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REVIEW ARTICLE

# Alzheimer's disease and anaesthesia: implications for the central cholinergic system

**V. Fodale*, D. Quattrone, C. Trecroci, V. Caminiti and L. B. Santamaria**

*Department of Neurosciences, Psychiatric and Anaesthesiological Sciences, University of Messina, School of Medicine, Policlinico Universitario 'G Martino', via C.Valeria, 98125 Messina, Italy*

**Corresponding author: Department of Neurosciences, Psychiatric and Anaesthesiological Sciences, University of Messina, Policlinico Universitario, via C. Valeria, 98125 Messina, Italy. E-mail: vfodale@unime.it*

Alzheimer's disease (AD) is associated with a loss of cholinergic neurons resulting in profound memory disturbances and irreversible impairment of cognitive function. The central cholinergic system is involved in the action of general anaesthetic agents. Anaesthetic modulation of cholinergic transmission has profound effects on brain function *via* a cascade of synaptic and postsynaptic events by binding both nicotinic and muscarinic receptors. During general anaesthesia, decrease in acetylcholine release and depression of cholinergic transmission facilitates the desirable effects of general anaesthetics, such as loss of consciousness, pain, voluntary movements and memory. From this point of view, patients with AD, characterized by a compromised neuronal transmission, represent particular cases in which the choice of anaesthesia drugs may have a negative effect on the postoperative outcome. A future challenge may be the identification of brain targets of general anaesthetics which do not expose patients to postoperative cognitive dysfunction, nor interfere with prognosis of brain degenerative disease.

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## Alzheimer's disease

Alzheimer's disease (AD) is a common form of dementia, characterized by the degeneration of basal forebrain cholinergic neurons innervating the cortex amygdale and hippocampus, with difficulty in maintaining and sustaining attention, and with profound cognitive impairment, such as loss of memory and learning ability.[9] Four different forms of AD are reported: with delirium, with delusions, with depressed mood and uncomplicated, each indicating the predominant feature of clinical presentation. The course of the disease is fluctuant, and cognitive impairment, personality change, psychotic symptoms, incontinence, gait and motor disturbance, seizures and myoclonus can occur.[14] These cognitive deficits cause significant impairment in social and occupational function. AD also increases mortality of the population affected, by up to 40%, so it is considered a leading cause of death '*per se*' and a predictor of mortality.[25]

Increasing longevity will inevitably lead to an increase in the number of patients with AD, the prevalence of which increases markedly after the age of 65.[23] In the Italian population, the incidence of dementia is increasing in line with trends in other western countries: more than 400 000 new cases of dementia are expected per year and most of them will be represented by AD cases.[47 51] Given the substantial number of people affected by this disease, it is likely that anaesthetists will encounter many patients with AD.[19 47]

General anaesthetic agents, and several drugs administered during anaesthesia, interact with the central cholinergic system, and degenerative diseases of the brain are associated with deficits in the cholinergic system.[20 21 44] This review describes the implications of anaesthesia on the central cholinergic system in patients with AD.

## AD and central cholinergic system

All regions of the cerebral cortex receive intense cholinergic innervation. In AD, there is reduced activity of cholinergic projections to the hippocampus and cortex, while the visual hallucinations experienced by subjects with dementia with Lewy bodies (DLB) are associated with reductions in neocortical acetylcholine (ACh)-related activity.[44]

High cognitive functions such as memory and learning are strictly related to molecular events which are

consequences of the expression of early gene products.[45] These include the activation of cholinergic receptors, long-term potentiation (LTP) and long-term depression, synaptic plasticity, and maintenance and differentiation of neurons.

The cholinergic hypothesis of memory dysfunction in the elderly was proposed by Bartus and colleagues[3] in 1982 and was based on two central notions. The first is that forebrain cholinergic systems sustain a wide variety of cognitive processes, particularly those involved in learning and memory, and second is that the age-related cognitive deficits are, at least in part, caused by a decline in the functional integrity of these forebrain cholinergic systems. From this point of view, the cholinergic hypothesis should be taken into consideration both in the context of normal ageing and as a key element of pathogenesis of degenerative disease (e.g. AD) in which loss of cortical cholinergic neurons is considered marker of disease.

