Long-Term Post-Operative Cognitive Decline in the Elderly: The Effects of Anesthesia Type, Apolipoprotein E Genotype, and Clinical Antecedents

Marie-Laure Ancelin, Guilhem de Roquefeuil, Jacqueline Scali, François Bonnel, Jean-François Adam, Jean-Claude Cheminal, Jean-Paul Cristol, Anne-Marie Dupuy, Isabelle Carrière and Karen Ritchie

Inserm, Montpellier, France; Univ Montpellier 1, Montpellier, France
CHU Montpellier, Service d’Orthopédie 3, Hopital Lapeyronie, Montpellier, France
CHU Montpellier, Service Anesthésie, os et articulations, Hopital Lapeyronie, Montpellier, France
CHU Montpellier, Laboratoire de Biochimie, Hopital Lapeyronie, Montpellier, France

Accepted 25 June 2010

Abstract. Cognitive dysfunction in the elderly commonly observed following anesthesia has been attributed to age-related neuronal changes exacerbated by pharmacotoxic effects. However, the extent to which these changes may persist following recovery from surgery is still largely unknown. This study investigates the long-term effects of anesthesia on cognitive functioning after orthopedic surgery in 270 elderly patients over the age of 65 who completed a computerized cognitive battery before and 8 days, 4 and 13 months after surgery. Their performance was compared to those of 310 elderly controls who completed the same neuropsychiatric evaluation at baseline and one-year interval. Multivariate analyses adjusted for socio-demographic variables, depressive symptomatology, vascular pathology as well as baseline cognitive performance. We found early and transient post-operative decline in reaction time and constructional praxis. With regard to long-term changes we observed improvement compared to controls in most verbal tasks (probably due to learning effects). On the other hand, a clear dissociation effect was observed for several areas of visuospatial functioning which persisted up to the 13-month follow-up. This specific pattern of visuospatial deficit was found to be independent of apolipoprotein E genotype and closely resembles what has recently been termed vascular mild cognitive impairment, in turn associated with subtle sub-cortical vascular changes. The observation of only minor differences between persons operated by general and regional anesthesia makes it difficult to attribute these changes directly to the anesthetic agents themselves, suggesting that cognitive dysfunction may be attributable at least in part to peri-operative conditions, notably stress and glucocorticoid exposure.

Keywords: Anesthesia, apolipoprotein E, mild cognitive impairment, post-operative cognitive decline

INTRODUCTION

Although cognitive decline in elderly persons following anesthesia has been reported in the literature for over a century, there is still lack of consensus as to whether anesthetic agents may directly cause permanent cognitive loss. The general concern has been that while the potential neurotoxicity of anesthetics may be well tolerated by younger persons, age-related losses in cerebral reserve, increased permeability of the blood-brain barrier and slower drug elimination rates may lead to adverse effects and perhaps also precipitate neurodegenerative disorders. Some neuropathophysio-

*Correspondence to: Karen Ritchie, Inserm U888, Hopital La Colombière, 39, avenue C. Flahaut, BP 34493, 34093 Montpellier Cedex 5, France. Tel.: +33 4 99 61 45 60; Fax: +33 4 99 61 45 79; E-mail: karen.ritchie@inserm.fr.
clinical studies have suggested that post-operative cognitive disorder (POCD) may even share common mechanisms with Alzheimer’s disease (AD) through plasma amyloid-β (Aβ) deposition and tau phosphorylation [1–3]. The principal methodological problem for research in this area lies in controlling for the many other causes of cognitive dysfunction which may confound results, notably clinical antecedents, co-morbidity and genetic vulnerability (see for reviews [4–6]). Most early studies were carried out on patients undergoing cardiac surgery revealing extensive cognitive disorder in a wide range of functions, most of which, however, were attributable to pre-existing cardiac insufficiency, peri-operative hemodynamic instability and very high rates of post-operative depression.

While subsequent studies conducted on non-cardiac surgery have generally agreed POCD to be quite common in the short-term (up to several weeks after surgery) with no differences between regional (RA) and general anesthesia (GA) [7–9], there have been few non-cardiac studies of long term consequences (over a year) [4–6]. While there is limited evidence of POCD 6 months after surgery, the validity of the results remains questionable due not only to failure to take into account the confounding factors described above but also a too narrow a range of cognitive tests (often restricted to tests used to diagnose dementia) and underpowered statistical analyses [4]. In addition, most studies have excluded patients with pre-existing cognitive, psychiatric, or central nervous system disorders, as well as patients taking tranquilizers or antidepressants, making them not only non-representative of elderly populations undergoing anesthesia, but also excluding the possibility of examining interaction effects [10,11]. Cognitive difficulties are, however, also common in elderly persons who do not undergo anesthesia, so that the failure of previous studies to provide a non-operated control groups may have led to an overestimation of anesthetic effects especially when long-term effects are examined. To date only one long-term study of POCD after major non-cardiac surgery has made a comparison between those cases with and without pre-existing cognitive dysfunction (regional or general). Subjects are compared with elderly persons with stable cognitive functioning over the past year at baseline, and no exposure to anesthetic agents over the one-year study period.

METHODS

Selection of patients and control subjects

Two hundred and seventy patients over the age of 65 coming for elective orthopedic surgery (hip or knee replacement for 94.1% of the subjects) were recruited into the study between October 1998 and January 2002. Persons with dementia, auditory, or visual impairment that would preclude cognitive testing or non-fluent French speakers were excluded from the study. Ethics approval was given by the national ethics committee and written informed consent was obtained from all participants. For ethical reasons, randomization to RA or GA was not possible and furthermore the study aimed to observe current clinical practice. The anesthetists in the study declared the principal reason for allocation to RA or GA were the physical and mental status of the patient and these factors are included as co-variates in the analyses relating to anesthesia type. The 310 subjects constituting the comparison group are taken from the Eugeria longitudinal study of cognitive ageing. These were persons over 60 years of age recruited through 63 randomly selected general practitioners in the Montpellier region [29]. Subjects selected for the control group were free of dementia and without pre-existing cognitive deterioration at baseline (DECO Score > 30, see below) and did not undergo anesthesia during follow-up. Control subjects had been given the same neuropsychological examination as the anesthetized patients at baseline and one year later.
Cognitive evaluation

Each subject was examined pre-operatively, and at eight days [median (IQR): 8 (7–8) days], four months [112 (98–145) days], and 13 months [391 (372–410) days] after surgery using a comprehensive computerized cognitive battery. This examination, ECO (Examen Cognitif par Ordinateur) assesses primary memory, verbal and visuospatial secondary memory, implicit memory, language skills (naming, verbal fluency), visuospatial performance (ideational, ideomotor and constructive apraxia), functional and semantic categorization of visual data, visual reasoning and form perception, and focused and divided attention (visual and auditory modalities) [29]. Reaction time and response latencies were recorded using a tactile screen. The following summary cognitive domains were examined in the present study:

Reasoning
Assessed by a multiple choice task requiring completion of a logical visual series with increasingly complex decision rules

Attention
Measured by response time on a dual task (simultaneous visual selection and counting of auditory stimuli)

Primary memory
Assessed by immediate recall of a list of first names (verbal memory) and recall of a trail traced on the computer screen (visuospatial memory)

Secondary verbal and visual memory
Measured by (i) delayed recall of proper names with and without semantic and phonetic cueing; (ii) delayed recall of faces associated with the proper names; and (iii) recall of two narratives – one with a logical sequence and the other a description requiring visual recall

Implicit memory
Time taken to recognize the previously learnt proper names and distracters progressively built up by random pixels on the computer screen

Visuospatial ability
Measured by the number of elements correct in the copying of complex meaningful and meaningless figures

Language
Assessed by object naming and verbal fluency.

In addition to cognitive assessment at the time of admission, pre-existing cognitive deterioration is established by an informant questionnaire completed by care-givers (DECO - Détérioration Cognitive Observée) which measures changes in cognitive performance over the past year. Previous validation studies in both clinical and population settings have shown this instrument to be highly sensitive to early modifications in cognitive functioning due to multiple causes [30]. DECO scores have a maximum of 38 (no change over the past year) down to 0 (significant change over the 19 areas of cognitive performance examined). A score lower than 30 has been established by Receiver Operating Characteristics analysis to indicate a high probability of dementia within a general population sample [30].

General questionnaire

A general questionnaire obtained information on socio-demographic status, current pathologies and treatment, previous surgical interventions, pre-operative physical status using the American Society of Anesthesiologists’ (ASA) classification, surgical procedures, type of anesthesia, duration of hospitalization and management after discharge. The Center for Epidemiologic Studies-Depression Scale (CES-D) [31] was used to detect levels of current depressive symptomatology with a cut-off score equal or above 16 indicating clinical levels of depression. Ability to perform activities of daily living was assessed by the Adaptation and Behaviour scale (ECA – Echelle de Comportement et d’Adaptation) [32]. This questionnaire is completed by relatives and has been constructed with reference to the disability classifications given by the W.H.O. in the International Classification of Impairments, Disabilities and Handicaps [33]. Venous blood samples were taken for ApoE genotyping as described previously [34].

Statistical analysis

Logistic regression was used to compare cognitive decline between inclusion and each follow-up with one-year changes in cognitive functioning in the control group (reference, OR = 1). ORs were adjusted for age, gender, education level, depressive symptomatology, cerebrovascular and cardiac pathology, and baseline cognitive score (i.e., covariates that were associated with cognitive decline at p < 0.10). Cognitive
Table 1
Comparison of subjects exposed to general and regional anesthesia with controls

<table>
<thead>
<tr>
<th>Subjects with anesthesia (n = 270)</th>
<th>Subjects without anesthesia (n = 310)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>71 (66–76)</td>
<td>74 (69–81)</td>
</tr>
<tr>
<td>Gender (female %)</td>
<td>60.4</td>
<td>70.6</td>
</tr>
<tr>
<td>Education level (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>25.9</td>
<td>4.2</td>
</tr>
<tr>
<td>9 years</td>
<td>45.6</td>
<td>45.2</td>
</tr>
<tr>
<td>12 years</td>
<td>17.8</td>
<td>32.9</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>10.7</td>
<td>17.7</td>
</tr>
<tr>
<td>CESD ≥ 16 (%)</td>
<td>17.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Cerebrovascular and cardiac pathology</td>
<td>6.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*p* Chi² or Mann Whitney.

Post-operative cognitive change across time

In multivariate logistic models, anesthesia exposure was associated with specific cognitive changes (Table 2). Eight days after anesthesia, a decline was observed in reaction time (OR = 1.74, p = 0.01), constructional praxis (OR = 3.6, p < 0.0001) and geometr-
Decline after 8 days was observed in patients undergoing GA in reaction time (OR = 1.97, \( p = 0.006 \)) and verbal fluency (OR = 1.54, \( p = 0.04 \)) and in immediate visual memory for RA patients (OR = 2.13, \( p = 0.01 \)) (data not shown). Decline in constructional praxis was observed both with RA (OR = 2.19, \( p = 0.03 \)) and GA (OR = 4.61, \( p < 0.0001 \)), but returning to normal levels at 4 or 13 months. Decline in immediate visual memory was observed for GA at 13 months (OR = 2.15, \( p = 0.002 \)). Decline in geometric form association persisted even at 13-month follow-up in RA (OR = 2.96, \( p = 0.002 \)) or GA patients (OR = 2.60, \( p = 0.0002 \)).

Mixed models were used to compare the global cognitive evolution of persons receiving GA compared to RA over the observation period (Table 3). Persons receiving GA appeared to undergo a slightly more rapid recovery in constructional praxis (OR = 0.88, \( p = 0.01 \)) during the 13 month follow-up compared to those with RA. No significant differences were observed on other cognitive tasks. The same results were obtained when the ApoE variable was not included as a confounding factor.

**DISCUSSION**

**Post-operative cognitive change across time**

This study, using a wider range of neuropsychological tests than in previous reports, suggests that anesthesia during orthopedic surgery has adverse effects on reaction time, constructional praxis, geometric form association, and immediate visual memory. These effects appeared to be independent of ApoE genotype as observed by previous studies of both cardiac [24–26] and non-cardiac [27,28] surgery.

Early and transient post-operative decline was observed for reaction time and constructional praxis as previously reported [35], suggesting reversibility of the deleterious effect of the anesthesia and/or complete elimination of residual anesthetics. On the other hand, a highly significant deterioration in geometric form association and visual memory were observed to persist even after 13-month follow-up suggesting more permanent effects on brain functioning. In contrast improve-
ment was observed on some verbal tasks (naming, immediate and delayed verbal recall, narrative, and name-face pair recall). Improvement on verbal tasks compared to the control group is most likely due to practice effects as controls only completed the battery at baseline and one year whereas the patients exposed to anesthesia completed it four times. Indeed, the control group used had already been assessed in the year before this study so it was not possible to have equal number of administrations. This learning effect is likely on the other hand to have led to an underestimation of the decline observed on visuospatial tasks. Our study shows a probable unilateral effect which is consistent with observations that even in normal aging visuospatial functions may be particularly vulnerable, and are amongst the earliest signs of mild cognitive impairment [36, 37]. A distinction has recently been made between vascular and non-vascular mild cognitive impairment; the former showing significant deterioration in visuospatial functions whereas the latter concerns primarily verbal memory [38] indicating a possible double dissociation. Cases of vascular mild cognitive impairment are more likely to evolve towards either vascular or mixed vascular and AD dementia. Furthermore a distinctive pattern of predominantly visuospatial dysfunction has been shown to be related to microalterations in white matter lesions and other subcortical vascular changes [39]. This would suggest that anesthesia may have initiated or accelerated subtle vascular lesions leading to more permanent effects. The question remains as to whether the changes we have observed in visuospatial functioning can be directly attributed to the anesthetic agents themselves. Indeed, corticosteroid secretion, whether endogenous (stress reaction which may be consecutive to illness, pain and surgery) or exogenous (as frequently used in orthopedic geriatric patients) has previously been associated with cognitive decline [40–45].

**Effect of anesthesia type**

No significant differences were found on most neuropsychological tests according to the type of anesthesia used. An increased risk of cognitive decline was observed after 8 days only in reaction time and verbal fluency with GA and in immediate visual memory for RA. Constructional praxis was found to decline in both GA and RA, with GA patients appearing to have a more rapid recovery during the 13-month follow-up compared to those with RA. The few randomized studies which have previously been conducted failed to observe significant differences in cognitive impairment as a function of anesthesia type [7–9]. Recent in vivo and in vitro NMR studies have shown selective neurotoxic effects, including increased capacity to oligomerize Aβ peptide, after GA by inhalation with halogenated anesthetics of small molecular weight compared to intravenous anesthetics such as propofol or thiopental [1,46–48]. In our sample, 95.7% of the patients who had GA received a combination of both halogenated and intravenous anesthetics and we could not address this specific question. While a pattern of visuospatial decline consistent with vascular changes

### Table 3

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>GA effect</th>
<th>GA*Time effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time(^{a})</td>
<td>-0.014(0.019)</td>
<td>0.46</td>
</tr>
<tr>
<td>Geometric form association</td>
<td>-0.18 (1.55)</td>
<td>0.91</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>-0.92 (1.21)</td>
<td>0.45</td>
</tr>
<tr>
<td>Implicit memory</td>
<td>-0.56 (0.27)</td>
<td>0.04</td>
</tr>
<tr>
<td>Narrative recall</td>
<td>-1.15 (0.96)</td>
<td>0.23</td>
</tr>
<tr>
<td>Logistic Mixed Model</td>
<td>OR [95%CI]</td>
<td>p</td>
</tr>
<tr>
<td>Attention dual task</td>
<td>0.97 [0.57–1.65]</td>
<td>0.90</td>
</tr>
<tr>
<td>Constructional praxis</td>
<td>2.06 [1.03–4.12]</td>
<td>0.04</td>
</tr>
<tr>
<td>Logical visual series</td>
<td>0.79 [0.42–1.51]</td>
<td>0.48</td>
</tr>
<tr>
<td>Object naming</td>
<td>0.78 [0.41–1.49]</td>
<td>0.45</td>
</tr>
<tr>
<td>Immediate verbal recall</td>
<td>1.58 [0.85–2.94]</td>
<td>0.15</td>
</tr>
<tr>
<td>Visuospatial span</td>
<td>1.10 [0.66–1.82]</td>
<td>0.72</td>
</tr>
<tr>
<td>Delayed verbal recall</td>
<td>1.52 [0.67–3.46]</td>
<td>0.32</td>
</tr>
<tr>
<td>Delayed visual recall</td>
<td>1.04 [0.60–1.82]</td>
<td>0.88</td>
</tr>
<tr>
<td>Name-face pair recall</td>
<td>0.87 [0.45–1.70]</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Each (linear or logistic) model included age, gender, education level, time, ASA score, ApoE4, anesthesia type, and, the interaction between time and anesthesia.

\(^{a}\)time = number of months between inclusion and follow-up, \(^{b}\)log-transformed values.

A distinction has recently been made between vascular and non-vascular mild cognitive impairment; the former showing significant deterioration in visuospatial functions whereas the latter concerns primarily verbal memory [38] indicating a possible double dissociation.
suggests anesthesia may be responsible for subtle subcortical damage, failure to find a difference according to anesthesia type suggests that it may not be the anesthetic compounds per se which precipitate POCD, but rather the peri-operative effects of surgery, anxiety, stress, pain, prolonged starvation, all of which may be cumulative [49].

Limitations and strengths

Although the dropout rate between eight days and 13 months (21.1%) in this study was a cause of concern, analysis of the various demographic variables suggested that non-returners were not significantly different in terms of socio-demographic or clinical variables and there was no interaction between return/no return and anesthetic choice.

Unlike most previous studies, the absence of exclusion criteria concerning the initial health status of the patients permitted the evaluation of cognitive change under externally valid conditions, reflecting fairly well the geriatric orthopedic surgery population, and also allowing us to examine the individual effects of these variables. Lastly, since the same test battery was used on all four test occasions, repeated examination could have led to an underestimation of the proportion of subjects with cognitive decline, considering that subjects who did not decline could be those for whom a learning effect did not occur.

In this study, the subjects were not randomly assigned to anesthesia type and the proportion of subjects at risk (older and more frequently with severe comorbidity) was higher in the RA than in the GA group, which may reflect the existing concerns of anesthetists and patients as to the possible effects of GA. This may be a significant indication bias both in our study and previous observations. Even in randomized studies the rate of subjects excluded due to contraindications to one given type of anesthesia is high (for instance 37% in [7]). On the other hand age, health status and cognitive functioning at the time of surgery, which anesthetists declared to be the principal criteria for anesthesia type, were taken into account in the multivariate analyses.

Despite these limitations, this study has several strengths, namely a larger sample size (270 patients) than in most previous long-term controlled studies and longer duration of follow-up (up to 13 months). The study used a neuropsychological battery which aimed at detecting changes in the full range of information-processing functions and not just confined to tests used in dementia screening. We also had access to a cognitively healthy control group and were able to adjust for a large range of confounding factors (age, gender, education level, depressive symptomatology, cerebrovascular, and cardiac pathology, genetic vulnerability to cognitive decline, and baseline cognitive performance). However, we could not control for other preoperative factors (such as pain or stress) which may have led to an under-estimation of post-operative cognitive decline.

CONCLUSION

In this study, transient cognitive decline was observed in the early post-operative period in reaction time and constructional praxis, with decline on certain visuospatial functions persisting to over one year follow-up. Improvement on the other hand in verbal domains probably reflects learning effect. This dissociation between verbal and visuospatial skills is suggestive of underlying sub-cortical vascular damage but as few clinically significant differences were observed according to anesthesia type it is difficult to attribute this detriment to anesthesia per se as cumulative peri-operative factors may also have played a role. Neuroimaging studies for the detection of subtle cerebrovascular changes before and after surgery are required to confirm the link with visuospatial deficits.

ACKNOWLEDGMENTS

We owe special thanks to Daniele Dietz and Christophe Bonnel for their help in interview and data acquisition as well as to Annie Fraysse for data monitoring and to Hill Rom France for the provision of a mobile arm permitting subjects to respond to a computer screen in a reclining position. The study was supported by a university hospital clinical research grant (PHRC 1996 and AOI 2002 U.F. 7549).


REFERENCES


Cholinergic Central System, Alzheimer’s Disease, and Anesthetics Liaison: A Vicious Circle?

Daniela Schifilliti, Letterio B. Santamaria, Giovanni Rosa, Gianfranco Di Nino, Pravat K. Mandal and Vincenzo Fodale

Department of Neurosciences, Psychiatric and Anesthesiological Sciences, University of Messina, Policlinico G. Martino, Messina, Italy

Department of Anesthesiology, Critical Care and Pain Medicine, Neuroanaesthesia and Neurocritical care, University of Rome “La Sapienza”, Rome, Italy

Department of Surgical and Anesthesiological Sciences, University of Bologna, Bologna, Italy

Neurospectroscopy and Neuroimaging Laboratory, National Brain Research Center, Manesar, Gurgaon, India

Accepted 12 August 2010

Abstract. Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by the accumulation and aggregation of amyloid-β peptide and loss of forebrain cholinergic neurons, resulting in progressive loss of memory and irreversible impairment of higher cognitive functions. Several studies have accounted for the close relationship between AD and the central cholinergic system, suggesting that a dysfunction of acetylcholine containing neurons in the brain contributes significantly to the cognitive deficit of individuals with AD. The aim of the present review is to survey current literature on this topic in order to provide a clear understanding of the role of the cholinergic system in the development and neurodegenerative process of AD. The implications for anesthesia are also discussed. This knowledge could be valuable to improve anesthesia performance and patient safety.

Keywords: Alzheimer’s disease, amyloid-β peptide, anesthesia, anesthetics, central cholinergic system, cholinergic receptors, liaison, neurodegenerative disorders, oligomerization

INTRODUCTION

First described in 1906 by German psychiatrist and neuropathologist, Aloysius Alzheimer, Alzheimer’s disease (AD) is the most common form of dementia in elderly people, accounting for around 50–60% of all cases of mental deterioration among persons over 65 years of age. It is clinically characterized by a progressive loss of memory, which begins early in the disease process, and a decline in higher cognitive functions. Other cognitive (disorientation, confusion, and problems with reasoning) and behavioral (agitation, anxiety, delusion, depression, and insomnia) disturbances appear as the disease progresses, and impair functions in activities of daily living. The mean duration of AD is around 8.5 years (time between onset of clinical symptoms and death), but the course of the disease is fluctuant.

In the last three decades, a considerable research effort has been directed towards discovering the cause of AD, with the ultimate hope of developing safe and effective treatments.
effective pharmacological treatments. The postmortem and antemortem systematic investigations of the brains of patients with AD have consistently demonstrated that the brain of an affected individual exhibits extracellular plaques of aggregated amyloid-β (Aβ) protein, intracellular neurofibrillary tangles that contain hyperphosphorylated tau protein, and a profound loss of basal forebrain cholinergic neurons that innervate the hippocampus and the neocortex, which are associated with higher mental functions [4]. As a result, the so-called “cholinergic hypothesis” of AD was developed. It posits the degeneration of the acetylcholine containing neurons in the basal forebrain and the loss of cholinergic transmission in the cerebral cortex, and other areas, as the principal cause of the cognitive decline observed in patients with AD [2,4,6–10].

The aim of this short review is to survey available up-to-date information about the plausible links between cholinergic system and AD, for a clear understanding of the behavioral role of the former, and a more detailed understanding of the molecular pathology of the disease. The implications for anesthesia are also discussed. General anesthetic agents, and several drugs administered during anesthesia, interact with the central cholinergic system (CCS) [11], and, given the substantial number of people affected by this disease, it is likely that anesthetists will encounter many patients with AD [12,13]. Therefore, we believe that this kind of knowledge could be a useful means to decrease the risk of unwelcome events and increase anesthesia performance, patient safety and, in the future, maybe outcome.

CHOLINERGIC SYSTEM

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain. It regulates high cognitive functions such as memory, learning, dendrite arborization, neuronal development, and differentiation [11,14]. Acetylcholine (ACh) was the very first neurotransmitter to be identified, acting both in the central nervous system (CNS) and in the peripheral nervous system (PNS). ACh evokes responses similar to those of nicotine or muscarine, and therefore, its receptors are subdivided into nicotinic receptors and muscarinic receptors [11].

Nicotinic receptors

Nicotinic receptors (nAChRs) are members of a superfamily of ligand-gated ionic channels, and are present in the neuromuscular junction of the skeletal muscle, in autonomous ganglions, in the adrenal medulla, and in the CNS [15]. They are characterized by a pentameric structure formed by homomeric alpha (α) and beta (β) subunits: in humans eight α-subunits (α2 – α7, α9 and α10) and three β-subunits (β2 – β4) have been identified [15,16]. Depending on their distribution, nAChRs are divided into muscular and neuronal. They share structural and functional properties with other ligand-gated channels such as GABAA receptor, 5-HT3, and glycine [15]. Muscular and neuronal subunits share the same basic layout of a large extracellular N-terminal domain, which contributes to the linkage of the agonist, four hydrophobic transmembrane domains (from TM1 to TM4), a large cytoplasmic loop between TM3 and TM4, and a short C-terminal extracellular domain. It is believed that the transmembrane region, M2, forms the ionic pore of nAChRs [15]. The autonomous ganglions form, instead, homomeric complex α7 and heteromeric complex α3/β4, among which the compound (α3)2(β4)3 is predominant. Electrophysiological studies on interneurons have documented that α7 receptors subtypes are presynaptic, while α4/β2 are both presynaptic and postsynaptic [11]. Numerous studies have revealed a wide, but non-uniform, distribution of nAChRs in the brain. For example, α7 are located across all layers in the cingulated, temporal and frontal cortex, hippocampus, substantia nigra, while α4/β2 are located in the deeper layers of the cerebral cortex [11]. Other locations include the thalamus, putamen, and cerebellum, with a wide variation in density relative to physiological age-related brain decline [17].

Muscarinic receptors

Muscarinic cholinergic receptors (mAChRs) are a family of the ligand-gated K+ channels with a metabotropic function. In the peripheral system, mAChRs regulate the classical muscarinic actions of ACh in the organs and tissues innervated by parasympathetic nerves, although they may also be present in places where parasympathetic innervations are missing (smooth muscular and endothelial cells of most blood vessels) [15]. In the CNS, instead, mAChRs are involved in the regulation of numerous functions: cognitive, behavioral, sensory, motor, and autonomic [15,
The basic functions of muscarinic cholinergic receptors are mediated by interaction with protein G and, therefore, the changes induced by G proteins in the function of different effector molecules. mAChRs can be classified into five different subtypes (M₁-M₅), according to their primary structure and property of activating/inhibiting cation transmembrane current [18]. M₁, M₃, and M₅ subtypes are postsynaptic receptors and are coupled with a G-protein alpha subunit (11/1q) that activates adenylate cyclase and phospholipase C, generating inositol 1,4,5-triphosphate (IP₃) and diacylglycerol with subsequent activation of Ca²⁺ dependent phenomena [15,18]. The activation of M₁, M₃, and M₅ can also produce the activation of phospholipase A2 leading to the release of arachidonic acid and subsequent synthesis of eicosanoids, which finally leads to autocrine/paracrine stimulation of the adenyl-cyclase [15]. M₂ and M₄ subtypes, instead, are presynaptic receptors that interact with G-protein, with adenylyl cyclase inhibition, decrease of the cyclic AMP, activation of K⁺ channels, and inhibition of the voltage-gated Ca²⁺ channels [11,15]. The functional consequences of these effects are excitable membrane hyperpolarization and inhibition. Following activation by classical or allosteric agonists, mAChRs can be phosphorylated by various kinases, associated with receptors or regulated by second messengers. Once phosphorylated, the muscarinic cholinergic receptors may interact with different adapter proteins, with the result that the signals generated by mAChRs may be modulated differentially, leading to a short-or long-term desensitization of a particular way, or the activation of the MAPK pathways, downstream phosphorylation of mAChRs, or long-term potentiation of the stimulation of PLC associated with mAChRs [15].

CENTRAL CHOLINERGIC SYSTEM AND AD

Biochemical investigation of AD began between the late 1960s and early 1970s. The hope was that a clearly defined neurochemical abnormality would be identified, providing the basis for the development of rational therapeutic interventions [2].

In the mid 1970s, several authors demonstrated substantial neocortical deficits in the enzyme responsible for the synthesis of acetylcholine (ACh) and choline acetyltransferase [2,19–22]. Subsequent discoveries of reduced choline uptake [23], ACh release [24] and loss of cholinergic perikarya from the nucleus basalis of Meynert [25] confirmed a substantial presynaptic cholinergic deficit. As result, the so-called “cholinergic hypothesis” of AD was proposed. It was based on two central notions: the first is that the forebrain cholinergic system sustains a wide variety of cognitive processes; the second is that a dysfunction of cholinergic neurons in the brain contributes significantly to cognitive decline in AD [11]. The involvement of the cholinergic system in cognitive functions (learning and memory) is widely documented in animal and human research. For example, antimuscarinic agents, such as scopolamine and atropine, have been shown to impair memory performance in a variety of behavioral paradigms in rodents [6]. Similarly, nicotinic antagonists can acutely impair memory and learning [11], while acute or chronic treatment with nicotine or nicotinic agents significantly improves memory performance of rats [11,26, 27]. Epidemiological studies on patients who smoke have also demonstrated the benefits of nicotine on cognitive processes, improvement in attention capacity, and acquisition and retention of verbal and non-verbal information [28].

In the last few decades, several studies have explained the close relationship between AD and the central cholinergic system. Primarily based on the post-mortem analysis of the brain of patients with AD, these studies highlighted the presence of extracellular neuritic plaques, intracellular neurofibrillary tangles, and loss of neurons and synaptic integrity in specific brain areas [3,4,29–33]. Neuritic plaques are multicellular lesions that contain a compact deposit of A/β surrounded by distrophic neurites, activated microglia and reactive astrocytes [4]. A/β derives from an amyloid-β protein precursor (AβPP) by proteolytic cleavage, and there are two forms of neuritic plaques: amyloid-β₁₋₄₂ (A/β₁₋₄₂) and amyloid-β₁₋₄₀ (A/β₁₋₄₀) [11]. In the brain with AD, the former is deposited first and is the predominant form in senile plaques, whereas the latter is deposited later in the disease process [4]. Neuritic plaques are prominent in the entorhinal cortex, hippocampus and association cortices [33–36]. Their number does not appear to be associated with the severity of dementia, although a clinical correlation between elevated level of A/β peptides in the brain and cognitive decline has been reported [4,37]. Neurofibrillary tangles are composed of paired helical filaments (PHF) and occasional single straight filaments, mainly containing an abnormal hyperphosphorylated form of the microtubule associated protein tau [4]. Formation of PHF-tau reduces the ability of tau to stabilize microtubules, leading to disruption of neuronal transport and eventually to the death of affected neurons [4,38–40]. Simi-
larly to the senile plaques, in the brain of an individual with AD, they are particularly abundant in the entorhinal cortex, hippocampus, amygdala, association cortices of the frontal, temporal and parietal lobes, and certain subcortical nuclei that project to these regions [4]. The number of cortical neurofibrillary tangles is strongly correlated with the severity of dementia [4]. Finally, degenerating neurons and synapses in the brain of patients with AD have been reported, especially within regions characterized by high densities of plaques and tangles. Biochemical investigations of tissues from biopsy and autopsy indicate that various neurotransmitters and modulators including ACh, serotonin, noradrenaline and somatostatin are differentially altered in the brains of individuals with AD [2,4,41]. The early and most consistently reproduced finding is a profound reduction in the activity of the ACh-synthesizing enzyme, choline acetyltransferase (ChAT), in the neocortex, which correlates positively with the severity of dementia [4,7,20]. Reduced choline uptake, ACh release and loss of cholinergic neurons from the basal forebrain region further indicate a selective presynaptic cholinergic deficit in the hippocampus and neocortex of brains of individuals with AD [2,4,42]. Extensive studies on cholinergic receptors demonstrated that M_2 muscarinic receptors, most of which are located on presynaptic cholinergic terminals, are reduced in the brains of individuals with AD [4,7,43]. The density of postsynaptic M_1 receptors remains unaltered, while the profiles of M_3 and M_4 receptors in the brains of patients with AD remain equivocal [4]. Mostly composed of α_4/β_2 subunits, high-affinity nicotinic binding sites are markedly reduced in the hippocampus and cortex of postmortem brains of individuals with AD [2,44]. A significant decrease in α_7 protein expression in the hippocampus has also been reported [4,45], although a recent immunocytochemical study demonstrated an increase in the proportion of astrocytes expressing α_7 immunoreactivity in the hippocampus and entorhinal cortex of the brain with AD relative to age-matched controls [4,46].

CENTRAL CHOLINERGIC SYSTEM AND AD: A VICIOUS CIRCLE

Because Aβ deposits precede any other lesion in the brain of individuals with AD, it is likely that the overexpression and deposition of Aβ play a critical role in the development and neurodegenerative process of AD [29]. The relationship between Aβ deposits and central cholinergic system is, therefore, of enormous interest.

Concentrations of Aβ seem to have a neuromodulatory role in the regulation of various cholinergic neurotransmitter functions through adverse effects on multiple aspects of ACh synthesis and release [4,5,47]. In particular, a treatment with very small concentrations of Aβ peptide significantly decreases the number of nicotinic receptor binding sites in cell lines [48] and, after long-term exposure, induces cholinergic cell toxicity [4].

Conversely, the activation of selected cholinergic receptors appears to be involved in the regulation of AβPP metabolism to Aβ peptide production, as well as phosphorylation of the tau protein [5,49]. Selective agonists of M_1 receptors lead to the processing/transformation of AβPP into non-amyloidogenic products [5,50], suggesting that agonists of M_1 receptors might mediate a dual action (increasing AβPP release and decreasing Aβ formation) capable of modifying the neuropathogenic process of AD [51]. Moreover, M_1 agonists decrease the phosphorylation of tau protein [4,50]. Also the activation of nicotinic cholinergic receptors may produce disease-modifying actions in AD [6]. The ability of nicotine to evoke neuroprotective effects has been demonstrated in both in vitro and in vivo models of neural toxicity [52,53], highlighting how it inhibits the development of cellular toxicity induced by Aβ peptide [54].

In other words, it appears that AD may be associated with a “vicious circle” whereby lesions of the basal forebrain cholinergic neurons or transient inhibition of cortical ACh release can elevate local AβPP synthesis, intensifying both the production and neurotoxicity of Aβ peptide which, in turn, further increases the phosphorylation of tau protein and, consequently, the cholinergic deficit [4,55].

CENTRAL CHOLINERGIC SYSTEM AND AD: IMPLICATIONS FOR ANESTHESIA

During anesthesia, decrease in ACh release and depression of cholinergic transmission facilitate all the desirable effects of general anesthetics, such as loss of consciousness, pain, voluntary movements and memory [56].

Most anesthetic agents and drugs administered during anesthesia, with few exceptions, interact with both nicotinic and muscarinic receptors [11]. Volatile anesthetics and ketamine are potent inhibitors of nAChRs;
desflurane selectively binds $M_1$ receptor subtype enhancing the signal for low concentrations and depressing the pathway for higher doses; sevoflurane depresses $M_1$ and $M_3$ signaling in a dose-dependent manner, while isoflurane interferes only with $M_3$ [5, 18]. Barbiturates are strong competitive antagonists of $m$ACHRs, while propofol acts on nicotinic and muscarinic cholinergic receptors only at concentrations much higher than used clinically [5]. Opioids (morphine, fentanyl) depress cholinergic signals mediated by $n$AChRs and $m$ACHRs, whereas remifentanil does not alter acetylcholine release in cholinergic synapses [62]. Similarly, desflurane can induce $A_3$ production only at concentrations much higher than used clinically [5]. These inhaled anesthetics act in the processing of $A_3$ protein. Moreover, recent in vitro experiments have demonstrated that some anesthetics act directly in the processing (i.e., production and oligomerization) of $A_3$. Clinical concentrations of isoflurane cause altered processing of $A_3$PP, increasing $A_3$ peptide production in both human neuroglioma and mice brain cell lines [61, 62]. Similarly, desflurane can induce $A_3$ peptide production, but only in the presence of hypoxia [63], whereas the inhaled anesthetics halothane and isoflurane, at higher concentrations, encourage clumping of $A_3$ protein. In particular, in nuclear magnetic resonance spectroscopic studies, it has been noted that halothane and isoflurane induce structural alteration of $A_3$ peptides from the soluble monomeric $\alpha$-helical form to oligomeric $\beta$-sheet conformation oligomerization, which may hasten the onset of AD [5,64,65]. Finally, studies have been conducted also on intravenous anesthetics, highlighting how propofol, at very high concentrations, induces oligomerization, while clinical concentrations of propofol inhibit it [4,66]. Similarly thiopentone, also at high concentrations, does not interact with $A_3$, which remains in its monomeric form [67,68]. Propofol and thiopental can, therefore, be considered relatively safe [69].

CONCLUSIONS

The brain of an individual with AD is characterized by the accumulation of $A_3$ peptide, and loss of basal forebrain cholinergic neurons [70,71]. The relationship between $A_3$ deposits and the central cholinergic system has been widely investigated. Activation of selected acetylcholine containing receptors is involved in the regulation of $A_3$PP metabolism to $A_3$ production [49]. Conversely, very low concentrations of $A_3$ can inhibit various cholinergic neurotransmitter functions independent of its apparent neurotoxicity [72]. Therefore, it seems justified to say that AD is associated with a “vicious circle” whereby lesions of the basal forebrain cholinergic neurons or transient inhibition of cholinergic neurotransmission intensify $A_3$PP metabolism, increasing the production of amyloidogenic $A_3$ peptides which, in turn, further increase the cholinergic deficit [4,55].

