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Review

Neuronal nicotinic acetylcholine receptor–cholesterol crosstalk in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is one of the most devastating diseases of the central nervous system (CNS). It is characterized by two neuropathological findings: amyloid plaques and neurofibrillary tangles. AD is also accompanied by an extensive functional deficit in the cholinergic system, involving the neuronal-type nicotinic acetylcholine receptor (AChR). Furthermore there is increasing evidence showing a misregulation of cholesterol metabolism in the development of the disease. Since cholesterol affects AChR protein at multiple levels, the cognitive impairment and other neurological correlates of AD might be partly associated with an abnormal crosstalk between the receptor protein and the sterol in this synaptopathy.

1. Introduction

Alzheimer's disease (AD) is one of the most common aging-related diseases of the central nervous system (CNS). AD, dementia with Lewy bodies, and Pick's disease are three forms of dementia associated with pathological protein aggregation and inclusion body formation. In AD the two prevailing neuropathological findings in postmortem brains are senile-amyloid-plaques, mainly composed of deposits of the amyloid peptide (Aβ), and neurofibrillar tangles, composed of hyperphosphorylated tau protein. Aβ is generated from the amyloid precursor protein (APP) by enzymatic cleavage through β and γ secretases. In normal individuals Aβ40 represents the major component of the total Aβ pool in brain, whereas in brains of patients suffering from AD this ratio is altered and the levels of Aβ42 are much higher. Aβ42 is highly fibrillogenic and has toxic effects on neurons [1]. AD is also accompanied by extensive neuronal loss, especially in the cholinergic system, involving most conspicuously the neuronal-type nicotinic acetylcholine receptor (AChR).

Historically, the "cholinergic hypothesis" of AD is based on one of the earliest neuropathological abnormalities in this disease: the degeneration of cholinergic neurons located in the basal forebrain [2]. Abundant postmortem and antemortem studies in elderly humans and AD patients have reported a large number of cholinergic abnormalities including decreases in choline acetyltransferase activity and acetylcholine release, loss of AChR and muscarinic receptor expression early in the disease, defective high-affinity choline uptake or dysfunctional neurotrophin support, all of which positively correlate with cognitive decline and non-cognitive behavioral disturbances as well as with the deposition of toxic neuritic plaques [2]. More recent studies provide a new twist to the cholinergic hypothesis, focusing on a particular subtype of neuronal cholinergic receptor: Aβ binds with high affinity to the α7 AChR on neuronal cell surfaces, a process that may constitute a precipitating event in the formation of amyloid plaques [1].

The α7-type of neuronal AChR is an homopentameric ligand-gated ion channel that belongs to the family of Cys-looped receptors. It transduces the binding of at least two acetylcholine (ACh) molecules into a rapidly desensitizing Ca^{2+} influx. This type of receptor is widely expressed throughout the mammalian brain and is involved in sensory gating, learning, memory formation and neuroprotection. Due to its high Ca^{2+} permeability it participates in various signal transduction mechanisms such as the ERK/MAPK and the JAK2/PIP3K cascades, promoting neuronal survival by inducing the production of the anti-apoptotic proteins Bcl-s and Bcl-x [1] (see Fig. 1).

There is increasing evidence that lipid homeostasis is misbalanced in brains of AD patients. In particular, cholesterol metabolism seems to be affected and has recently become an important