A correlation between anatomical (degeneration of the forebrain cholinergic systems) and biochemical changes and mental test scores in AD patients led Coyle and colleagues[13] to extend the cholinergic hypothesis to AD. However, many other neuroanatomical and neurochemical systems also degenerate in AD, so it is extremely difficult to establish a causal relationship specifically with cholinergic decline.

The involvement of the central cholinergic system in cognitive functions is amply documented in animal and human research. For example, acute or chronic treatment with nicotine or nicotinic agonists significantly improves memory performance of rats.[35 36] Conversely, nicotinic antagonists can impair memory and learning acutely. Epidemiological studies on patients who smoke have demonstrated the benefits of nicotine on cognitive processes, on improvement in attention capacity, and on the acquisition and retention of verbal and non-verbal information.[31]

Several studies have accounted for the close relationship between AD and the central cholinergic system by consistent deficits in cholinergic neurotransmission and impaired cognitive function in AD patients. Cognitive impairments are a consequence both of a marked reduction (over and above the normal age-related decline) in cortical cholinergic transmission[1] and of a perfusion deficit of cerebral blood flow (CBF).[46] CBF is modulated by nicotinic acetylcholine receptors (nAChRs) neurotransmission,[9] and a decrease causes white matter lesions (WML), which are frequent in both Alzheimer's and ischemic disease.[40] WML are characterized by reactive astrogliosis and activation of microglia cells, which are a key source of cytokines, proteases and nitrogen intermediates.[39]

The degeneration of cholinergic neurons represents the earlier, pathological events in AD, and, above all, involves the structures of the basal forebrain cholinergic system (BFCS) (Fig. 1). The BFCS is composed of nucleus basalis of Meynert (NBM), the horizontal and vertical diagonal bands of Broca (HDBB and VDBB) and the medial septal

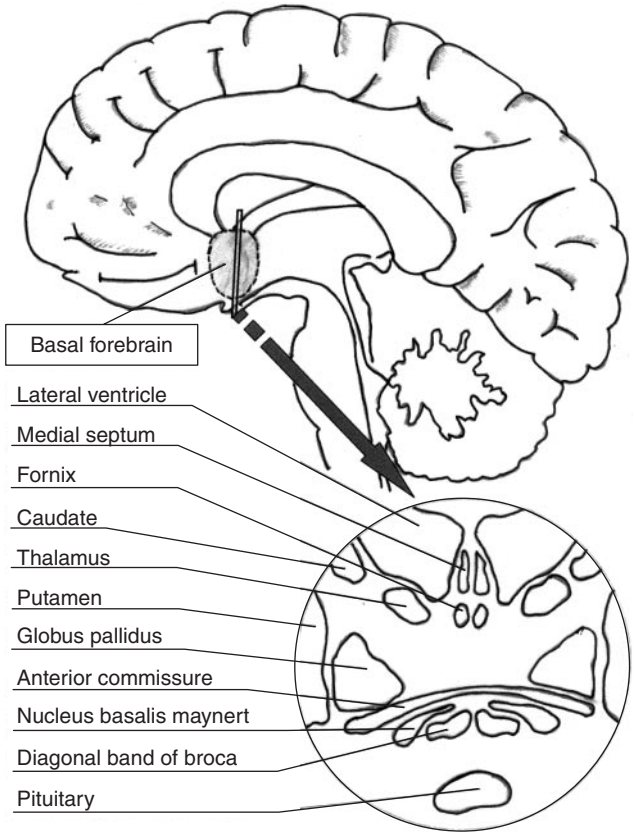


**Fig 1** Structures of the basal forebrain cholinergic system.

(MS) nucleus. This system represents the cholinergic innervations of limbic and cortical brain layers. Neurons of the MS innervate the hippocampus, and the neurons of VDBB and HDBB are directed to the anterior cingulated cortex and olfactory bulb; the VDBB project to the hippocampus as well. The NBM sends projections to amygdale, to the rest of the cortical mantle, to the frontoparietal operculum and to medial cortical regions. The frontal, parietal and temporal cortex receive cholinergic innervations from intermediate and posterior divisions on NBM.[2]