In terms of anesthesia, this premise suggests prudence when selecting an anesthetic agent. Most anesthetics and drugs administered during anesthesia interact with the central cholinergic system. They can, therefore, affect $A_3$PP metabolism leading to persistent increase in concentrations of AD-associated $A_3$ peptides [59,60]. Moreover, recent in vitro experiments have demonstrated that some anesthetics act in the processing of $A_3$ in a straightforward way. For example, inhaled anesthetics such as halothane, isoflurane and desflurane cause $A_3$ peptide oligomerization more than others (i.e., propofol and thiopental) [5].

However, further clinical and experimental evidence is imperative in order to help anesthesiologists make the best choice.

ACKNOWLEDGMENTS

The research is supported by a grant from the Italian Ministry for University and Research, Program for the Development of Research of National Interest (PRIN Grant #2007H84XNH – Scientific coordinator: V. Fodale).


REFERENCES


[40] Billingsley ML, Kincade RL (1997) Regulated phosphorylation and dephosphorylation of tau protein: effects on micro
D. Schifilliti et al. / Cholinergic Central System, Alzheimer's Disease, and Anesthetics Liaison

S41


Over 35 million people worldwide are reported to suffer from Alzheimer’s disease (AD). With health-care advances and marked increase in life expectancy, there is an ever-increasing incidence of AD. Longevity and the continuous improvement of peri-operative medicine, reducing mortality and morbidity, have led to an exponential increment in surgery and, as a consequence, a larger number of aged patients are undergoing surgery. While anesthetics are indispensable clinical tools and generally considered safe and effective, in some situations there is a growing concern about the potential neurotoxicity of these agents. Particularly among the elderly, a number of cases of post-operative cognitive decline (POCD), both short-term and long-term, have been globally reported. It is argued, and justifiably so (with regard to cardiac surgery in particular, having several risk factors which could result in cognitive decline), that it is not possible to dissociate the effects of surgery and anesthesia. However, significant reports of cognitive decline on follow up of patients undergoing non-cardiac, prolonged surgical procedures under general anesthesia have resulted in several scientific groups focusing greater attention on the possible neurotoxic effect of anesthetics in POCD.

The overwhelming response to the call for articles for this supplemental issue is proof enough of the common note of concern and urgency shared by the scientific community to scrutinize the possible toxic effects (if any) of anesthesia in POCD (the long-term form simulating the clinical and molecular mechanisms involved in AD), particularly in the aged population. Scientists, anesthesiologists, neurologists, neuropsychologists and surgeons have expressed their expert views on various aspects of the pathophysiology of AD, and the role of anesthetics as a possible risk factor. These efforts, when viewed as a whole, will inevitably stimulate rethinking on the subject.

The introductory article by Dr. Finder provides a panoramic view of the classic and recent literature on the complex cellular and molecular mechanisms underlying AD, supported by subsequent articles which focus on the more recent observations in specific areas of molecular research. Amyloid-β (Aβ) plaques were considered the pathogenic species in AD; however, accumulating evidence suggests that plaques could represent final waste deposits, with the oligomeric intermediates representing the key toxic players since the severity of cognitive deficits in AD correlates with the level of oligomers in the brain but not with the total Aβ burden. The proposed neurotoxic effects of Aβ oligomers are synaptic failure, membrane disruption with Ca²⁺ influx, mitochondrial failure and oxidative stress, and recruitment of cellular factors or activation of cellular processes such as apoptosis and inflammation.

Aβ has a natural role in many functions of the nervous system. There is evidence that Aβ is part of the innate immune system of the brain and natural antibodies against oligomeric, fibrillar Aβ and plaques have been identified. However, with the aging process, there is a decrease in the level of these antibodies that could account for the reduced efficiency of the immune system, leading to decreased Aβ plaque clearance. An imbalance between production and clearance causes Aβ to accumulate and this may lead to AD. The elaborate review on anesthetics promoting in vitro AβPP metabolism and Aβ toxicity, by Dr. Barbara Eckel and colleagues, provides convincing evidence for the possible role of anesthetics in AD pathophysiology, while acknowledging the limitations of such in vitro studies. Dr. Gong and his team members stated in their article that inhaled anesthetic-induced hyperphosphorylation of tau protein is also a significant observation in animal model studies.

Systematic biophysical studies by Dr. Mandal and colleagues, using state-of-the-art NMR technique for Aβ peptide interactions with a range of varying sized anesthetics, have led to the conclusion that only smaller sized (e.g., isoflurane, desflurane, etc.) anesthetics (many of which are widely used in anesthesia today) can access the cavity containing critical amino acid...
residues (G29, A30, and I31) whose perturbation leads to Aβ peptide aggregation (oligomerization). This observation emphasizes the association of the size factor of anesthetics and their profound role in Aβ peptide aggregation. Based on this in vitro research, the thought-provoking novel concept put forward to the scientific community and the pharmaceutical industry is that it may be crucial to focus efforts on the development of new larger sized (~191 Å3) inhaled anesthetics. The novel NMR technique can be used to screen new generation anesthetic molecules.

Animal studies, conducted by Dr. Mena and her team, as well as many other investigators, show that plaque formation due to exposure to isoflurane is of significance. The exact mechanism(s) underlying AD are under great research scrutiny at the molecular and cellular level but continue(s) to evade total scientific understanding. This knowledge gap, if filled, could facilitate early intervention, better preventive measures, and more effective drug formulations to stem the progress of AD. The role of Aβ, tau, and S100β as biomarkers of cognitive decline is being currently evaluated.

Cardiac anesthesiologists have been perturbed by the reported cases of long-term POCD and procedures ensuring optimal perfusion, neuroprotective methods and stricter anesthetic protocol to mitigate this have not been as successful as desired. It is of interest to note that off-pump CABG has not significantly reduced the occurrence of POCD compared to on-pump. The clinical research report, by Dr. Karen Ritchie and her team, with close attention to study design, statistical and analytic procedures, on the long-term effects of anesthesia on cognitive functioning after orthopedic surgery in a large number of elderly patients, stresses the observation that POCD is not confined to cardiac surgery. As highlighted by Dr. Tripati and colleague, from a neurological diagnostic point of view, clinical awareness of the emerging metabolic, nutritional, endocrinical, toxic, autoimmune, cerebrovascular, genetic, infectious, and hemorheological factors need to be kept in mind in the differential diagnosis of dementia, to add to the already established causes of dementia, which require consideration when faced with POCD.

A review by Dr. Rasmussen and co-workers, with general considerations concerning geriatric patients and specific features of perioperatively used drugs and anesthetics which might have an impact on patients with AD, covers the whole range of strictly-followed procedural details. These also include the legal aspects of obtaining informed consent in the demented patient, decisions on the use of premedication, choice of anesthetics, the depth of anesthesia and how to monitor it with precision, and the management of postoperative pain.

In this scenario of incomplete knowledge about what triggers AD on one hand and an incriminating finger pointing to the possible role of anesthetics on the other, abundant caution in the choice of anesthetics and the procedure is perhaps the key to avoid adding yet another factor to the armamentarium of risk factors for AD. A consistent part of funding for research in AD is currently aimed at delaying the clinical manifestations of the disease; however, during the past half-century, the inhaled anesthetics, suspected of potentially accelerating the AD onset, are the agents of choice in general anesthesia. Surprisingly, faced with this situation, whether anesthesia influences the development or even causes AD, is rarely evaluated and enmeshed in controversy. The medical field needs to adopt a more rigorous approach to codify the frequency and extent of early and delayed POCD against data on the anesthetic employed.

This supplemental issue sees the convergence of evidence from various groups on the possible neurotoxicity of anesthetics, especially in the elderly, even as our understanding of the pathomechanism of AD increases. We thank the Editors and contributors to the issue and Dr. Subbulakshmi Natarajan, MBBS, Ph.D and Dr. Poonam Malhotra, MD for suggestions which gave us unique opportunity to put together the many pieces of the jigsaw puzzle to present a comprehensive picture. We wish to express our appreciation to Dr. John P. Williams, MD, Safar Professor and Chair Anesthesiology, University of Pittsburgh, USA for discussion. It must be noted that this is no attempt to raise a ‘fear of anesthesia’, but an earnest quest for the ‘safe anesthetic’ for the elderly. It is most heartening that the contributors for this issue have joined efforts in this crusade against AD, and in pursuing the dialogue on anesthetics as a possible risk factor for AD. It is hoped that this special issue of the Journal of Alzheimer’s Disease sends out a message to the scientific community to give a serious rethinking on the topic ‘Anesthetics and AD’ and add new knowledge and value to this emerging area of research.
Peri-Operative Risk Management in Patients with Alzheimer’s Disease

Gianfranco Di Ninoa,∗, Marco Adversiba, Boaz G. Samolsky Dekela, Vincenzo Fodaleb, Giovanni Rosac and Rita M. Melottia

aDepartment of Surgical and Anesthesiological Sciences, University of Bologna, Bologna, Italy
bDepartment of Neuroscience Psychiatric and Anesthesiological Sciences University of Messina, Messina, Italy
cDepartment of Anesthesiology, Critical Care and Pain Medicine, Neuroanaesthesia and Neurocritical care, University of Rome “La Sapienza”, Rome, Italy

Accepted 9 September 2010

Abstract. The aim of this review is to identify an evidence-based perioperative management for patients affected by Alzheimer’s disease (AD) that are scheduled to undergo surgery. This will minimize the negative effects of anesthesia and postoperative sedation and correct those perioperative variables possibly responsible for a decline in cognitive status and a worsening of AD. We here gather evidence on the importance of correct preoperative assessment regarding cognitive and functional status and the presence of preoperative delirium. The potential role of anesthesia, surgery, and postoperative analgosedation as risk factors for development of delirium are herein outlined. Finally, pain assessment instruments, as well as principles of management strategies for postoperative delirium in subjects with AD, are suggested.

Keywords: Alzheimer’s disease, anesthesia, anesthetics, delirium, dementia, pain, pain measurement, POCD, postoperative care

INTRODUCTION

The so called “great elderly” patients with numerous co-morbidities, including Alzheimer’s disease (AD) or progressive dementia, are more and more often scheduled to undergo surgery for various pathologies. The anesthesiologist, who is aware of the fragility and the precarious equilibrium of such patients, must implement preventive strategies and take adequate measures to minimize negative perioperative events in these patients. The main aims are to avoid deterioration of underlying mental diseases, the development of Postoperative Cognitive Dysfunctions (POCD), and the increase of morbidity and hence, the economical cost of patient care. The negative influence of surgery, anesthesia, and care on this category of patients is often underestimated or neglected.

The aim of this review is to analyze scientific literature regarding the relationship between AD, anesthesia, and perioperative management, according to Evidence Based Medicine (EBM) criteria, following the systematic review principle. In particular, we have selected and examined in detail: 9 guidelines, 14 reviews, 1 consensus conference, and 2 observational prospective studies, all of which dealt with the perioperative management of patients with AD.

METHOD

The method followed the principles of systematic reviews. The arrangement of the present systematic review was made in order to satisfy the requisites of the Critical Appraisal Skills Programme (CASP), which is the EBM tool for evaluation of published systematic reviews.
The examined population: patients affected by AD scheduled for surgery.

The examined interventions: influence of anesthesia, surgery, and perioperative hospitalization on patients with AD who are scheduled for surgery, and the identification of strategies for perioperative management.

Outcomes: perioperative clinical and laboratory evolution of AD, amyloidogenic potential of surgery and anesthesia and therapeutic strategies, incidence of postoperative delirium or POCD in AD patients, and therapeutic strategies.

Examined database and the bibliographical search strategy are described hereafter:


Scientific societies that produce Systematic Reviews: Cochrane Library: http://www.cochrane.org; Joanna Briggs Institute: http://www.joannabriggs.edu.au; Centre for Reviews and Dissemination: http://www.crd.york.ac.uk.


Search strategy: Keywords: Dementia, Alzheimer, Delirium, POCD, Anesthesia, Anesthetics, Surgery, Operational, Postoperative, Pain, Pain measurement, Pain Scale.

When possible, an advanced bibliographical search was conducted based on MeSH terms and operational Booleans:


Nine Guidelines and six Systematic Reviews [1–15] were selected and positively graded according to the AGREE (Appraisal of Guidelines for Research and Evaluation) and the CASP (Critical Appraisal Skills Programme) methods, respectively. In addition, we selected: 7 non-systematic reviews, 1 consensus conference, and 2 observational prospective studies.

The quality, systematic aspects and internal validity of the selected guidelines were evaluated according to the AGREE method (http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/doss060/link/doss60.pdf).

The quality, systematic aspects and internal validity of the selected systematic reviews were evaluated according to the CASP method (http://www.casp-birmingham.org). Every statement is followed by bibliographical references. For statements derived from the clinical experience of our operational unit but without clear support from literature we added the term ‘expert opinion’ in parenthesis. Such statements are complementary to this EBM review.

RESULTS AND DISCUSSION

Preoperative management

Cognitive, clinical, and instrumental assessment

Cognitive scales: Mini Mental State Examination (MMSE), Addenbrooke’s Cognitive Examination, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), SPSMQ.

There is a body of evidence showing that diagnostic criteria for probable AD, such as those based on definitions contained in the Diagnostic and Statistical Manual, 4th edition (DSM-IV criteria), the National Institute of Neurologic, Communicative Disorders and Stroke–AD and related Disorders Association Work Group (NINCDS-ADRDA criteria), and the diagnostic criteria of ICD-10 have reasonably good diagnostic accuracy. However, in daily practice, anesthetists often lack the knowledge and the time required to accurately verify the signs and symptoms necessary for a correct
diagnosis, and require a less accurate but friendlier and faster diagnostic tool to assess the initial cognitive status of the patients and the probability of an underlying dementia, in order to decide the appropriate perioperative management. The MMSE was developed as a screening instrument for dementia and is widely used. The brevity of the MMSE results in superficial assessment of memory, language, and visuoperceptual function. Processing speed and executive function are not tested. Evidence from a systematic review has shown that the MMSE is suitable for the detection of dementia in individuals with suspected cognitive impairment.

Initial cognitive evaluation can be improved by Addenbrooke’s Cognitive Examination. The IQCODE, compiled by the patient’s relative or a friend, can be used for the diagnosis of dementia and can additionally help the direct cognitive test [1–3]. Once the anesthetist has assessed that the patient has an impaired cognitive status, through MMSE, Addenbrooke’s Cognitive Examination and IQCODE, and is likely to be affected by dementia, he/she should accurately plan a post-operative psychiatric examination in order to accurately define the cognitive status of the patient and plan the most appropriate treatment [expert opinion].

Screening for the presence of delirium and favoring factors
The high risk for development of post-operative delirium or POCD in patients with AD implies a preoperative search for signs of delirium. The purpose is to monitor evolution, uncover signs of psychiatric impairment and optimize psychiatric therapy before surgery. Preoperative Delirium can be diagnosed quickly and accurately by non-psychiatrically trained clinicians, using the Confusion Assessment Method (CAM) screening instrument. The CAM scale, useful to differentiate delirium from dementia, has also been validated to monitor delirium [3–6,16]. Delirium is proportional to the severity of the patient’s co-morbidities: this parameter is easily analyzed with the Cumulative Illness Rating (CIRS) scale [16]. Mood alterations are often concomitant to the manifestation of postoperative delirium; signs of depression, anxiety and psychomotor agitation can be detected with the Hospital Anxiety and Depression (HADS) scale [16].

Preoperative evaluation of residual functional autonomy
For this, the following evaluation scales have been validated: Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) [8,16]. The objectives are to adequately plan rehabilitation and postoperative assistance.

Nutritional evaluation
This consists of the evaluation of the following clinical and laboratory parameters: dysphasia, recent weight loss, anorexia, total proteins count, and the presence of ongoing enteral or parenteral nutrition. In disease-advanced stages, the risk of complications is high and may include, malnutrition, dehydration, infectious diseases (ab ingestis pneumonia), fractures and bedsores [2,8]. Some of the preventive strategies for such complications are: to optimize patient’s nutritional state, personalize daily diet and integrating it, if insufficient, with the prescription of enteral or parenteral additional nutrition [expert opinion].

Caregivers’ evaluation and suitable education
The Scottish Intercollegiate Guidelines Network (SIGN) underlines the importance of a suitable education for caregivers who assist AD patients, with the purpose of delaying, for as long as possible, definitive institutionalization of these patients [1]. It is reasonable to extend such recommendations to caregivers who assist surgical patients with AD, in the perioperative context. These caregivers should be extensively informed about the specific post-operative care interventions that surgery on such patients may require and should be involved with the intra- and extra-hospital care of this category of patients. Such involvement may lead to building together a suitable rehabilitation path [1,9].

Correction of pre-operative hypo/hyper-glycaemia
Pre-operative glycaemia alterations appear to correlate with the development of Postoperative Delirium or POCD [16]. At present, there is emerging evidence for a pathophysiologic, as well as a clinical link between hyperglycemia and POCD. Pathophysiologically, elevated glucose levels allow higher substrate availability for the production of lactate during anaerobic metabolism consequent with cerebral ischemia during surgery and postoperative period. Intracellular lactic acidosis interferes with glycolysis, protein synthesis, and enzyme function, among other intracellular processes. In addition, hyperglycemia has also been demonstrated during cerebral ischemia to increase the release of excitotoxic amino acids glutamate and aspartate. These amino acids are key mediators in the ischemic cascade and hyperglycemia significantly augments this injurious response, a critical means by which cerebral outcome may be influenced. In addition, inflammatory pathways have been shown to be important in the pathophysiology of POCD. Hyperglycemia may also enhance the inflammatory response, increas-
ing perioperative C-reactive protein levels. Additional hyperglycemia – mediated inflammatory responses could augment inflammation-mediated POCD. Indeed, it is via both the ischemia and inflammatory pathways that there is a plausible biologic link between POCD and hyperglycemia. However, it is uncertain at what blood glucose level concern should be raised, and what therapy is appropriate. Common sense dictates that normoglycemia should be the goal, but inadvertent hypoglycemia could be just as injurious [16,17].

Intraoperative management

AD medications and interaction with anesthetic drugs

In AD patients, cholinesterase inhibitors are designed to hold back acetylcholine catabolism through inhibition of hydrolysis by acetylcholinesterase and consequently, increase cholinergic neurotransmitter activity in the central nervous system. These drugs are not organ selective and thus interfere with acetylcholine catabolism in other organs and tissues. Nevertheless, in most cases, their effect is reversible with the resumption of cholinesterase activity once inhibitor administration is suspended.

During anesthesia, the cholinesterase inhibitors, donepezil and rivastigmina, may increase the effects of succinylcholine. Donepezil is a reversible, noncompetitive, piperidine-type cholinesterase inhibitor. It is more selective for acetylcholinesterase than pseudocholinesterase, which is, nevertheless, partially inhibited. Suxamethonium is generally short acting, as it is rapidly hydrolyzed by plasma pseudocholinesterase. By inhibiting pseudocholinesterase, cholinesterase-inhibitors prolong the half-life of succinylcholine up to 50 min.

Cardiovascular system: for their pharmacological action cholinesterase inhibitors can induce bradycardia by inducing hyperactivity of parasympathetic system. In patients with sinus node disease or with other supraventricular conduction anomalies (e.g., sinoatrial or atrioventricular block) the effect of an excessive cholinergic state may be clinically evident. Cases of syncopies and convulsions have been reported. When these patients are being examined, one should take into consideration the eventuality of cardiac block or prolonged sinus pauses.

Gastro-intestinal system: patients at risk for ulcer, similar to those with a history of ulcerous disease or those with concomitant therapy with non-steroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptom onset. Clinical studies, comparing donepezil versus placebo, failed to demonstrate an increase in the incidence of peptic ulcer or gastrointestinal bleeding episodes.

Urogenital system: substances with cholinergic activity can cause detrusor hyperactivity, a condition characterized by an increase in contractile activity of the detrusor muscle of the bladder, resulting in urinary incontinence; nevertheless, this has not been observed in clinical studies with donepezil.

Nervous system: convulsions: substances with cholinergic activity can cause generalized convulsions. However, convulsive episodes can also be due to AD. Respiratory system: because of cholinergic induced activity, cholinesterase inhibitors should be prescribed with caution in patients with asthma or with obstructive pulmonary disease [18].

Amyloidogenic potential of inhalational and intravenous anesthetics

Evidence from animal studies suggests that exposure to inhalational anesthetics enhances the clinical and laboratory indicators of AD. It has been argued that potential pathogenetic mechanisms for such aggravation may include: a deregulation of neuronal calcium, an increase in the production and aggregation of amyloid-β, and an abnormal tau-phosphorylation. These hypotheses, to date, have not been confirmed in the clinical setting. Indeed, literature on this issue lacks human studies, and studies on the amyloidogenic and toxic potential of inhalational (apart from isoflurane) and intravenous anesthetics [19–30].

Opioids and benzodiazepines constitute a risk factor for the development of postoperative delirium and POCD

Numerous studies have acknowledged the relationship between the use of benzodiazepines/opioids and the development of delirium, apparently drug induced. Most of these studies have analyzed the role of postoperative sedation, and those others which have analyzed the role of intraoperative sedation have not found any protective role of regional anesthesia vs general anesthesia regarding the development of postoperative delirium. However, general anesthesia would seem to be preferable when it is feasible to deliver a blended anesthesia (combination of general-epidural anesthesia, where epidural anesthesia, supported by inhalatory or endovenous hypnosis, provides optimal locoregional anesthesia) in order to reduce the opioid load, both intra- and postoperatively (expert opinion). If such option is not practicable, it appears reasonable to use short
half-life opioids and anesthetics (i.e., short-term sedation with remifentanil and propofol), readily manageable according to the clinical needs of the patient and the onset of delirium (expert opinion) [4–6,16].

Intra- and post-operative hypothermia and AD

In animals, hypothermia causes tau-hyperphosphorylation. Given the role of tau-phosphorylation in the development of AD, frequent intra- and post-operative hypothermia play a major role in the development of post-operative delirium or AD. Nevertheless, unless data on human beings confirm these findings, we cannot at the moment make any recommendations about optimal peri-operative temperature management [20].

Surgery duration and AD

The risk for postoperative delirium or POCD increases with the increase of duration of surgery. This is explained by the increased exposure to anesthetic drugs, hypothermia and surgical stress [expert opinion based on references previously quoted].

Cardiac and orthopedic surgery: risk factors for the development of POCD and aggravation of AD [20,31] (i.e., transfusions of blood components and postoperative Delirium)

The amount of blood components transfusions intra- and post-operatively appears to be correlated to the development of postoperative delirium [16]. It is recommended that anesthesiology and surgery strategies be adopted to minimize blood loss, also for the prevention of delirium in the AD surgical patient.

Postoperative Management

Postoperative psychiatric/neurologic monitoring

Postoperative delirium or POCD usually appear within 5 days after surgery and it appears reasonable to monitor the advent, during that period, using the already discussed evaluation scales. Monitoring should be performed by appropriately trained clinicians and nursing staff (e.g., CAM) [3–7,16].

Reduction of pain perception in the AD patient and analgesia/sedation

Pautex and colleagues [32] found a negative association between the severity of the patient’s dementia and his ability to understand the use of pain self-evaluation scales (visual analogue scale, numerical rating scale, etc). In his study, only 15% of the participants (mean age, 83 years; MMSE < 11) were able to use at least one of these scales. For this reason, recently, objective pain evaluation tools have been proposed. These tools are based on the systematic observation of the patient at rest and during movement or care activities. In literature, 7 scales, suitable for elderly patients with cognitive or communication deficit, have been retrieved: Checklist of Not-Verbal Pain Indicator (CNPI); Doloplus-2 Scale; Pain Assessment in Advanced Dementia (PAINAD); Pain Assessment for the Dementing Elderly (PADE); Abbey Pain Staircases; Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PAC-SLAC); Not-communicative Patient’s Pain Assessment Instrument (NOPPAIN).

It has been argued that Pain Assessment in Advanced Dementia (PAINAD) is the most suitable. It is divided into five sectors that explore different modalities of pain expression: breathing, vocalizations, face expressions, body language, and person consolation. Each sector of investigation has a severity score: 0 (absent), 1 (mild-moderate), 2 (severe). The total score goes from 0 to 10 (0–1: absence of pain, 2–4: mild pain, 5–7 moderate pain, 8–10 severe pain).

It appears reasonable to plan a postoperative analgesia/sedation based on the principles of locoregional analgesia (central or peripheral nerve blocks) or short-term analgesia/sedation. The aim of such approach is to reduce the consumption of long half-life opioids and benzodiazepines and thus the incidence of postoperative delirium or POCD, and readily adjust analgesia treatment in the case of psychiatric impairment onset [expert opinion].

Days of invasive ventilation and delirium incidence

Prolonging mechanical ventilation administered through an endotracheal tube, would appear to constitute a risk factor for the development of POCD, apparently related to deeper sedation (opioids and benzodiazepines) administered, to lower PaO₂/FIO₂ ratios – oxygen delivery and often to baseline differences in disease severity [10]. It appears reasonable that the elderly patient with AD will benefit, when possible and feasible, from early progressive reduction of the analgesia/sedation regime and early extubation [expert opinion].

Pharmacological treatment of delirium

The correct treatment of postoperative delirium includes the use of neuroleptics and olanzapine. Benzodiazepines should be avoided as they may deteriorate symptoms, worsening acute confusion and delirium, increasing sedation and prolonging coma. Further-
more, the development of ataxia in hospitalized AIDS patients affected by hypoactive delirium, treated with lorazepam, has been reported [11,15].

CONCLUSIONS

The aim of this review is to offer the physician a proposal of perioperative management of AD patients in order to sensitize the physician to this theme and offer the patient the best treatment, avoiding preventable adverse effects related to the multiple interactions between anesthesia, AD and surgery. We acknowledge the limits of this review, first of all, the small number of original studies related to this subject. We hope to close this gap by updating this review through exploring new databases of primary studies and periodically reviewing the databases here summarized, in search of new trials on human beings with AD patients, scheduled to undergo surgery.

ACKNOWLEDGMENTS

The research is supported by a grant from the Italian Ministry for University and Research, Program for the Development of Research of National Interest (PRIN Grant #2007H84XNH – Scientific coordinator: V. Fodale).


REFERENCES


Comprehensive Nuclear Magnetic Resonance Studies on Interactions of Aβ with Different Molecular Sized Anesthetics

Pravat K. Mandal* and Manisha Ahuja
Neurospectroscopy and Neuroimaging Laboratory, National Brain Research Centre, Manesar, Gurgaon, India

Abstract. Laboratory research on anesthetic-induced structural changes of amyloid beta (Aβ) peptide, from normal monomeric α-helix to the micro-aggregated form, has generated much interest in the scientific community as Aβ oligomerization is considered a key step in Alzheimer disease pathogenesis. A comprehensive review of the interactions of Aβ peptide with anesthetics of different molecular sizes is summarized as follows. Smaller sized anesthetics could access and perturb the cavity containing crucial amino acid residues G29, A30 and I31 of Aβ peptide leading to Aβ oligomerization. However, bulkier sized anesthetics are sterically hindered from accessing the cavity containing these crucial residues and do not initiate Aβ oligomerization. Notably, when a small sized anesthetic is co-administered with a larger sized one, the latter does not prevent access of the small sized anesthetic to the cavity. The results of these biophysical studies are supported by animal model studies which indicate that inhaled small molecular anesthetics induce enhanced Aβ plaque deposition in transgenic mice with AD pathology. In this review, a molecular pathway for the Aβ-anesthetic interaction at the atomic level is presented.

Keywords: Anesthetics, molecular size, NMR, Abeta, oligomerization, Alzheimer disease

INTRODUCTION

Anesthetic-induced structural changes of amyloid beta (Aβ) peptide from normal monomeric α-helix to the toxic oligomeric form is a significant area of research to the scientific community as Aβ oligomerization is a crucial event in Alzheimer disease pathogenesis. Light scattering experiments have shown that inhaled anesthetics enhance toxicity in cultured neuronal cells [1]. Reports suggest that some of the commonly used inhaled anesthetics may cause brain damage that accelerates the onset of Alzheimer’s disease [2]. Synthetic Aβ oligomers have been reported to impair long-term memory in animal models [3]. Halothane treated transgenic mice (Tg2576) present more amyloidopathy compared to isoflurane treated transgenic mice (Tg2576) [4]. Cognitive impairment due to these anesthetics is also reported in non-transgenic mice [4]. Based on a further in vivo study using isoflurane, it has been concluded that isoflurane may promote AD neuropathogenesis [5]. Interestingly, repeated administration of inhaled anesthesia (dose: twice a week, for 3 months) to 7–10 months old wild type and APPswe transgenic mice revealed that the deleterious impact of isoflurane on behavior, survival, neuronal cell death and processing of proteins involved in neurodegeneration is restricted to mice with special susceptibility [6].

Hence, it is important to trace the molecular mechanism for anesthetic-induced Aβ oligomer formation, through biophysical studies, in order to reveal the molecular process of amyloidogenesis. In this global search for ‘better’ anesthetics, in vitro biophysical experiments (e.g. NMR) offer one channel of investigation to study the Aβ peptide interactions with different sized anesthetic molecules. This review assimilates the present knowledge available to suggest a novel course
Fig. 1. Detailed overview of anesthetics and anesthesia adjuvants. Two representative substances of each group of opioids are shown due to space limitations. Further members of the respective groups are abbreviated as follows: $ \text{thebaine}; $ $ \& $ oxycodone, oxymorphone, desomorphine, diacetylmorphine (heroin), and nicomorphine; $ \# $ methadone, tramadol, and dextropropoxyphene. Analogues fentanyl compounds are sufentanil, alfentanil, and remifentanil.

of scientific research for testing a new anesthetic drug before it is chosen for animal or clinical trial.

BIOPHYSICAL AND BIOCHEMICAL CHARACTERISTIC OF ANESTHETICS

Anesthetics are broadly classified into two categories, inhaled and intravenous. A detailed classification of various anesthetics and anesthesia adjuvants are provided in Fig. 1. Certain features of size, structure and chemical properties of some anesthetics are detailed below. The inhaled anesthetic halothane belongs to the halogen-alkane group, whereas isoflurane, desflurane, sevoflurane and enflurane are halogen-ethers. Xenon is a noble gas and nitrous oxide is an inorganic gas. Boiling points of these inhaled anesthetics range from 23°C to 58°C and the boiling points of nitrous oxide and xenon are −89°C and −107°C, respectively.

Morphine is a T-shaped molecule. Propofol, a non-opioid anesthetic, consists of substituted phenol while thiopental consists of a cyclic ring with electronegative sulphur and oxygen atoms.

The molecular size of halothane and isoflurane are 110 Å³ [7] and 144 Å³ [7], respectively. The molecular size of propofol belonging to the non-opioid category is 191 Å³ [8]. The molecular size of opioids is much larger when compared to all inhaled and non-opioid category. Among the opioids, the fully synthetic opioid (e.g. fentanyl), is generally larger in size than natural opioid (e.g. morphine). The exact molecular mechanism of anesthesia is not understood but it is well accepted that anesthetics act on different receptors (e.g. N-methyl-d-aspartate (NMDA), γ-aminobutyric acid (GABA), glycine and acetylcholine etc.).

The calculated cerebral concentration of the inhaled anesthetics are in the range of 0.26–0.57 mmol l⁻¹ [9]. On the other hand, the calculated cerebral concentra-
P. K. Mandal and M. Ahuja / Comprehensive Nuclear Magnetic Resonance Studies on Interactions of Amyloid-β

Fig. 2. Experimental flowchart for preparation of clinically relevant concentration and measurement of inhaled anesthetics. In this setup, an experimental solution is kept in a 5 mm NMR tube and the reference solution trifluoro acetic acid (TFA) is kept in the 3 mm tube which is coaxially arranged with the 5 mm tube. The final inhaled anesthetic concentration upon dilution from aqueous solution is determined by measuring the peak area of the CF$_3$ moiety of TFA and the CF$_3$ moiety of inhaled anesthetics present in the experimental solution [12].

ions of intravenous anesthetics (propofol and thiopental) are approximately 0.15 mmol l$^{-1}$ and 0.075 mmol l$^{-1}$, respectively [9]. The clinically relevant concentration (CRC) of opioids is lower than CRC of the non-opioids anesthetics in the intravenous anesthetic family.

AMYLOID BETA PEPTIDE (Aβ)

Aβ is primarily a 40 or 42 amino acid containing peptide and is the constituent of amyloid plaques in the brain. Aβ is produced by the proteolytic cleavage of the amyloid precursor protein (APP) located on the plasma membrane, trans-Golgi network, endoplasmic reticulum (ER) and endosomal, lysosomal and mitochondrial membranes [10]. It has been suggested that low-molecular weight Aβ oligomers could be the fundamental building blocks of larger oligomers [11]. Synthetic Aβ spontaneously aggregates into β-sheet-rich fibrils, resembling those in plaques [3]. This provides the basis for investigating the influence of different agents (e.g. certain anesthetics) which may induce the formation of Aβ oligomers. NMR provides an excellent experimental tool to investigate the molecular pathway for Aβ oligomerization by different anesthetics at clinically relevant concentration range.

Clinically relevant concentration (CRC) for inhaled anesthetics

Generally, neat inhaled anesthetics are too concentrated and the addition of these into the experimental solution yield more than the CRC of the respective inhaled anesthetic. In order to attain CRC levels of inhaled anesthetic in the experimental solution, it is preferable to add the desired amount of aqueous inhaled anesthetics to the experimental solution. The determination of the final concentration of the inhaled anesthetic in the experimental solution is schematically presented in Fig. 2, which is based on our earlier work [12]. The advantage of this setup is that the effective concentration of the inhaled anesthetic in the experimental solution...
can be measured at different time points without disturbing the reference sample and experimental solution as both NMR tubes are coaxially aligned and remain in this position throughout the experimental period.

**INTERACTION PATTERN OF Aβ PEPTIDE WITH ANESTHETICS**

We hereby review the specific effect of inhaled (halothane, isoflurane, desflurane etc.) and intravenous (propofol, diazepam and thiopental) anesthetics on Aβ peptide at various time points by one, two and three dimensional heteronuclear NMR experiments as well as by two dimensional heteronuclear single quantum coherence (HSQC) experiments [13].

**Aβ Peptide Interaction Studies with different sized Anesthetics**

The smaller sized anesthetic isoflurane, at high concentration, induces chemical shift change of three critical residues (G29, A30 and I31) of Aβ peptide, which is linearly correlated with the addition of isoflurane. The NH peak chemical shift change due to isoflurane was 50 Hz, 45 Hz and 12 Hz for G29, I31 and A30, respectively [14]. However, at clinically relevant concentration (CRC) of isoflurane the chemical shifts of the critical residues show NH chemical shift change 9 Hz and 4 Hz for G29 and I31, respectively. Aβ oligomerization was found after 9 days in the presence of CRC of isoflurane [15] (Fig. 3), whereas Aβ oligomerization was observed after 25 days in the presence of CRC of desflurane [15].

Intermediate sized anesthetic, propofol, at high concentration, induced NH chemical shift changes of the same critical residues (I31, G29 and A30) and oligomerization of Aβ peptide was observed [14]. However, at CRC of propofol, no chemical shift change of the critical residues and no subsequent oligomerization of Aβ was observed even after 69 days [16].

Interestingly, a larger anesthetic thiopental, even at very high concentration, did not perturb the critical residues (G29, A30 and I31) and no Aβ oligomerization was observed [14]. A similar effect was observed with another bigger sized anesthetic, namely diazepam where, again, no Aβ oligomerization was observed. It is important to note that these two bigger sized anesthetics, thiopental and diazepam, do not cause in vitro Aβ peptide oligomerization at any concentration or time frame.

However, certain other amino acid residues (i.e. F20 and Q15) are perturbed and show chemical shift change due to addition of thiopental but these did not influence the process of Aβ oligomerization. This finding indicates that perturbations of the three critical residues G29, A30 and I31 is essential for the induction of Aβ oligomerization.

When a smaller sized anesthetic, halothane, is co-administered with a bigger sized anesthetic, diazepam or thiopental, the critical residues (G29, A30 and I31) show chemical shifts and subsequent Aβ oligomerization. However, in the presence of either diazepam [17] or thiopental [14] alone, no change in chemical shift of those critical residues and no subsequent Aβ oligomerization was observed.

**DISCUSSION**

Biophysical studies (e.g. size exclusion chromatog-
Fig. 4. Schematic diagram for interaction studies of Aβ peptide with bigger sized anesthetic (e.g. diazepam) co-administered with smaller sized anesthetic (e.g. halothane). Due to steric hindrance, diazepam could not access the helix-loop-helix region containing critical residues G29, A30 and I31. Diazepam also could not block the entry of the smaller sized halothane. Hence Aβ oligomerization was initiated when halothane is co-administered with diazepam. This model works in a same fashion with inhaled anesthetics alone or other bigger sized anesthetics (e.g. thiopental and propofol) when halothane is co-administered with them separately. The figure is adapted and revised from our earlier works [15–17].
three crucial residues (G29, A30 and I31). The conclusion drawn from these experiments is that oligomerization of Aβ is induced whenever inhaled anesthetics are given alone or co-administered with bigger sized anesthetics.

**Hydrophobic Interaction between Anesthetics and Critical Amino Acid Residues**

Studies in various systems have reported the hydrophobic nature of interactions between anesthetics and proteins [18]. In our dose-dependent study with inhaled anesthetic (i.e. isoflurane at four different concentrations), the three critical residues (G29, A30 and I31) were perturbed in a systematic manner. Similarly, with intermediate sized intravenous anesthetic (propofol), the critical residues were perturbed to a different extent with varying concentrations, except at CRC of propofol where no Aβ oligomerization was observed. The concentration dependence on the perturbation of the critical residues with propofol, clearly indicate the hydrophobic nature of interactions of the critical residues with both isoflurane and propofol. In the case of diazepam and thiopental, these critical residues were not perturbed as these bulkier anesthetics could not access the cavity containing the three critical residues due to steric hindrance.

Biophysical studies involving light scattering and fluorescence studies [1,19] could not provide specific molecular interaction pattern of the anesthetics and Aβ peptide. However, NMR studies with various anesthetics provide crucial additional information on the size of the cavity containing the three critical residues [16]. From published results, it is reasonable to assume that this cavity size is comparable to the propofol molecular volume which is 191 Å³. This information should serve as a significant indicator of molecular size while designing new generation anesthetics, keeping in mind that the molecular size should be equal to or slightly higher than that of propofol in order to prevent the anesthetics from reaching the cavity and causing subsequent Aβ oligomerization.