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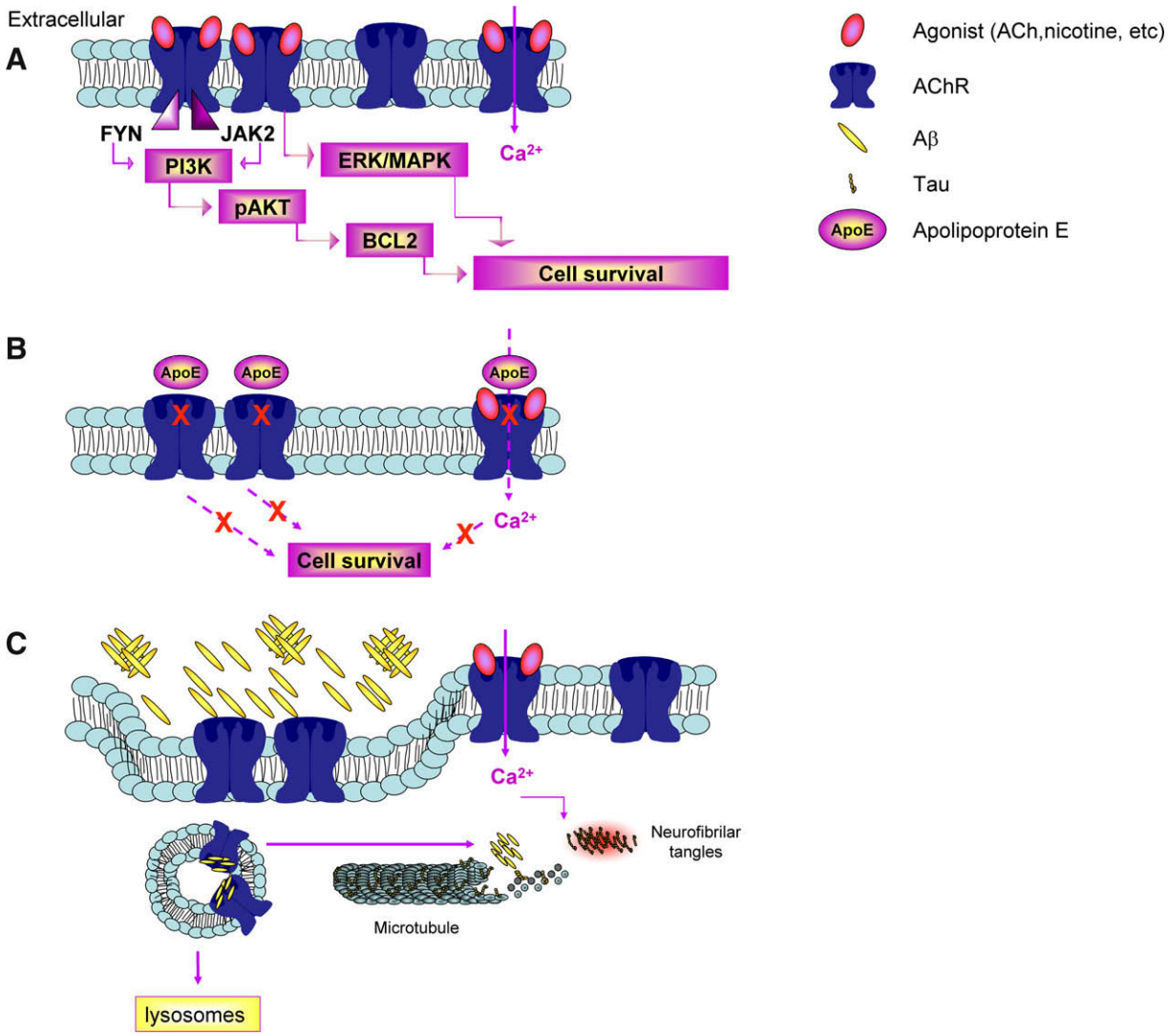

Fig. 1. Involvement of the neuronal α7 AChR in signal transduction cascades. Cholinergic transmission mediated by the α7 AChR is important in sensory gating, learning, and memory formation, and its derangement is increasingly acknowledged as a hallmark of AD. (A) When two molecules of the natural neurotransmitter ACh or other cholinergic agonists bind to the α7 AChR at the neuronal surface, the channel opens and a rapidly desensitizing Ca^{2+}-driven ion current ensues. Calcium ions can participate in a variety of intracellular processes; the diagram schematically depicts two key signal transduction cascades associated with α7 AChR gating: the ERK/MAPK and the JAK2/PI3K cascades, activation of which promotes neuronal survival. In AD, chronic α7 AChR-dependent activation of the ERK/MAPK cascade by Aβ overburdens the cascade and signal transduction fails [1,26]. (B) ApoE peptides behave as non-competitive antagonists of α7 AChRs. ApoE may thus contribute to the cognitive decline characteristic of AD by interfering with cholinergic neurotransmission. (C) The amyloid peptide Aβ42 binds to the α7 AChR at the surface of neurons with very high (pM) affinity, competing with the normal Ca^{2+} activation, and resulting in endocytic internalization of the AChR–Aβ42 complex, especially in neurons with high levels of expression of α7 AChRs, and intracellular accumulation in the lysosomal compartment. Aβ42 aggregation can in turn promote phosphorylation of the microtubular tau protein and the formation of neurofibrilar tangles.

