

Review

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

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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, Aloisius Alzheimer [1], 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 [2–4]. It is clinically characterized by a

progressive loss of memory, which begins early in the disease process, and a decline in higher cognitive functions [5]. 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 [4,5]. 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 [2].

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

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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 ($A\beta$) 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 ($\alpha_2 - \alpha_7$, α_9 and α_{10}) and three β -subunits ($\beta_2 - \beta_4$) 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 α_7 and heteromeric complex α_3/β_4 , among which the compound $(\alpha_3)_2(\beta_4)_3$ is predominant. Electrophysiological studies on interneurons have documented that α_7 receptors subtypes are presynaptic, while $\alpha_4\beta_2$ are both presynaptic and postsynaptic [11]. Numerous studies have revealed a wide, but non-uniform, distribution of nAChRs in the brain. For example, α_7 are located across all layers in the cingulate, temporal and frontal cortex, hippocampus, substantia nigra, while $\alpha_4\beta_2$ 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,

18]. 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 (M_1 - M_5), according to their primary structure and property of activating/inhibiting cation transmembrane current [18]. M_1 , M_3 , and M_5 subtypes are postsynaptic receptors and are coupled with a G-protein alpha subunit (11/q) that activates adenylate cyclase and phospholipase C, generating inositol 1,4,5-triphosphate (IP3) and diacylglycerol with subsequent activation of Ca^{2+} dependent phenomena [15,18]. The activation of M_1 , M_3 , and M_5 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 adenylyl-cyclase [15]. M_2 and M_4 subtypes, instead, are presynaptic receptors that interact with G-protein, with adenylate cyclase inhibition, decrease of the cyclic AMP, activation of K^+ channels, and inhibition of the voltage-gated Ca^{2+} 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 $A\beta$ surrounded by dystrophic neurites, activated microglia and reactive astrocytes [4]. $A\beta$ derives from an amyloid- β protein precursor ($A\beta$ PP) by proteolytic cleavage, and there are two forms of neuritic plaques: amyloid- β_{1-42} ($A\beta_{1-42}$) and amyloid- β_{1-40} ($A\beta_{1-40}$) [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 $A\beta$ 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 $\alpha_4\beta_2$ 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 $A\beta$ deposits precede any other lesion in the brain of individuals with AD, it is likely that the overexpression and deposition of $A\beta$ play a critical role in the development and neurodegenerative process of AD [29]. The relationship between $A\beta$ deposits and

central cholinergic system is, therefore, of enormous interest.

Concentrations of $A\beta$ seem to have a neuromodulatory role in the regulation of various cholinergic neurotransmitter functions through adverse effects on multiple aspects of ACh biosynthesis and release [4,5,47]. In particular, a treatment with very small concentrations of $A\beta$ 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 $A\beta$ PP metabolism to $A\beta$ peptide production, as well as phosphorylation of the tau protein [5,49]. Selective agonists of M_1 receptors lead to the processing/transformation of $A\beta$ PP into non-amyloidogenic products [5,50], suggesting that agonists of M_1 receptors might mediate a dual action (increasing $A\beta$ PP release and decreasing $A\beta$ 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 $A\beta$ 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 $A\beta$ PP synthesis, intensifying both the production and neurotoxicity of $A\beta$ 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 mAChRs, 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 nAChRs and mAChRs, whereas remifentanyl does not alter acetylcholine release in cholinergic synapses [57]. Other drugs administered during anesthesia, such as anticholinesterase drugs and neuromuscular blocking agents, exert an ambiguous pattern of effects on cholinergic transmission depending on drug characteristics and cerebrospinal fluid concentrations [5]. Physostigmine activates only the M_1 receptor, neostigmine activates only M_3 , while pyridostigmine activates both subtypes [58].

The use of one drug rather than another assumes, therefore, a crucial role. Through interaction with the central cholinergic system, an anesthetic agent can affect A β PP metabolism, leading to persistent increase in concentrations of AD-associated A β peptides [59, 60].

Moreover, recent *in vitro* experiments have demonstrated that some anesthetics act directly in the processing (i.e., production and oligomerization) of A β . Clinical concentrations of isoflurane cause altered processing of A β PP, increasing A β peptide production in both human neuroglioma and mice brain cell lines [61, 62]. Similarly, desflurane can induce A β peptide production, but only in the presence of hypoxia [63], whereas the inhaled anesthetics halothane and isoflurane, at higher concentrations, encourage clumping of A β protein. In particular, in nuclear magnetic resonance spectroscopic studies, it has been noted that halothane and isoflurane induce structural alteration of A β peptides from the soluble monomeric α -helical form to oligomeric β -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 β , 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 β peptide, and loss of basal forebrain cholinergic neurons [70,71]. The relationship between A β deposits and the central cholinergic system has been widely investigated. Activation of selected acetylcholine containing receptors is involved in the regulation of A β PP metabolism to A β production [49]. Conversely, very low concentrations of A β 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 β PP metabolism, increasing the production of amyloidogenic A β 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 β PP metabolism leading to persistent increase in concentrations of AD-associated A β peptides [59,60]. Moreover, recent *in vitro* experiments have demonstrated that some anesthetics act in the processing of A β in a straightforward way. For example, inhaled anesthetics such as halothane, isoflurane and desflurane cause A β 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.

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