**Molecular Pathway leading to anesthetic induced Aβ oligomerization**

The topological co-existence of both Aβ and anesthetics in the extracellular space makes anesthetics available for interaction with Aβ peptide. Figure 4 presents the schematic diagram [9,14,15,17] for the interaction of Aβ peptide and diazepam (at CRC) co-administered with halothane. Aβ peptide is generated via the proteolytic cleavage action of β- and γ-secretase on APP protein located in the transmembrane region. The cleavage of APP to Aβ peptide and its subsequent release to the extracellular domain is a normal biological process. Aβ peptide accumulates in abundance in the aged brain. Consequently, anesthetic interactions with Aβ in the older population could be more relevant than in a younger control group. This schematic model based on NMR studies provides vital information regarding the molecular pathway for anesthetic-induced Aβ oligomerization.

**Animal Model Studies: Plaque Load and Cognition**

The results of current animal model studies concur with the findings of NMR and other biophysical studies that small molecular anesthetics do indeed play a role in Aβ oligomerization. Transgenic mice, Tg2576 with APP Swedish mutation expressing AD pathology, on exposure to halothane at CRC showed enhanced amyloid beta plaque deposition compared to isoflurane, an anesthetic of bigger size [4]. No detectable alteration in cognitive performance of aged transgenic mice (12 months old) was found with either anesthetic but isoflurane exposure impaired cognitive function in non-transgenic mice [4]. The supportive explanation given for this ambiguous finding is that twelve months old transgenic mice were of advanced age and already had significant cognitive decline at the time of exposure to anesthetic. Consequently any further effect on the cognition due anesthetic induced Aβ oligomerization was difficult to detect. Quoting the study group, “The clinical correlate of this study might be those patients with a diagnosis of Alzheimer disease at the time of surgery (quite common)”. It is interesting to note that the results of a controlled laboratory experiment on animals is being directly extrapolated to a clinical scenario [4] where the development of the disease is characterized by multifactorial etiology and the susceptibility to it based on a complex interaction of genetic and environmental conditions. It was thus crucial that the effect of these anesthetics be investigated on younger mice. In another study, 7 to 10 month old transgenic mice were exposed to isoflurane over a cumulative period of 8 hours spread over three months [6]. Reports show that isoflurane exposure not only produced cognitive decline in transgenic mice but was found to be life threatening in some cases, while the non-transgenic mice remained resistant to the effects of anesthesia [6]. This study highlights the nature of individual susceptibility to certain anes-
Table 1
Comparative analysis of animal model studies on the effect of inhaled anesthetics

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of transgenic mice</strong></td>
<td>APP Swedish Tg2576</td>
</tr>
<tr>
<td><strong>Mice gender</strong></td>
<td>Male</td>
</tr>
<tr>
<td><strong>Age at the time of experiment</strong></td>
<td>7 to 10 months</td>
</tr>
<tr>
<td><strong>Type of inhaled anesthetics used</strong></td>
<td>Isoflurane only</td>
</tr>
<tr>
<td><strong>Anesthetic treatment</strong></td>
<td><strong>Dose:</strong> Induction with 4% isoflurane for 1 min, and then 2% isoflurane with 98% oxygen for 20 min as maintenance. <strong>Duration:</strong> Repetitive anesthesia, twice a week, for 3 months, from 7 to 10 month of age. Total time of exposure = 8 hours.</td>
</tr>
<tr>
<td><strong>Observation (Histopathology)</strong></td>
<td>Isoflurane exposure causes increased levels and aggregation of Aβ peptides, increased mortality and neuronal cell apoptosis in transgenic mice, but no increase in plaque deposition found. No effect on wild type mice.</td>
</tr>
<tr>
<td><strong>Outcome in terms of cognition etc.</strong></td>
<td>Isoflurane exposure produces significant reduction in cognitive behavior of Tg2576 mice compared to wild type. Continuous exposure to isoflurane (dose mentioned above) found to have deleterious impact on behavior, survival, neuronal cell death.</td>
</tr>
<tr>
<td><strong>Clinical relevance</strong></td>
<td>The study suggests that the risk of some inhaled anesthetics may be limited to subjects with special genetic and environmental risk factors for AD; aspiring to ensure proper selection of patients, and the type of anesthetics and anesthesia to be used for them.</td>
</tr>
</tbody>
</table>

ACKNOWLEDGMENTS

Dr. Subbulakshmy Natarajan, MBBS, Ph.D and Dr. Sreedevi Sugunan, MBBS are appreciated for comments. Dr. Vincenzo Fodale, MD is highly appreciated for valuable suggestions. Dr. Mandal is thankful to National Brain Research Center for providing research support.

REFERENCES


The Impact of General and Regional Anesthesia on the Incidence of Post-Operative Cognitive Dysfunction and Post-Operative Delirium: A Systematic Review with Meta-Analysis

Sam Ewan Mason\textsuperscript{a}, Anna Noel-Storr\textsuperscript{b} and Craig William Ritchie\textsuperscript{a,*}

\textsuperscript{a}Centre for Mental Health Claybrook Centre, Imperial College London, Hammersmith, London, UK

\textsuperscript{b}Cochrane Collaboration Centre, John Radcliffe Hospital, Oxford, UK

Accepted 10 August 2010

Abstract. Post-operative cognitive complications such as delirium have been consistently associated with poor short and long term outcomes, and the role of anesthesia, particularly the role of general versus regional anesthesia, remains unclear. The objective of this systematic review with meta-analysis was to compare the influence of general, regional, or a combination of anesthesia on the development of Post-Operative Cognitive Dysfunction (POCD) and Post-Operative Delirium (POD). Standard bibliographic databases were searched and complimented by hand searching of original and review article references. Included studies were randomized controlled trials comparing general to regional (spinal, epidural, or intravenous block) or a combination of these in a cohort who were pre-operatively cognitively normal and had an average age exceeding fifty. Where POD was the principle outcome, studies must have employed the DSM or ICD criteria. Where POCD was the principal outcome, this was defined as any objective cognitive impairment. Twenty one studies were considered suitable for inclusion. There was no effect of anesthesia type on the odds ratio of developing POD (0.88, 0.51–1.51 with 95% confidence) however general anesthesia was marginally non-significantly associated with POCD (odds ratio of 1.34, 0.93–1.95 with 95% confidence). There was no evidence of publication bias. In conclusion, it appears that general anesthesia, compared to others, may increase the risk of developing POCD; however this has not been shown for POD. Possible reasons for this finding have been explored. This data would advocate for the use of regional anesthesia wherever possible especially in people otherwise vulnerable to developing cognitive symptoms.

Keywords: Confusion, delirium, epidural anesthesia, general anesthesia, post-operative period, spinal anesthesia

INTRODUCTION

The role of anesthesia in the development of post-operative cognitive complications remains unclear. It is remarkably common, especially in the elderly, to experience a varying degree of cognitive dysfunction post-operatively, which can vary from mild and short-lived to severe and permanent. Such manifestations are described as post-operative cognitive dysfunction (POCD) which describes a range of abnormalities, one of which is post-operative delirium (POD). Delirium is a condition with a wide range of etiologies and whether it is seen in those having undergone surgery or not, has consistently been associated with a poor short and long...
The diagnostic criteria for post-operative delirium are remarkably similar between the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV and International Classification of Diseases (ICD) 10, which include fluctuating consciousness, inattention, memory impairment, and perceptual abnormalities. A key point to note is that post-operative delirium is not attributed to anesthetic agents, in which case it would be referred to as emergence delirium, a subtype of substance-induced delirium. Emergence delirium is considered more of a concern in pediatric patients and this review is interested in interval delirium (referred to as post-operative delirium) in which patients emerge from anesthesia normally. Clinical diagnostic batteries include the Delirium Symptom Interview and Confusion Assessment Method (CAM), with further tests such as the Delirium Rating Scale (DRS) available to assess the severity, a prognostic indicator [5]. The natural history of POD often involves a lucid post-anesthetic phase which lasts 1–3 days, where after the fluctuation of cognitive abilities becomes apparent and objective recognition of the condition is possible within this first post-operative week. Studies have demonstrated a wide variance in the incidence of POD, rates of between 5–15% have been reported [6] and we demonstrated that rates of POD were highly variable in a post operative hip surgery population (3.6–28.3% of elective and 4–53.3% of trauma patients) [7]. Such a disparity in results may be attributed to the varying methodologies used in previous studies.

In comparison to the validated criteria for POD, the definition of POCD is much looser. For instance, there are no diagnostic criteria in the DSM-IV or ICD-10 and in previous studies the neuropsychological test batteries employed and the thresholds considered significant have varied considerably [8,9]. One of the largest studies, ISPOCD 1 [10] described POCD in 25.8% of patients using a variety of well recognized tests. Such test batteries often assess a variety of cognitive dimensions such as memory, attention and executive function; many of which may be insensitive to POCD or vary widely within this group [11]. There are a large number of risk factors for POCD and POD that overlap, which suggests a shared pathogenesis with POD being a more severe manifestation of the same process.

Many authors have suggested that POD is a manifestation of a central cholinergic deficit [12,13], which may be an end point of many up-stream mechanisms. A functional cholinergic impairment can occur as a result of energy failure intra- and post-operatively due to hypoxia or ischemia of several causes, and this is likely augmented by the direct action of anti-cholinergic medications. Later, peripheral inflammation, as a result of surgery and the consequent release of pro-inflammatory cytokines such as interleukin 1β and tumor necrosis factor α (TNFα), may activate CNS microglia. The latter then further release pro-inflammatory cytokines and cause neuronal dysfunction [14,15]. Cognitive reserves to compensate during neuronal dysfunction post-operatively may also be diminished by extant but clinically occult Alzheimer’s disease, Lewy Body, or other central neurodegenerative pathology, resulting in a cognitive dysfunction such as delirium. Finally, symptom manifestation may be mediated by alteration in the balance of the reciprocal dopaminergic and cholinergic systems, as cytokine release has been shown to increase dopamine levels centrally [16].

The method of anesthetic administration though is a potentially modifiable risk to avoid POCD. Beyond their central pharmacological effect, general anesthetics (GA) influence neuronal processes such as gene transcription, receptor efficacy, synaptic vesicle cycling, and intracellular calcium homeostasis [17–20]. GA’s also appear to specifically influence pathways currently linked to POCD through anti-cholinergic effects [21,22]. These effects are not shared by regional anesthetic (RA). There have been numerous trials comparing anesthetic routes viz a viz the development of POCD (Table 1), though there remains an absence of consensus with regards to the association between route of anesthetic administration and POCD. This may be mediated partially through methodological problems; challenges in randomizing patients into different arms of a study, maintenance of blinding, the combination of anesthetics used in clinical practice, poor collection of baseline confounders, small study size and the effect of post-operative interventions such as narcotic analgesia with known cognitive effects all play their part in the genesis of this lack of conclusion.

OBJECTIVES

The aim of this study was to undertake a systematic review of the literature with meta-analysis to determine the influence of method of anesthetic administration on the development of POCD and POD comparing GA, RA, and a combination of these methods.
Table 1
Summary of reviews assessing the role of anesthetics on the post-operative cognitive outcome

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Design of included studies</th>
<th>Anesthesia studies assessed</th>
<th>Methodology of included studies</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryson 2006 [23]</td>
<td>RCT</td>
<td>GA, RA, RBB</td>
<td>Surgeries: non-cardiac Outcome: delirium (including any confusion), any POCD Follow-up: Unclear</td>
<td>No difference between GA and RA</td>
</tr>
<tr>
<td>Parker 2004 [24]</td>
<td>RCT</td>
<td>GA, RA</td>
<td>Surgeries: Orthopedic Outcome: any confusional state Follow-up: 3–365 days</td>
<td>A risk ratio of 0.5 (0.26–0.95 95% CI) favoring RA over GA</td>
</tr>
<tr>
<td>Wu 2004 [25]</td>
<td>RCT, OBS</td>
<td>GA, RA, LA</td>
<td>Surgeries: all Outcome: any POCD Follow-up: 0–365 days</td>
<td>No difference between GA and RA</td>
</tr>
</tbody>
</table>

RCT = Randomized Controlled Trial; OBS = Observational; GA = General Anesthetic; RA = Regional Anesthetic; RBB = Retro-Bulbar Block; LA = Local Anesthetic; POCD = Post-Operative Cognitive Dysfunction; CI = Confidence Interval.

METHODS

Both electronic and hand searching techniques were used to identify appropriate literature. MEDLINE, EMBASE, PsycINFO, and ISI Web of Knowledge, all via OvidSP were used. Relevant references from the studies identified from the electronic search were located. A study was excluded at this stage if the abstracts identified an inappropriate intervention or incorrect outcome. The manuscripts for all remaining abstracts were sought and assessed to pre-determined criteria. For foreign language studies a translator was sought. To be included, the study had to be a RCT presenting data on a cohort of patients with a mean age exceeding 50 who received either a general, regional (epidural, spinal or iv block), or combination of anesthetics. Studies were excluded if participants had pre-operative cognitive dysfunction (as defined by the reporting author), where there was neurosurgery or had received an intervention designed to decrease the risk of post-operative cognitive dysfunction. If the principle outcome was POD, the study must have employed either the DSM or ICD criteria. However for any post-operative cognitive dysfunction, it was anticipated that a large number of neuropsychological tests and thresholds will be employed. In order for a test to be considered acceptable, the reporting author must state that it is able to measure the presence or absence of cognitive dysfunction and this must be achieved in an objective manner. All scales for POD and POCD had to have been applied within three to seven days post-operatively to avoid studies capturing the etiologically distinct emergent delirium described previously. Studies included by this systematic review process are described.

In the meta-analysis a fixed effect assumption was made, pooling the odds ratios between studies with similar interventions being compared. In PODC studies, where an odds ratio was not presented (or could not be calculated), group mean change for a test were described and contextualised with the meta-analysis findings. Quality of the included studies was assessed using the Jadad score which has been adapted to increase its use in this review (Appendix 1).

It was anticipated that authors would compare general anesthesia to epidural, spinal, regional (spinal or epidural), and intravenous block distal to a cuff and combination anesthesia (both regional and general). General anesthesia will also be compared to all other anesthesia methods (regional and combined), in a group entitled ‘non-general’. The heterogeneity of the sample is defined using a $X^2$ test.

The apparent influence of covariates such as the number and type of neuropsychological tests used and frequency of assessment will be described. All analysis was conducted using Stata 11.0.

RESULTS

The original search yielded 6968 abstracts, the vast majority of which could be excluded due to an inappropriate study design, population, intervention, or outcome measure. Seventy-five remained and the studies were reviewed yielding 21 studies which satisfied the final inclusion criteria. Table 2 describes the characteristics of some of the studies that were excluded and Table 3 summarizes those that have been included. Studies included are listed in Table 4 and those not
Table 2
Selection of excluded studies with a brief description of their methodologies and reason for exclusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics of the study and reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benoit 2004 [26]</td>
<td>This cohort study assesses post-operative delirium in 102 patients receiving combined general and epidural anesthesia. As there is no group randomized to general anesthesia for comparison, it has been excluded.</td>
</tr>
<tr>
<td>Bracco 2007 [27]</td>
<td>This study follows a 1293 patient cohort with general versus general with thoracic epidural anesthesia in cardiac surgery. The participants were controlled however not randomized and therefore this study was excluded.</td>
</tr>
<tr>
<td>Campbell 1993 [28]</td>
<td>This study explores cognitive function in 169 patients undergoing cataract after being randomized to either general or local anesthesia. This study is designed to assess the impact of anesthetic agents on neuronal function centrally and largely local anesthetics are not considered to be able to enter the central nervous system to influence cognitive function.</td>
</tr>
<tr>
<td>Crul 1992 [29]</td>
<td>This study describes subjective physical well-being and mental function in elderly patients after being randomized to general or spinal anesthesia for urological surgery. However patients who were unsuitable for randomization due to a heavy co-morbidity load have been added to the spinal group for analysis, without presenting data only for those who were randomized.</td>
</tr>
<tr>
<td>Haan 1991 [30]</td>
<td>This study explores general and spinal anesthetics for urological surgery in elderly men. Only those that did not express a preference were randomized and the incidence of post-operative cognitive dysfunction was only stated including those that had not been randomized.</td>
</tr>
<tr>
<td>Handley 1997 [31]</td>
<td>This study is a randomized controlled trial of general versus general and epidural anesthesia in patients aged 18–74 for abdominal surgery. Not only was the study population too young but the psychological testing to determine post-operative cognitive dysfunction was on the first post-operative day only and as such an incidence was not reported within the required 3–7 post-operative day window.</td>
</tr>
<tr>
<td>Jones 1990 [32]</td>
<td>This randomized study compares general and regional anesthesia in 146 patients undergoing elective knee or hip replacement. However the psychological outcome measures were employed at 3 months post-operatively only and not within the required 3–7 day window.</td>
</tr>
<tr>
<td>Marcantonio 1998 [33]</td>
<td>This study describes the incidence of post-operative delirium in 1341 patients who have undergone non-cardiac surgery, by looking at their medical records. Therefore this paper is non-randomized, non-controlled and retrospective.</td>
</tr>
<tr>
<td>Nielson 1990 [34]</td>
<td>This randomized study evaluates cognition of 98 patients after randomization to general or regional anesthesia for elective knee arthroplasty. The outcome measures were used at 3 months post-operatively only and therefore were not within the 3–7 day timeframe as required.</td>
</tr>
<tr>
<td>Ryhanen 1978 [35]</td>
<td>This study assesses the effects of halothane, methoxyflurane, combined analgesic-relaxant anesthesia and epidural anesthesia for varicose vein stripping in women. Although the patients were controlled they were unrandomized.</td>
</tr>
<tr>
<td>Yoshida 2008 [36]</td>
<td>This randomized controlled trial assessed the influence of general and spinal anesthetics in eighty men undergoing urological surgery. However no objective assessment of cognitive outcome was made.</td>
</tr>
</tbody>
</table>

Table 3
The number and nature of the included studies, comparing the outcome measures of post-operative delirium and post-operative cognitive dysfunction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies which report incidences</th>
<th>Mean Study size (Range)</th>
<th>Type of surgeries (in order of frequency)</th>
<th>Volume-weighted mean age (Range)</th>
<th>Volume-weighted mean % male (Range)</th>
<th>Mean adapted Jadad score (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Outcomes</td>
<td>21</td>
<td>14</td>
<td>103 (30–408)</td>
<td>ORTH, URO, VASC, ABDO, CARD</td>
<td>67 (52–84)</td>
<td>51 (6.7–100)</td>
</tr>
<tr>
<td>Post-Operative Delirium</td>
<td>5</td>
<td>5</td>
<td>109 (30–262)</td>
<td>ORTH, ABDO</td>
<td>72 (69–78)</td>
<td>28 (10–64)</td>
</tr>
<tr>
<td>Post-Operative Cognitive Dysfunction</td>
<td>16</td>
<td>9</td>
<td>101 (30–408)</td>
<td>ORTH, URO, VASC, ABDO, CARD</td>
<td>66 (52–84)</td>
<td>59 (6.7–100)</td>
</tr>
</tbody>
</table>

ORTH – orthopedic; URO – urological; VASC – vascular; ABDO – abdominal; CARD – cardiac.

measuring the odds of POD or POCD are listed in Table 5. Studies tended to present risk ratios rather than odds ratios and for consistency these are presented in the tables.

**Comparison of GA with all non-GA for POD**

In the five studies whose outcome was POD, GA was compared to epidural in two cases [44,56], regional in one case [54] and a combination of either general with spinal [51] or general with epidural [52]. The pooled estimate shows no difference between the groups (0.88, 95% CI = 0.51–1.51) (Fig. 1).

**Comparison of GA with spinal anesthesia for POCD**

Of the five studies which explored general versus sp-
Table 4
Included papers which present incidences of post-operative delirium or cognitive dysfunction

<table>
<thead>
<tr>
<th>Paper</th>
<th>Surgery</th>
<th>Anesthesia</th>
<th>Outcome</th>
<th>Number</th>
<th>Gender (%M)</th>
<th>Age</th>
<th>Assessment timing (days)</th>
<th>Jadad score</th>
<th>Adapted Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berggren 1987 [44]</td>
<td>ORTH</td>
<td>GA, EPI</td>
<td>Delirium</td>
<td>57</td>
<td>19</td>
<td>78</td>
<td>1, 7</td>
<td>3</td>
<td>0.70 (0.23–2.07)</td>
</tr>
<tr>
<td>Bigler 1985 [45]</td>
<td>ORTH</td>
<td>GA, SPI</td>
<td>POCD</td>
<td>40</td>
<td>18</td>
<td>79</td>
<td>7, 90</td>
<td>4</td>
<td>1.0 (0.06–17.18)</td>
</tr>
<tr>
<td>Casati 2003 [46]</td>
<td>ORTH</td>
<td>GA, SPI</td>
<td>POCD</td>
<td>30</td>
<td>7</td>
<td>84</td>
<td>1, 7</td>
<td>5</td>
<td>3.5 (0.32–32.23)</td>
</tr>
<tr>
<td>Chung 1987 [47]</td>
<td>URO</td>
<td>GA, SPI</td>
<td>Confusion</td>
<td>44</td>
<td>50</td>
<td>72</td>
<td>1, 3, 5, 30</td>
<td>2</td>
<td>2.86 (0.27–29.80)</td>
</tr>
<tr>
<td>Chung 1989 [48]</td>
<td>URO</td>
<td>GA, SPI</td>
<td>POCD</td>
<td>44</td>
<td>100</td>
<td>72</td>
<td>1, 3, 5, 30</td>
<td>4</td>
<td>1.46 (0.44–4.88)</td>
</tr>
<tr>
<td>Cook 1986 [49]</td>
<td>VASC</td>
<td>GA, SPI</td>
<td>Confusion</td>
<td>101</td>
<td>70</td>
<td>67</td>
<td>Until discharge</td>
<td>1</td>
<td>0.61 (0.20–1.85)</td>
</tr>
<tr>
<td>Forster 1990 [50]</td>
<td>VASC</td>
<td>GA, RA</td>
<td>POCD</td>
<td>64</td>
<td>33</td>
<td>73</td>
<td>1, 7</td>
<td>4</td>
<td>0.22 (0.02–2.07)</td>
</tr>
<tr>
<td>Kudoh 2004 [51]</td>
<td>ORTH</td>
<td>GA, COM</td>
<td>Delirium</td>
<td>150</td>
<td>10</td>
<td>76</td>
<td>0–7</td>
<td>5</td>
<td>1.0 (0.14–7.29)</td>
</tr>
<tr>
<td>Nishikawa 2007 [52]</td>
<td>ABDO</td>
<td>GA, COM</td>
<td>Delirium</td>
<td>30</td>
<td>57</td>
<td>71</td>
<td>0–3</td>
<td>4</td>
<td>1.63 (0.23–11.46)</td>
</tr>
<tr>
<td>Pan 2006 [53]</td>
<td>ABDO</td>
<td>GA, COM</td>
<td>POCD</td>
<td>92</td>
<td>53</td>
<td>72</td>
<td>7</td>
<td>4</td>
<td>0.83 (0.37–1.90)</td>
</tr>
<tr>
<td>Papaioannou 2005 [54]</td>
<td>ABDO</td>
<td>GA, RA</td>
<td>Delirium</td>
<td>47</td>
<td>64</td>
<td>60+</td>
<td>0–3</td>
<td>4</td>
<td>1.45 (0.32–6.71)</td>
</tr>
<tr>
<td>Rasmussen 2003 [9]</td>
<td>ORTH</td>
<td>URO, GA</td>
<td>RA, POCD</td>
<td>314</td>
<td>41</td>
<td>71</td>
<td>7, 90</td>
<td>3</td>
<td>1.72 (0.97–3.04)</td>
</tr>
<tr>
<td>Scott 2001 [55]</td>
<td>CARD</td>
<td>GA, COM</td>
<td>Confusion</td>
<td>408</td>
<td>86</td>
<td>59</td>
<td>0–5</td>
<td>0</td>
<td>3.90 (1.07–14.18)</td>
</tr>
<tr>
<td>Williams-Russo 1995 [56]</td>
<td>ORTH</td>
<td>GA, EPI</td>
<td>Delirium</td>
<td>262</td>
<td>30</td>
<td>69</td>
<td>7, 180</td>
<td>4</td>
<td>0.76 (0.35–1.68)</td>
</tr>
</tbody>
</table>

ORTH – orthopedic; URO – urological; VASC – vascular; ABDO – abdominal; CARD – cardiac; GA – general anesthetic; EPI – epidural; SPI – spinal; RA – regional anesthesia; COM – combined; POCD – post-operative cognitive dysfunction; CI – confidence intervals.

Fig. 1. Forest plot of the five studies which compare GA with RA in the development of POD. GA – General Anesthesia; RA – Regional Anesthesia.

Test for heterogeneity: Q = 1.11; df=4 (p= 0.89)
Table 5
Papers which present only mean group changes in a neuropsychological test battery, with a summary of their findings

<table>
<thead>
<tr>
<th>Paper</th>
<th>Surgery</th>
<th>Anesthesia</th>
<th>Outcome</th>
<th>Number</th>
<th>Gender (%M)</th>
<th>Age</th>
<th>Assessment Timing (days)</th>
<th>Jadad Score</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anwer 2006 [37]</td>
<td>ORTH, URO</td>
<td>GA, RA</td>
<td>POCD</td>
<td>60</td>
<td>60</td>
<td>62</td>
<td>1, 3</td>
<td>3</td>
<td>Significantly less decline in RA compared to GA</td>
</tr>
<tr>
<td>Asbjorn 1989 [38]</td>
<td>URO</td>
<td>GA, EPI</td>
<td>POCD</td>
<td>40</td>
<td>100</td>
<td>69</td>
<td>4, 21</td>
<td>3</td>
<td>Equal risk from GA and EPI</td>
</tr>
<tr>
<td>Dahn 1999 [39]</td>
<td>ORTH</td>
<td>GA, SPI</td>
<td>POCD</td>
<td>30</td>
<td>37</td>
<td>70</td>
<td>0, 1, 3</td>
<td>3</td>
<td>Favors SPI compared to GA, significantly in 1 of 10 tests</td>
</tr>
<tr>
<td>Dahn 2003 [40]</td>
<td>ORTH</td>
<td>GA, SPI</td>
<td>POCD</td>
<td>40</td>
<td>43</td>
<td>65</td>
<td>0, 1, 3</td>
<td>3</td>
<td>Equal risk from GA and SPI</td>
</tr>
<tr>
<td>Ghoneim 1988 [41]</td>
<td>ORTH, URO</td>
<td>GA, RA</td>
<td>POCD</td>
<td>105</td>
<td>67</td>
<td>61</td>
<td>1–7</td>
<td>3</td>
<td>Equal risk from GA and RA</td>
</tr>
<tr>
<td>Riis 1983 [42]</td>
<td>ORTH</td>
<td>GA, EPI, COM</td>
<td>POCD</td>
<td>30</td>
<td>NR</td>
<td>70</td>
<td>2, 4, 7</td>
<td>3</td>
<td>Equal risk from GA, COM and EPI</td>
</tr>
<tr>
<td>Somprakit 2002 [43]</td>
<td>ORTH, URO</td>
<td>GA, RA</td>
<td>POCD</td>
<td>120</td>
<td>38</td>
<td>52</td>
<td>1, 3</td>
<td>3</td>
<td>Equal risk from GA and COM</td>
</tr>
</tbody>
</table>

ORTH – orthopaedic; URO – urological; GA – general anesthetic; RA – regional anesthesia; EPI – epidural; SPI – spinal; COM – combined; POCD – post-operative cognitive dysfunction; NR – not reported

Fig. 2. Forest plot of the five studies which compare GA and spinal anesthesia in the development of POCD. GA – General Anesthesia; SPI – spinal.

Comparison of GA with epidural anesthesia for POCD

There were no studies presenting incidences comparing general and epidural anesthesia, however there were two papers which presented mean group changes [38, 42], which both showed an equal risk for POCD between anesthesia methods.
Fig. 3. Forest plot of the two studies which compare GA and RA in the development of POCD. GA – General Anesthesia; RA – Regional Anesthesia.

Test for heterogeneity: $Q = 3.02; df = 1 \ (p = 0.08)$

Fig. 4. Forest plot of the two studies which compare GA and combination anesthesia in the development of POCD. GA – General Anesthesia.

Test for heterogeneity: $Q = 3.90; df = 1 \ (p = 0.05)$
Comparison of GA with RA for POCD

Two papers presented incidences for GA and RA [9, 50], with a pooled estimate of the odds ratio of 1.51 (95% CI = 0.87–2.64), non-significantly favoring RA (Fig. 3). Three studies presented mean group changes [37,41,43], with one [37] significantly favoring RA and two showing no difference between types of anesthesia.

Comparison of GA with combination anesthesia for POCD

Two papers presented an incidence of POCD after surgery under GA or combination (general and epidural) anesthesia [53,55], with a pooled odds ratio of 1.3 (95% CI = 0.65–2.60), non-significantly favoring combination anesthesia (Fig. 4). One paper presented mean group changes [42] which did not favor either method of anesthesia.

Comparison of GA with non-GA for POCD

Combining the 9 studies which presented incidences of POCD after GA compared to non-GA, the pooled estimate of the odds ratio is 1.34 (95% CI = 0.93–1.95), marginally non-significantly favoring non-general anesthesia (Fig. 5). In total, 7 studies showed mean group changes, with a significant finding reported in two [37,39]. The pattern of results from these 7 papers does not seem to differ substantially from the pattern observed in the studies which contributed to the meta-analysis.

The rating scales used to assess cognitive dysfunction across all studies have been categorized in Table 6. The 35 tests tended to be either global measures (the most commonly used was the mini-mental state examination), or recognized tests of specific cognitive domains which are normally found as components of comprehensive test batteries. The studies that did not present criteria derived definitions of POCD tended to employ many individual tests to cover domains of cognition including memory, executive function and calculation.

The adapted Jadad score giving an indication of methodological rigor varied from 0–5 across all studies and on average where delirium was the principal outcome, quality appeared higher in comparison to POCD studies (p = 0.11). However there appeared no clear relationship between the adapted Jadad score of studies and their findings for each outcome. Finally, Figs 6
Table 6

<table>
<thead>
<tr>
<th>Paper</th>
<th>Global function</th>
<th>Memory function</th>
<th>Verbal recognition</th>
<th>Visual recall</th>
<th>Visual recognition</th>
<th>Higher cognition function</th>
<th>Attention</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awmer 2006 [37]</td>
<td>WAIS</td>
<td></td>
<td>Digit span, paired associates, free recall</td>
<td>Paired associates</td>
<td>Author's</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asbjorn 1989 [38]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bigler 1985 [45]</td>
<td>AMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Backwards spelling, calculation, controlled word association</td>
</tr>
<tr>
<td>Casati 2003 [46]</td>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chung 1987 [47]</td>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chung 1989 [48]</td>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook 1986 [49]</td>
<td>Author's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahn 1999 [39]</td>
<td></td>
<td>Digit span, free recall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroop</td>
</tr>
<tr>
<td>Dahn 2003 [40]</td>
<td></td>
<td>Digit span, free recall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Backwards spelling, calculation, controlled word association</td>
</tr>
<tr>
<td>Ghorneim 1988 [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan 2006 [53]</td>
<td></td>
<td>Paired associates, digit span forward and backwards</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Digit symbol substitution, symbol cancellation</td>
</tr>
<tr>
<td>Rasmussen 2003 [9]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pegboard for the favored and unflavored hand, mental conorol</td>
</tr>
<tr>
<td>Riis 1983 [42]</td>
<td></td>
<td>Digit span, paired associates, story recall, selective reminding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott 2001 [55]</td>
<td>Author's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somprakit 2002 [43]</td>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WAIS – Weschler Adult Intelligence Scale; AMT – Abbreviated Mental Test; MMSE – Mini-Mental State Examination; Author’s – authors own test or adaptation of a recognized test.
and 7; though with small numbers of studies show little evidence of publication bias.

**DISCUSSION**

This study aimed to determine the impact of the route of anesthetic delivery on the development of either POD or the more restricted concept of POCD.

It was an objective to compare individual types of anesthesia in the development of POD, but as only five studies were suitable for inclusion, it was required that they were grouped into GA versus non-GA. The pooled estimate of the odds ratio showed no impact of anesthetic route on the incidence of POD. From review of individual studies, it would appear that orthopaedic surgery was more likely to favor general anesthesia, with the opposite the case for abdominal surgery. The small number of studies in this part of the analysis though
limits any opportunity to draw inference. What was not observed though is important, namely that in terms of delirium, the route of anesthetic would appear to have little bearing. A larger sample of studies was available for review where POCD was the principal outcome. However, differences in how this was defined limited the ability to draw any firm conclusions. Despite this, the meta-analysis on this occasion pointed towards regional anesthesia being less likely to cause POCD than GA, however this was non-significant. Comparing this finding to the one for POD suggests either that the subtle effects of anesthetic on cognition are measurable and apparent but insufficiently potent to cause delirium or that the genesis of delirium is multi-factorial and in RCT’s not manifest. This is not true for POCD work, where the impact of anesthetic route is more specific to the genesis of POCD.

The influence of other variables such as surgery type, age of sample, or duration of post operative observation could not be measured statistically due to the high degree of variability in these factors in a small sample of studies. Therefore, the ability to draw any conclusions regarding mapping anesthetic type onto subpopulations of patients is limited.

Standardization of outcomes in this type of work would help the field progress, indeed with a burgeoning interest in intervention studies to reduce the risk of POD and POCD, the use of a standardized cognition battery for POCD would be helpful. The validity and reliability of the rating scales used for POD have helped in this regard and similar scales for POCD are overdue. We found that 35 different tests were employed for measuring cognitive decline, often with different thresholds for impairment. Global measures such as the MMSE were most popular probably as they are fast and easy to perform, but they may be insensitive to the dysfunction seen post-operatively. It has been described that particularly tests of verbal memory are sensitive for post-operative cognitive dysfunction [11], but in a global assessment, the lack of impairment in other domains may hide the verbal memory dysfunction. Similarly, studies which employ many individual tests may have increased sensitivity, depending upon how one sets a threshold. In one study [9], the authors derived an incidence based on several tests and they interestingly reported a higher rate of POCD as well as a greater different between the groups than other studies in our sample.

The strengths and weaknesses of this study must be assessed in order to understand the implications of the findings. We had a clear aim to only include RCTs using robust outcome measures applied in the critical window for POD and POCD namely between 3 and 7 days post operatively. These specific requirements along with the sensitive search strategy and hand-searching of original and review article bibliographies should have ensured that this review only incorporates the most relevant, high quality evidence. However, by strictly defining the criteria for inclusion in this study, it has been impossible to assess specific covariants due to a lack of studies to use for metaregression analysis. The study could have been improved further if experts in the field were contacted to locate relevant grey literature.

CONCLUSION

This meta-analysis has demonstrated that rates of delirium are unlikely to be influenced by the route of anesthesia. This is reassuring in some regards because of the work linking delirium to increased morbidity and mortality post operatively as well as with regards to the longer term risks of neurodegeneration. Perhaps though this optimistic observation should be balanced against the likely risk our work demonstrated of generating POCD with GA when compared to anesthesia that has no central effect. The short, mid, and long term consequences of POCD need qualifying and quantifying. However, there is an urgent need for a consensus on the definition of POCD to aid both observational work as well as measuring the impact of interventions in this condition.

DISCLOSURE STATEMENT


Appendix 1

The adapted Jadad score is as follows.

Randomization:
- +1 if the study uses the word randomized, random allocation or similar
- +1 if the method of randomization is adequate e.g., random number generation
- -1 if the method of randomization is inadequate e.g., based on date of operation

Blinding:
- +1 outcome assessor blinded
- Outcome assessor clearly unblinded
- Objective measures of cognitive performance are clearly stated
- Measures are not adequately stated such that replication is difficult

Were both groups treated equally:
- Patient characteristics well documented and different between groups
- Patient characteristics in each group are not reported

REFERENCES

Anesthetics Promoting in vitro AβPP Metabolism and Amyloid-β Toxicity

Barbara Eckel*, Manfred Blobner and Gerhard Rammes
Klinik für Anästhesiologie, Klinikum rechts der Isar, Technische Universität München, Ismaningerstr. München, Germany

Accepted 25 June 2010

Abstract. At present, more than 35 million people worldwide have Alzheimer’s disease (AD). With increasing incidence and a growing number of aged patients undergoing surgery, the relevance of a possible interaction between anesthetics and AD is growing as well. Below, we review in vitro studies investigating the effects of anesthetics on the metabolism of amyloid precursor protein and its metabolite amyloid-β.

Keywords: Alzheimer’s disease, amyloid, amyloid-β protein precursor, anesthetics, in vitro

INTRODUCTION

Alzheimer’s disease (AD) is one of the most serious health problems in western countries. In 2006, the worldwide prevalence of AD was 26.6 million. It is estimated, that the prevalence will quadruple by 2050, by which time 1 in 85 persons worldwide will be living with this disease [1]. Since the number of aged patients undergoing surgery is growing due to demographic changes in population, the number of aged patients and specifically those with AD needing anesthesia is increasing as well. Accordingly, a possible interaction between anesthetics and AD is of major interest. However, whether anesthesia influences the development or even causes AD is hardly evaluated and discussed controversially [2,3]. Clinical studies bear the problem that it is not possible to dissociate the effects of anesthesia and surgery. Therefore, due to the possibility to manipulate experimental factors in a controlled manner, several research groups prefer to evaluate the anesthesia-AD interaction in animal models or in in vitro experiments. In vitro studies offer the possibility to study distinct questions in detail but lack the interrelation with other systems of the body. Therefore, they are valuable to investigate cellular mechanisms but it is hazardous to draw general conclusions.