focus of study of the physiopathology of the disease. Cholesterol synthesis in the brain does not appear to depend on the circulating pool of steroids and furthermore, plasma lipoproteins cannot cross the blood–brain barrier (BBB) [3]. In the adult brain mature neurons progressively lose the ability to synthesize cholesterol and therefore acquire it from glial cells, particularly from astrocytes [4]. Therefore, astrocytes can be envisaged as the locus of cholesterol homeostasis in the adult brain since they are able not only to synthesize, but also to internalize and recycle the cholesterol released from degenerating nerve terminals to deliver it back to neurons [5]. In healthy people the exchange of cholesterol between the CNS and the circulating blood is hindered by the BBB, whereas in AD patients the reverse passage of cholesterol from the CNS to the venous circulation appears to be reduced, and transport of cholesterol coming from degenerating neurons appears to be increased. This latter activity requires cholesterol binding to apolipoprotein E (ApoE) [5].

In this short overview we discuss available evidence pointing to the possible involvement of, and mutual interactions between, α7 AChR and cholesterol in AD.

2. α7 AChR, cognitive brain functions and AD

Several lines of evidence link brain α7 AChR with the development of AD [6]. Firstly, the α7 AChR subunit gene (CHRNA7) is located in the highly duplicated 15q13–q14 region implicated in several neuropsychiatric disorders, including schizophrenia and bipolar affective disorder. The CHRNA7 gene is duplicated from exons 5 to 10, with more than 99% identity at the nucleotide level [7]. Biochemical analyses of postmortem brains show decreased amounts of AChRs in AD patients. The most vulnerable neurons appear to be those expressing high levels of α7 AChR [8]. Furthermore, the α7-type AChR is highly expressed in brain regions

relevant to memory functions and involved in the processing of sensory information, such as the basal forebrain cholinergic neurons that project to the hippocampus and cortex [9].

A distinctive property of the α7 AChR is its ability to modulate Ca^{2+} homeostasis and the release of the natural neurotransmitter, ACh, two functions playing a major role in cognition and memory. AChRs have also been postulated to exert a neuromodulatory role on glutamate-mediated excitatory synaptic transmission [10]. If one further considers the involvement of α7 AChRs in synaptic plasticity [11] this subtype of receptors constitutes a key target for understanding the molecular dysfunctions involved in AD and for the development of new drugs to ameliorate or treat this disease. It is worth mentioning that nicotine treatment has been shown to improve attention, as well as learning and memory performance in patients with mild to moderate AD, as do drugs that potentiate central cholinergic function [12].

The mechanistic link between the affectations of nicotinic cholinergic pathways with the cognitive decline in AD is still far from being understood. One of the obvious inferences is that at least some of the pathognomonical behavioral alterations, such as the episodic memory impairment observed in AD, reflect compromised cholinergic neurotransmission and this in turn is a sign of abnormal AChR function. Indeed, nicotinic ligand binding studies of postmortem brains as well as in vivo positron emission tomography have shown that there is a marked reduction in the number of different subtypes of AChRs in various brain areas of individuals with AD [13,14]. Cholinergic input to the hippocampus and neocortex stems mainly from the basal forebrain, including the medial septal nucleus, diagonal band nuclei, and nucleus basalis. Cholinergic projection neurons within cortical areas are deficient in AChR. In particular, there is evidence that Aβ42 binds to the α7 AChR with very high (pM) affinity and that both are present in neuritic amyloid plaques of human brains with AD [1]. Short exposure times and moderate concentrations (pM–nM) of Aβ42 do not lead to permanent changes in α7 AChR or the ERK MAPK cascade; higher doses and extended exposure time lead to dysregulation of α7 AChR, ERK MAPK, and CREB, as well as deficits in memory and learning. The intraneuronal accumulation of Aβ42 is apparently facilitated by its high-affinity binding to the α7 AChR. Activation by the latter mediates Aβ-induced tau protein phosphorylation, which in turn involves the activation of the ERK MAPK and JNK-1 MAPK cascades (Fig. 1). A significant decrease in α7 AChR protein expression – but not in the amount of mRNA – takes place in the temporal cortex of AD brains, suggesting that the loss of α7 AChR does not occur at the transcriptional level. Reports that correlate deficits in synaptic plasticity, learning, and memory with increases in intraneuronal Aβ may reflect the consequences of the interaction between Aβ and α7 AChR [15]. A recent study using a transgenic mouse model of AD overexpressing a mutated form of the human APP [16] on the background of a knockout mouse for the α7 AChR [17] established that deletion of the α7 AChR gene leads to a reduction in cognitive deficiency and an improvement in synaptic physiology [18]. It is interesting to note that this occurs despite the presence of high amounts of APP and amyloid deposits, further highlighting the importance of α7 AChR in the pathology of AD and suggesting that α7 AChR is required to develop the cognitive impairment observed in AD [18]. Deletion of α7 AChR also protected from loss of the synaptic markers synaptophysin and MAP2 and preserved the ability to elicit long-term potentiation otherwise deficient in APP mice. The authors speculate that interfering with α7 AChR function could be beneficial in the treatment of AD.