Biochemical studies reveal that BFCS impairments are related to several structural and functional changes. NBM neurons present low activity and low mRNA expression of choline acetyl transferase (ChAT) enzyme.[6] However, in other cortical areas ChAT is significantly and variably reduced, especially in the later stages of the disease, indicating the loss of cholinergic neurons. In BFCS neurons, functional changes (decrease in ChAT activity and ACh release) are also related to soma size and to the level of nerve growth factor. As a result, cholinergic dysfunction is responsible for an impaired trophic support.[2] In patients with AD, the brain demonstrates the following features: extracellular beta-amyloid (beta-A) peptide-containing plaques, intracellular neurofibrillary tangles of abnormally phosphorylated tau, astrocytic gliosis, reactive microglia and inflammation, and neuronal and synaptic losses.[34 52 53]

Most of the lesions which are characteristic of AD can be reproduced in animal disease models[2 11 30] but the interrelationship of these pathological changes is poorly understood.

Beta-A derives from an amyloid precursor protein (APP) by proteolytic cleavage and exists in two forms, 40-residue beta-$A_{(1–40)}$ and 42-residue beta-$A_{(1–42)}$. Both may bind nAChRs and cause neuronal damage by different mechanisms which have not as yet been completely defined. Dineley and colleagues[15] have proposed chronic stimulation of $\alpha7$ and $\alpha4\beta2$ receptors by beta-$A_{(1–42)}$ as the central event. The mechanism involves $Ca^{2+}$ release, the chronic activation of the cellular cascade of extracellular signal-regulated kinase (ERK2)[15] and the derangement of ERK2–MAPK signalling,[5] and may explain, in part, the memory impairment observed in AD. Oxidative stress or destabilization of $Ca^{2+}$ activates the nuclear factor NF-$\kappa$B and leads to a rapid and sustained activation of different protein kinases and c-Fos transcription factors in the hippocampus cell line.[27]

Beta-A negatively regulates the synthesis and release of acetylcholine, inhibiting pyruvate deydrogenase that generates Acetyl-CoA from pyruvate, the mechanism of synthesis and release of ACh, and glucose uptake. It interferes with both cholinergic neurotransmission and the neuromodulatory effect of ACh, probably through an ion-mediated mechanism.[2] An increase in the soluble form of beta-A is considered a predictor of synaptic degeneration in AD patients, while insoluble beta-A is related to cognitive impairment.[2] Having limited access to choline, the BFCS neurons are more vulnerable and, deprived of this component for ACh biosynthesis, usually act as a sort of irreversible autocannibalism. The trophic properties of ACh are widely recognized as it is essential to neuronal morphology and survival promotion in response to neurotoxic changes.[33] Soluble beta-A impairs M1ACh receptor signalling, $Ca^{2+}$ release, inositol generation and second messenger activation. Beta-A probably interacts with G-protein coupled to receptor, but the unfavourable effect seems limited by administration of antioxidants such as vitamin E, and it interferes significantly with processes of LTP, learning, memory and all cognitive functions.

## Cholinergic pathway: receptor, topography, functions

Cholinergic receptors can be divided into nicotinic (nAChRs) and muscarinic (mAChRs) receptors, based on the agonist activities of the natural alkaloids, nicotine and muscarine (Table 1).

nAChRs are a family of the ligand-gated cation channels, which also includes GABA-A, 5-HT3 and glycine receptors. They are characterized by a pentameric structure and, in vertebrates, 11 genes encode for neuronal nAChRs subunits, suggesting a large number of possible different nAChRs. Eight of these genes encode for alpha subunits ($\alpha2–\alpha9$); three non-alpha genes encode for beta units ($\beta2–\beta4$).[29] Alpha and beta units, arranged around a pseudo-axis of symmetry, are assembled to compound a transmembrane glycoproteic heterologous pentamer composed generally of two alpha and three beta subunits. The receptors, after the binding of an agonist in the specific site, change their conformation and open the inner pore, permitting cations to flow.[29]

nAChRs are expressed in both the peripheral and central nervous system. The neuromuscular junction is the main peripherical location, but nAChRs are located on ganglionic cells and on non-neuronal cells. The best characterized subtypes in the human brain are both the $\alpha4\beta2$ and $\alpha7$ receptor subtypes.[12] Electrophysiological studies on interneurons have documented that $\alpha7$ receptor subtypes are presynaptic, while $\alpha4\beta2$ are both presynaptic and postsynaptic. Numerous studies have revealed a wide, but non-uniform, distribution of nAChRs in the brain. For example, $\alpha7$ are located across all layers in the cingulated, temporal and frontal cortex, hippocampus, substantia nigra, while $\alpha4\beta2$ are located in the deeper layers of the cerebral cortex. Other locations include the thalamus, putamen and cerebellum, with a wide variation in density relative to the physiological age-related brain decline.[44]