Below, we review in vitro studies investigating the effects of anesthetics on the metabolism of amyloid precursor protein and its metabolite amyloid-β (Aβ).

Aβ AND AβPP METABOLISM IN ALZHEIMER’S DISEASE

AD is an age-dependent devastating neurodegenerative disorder characterized clinically by a progressive cognitive decline, and pathologically by senile plaques, neurofibrillary tangles, and neuronal loss in selected brain regions. The major component of the senile plaques (amyloid deposits) is an amphiphilic peptide (Aβ) derived from proteolysis of a large membrane spanning amyloid-β protein precursor (AβPP) [4]. This Aβ plays an important role in the most common theory of genesis of AD, the “amyloid hypothesis”.
This hypothesis states that an imbalance between production and clearance causes Aβ to accumulate and this excess may lead to AD (AD) [5].

Aβ peptides originate from proteolysis of AβPP by the sequential enzymatic actions of beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1), a β-secretase and γ-secretase, a protein complex with presenilin at its catalytic core. BACE generates C-terminal fragments (CTF/β) from membrane bound AβPP. Cleavage of CTF/β by γ-secretase releases Aβ monomers into the extracellular and cytosolic space [6, 7]. Depending on the exact point of cleavage by γ-secretase, three principal forms of Aβ, comprising 39, 40 and 42 amino acid residues, respectively, are produced. Monomers of Aβ40 are much more prevalent than aggregation prone and damaging Aβ42 species [8]. Soluble Aβ is thought to undergo a conformational change to high β-sheet content, rendering it prone to aggregate into soluble oligomers and larger insoluble fibrils in plaques. In this process, the fibrillogenic Aβ42 isoform triggers the misfolding of other Aβ- species [8]. Initially, it was assumed that primarily Aβ derived fibrillar plaques were responsible for neurotoxicity. More recent findings, however, suggest that soluble Aβ oligomers might be the culprit, inhibiting hippocampal long-term potentiation and disrupting synaptic plasticity [9]. In brain-slice preparations, dimers and trimers of Aβ are toxic to synapses [10, 11]. In transgenic AD mice, 12-mers of Aβ-peptides also seem to contribute to cognitive deficits in independently of plaques or neuronal loss [12]. The severity of cognitive deficits in AD correlates with levels of oligomers in the brain not the total Aβ burden [13].

Aβ solubility, and consequently its likelihood to oligomerize, can be influenced by different factors. First of all, oligomerization starts if Aβ burden exceeds a solubility threshold and Aβ begins to self-associate [5]. An increased production as well as a decreased clearance increase Aβ levels. Typical increases are due to genetic variability like mutation in the AβPP gene. Another example would be the Down syndrome as the AβPP gene. Cleavage of the chromosome 21 which is present as an extra copy (in whole or as a part) in suffers from AD. The microdialysate revealed an Aβ1–40 and Aβ1–42 concentration of 1.38 nM and 0.14 nM, respectively [21].

In addition, it has to be taken into account that most of the studies have been conducted using the synthetic Aβ1–40 and Aβ1–42 peptides, whereas naturally generated Aβ species are considerably more heterogeneous in length [22–24]. Also, synthetic Aβ peptides are often solubilized initially in highly non-physiological solvents which may affect the oligomerization profile.

All these caveats have to be considered for interpretation and/or extrapolation and may provide an explanation for the occurrence of contradictory results concerning Aβ toxicity and the interaction with anesthetics.

**DO ANESTHETICS ENHANCE Aβ-FORMATION?**

It is still a matter of debate, whether inhalational anesthetics induce neuroprotection or neurotoxicity.
Depending on the specific cell line used, duration of exposure and the concentrations applied, anesthetics protect against apoptosis (for review see [25,26]), but the opposite has also been reported (for review see [27,28]). The neuroprotective potential of inhaled anesthetics probably results from their pharmacological properties contributing to the decrease or inhibition of neuronal excitability and enhancing GABAA receptor function. However, the mechanisms by which inhaled anesthetic mediated toxicity in the animal and cell culture studies are still unknown. A more recent mechanism proposes that inhalational anesthetics induce apoptosis by a disruption of intracellular calcium homeostasis (for review see [29]). Disruption in calcium homeostasis plays a central role in the pathophysiology of AD (for review see [30]). Therefore, it has been hypothesized that a detrimental interaction between anesthetic exposure and ADs neuropathology may exist. Indeed, studies in cell culture models demonstrate an increase in the production and aggregation of Aβ after inhaled anesthetic administration. In H4 human neuroglioma cells stably transfected to express human AβPP (H4-AβPP cells), the application of various inhaled anesthetics, mostly isoflurane, increased caspase-3 activation [31–35], induced apoptosis [31–36] and elevates Aβ production [31–33,35]. The molecular mechanism by which isoflurane induces apoptosis still remains unclear. Anesthetic exposure to H4-AβPP cells is accompanied by an increase in levels of BACE [31,32] and γ-secretase [31], thereby increasing the levels of intracellular Aβ and decreasing CTFβ levels [31–33]. Interestingly, it has been found recently that caspase-3 stabilizes BACE [37] providing an additional pathway for elevating Aβ generation in H4-AβPP cells. Finally, the increased Aβ generation/accumulation further potentiate the isoflurane-induced caspase activation and apoptosis [32]. Collectively, all these data imply synergistic mechanisms triggering the neurodegeneration that underlies the pathophysiology in AD. However, there are obviously some caveats in the proposed vicious cycle [29] of some inhaled anesthetic-induced apoptosis and Aβ generation. Firstly, all these experiments were performed in cultured cells. Unfortunately, there is currently no satisfactory way to extrapolate anesthetic-induced apoptosis-related mechanisms found in cultured cells to the in vivo aging brain. Secondly, inhaled anesthetics were applied at doses and durations which may exceed clinical standard exposures. In the above mentioned studies, H4-AβPP cells were mostly treated with 2% isoflurane [31,32,34–36]. Some groups used 12% desflurane and hypoxia (18% O2 [33], 70% nitrous oxide and 1% isoflurane [38] or 4.1% sevoflurane [35]). All these concentrations lay more or less within the clinical range. However, in all studies, cells were exposed to the anesthetic for 6 h which, when extrapolated, is clearly above the average duration for surgery. Thirdly, the same doses of anesthetics which were applied to H4-AβPP cells, also induced caspase-3 activation and decreased cell viability in naïve H4 cells without detectable changes in AβPP processing and Aβ generation [32,33,35,38]. This indicates that apoptosis induced by anesthetics can occur independently of alterations in AβPP processing and Aβ generation. Finally, H4 neuroglioma cells are non-differentiated cells. Considering that a specific fraction of cultured cells is always entering or is still within the mitotic phase, long-term exposure to anesthetics may also affect mechanisms crucial for cell cycling and may therefore induce apoptotic processes.

**DO ANESTHETICS INDUCE Aβ OLIGOMERIZATION?**

The analysis of the assembly pathway of Aβ in vitro and biochemical characterization of Aβ deposits isolated from AD brains indicate that Aβ oligomerization occurs via distinct intermediates. Of these, the most toxic species appear to be small Aβ oligomers. Anesthetic agents are widely used in clinical medicine and are hypothesized to be associated with postoperative cognitive dysfunction (POCD). Patients with pre-existing cognitive deficits are at the highest risk for the development of POCD. However, whether anesthesia influences the development or even causes AD is hardly evaluated and discussed controversially. It is obvious that apart from intrinsic properties of Aβ aggregation (see above) a potential acceleration of Aβ oligomerization by anesthetics and thereby promoting Aβ toxicity would have critical implications for clinical anesthesia. First evidence came from in vitro studies showing that inhaled anesthetics can interact with Aβ monomers to promote the formation of small soluble oligomers. In cultured neuronal cells, halothane (0–10 mM) and isoflurane (0–10 mM) when applied to synthesized Aβ1–40 and Aβ1–42 monomers (15 μM) accelerate amyloid fibril formation and enhance cytotoxicity as measured by LDH release [39]. It has been proposed that halothane and isoflurane bind to protein complexes with interfacial hydrophobic cavities [40] and stabilize population of diffusible Aβ oligomers relative to monomers and fibrils [41]. Indeed, biophysical experi-
ments with Aβ1−40 protein samples (200 µM) revealed that halothane (10 mM) and isoflurane (15 mM) may lower the necessary concentration of Aβ monomers to initiate oligomer formation [41]. Further evidence for an involvement of general anesthetics in promoting Aβ oligomerization came from studies using H4 human neuroglioma cells overexpressing human AβPP [36]. When cells were exposed to 2% isoflurane for 6 h the Aβ fibrillar aggregation inhibitor Congo red inhibits apoptosis. These results led to the conclusion that isoflurane-induced Aβ oligomerization and apoptosis may contribute to the risk of postoperative cognitive dysfunction and provide a potential pathogenic link between delirium and dementia. In addition, in vitro multidimensional NMR spectroscopy revealed that the anesthetics halothane, isoflurane and propofol (beyond the clinical range) interact with Aβ1−40 and induce Aβ oligomerization [42]. Aβ1−40 (0.2 mM) oligomerization has also been shown when isoflurane and desflurane was applied at clinically relevant concentrations [43]. Interestingly it has been shown using NMR spectroscopy at clinically relevant concentration of diazepam and propofol do not oligomerize abeta peptide [44–46]. Size factor of anesthetics are believed to be played an important role for abeta oligomerization [46]. However, it has to be considered that Aβ assembly occurs in a very complex and dynamic environment; characterized by the presence of different proteins, membranes, metal ions etc., while in vitro experiments are done with extremely simplified conditions that may bias toward amyloid aggregation [47].

CONCLUSION

There is growing evidence that small soluble Aβ oligomers are playing a prominent role in the pathophysiology of AD. Anesthetics are widely used in clinical practice and a possible promotional interaction of anesthetics with Aβ aggregation or even Aβ formation is therefore intensively discussed. The advantages of in vitro investigations are obvious. Indeed, in vitro experiments showed that inhaled anesthetics can interact with Aβ and promote its oligomerization and enhance the apoptotic properties of this “peptide from hell” [48–50] in cell culture. Unfortunately, the pharmacological design of those in vitro experiments are not adequate adapted to pathophysiological and/or clinical conditions thus making the interpretation complicated. Nevertheless, based on existing studies (biophysical using NMR, molecular and animal model), the suggested synergistic mechanisms resulting in the elevation of Aβ levels after exposure of inhaled anesthetics should be taken seriously.

DISCLOSURE STATEMENT


REFERENCES


Alzheimer’s Disease: A General Introduction and Pathomechanism

Verena H. Finder*
Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich, Zurich, Switzerland

Accepted 20 July 2010

Abstract. Alzheimer’s disease (AD) is the most common form of dementia, which affects more than 35 million people worldwide with increasing tendency. Satisfying therapies and prevention are not available. Since the first description of the fatal progressive neurodegenerative disease in 1907, however, major findings on the molecular mechanisms have been reported. Current clinical trials target diverse aspects and principles of AD, such as the generation and aggregation of amyloid-β (Aβ). Extracellular amyloid plaques, predominantly consisting of Aβ, and intracellular neurofibrillar tangles, formed by hyperphosphorylated tau, are the major pathological hallmarks in the brain of AD patients. AD is consequently one of about 40 identified amyloidoses – protein misfolding diseases, which share as their main pathogenic mechanism the aberrant deposition of endogenous proteins as amyloid fibrils. This article aims principally to introduce AD and its identified key players, to summarize classic and recent publications on the complex molecular mechanisms underlying the disease, and to discuss challenges that need to be faced for the development of improved therapeutic strategies.

Keywords: Alzheimer’s disease, amyloid-β, amyloid-β protein precursor, fibrils, protein misfolding, oligomers, neurotoxicity, tau

INTRODUCTION TO ALZHEIMER HISTORY

Alzheimer’s disease (AD) is the most common form of dementia, accounting for 60–80% of all cases [1] and affecting people aged 85 or older with an incidence of 25–50% [2]. Currently, every 70 seconds one person in America develops dementia, which corresponds to about 450,000 new cases per year. It is estimated that this number will more than double by 2050 [1], mainly due to increased life expectancy.

The exact mechanism(s) underlying AD are subject to enormous research efforts. Until now, approximately 72,000 papers on AD have been published (July 2010, PubMed). About 18% of all actively publishing scientists in neuroscience have published at least one paper in the field [3]. As yet, neither a satisfying therapy nor a preventative cure is available. Furthermore, AD can only be precisely diagnosed postmortem on a neuropathological basis, the so-called Braak stages classify the progress of the disease [4].

AD is one of about 40 identified amyloidoses, which share as their main pathological hallmark the aberrant deposition of endogenous, normally soluble proteins as amyloid fibrils in various tissues. Each of these diseases involves a specific protein and clinical profile, among them Parkinson’s disease, the prion diseases, diabetes type II, Huntington’s disease, and amyotrophic lateral sclerosis [5]. The major pathological hallmarks in the brain of AD patients are amyloid plaques, consisting predominantly of the Amyloid-β (Aβ) peptide, and neurofibrillary tangles (NFTs), formed by hyperphosphorylated tau protein. These lesions occur in brain regions involved in learning and memory, i.e. the
hippocampus, the amygdala, and in the association cortices of the frontal, temporal and parietal lobes. Further Aβ accumulation is observed in the small blood vessels of the meninges and cerebral cortex, also termed cerebral amyloid angiopathy [6].

The first AD case was described in 1907. Since then, major developments and findings mark the history of AD research in the general context of amyloid-associated disorders. The term amyloid was first introduced by Virchow in 1854 to describe the macroscopic abnormalities associated with clinical symptoms, which appeared to represent the amylaceous constituents of plants upon staining with iodine [7]. Five years later, Friedreich and Kekule suggested that amyloid is a protein rather than starch according to the high nitrogen content [8]. The plaques in the AD brain were first described in 1898 [9], the aniline dye Congo red facilitated specific discrimination from non-amyloid plaques in 1922 [10]. In 1907, Alois Alzheimer’s lecture about the first case of the fatal progressive dementia including extracellular plaque and intraneuronal NFT pathology did not receive special attention [11], although as a psychiatrist he was a pioneer at this time by associating pathological changes with dementia symptoms. Alzheimer’s colleague, Kraepelin, finally gave the disease its official name in 1910 [12]. Amyloid fibrils from tissue were first visualized by electron microscopy in 1959 [13]. X-ray diffraction studies of isolated fibrils in 1968 revealed the so-called cross-β structure as a common motif [14]. In the 1970s, the availability of amino acid analysis and protein sequencing tools revealed that each amyloidosis is linked to a specific protein [15].

In 1984, Aβ was identified as the major component of plaques from AD and Down syndrome patients [16, 17]. Tau had already been described in 1975 as an essential protein for microtubule assembly [18], but it was not until one year after the identification of Aβ that it was identified as the NFT-forming protein [19]. The corresponding MAPT gene was cloned in 1988 [20], again one year after the amyloid-β protein precursor (AβPP) gene containing the Aβ sequence was cloned from chromosome 21 [21].

AD cases can be categorized into two main categories, the (pseudo-) sporadic late-onset AD (LOAD) and early-onset familial AD (FAD). LOAD is characterized by disease manifestation at ages above 65 years, whereas FAD occurs earlier, sometimes already in the twenties. Increasing age is the major risk factor for LOAD. In addition, the apolipoprotein E (ApoE) gene on chromosome 19 has been demonstrated to represent a major genetic risk factor. FAD cases likely constitute less than 1% of all AD cases [1]. The usual suspects of FAD are primarily AβPP and presenilin (PS) 1 and 2. Aβ is generated from AβPP by β- and γ-secretase cleavage. PS resembles the active site of the γ-secretase, which is composed of one PS, nicastrin, APH-1, and PEN-2. In 1991, the first FAD cases were linked to mutations in the AβPP gene [22]. One year later, FAD-causing mutations were mapped to chromosome 14 and in 1995 to chromosome 1 [23], where the genes encoding PS 1 and 2 are localized, respectively. The first transgenic mouse model for AD, which developed plaques caused by AβPP mutation, was presented in 1995 [24]. In 2003, the first Aβ vaccination trial was eventually performed [25]. However, due to the occurrence of meningoencephalitis in some of the AD patients, this initial trial had to be suspended.

THE AMYLOID HYPOTHESIS

In the early 1990s, the amyloid hypothesis was formulated [26–28]. It proposes that Aβ deposition represents the central hallmark of AD pathogenesis and states that Aβ aggregation is the cause rather than an effect of AD, which was initially based on FAD cases and Aβ toxicity [26–28]. Major evidence came from the analysis of Down syndrome patients, who carry an additional AβPP allele and develop FAD likely because of a dose-dependent effect. Duplication of the AβPP locus was eventually reported to cause FAD in 2006 [29]. Moreover, FAD-associated mutations identified at this time in AβPP where shown to alter its metabolism, leading to increased Aβ production [28]. Aβ aggregates are toxic in cell culture and animal models [30] and disaggregation of Aβ by antibody treatment reverses its toxicity [31]. Arguments against a causative role of tau in AD are that Aβ aggregates occur earlier than the NFTs [32], tau hyperphosphorylation and aggregation can be triggered by Aβ aggregation [33, 34], and mutations in tau cause frontotemporal dementia with Parkinsonism, not FAD [35]. Aβ aggregation was therefore concluded to initiate a neurodegenerative cascade, leading to neuron loss and dementia, which is also termed the amyloid cascade hypothesis [26,28].

More than 25 years after the identification of Aβ, the enzymes that generate Aβ from AβPP, the proteases that clear Aβ from the brain, as well as other proteins that interact with Aβ to regulate its abundance, have been characterized. This information provides further support for the amyloid hypothesis [36]. There is, how-
However, some controversy as to whether Aβ aggregation exclusively causes AD, which role Aβ/PP tau, and other proteins play in AD, and how they interact. The toxic key players in the Aβ aggregation pathway(s) still have to be identified. The amyloid hypothesis implies that Aβ aggregation is upstream of all obvious pathological events and that inhibition of Aβ aggregation can prevent AD. So far, a satisfactory therapy based specifically on targeting Aβ could not be established. However, several promising approaches have now reached the clinic [37].

**Aβ, THE PATHOGENIC KEY PLAYER?**

Aβ aggregation is considered a key event in the pathogenesis of AD [30] as well as sporadic inclusion-body myositis, which is the most common cause of muscle degeneration in elderly people [38]. Aβ is generated as a normal product of Aβ/PP metabolism via sequential cleavage by β- and γ-secretase, releasing the N- and C-terminal fragments of Aβ/PP, respectively [39,40]. This procedure is called the amyloidogenic pathway of Aβ/PP processing. In an alternative, non-amyloidogenic pathway, Aβ/PP is cleaved by α-secretase between position 15 and 16 of the Aβ segment, followed by γ-secretase processing, which prevents Aβ formation [39,40] (Fig. 1).

In the cortex of AD patients and healthy controls, the average Aβ concentrations of 406 and 221 mg/g were determined, respectively [41]. This extrapolates to several hundred milligrams of Aβ in a human brain and suggests a non-transient physiological function. Depletion of Aβ specifically led to neuron death in cell cultures [42]. In mice, Aβ was shown to have an important role for learning and memory in younger individuals [43]; it may generally regulate cell survival and excitability. Notably, β-secretase knockout mice do not show any deficits, although the Aβ load is dramatically decreased [44]. After traumatic brain injury (TBI), increased Aβ, Aβ/PP, and plaque loads are found, which can occur within hours after the initial trauma [45].

Furthermore, there is recent evidence that Aβ is part of the innate immune system of the brain and functions as an antimicrobial [46]. It has also recently been reported that the Aβ content in the interstitial fluid is regulated by the sleep-wake cycle and increases upon sleep deprivation [47].

Several proteases have been identified that clear Aβ from the brain. Insulin degrading enzyme (IDE) and neprilysin are primarily important for regulation of the steady-state levels of Aβ. IDE is a thiol metalloendopeptidase that degrades monomeric Aβ. Deletion of IDE reduces Aβ degradation by more than 50% in mice [48]. Neprilysin is a membrane-anchored zinc endopeptidase that degrades Aβ monomers and oligomers. Depletion of neprilysin causes cerebral accumulation of Aβ [49]. Further identified proteases for Aβ degradation are plasmin and cathepsin [50,51], endothelin-converting enzyme [52], and the matrix-metalloproteinase family [53]. Moreover, the Aβ load is in equilibrium across the blood-brain barrier (BBB) with its efflux mediated by the low-density lipoprotein receptor related protein (LRP1) and its influx mediated by the receptor for advanced glycosylation end products (RAGE) [54]. In the periphery, Aβ is primarily degraded in the liver and to a lesser extent in the kidneys [55].

In the brain, Aβ is produced mainly in various cellular compartments of neurons, but has also been detected in glial cells and astrocytes [56]. In vitro, “the peptide from hell” [57] rapidly forms amyloid fibrils in aqueous solution and is hard to handle due to its amphipathic character and distinct tendency to aggregate [30]. In vivo, Aβ variants with lengths of 38–43 amino acids, differing in their C-terminus, are produced due to differential cleavage of Aβ/PP by γ-secretase, following a mechanism termed regulated intramembrane proteolysis [58]. The most abundant variants are Aβ1–40 and the more amyloidogenic Aβ1–42, with an approximate ratio of 10:1 [30]. Aβ1–42 is considered to be a key player in the initiation of AD [30].

FAD-causing mutations flanking the Aβ segment in Aβ/PP, and in PS 1 and 2 generally modulate Aβ production and frequently underlie a selective increase in production of Aβ1–42 [59]. About ten FAD-underlying mutations within the Aβ sequence have been identified (Fig. 1). These variants generally exhibit higher amyloidogenicity and lead to distinct neuropathology [60]. Most of these mutations are localized at positions 21–23, but there are also FAD-related amino acid replacements in the N-terminal segment, such as the Tottori (D7N), English (H6R), and A2V mutation [61, 62]. The identified Aβ mutations mostly cause autosomal dominant FAD, but two apparently recessive mutations have been reported: A2V [62] and the Japanese mutation E22Δ [63]. Molecules of the Aβ population can undergo posttranslational modification, e.g. oxidation of methionine 35 to methionine sulfoxide or N-terminal truncation by aminopeptidases and pyroglutamate formation, i.e. lactam formation of N-terminal glutamate [30,64,65]. Taken together, the Aβ population in the brain is a heterogeneous peptide pool.
AβPP processing and Aβ. AβPP has a length of 695-770 amino acid residues, the variants differing in their N-terminal segment. AβPP can be metabolized in a non-amyloidogenic pathway by sequential α- and γ-secretase cleavage (upper part of the scheme). Processing in the amyloidogenic pathway by sequential β- and γ-secretase occurs in lipid rafts and yields Aβ (lower part). The sequence of Aβ₁₋₄₂ is shown, with the identified FAD associated mutations within or flanking the Aβ sequence indicated below.

AβPP – MORE THAN A SOURCE OF Aβ

AβPP is produced in a variety of cells throughout our body, with its expression level depending on the respective developmental state. AβPP is found mainly at the plasma membrane, but also in the trans-Golgi network, the endoplasmic reticulum, and at endosomal, lysosomal and mitochondrial membranes [66]. Different isoforms of AβPP with lengths of 695–770 amino acid residues exist. The shortest one – AβPP695 – is the predominant form in the brain. The larger extracellular N-terminal segment consists of several domains, is glycosylated, and constitutes 88% of AβPP695. The small cytoplasmic C-terminal segment comprises the AβPP intracellular domain (AICD). The Aβ segment includes partly the N-terminal and the transmembrane segment [67]. Assessment of AβPP metabolism has shown that it undergoes rapid turnover in cells [68], with the majority of AβPP molecules being cleaved by α-secretase [39].

The physiological functions of AβPP and its metabolic products are subject to intensive research [67]. AβPP knockout mice are viable but have been shown to display synaptic, learning and memory deficits. The presence of the other APP family members, namely APLP1 and APLP2, has been shown to compensate for the loss of AβPP itself [69]. However, triple AβPP/APLP1/APLP2 knockouts are embryonic lethal [70]. The number of functional synapses generally seems to be modulated by AβPP in a dose-dependent manner [71]. AβPP has been shown to be important for the regulation of neuronal survival, neurite outgrowth, synaptic plasticity, and cell adhesion [72]. It can be phosphorylated by different kinases in the extra- and intracellular segment. Phosphorylation at T668 has received special interest as it leads to altered AβPP processing and Aβ production [73].

Upon cleavage with α-secretase (Fig. 1), the extracellular sAβPPα is secreted and C83, a C-terminal fragment of 83 amino acid residues also termed AβPP-CTFα, remains at the membrane. Secretion of sAβPPα from presynaptic terminals is triggered by electrical activity and activation of muscarinic acetylcholine receptors. Hence, neuronal activity may increase non-
amyloidogenic processing of Aβ/PP [72]. sAβ/PPα regulates neuronal excitability and increases synaptic plasticity, leading to enhanced learning and memory. C83 is either degraded in lysosomes [74] or sequentially processed by γ-secretase to AICD/C59 and C-terminal Aβ/PP fragments of approximately 3 kDa termed p3 [40].

Amyloidogenic processing of Aβ/PP (Fig. 1) involves sequential cleavage by β-secretase (also termed BACE1) and γ-secretase. Upon β-secretase cleavage, the extracellular sAβ/PPβ segment is released and the remaining C-terminal C99 fragment can be further processed by γ-secretase, producing Aβ and AICD, or by caspases to release the neurotoxic peptide C31 [75]. AICD can translocate to the nucleus, where it regulates gene expression and potentially induces production of apoptotic proteins [76].

TAU – A LATECOMER IN AD?

Hyperphosphorylated tau is the major component of NFTs in pyramidal neurons and neuropil threads in distal dendrites in AD. Additionally, tau inclusions are observed in several sporadic disorders, termed tauopathies [35].

The physiological function of tau is to promote the assembly of microtubules and to stabilize them, entailing a role in vesicle transport. Tau has a length of 352-441 amino acid residues and is present in a total of six different isoforms in the human brain [77]. Within three of these isoforms the microtubule-binding domain is encoded by three repeat sequences, whereas the others contain four sequence repeats. The isoforms within these subgroups differ in their N-terminal segments. Phosphorylation and dephosphorylation of tau is catalyzed by various kinases and phosphatases, respectively [78]. Hyperphosphorylated tau spontaneously aggregates into paired helical filaments, which can subsequently form NFTs [79].

Oligomers of tau exhibit cytotoxicity and cause cognitive deficits [80], suggesting a toxic gain of function. Additionally, tau has been described as a prerequisite for Aβ toxicity [81] and there is evidence that tau aggregation could be seeded in mice by injection of extracted tau aggregates [82]. The number of NFTs correlates with the extent of disease progression in AD, but does not correspond to the neuron loss [83]. Importantly, aggregation of tau also leads to disturbance of axonal transport through its loss of function.

UNDERLYING MECHANISM(S) OF AD

The biological functions of a cell depend on folding of thousands of diverse proteins and hence misfolding underlies the pathology of various diseases. According to the amyloid hypothesis, the key event in the initiation of AD is misfolding and aggregation of Aβ (Fig. 2). Factors for the misfolding probability of a protein can be intrinsic (based on the amino acid sequence) or extrinsic (based on mostly unidentified external circumstances) [84]. The intrinsic aggregation tendency primarily depends on the charge, hydrophobicity, and on secondary structure propensities [85]. Particularly, high propensity to form β-sheets and low propensity to form α-helices favors amyloid formation [86]. Environmental factors for the misfolding propensity are parameters such as temperature, ionic strength, pH, oxidative stress, macromolecular crowding, and increased concentration of the misfolding protein [85]. For instance, increase in the protein production rate [17] or decrease of protein clearance, or both, can be directly associated with pathogenic misfolding. Misfolded proteins in the cell are either naturally rescued by the cellular quality control machinery or degraded. The latter can be mediated by the proteasome [87], chaperones, and autophagy/lysosomal pathways [88]. The capability of the immune system to recognize and clear protein aggregates requires further investigation. Aggregated Aβ seems to be a natural target of the immune system. Natural antibodies against oligomeric, fibrillar Aβ and plaques have been identified and their abundance shown to decrease with increasing age [89, 90]. These findings suggest that reduced efficiency of the immune system could lead to decreased Aβ plaque clearance.

Amyloid formation is not necessarily an undesired event. In fact, functional amyloid structures exist in many living organisms for manifold specific purposes, e.g. in spider silk [85]. The highly ordered fibril structure carries information, which self-propagates the morphology by seeding and cooperative binding of further subunits. Amyloid fibrils share their cross-β structure with β-sheets aligned perpendicular to the fibril axis. Diverse morphologies, however, can even be formed by the same protein, such as Aβ[1-40] [91]. It has been proposed that all proteins can form amyloid fibrils under appropriate conditions. As in a simple polymer, stability of the β-sheets of the fibril is built by hydrogen bonds between the β-strands, but not by specific interactions between amino acid residues [84]. Deciphering
the “amylome” should reveal, which proteins can form amyloids under naturally occurring conditions [92].

The only accepted genetic risk factor for sporadic AD identified so far is the ApoE4 allele, of which one and two copies lead to 3–4 times and 15–19 times increased risk, respectively [93]. In addition, ApoE4 lowers the age of onset by about ten years per allele [94]. Although the exact mode of action is unclear, ApoE4 binds to Aβ and seems to trigger Aβ and tau aggregation [95]. Recently, three further genes have been reported to represent risk factors for LOAD: CLU/APOJ, PICALM, and CR1 [96,97].

Extrinsic risk factors for AD include high cholesterol, diabetes mellitus, a low educational level, TBI, consumption of a high calorie diet, sedentary lifestyle, cardiovascular disease and risk factors thereof, and reduced cognitive reserve capacity of the brain [98]. The mechanisms are unclear. It is known that cholesterol is essential in neuronal membranes and concentrated in lipid rafts, where the β- and γ-secretase are assembled and Aβ is generated [99]. ApoE is the main cholesterol transporter in the brain, whereby ApoE4 has the lowest efficiency in maintaining healthy lipid turnover in the membranes [100]. High cholesterol increases Aβ-associated pathology in transgenic mice, whereas cholesterol-lowering drugs decrease it [101] and also cause a lower incidence of AD in humans [102].

The various Aβ variants in the brain could follow different assembly pathways, with different relevance in the initiation of AD. The 20 so far identified FAD-causing AβPP mutations flanking the Aβ segment generally lead to increased or modified Aβ production. Over 150 mutations in PS 1 and about 20 in its homologue PS 2 have been identified to mainly cause FAD by increasing the production of Aβ1–42 [103] (see http://www.alzforum.org/ and http://www.molgen.ua.ac.be/ADMutations/default.cfm?MT=0&ML=0&Page=Home for AD-associated mutations). There is evidence that Aβ1–40 plays a protective role rather than being a key player in the pathogenesis of AD, most likely by exhibiting low amyloidogenicity and the potential to inhibit aggregation of other Aβ variants [104]. Vascular Aβ deposits, however, contain mainly Aβ1–40 [105]. It has also been suggested from in vitro experiments that pyroglutamate Aβ seeds pathogenic aggregation in vivo. Inhibition of the glutaminylcyclase - the enzyme that catalyzes N-terminal pyroglutamate formation – inhibits Aβ aggregation and toxicity in rodents [65].

The ordered misfolding pathways of different proteins seem to be similar, proceeding from (partially) unfolded monomers to oligomers and finally to fibrils that accumulate. This process follows the mechanism of a nucleated polymerization [30,106], involving an initial lag phase followed by a phase of seeded aggregation, which is in agreement with typical Aβ aggregation kinetics [107]. The lag phase, as in crystallization processes, can be eliminated or shortened by seeding, explaining the transmission propensities of prion-related misfolding diseases. Recently, a mathematical model involving the possibility of fibril breakage associated with acceleration of the aggregation reaction was described [108].

An important question to address is whether Aβ exhibits the strain phenomenon observed for prions. Prions form aggregates with differences in structure, transmissibility, and protease resistance. These strains are propagated by seeding of monomeric populations of molecules [109]. Transmission of amyloidoses in the classical way was only shown for prion diseases. AD and other amyloidoses may be transmissible as well, as shown by inoculation of brains [110] and cell to cell transmission [111].

The elucidation of the pathogenic mechanisms in AD is challenging. Amyloid formation by a peptide or protein immediately results in loss of function. If the aggregates exhibit toxic effects this event can additionally be considered a toxic gain of function, which can also be caused by modified function, e.g. missense mutations in PS shift the cleavage of AβPP to residue 42 of Aβ, thereby favoring aggregation of Aβ [58,112]. AD involves a huge complexity of pathological processes and protein interactions, which result in manifold disturbances of the cellular function. Initially, Aβ plaques were considered the pathogenic species in AD. However, accumulating evidence suggests that they could represent final waste deposits, with the oligomeric intermediates representing the key toxic players [58]. In support of this concept, oligomeric species have been shown to be elevated in AD and correlate with cognitive dysfunction [113]. Plaques could, however, provide a source for soluble toxic species [58].

Oligomers of various proteins involved in amyloidoses have been shown to exhibit toxic characteristics and could therefore be generic toxins [114]. Numerous studies on toxic Aβ oligomers identified dimers [115], pentamers [116], ADDLs, pores/annular oligomers, Aβ*56 (56 kDa), globulomers, and others [117]. The exact aggregation pathway(s) and the mechanisms of oligomer toxicity, their relevance, and whether these oligomers are on- or off-pathway intermediates remains to be elucidated.
AD is a complex neurodegenerative disease. Aβ aggregation is considered the key event in the initiation of AD and can be caused by intrinsic/genetic factors (e.g., traumatic brain injury, neural reserve, vascular/heart disease, lifestyle) or extrinsic factors (e.g., AβPP, PS1 or 2, degradation/rescue machinery), shown in yellow and green/black font in white ovals. The former are associated with FAD, whereas the latter rather cause sporadic AD. Aβ aggregation can trigger aberrant tau phosphorylation and aggregation. Aggregation of tau leads to loss of function, which causes axonal transport disruption by microtubule disassembly. The intermediates and products of the ordered aggregation mechanisms (blue/black font in grey ovals), with Aβ oligomers as key players causing various potential pathological and toxic events (indicated in orange/white font in grey ovals), which eventually lead to neuronal loss, presenting as dementia (red/white font in black ovals).

The proposed neurotoxic effects of Aβ oligomers are synaptic failure, membrane permeabilization, mitochondrial failure and oxidative stress, recruitment of cellular factors or activation of cellular processes such as apoptosis and inflammation [78] (Fig. 2).

Oligomeric Aβ is synaptotoxic, which could lead to subsequent death of neurons [118,119]. In AD, the number of synapses is significantly reduced and synapse reduction correlates better with cognitive deficits than plaque load [120]. Several mechanisms for the disruption of synapse function have been described. Oligomeric Aβ, for example, has been reported to disrupt phosphatidylinositol metabolism [121] and glutamate uptake [113]. Aβ aggregation in AD has moreover been associated with specific disturbance of the activity of the default network [122].

Membrane disruption by Aβ oligomers is a likely pathogenic mechanism. The channel theory, or amyloid pore hypothesis, states that Aβ forms channels or pores in the cellular membrane, which render them more or less specifically permeable for ions such as Ca²⁺, and lead to disturbed ion homeostasis, resulting in apoptosis [123]. The disturbance of Ca²⁺ homeostasis has been reported to be a hallmark of AD [124], and can be caused by Aβ oligomers. Pores were observed in samples from AD patients by high resolution transmission electron microscopy [125], and in vitro by atomic force microscopy [126]. Further support for these findings is provided by a study showing that inhibitors of predicted Aβ Ca²⁺ channels reduced neurotoxicity of Aβ in vitro [127]. There is also evidence that Aβ increases Ca²⁺ influx through receptor targeting
and that Aβ aggregation can be triggered by increased Ca²⁺ [128].

20% of the body’s total basal oxygen consumption occurs in the brain, which makes it particularly prone to the generation of oxidative stress, resulting from mitochondrial dysfunction [129]. Reactive oxygen species can damage a variety of the biomolecules in the cells, such as DNA/RNA, lipids, and proteins. Increased oxidative stress is described as a common phenomenon in AD [130]. There is evidence for oxidative DNA damage [131] and lipid peroxidation in the presence of plaques in transgenic mice and in AD brain [53,132]. Many proteins are found to be excessively oxidized in AD, which could result in neuronal death upon loss of function [130]. There is already evidence for increased oxidative stress in individuals with mild cognitive impairment (MCI), a transitional stage to AD from which about 10–15% of patients convert per year [133], suggesting a rather early role in the development of AD [130].

Post-mortem studies of AD brains revealed altered mitochondrial enzyme activities, morphology, and reduced numbers of mitochondria, even before NFTs occurred [53,134]. Moreover, Aβ has been shown to accumulate in structurally disrupted mitochondria in AD [134], to be toxic to mitochondria, and to disrupt their function at the synapse [135], leading to disturbed energy metabolism, generation of reactive oxygen species, and ultimately to apoptosis.

Human Aβ may play a role in the generation of reactive oxygen species. Three histidine residues at positions 6, 13, and 14 of the Aβ sequence can chelate Cu²⁺ and Fe³⁺ ions, which can be reduced by oxidation of methionine 35, leading to the generation of reactive oxygen species. The data on the role of oxidized methionine 35 for Aβ toxicity are contradictory. Clinical trials with antioxidative substances and metal chelators gave inconsistent results [136]. Taken together, the general consequences of increased oxidative stress, potentially mediated by Aβ, seem to have a more pronounced impact on the AD pathology than the oxidation of Aβ itself.

The role of intracellular tau aggregation and its localization within or beside the pathological cascade needs further clarification. Similar to the findings with Aβ oligomers and plaques, there is evidence that tau oligomers rather than the NFTs act as the neurotoxic species [137].

It is under investigation whether intracellular Aβ aggregation is the key event in the pathogenesis of AD. Intracellular Aβ has been detected in nerve tissue of AD patients and healthy individuals since the eighties [138]. There is evidence from human brain tissue and mouse models that intracellular Aβ accumulation, particularly of Aβ₁₋₄₂, precedes extracellular Aβ aggregation and correlates better with the appearance of disease symptoms in mice [139,140]. In inclusion body myositis, Aβ exclusively accumulates intracellularly [66].

The toxic mechanisms are as unclear as the assembly states of intracellular Aβ, but hypothetic pathways involve the damage of cellular structures and activation of apoptotic pathways [56,66]. Aβ can be generated in early endosomes and secreted in association with exosomes. Exosomal proteins accumulate in plaques, which could indicate an intracellular basis for a pathogenic Aβ aggregation mechanism. Lipid rafts could serve as a seed production site for Aβ aggregation [141,142]. Moreover, Aβ uptake by interaction with various receptor proteins and potential intracellular seed formation has been described [143].

A further explanation for the cognitive deficits in AD is the loss of cholinergic neurons. This results in reduced levels of acetylcholine, which has been ascribed to the neurotoxic effect of Aβ and is also observed for some anesthetics targeting acetylcholine-sensitive cells [144]. Furthermore, inflammation in AD brains causes elevated markers for activated microglia and reactive astrocytes, which surround amyloid plaques [145], and led to consideration of anti-inflammatory drugs as AD therapeutics.

Surgery under anesthesia can cause transient reversible AD-like symptoms in elderly patients and after prolonged anesthesia, which is termed postoperative cognitive dysfunction (POCD) [146]. In vitro studies aimed at elucidating the involvement of AD mechanisms showed that several anesthetics – particularly the small-sized inhaled anesthetics isoflurane and halothane – could promote Aβ aggregation. In contrast, the interaction of Aβ with the bulkier injected anesthetics such as thiopental and diazepam seems to be sterically hindered [146–149]. Isoflurane and halothane were shown to increase the plaque load in a murine AD model [150], and isoflurane has recently been shown to accelerate neurofibrillar pathology in a murine tauopathy model [151]. These findings point to the importance of further investigation of cognitive dysfunction after anesthesia or reconsideration of anesthetic protocols for patients with increased AD risk, (i.e. due to increased age, TBI, or genetic predisposition).

In summary, AD is a very complex disease. The manifold pathomechanisms and pathologic observa-
CHALLENGES ON THE ROAD TOWARDS THERAPEUTIC APPROACHES

Major roads, which have so far been followed for the development of therapeutic approaches, include the intervention in Aβ generation and aggregation as well as the prevention of neuronal loss. The long list of current and future challenges include the ability to bridge the in vitro-in vivo gap, i.e. to appraise the relevance of findings from in vitro studies, to reproduce these findings in animal studies and finally also in clinical trials [152]. Reproducibility of in vitro studies with Aβ is challenging to obtain since proper handling and the quality of the applied material are crucial [107]. Variation of the fibrillation conditions in vitro leads to fibril polymorphism [91], which challenges the in vivo relevance of these studies. In vitro preparations, however, proved to be toxic in transgenic mice [107]. The peptide concentration in in vitro experiments usually exceeds the physiological condition, but local concentrations in vivo could be considerably higher as well [143].

The role of the various Aβ variants found in vivo needs further elucidation to separate the guilty parties from the innocent bystanders. The study of potential co-aggregation and cross seeding of the different natural Aβ variants may reveal the existence of fibril strains. It will also be important to investigate whether intra- or extracellular Aβ causes the major risk.

It is challenging to detect and identify the transient oligomers in the pathway(s) of Aβ aggregation. Cross-linking of aggregating Aβ yielded ambiguous results [153]. Enzyme-linked immunosorbent assays were found to detect oligomers inefficiently [154] and application of different antibodies, combined with the uncertainty of the detected oligomeric state challenge their reproducibility. So far, oligomeric intermediates have been separated via Western blotting, where oligomer formation can be caused by sodium dodecyl sulfate added to the samples [155]. Application of further methods for the structural characterization of prefibrillar intermediates is, however, emerging with increasing success, e.g. nuclear magnetic resonance [156].

The inhibition of Aβ generation is promising but also challenging in different aspects. Inhibition of the β-secretase is technically challenging as the active site is large and inhibitors have to be sufficiently small to cross the BBB [157]. Moreover, inhibition of β- and γ-secretase leads to severe side effects due to the existence of various substrates other than AβPP [39]. An activator of α-secretase to favor the non-amyloidogenic pathway of AβPP processing will be challenging to develop, which also applies for the activation of the Aβ degrading enzymes. Overexpression of both IDE and neprilysin has, however, been reported to prevent plaque formation in mice [158].

Animal models do not normally exhibit all aspects and forms of the disease. For example, AβPP based transgenic mouse models do not include NFTs and many of them are based on rare FAD forms. Furthermore, murine Aβ is present in addition to the transgenic human AβPP variants in these models and could hence interfere with the aggregation process. Despite this setback, many of the pathological features of AD could nevertheless be included in mouse models over the years. In fact, a variety of different animal models are now available, enabling various applications, including zebrafish, C.elegans, drosophila, and yeast [159].

Active or passive vaccination against Aβ seems to be the most promising therapeutic approach to date. The modes of action involve clearance of plaques, inhibition of aggregation, and causation of a peripheral sink to clear Aβ from the brain. To date, at least 13 Aβ immunotherapies are in clinical trials [160]. Antibodies binding to Aβ have the risk of targeting AβPP as well. Thus, the development of conformation-specific antibodies may be promising, with the added advantage that they could also serve in diagnostics.

Aβ aggregation had been suggested to take place several decades before the first AD symptoms occur. In 2008, it was shown that plaques can be formed within 24 hours [161], which provides space for previous causes of Aβ-associated AD. Moreover, cognitively normal aged individuals with pronounced plaque load were identified [162], which could indicate a non-toxic pathway of plaque formation. Clearance of plaque burden does not necessarily lead to improvement of cognitive performance and expansion of life span [163]. Consequently, vaccination and other therapies may only be efficient before plaque formation.
Antemortem diagnostic tools are limited, but promising imaging techniques for the diagnosis of AD have been described. Imaging of the plaque load with Pittsburgh compound B (PiB) proved to be useful, although the binding capacity for different fibril morphologies could differ [164]. Furthermore, positron emission tomography represents a promising tool for monitoring the disease stage [165]. Functional magnetic resonance imaging (fMRI) [166] seems to be promising for early and specific diagnosis of AD by measuring the brain volume and prediction of conversion from MCI to AD. Diagnosis via biochemical analysis of cerebrospinal fluid (CSF), involving the analysis of the distinct A/β variants, oligomeric A/β, increased phosphorylation and tau load are promising, although there is some controversy [167].

Finally, it is important to carefully choose (control-) patients for clinical trials, as it is not yet clear how many different forms of AD exist and heterogeneity in the subject population complicates the evaluation.

CONCLUSION

AD is a complex disease and represents a tremendous problem in our aging populations, where the major aim is to cure and prevent AD. Collaboration of experts with different backgrounds will be required to further elucidate the molecular mechanism(s) and interactions of different pathological aspects of AD. It remains to be elucidated to which extent the different A/β fractions and tau contribute to AD, how many forms of the fatal progressive dementia exist, and how and when to interfere efficiently. The emergence of early and precise diagnosis is of paramount importance for a more specific and opportune intervention in AD.

ACKNOWLEDGMENTS

I am grateful to Zoe Goodger for critical reading of the manuscript. Fruitful discussions with my colleagues are greatly acknowledged.

The author’s disclosure is available online (http://www.j-alz.com/disclosures/view.php?id=545).

REFERENCES


S16 

V.H. Finder’s Alzheimer’s Disease, Introduction


Iatrogenic Risk Factors for Alzheimer’s Disease: Surgery and Anesthesia

Tara Vanderweyde, Martin M. Bednar, Stuart A. Forman and Benjamin Wolozin

aDepartment of Pharmacology, Boston University School of Medicine, Boston, MA, USA
bNeuroscience Research Unit, Pfizer Inc. Groton, CT, USA
cDepartment of Anesthesia Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
dDepartment of Neurology, Boston University School of Medicine, Boston, MA, USA

Accepted 2 July 2010

Abstract. Increasing evidence indicates that patients develop post-operative cognitive decline (POCD) following surgery. POCD is characterized by transient short-term decline in cognitive ability evident in the early post-operative period. This initial decline might be associated with increased risk of a delayed cognitive decline associated with dementia 3 to 5 years post-surgery. In some studies, the conversion rates to dementia are up to 70% in patients who are 65 years or older. The factors responsible for the increased risk of dementia are unclear; however, clinical studies investigating the prevalence of POCD and dementia following surgery do not show an association with the type of anesthesia or duration of surgery. Epidemiological studies from our group support this observation. The adjusted Hazard Ratios for developing dementia (or AD specifically) after prostate or hernia surgery were 0.65 (95% CI, 0.51 to 0.83, prostate) and 0.65 (95% CI, 0.49 to 0.85, hernia) for cohorts of subjects exposed to general anesthesia compared to those exposed only to local anesthesia. Animal studies suggest that prolonged exposure to some volatile-inhalational anesthetics increase production of amyloid-β and vulnerability to neurodegeneration, but these results are weakened by the absence of clinical support. Inflammation and a maladaptive stress response might also contribute to the pathophysiology of this disorder. Future research needs to identify predisposing factors, and then strategies to protect against POCD and subsequent dementia. The field also needs to adopt a more rigorous approach to codifying the frequency and extent of early and delayed post-operative cognitive decline.

Keywords: Alzheimer’s disease, amyloid-β protein, anesthetics, coronary artery bypass operation dementia, surgery

INTRODUCTION

This review focuses on a group of risk factors that are a byproduct of medical advances in healthcare technology: surgery, anesthesia, and increased longevity, and their possible interdependent role in the emergence of dementia. Worldwide, 200 million patients undergo surgery with anesthesia each year, and this number is only expected to grow with increasing lifespan and growing populations. While major surgical procedures, such as coronary artery bypass grafts (CABG), offer tremendous health benefits for the population, our understanding of the side effects of these procedures continues to evolve. Increasing lifespan has also led to increasing rates of dementia. The causes of dementia are multi-factorial, and reducing rates of dementia in the elderly might require correspondingly multifaceted interventions. Prevention by identifying risk factors and adapting lifestyles to reduce these risk factors is a very promising approach for reducing rates of
dementia. Major surgery has been recently proposed as a potential risk factor for Alzheimer’s disease (AD), with accumulation of the toxic amyloid-β (Aβ) peptide representing a potential causative factor. Clarifying the linkage between surgical factors and cognitive decline is critical to optimizing long-term outcomes from major surgery and reducing the risk of dementia. This article will present an overview of past and current research that has been done on POCD, anesthesia, and its implications on the development of dementia.

### Alzheimer’s disease and dementia: basic concepts

The two most common causes of dementia are vascular dementia and AD, although most cases of dementia have both types of pathology. Risk factors for vascular dementia are similar to those of other vascular diseases and are discussed below. The pathophysiology of vascular dementia is not explicitly reviewed in this manuscript, but is reviewed by Kalaria [1]. The pathophysiology, etiology, and risk factors for AD are described below.

Dementia is the most common age-related disorder of the brain. The prevalence of dementia is 13% by age 65, and nearly 50% by age 85 (http://www.alz.org). The most frequently diagnosed type of dementia is AD, which is characterized by progressive cognitive and functional decline associated with specific pathological changes in the brain. These pathological changes include extracellular neuritic plaques, composed of amyloid-β (Aβ), intracellular neurofibrillary tangles, composed of hyperphosphorylated tau, astrocytic gliosis, reactive microglia and inflammation, synaptic loss, and neuronal death [2–4]. The accumulation of aggregated Aβ is thought to lead to neurodegeneration and the associated accumulation of aggregated tau protein. The major genetic risk factor for AD is the apolipoprotein E ε4 genotype (ApoE ε4, located on chromosome 19), which is present in approximately 15% of the population [5]. Possession of the ApoE ε4 allele was identified as a risk factor for late-onset AD in 1993, and is associated with an odds ratio for incident AD of about 3.7 [6]. All other genetic risk factors identified to date exert only minor effects in comparison (odds ratios of 1.2–1.3). Genetic risk factors for AD are reviewed and updated at the web site: http://www.alzgene.org. Vascular diseases represent another strong source of risk for AD. These factors include hypertension, hypercholesterolemia, diabetes, and obesity. Interestingly, hypertension and elevated cholesterol need to be present at midlife, well before the onset of disease, to exert influence on the incidence of AD. Subjects with midlife hypertension, hypercholesterolemia, or midlife obesity exhibit roughly a 50% increase in the risk of AD in later life, while none of these factors are associated with AD when examined in the year preceding disease incidence [7,8]. The temporal disconnect between vascular damage and dementia emphasizes the importance of studying risk factors over an extended longitudinal range, rather than focusing on acute effects occurring within one year of the documented risk factor.

### POST-OPERATIVE COGNITIVE DECLINE (POCD)

Accumulating evidence suggests that major surgical procedures are associated with acute and chronic consequences for the brain. Multiple studies document the acute occurrence of post-operative cognitive decline (POCD), which is a transient cognitive impairment that is typically manifest in the immediate postoperative period and usually resolves by one year after surgery. POCD is characterized neuropsychologically by impairments in memory, concentration, language comprehension, and social integration. Pathological changes in the brain that are associated with these changes in cognitive function have been quantified through the use of imaging and biochemical modalities. Magnetic resonance imaging (MRI) indicates the presence of brain edema, diffusion tensor imaging suggests injury to white matter tracts, and magnetic resonance spectroscopy (MRS) indicates reductions of biomarkers such as N-acetyl aspartate (NAA), a marker of neuronal integrity as well as by other biomarkers such as S-100B [9–11].

The prevalence of POCD increases with age, and in elderly patients is approximately 33% at 2–10 days post-operatively, but POCD gradually resolves between 3 months and 1 year [12–18]. One exception to this generally consistent story is a study by Rasmussen et al., which failed to observe POCD at the earliest time point (3 months) [12,19]. The causes of POCD are poorly understood, but factors such as anesthesia, heart-lung devices, and embolism have all been suggested as potential causes. Patients undergoing major cardiac surgery have the highest risk of POCD, and this risk increases with age. The association between POCD and CABG surgery was originally thought to be attributable to the cardiopulmonary bypass machine (CPB); however, POCD can occur in patients undergoing cardiac surgery as well as in non-cardiac surgery patients [12].
Despite the transient nature of POCD, these major surgical procedures also appear to accelerate cognitive decline following a delay of several years after the operation, with a resulting increase in the incidence of dementia.

**Brain reserve might modify identification of POCD**

The importance of midlife vascular risk factors suggests that the onset and progression of AD are initiated decades prior to the manifestation of the clinical symptoms of dementia. This important point is now well accepted and suggests the importance of a concept termed, “cognitive reserve” or “brain reserve”. This internal resilience of the brain is thought to modify POCD, as well as the delayed dementia occurring after POCD. Brain reserve originally referred to differences in brain size, or neuronal density contributing to resilience of the brain to trauma or degenerative insults [20]. Brain reserve is thought to modify the appearance of AD because approximately 25% of elderly patients show no cognitive decline prior to death, yet meet the full pathogenic criteria for AD upon examination of brain pathologies [21]. Education and social networking appear to increase brain reserve, presumably because they increase synaptic density, the loss of which is associated with the onset of AD. Conversely, subjects from a low educational background are more susceptible to POCD, possibly because of lower cognitive reserve, which would provide less buffer from brain insults before falling below the threshold of cognitive loss used to define POCD [13,14,16,22]. Quantifying brain reserve might ultimately facilitate identification of subjects at increased risk of POCD or dementia after CABG surgery, although such measurements are currently not technically feasible.

**POCD risk factors**

Many of the risk factors for POCD are also risk factors for AD. These factors include: age, low education, diabetes, and severity of atherosclerotic disease. The association of POCD with a lower educational background might reflect greater cognitive reserve among individuals with higher levels of education [13,14,16,22]. Although elderly subjects are most susceptible to POCD, in a study of middle-aged subjects (40 to 60 years), 19% were found to have POCD at 7 days after surgery (95% CI, 15.7–23.1), compared with a rate of cognitive impairment of only 4% (95% CI, 1.6–8.0, \( P < 0.001 \)) in age-matched control subjects [23]. These results suggest that POCD might be a general problem for the population, although those over age 60 are likely at increased risk. Potential iatrogenic factors such as intra-operative cerebral hypoxia, hypocapnia, hypoperfusion with loss of autoregulation, cerebral emboli, and an increased brain amyloid burden (risk factors not mutually exclusive) might accelerate AD pathogenesis associated with POCD. The extent to which such events occur is not currently known.

The incidence of POCD shows a surprising absence of linkage to the ApoE\(\varepsilon4\) genotype. A 2004 study done by Abildstrom and colleagues found that the presence of the ApoE\(\varepsilon4\) allele was not a risk factor for POCD at 1 week (\( p = 0.33 \)) or 3 months (\( p = 0.57 \)) postoperatively [24]. A possible explanation for this involves the observation made by Hsiung that the APOE\(\varepsilon4\) genotype significantly increases the risk of developing AD in the already cognitively impaired; however, the possession of the APOE\(\varepsilon4\) genotype was not associated with increased risk of developing cognitive impairment [25]. On a mechanistic level, the ApoE4 protein likely increases the tendency of \(A_\beta\) to aggregate. Although AD is associated with aggregation of \(A_\beta\), there is no clinical evidence linking POCD with the accumulation of aggregated \(A_\beta\); however, there is animal data suggesting that some anesthetics can increase production of \(A_\beta\) (see below). If POCD is not associated with \(A_\beta\) aggregation (it may relate to cerebral edema, neuronal/synaptic drop-out with temporary compensation), then one might not expect any linkage with the APOE\(\varepsilon4\) genotype. On the other hand, the importance of the APOE\(\varepsilon4\) genotype to the incidence of AD suggests the possibility that subjects carrying one or two APOE\(\varepsilon4\) alleles will have increased risk and earlier onset of AD following POCD.

Studies described below show that dementia associated with major surgery requires years (> 3) to become apparent. Since the ApoE\(\varepsilon4\) allele is specifically associated with dementia, the lack of association of ApoE\(\varepsilon4\) with POCD raises the possibility that the pathophysiology of POCD and dementia occur through differing mechanisms, although both may be the result of the same upstream event of surgical intervention.

The type of anesthesia is another risk factor that has been examined. Although animal models present clear evidence that some forms of anesthesia increase vulnerability to neurodegeneration (see below), the clinical evidence is ambiguous. For instance, Rasmussen and colleagues completed a study involving 364 elderly patients undergoing major surgery with either general or regional anesthesia [12]. They found no clini-
A summary of studies investigating POCD is presented in Table 1. The methodologies (e.g., specific tests used, number of tests used, frequency and duration of testing, and the criteria for declaring cognitive decline) and results obtained in each study vary greatly. Early studies used the Mini-Mental State Examination (MMSE), however some argue this test is not sufficiently sensitive to capture all cases of POCD; scoring systems such as the AD-8, or that recently described by Inzitari and co-workers, to detect subtle neurologic abnormalities are now being developed [29–32]. Recently, studies involving both cardiac and non-cardiac patients have begun to overcome the flaws in previous methodologies by utilizing cohorts with better-defined cognitive function before and after surgery for defining the incidence of POCD and delayed dementia [33,34]. These studies emphasize the need for a consistent and comprehensive approach to assess subjects’ baseline (pre-operative) status, the use of control groups, use of careful cognitive monitoring, and the need to control for learning effects of repeated testing. There also remains a need for a strict definition of POCD and the use of sensitive, standardized methods of measurement.

Clinical evidence of POCD

A possible relationship between neurodegenerative disorders, anesthesia, and surgery was first revealed in a study conducted by Savageau in 1982 examining 227 men and women, aged 25–69 years, before and after major cardiac surgery to determine the incidence of POCD. A decline in cognition of at least 1 SD was found in each of four domains in 11%–17% of the patients [35]. However, 70% of patients showed no significant decline in all four areas, although this figure might reflect the wide age range of the cohort, which included young, middle-aged, and elderly participants [35]. In a related study Savageau studied 245 men and women, aged 25–69 years undergoing CABG surgery and found that 28% of patients showed deterioration in at least one test score 9 days post-operatively. The decline was transient, with 80% of the patients returning to a normal range by 6 months post-surgery. After 6 months, 19% had a significant decrease in at least one area, but the majority of these patients acquired this cognitive deficit after the first post-operative assessment. Only 5% of patients showed consistent decline at both 9 days and 6 months [36], suggesting that POCD is reversible.

Another study investigating the relationship between POCD and dementia, was the international study of post-operative cognitive dysfunction (ISPOCD), organized by Moller [14]. This study was a large-scale study to investigate the prevalence and risk factors associated with POCD. The study involved 1218 patients over age 60, whose cognitive function was monitored before, and 1 week and 3 months after major surgery. Moller and colleagues concluded that POCD did occur, and that age was a major risk factor. Other POCD risk factors were duration of anesthesia and poor education [14]. In a retrospective study two years later, 336 patients from the original ISPOCD study were examined for the incidence of cognitive decline 1–2 years post-surgery, where 10.4% (95% CI: 7.2–13.7%) showed decline, but this fraction was not statistically significant when compared to a control group of subjects who had not had surgery. This percentage was consistent with the values observed at 3 months by Moller in the original study, indicating POCD is transient, and patients tend to recover within the first few months [17].
Table 1

Summary of clinical studies done investigating the incidence of POCD from 1 week to 5 years post-surgery (*Relative risk of AD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of Surgery</th>
<th>Total # Patients</th>
<th>1 week (% with POCD)</th>
<th>3 months (% with POCD)</th>
<th>6 months (% with POCD)</th>
<th>1–2 years (% with POCD)</th>
<th>5 years (% with POCD)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abildstrom et al.</td>
<td>2000</td>
<td>Major Noncardiac</td>
<td>336</td>
<td>10.4</td>
<td>10.6</td>
<td>9.9</td>
<td>25.8</td>
<td>3.4</td>
<td>POCD is reversible, there is no statistical difference in cognitive decline between surgical and control patients 1–2 years after surgery. Statistics: Surgery: 95% CI: 7.2–13.7%, Control: 95% CI: 1.8–19.4%. [17]</td>
</tr>
<tr>
<td>Ancelin et al.</td>
<td>2001</td>
<td>Major Noncardiac</td>
<td>140</td>
<td>7.1</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td>Found an alarmingly high incidence of POCD at both 1 week and 3 months post-surgery, perhaps due to their testing standards [13]</td>
</tr>
<tr>
<td>Moller et al.</td>
<td>1998</td>
<td>Major Noncardiac</td>
<td>1218</td>
<td>25.8</td>
<td>9.9</td>
<td></td>
<td></td>
<td></td>
<td>POCD is transient with almost complete recovery by 3 months post-surgery. Statistics: Surgical: 1 week: 95% CI: 23.1–28.5, p &lt; 0.0001, 3 months: 95% CI: 8.1–12.0, p = 0.0037 [14]</td>
</tr>
<tr>
<td>Rasmussen et al.</td>
<td>2003</td>
<td>Major Noncardiac</td>
<td>438</td>
<td>19.7</td>
<td>14.3</td>
<td></td>
<td></td>
<td></td>
<td>No statistical difference 3 months post-operatively. Greater risk for short-term POCD with general than regional, but not statistically significant. Statistics: General: 1 week 95% CI: [14.3–26.1%], 3 months 95%: [9.5–20.4%], Regional: 1 week 95% CI: [8.0–18.3%], P = 0.06, 3 months 95% CI: [9.0–20.2%], P = 0.93 [12]</td>
</tr>
<tr>
<td>van Dijk et al.</td>
<td>2008</td>
<td>CABG</td>
<td>281</td>
<td>34.2</td>
<td></td>
<td>16.2</td>
<td></td>
<td></td>
<td>After statistical adjustments CABG patients were 1.37 times more likely to have cognitive decline after 5 years. (95% CI, 0.65 to 2.92) [37]</td>
</tr>
<tr>
<td>van Dijk et al.</td>
<td>2002/2007</td>
<td>CABG</td>
<td>281</td>
<td>29</td>
<td>33.6</td>
<td>50.4</td>
<td></td>
<td></td>
<td>The use of CPB is not a risk factor in long-term POCD. Patients who received their first CABG surgery without CPB had improved cognitive outcomes 3 months after the procedure, but the effects became negligible at 12 months. Statistics: 3 months Relative Risk = 0.65 (95% CI, 0.36–1.16; p = 0.15), 12 months RR = 0.88 (95% CI, 0.52–1.49; p = 0.69)</td>
</tr>
<tr>
<td>Newman et al.</td>
<td>2001</td>
<td>CABG</td>
<td>281</td>
<td>53</td>
<td>36</td>
<td>24</td>
<td></td>
<td>42</td>
<td>Indicates bimodal pattern of cognitive decline [16]</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2005</td>
<td>Cardiac CABG</td>
<td>9170</td>
<td>1.5*</td>
<td></td>
<td></td>
<td></td>
<td>1.0*</td>
<td>Patients undergoing CABG surgery are 1.71 times more likely to have an AD diagnosis at 5 years post-operation (95% CI, 1.02–2.87, p = 0.04) [43]</td>
</tr>
</tbody>
</table>
Table 2  
Studies using animal models to investigate the AD-like pathogenesis due to major surgery and anesthesia

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Animal</th>
<th>Transgenic</th>
<th>Anesthesia</th>
<th>Dose</th>
<th>Time (min)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bianchi et al.</td>
<td>2008</td>
<td>Mouse</td>
<td>Tg2576</td>
<td>Isoflurane</td>
<td>Clinical</td>
<td>120 (x5 days)</td>
<td>Halothane enhances Aβ plaque deposition in Tg, while isoflurane does not [46]</td>
</tr>
<tr>
<td>Bianchi et al.</td>
<td>2008</td>
<td>Mouse</td>
<td>WT</td>
<td>Isoflurane</td>
<td>Clinical</td>
<td>120 (x5 days)</td>
<td>Isoflurane causes a decrease in cognitive performance in WT, halothane does not [46]</td>
</tr>
<tr>
<td>Dong et al.</td>
<td>2009</td>
<td>Mouse</td>
<td>WT</td>
<td>Sevoflurane</td>
<td>Clinical</td>
<td>120</td>
<td>Induced apoptosis and elevated levels of β-site AβPP-cleaving enzyme and Aβ [47]</td>
</tr>
<tr>
<td>Perucho et al.</td>
<td>2010</td>
<td>Mouse</td>
<td>APP (swe)</td>
<td>Isoflurane</td>
<td>Clinical</td>
<td>2x/week, 3 months</td>
<td>Compared to WT, the APP mice had increased mortality, less responsiveness, increased Aβ aggregates, &amp; abnormal chaperone responses [48]</td>
</tr>
<tr>
<td>Planel et al.</td>
<td>2007</td>
<td>Mouse</td>
<td>WT</td>
<td>Isoflurane</td>
<td>Clinical</td>
<td>60</td>
<td>Increases hyperphosphorylation of tau [55]</td>
</tr>
<tr>
<td>Planel et al.</td>
<td>2009</td>
<td>Mouse</td>
<td>JNPL3: mut. TauP301L</td>
<td>Isoflurane</td>
<td>Clinical</td>
<td>240</td>
<td>Increase in tau hyperphosphorylation [57]</td>
</tr>
<tr>
<td>Xie et al.</td>
<td>2008</td>
<td>Mouse</td>
<td>WT</td>
<td>Isoflurane</td>
<td>Clinical</td>
<td>120</td>
<td>Time-dependent cascade of caspase activation, elevated BACE levels, and increased Aβ levels [49]</td>
</tr>
</tbody>
</table>

POCD has been most commonly studied following major surgeries, such as CABG surgery, where the incidence is especially high. The average incidence rates across studies was 53% at discharge, 28.7% at 6 weeks, 24% at 6 months, 32.3% at 1–2 years, and 39.1% at 5 years, where an early decline is associated with increased risk of a late decline [15,16,27,37]. The POCD observed is transient and reversible, with there being no significant difference between the performance of the control and surgical groups at both 3 months and 1 year post-operatively [18]. The presence of POCD might be associated with underlying damage or fragility because patients with POCD at hospital discharge are more likely to die within the first 3 months after surgery (p = 0.02), and patients with POCD at both hospital discharge and 3 months are more likely to die in the first year after surgery (p = 0.02). This fragility may skew the percentage of patients with cognitive decline over time due to increased mortality rates [38]. The increased vulnerability of subjects with POCD might be a harbinger of future vulnerability to AD or dementia.

The concern over the potential delayed effects of POCD on dementia derives partly from growing awareness of the relationship between mild cognitive impairment and dementia. Increasing evidence indicates that dementia (particularly AD) presents gradually, with most patients experiencing mild cognitive impairment before the overt onset of dementia (reviewed in [39]). There is now mounting evidence that AD can be detected decades before the emergence of significant clinical symptoms. One example is the use of amyloid imaging agents to study brain amyloid burden in life. Using this PET technology, studies consistently demonstrate an amyloid burden consistent with the distribution of AD brain pathology post-mortem that may be best characterized as a “rule of thirds”: approximately 1/3 of healthy elderly subjects, 2/3 of those with mild cognitive impairment (MCI), and essentially all AD subjects had a significant amyloid burden [40,41].

**DOES POCD PRECIPITATE AD?**

*Studies focusing on CABG surgery*

Studies of POCD consistently document a temporary decline in cognition present 1 week post-operatively, but also indicate that patients recover by 3–12 months post-surgery. The acute changes associated with POCD, both neuropsychologically as well as structurally (cerebral edema, reduced NAA, reduced anisoptropy by diffusion tensor imaging) and biochemically (S-100b) might also predispose to chronic changes associated with dementia and its structural MRI correlates (brain...
We observed an odds ratio of 1.71 (95% CI, 1.02 to 2.87; \( p = 0.04 \)) for the development of AD subsequent to CABG surgery 5 years earlier [16]. Our group observed that 5 years after CABG surgery, there was a 70% increase in the risk of dementia among CABG subjects compared to subjects receiving stents under local anesthesia [43]. In this study we used the Decision Support System of the Veterans Affairs Health System, which follows all subjects in the Veterans Affairs Health System longitudinally. Our results showed a striking relationship between CABG surgery and subsequent dementia. The study followed 9,170 patients and compared the emergence of AD after CABG surgery under general anesthesia, and non-surgical percutaneous transluminal coronary angioplasty (PTCA) under mild sedation. The PTCA group was selected because they exhibited health co-morbidities that were similar to subjects having CABG surgery. We observed an odds ratio of 1.71 (95% CI, 1.02 to 2.87; \( p = 0.04 \)) for the development of AD subsequent among patients having CABG surgery compared to patients having PTCA [43]. This data suggest that some aspect of the CABG surgery procedure leads to a delayed increase in the risk of dementia. Taken together, these studies suggest a bimodal pattern of cognitive decline, where an initial early decline with improvement to 1 year is associated with increased risk of a late period of decline in all cognitive domains between 1 and 5 years.

The occurrence of dementia following cardiac surgery was not observed in a recent study. Selnes and colleagues performed a long-term follow up on subjects exposed to major operations [62,63,65]. They observed a pattern of POCD similar to that found by others, documenting the initial occurrence of POCD followed by recovery by 1 year after surgery. However, as they extended the observations out to 5 years, they observed significant decline across all cognitive domains, with the exceptions of attention and executive function [44]. The declines were similar among cohorts with similar cognitive function and morbidity who were hospitalized for reasons other than cardiac surgery. These data therefore raise the possibility that the delayed cognitive decline seen among subjects undergoing CABG reflects co-morbidities other than surgery.

Analysis of hernia and prostate procedures: A study of brief exposure to anesthesia

Whether the putative increased risk results from the stress of the CABG surgery itself, an inflammatory event, the prolonged exposure to anesthesia, or other factors (not mutually exclusive) was not addressed in our study and has become an important question in the field. We have performed additional studies to provide insight related to the question of duration and type of anesthesia. We examined risk of AD or dementia among subjects undergoing hernia operations (98% male) under general \((n = 2,658)\) or local \((n = 1,111)\) anesthesia, as well as subjects undergoing prostate operations under general \((n = 2,820)\) or local \((n = 3,691)\) anesthesia. Surprisingly, the data demonstrated that subjects exposed to general anesthesia showed a lower risk of AD and dementia using either an unadjusted model or after adjusting for age, length of hospital stay, number of procedures, and number of diagnoses during the index hospitalization. The differential risk is difficult to ascribe to bias in patient selection or co-morbidities because the general anesthesia groups showed slightly higher rates of chronic illness (judged by the Charlson index [45]), although they were slightly younger. The data is described below.

**Hernia study**

Over 98% of the patients in the Hernia study were male, and all of the subjects in the prostate study were male. There were 3769 patients included in the Hernia Cohort, of which 2658 (70.5%) were exposed to general anesthesia, and 1111 (29.5%) were in the non-general anesthesia group. Patients exposed to general anesthesia were younger than patients in the non-general anesthetic cohort (68.5 yrs vs. 70.9 yrs, \( p < 0.001 \)). The general anesthesia group had longer lengths of hospital stay (8.4 days vs. 6.7 days, \( p < 0.001 \)). The patients in the general anesthesia cohort had more diagnoses at their index hospitalization and higher Charlson Index scores.

The follow-up time was slightly longer in the patients exposed to general anesthesia (1685.5 days vs. 1628.6 days, \( p = 0.011 \)). The proportion of patients that died during the follow-up period was similar between the groups (General = 30.6% vs. Non-general = 32.8%, \( p = 0.190 \)). The proportion of patients experiencing an...
The incidence rate of either a senile dementia or AD diagnosis was 10.4 per 1000 person-years in the general anesthesia group, and 18.2 per 1000 person-years in the non-general anesthesia group. The adjusted Hazard Ratios, comparing the risk of events in the general anesthesia group compared to the non-general anesthesia group after adjusting for age, length of stay, number of procedures, and number of diagnoses during the index hospitalization, show that patients exposed to general anesthesia were at lower risk for events than those exposed to non-general anesthetics. The risk when the events were dementia or AD was 0.65 (95% CI, 0.49 to 0.85), and when only AD was considered the risk was 0.65 (95% CI, 0.43 to 0.98).

Prostate study
A total of 6511 patients were included in the Prostate Cohort with 2820 (43.3%) exposed to general anesthesia and 3691 (56.7%) exposed to non-general anesthetics. Because of the cohort, all of the patients were male. Patients exposed to general anesthesia were younger than patients exposed to non-general anesthesia (67.6 yrs vs. 70.8 yrs, \( p < 0.001 \)). The general anesthesia group had shorter lengths of stay (7.5 days vs. 8.3 days, \( p = 0.013 \)), due to shorter lengths of stay prior to their procedures (1.5 days vs. 2.3 days, \( p < 0.001 \)). Also, the patients in the general anesthesia cohort had fewer diagnoses at their index hospitalization, but slightly higher Charlson Index scores.

The unadjusted rate ratio comparing the general anesthesia prostate group to the non-general anesthesia prostate group was 0.52 (95% CI. 0.36 to 0.76). The adjusted Hazard Ratio for developing either dementia or AD after prostate surgery was 0.65 (95% CI. 0.51 to 0.83) for the cohort exposed to general anesthesia compared to a cohort exposed only to local anesthesia. In the AD-specific analysis the adjusted ratio was 0.71 with a confidence interval that includes 1.00 (95% CI, 0.49 to 1.04).

Interpreting these data is difficult because they might reflect an unanticipated bias in the patient selection, or in the subsequent diagnosis of AD or dementia. However, these data support a hypothesis that short-term exposure to general anesthesia does not predispose to AD. This conclusion is supported in recent work by Steinmetz, discussed above, which does also not show any relationship between depth of anesthesia and POCD [26].

ANIMAL MODELS

The tenuous link between anesthesia and AD evident in the current clinical data is contrasted by provocative data from animal models suggesting that anesthetics can increase Aβ plaque formation, increase tau hyperphosphorylation, and impair memory. The amount of Aβ accumulation is dependent upon the balance of generation and clearance. Accumulation of Aβ can trigger synaptic loss and neuronal dysfunction, a hallmark of AD.

Studies performed in vitro and in vivo suggest that anesthetics can increase AD pathology in the brain, although the effect is specific to particular anesthetics and cannot be generalized to all anesthetics [46–49]. Several studies from the Mandel group suggest that small-sized anesthetics can promote Aβ aggregation in vitro [50,51]. In animal models of AD, isoflurane exposure causes significant memory impairment in the elderly rodent that leads to a long-term deficit in learning and memory in rats in an already-learned spatial memory task [52]. In wild type (WT) mice, sevoflurane was found to induce apoptosis, and elevated levels of amyloid-β precursor protein, β-site cleaving enzyme, and Aβ (AβPP; BACE; β-secretase) [47]. With halothane, Bianchi et al. found an increased Aβ plaque formation in the Tg2576 mouse model of AβPP overexpression one week after exposure [46]. On the other hand, the effects of the anesthetic propofol are more complex. Propofol inhibits Aβ oligomerization at clinical concentrations, but enhances oligomerization at high concentration, suggesting the possibility of a neuroprotective effect with respect to AD pathogenesis [53]. Further studies have shown that neither thiopental nor propofol interfere with AβPP metabolism, and do not facilitate Aβ toxicity, supporting the hypothesis that these anesthetics might not promote Aβ pathology [54].

The microtubule associated protein tau, is also an important mediator in the pathogenesis of AD. In the wild type (WT) mouse brain, regardless of the inhalational anesthetic used, anesthesia induced rapid increases in hyperphosphorylation of tau via the inhibition of the serine/threonine protein phosphatase 2A (PP2A) [55]. In a more recent study, clinically relevant doses of isoflurane increased short and long-lasting tau hyperphosphorylation, producing long-lasting detachment of tau from microtubules, and the accumulation of insoluble tau in JNPL3 tau mice [56]. These findings provide researchers with a link between anesthesia and AD pathogenesis. Thus, there is strong evidence indicat-
ing that inhalational anesthetics, especially isoflurane, increase A/β plaque load and tau hyperphosphorylation in non-transgenic models [47,49,52,55]. This effect is exacerbated in transgenic models, although the type of anesthetic damage in the brain might be multi-faceted, and might vary between non-transgenic and transgenic models [46,48,57]. However, the contradictory clinical data bring into question about whether the studies on transgenic mice extrapolate to the human condition.