Thus, location, functions and interactions indicate the importance of central cholinergic neurotransmission in fast synaptic transmission, axo-axonic transmission, modulation of membrane potentials, and regulation of release of both excitatory and inhibitory transmitters such as ACh, dopamine, GABA, glutamate, norepinephrine and serotonin.[41] mAChRs are a family of the ligand-gated $K^+$ channels with a metabotropic function. They are classified into five different subtypes ($M_1–M_5$), according to their primary structure and property of activating/inhibiting cation transmembrane current.[45]

$M_1$, $M_3$ and $M_5$ subtypes are postsynaptic receptors and are coupled with a G-protein alpha subunit (11/q) that generates diacylglycerol and inositol 1,4,5-triphosphate (IP3) (via adenylate cyclase and phospholipase C). Second messengers increase $Ca^{2+}$ concentrations and activate protein kinase C, the mitogen-activated protein kinases (MAPKs) pathway and the phospholipase A2 and D.[45] Conversely, $M_2$ and $M_4$ ACh receptors are presynaptic and function as autoreceptors both in cholinergic and in dopaminergic neurons. They are coupled with the G-protein alpha (i/o) that inhibits the adenylate cyclase and stimulates the phospholipase C and the inward rectifying K current.

Receptor binding by agonists causes the activation of several cytoplasmatic and nuclear factors, such as specific tyrosine kinases, focal adhesion kinase, MAPK, extra cellular signal-regulated kinases (ERKs) and c-Jun N-terminal kinases (JNKs, or stress-activated protein kinases).[45]

High cognitive functions such as memory and learning, neuronal rearrangement and evolution are strictly related to LTP and long-term depression, synaptic plasticity, maintenance and differentiation of neurons. All these functions

**Table 1** Description of types and functions of nicotinic (nAChRs) and muscarinic (mAChRs) acetylcholine receptors[17 45 60]

| Receptor subtype | Location | Action | Function |
|---|---|---|---|
| nAChRs $(\alpha4)_2,(\beta2)_2$ | Hippocampal fields CA1 and CA3, dentate gyrus, hypothalamus, inferior colliculus, periaqueductal gray, interpeduncular nucleus, lateral part, red nucleus | Activation cation-selective channel activity. Synaptic transmission, paracrine transmission | Memory and learning |
| nAChRs $(\alpha4)_3,(\beta2)_2$ | Cortex, hippocampal neurons, thalamus and the habenula, interpeduncular system | Activation cation-selective channel activity. Synaptic transmission, paracrine transmission | Memory and learning, maintenance and differentiation of neurons |
| nAChRs $(\alpha3)_3,(\beta2)_2$ | Homogeneously in the ventral portion of the medial habenula, Hippocampus | Activation cation-selective channel activity. Synaptic transmission, paracrine transmission | Memory and learning |
| nAChRs $(\alpha6)_3,(\beta3)_2$ | Ventral mesencephalon and locus coeruleus, catecholaminergic nuclei | Activation cation-selective channel activity. Synaptic transmission, paracrine transmission | Memory and learning, nicotine crowing |
| nAChRs $(\alpha7)_5$ | Parietal cortex, frontal cortex, hippocampus, temporal cortex, limbic area and cerebellum | Activation cation-selective channel activity. Synaptic transmission, paracrine transmission | Memory and learning |
| nAChRs $(\alpha3)_2,(\beta4)_3$ | Medial habenula; dorso-caudal medulla oblongata, and pineal gland | Activation cation-selective channel activity. Synaptic transmission | Memory and learning, nicotine crowing |
| nAChRs $(\alpha3)_2,(\beta4)_2,\alpha5$ | Medial habenula, dorsal medulla, interpeduncular nucleus | Activation cation-selective channel activity. Synaptic transmission | Memory and learning, nicotine crowing |
| mAChRs $M_1$ | Cortex, hippocampus, thalamus, forebrain, caudal regions of the brain | $G_{alphaq/11}$, Phospholipase Cbeta, diacylglycerol and inositol 1,4,5-trisphosphate (IP3) | Memory and learning, long-term potentiation (LTP) and long-term depression, synaptic plasticity, maintenance and differentiation of neurons that are consequences of expression of early gene products |
| mAChRs $M_2$ | Presynaptic side, thalamus, cerebellum, corpus striatum, rostral regions of the brain, medulla pons. | $G_{alphai/o}$ Adenylyl cyclase inhibition, inward rectifying K current | Synapses modulation |
| mAChRs $M_3$ | Telencephalic structures, corpus striatum | $G_{alphaq/11}$ Phospholipase Cbeta, diacylglycerol and inositol 1,4,5-trisphosphate (IP3) | Memory and learning, LTP and long-term depression, synaptic plasticity, maintenance and differentiation of neurons that are consequences of expression of early gene products |
| mAChRs $M_4$ | Presynaptic side, telencephalic structures, corpus striatum, neostriatum | $G_{alphai/o}$ Adenylyl cyclase inhibition, inward rectifying K current | Synapses modulation |
| mAChRs $M_5$ | Substantia nigra, corpus striatum | $G_{alphaq/11}$ Phospholipase Cbeta, diacylglycerol and inositol 1,4,5-trisphosphate (IP3) | Memory and learning, LTP and long-term depression, synaptic plasticity |