**MECHANISMS**

This review has outlined evidence linking POCD and dementia. The published studies help to prioritize attention to particular mechanisms. Work in animal models raises the possibility that anesthetics can promote accumulation of A/β, however, the current clinical data do not provide any support for this hypothesis. The use of the CPB machine represents an alternative possibility, and is a strong candidate contributing to the risk of POCD. The CPB machine can cause embolization with micro-emboli and macro-emboli, as well as activate systemic inflammatory pathways [58], although this increased risk has not been correlated to cerebral micro-emboli. A study done in the Chinese population shows that although CPB increased the number of cerebral micro-emboli, it did not increase the incidence of POCD compared with the off-pump group [28], suggesting another etiology for cognitive decline, perhaps by the activation of inflammatory pathways.

Emboli generated by the CPB machine might also act by exacerbating ischemia or hypoxia during surgery. Ischemia and hypoxia are both thought to exacerbate cognitive decline and AD. Elevated levels of A/βPP and A/β occur in animal models subjected to mild to severe ischemia [59–61]. The enhanced accumulation of A/β is associated with a corresponding increase in apoptosis [62,63]. Population-based studies indicate that a history of ischemic stroke increases the risk of AD, as well as associated AD pathology among patients who have suffered from prolonged hypoxia or ischemia [64, 65]. The link between ischemia, hypoxia, and cognitive decline suggested by these studies raises the possibility that mild ischemia or hypoxia occurring from CABG or from use of the CPB machine might also promote POCD and/or AD.

Another possible mechanism is the type or duration of anesthesia used. Work in animal models raises the possibility that anesthetics can promote accumulation of A/β. Elevated levels of A/βPP and A/β occur in animal models subjected to mild to severe ischemia [59–61]. Although the current clinical data do not provide any support for this hypothesis, a comprehensive assessment on CNS A/β accumulation has not been conducted.

Finally, inflammation presents an alternative and appealing mechanism exacerbating cognitive decline. Pro-inflammatory cytokines that are released in response to surgery include TNF-α and IL-1/β, which can then induce the production and release of other pro-inflammatory cytokines, including IL-6 [66,67]. Neutrophils are known to be associated with AD pathology, and the inflammatory response occurs in close vicinity of A/β plaques. The presence of A/β induces the expression of cytokines, but the cytokines can also promote the accumulation of A/β into plaques [68]. Systemic inflammation also might exacerbate cognitive symptoms of neurological diseases, and thereby accelerate the disease progression [69].

**Progress in prevention: Next generation anesthesia**

Although a definite mechanism for the surgical and anesthetic induced pathogenesis of POCD is not fully known, there have been various observations and ideas that may be able to reduce the incidence of POCD by targeting certain pathways associated with anesthesia or surgery. Several drug and chemical based interventions have been proposed. Barbiturates have been used for neuroprotection, which may be mediated by their activity as allosteric potentiators of GABA_A receptors or by inhibition of NMDA receptors [70–72]. Xenon has been shown to be neuroprotective due to its antagonism of the NMDA receptor [73]. Increased glutamate levels in brain microdialysate are associated with cognitive decline in preclinical models of circulatory arrest. Actracurium, and its metabolite laudanosine, activate α4/β2 nicotinic acetylcholine receptors to levels of normal function in the CNS peri-operatively, and several hours post-operatively yielding neuroprotective effects [74,75].

One of the more promising avenues of research lies in the development of anesthetics that do not increase A/β or otherwise injure the brain. Development of improved general anesthetics with the potential to improve post-operative neurological function, or at least have intrinsic properties that are less detrimental to the brain, has evolved in three directions during the last decade. One group has focused on xenon as an anesthetic agent that also may have unique neuroprotective activity. In both cellular and animal models, xenon at-
tenuates hypoxia-induced damage, such as that which may occur with traumatic brain injury, during CABG or cerebrivascular surgery, or when systemic ventilation or perfusion are otherwise impaired [76,77]. A variety of molecular mechanisms have been invoked to explain xenon neuroprotection, but at the concentrations used clinically (up to 0.6 atm), this small molecule can inhabit many protein pockets and potentially affect many molecular signaling pathways. Clinical trials to assess xenon’s potential value in preventing POCD are underway, but one such trial has reported negative results [78, 79]. Other trials are investigating xenon neuroprotection in CABG surgery and in neonatal asphyxia.

Most of the data implicating anesthetics as neurotoxic agents have focused on the role of volatile inhaled anesthetics, which are small amphiphilic molecules that affect many biological systems. It is possible that the protective or degenerative actions of an anesthetic are unrelated to its size but rather are more related to other characteristics, such as its lipohilicity and/or being an amphiphilic molecule. Intravenous agents such as propofol and etomidate are known to act primarily by enhancing the activity of GABA$_A$ receptors, and their potential for toxic side-effects is less than that of volatile anesthetics. Etomidate, in particular, shows significant specificity for a subgroup of GABA$_A$ receptors containing $\beta$2 and $\beta$3 subunits [80], and it produces less cardiovascular and ventilatory depression than other general anesthetic drugs. However, etomidate is infrequently used, and is only used for anesthetic induction, because as the only anesthetic imidazole, it also produces a unique toxic side-effect: inhibition of adrenal corticosteroid synthesis [81].

Recently, two structural analogs of etomidate have been reported that appear to retain anesthetic potency and safety, while minimizing adrenal suppression. Methoxycarbonyl-etomidate [82] is a “soft analog” of etomidate, designed for rapid metabolism by non-specific esterase enzymes in blood and other tissues. It produces short-lived anesthesia after bolus administration, and can be infused for maintenance of anesthesia. Because its metabolism is about 100-fold faster than that of etomidate, any adrenal suppression that it produces is expected to reverse soon after termination of its administration. A second derivative, carboxetomidate [82], replaces the imidazole ring of etomidate with an isoetric pyrazole that lacks the ability to interact with the heme-based adrenal enzymes that synthesize corticosteroids. Carboxetomidate has anesthetic potency near that of etomidate, produces minimal cardiovascular and respiratory depression, yet adrenal suppression is minimal in both cellular and animal models. Neither of these drugs has been tested in models of anesthetic neurotoxicity or POCD.

Looking further into the realm of possibility, a third research group has combined a surrogate molecular binding target for anesthetics that act at GABA$_A$ receptors [83] with a fluorescent anesthetic ligand [84] to create a high-throughput screening method to identify novel classes of anesthetics [85]. Maintaining a focus on anesthetics that do not promote A$\beta$ aggregation might represent a prudent consideration given the prevalence of surgery in the elderly population. In this context, it is relevant to note that smaller sized anesthetics promote A$\beta$ aggregation in vitro [50,51]. The variety of approaches being examined suggests strong promise for discovery of new classes of general anesthetics that may prove to have fewer neurotoxic effects than current drugs.

**CONCLUSION**

Major surgery, such as CABG, appears to promote POCD. The factors contributing to POCD could include hypoxia, ischemia, micro-emboli, activation of NMDA receptors and/or GABA$_A$ receptors, increased accumulation of brain A$\beta$ (reduced clearance, increased synthesis, facilitate amyloid aggregation/shunt away from soluble amyloid monomers), tau hyperphosphorylation, inflammation, reduced immunocompetence, as well as maladaptive stress responses. Many of these factors are also thought to contribute dementia. Studies from the basic science literature demonstrate that gaseous anesthetics promote aggregation of A$\beta$ in vitro and in animal models. The putative mechanistic similarities and supportive laboratory data provide a theoretical basis to hypothesize that major surgery might promote delayed cognitive decline and dementia. However, there appears to be no evidence in the clinical literature indicating that anesthetics increase the risk of dementia. In addition, although retrospective studies show increased risk for delayed cognitive decline 3 to 5 years after major surgery, a prospective clinical trial did not confirm these retrospective observations. The ApoE e4 polymorphism is not associated with increased risk of POCD, but has not been studied to assess the risk of dementia in subjects with prior POCD. Thus, a conclusive assessment cannot be made at this point.

Despite ambiguous data about the risks of anesthetics or CABG for subsequent dementia, there are at least
two rationales for the development of neuroprotective therapeutics for POCD. The first rationale is that this putative brain stress demonstrated anatomically and biochemically, is to a great extent, iatrogenic, and is one of the few brain insults that can be treated prophylactically. Use of neuroprotective agents would be analogous to the use of pre-operative antibiotics for individuals who undergo surgery, assuming that such agents would have an acceptable therapeutic index. This is particularly important as most acute brain injuries (e.g., traumatic brain injury and stroke), even with short time windows post-insult, have yet to see even one therapeutic approved for acute neuroprotection when administered following the insult. The second rationale is the serious, life-threatening nature of the disease. AD and dementia in general is reaching epidemic proportions worldwide. The advancing age of the population along with the increasing need for surgical intervention highlights the potential risks of iatrogenically-induced increase in POCD, and ultimately, AD/dementia.

With increasing lifespan, surgical interventions will become increasingly common in older patients. Understanding the effects of surgery and anesthesia on cognitive function, and preventing deleterious effects of surgery and/or anesthesia on subsequent cognitive function is clearly a major public health issue and should be a major focus of research efforts in the future. In 2011, the first baby boomers in the United States will reach age 65. This group, totaling an estimated 70 million people, will have a significant impact on the U.S. healthcare system. The interaction between surgical intervention, cognitive decline, and AD could be problematic for our society. Further research is necessary to protect patients during surgery, to decrease the risk of POCD, and to protect against the potential of an earlier emergence of dementia.

ACKNOWLEDGMENTS

This work was supported by grants to BW from the Retirement Research Foundation and the Casten Foundation.


REFERENCES


Cognitive Dysfunction after Cardiac Surgery

Yatin Mehta* and Raveen Singh
Medanta Institute of Critical Care and Anaesthesiology, Medanta The Medicity, Gurgaon, India

Accepted 20 July 2010

Abstract. Both short and long term cognitive changes occur after cardiac surgery but the pathophysiology of these neurobehavioral changes remain incompletely understood. The cause of cognitive decline is most likely multifactorial and probably represents a complex interaction between cerebral microemboli, global cerebral hypoperfusion, inflammation, and genetic susceptibility. The problem of cognitive decline after cardiac surgery continues to increase as the surgical population becomes older and has more prevalent comorbid diseases. A better understanding of the etiology is essential to finding new preventive strategies as no definitive therapy exists for cognitive dysfunction.

Keywords: Cardiac surgery, cardiopulmonary bypass, neurologic dysfunction, pathophysiology

INTRODUCTION

Advancements in cardiac surgery and anesthesia over the last two decades has led to greatly reduced mortality rates for elective cardiac surgery (1–2%). The focus has now shifted to reducing cardiac, cerebral, renal, and pulmonary morbidity which lead to human suffering and a high financial burden on health care system.

Adverse cerebral outcomes after cardiac surgery encompass a wide spectrum, from subtle cognitive impairment to deadly stroke. Neurological injury after cardiac surgery may manifest as stroke (1.5 to 5.2%); delirium (10 to 30%); short-term (33 to 83%) as well as long-term cognitive changes (20 to 60%) [1–6]. There is a wide variation in the reported incidence of neurologic injury after cardiac surgery. These differences are mainly due to the designs of studies (prospective or retrospective), type of surgery (open heart or coronary), the presence of comorbidities, differences in definitions of cognitive dysfunction, the method of psychological testing and time of evaluation of neurological disturbances.

Post-operative cognitive dysfunction after cardiac surgery is a well described complication and is characterized by impairment of memory, concentration, language comprehension, information processing, and social integration [7,8]. It may manifest as difficulties in memory and in handling daily activities at home and work. Cognitive dysfunction is difficult to properly assess on routine clinical work and subtle signs are detectable only with sophisticated tests. The cognitive decline may sometimes be so subtle that patients themselves may be unaware of their cognitive decline or they may not report it due to embarrassment. Longitudinal follow up of patients who develop cognitive dysfunction has shown that these patients have a lower quality of life and a less productive work status [7,8].

PATHOPHYSIOLOGY

The processes involved in cognitive decline are still not completely elucidated, though its multifactorial character is known [9]. The etiology behind cognitive decline probably represents a complex interaction between cerebral microemboli, global cerebral hypoper-
fusion, inflammation, and genetic susceptibility [10–13].

Risk factors for cognitive dysfunction after cardiac surgery are: 1) Pre-operative factors (advanced age, lower education, previous cerebral diseases, severe atherosclerotic disease, comorbid diseases); 2) Intra-operative (number of emboli, duration and type of procedure, arterial pressure, temperature, stress response); and 3) Post-operative (temperature, arrhythmias).

Age is the most important risk factor with higher cognitive decline seen in elderly [6,9,14]. Progressive atherosclerosis in elderly may lead to altered cerebral autoregulation predisposing them to greater cognitive decline. Early post-operative dysfunction is more common in elderly because the aged brain is different from the younger brain in several important aspects, including size, distribution and type of neurotransmitters, metabolic function, and capacity for plasticity [15]. In a review of 67,764 cardiac surgical patients (4748 octogenarians), the incidence of neurologic injury was 10.2% in patients older than 80 years versus 4.2% in patients less than 80 years [16].

The protective effect of the number of school years in preventing cognitive decline seems similar to that suggested in recent studies on Alzheimer’s disease (AD), although the mechanism by which this is possible requires further elucidation [17,18]. One hypothesis, that may explain this association, is based on the fact that education increases the synaptic density in the neocortex, increasing the neuronal communication and minimizing the signs of cognitive and functional impairment [19].

Comorbidities like peripheral vascular disease, diabetes mellitus, systemic hypertension, and chronic renal failure all lead to cerebral vascular disease, thus increasing the risk of cognitive decline after cardiac surgery [9,20].

Peri-operative inflammatory response is believed to be an important factor in pathogenesis of cognitive dysfunction [21,22]. Activators of the inflammatory response during surgery, e.g., cardiopulmonary bypass (CPB), surgical trauma, blood loss, transfusion, and hypothermia might enhance this response leading to cognitive decline. The key players in this brain inflammation are various pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF), cyclooxygenase 2 (COX-2), and matrix metalloproteinases (MMP) [22,23]. Selective inhibition of COX-2, inflammatory cascade, and MMP proteolytic cascade may offer possible preventive approaches in preventing brain injury [24,25].

The release of inflammatory mediators via the CPB procedure appears to be temperature dependent, with warm CPB and hyperthermia associated with an increased inflammatory response (and increased cognitive decline) compared to hypothermic CPB [26]. Surgery itself is also associated with a stress response, with increasing secretion of cortisol and catecholamines. Persistently high levels of stress may inhibit memory and interfere with hippocampal function. Minimally invasive surgeries by decreasing the inflammatory response may result in less cognitive decline.

Neurocognitive dysfunction occurs frequently in non-cardiac surgery patients, though the incidence is less as compared to cardiac surgery, indicating that some element of surgery and/or anesthesia contributes to this condition [27]. Advanced age and the type of surgery are the most important risk factors; the incidence of cognitive dysfunction being higher in major non-cardiac surgery (e.g., hip replacement) [28]. The risk of cognitive dysfunction appears to be similar after both general and regional anesthesia though some studies have favored regional anesthesia [28]. Short-term impairment of cognitive and psychomotor performance after general anesthesia is typically attributed to incomplete drug clearance. Modern day fast track cardiac anesthesia technique is tailored to early extubation and effective early post-operative analgesia. Volatile inhalational based anesthesia is used (1 MAC, provides myocardial preconditioning) with small amount of opioid anesthetics (fentanyl 5–10 µg/kg) and minimal use of muscle relaxants. Evidence from animal models suggests that exposure to inhaled anesthetics (isoflurane, halothane) may lead to cognitive decline but human studies are lacking [29]. The proposed mechanism is increased aggregation of amyloid-β oligomerization, as revealed by NMR studies [30–32], which enhances neurocognitive dysfunction.

Intra-operative formation of gaseous microemboli and aggregated platelets, atheromatous debris, long surgical duration all enhance the risk of cognitive dysfunction after cardiac surgery [9]. Intra-operative hypotension and consequent hypoperfusion, hyperglycemia, hyperthermia all potentially worsen the neurologic damage and should be avoided [33–35]. Hyperthermia (intra-operative and post-operative) leads to cognitive decline by exacerbating neurologic injury. Grocott and colleagues demonstrated that peak temperature in post-operative period (24 h after surgery) was related to cognitive decline 6 weeks after cardiac surgery [36].

Open chamber procedures (valve surgery) or complex combined procedures (Valve + CABG, arch replacement) are associated with increased risk of cerebral injury as compared to coronary artery bypass graft-
ing (CABG) [37]. Studies comparing off pump coronary artery bypass grafting (OPCAB) with conventional on pump bypass surgery have shown equivocal results [38,39]. OPCAB avoids effects of bypass machine and despite a much lower incidence of embolic events; the incidence of cognitive dysfunction is similar to that seen in conventional surgery suggesting that inflammation may be more important in pathogenesis of cognitive dysfunction.

Genetics plays a crucial role, modifying the degree of central nervous system injury as well as its ability to recover from insult. Researchers have reported a genetic influence, in particular related to the presence of the apolipoprotein E4 allele [40,41]. This gene has been implicated in increasing the risk of AD as well as influencing the outcomes after head injury. PLA2 positive patients have also demonstrated worse impairment in Mini-Mental Status Examination after cardiac surgery [42]. Some researchers have suggested that cognitive dysfunction occurring after CPB with coronary artery grafting or valve repair/replacement is a functional sequel of AD-like neuropathology [43,44].

**BIOLOGICAL MARKERS**

Biochemical markers and new sensitive methods are needed to detect early cognitive dysfunction after cardiac surgery [45]. It has been demonstrated that preoperative and post-operative plasma concentrations of stable NO products (nitrate/nitrite) are associated with the early detection of cognitive dysfunction after cardiac surgery [46]. A significant positive correlation has been established between neuropsychological function and serum concentrations of S100B protein in patients with traumatic head injuries, stroke, and after non-cardiac or cardiac surgery [47].

**NEUROPSYCHOLOGICAL TESTING**

Patients may have a decline in cognitive performance without any evidence of neurological abnormalities, therefore necessitating the need for highly sensitive neuropsychological tests. Ideally specialized tests should cover the entire spectrum of cognitive functions, but for practicality cognitive assessment tests usually focus within specific cognitive domains like attention/concentration, psychomotor speed, motor dexterity or verbal learning [48]. Various neuropsychological tests like the Grooved Pegboard test (motor dexterity), Digit Span (concentration), Paired Associate verbal learning, Halstead Reitan Trail making test (Trails A and B), among others, have been used for assessment of cognitive impairment after cardiac surgery [3,17,35,37]. These tests should be applied both pre-operatively and post-operatively (prospective study) by trained individuals to enable the detection of cognitive decline. Ideally the pre-operative testing should be done several days before surgery as anxiety and worry prior to surgery may lead to underestimation of cognitive performance. Retrospective studies are less sensitive in detecting cognitive dysfunction. Sotaniemi and colleagues showed a 37% incidence of cognitive decline by careful neurologic examination while the prevalence of cerebral abnormalities detected by retrospective analysis of the same patient pool was only 4% [49]. The test results may also be influenced by factors such as variability, practice effects.

**PREVENTION OF COGNITIVE DYSFUNCTION**

- Early identification of at risk individuals.
- Intra-operative management: emboli reduction, maintain hemodynamic stability and organ perfusion, temperature management and rewarming strategy, glucose control, minimal surgical invasiveness.
- Pharmacoprevention (lidocaine, remacemide).

**Emboli reduction**

Use of arterial filters in CPB circuit helps reduce microemboli but its capacity to remove all sources of microemboli (gaseous and particulate) has limitations. Special aortic cannula and designs (contain filtering technologies and other means to deflect embolic load away from cerebral circulation) may be helpful in reducing embolic load [50,51]. Use of echocardiography and epiaortic scanning can help avoid atheromas during cannulation, clamping and vein graft anastomosis.

**Perfusion pressure**

Maintaining adequate cerebral perfusion during perioperative period (50–80 mmHg) can help reduce hypoperfusion injury [33]. In hypertensive, elderly and high risk individuals the autoregulatory curve is shifted to right and require higher perfusion pressures (70–100 mmHg).
Acid base management

Alpha stat pH management (pH maintained at 37°C) maintains normal cerebral blood flow autoregulation allowing adequate oxygen delivery while minimizing potential for emboli. pH stat management (i.e., carbon dioxide is added to maintain pH at hypothermic temperatures) leads to luxury perfusion with risk of excessive delivery of embolic load. Most studies support the use of alpha stat acid base management for adult cardiac surgery while pH stat management is used in pediatric surgeries and complex surgeries requiring circulatory arrest as it leads to homogenous brain cooling [52,53].

Temperature and rewarming strategy

Use of hypothermia for cerebral protection during cardiac surgery has been used as it leads to decreased cerebral metabolism (6–7% decline for every 1°C fall in temperature). The beneficial effects of hypothermia may also be mediated by non metabolic effects like reduction in calcium influx, blocking release of glutamate, decreased free radical formation [54]. Active warming at the end of surgery may, however, increase the risk of cerebral injury and cerebral hyperthermia must be avoided at all costs. Slower rewarming leads to lower peak cerebral temperatures and lower incidence of neurocognitive dysfunction [35,36].

Peri-operative glucose control

Hyperglycemia (> 200 mg%) worsens neurologic injury and should be avoided during perioerative period. Hyperglycemia in the setting of anaerobic metabolism leads to intracellular acidosis along with release of excitatory amino acids and a greater inflammatory response.

Pharmacological protection

There is no approved drug therapy for neuroprotection during cardiac surgery. Variety of agents like thiopentone, propofol, aprotinin, NMDA receptor antagonists (ketamine, remacimide), and steroids have been used but results have been equivocal [55–58].

Ultrafiltration and leucocyte depletion

Ultrafiltration helps in removing inflammatory mediators released during CPB and leucocyte depletion reduces oxygen free radical formation, both these measures may help reduce secondary brain injury.

CONCLUSIONS

Cognitive dysfunction after cardiac surgery remains an important complication and leads to decline in quality of life. In spite of many studies, the physiopathology of these neurological events has not been clearly determined yet. Further research to elucidate pathogenesis can help develop targeted interventions that can minimize cognitive dysfunction.

DISCLOSURE STATEMENT


REFERENCES


Review

Unusual Risk Factors for Cognitive Decline

Manjari Tripathi a,* and Deepti Vibha b
 aDepartment of Neurology, All India Institute of Medical Sciences, New Delhi, India
 bDepartment of Neurology, Institute of Liver and Biliary Sciences, New Delhi, India

Accepted 12 August 2010

Abstract. The evaluation and management of patients with cognitive decline pose many diagnostic and therapeutic challenges. While most cognitive disorders need a standard screening for common reversible causes, the diagnosis of ‘not so usual’ causes are delayed and often missed. It is important to be aware of such clinical scenarios, especially since a lot of these are reversible. Many coexisting metabolic, nutritional, endocrinial, toxic, and infectious causes mask the subtle and progressive cognitive changes that become apparent with stress and in the post operative period, often after a major surgery. Many more metabolic, nutritional, endocrinial, toxic, post operative, autoimmune, cerebrovascular, genetic, infectious, and hemorheological factors are now emerging as unusual causes. This review deals with the recognition and evaluation of these unusual causes of cognitive decline.

Keywords: Cognition, dementia, risk factors

INTRODUCTION

Cognitive decline in adults and in the elderly has been attributable to various reversible and non reversible risk factors. While the common risk factors are easily recognized, the uncommon or unusual ones are usually missed or overlooked. While epidemiological studies traditionally divide risk factors into three categories (i.e., familial and genetic factors, environmental factors and socio demographic factors [1]), it is practical to look at common factors first and then identify the less causative or contributing causes depending upon the clinical setting.

The most common causes of dementia are Alzheimer’s disease (AD) and vascular disease. Both of these are progressive illnesses that lead to functional dependence [2]. The search for unusual causes is thought futile, but may not be so. Many of the uncommon causes of dementia can be improved or even reversed if adequate treatment is introduced promptly (for example, when dementia is associated with certain types of infections). Effective preventive strategies are also possible once the pathogenetic mechanisms are understood. Public health measures introduced to control the spread of the new variant of Creutzfeldt-Jakob disease is one such an example. A better understanding of the steps that lead to the development of dementia in some of these uncommon conditions may provide valuable information about the pathogenetic processes involved in the causation of conditions [3]. This review deals with the lesser known risk factors of cognitive decline.

RISK FACTORS

Risk factors stratification

For the purpose of description, we have divided the risk factors into two groups- established risk factors and unusual risk factors. These are further grouped as modifiable and non modifiable to increase clinical applicability (Table 1).
Table 1
Risk factors for cognitive decline

<table>
<thead>
<tr>
<th>Established risk factors</th>
<th>Unusual risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modifiable</td>
<td>Non modifiable</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Non modifiable</strong></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Aging</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Genetic (Down's Syndrome,</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Huntington's disease)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Parkinon's disease</td>
</tr>
<tr>
<td>CNS infections (bacterial,</td>
<td>Apo ε 4 allele</td>
</tr>
<tr>
<td>fungal, protozoal)</td>
<td></td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>Less common</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Hallervorden-Spatz disease</td>
</tr>
<tr>
<td>Wernicke's encephalopathy</td>
<td>Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)</td>
</tr>
<tr>
<td>B12 deficiency</td>
<td>ALS–Parkinson’s–Dementia complex of Guam</td>
</tr>
<tr>
<td>Hypo and hyperparathyroidism injury</td>
<td>Hereditary ataxias (some forms)</td>
</tr>
<tr>
<td>Adrenal insufficiency and Cushing’s Syndrome</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Whipple’s disease</td>
<td></td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td></td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Vasculitis CADASIL</td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td></td>
</tr>
<tr>
<td>Recurrent nonconvulsive seizures</td>
<td></td>
</tr>
<tr>
<td>Aluminum</td>
<td></td>
</tr>
</tbody>
</table>

**Metabolic causes**

Patients are considered to have a metabolic syndrome if they meet ≥ 3 of the following criteria: 1) Abdominal obesity (waist circumference > 88 cm for women and > 102 cm for men); 2) Hypertriglyceridemia (≥ 150 mg/dL); 3) Low HDL cholesterol (< 40 mg/dL for men and < 50 mg/dL for women); 4) High blood pressure (systolic ≥ 130 mm Hg, diastolic ≥ 85 mm Hg) or use of antihypertensive medication; and 5) High fasting blood glucose (≥ 110 mg/dL) or use of antidiabetic medication [4]. Although some individual components of the metabolic syndrome have shown definite risk of developing dementia and cognitive impairment, few studies have looked at the components of the metabolic syndrome as a whole [5]. Several possible mechanisms may explain an association between the metabolic syndrome and cognitive decline, including microvascular and macrovascular disease, inflammation, adiposity, and insulin resistance.

**Hepatic disease**

Although it is well established that advanced forms of liver disease are frequently accompanied by overt and global cognitive deficits (hepatic encephalopathy), liver-derived circulating insulin-like growth factor–1 affects crucial aspects of mature brain function, and may exert a significant pro-cognitive function in adults [6]. Literature also shows that patients with chronic hepatitis C virus infection frequently show a decline in power of concentration and speed of working memory [7], and that they perform significantly worse than healthy controls on verbal learning and memory [8]. A recent study found that elevated gamma glutamyltransferase, a common biochemical finding in non alcoholic fatty liver disease, may be involved in the pathogenesis of AD by promoting oxidative stress [9].

**Chronic obstructive pulmonary disease (COPD)**

Neuropsychological deficits for COPD subjects include impairments in attention, verbal memory, and...
Table 2
Unusual risk factors discussed in this review

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Endocrinial</th>
<th>Nutritional</th>
<th>Post operative</th>
<th>Toxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>Addison’s disease</td>
<td>B12, folate and homocysteine</td>
<td>Cardiac surgery</td>
<td>Heavy metals (lead, mercury, aluminum)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>Hypercortisolism</td>
<td>Vitamin B3</td>
<td>Non cardiac surgery</td>
<td>Solvents</td>
</tr>
<tr>
<td>COPD</td>
<td>Hypo and hyperparathyroidism</td>
<td>Hypo and hyperthyroidism</td>
<td></td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Hypertension and hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Cerebrovascular</td>
<td>Genetic forms of degenerative disease</td>
<td>Prion disease</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>White matter hyperintensities (WMH) or leukoaraiosis</td>
<td>Altered lipid metabolism</td>
<td>HIV associated dementia</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
<td>Wilson’s disease</td>
<td>Herpes Encephalitis</td>
<td></td>
</tr>
<tr>
<td>Behcet’s disease - Sjogren’s syndrome.</td>
<td></td>
<td>Mitochondrial cytopathy</td>
<td>Cryptococcal meningitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neurocysticercosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lyme’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Whipple’s disease</td>
<td></td>
</tr>
</tbody>
</table>

COPD, Chronic obstructive pulmonary disease.

Deductive thinking. There are no recent randomized trials of treatment of long-term cognitive decline associated with COPD except compared neuropsychological functioning and single photon emission tomography (SPECT) of patients with COPD, with and without hypoxemia [10].

Diabetes mellitus in young
Clinically relevant cognitive decrements in relation to diabetes occur during two crucial periods in life: the period of brain development in childhood, and the period when the brain undergoes neurodegenerative changes associated with ageing. Outside these periods, cognitive decrements mainly occur in patients with substantial diabetes-related comorbidity, in particular microvascular or macrovascular complications [11]. Prospective cohort studies have identified an association between the presence of diabetes mellitus and incident cases of dementia, which seems likely to represent an increased risk for both AD and VaD [12,13].

Hypertension and hypotension
In addition to age, diabetes, hypercholesterolemia, and presence of an apolipoprotein E4 (ApoE4) allele, all characterized by vascular pathology, hypertension is now considered an important risk factor for the sporadic, prevalent form of AD [14]. Although treatments to lower blood pressure can enhance cognition, an aggressive reduction in blood pressure must be approached with caution, given the unanticipated negative cognitive consequences in the very old. Whether relatively low blood pressure is a complication of dementia of the AD type or whether it merely predisposes a subpopulation to an increased dementia risk needs further clarification [15].
The screening laboratory test for dementia, TSH, has long been part of the association between hypo- or hyperthyroidism and AD. This decline could be thyroxine-mediated (thyroid dysfunction as a consequence of AD neuropathology) or the direct effect of TSH on amyloid-β (thyroid dysfunction as a contributing factor to AD neuropathology) [22].

Nutritional

Folate, B12, and homocysteine
The prevalence of reduced levels of vitamin B12 is about 10% among persons aged 65–74 and rises to 20% with age > 75 years [23]. Deficiencies of vitamin B12 and/or folate and their clinical consequences for old people have been described extensively and elevated homocysteine has been associated with increased risk of vascular events and dementia [24]. Despite some evidence for a possible association between vitamin B12 deficiency and cognitive impairment, there is currently no evidence that supplementation of vitamin B12 prevents development or progression of cognitive decline [25]. Thus a finding of low cobalamin levels warrants treatment but its implications may not be clinically significant [26]. However, a recent study found that serum methylmalonic acid and vitamin B12 concentrations may be the more important risk factors for cognitive decline when compared to serum homocysteine concentrations, particularly in older populations exposed to food fortification and possible supplements containing folic acid [27].

Niacin (B3) deficiency
Early symptoms of niacin deficiency cause lassitude, weakness, loss of appetite, anxiety, irritability, and depression. Later neurologic changes include psychotic features, psychomotor retardation or agitation, tremor, ataxia, and insomnia, eventually leading to encephalopathy [20]. A prospective cohort study also showed protective effect of niacin preventing AD and cognitive decline within normal levels of dietary intake [28].

Post operative (cardiac and non cardiac surgery)
A wide variety of neurocognitive impairment ranging from stroke, postoperative delirium, depression, and early and delayed impairment in memory and visuospatial functions has been reported after coronary artery bypass surgery [29]. While the etiology of short term cognitive decline has been implicated to be microemboli, hypoperfusion, systemic inflammatory response syndrome (SIRS), anesthesia, depression, and genetic factors, long term changes are associated with associated cerebrovascular risk factors. However, in a study of non cardiac surgeries, 13% of the elderly group demonstrated cognitive dysfunction at 3 months after surgery and this was associated with advanced age, lower educational level, previous stroke with no residual impairment, and post operative cognitive decline (POCD) at hospital discharge [30].

Toxic causes

Heavy metals (lead, mercury, aluminum)
It has been shown that individuals exposed to lead as adults (former organo-lead manufacturing workers), had cognitive decline, particularly of new learning and memory functions, raising the possibility that lead might exert detrimental effects on cognitive function long after the initial exposure [31].

Occupational exposure to elemental mercury occurs in miners and workers in a variety of manufacturing industries. Significant decrement in performance on cognitive tests when exposed to high mercury levels has been found in these studies [32,33]. However, in a meta analysis relative deficits were seen for mercury-exposed subjects in the domains of motor speed, attention and visual memory but these effect sizes were small (< 0.5) [34].

Although the entity of dialysis dementia is well known, the role of aluminum as a risk factor for AD is still speculative, and epidemiological studies with positive and negative associations have been published [35, 36]. Manganese, tin, and arsenic has also been implicated in dementia causation but the definite evidence is lacking.

Carbon monoxide (CO)
In a retrospective study of patients with CO poisoning [37], 12% experienced delayed neurologic sequelae with an intervening “clear” period that lasted between 2 and 40 days. Cognitive deterioration (99%), urinary and fecal incontinence (88%), gait disturbance (53%), and mutism (32%) were the most common delayed sequelae. However, chronic poisoning from CO may not be obvious, and a high level of suspicion is required [38].
Solvents

Organic solvents are widely used in industries and chronic exposure causes cognitive impairment, pyramidal, cerebellar, and cranial nerve or brainstem signs in varying combinations [39]. Acute effects of solvents reflect their lipophilic properties and direct effects on neuronal cell membranes. Evidence is not very clear but suggests that a chronic low-level occupational exposure to solvents may have a negative impact on cognitive and psychological functioning [40]. Methodologically more rigorous studies have not uniformly supported the hypothesis that chronic low-level exposure to solvents causes cognitive impairment [41].

Autoimmune

Multiple sclerosis

Cognitive domains primarily affected in multiple sclerosis are attention, psychomotor speed, memory, and executive functioning. Neuropsychological testing shows some degree of cognitive impairment in approximately 43–65% of patients with MS, 20–30% of these may have severe dementia [42].

Systemic lupus erythematosus (SLE)

Clinical manifestations of CNS involvement comprise a broad spectrum of neuropsychiatric conditions, the most common of which is cognitive impairment; this is present in up to 50% of individuals with the disease. However, cognitive impairment correlates poorly with indices of disease activity, organ involvement or serological status, and is common in patients without a history of recognized CNS involvement [43]. Other chronic autoimmune conditions associated with cognitive decline are Behcet’s disease and Sjögren’s syndrome. This would suggest an immune mechanism for cognitive decline.

Cerebrovascular

Although cerebrovascular risk factors are a common cause of vascular dementia, unsettled risk factors are white matter hyperintensities (WMH) or leukoaraiosis. WMH are present in healthy elderly subjects and in patients with dementia, and their relevance to cognitive decline has not yet been fully established. In a 10-year follow-up study, Swan et al. [44] reported that healthy subjects with large WMH had greater decline on measures of planning, sequencing, response set, shifting, psychomotor speed, working memory, selective attention, and response selection than individuals without WMH. Later studies have used newer imaging modalities like diffusion tensor imaging, computation of brain parenchymal fraction, and brain volumetry, to correlate with cognitive changes over time, and found that increased WMH speed up the progression from normal to mild cognitive impairment [45,46].

Genetic causes

Developments in the field of genetics are contributing to expand our knowledge of the complex physiopathological mechanisms leading to neurodegeneration and cognitive decline (Table 3). While most of them are irreversible, a few like Wilson’s disease and mitochondrial cytopathies and dysfunction are partially reversible and are also commonly missed.

Infections

Infectious diseases are very common in developing countries and central nervous system affection commonly manifests as delirium or encephalopathy rather than cognitive decline. The central nervous system can be infected by prions, viruses, bacteria, fungi, and parasites. With the rise of human immunodeficiency virus (HIV) infection, some of the “historical” causes of dementia, such as neurosyphilis, have re-emerged and now feature alongside modern infectious causes of mental disorders, such as variant Creutzfeldt–Jakob disease [47].

Prion disease

All prion diseases are associated with the accumulation in the brain of an abnormal isoform of a host-encoded glycoprotein known as the prion protein (PrP). These affect 0.5 to 1.0 persons per million per year, with 90 deaths being attributed to such diseases in the U.K. every year [48]. All present a dementia syndrome plus a constellation of symptoms varying from ataxia, psychiatric symptoms, myoclonus, visual symptoms. Identification of these is accomplished by high index of clinical suspicion and supported by magnetic resonance imaging, electroencephalography, and cerebrospinal fluid (CSF) findings. Brain biopsy is confirmatory.

Herpes encephalitis

Although herpesviruses, arboviruses, and enteroviruses are the most frequent cause of acute viral encephalitis, the herpes simplex virus 1 (HSV1) affects mostly the frontal and temporal lobes (including the hippocampus), these brain areas are known to be vulnerable to AD pathology. There is however no evidence that herpesvirus increases the risk of AD [49].
Table 3  
Rare genetically defined causes of dementia

<table>
<thead>
<tr>
<th>Protein aggregation disease</th>
<th>Gene</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Alzheimer’s disease (FAD)</td>
<td>PS1, PS2, AβPP, and ApoE</td>
<td>Increased amyloid-β production</td>
</tr>
<tr>
<td>Familial diffuse Lewy body dementia (DLB)</td>
<td>A–Synuclein gene (SNCA)</td>
<td>Tripplication of SNCA</td>
</tr>
<tr>
<td>Parkinson’s disease (PD)</td>
<td>SNCA, parkin, VCH-L1, DJ-1, PINK1 and dardarin/LRRK2</td>
<td>Tripplication of SNCA, missense of PARK</td>
</tr>
<tr>
<td>Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T)</td>
<td>Microtubule-associated protein tau (MAPT)</td>
<td>14 missense mutations, a 3 base pair deletion (deltaK280) and 7 splice site for FTDP, mechanism still speculative for others</td>
</tr>
<tr>
<td>Progressive supranuclear palsy (PSP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical basal ganglionic degeneration (CBD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial frontotemporal dementia (FFD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease (HD)</td>
<td>Huntingtin</td>
<td>CAG trinucleotide repeats</td>
</tr>
<tr>
<td>Spinocerebellar ataxias (SCA)</td>
<td>SCA DRPLA</td>
<td></td>
</tr>
<tr>
<td>Altered lipid metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachromatic leukodystrophy (MLD)</td>
<td>Arylsulfatase A alleles</td>
<td>Three mutations in arylsulfatase A allele</td>
</tr>
<tr>
<td>Adrenoleukodystrophy (ALD)</td>
<td>ABCD1</td>
<td>More than 500 distinct mutations in ABCD1</td>
</tr>
<tr>
<td>Cerebroretinoid xanthomatosis (CTX)</td>
<td>Sterol 27-hydroxylase</td>
<td></td>
</tr>
<tr>
<td>Kufs disease</td>
<td>CLN4</td>
<td></td>
</tr>
<tr>
<td>Lafora body disease</td>
<td>EPM2A</td>
<td>Encodes two isoforms of laforin protein tyrosine phosphatase</td>
</tr>
<tr>
<td>Metal metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>ATP7B</td>
<td>More than 200 mutations</td>
</tr>
<tr>
<td>Pantethein kinase-associated neurodegeneration</td>
<td>PANK2</td>
<td></td>
</tr>
<tr>
<td>Energy metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial encephalomyopathies (ME)</td>
<td>Mitochondrial DNA (mtDNA)</td>
<td>Maternally inherited mitochondrial genome, or by nuclear DNA mutations</td>
</tr>
<tr>
<td>Other degenerative dementias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial encephalopathy with neuroserpin inclusion bodies (FENIB)</td>
<td>Serine protease inhibitor neuroserpin</td>
<td>Results in unstable neuroserpin protein that aggregates into Collins bodies</td>
</tr>
</tbody>
</table>

**HIV associated dementia**

HIV dementia has been described as a subcortical dementia associated with neuropathological changes to the basal ganglia. Patients with HIV who develop cognitive impairment should also be investigated for opportunistic infections of the central nervous system, such as neurosyphilis, cerebral toxoplasmosis, cryptococcal meningitis, tuberculous meningitis, and cytomegalovirus encephalitis. The classification criteria for HIV-associated dementia complex (HAD) introduced by the American Academy of Neurology AIDS taskforce, 1991 is commonly used [50].

**Cryptococcal meningitis**

Cryptococcal meningitis is caused by an infection with the yeast Cryptococcus neoformans. The meningitis is usually subacute and follows a pulmonary infection. The fungus can be visualized in the CSF with India ink staining. Although case reports abound for presentation of cryptococcal meningitis as cognitive impairment [51–53], routine CSF examination is still not practiced for the diagnosis or screening in a patient of dementia.

**Neurosphylis**

The underlying pathology of neurosyphilis involves diffuse inflammatory processes of the cerebrovascular system and the meninges, which can also lead to cranial nerve lesions, hydrocephalus, hypothalamic involvement, epilepsy, and strokes. Although a rare cause of dementia after the advent of penicillin, the disease has resurfaced after increase in prevalence of HIV. The key is clinical suspicion and CSF Venereal Disease Research Laboratory (VDRL) test confirms the diagnosis.

**Neurocysticercosis**

It is relatively common in developing countries and remains clinically silent in a large proportion of patients, but in many it will express itself through neurological deficits, seizures or psychiatric symptoms. A hospital study on 124 patients > 60 years of age to ascertain the cause of dementia showed that 8% of all
dementia were caused by tuberculosis and neurocysticercosis [54].

Other known causes of dementia with an underlying infective etiology are Whipple’s disease and Lyme’s disease.

Hemorheological

The Caerphilly study reported a U-shaped relationship between hematocrit and general cognitive function and a linear relationship with reaction time [55]. Fibrinogen has been implicated as a risk factor for cognitive decline in mildly cognitively impaired people [56]. The rheological properties of blood are important determinants of circulatory flow behavior and a recent study shows that these are also independently associated with cognition function [57]. The impact of blood rheology on cognition may be at a par with more established CVD risk factors. Future studies need to determine whether these markers can be considered as targets for strategies aiming at preventing or delaying cognitive decline in older people.

CONCLUSION

The work up of a patient with declining cognitive faculties becomes a challenging task in an era where knowledge is fast emerging on novel and unusual factors. This becomes more challenging when the patient is young and the cognitive decline is rapid. While it becomes the responsibility of a clinician to look for all possible fully or partially reversible causes, it is also necessary to define the dementia syndrome and the most probable etiology. This not only helps in paving the path for a smooth future management but also in prognosticating and guiding the patient and the care givers about the course of disease. Recent research on the effect of anesthetics induced amyloid beta oligomerization using biophysical studies [58–62] and animal model studies [63,64] is very interesting. Further research is necessary to know whether anesthetics have any role for POCD, which is common in elderly patients.

Hence this special issue on anesthetics and Alzheimer disease is very timely and most appropriate to rethink all other possible risk factors.

DISCLOSURE STATEMENT


REFERENCES


[38] Charlton RA, Schiavone B, Barrick TR, Morris RG, Markus HS (2010) Diffusion tensor imaging detects age related white matter change over a 2.2 year follow-up which is associated with working memory decline. *J Neurol Neurosurg Psychiatry* 81, 13-19.


Postoperative Cognitive Dysfunction: Toward the Alzheimer’s Disease Pathomechanism Hypothesis

Federico Bilotta\textsuperscript{a,b}, Andrea Doronzio\textsuperscript{a}, Elisabetta Stazi\textsuperscript{a}, Luca Titi\textsuperscript{a}, Vincenzo Fodale\textsuperscript{b}, Gianfranco Di Nino\textsuperscript{c} and Giovanni Rosa\textsuperscript{a}

\textsuperscript{a}Department of Anesthesiology, Critical Care and Pain Medicine, Neuroanaesthesia and Neurocritical care, University of Rome “La Sapienza”, Rome, Italy
\textsuperscript{b}Department of Neurosciences Psychiatric and Anesthesiological Sciences, University of Messina, Policlinico Universitario “G.Martino”, Messina, Italy
\textsuperscript{c}Department of Surgical and Anesthesiological Sciences, University of Bologna. Bologna, Italy

Accepted 1 September 2010

Abstract. Alzheimer’s disease (AD), a chronic and progressive deterioration of memory and other cognitive domains, is the most common form of dementia. Because of related health and social impact, there is growing interest in assessing potential relationship between anesthesia and the onset and progression of chronic neurodegenerative disorders, including AD. Currently, preclinical and clinical research is addressed to identify underlying pathomechanisms, patient risk factors, and the use of the least provocative drugs and techniques, to minimize the incidence of chronic neurodegenerative disorders. Preclinical studies are providing an increasing body of evidences on some of the mechanisms that link anesthetics to neuronal programmed cell death (apoptosis) and accumulation of misfolded proteins in the aging brain. Therefore, risk factors and pathomechanisms of chronic neurodegenerative disorders, including AD, and persistent postoperative-postanesthesia cognitive dysfunction may overlap.

Keywords: Alzheimer’s disease, postanesthesia cognitive dysfunction, postoperative delirium

INTRODUCTION

Alzheimer’s disease (AD), a chronic and progressive deterioration of memory and other cognitive domains, is the most common form of dementia [1,2]. Because of related health and social impact, there is growing in-
ic neurodegenerative disorders, including AD, and persistent postoperative-postanesthesia cognitive dysfunction (POCD) may overlap [4].

The aim of this review is to present preclinical evidence, including in vitro and in-vivo studies, and clinical studies on early and long-term POCD, and to provide a hypothesis on the pathomechanism that link anesthesia to AD.

PRECLINICAL EVIDENCE

In vitro studies -defined as those using isolated proteins, cells in culture, and brain slices- provide evidence that inhaled anesthetics interact with AD pathogenesis with various mechanisms including: protein abnormalities, synaptic failure, mitochondrial dysfunction, and cellular apoptosis.

Protein abnormalities

Inhaled anesthetics are possibly related to AD pathogenesis with two principal mechanisms: increase in the production and aggregation of amyloid-β peptide (Aβ) and induction of hyperphosphorylation and polymerization of the microtubule-associated tau protein [8,9].

Aβ peptides are natural products of metabolism consisting of 36 to 43 amino acids, the excessive accumulation generated via sequential cleavage of the amyloid-β protein precursor (AβPP) by β- and γ-secretase, is a key pathogenic event in AD [10,11]. Several studies support that inhalational anesthetics may contribute to this AD neuropathogenetic mechanism also in human cells, since clinically relevant concentration of isoflurane induces apoptosis, alters AβPP processing, and increases Aβ production in a human neuroglioma cell line [12,13]. In detail, the effects of isoflurane on apoptosis are linked to Aβ generation and aggregation but can induce caspase-3 activation in naïve H4 cells that further favor cell apoptosis [11]. These findings may suggest avoiding these anesthetic agents in individuals with excessive levels of cerebral Aβ and in elderly patients at increased risk for postoperative cognitive dysfunction [5].

Tau is an abundant soluble protein in axons that promotes assembly and stability of microtubules and vesicle transport, abnormal hyperphosphorylation and aggregation of microtubule-associated protein tau play a crucial role in neurodegeneration of AD [14,15]. Anesthesia, even for short periods (30 s to 5 min), induces tau phosphorylation at various amino acid sites, which result from stress-activated protein kinases. Anesthesia for a longer time (> 1 h) induces more dramatic phosphorylation of tau at the same sites, and the further phosphorylation may be associated with anesthesia-induced hypothermia [9].

Synaptic failure

According the “synaptic Aβ hypothesis” AD may be primarily a disorder due to synaptic failure; synapses loss and dysfunction correlate with cognitive decline and with the degree of clinical dementia [16]. The synaptic Aβ hypothesis of AD states that Aβ can compromise synaptic function and decrease synaptic long-term potentiation [10]. Aβ can facilitate NMDA receptor endocytosis and there is a reduction in the amount of surface NMDA receptors in the neurons of AβPP-Swedish transgenic mice that has elevated Aβ levels. Exposure to isoflurane induces changes in both NMDA and GABA_A receptors by increasing GABAergic neurotransmission and antagonizing glutamate at the NMDA receptor, evoking neurotoxic mechanism through both receptor systems [7,17,18].

Mitochondrial dysfunction

Aβ peptide is a potent mitochondrial poison that induces mitochondrial morphological changes and dysfunction through swelling and intense small synaptic vesicles depletion due to aberrant intraneuronal Ca^{2+} homeostasis [19]. An alternative mechanism of neurodegeneration mediated by mitochondrial dysfunction relates to mutated presenilin-1, which is found in more than 50% of the cases of early-onset of familiar AD, that decrease calcium level in endoplasmic reticulum [20, 21].

Cellular apoptosis

Human H4 neuroglioma cells stably transected to express human full-length wild type AβPP when exposed to a clinically active concentration of isoflurane (2%) for 6 h have an altered AβPP processing (by decreasing AβPP/C-terminal fragments levels), increased Aβ level, and a higher apoptosis rate [4]. These results further confirm that exposure to isoflurane, beside the direct effect on the biosynthesis of a protein implicated in the pathogenesis of AD, increases cellular apoptosis [22–25].

The above mentioned changes (protein abnormalities, synaptic failure and mitochondrial dysfunction,
cellular apoptosis) can be triggered or modulated by the interaction between inhaled anesthetics and internal protein cavities through two mechanisms: favoring protein intermediates with enlarged cavities prone to molecular destabilization; formation of hydrophobic cavities of suitable volume at oligomeric interfaces that provide free energy for oligomerization [26,27]. These mechanisms can partially contribute to explain why a temporary exposure to the anesthetics could translate into a durable effect on the distribution of molecular population. Of interest, according recent evidences collected with nuclear magnetic resonance (NMR) studies, the molecular size of the anesthetics have a critical role in inducing oligomerization [28]. Namely inhalational anesthetics with molecular sizes of 90–140 Å interact with amino acid residues located in the loop region of the helices of Aβ peptides (G29, A30, and I31) favoring oligomerization [29–32]. These oligomerization effects were not found in studies with intravenous anesthetics that have molecular size > 190 Å that include thiopental, propofol and diazepam, since these molecules cannot fit into the pocket that contains the three critical amino acids [31–33].

Preclinical in vivo studies

To determine whether the above described "in vitro" effects have an "in vivo" correlate, AD Tg2576 mice and their nontransgenic littermates, were exposed to isoflurane and halotane at 12 months of age and subsequent behavior and changes in brain Aβ plaque burden and caspase-3 mediated apoptosis were studied [34,35]. This study showed that moderate exposures to inhaled anesthetics can produce subtle but durable alterations in the aging rodent central nervous system; halotane enhanced plaque deposition in the Tg2576 mouse model, but isoflurane did not [34]. These results confirm "in vivo" that anesthetics may have effects on the central nervous system that outlast the period of anesthetia itself. Other animal models suggest that exposure to inhaled anesthetics induce decrements in learning and memory that persist for weeks or months, along to neurodegenerative disease-associated proteins including compounds with pathogenic relevance in AD [36]. Isoflurane, alone or in combination with midazolam or nitrous oxide, was associated with remarkably enhanced apoptosis in the 7-day-old developing rat brain, which was accompanied by subsequent cognitive impairments. It is still not clear if anesthetics mediated neurodegeneration contributed to the subsequent impairment of memory and learning in the above animal models. Acute exposure of infant rats or mice to several classes of drugs, including those that block N-methyl-D aspartate glutamate receptors and those activate γ-aminobutyric acid-mimetic properties, triggers widespread apoptotic death of neurons in the developing brain [37,38]. The window of peak vulnerability to the apoptogenic mechanism coincides with the developmental period of rapid synaptogenesis [39,40], also known as the brain growth spurt period, which in mice and rats occurs primarily during the first 2 weeks after birth, but in humans extends from about mid-gestation to several years after birth 6. The cell death process triggered by these drugs has been demonstrated at both light and electron microscopic level to have classic morphologic characteristics of apoptosis [41,42]. Exposing P6 infant rhesus macaques, endotracheally intubated and mechanically ventilated, to anesthesia for 5 h with isoflurane (maintained between 0.7–1.5% end-tidal) or control exposed for 5 h to room mechanical ventilation without further intervention, while maintaining physiologic stability, is associated with a 3-fold increase in the rate of neuroapoptosis compared with nonanesthetized controls. The increased neurodegeneration was demonstrable in widespread distribution across all division of the cerebral cortex [43]. Moreover, recent experimental studies have linked anesthetic exposure to changes in dendritic spine architecture, raising the question whether anesthetics may interfere with neuronal network formation [44]. The issue of anesthetic-induced neurotoxicity in the developing brain seems to extend beyond inhalational anesthetics to all the drugs that exert an antagonist effect on N-methyl-D aspartate glutamate and gamma-aminobutyric acid agonists [45,46]. In neonatal rat intrathecal administration of ketamine induced accelerated neuroapoptosis within the dorsal horn, long-term effects on mechanical withdrawal (hyperalgesia), and gait disturbance [47]. This study describe the development and validation of a model for investigating the effects of intrathecal anesthetics on early postnatal development and, since the literature in this field is not entirely consistent, can contribute to better define an issue with extremely relevant clinical implications [46,48].

CLINICAL EVIDENCE

The clinical evaluation of postanesthesia early and long-term neurocognitive impairment is biased by the multiple variables that can complicate or characterize the perioperative period. The clinical study of the neu-
rotoxic effects of anesthetics lacks a robust biomarker for neurodegeneration; neuropsychological testing is likewise difficult, and their time course changes are not clear. Postoperative cognitive dysfunction can complicate the postanesthesia course leading to abnormalities on neuropsychological testing, that may manifest as memory loss, psychomotor derangement, dementia, delirium, or depression, difficulties with fine-motor coordination, and impaired higher-level cognitive functions [49–54]. In this section we will presents some of the most recent and relevant clinical studies that have addressed the issue of postoperative postanesthesia neurocognitive impairment including those that have reported a delay in early postoperative cognitive recovery, postoperative delirium (PD) and long-term postoperative neurocognitive dysfunction (POCD) after anesthesia.

Anesthesia should induce a “transient” and “fully reversible” loss of consciousness and of neurocognitive functions, nevertheless, depending also on the anesthetic regimen adopted and on accessory drugs used, early postoperative cognitive recovery can be delayed. Anesthetic drugs with longer half life or patients-related and procedural issues can determine a delay in the early postoperative neurocognitive recovery and increase the risk of PD [55,56]. Cognitive changes are usually transient, returning to normal function within hours or days, but the cognitive impairment can persist for weeks (in up to 25% of patients one week after anesthesia and in almost 10% up to 3 months after) and in some cases may be a precursor for further deterioration [53–59]. Currently the term POCD is reported in the literature to include acute (<1 week), intermediate (<3 months), and long-term (1–2 years) cognitive decline after surgery [59]. Persistency of POCD 3 months after noncardiac surgery is associated with worse outcome including increased mortality, risk of leaving labor market prematurely and dependency on social transfer [60,61].

Early postoperative cognitive recovery

The pathogenesis of early and long-term postoperative cognitive dysfunction is unclear; however, age, alcohol abuse, low baseline cognition, hypoxia, hypotension and type of surgery have been alleged to contribute to this problem. The choice of anesthetic drugs can also affect postoperative cognitive behavior because residual levels of anesthetics can produce change in central nervous system activity [55,56]. The use of anesthetics that are rapidly eliminated with minimal metabol-
the memory performance and amount of nitrazepam given during the postoperative week [66].

There are several non-modifiable and modifiable risk factors for PD including, advanced age, high blood urea levels and cardiothoracic index, hypertension, smoking habits, blood replacement during bypass, atrial fibrillation, pneumonia, and postoperative blood fluid balance, but also preoperative cognitive impairment and reduced haemoglobin and haematocrit levels [67,68]. Among the modifiable risk factors should be mentioned the duration of preoperative fluid fasting and the choice of intraoperative opioid are independent risk factors for early PD [69,70]. The risk of PD can be predicted and effective strategies exist to reduce this risk. In 126 patients undergoing hip fracture repair to receive usual care alone or supplemented by several additional measures (including: supplemental oxygen during surgery, optimizing electrolytes, and blood glucose preoperatively, discontinuing high-risk medications, maintaining adequate nutritional intake, encouraging patients to get out of bed on the first postoperative day, treating severe pain), reduce the incidence of delirium from 50% to 32% in the intervention group and the incidence of severe delirium from 29% to 12% [71]. Notably, among non-modifiable risk factors preoperative executive dysfunction and depressive symptoms are predictive of PD in patients undergoing non-cardiac surgery [72,73].

Delirium is associated with significant reductions in global cerebral blood flow and systemic neurotransmitter dysfunction [74]. Although the pathophysiology of delirium is multifactorial the neurotransmitter systems based on gamma-aminobutyric acid, acetylcholine [75], and serotonin appear to be principally involved [76]. Recent evidence suggests that dysregulation in the homeostasis of tryptophan, the precursor to serotonin, may also play a critical role in the pathogenesis of postoperative delirium [77]. Because abnormalities in the regulation of serotonin have been consistently linked with depression, this may have important implications for elucidating the relationship between depression and delirium. Furthermore, in patients with AD following an episode of delirium there is a significant acceleration of the slope of cognitive decline [78]. Hence the importance of aggressively prevent PD and the underling possible triggering pathomechanism toward the development or modulation of AD [79,80].

Long-term postoperative neurocognitive dysfunction

The International Study of Postoperative Cognitive Dysfunction 1 (ISPOCD1) demonstrated that general anesthesia is related to a postoperative cognitive dysfunction at 1 week and 3 months postoperatively in 25.8% and 9.9% of patients [51]. The ISPOCD 2 study reported, in 438 elderly patients, no significant differences in POCD between general anesthesia and local anesthesia at 3 months follow up (14.3% and 13.9%; p = 0.93) [81]. Age distribution of late POCD after surgery (3 months follow up) shows that prevalence in elderly patients (> 60 years) is significantly higher compared to an age-matched control group [82]. In this study 30–41% of adult patients experienced POCD at hospital discharge in all age groups (young 18–39 years; middle 40–59 years; elderly 60 years or older), but the prevalence of late POCD was significantly higher in elderly patients, in patients with an history of stroke even when asymptomatic and in the subgroup of patients that developed PD. Notably, patients who exhibited POCD at both hospital discharge and at 3 months after surgery were more likely to die in the first year after surgery compared to patients with no POCD (10.6% vs 2.1%; p = 0.02) [83]. A subgroup analysis of the types of cognitive impairment (namely: memory, executive functions and combined executive functions/memory), at hospital discharge and after 3 months follow-up in patients aged 60 years or older undergone non cardiac surgery, showed that only those patients with executive and combined executive/memory decline had functional limitations in daily living [82]. These findings can contribute to clarify the conflicting evidences reported in the literature regarding the relationship between POCD and daily living impairment, since executive functions and memory systems are intimately related but have dedicated neuroanatomical localization. Executive functions are most commonly associated with the frontal cortex, subcortical nuclei and white matter fibers [84,85]. Memory functions are associated with medial temporal lobe (hippocampus, entorhinal cortex), thalamus (dorsomedial and anterior nuclei), and basal forebrain (which innervate the hippocampus with cholinergic neurons) [86]. Disruption of any of these brain regions during the perioperative period can lead to selective deficits with various impact on daily life abilities. Understanding the etiology of the cognitive impairment can help to develop dedicated strategies for preventing and rehabilitate patients with different types of POCD [61,87].

In a retrospective cohort study, that included also patients with early AD, the effects long-term cognitive functions were evaluated in three groups: noncardiac surgery, illness, and none of the above [88]. Cognitive trajectories did not differ among the three groups. Al-
though in demented participants cognitive function declined more markedly compared to nondemented participants, surgery or illness did not independently contribute to cognitive decline. This study provides results partially conflicting with previous evidences and concluded that is necessary to conduct further studies properly designed appropriately designed with meaningful clinical end point to determine whether surgery, anesthesia or patients characteristics might be associated with long-term postoperative cognitive decline [88].

Among other factors that can contribute to POCD there might be individual genotype, in particular apolipoprotein E4 (APOE4) subtype; nevertheless, a large prospective study in 350 patients aged > 55 years that completed 6-weeks neurocognitive testing after noncardiac surgery there were no differences in patients with or without APOE4 allele [89].

DISCUSSION

In this paper we have revised the preclinical and clinical evidences on early and long-term POCD. Available preclinical evidences support that inhalational anesthetics do play a role in modulation and triggering AD. Clinical evidences also demonstrate that some anesthetics (including opioids and inhalational hypnotics) and various other drugs frequently used in the perioperative period (including atropine, ketamine, benzodiazepines, etc.) can delay postoperative cognitive recovery, and are associated to an increased risk of PD and persistent POCD.

Robust preclinical evidences and several clinical studies provide the support for increasing concern over anesthetics-induced long-term detrimental effects on brain functions, such as neurotoxicity, neurodegeneration and persistent POCD. The central cholinergic system has a key role in regulating consciousness, memory and learning; its dysfunction may play an important role in the pathogenesis of POCD [90–92]. Different anesthetic agents, and in particular inhalational anesthetics, act on the central cholinergic system. Clinical concentrations of isoflurane, and desflurane in presence of hypoxia, cause altered processing of amyloid precursor and increase Aβ production and induce apoptosis in both human neuroglioma and mice brain cell lines [92–96]. These two mechanisms, induced by isoflurane, can trigger a vicious cycle that lead from apoptosis to Aβ generation to further apoptosis [12]. Furthermore, Aβ have acute adverse effects on multiple aspects of acetylcholine synthesis and release [96].

AD is clinically characterized by progressive memory loss, declined cognitive functions and behavioral disturbances, accompanied by spatial-temporal disorientation, confusion, agitation, anxiety, depression, and insomnia, that progress and impair abilities in daily activities [97]. In these patients progressive neuronal loss results in reduced brain levels of acetylcholine and choline acetyltransferase that correlates with the severity of the cognitive dysfunction [96–98]. A similar mechanism based on the functional relationship between Aβ and the central cholinergic system can underlie POCD, a better understanding of this relationship can contribute to disclose the pathomechanisms of anesthesia and AD [4].

Another possible pathomechanism that can contribute to explain the relationship between anesthesia and long-term and persistent POCD refers to preoperative “cognitive reserve”. As reported in the study by Monk and colleagues, asymptomatic patients with an history of stroke are exposed to an increased risk of prolonged POCD despite having no residual neurologic deficits at the time of surgery, these patients may have lost a critical neural mass with their stroke leading to a decreased cognitive reserve and an increased susceptibility to POCD [99]. Preexisting brain dysfunction is an established risk factor for PD and POCD especially in the elderly [100].

In our opinion, despite anesthetics can trigger and modulate chronic neurocognitive impairment through various mechanisms, it remains difficult to drive conclusive evidences since various physiologic and environmental factors can contribute to postoperative persistent POCD and PD. In particular, hypotension, hypoxia and hypocapnia can favor brain hypoperfusion and induce neurocognitive impairment. On the other hand, especially in elderly patients, environmental factors (including changes due to hospitalization, sleep deprivation, etc) can play a critical role in PD.

Chronic cognitive impairment and AD have some of the highest healthcare and non healthcare social costs, with the costs being especially high for the patient’s family. Whether POCD represents another subgroup of AD is still unknown. Preclinical and clinical studies provide solid and consistent evidence that several perioperative factors, including anesthetics, could contribute to AD pathogenesis.

CONCLUSIONS

Anesthesia allows surgical procedures of increasing complexity in sicker patient populations. Further re-
search is needed to determine whether different classes of anesthetics are related to changing risk profiles in inducing deleterious effects on long term cognitive abilities in defined subgroup of patients.

DISCLOSURE STATEMENT

Authors’ disclosures available online (http://www.j-alz.com/disclosures/view.php?id=599).

REFERENCES

Studies in Animal Models of the Effects of Anesthetics on Behavior, Biochemistry, and Neuronal Cell Death

María Ángeles Mena, Juan Perucho, Isabel Rubio and Justo García de Yébenes

Department of Neurobiology, Hospital Ramon y Cajal, and CIBERned, Madrid, Spain

Department of Neurology, Hospital Ramon y Cajal, and CIBERned, Madrid, Spain

Accepted 29 June 2010

Abstract. Recent clinical studies have suggested that there is an increased risk of Alzheimer’s disease (AD) in patients undergoing surgical interventions, but it is unknown whether this effect is related to anesthesia, cardiovascular complications of surgery, or associated conditions such as hypothermia. In addition, many patients, especially the elderly, present persistent post-operative cognitive deterioration after anesthesia, without clear complications during surgery. Experimental studies in animals may be helpful to dissect the pathogenic role of the different factors involved in surgery. Here, we review studies on the effects of anesthesia on neuronal function performed in tissue culture and in experimental animals. Several studies have shown that a small inhalation of anesthetics induces activation of caspases and cell toxicity on glioma and pheochromocytoma cells in culture, which is prevented by treatment with the metal chelating agent clioquinol. Exposure of old rodents to anesthesia produced memory deficits and increased levels of amyloid-β (Aβ) peptide and phosphorylated tau in brain. The effects of long term or short term repetitive exposure to small molecular weight anesthetics are more severe in transgenic AβPPswe mice than in wild type mice. In the former, low molecular weight increased the number of TUNEL+ apoptotic cells and the ratio of pro-apoptotic proteins in hippocampus; reduced astroglial and increased microglial responses; increased Aβ aggregates and high molecular weight peptides; abnormal chaperone responses and reduced autophagy. In conclusion, anesthetic gases induce changes which may reproduce AD pathology in mice with mutations which produced AD. It would be interesting to know whether anesthetics are risky for subjects with special genetic risk factors.

Keywords: Alzheimer’s disease, amyloid pathology, AβPPswe mice, apoptotic cell death, autophagy, cognitive deficits, chaperones, glial cells, isoflurane, post operative cognitive dysfunction, presenilin-1

INTRODUCTION

There is a great interest in the effects of anesthetics in the brain. While it is evident that anesthetics have been used safely in billions of surgical interventions performed in many patients in the last two centuries,
play complementary roles. In addition to the specific effects of anesthetics (compounds which alter neuronal function) on the brain, other factors should be taken into consideration including cardiovascular complications, hypoxia and hypothermia among others [7–10].

Furthermore, after surgical procedures, many elderly patients present an acute syndrome of memory loss, disorientation, difficulties in learning and inability to concentrate, of variable duration, called post operative cognitive dysfunction (POCD), which has been related to changes in brain function similar to those which take place in patients with AD [11–13]. It is not clear whether POCD is a transient first event for development of AD and, in addition as mentioned above, the pathogenic factors of POCD may be multifactorial and not restricted to those of anesthetics. For this reason, it is very important to test the effects of anesthetics, without surgery and under careful temperature control and cardiovascular and respiratory parameters, on animal behavior and neuronal cell function. Here we review the effects of anesthetics in vitro and in vivo animal models and the impact of these effects on the putative pathogenesis of AD.

**EFFECTS OF ANESTHETICS ON NEURONAL CELLS IN CULTURE**

The effects of anesthetics have been tested in neuronal cells in culture. Zhang and colleagues [14,15] reported that the combined effects of hypoxia and desflurane, but not the isolated effect of any of these two factors, increased the levels of amyloid-β (Aβ) peptide and the levels of caspases in neuroglioma cells in culture. The mechanism of toxicity was considered related to activation of the processing of the amyloid-β protein precursor (AβPP) through the β-secretase and it could be blocked by the antidiarrheic metal chelator clioquinol and by γ-secretase inhibitor L-685458, which reduced caspase activation.

Isoflurane, but not sevoflurane, induced cytotoxicity in rat PC12 pheochromocytoma cells and primary cortical neurons as determined by both lactate dehydrogenase (LDH) release and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reduction assays [16]. Isoflurane significantly decreased the anti-apoptotic Bcl-2/Bax ratio. Isoflurane cytotoxicity was suppressed by dantrolene, a ryanodine receptor antagonist that inhibits abnormal calcium release from the endoplasmic reticulum (ER) suggesting that its toxic effects were mediated through excessive calcium release. PC12 cells transfected with the presenilin-1 mutation L286V were more vulnerable to isoflurane toxicity [17] suggesting that susceptibility to anesthetics increases in animals with genetic risk factors for AD.

Exposure to isoflurane induced neuronal degeneration in postnatal organotypic hippocampal slice cultures [18]. The severity of toxicity was related to the age of the pup and to the length of exposure to isoflurane. Toxic effects of anesthetics on cells in culture is not restricted to neurons but also involves other cells such as fibroblasts [19], lymphocytes [8,20] and liver cells [21].

**EFFECTS OF ANESTHETICS ON ANIMAL BEHAVIOR**

Several studies have shown that anesthetics produce persistent learning deficits in developing rodents [22, 23]. Similarly, in aged rodents, exposure to isoflurane produced persistent memory deficits [24,25]. In normal young adult mice, repetitive exposure to isoflurane does not produce persistent cognitive deficits but in transgenic mice with amyloid precursor protein mutations, isoflurane increases the rate of mortality during and after anesthesia; increases the emergence time after anesthesia; decreases the responsiveness to the sensorial stimulation; and produces a long lasting reduction of exploratory behavior [26] (Table 1).

The amnesic effects of isoflurane are mediated, at least in part, throughout enhancement of GABA neurotransmission, since the knockout mice for the α4 subunit of the GABA type A receptor are much more resistant [27]. Other effects of isoflurane such as depression of breathing and righting response appear to be related to changes in other proteins such as regulatory G signalling protein [28].

**EFFECTS OF ANESTHETICS ON THE METABOLISM OF PROTEINS INVOLVED IN AD**

The most important proteins involved in neurodegeneration in AD are the Aβ peptides and protein tau. The Aβ peptides are a number of peptides from 38 to 43 amino acids, derived from the extracellular portion of AβPP by processing via the β- and the γ-secretases. Several studies have shown that small anesthetics such as isoflurane and sevoflurane increase Aβ levels [29, 30]. Toxicity of Aβ has been related to the oligomers of
### Table 1

**Effects of anesthesia in animal models**

<table>
<thead>
<tr>
<th>Animal models</th>
<th>Type of Anesthesia</th>
<th>Parameters of study</th>
<th>Results</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague Dawley rats (7-days-old)</td>
<td>Midazolam, nitrous oxide, Isoflurane (6 hours)</td>
<td>LTP, Behaviour, IHQ, Electron microscopy, Western Blot</td>
<td>Neurodegeneration, memory impairments, deficit synaptic function</td>
<td>Jevtovic-Todorovic et al. 2003 [22]</td>
</tr>
<tr>
<td>Sprague Dawley rats (7-days-old)</td>
<td>Xenon 30–75%, Isoflurane 0.75%, nitrous oxide 35–75%</td>
<td>Caspase activation, IHQ, Western Blot,</td>
<td>Xenon prevents isoflurane-induced neonatal neuronal apoptosis</td>
<td>Ma et al. 2007 [23]</td>
</tr>
<tr>
<td>Tg2576 transgenic and non transgenic mice (females, 12-m-old)</td>
<td>Isoflurane, Halothane, (0.8 MAC) 120 min, repeated 5 days</td>
<td>IHQ, Morris water maze</td>
<td>Halothane affects behaviour but not amyloidogenesis</td>
<td>Bianchi et al. 2008 [42]</td>
</tr>
<tr>
<td>C57B6 mice</td>
<td>1.4% Isoflurane, (2 hours)</td>
<td>Caspase activation, IHQ, BACE levels, Western Blot</td>
<td>caspase-3 and BACE increased 24 hours after anesthesia</td>
<td>Xie et al. 2008 [38]</td>
</tr>
<tr>
<td>Rats (neonates and 16-m-old)</td>
<td>Isoflurane MAC (4 hours)</td>
<td>Fear condition, Morris Water Maze, neurogenesis and cell death</td>
<td>Cell death neurogenesis and LTNO not affected</td>
<td>Stratman et al. 2010 [39]</td>
</tr>
<tr>
<td>AβPPswe/Tau/PS1 (3xTgAD); C57B6 mice (12 and 14-m-old)</td>
<td>Isoflurane, Sevorane, Halothane (MAC)</td>
<td>Emergence patterns and MAC test</td>
<td>Less sensibility of 3xTgAD mice in MAC levels</td>
<td>Bianchi et al. 2010 [40]</td>
</tr>
<tr>
<td>AβPPswe Tg2576 mice (10.5-m-old)</td>
<td>Isoflurane 2% 30min. Twice per week x 3 months</td>
<td>Western Blot, IHQ, Behaviour</td>
<td>Increased susceptibility in AD pathology in transgenic mice</td>
<td>Perucho et al. 2010 [26]</td>
</tr>
</tbody>
</table>

BACE (β-secretase); IHQ (Immunohistochemistry); LTNO (Long-term neurocognitive outcome); LTP (Long Term Potentiation); MAC (Minimal Alveolar Concentration); POCD (Post-operative cognitive decline); POR (Post-operative recovery); RT-PCR (Reverse transcriptase Polymerase Chain Reaction).

These peptides rather than to the soluble monomers. It has been shown, by NMR techniques, that these small anesthetics increase the oligomerization of Aβ [31–33]. Anesthetics and amyloid interact, therefore, through several mechanisms which may lead to neuronal degeneration and AD.

Tau protein is involved in the stabilization of microtubules where it interacts with many other proteins and plays a very important role in cellular transport. In AD, tau protein is characteristically hyperphosphorylated. Hyperphosphorylated tau protein binds abnormally to microtubules and does not allow for normal transport function. Hyperphosphorylation of tau has been attributed to hyper activation of several kinases, specially to glycogen synthase kinase β (GSK/β) but several recent studies have suggested that there is also a deficiency of phosphatase, namely phosphatase 2 A (P2A).

Several recent studies have suggested that anesthesia increases the phosphorylation of tau [34,35]. We also know that anesthesia-induced hyperphosphorylation detaches 3-repeat tau from microtubules [36]. These changes, at least partly, have been related to inhibition of phosphatases which takes places when hypothermia occurs in anesthesia [7]. Anesthesia accelerates and aggravates neurofibrillary pathology in mouse models of taupathy. In these animals anesthesia induces hyperphosphorylation of tau, the detachment of 3-R tau from microtubules and the production of neurofibrillary pathology [36,37].

Both Aβ peptides and aggregated Aβ forms increase, but not p-tau or total tau brain levels, in transgenic mice with AβPP mutations when exposed to isoflurane under temperature control [26]. Furthermore, isoflurane induces caspase activation and increased β-protein levels in vivo [38] (Table 1).

### EFFECTS OF ANESTHETICS ON NEURONAL CELL BIOLOGY AND FUNCTION

There is a debate about the effects of anesthetics on neuronal cell biology and the variations in results ob-
tained in different experiments may be explained by distinct methods, doses of anesthetics, time of exposure, presence or absence of hypothermia or cardiovascular complications, age of experimental animals, species, and genetic backgrounds. Isoflurane does not affect brain cell death, hippocampal neurogenesis, or long-term neurocognitive outcome in aged rats [39]. Similarly, mice with three transgenes of proteins involved in AD (AβPPswe, tauP301L, and PS-1M146V) after single exposure to inhaled anesthetics present mild resistance to the anesthetics but a normal pattern of emergence [40].