are consequences, at least in part, of the activation of the second messenger system, of tyrosine kinases cascade and promotion of genic transcription.

## Anaesthesia, anaesthetic agents and the central cholinergic system

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain and controls activities that depend on selective attention, which are an essential component of conscious awareness. ACh is one of the main neurotransmitters acting in the central forebrain system and its projections. It regulates high cognitive functions such as memory, learning, dendrite arborization, neuronal development and differentiation. Psychopharmacological and pathological evidence supports the concept of a 'cholinergic component' of conscious awareness. It backs up the statement that alleviation of a range of cognitive and non-cognitive symptoms by drugs modulating the cholinergic system, developed for the treatment of AD and related disorders, could be caused by changes in consciousness.[44]

Despite notable progress in the identification of the most likely target of general anaesthetic agents, brain mediation of anaesthesia is still not clear. Nevertheless, sensitivity of cholinergic receptors to anaesthetic drugs plays a pivotal role in determining various stages of narcosis (e.g. amnesia, inattentiveness, hypnosis).[44 58]

During general anaesthesia, decrease in ACh release and depression of cholinergic transmission facilitate all the desirable effects of general anaesthetics, such as loss of consciousness, pain, voluntary movements and memory.[37] Anaesthetics modulation of cholinergic transmission has profound effects on brain function *via* a cascade of synaptic and postsynaptic events by binding both mAChRs and nAChRs. The nicotinic receptor is implicated as being involved in the mechanism of action of general (inhalation) anaesthetic agents,[44] and investigation of the mode of action on the cholinergic receptors provides important information as to the mechanisms of anaesthesia.[57] The main effect of anaesthetic agents on nAChRs is inhibitory.[56]

Most of the drugs administered during anaesthesia, with a few exceptions, interact with both nicotinic and muscarinic receptors. The volatile anaesthetics, desflurane, isoflurane and sevoflurane can bind both nicotinic and muscarinic receptors in a dose-related manner.[22] Barbiturates are strong competitive antagonists of mAChRs but propofol acts on the nAChRs and mAChRs only at concentrations higher than in clinical use.[22] The opioids, morphine and fentanyl, may block mAChRs and nAChRs, while the newest opioid, remifentanil, does not interfere with ACh release.[45]

Atracurium and the atracurium and cisatracurium metabolite laudanosine activate $\alpha 4\beta 2$ nAChRs at concentrations comparable to those measured in the central nervous system during and for several hours after general anaesthesia.[55] As the $\alpha_4\beta_2$ nAch subtype receptor activation elicits neuroprotective effects,[4,28] laudanosine, at clinical concentrations reported in CSF after administration of atracurium, could elicit neuroprotective effects.[20,22]

Therefore, it has been hypothesized that the pathogenesis of postoperative cognitive dysfunction and delirium are possible consequences of anaesthetic drugs interacting with AChRs to produce inhibition of central cholinergic transmission, which is already impaired because of age-related changes.[45] From this point of view, patients with AD, characterized by a compromised neuronal transmission, present particular problems in the choice of anaesthetic drugs which may have different effects on postoperative outcome.

## Anaesthesia and development of AD: is there a relationship?

There has been speculation about a possible relationship between anaesthesia and AD. In a retrospective study performed to evaluate the association between exposure to anaesthesia and AD, no association between the risk of AD and exposure to anaesthesia in the 1 and 5 yr preceding disease onset was found, nor between the risk of AD and the number of surgical operations.[26] Similarly, other studies have concluded that it seems unlikely that multiple exposures to general anaesthesia increase the risk of AD.[7,10]

Conversely, data shown by Eckenhoff and colleagues[16] indicate that inhalation anaesthesia may be implicated in the evolution of neurodegenerative disorders such as dementia. Inhaled anaesthetics are associated with long-term cognitive problems and may enhance beta-A oligomerization rates, while propofol inhibits oligomerization at low concentrations but enhances beta-A toxicity at very high concentrations.[16]

Palotas and colleagues[43] investigated the possible interference of thiopental and propofol with APP metabolism and assessed that neither agent had an impact on APP metabolism. In addition, treatment with these agents resulted in stable APP levels. As a consequence, the authors are inclined to consider thiopental and propofol safe with respect to APP metabolism, as they do not facilitate APP production. However, the study also shows the controversial role of anaesthesia in the development of cognitive decline. The incidence of postoperative cognitive dysfunction (POCD) is increased after cardiac surgery and reflects severe neuronal injury and mimics pathogenetic events seen in AD patients.

Bohnen and colleagues[7,8] have evaluated whether external factors, such as general and spinal anaesthesia, interfere with individual susceptibility and contribute to the development of AD. They identified an inverse relationship between age of onset and cumulative exposure to general and spinal anaesthesia before the age of 50, but did not find a correlation with anaesthetic exposure after 50 yr. These findings are indicative of a possible relationship between dementia and exposure to external factors at an earlier age.

Knowledge of the pathophysiology of neurodegenerative disorders has been dramatically improved by progress in genetics and molecular biology.[38] Prospective epidemiological studies investigated levels of exposure to anaesthesia and any possible relationship between anaesthetic exposure, genetic factors (e.g. APOEepsilon4 genotype) and AD.[26]

Apolipoprotein E (APOE, gene; ApoE, protein) is the major genetic susceptibility locus for the common forms of AD.[48] There are three common polymorphisms in the population (Table 2). APOE alleles have also been

**Table 2** Common polymorphisms in the population of Apolipoprotein E (APOE), the major genetic susceptibility locus for the common forms of AD. APOE-epsilon 4 has a high positive predictive value for AD and is clinically useful as an adjunct in the early diagnosis of cognitively impaired patients[18,42,48]

| Polymorphisms | Frequencies in population (%) | Significance |
|---|---|---|
| epsilon 2 | 6.9 | It lowers the risk and increases the age of onset distribution |
| epsilon 3 | 76.2 | Histopathological onset 1–2 decades later than polymorphism epsilon 4, but same speed in progression |
| epsilon 4 | 16.9 | The inheritance of each dose of epsilon 4 increases the risk and lowers the age of onset distribution for AD |

associated with risk of AD and with recovery of psychological parameters after general cardiac anaesthesia.[48]

All these aspects, taken together, open new, intriguing scenarios considering that not only neuronal changes (ageing, genetic factors) but also cellular distress (injury, surgery) can determine functional decline. Thus, the relationship between general anaesthesia and AD has not yet been clarified. Nevertheless, we would like to focus our attention on the possibility that anticholinergic properties of drugs administered during anaesthesia alter cellular balance and functions facilitating cognitive decline. As a consequence, anaesthesia drugs could be highly discriminative for the postoperative outcome and could explain the varying conclusions which emerged in the above mentioned studies. Epidemiological prospective studies are required on exposure to anaesthesia, predisposing individual factors and development of AD.