However, the repetitive exposure to isoflurane did not have deleterious effects on neuronal cell survival in young adult wild type mice. But in mice with mutations of the AβPP protein, exposure to isoflurane produces alteration of neuronal biology both after chronic repetitive exposure and after only three exposures to low isoflurane concentrations (Perucho et al., unpublished). The changes observed in these AβPP mutant mice include increase in the number of apoptotic cells and a reduction of the Bcl2/Bax, anti-apoptotic/pro-apoptotic ratio.

### Differential Effects of Anesthetics According to the Genetic Risk Susceptibility for AD

We investigated the effects of repetitive anesthesia with isoflurane on survival, behavior, apoptosis in hippocampal cells, Aβ peptide and tau patterns, chaperones and autophagy in wild-type (WT) and AβPPswe mice. The mice were anesthetized with isoflurane, 2%, and oxygen, 98%, for periods of 20 min, under control of temperature and cardiovascular parameters. The experiments were repeated twice a week, for 3 months, in animals aged from 7 to 10 months.

During isoflurane treatment, AβPPswe mice had a slightly higher but not significantly different heart rate than WT from the beginning of the anesthesia, which did not increase during the exposure to isoflurane. Similarly, AβPPswe had less but not a significantly different number of respirations per minute and, under the experimental conditions of anesthesia with isoflurane, 2%, and O2, 98%. Both groups of animals had full and equal saturation of O2 in blood.

We found that AβPPswe mice treated with isoflurane have increased mortality; less responsiveness after anesthesia; long-lasting reduced exploratory behavior; increased number of TUNEL+ apoptotic cells and increased ratio of pro-apoptotic proteins in hippocampus; reduced astrogial and increased microglial responses; increased Aβ aggregates and high molecular weight peptides; abnormal chaperone responses and reduced autophagy. These effects were not present in WT mice, suggesting that the deleterious impacts of isoflurane on behavior, survival, neuronal cell death, and processing of proteins involved in neurodegeneration are restricted to subjects with special susceptibility, and not normal subjects [26,41].

Many of these responses are present in patients with AD and, therefore, we assume that the treatment with isoflurane aggravates the clinical phenotype observed in less than one-year-old AβPPswe mice and accelerates the pathological and molecular findings observed in the brains of these animals.

In addition to reducing exploratory behavior in the Y-maze, isoflurane increased the emergence time in AβPPswe mice. In our study, lengthening of the emergence time appears only in AβPPswe but not in WT mice, which suggests that it is not related to cardiovascular complications of anesthesia, and is dependent on the time of anesthesia, which implies that it is not related to immediate isoflurane effects on neuronal function. Emergence time is a parameter which could be related to the so-called POCD observed in patients after surgery. POCD is considered a cognitive disorder with some risk factors in common with AD.

Our data suggest that isoflurane exposure produces cognitive changes and it is life-threatening for AβPPswe mice. Our experiment is very different to that of Bianchi et al. [42], since they used 12-month-old females, which already express cognitive changes and amyloid pathology in their brain, and we have used 7 to 10-month-old males, which are presymptomatic. Bianchi et al. treated their animals with a total cumulative exposure to anesthesia of 10 h and we exposed the animals to isoflurane for a cumulative time of 8 h. However, their procedures were applied in 5 days while ours were applied in 3 months. Our experimental protocol was, therefore, less likely to produce cardiovascular complications of anesthesia. The apparent discrepancy of Bianchi et al. (2008) and our results is solved if we take into consideration that they found impaired cognitive changes in aged WT animals exposed to isoflurane, similar to our finding of abnormal behavior of presymptomatic AβPPswe mice. In summary, the results of both studies suggest that isoflurane increases cognitive deterioration in elderly mice, accelerates it in presymptomatic AβPPswe, but does not increase it in AβPPswe mice after they develop amyloid pathology in brain.
In order to study if acute exposure of isoflurane has differential effects according to the genetic risk susceptibility for AD, we have performed new experiments with 10-month-old female WT and A/βPPsw mice treated 3 times with isoflurane (1.5%, and oxygen 98.5%, for 90 min). The isoflurane treatments were performed every 2 days and the mice were sacrificed 24 h after the last dose. Acute isoflurane treatment increased the pro-apoptotic Bax/Bcl2 index and the A/β aggregated forms in the A/βPPsw mice, but not in the WT (Perucho et al., unpublished results).

CONCLUSIONS

Experimental studies of the effects of anesthesia on neuronal function suggest that in normal animals and under normal conditions, anesthesia is safe. There are, however, certain circumstances such as experiments performed on animals with genetic risk factors for AD, aged, or suffering hypothermia simultaneous to anesthesia, where the exposure to small inhaled anesthetics produces changes similar to those found in AD. Determining the risk factors of anesthesia in patients undergoing surgery would be critical for the safety of anesthesia.

FUTURE DIRECTIONS

The relative risk of the different anesthetics for cognitive impairment should be tested in prospective studies performed in patients with strict control of many variables. These studies should be performed in subjects undergoing anesthesia for surgery not involving the central nervous system or the cardiovascular system. Logistic regression analysis of several variables should be investigated. These variables should include the type of surgery, the duration, the type of anesthetics, the presence of absence of cardiovascular complications and the presence of genetic risk factors for dementia.

We have performed a pilot study in nearly 100 patients, undergoing orthopaedic surgery, without cardiovascular complications, not exposed to small molecular size inhaled anesthetics, and found out that these patients do not develop cognitive deterioration, nor postoperative elevation of plasma amyloid levels, with the exception of apolipoprotein E4 homozygotes, who increased A/β levels [41]. But the number of patients is too small to draw definitive conclusions.

ACKNOWLEDGMENTS

This study has been supported in part by grants from the Spanish Ministry of Health, FIS 2007/0037, CAM 0202/2006 and CIBER 2006/05/0059. JP and IR have a CIBER predoctoral and postdoctoral fellowships, respectively. The authors thank Ana Gomez, Laura Rodriguez, Izaskun Rodal and M. Paz Muñoz for excellent technical assistance, and Mrs. Claire Marsden for editorial help.


REFERENCES


Anesthetics and Tau Protein: Animal Model Studies

Xiaoqin Run\textsuperscript{a,c}, Zhihou Liang\textsuperscript{b,c} and Cheng-Xin Gong\textsuperscript{c,*}

\textsuperscript{a}Department of General Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
\textsuperscript{b}Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
\textsuperscript{c}Department of Neurochemistry, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA

Accepted 10 August 2010

Abstract. Recent studies have suggested that general anesthesia may initiate or accelerate cognitive impairment and Alzheimer’s disease (AD). To understand the possible underlying mechanisms, several studies have been carried out in animal models. In this review, we first briefly discuss the mechanisms leading to neurodegeneration and cognitive impairment in AD, with an emphasis on tau abnormalities in this pathological process. Subsequently, we review the role of anesthesia in inducing tau abnormalities and the possible mechanisms. Recent studies suggest that anesthesia may accelerate the development of AD by promoting abnormal hyperphosphorylation of tau. Further studies are certainly needed to understand the molecular mechanism by which anesthesia may initiate or accelerate cognitive impairment and AD. An understanding of the mechanism will help develop strategies for preventing or eliminating this adverse effect of anesthesia.

Keywords: Alzheimer’s disease, anesthesia, phosphorylation, tau

INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disease with cognitive impairment and is the most common form of dementia in adults. It affects approximately 27 million people worldwide and has an expected prevalence of 100 million by 2050 [1]. The warning signs of AD include memory loss, difficulty performing familiar tasks, problems with language, disorientation in time and place, poor or decreased judgment, problems with abstract thinking, changes in mood or behavior, changes in personality, and loss of initiative [2].

It is well known that only a small proportion of AD is attributed to mutations of amyloid-β (Aβ) precursor protein, presenilin-1, or presenilin-2. Most AD cases (> 95%) are sporadic with a late onset. The causes of sporadic AD are multifactorial, with external factors interacting with biological or genetic susceptibility to accelerate the manifestation of the disease. The exact mechanisms of AD are still unclear. However, among the possible etiological factors contributing to AD, anesthesia has been reported to cause cognitive impairment and increase the risk for AD [3,4]. Recent investigations have attempted to address the underlying mechanisms. In this review, we first summarize briefly the possible mechanisms, especially the tau-mediated mechanism, of AD. Then, we review and discuss the role of anesthetics in tau pathology.
POSSIBLE MECHANISMS OF AD

Studies in the last three decades have led to several hypotheses about the mechanism of AD, including the amyloid cascade hypothesis [5], cholinergic hypothesis [6], metabolic hypothesis [7,8], oxidative stress hypothesis [9,10], excitotoxicity dysfunction hypothesis [11], and calcium hypothesis [12]. Among these hypotheses, the amyloid cascade hypothesis has been the leading hypothesis guiding the majority of the modern AD research in the last two decades. According to it, the accumulation of Aβ in the brain is the primary cause driving AD pathogenesis. The rest of the disease process, including formation of neurofibrillary tangles, may result from Aβ overproduction and aggregation [5]. Over the last two decades, this hypothesis has refined according to new discoveries in the field [13]. However, in spite of numerous clinical trials based on the amyloid cascade hypothesis, lack of success in any of these trials has posed a big challenge to this hypothesis. On the other hand, neurofibrillary degeneration, which is characterized by tau abnormalities, causes neuronal death and directly correlates to the dementia symptom [14]. It appears that more than one insult is needed for development of sporadic AD and that different sporadic AD cases might have different etiological factors.

TAU PROTEIN IN AD PATHOGENESIS

Hyperphosphorylated microtubule-associated protein tau is the main constituent of neurofibrillary tangles [15], one of the two hallmark histopathological features of AD [15–18]. The normal biological function of tau is to stimulate microtubule assembly and stabilize microtubules. In the adult human brain, six isoforms of tau are expressed as a result of alternative splicing of tau mRNA from a single gene located on the long arm of chromosome 17. They differ by the presence of three or four tandem repeats of 31 or 32 amino acids in the carboxyl-terminal region in conjunction with 0, 29, or 58 amino acid inserts located in the amino-terminal region [19]. The repeat regions of tau and the sequences flanking the repeats constitute the microtubule-binding domains, while the functions of the amino-terminal regions remain uncertain. Tau mRNA is expressed predominantly in neurons and some oligodendrocytes. Within nerve cells tau is present mainly in axons. However, tau is not an essential protein: inactivation of its gene by homologous recombination leads to no overt phenotype, except for a reduction in the number of microtubules in some small-caliber axons [20]. Tau expression is developmentally regulated in that only the tau isoform with three repeats and no amino-terminal inserts is present in the fetal brain [21]. Yet, there exist true species differences in the expression of tau isoforms in adult brain. All six tau isoforms are expressed in adult human brain, whereas mainly tau isoforms with four repeats are expressed in adult rodent brains.

Tau is a phosphoprotein, and its biological activity to stimulate microtubule assembly is regulated by phosphorylation [22,23]. Though tau is abnormally modified extensively in AD brain [24], hyperphosphorylation is the major and the most significant abnormal modification. Abnormal hyperphosphorylation of tau not only inhibits its biological activity, but also makes it gain a toxic activity to sequester normal microtubule-associated proteins and disrupt microtubules [25,26]. Many studies have demonstrated that abnormal hyperphosphorylation and aggregation of tau are crucial to neurodegeneration in AD [14,27]. The abnormal hyperphosphorylation of tau may also trigger neurodegeneration in the mouse brain, because neurodegeneration has been observed in several tau transgenic mouse models in which tau is hyperphosphorylated [28–31].

The detailed mechanism leading to abnormal hyperphosphorylation of tau in AD and other tauopathies is not clear. Studies have demonstrated that multiple pathways can lead to hyperphosphorylation of tau, including up-regulation of tau kinases [32], down-regulation of tau phosphatases [33–37], and impaired brain glucose metabolism [38–40]. Other factors, such as stress [41–43] and Aβ [44–46], can also contribute to tau hyperphosphorylation by modulation of tau kinases and tau phosphatases. Recent studies have demonstrated that anesthesia also promotes hyperphosphorylation of tau [47–51]. As tau hyperphosphorylation is crucial to neurodegeneration, this could be the underlying mechanism by which these factors contribute to AD.

TAU ABNORMALITIES INDUCED BY ANESTHESIA

Panel and his colleagues had investigated the relationship between tau and anesthesia in great detail. First, they studied the effect of anesthesia on tau phosphorylation and amyloid-β protein precursor (AβPP) metabolism in the mouse brain. They observed that anesthesia, including intraperitoneal administration of
chloral hydrate or sodium pentobarbital and exposure to vapors of isoflurane, induced rapid and massive hyperphosphorylation of tau, rapid and prolonged hypothermia and inhibition of protein phosphatase 2A (PP2A) [48]. However, there were no changes in Aβ metabolism or Aβ accumulation. Re-establishing normothermia during anesthesia completely rescued tau phosphorylation to the normal level. Thus, the authors concluded that changes in tau phosphorylation were not a result of anesthesia per se, but a consequence of anesthesia-induced hypothermia, which led to inhibition of phosphatase activity and subsequent hyperphosphorylation of tau.

Secondly, they exposed a mouse model of tauopathy to anesthesia and monitored the outcome at two time points during anesthesia and 1 week latter to investigate whether anesthesia enhances the long-term risk of developing pathological forms of tau. Their studies showed that exposure to isoflurane at clinically relevant doses led to increased levels of phosphorylated tau and insoluble, aggregated forms of tau, and detachment of tau from microtubules [50]. The levels of phospho-tau distributed in the neuropil and in the cell body were also increased. The increased level of insoluble tau was seen 1 week following anesthesia, suggesting that anesthesia precipitates changes in the brain that provoke the later development of tauopathy. These studies suggest that anesthesia could lead to an acceleration of tau pathology in vivo, which could have significant clinical implications.

Thirdly, they investigated the effects of anesthesia on the microtubule-binding of tau in transgenic mice that express normal human tau isoforms. They found that after anesthesia-induced hypothermia, microtubule-free tau was hyperphosphorylated, which impaired its ability to bind to microtubules and to promote their assembly [49].

By using ether anesthesia, Ikeda et al also reported hyperphosphorylation of tau in the mouse hippocampus [47]. Robust tau phosphorylation was observed immediately and 10 min after ether vapor exposure at Ser198/Ser199 (Tau-1 sites), Ser202/Thr205 and Thr231/Ser235, sites that are typically hyperphosphorylated in AD brain. However, tau phosphorylation levels returned to the baseline by 40 min after ether exposure. They also studied glycogen synthase kinase-3β (GSK-3β), the most likely tau kinase, but found that this kinase was inhibited, rather than activated, as determined by alteration of its Ser9 phosphorylation, when tau was hyperphosphorylated. They concluded that tau phosphorylation, as well as GSK-3β inhibition, is a rapid physiological response to stress induced by anesthesia and other means.

To investigate the site-specific effects of anesthesia on tau phosphorylation, we anesthetized mice with ether or pentobarbital and found that anesthesia for short periods (30 s to 5 min) induces tau phosphorylation at Thr181, Ser199, Thr205, Thr212, Ser262, and Ser404, but not at Ser202, Ser214, Thr217, Thr231, Ser396, or Ser422, to small extents [51]. This appears to result from anesthesia-induced activation of stress-activated protein kinases. Anesthesia for a longer time (1 hour) induces much more dramatic phosphorylation of tau at the above effected sites, and the further phosphorylation may be associated with hypothermia induced by anesthesia. Anesthesia-induced tau phosphorylation appears to be specific because the increased phosphorylation is only seen at half of the tau phosphorylation sites studied and is not observed in global brain proteins. These studies clarified the dynamic changes of tau phosphorylation at various sites and, thus, can serve as a fundamental guide for future studies on tau phosphorylation by using brains of anesthetized experimental animals.

In summary, several independent studies have now confirmed that anesthesia induces hyperphosphorylation of tau, and this effect is independent of the types of anesthesia used. The hyperphosphorylation of tau induced by anesthesia appears to be transient and reversible. However, considering the crucial role of abnormal hyperphosphorylation of tau in AD neurofibrillary degeneration, the anesthesia-induced hyperphosphorylation of tau might still facilitate and/or contribute to cognitive impairment and AD in those individuals already bearing other genetic, metabolic and environmental insults for AD.

**HOW ANESTHESIA INDUCES TAU HYPERPHOSPHORYLATION**

The mechanism by which anesthesia induces tau abnormalities is not well understood. By using ether as an anesthetic, Ikeda and colleagues concluded that anesthesia induces transient tau hyperphosphorylation as a result of ether-induced stress, because other stresses, such as starvation and cold water swimming, cause tau phosphorylation similarly [47]. In line with this conclusion, inhalation of ether vapor elicits rapid release of adrenocorticotropic hormone into the circulation, followed by corticosterone release from the adrenal cortex [52]. Ether-induced sharp rise of plasma corticos-
terone concentration attains a peak in about 30 min and reverts to basal levels by about 2 h after ether exposure in rodents [53]. Ether anesthesia is thus considered to elicit a typical stress response, and has been employed in numerous neuroendocrinological studies of stress [54–56]. Tau phosphorylation is a rapid physiological process integral to neural stress response system [47]. By using ether or pentobarbital, we observed that anesthesia induces activation of stress-related protein kinases JNK and MAP [51], which also support the notion that anesthesia causes tau hyperphosphorylation via a stress-associated mechanism. On the other hand, the inhibitory phosphorylation of Ser9 of GSK-3β, which is the major tau kinase, is increased, suggesting inhibition, rather than activation, of the kinase under anesthesia [47,51]. The fact of increased tau phosphorylation under anesthesia indicates that the activation of JNK and MAP may overcome the effect of GSK-3/β inhibition, leading to a net increase in tau phosphorylation. In a recent study, Lim et al. reported that, while Ser9 of GSK-3/β is phosphorylated, GSK-3/β inhibitors reduce okadaic acid–induced hyperphosphorylation of tau and of several other proteins in neuronal cultures, suggesting that GSK-3/β might still be active toward these proteins when its Ser9 is phosphorylated [57]. It is therefore also possible that GSK-3/β activity toward tau might not be much decreased even though its Ser9 is phosphorylated after anesthesia.

By using several anesthetics, Planel and coworkers [48] observed that tau hyperphosphorylation did not result from anesthesia per se, but from anesthesia-induced hypothermia, because reestablishing normothermia during anesthesia completely rescued tau phosphorylation to normal levels. Further studies pointed to protein phosphatase 2A (PP2A), as its activity is downregulated during hypothermia [48]. PP2A is the major tau phosphatase in the brain [58–60]. In AD, decreased PP2A expression [61] along with upregulation of its inhibitors [62] result in overall inhibition of its activity [33,37], contributing to abnormal hyperphosphorylation of tau [63].

However, when mice were anesthetized for a short period of time (30 s with ether or 5 min with pentobarbital), we found a significant increase in tau phosphorylation at several sites, but not hypothermia [51]. Brain stress-activated protein kinases are also activated under this condition. These results suggest that the shortterm anesthesia induces tau phosphorylation through a hypothermia-independent mechanism, which appears to involve stress-activated protein kinases. Hypothermia induced by longer period of anesthesia may exacerbate hyperphosphorylation of tau.

OTHER MECHANISMS BY WHICH ANESTHESIA PROMOTES COGNITIVE IMPAIRMENT AND AD

In addition to promoting tau hyperphosphorylation, anesthesia may also accelerate or trigger cognitive impairment and AD through other mechanisms [64,65]. These mechanisms include promoting Aβ production and aggregation [66–68], dysregulation of cholinergic system [69], dysregulation of neuronal calcium homeostasis [70–72], neuronal apoptosis [73–75], and neurodegeneration [76].

It is worth to note that Aβ production and aggregation are believed to be central to the pathogenesis if AD [5,13]. Promoting Aβ production and aggregation may be another important mechanism that links between anesthesia and AD [77]. In 2004, Eckenhoff and colleagues reported that the inhaled anesthetics isoflurane and halothane cause Aβ to stick together in cell cultures [66]. They further demonstrated that transgenic mice of brain amyloidosis develop more amyloid plaques after being exposed to these two anesthetics [67]. Another group also showed that isoflurane triggers Aβ accumulation and cell death in human cell cultures [68]. By using 2D nuclear magnetic resonance (NMR), Mandel et al. analyzed the interactions between anesthetics and Aβ at the molecular level and found that isoflurane and desflurane at clinically relevant concentrations induce Aβ oligomerization by inducing chemical shift changes of the critical amino acid residues (G29, A30, and I31) of Aβ [78,79]. They further demonstrated that smaller sized, but not large sized, anesthetics promote aggregation of Aβ [80,81], suggesting that different anesthetics may play different roles in promoting cognitive impairment and AD.

CONCLUSIONS

Every year, approximately 100 million people undergo surgery worldwide. General anesthetics have provided immeasurable health and societal benefits for almost two centuries. Although the safety of anesthesia has now been dramatically improved, there are still some adverse effects of anesthesia. A possible adverse effect of anesthesia to induce or accelerate cognitive impairment and AD has been noticed only recently. Several clinical studies suggest that exposure to anesthetics may increase the risk of AD [64,82], although inconsistent results were also reported [83–85]. Much less is known about the underlying mechanisms. Re-
cent investigation in animal models, as reviewed here, suggest that anesthesia-induced hyperphosphorylation of tau may be one of the major contributing factors by which anesthesia accelerates cognitive impairment and AD.

Sporadic AD is multifactorial and heterogeneous. Though it ends up with the same main pathologies and similar clinical symptoms, sporadic AD is likely the result of multiple causing and accelerating factors. Anesthesia appears to be one of these multi-factors, and it could accelerate the development of AD via different pathways. Further understanding of the molecular mechanism by which anesthesia initiates or accelerates cognitive impairment and AD will help develop strategies for preventing or eliminating this adverse effect of anesthesia.

ACKNOWLEDGMENTS

This work was supported in part by funds from the New York State Office of Mental Retardation and Developmental Disabilities, NIH grants (AG027429, TW008123), a NSFC grant (30901386), and a grant from Wuhan Science and Technology Bureau, China (200960323132). Authors’ disclosures available online (http://www.j-alz.com/disclosures/view.php?id=575).

REFERENCES

Anesthetics and Tau Protein: Animal Model Studies


Anesthesia for the Patient with Dementia

Kamilia S. Funder, Jacob Steinmetz and Lars S. Rasmussen

Department of Anesthesia, Centre of Head and Orthopedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Accepted 25 June 2010

Abstract. With a growing aging population, more patients suffering from dementia are expected to undergo surgery, thus being exposed to either general or regional anesthesia. This calls for specific attention ranging from the legal aspects of obtaining informed consent in demented patients to deciding on the use of premedication, choice of anesthetics, and management of postoperative pain. This review reflects on both general considerations concerning geriatric patients but also on the specific features of perioperatively used drugs and anesthetics that might have an impact on patients with Alzheimer's disease (AD).

Keywords: Aging, Alzheimer's disease, anesthesia, consent, postoperative pain

INTRODUCTION

The lifespan is increasing because of generally improved living conditions and the fraction of elderly people in the population is growing exponentially. Age-related changes in the brain cause alterations in biochemical processes and structural arrangement, which eventually can result in dementia. Alzheimer’s disease (AD) accounts for more than 50% of all dementia and is estimated to affect over 100 million people by 2050 [1]. With the increasing elderly population, the proportion of patients attending healthcare services is expected to rise as well. Surgery will consequently be needed in a very high number of elderly persons due to cancer, chronic disease such as arthritis, or acute conditions like fractures and gastrointestinal diseases. Regional or general anesthesia calls for special considerations, as elderly and demented patients are particularly vulnerable.

CONSENT

As with any patient about to undergo surgery, it is imperative that all necessary information is obtained and that the ethical and legal issues of informed consent are taken into account. Preoperative assessment can be difficult because of inability to provide information about chronic disease and functional capacity. Low exercise tolerance and inability to cough are important predictors of the risk of postoperative cardiac and pulmonary complications.

Patients’ rights and choices regarding medical treatment require careful attention and all relevant information must be provided for the patient to allow consent. This is problematic in demented individuals and consequently, much patience is required. The patient must be able to express personal preferences and think rationally regarding medical alternatives when evaluating the risks, benefits and implications of surgery. The anesthesiologist should answer all questions and explain the procedure repeatedly if necessary [2]. To facilitate the patient’s perception, correction of presumed sensory deficits should be made, including eyeglasses, hearing aids, and adequate lightning in a room with minimal distracting stimuli like noise [3]. When a patient is incapable of making fully informed decisions, involvement of a family member, or a caregiver who is familiar with the patient, should be sought. Research on capacity for decision-making has shown that patients with moderate AD have impaired consent ability and difficulties in understanding medical treatment [4, 5]. In addition, severely demented patients may refuse treatment and other perioperative interventions without...
being fully aware of what they are actually declining. The anesthesiologist is therefore put in the dilemma of deciding, whether or not to proceed with the procedure, as some national legislation may prohibit such practice if the patient rejects repeatedly by saying no or actively expressing a lack of consent non-verbally.

PREMEDICATION AND CONCOMITANT MEDICATION

New surroundings are often associated with agitation, aggression, and anxiety in demented patients [6]. This behavior is inappropriate in the perioperative setting and precautionary measures are therefore needed. Anxiolytics may be used to calm demented patients before surgery, but anesthesiologists are often reluctant to prescribe premedication, as elderly patients tend to exhibit either an enhanced or altered response to CNS-active drugs. Consequently, the duration of action is often prolonged [7]. Studies of elderly people have shown an excess intake of psychotropic drugs such as sedatives, antidepressants, and antipsychotics [8, 9]. Therefore the physician should acquire a complete list of prescribed medication in addition to over-the-counter products and herbal medicine during the preanesthetic consultation to avoid unwarranted polypharmacy and possible drug interactions. Neuroleptics for instance, can have profound extra pyramidal side effects and induce parkinsonian symptoms in over 30% of patients [10, 11]. The incidence increases with advancing age and severity of dementia. If treatment with antipsychotic drugs is needed preoperatively, risperidone and clozapine are generally better tolerated compared to more traditional drugs such as haloperidol [12].

Ongoing medication should be continued perioperatively but there are important issues associated with antithrombotics. These drugs are commonly used in elderly patients because of atherosclerosis, atrial fibrillation, or a history of venous thromboembolism and typically Vitamin K Antagonists (VKA), Acetyl Salicylic Acid (ASA), and other platelet inhibitors are given. These drugs may cause an increased blood loss during surgery but they may also increase the risk of spinal and epidural hematoma after neuraxial block, which may therefore be contraindicated in case of impaired hemostasis. According to recent guidelines, such blocks are probably safe if VKA are discontinued for 1–5 days, depending on the International Normalized Ratio (INR) value, which must be determined before performing the neuroaxial block. INR decreases much slower in patients receiving very low doses of VKA. It is also recommended that ASA is stopped for 1–3 days before surgery and Non-Steroidal Anti-Inflammatory Drugs (NSAID) 12 h prior to surgery [13]. The available evidence, however, is very limited, and even less is known for antithrombotic drugs like clopidogrel and prasugrel. The risk-benefit ratio must be assessed on an individual basis with consideration of the risk of bleeding against the risk of thromboembolic events such as myocardial infarction or stroke. Consultation with a cardiologist or neurologist is strongly recommended before pausing antithrombotic drugs, especially if the patient has an artificial heart valve or a coronary artery stent.

PHARMACOLOGICAL CONSIDERATIONS

Most demented patients are elderly and many age-related changes occur in body composition and physiology, resulting in altered pharmacokinetics and pharmacodynamics. A smaller initial volume of distribution necessitates smaller doses for some induction agents, while a relative increase in body fat causes a greater volume for distribution of lipophilic drugs, such as diazepam and thiopental thereby increasing the half-life even if clearance is unchanged. A lower albumin concentration may allow more free drugs to reach target organs, making the patient more drug-sensitive. The age-associated decline in renal function will prolong recovery for water-soluble drugs.

Liver function is generally well preserved, but a reduction in diazepam clearance can potentially cause iatrogenic pseudo-dementia with a disturbance in attention, and flurazepam accumulation can produce a prolonged sleep [7]. A low dose of a short-acting benzodiazepine, such as triazolam, can be used preoperatively to avoid an excessive response [12]. Elderly are much more sensitive to depressants of the CNS and this pharmacodynamic change is partly explained by an altered receptor function. This means that the same effect is obtained at lower blood concentrations of for instance propofol and sevoflurane [14].

GENERAL ANESTHESIA

As neurodegenerative diseases such as AD cause a dysfunction of the central cholinergic system, it also impinges on the action of general anesthetics. The
cholinergic system is an important modulator of neurotransmitters in the brain, which controls all higher function such as general awareness, memory, and information processing [15]. Because general anesthetics modulate acetylcholine (Ach) release, they may contribute to the pathogenesis of neurodegenerative disorders and postoperative cognitive decline [16,17]. Anesthesia can possibly induce phosphorylation of the tau protein, and when these microtubules stabilizing proteins are defective they can contribute to the pathogenesis of AD [18]. In vitro studies of volatile, inhalational anesthetics like isoflurane and halothane have shown an interaction with amyloid-β (Aβ), being proteins forming small oligomers that can produce neuronal and synaptic damage and thereby worsen amyloidopathies like AD [19–24]. Inhaled anesthetics act on many receptors and ion channels, and isoflurane may have neurotoxic effects on the brain as it leads to apoptosis although the mechanism is not clear [25]. Desflurane and sevoflurane are less potent than isoflurane in this regard. It applies for most inhalational anesthetics that their possible toxic effects depend upon duration and concentration used in the experimental setting.

Intravenous induction agents like propofol and thiopental are less likely to bind to nicotinic and muscarinic receptors [23,26] thus considered relatively safe in respect to AD progression [12]. Opioids such as morphine and fentanyl may also block Ach receptors, while remifentanil does not interfere with Ach release [27].

**INFORMATION**

An increased sensitivity and altered pharmacokinetics with slower distribution are the main reasons for the recommended 50% dose reduction of propofol and thiopental. Induction agents should be given slowly because of a delay in onset to avoid excessive hemodynamic depression and prolonged recovery [28]. Variability is, however, very large, and the anesthesiologist must be prepared to give additional doses based on the patient’s response. Profound hemodynamic depression may occur after induction in the elderly as a result of vasodilatation, myocardial depression, and positive pressure ventilation. The age-related reduction in left ventricular compliance causes diastolic heart failure and less ability to compensate for changes in ventricular filling. Cardiac failure may, however, not be recognized preoperatively due to a lack of information about level of functioning and exercise tolerance. Vasopressor agents should therefore be readily available.

**AIRWAY MANAGEMENT**

A history of previous difficult intubation is a very important predictor of difficult airway management and one study found it to be an independent risk factor with an odds ratio of 9.46 [29]. Demented patients may be unable to provide information about previous difficulties, thus compromising safety in airway management. In addition, anatomical characteristics of elderly patients such as limited head and neck movement may challenge visualization of the vocal cords during laryngoscopy and impede tracheal intubation. A plan for an alternative airway management is therefore imperative, such as a technique based on fiber optics.

**NEUROMUSCULAR BLOCK**

Neuromuscular blocking agents (NMBAs) are used to provide optimal tracheal intubation conditions [28]. However, several reports have documented significant interactions between muscle relaxants and specific AD medication. Pharmacological treatment of AD is targeted on altering the cognitive impairment with acetylcholinesterase inhibitors like donepezil and rivastigmine [12]. This may have important consequences for NMBAs, which act on cholinergic receptors. In one case, donepezil triggered a prolonged paralysis of 50 min after 1 mg/kg intravenous (IV) dose of suxamethonium [30].

Succinylcholine should be given in the same dose as in young adults (1 mg/kg) but the dosage of the nondepolarizing NMBAs should be guided by objective, quantitative monitoring of neuromuscular transmission with a nerve stimulator. The duration of action is characterized by a huge variation in the elderly, especially for rocuronium [31] and consequently there is a risk of residual curarization. Reversal of neuromuscular block caused by rocuronium or vecuronium may be obtained by a new drug, sugammadex, a chelating agent [32,33].

**PERIOPERATIVE MAINTENANCE OF ANESTHESIA**

The minimum alveolar concentration (MAC), a well established measure of volatile anesthetics potency, declines progressively with age and is 30–50% lower in patients above 80 years of age [34]. End-tidal concentration can be used to maintain an adequate dose of anesthetic, but the drug administration can also be
POSTOPERATIVE PAIN RELIEF

Postoperative pain in demented, geriatric patients pose therapeutic challenges as cognitive impairment may mask the presence of pain, which is related to a higher incidence of depression, difficult behaviors, and increased care demands [44]. Effective pain management requires accurate assessment and appropriate interventions. Studies suggest that there are age-related differences in the perception of, and response to pain, thereby making elderly people more sensitive to severe pain [45]. Facial grimacing and restless body movements are common indicators used to assess pain, but both verbal and facial expressions may be reduced in demented patients [46]. Nevertheless, one study examined the association between self-reported pain and cognitive impairment among older institutionalized residents and found that self-reports were no less valid in the demented residents than that of the non-demented residents [47]. Therefore self-reports should be acted on in demented patients with intact communication skills, while behavioral tools might be better in patients who are unable to report verbally. Optimizing postoperative pain management is essential for decreasing length of hospital stay and criteria for selecting analgesics should include side-effect profile, onset of action and drug interaction.

CONCLUSION

Demented patients can be very challenging in the operative setting and many psychological as well as physiological aspects need to be considered. These patients are particularly sensitive to changes in their surroundings, and may be unable to articulate specific requests and provide sufficient information, and therefore assistance from a caregiver or family member is warranted. Furthermore, because of altered pharmacokinetics and pharmacodynamics, the administration of anesthetics and pain relieving treatments should be carefully modified to the individual – usually in lower doses compared to young adults. These initiatives should promote an uneventful recovery after surgery and a quick discharge from hospital.

DISCLOSURE STATEMENT

REFERENCES


Numerous anecdotal reports suggest that elderly subjects undergoing surgical procedures may experience long-term cognitive impairment with clinical features similar to those in patients with dementia, raising concerns that surgery and anesthesia could increase the risk of Alzheimer’s disease (AD) or accelerate the progression of the condition [1]. The population of surgical patients is aging and we are thus presently confronted by both increases in the number of persons at risk of developing AD and the number of elderly persons undergoing surgical procedures. Any possible association between the two therefore merits careful consideration.

Central nervous system complications have long been associated with cardiac surgery, where significant cognitive deficits have been observed in a high proportion of patients across a wide range of intellectual abilities weeks to months after the procedure. While the area of cardiac surgery has provided the first assessments of cognitive functioning, it has been difficult to attribute observed changes specifically to anesthesia given the number of likely confounding factors, notably extracorporeal circulation, vascular disease, pain, and stress. Moreover, while preventive pharmacological interventions aiming at cerebral protection have been repeatedly attempted in relation to cardiac surgery, it has been difficult to decrease the incidence of cognitive decline [2].

New interest in this area has been generated following observations of cognitive decline after non-cardiac surgery, in which the potential role of anesthetics has been highlighted [3,4].

In the last few decades, anesthesia management has clearly shown major advances in technology and drug development, permitting improvement of surgical techniques and the possibility of performing complex, prolonged surgical operations even in the very elderly and the critically ill. As a consequence, the evolution of anesthesia procedures has been considered to be amongst the greatest achievements in medicine.

In the absence of either a single coherent etiological model to explain the cause of AD or an effective treatment, recent research has focused on reduction of disease incidence through identification of risk factors. In this context the question of the association between AD and anesthesia has again been raised [5,6]. Accumulating clinical and epidemiological evidence has pointed to the potential adverse consequences of general anesthesia and a possible link with anesthesia-induced changes in molecules known to be involved in the pathogenesis of AD [7].

With regard to epidemiological evidence, the EURODEM Risk Factors Research Group performed a re-analysis of eight case-control studies exploring several
medical conditions that had previously been suggested as possible risk factors for AD. Among these, general anesthesia was not associated with AD [8], however, there was considerable variation in data collection methodology and type and duration of anesthesia was not taken into account.

Two years later, the California Alzheimer Disease Diagnostic and Treatment Center Program collected data on a large database of subjects with dementia (502 subjects with vascular dementia and 810 subjects with probable AD) examining differences in risk factors. They discovered that vascular dementia subjects were more likely to have a history of general anesthesia and concluded that general anesthesia is a risk factor for vascular dementia [9]. In 1994, the Bohnen group evaluated prior exposure to general anesthesia as a potential risk factor for AD. No significant difference in mean cumulative exposure (in minutes) to general anesthesia or exposure to six or more episodes of general anesthesia were significantly associated with AD [10]. Similar negative findings have been reported by other groups using neuropsychological testing within both cross-sectional and longitudinal study designs, however, this research has been limited by low statistical power, variability in the quality of cognitive testing, and inadequate data relating to type of surgery, the time interval between surgery and follow-up, and age at exposure to anesthesia [11–13].

Additionally, epidemiological studies have not till date been able to adequately separate out the effects of anesthetics from underlying disease and associated activation of inflammation and other responses [14, 15]. Several research groups are now investigating the neurotoxic effect of anesthetic drugs and combinations of drugs. Experimental findings suggest that certain anesthetic molecules can, in laboratory models, induce changes in protein expression in the brain of animals [16,17]. This research has led to many important findings notably that smaller sized, inhaled anesthetics oligomerize Aβ peptide [18–21] and increase other proteins which have been shown to play a role in AD [22,23]. AD is a devastating disease. After cancer, Americans fear AD most, but among adults aged 55 and older, the fear of getting AD is greater than the fear of cancer [24]. It is important, however, that such fears do not lead to an irrational rejection of surgery in later life. Surgery and anesthesia have done much to improve both the length and quality of life, so that the question of the relationship of dementia to anesthesia requires careful consideration and future recommendations backed by evidence-based argument. The current supplemental issue of the Journal of Alzheimer’s Disease thus hopes to contribute to this ongoing constructive debate.

REFERENCES