## Clinical aspects related to anaesthetic management

The percentage of aged and older patients that require surgical procedures is increasing and, generally, their cases may be considered more complex than those regarding adult and young patients. Impairment of one or more systems or organs may cause enduring disability and loss of autonomy.[24] For this reason, elderly patients require a careful evaluation of their physical and mental status. Indeed, a careful mental status evaluation seems mandatory in the light of evidence that long life expectancy exposes the elderly to the risk of developing dementia or mild cognitive impairments (MCI).[19] These patients have more systemic impairments (e.g. cardiovascular, pulmonary, renal, endocrine and metabolic) and clinically evident or borderline organ failure (Table 3). In addition to age-related changes, a chronic disease, smoking, alcohol and environmental toxins may contribute to the difficulties in managing these patients.[49]

**Table 3** Age-related variation detectable in elderly patients[24,49]

| Systems | Modifications |
|---|---|
| Nervous system | Decrease in brain volume, cerebral blood flow, cerebral oxygen consumption, cortical neuronal density, loss of dendrites and synapses, alteration of neurotransmitter systems |
| Cardiovascular system | Decreased cardiac output and left ventricular diastolic filling, reduction in perfusion of organs, increase in left ventricular after-load |
| Respiratory system | Loss of recoil forces, small holding airways open, major distribution of inspired gas to the apices rather than the base of the lung, increase of physiological dead space, high ventilation/perfusion mismatch |
| Renal system | Decreased renal blood flow, glomerular filtration rate, tubular function and creatinine clearance |
| Digestive system | Reduction of liver blood flow, hepatic function and drug metabolism |
| Physical characteristics | Loss of weight, height and body surface area |
| Body composition | Variation in total body water, decrease in the central compartment, decrease in lean body mass, increase in fat |

Patients affected by AD or MCI require careful management which takes into account such potential problems as informed consent, preoperative progression of disease and postoperative care and support. Patients with impaired mental function are probably not able to sign an informed consent,[59] so relatives should be consulted, where possible. Anaesthetists should also be aware of the possibility of pharmacokinetic and pharmacodynamic changes for administered drugs,[49] and of unfavourable drug interactions. For instance, the cholinesterase inhibitor donepezil and its metabolites block acetylcholine hydrolysis and antagonize the effects of atracurium.[50] Galantamine, which has been approved for the symptomatic treatment of senile dementia of the Alzheimer's type, has been used in anaesthesia to reverse neuromuscular paralysis induced by turbocurarine-like neuromuscular blocking agents.[54] Chronic use of tacrine, an anticholinesterase drug used to manage Alzheimer's dementia, could affect response to nondepolarizing neuromuscular blocking agents, as chronic tacrine therapy in rats causes resistance to D-tubocurarine, probably because of the down-regulation of postsynaptic acetylcholine receptors.[32]

All these aspects, taken together, account for both the different susceptibility of the aged patient to anaesthetics and the increased attention that anaesthesiologists must apply when confronted with a patient with AD requiring anaesthesia or sedation.

## Conclusions

Central nervous system complications remain a common problem after surgical procedures in patients with AD. Despite major advances in surgical techniques and anaesthetic management, a patient might not be able to return to their baseline status and could require more intensive care by the family or in a long-term care facility because of deterioration in cognitive function. This, in turn, can be an enormous cost to society in terms of suffering and consumption of resources.[43] Despite doubts about the involvement of anaesthesia in the development of AD, it is clear that drugs given during anaesthesia interfere with cholinergic function in the brain by several mechanisms. In addition, neurotoxic effects have been demonstrated for several anaesthetic agents.

Inhaled anaesthetics enhance peptide oligomerization and cytotoxicity of AD-associated peptides.[16] The majority of surgical patients receive inhaled anaesthetics. These results call for further evaluation of the interaction between neurodegenerative disorders, dementia and inhalation anaesthesia.

Propofol inhibits oligomerization at low concentrations but enhances only at very high concentrations. In addition, propofol does not enhance beta-A toxicity.[16] These and other results indicate that both propofol and thiopental

are considered to be relatively safe with respect to APP metabolism. One of the difficulties in human research in this area is the fact that anaesthesia is not administered as a sole procedure but is almost invariably given to facilitate surgery and, as reported above, often in emergency conditions. Surgical stress, in turn, may accelerate development of clinical signs and symptoms of AD.[43]

All these aspects make it very difficult to draw any conclusions, without risk of bias, about the anaesthetic agents to be used or avoided in patients with AD.

New clinical and experimental evidence is required to help anaesthetists make the best choice of anaesthetics for the patient with AD. We believe that investigation of the effects of drugs administered during anaesthesia on the central cholinergic system may open new scenarios on the possible interactions between AD and anaesthesia.

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