There is still uncertainty as to the nature of the pharmacological effects of Aβ on α7 AChR [19]. Some reports indicate that Aβ can act as an agonist of the α7 AChR whereas other reports point to inhibitory effects [1]. Aβ blocks long-term potentiation, a correlate of learning, through activation of MAPK and JNK. Other studies even suggest that Aβ does not interact at all with the α7 AChR but exerts its deleterious action by interacting with membrane lipids in the vicinity of the receptor [20]. Human neuroblastoma cells overexpressing α7 AChR are killed by Aβ42, α7 AChR agonists exerting a protecting effect on cell survival. Small et al. [20] reported that Aβ disturbs intracellular signal transduction mechanisms mediated by the α7 AChR in SH-SY5Y cells by decreasing plasma membrane fluidity. Studies from our laboratory and others have documented that changes in membrane fluidity or lipid distribution correlate with changes in AChR function (reviewed in Ref. [22]). Aβ has also been reported to inhibit α7 AChR-dependent calcium activation and ACh release [1]. Endocytosis of Aβ42 is enhanced by its binding to the α7 AChR; in fact the AChR–Aβ42 complex appears to be co-internalized and accumulated in lysosomes [8]. Aβ also affects the endocytosis of the NMDA receptor; upon α7 AChR stimulation, NMDA receptors are internalized in an Aβ-dependent manner, leading to a weakening of synaptic strength [21]. The observation that the interaction of Aβ peptides with α7 AChRs occurs at physiological concentrations of the peptide led to the suggestion that Aβ42 acts as an endogenous ligand of the α7 AChR [1]. Therefore, anomalous interactions of Aβ with the α7 AChR at high peptide concentrations have been invoked in the pathology of the AD. One possible consequence of this anomalous interaction could be the phosphorylation of tau, a critical step in the formation of neurofibrilar tangles. Interestingly, this process was shown to be blocked by α7-selective antagonists as well as by anti-sense knockdown of α7 AChR protein both in cell lines and human brain synaptosomes [23,24]. It was also reported that chronic nicotine intake causes a marked increase in the aggregation and phosphorylation state of tau in a transgenic model of AD [25]. The α7 AChR-mediated high Ca^{2+} permeability activated either by nicotine or by Aβ causes dramatic increases in intracellular Ca^{2+} levels [26]. This rise in intracellular Ca^{2+} activates Ca^{2+}-dependent kinases that could be responsible for tau phosphorylation [23,24]. The accumulation of intraneuronal Aβ occurs prior to plaque and neurofibrilar tangle formation and a selective decrease in Aβ42 markedly delays the progression of tau pathology [27]. Hence, tau hyper-phosphorylation and its deposit as neurofibrilar tangles seem to be a downstream event to aberrant processing of APP. The in vitro and in vivo data therefore suggest that α7 AChR can operate as a link between Aβ and tau pathology. Whether Aβ activates or inhibits the α7 AChR in vivo is still controversial; it is nonetheless clear from several studies using a variety of preparations that prolonged exposure to a moderate concentration of soluble Aβ leads to AChR antagonism, possibly through a desensitization mechanism. All studies conclude, however, that there is a direct or indirect interaction between the Aβ and the α7 AChR and that the latter may somehow catalyze the toxic effects exerted by the Aβ. All things considered, evidence of a link between Aβ and α7 AChRs is overwhelming. However the consequences of this interaction need to be clarified.

AD is a chronic disease with a very long asymptomatic period. In animal models of the disease, such as transgenic rat and mouse models with Aβ accumulation, deficits in synaptic transmission and plasticity occur before amyloid plaque accumulation [25,27,28], suggesting that it is the soluble, non-fibrilary species of Aβ that plays a major role in AD pathogenesis. The chronology of these events further suggests that AD is, ab initio and foremost, a "synaptopathy". To understand the mechanism for Aβ toxicity at the synaptic levels is, in our view, one of the core issues in the field of AD.

3. Cholesterol and the AChR

Cholesterol is a very abundant component of the synaptic membrane where the AChR is located [29]. Cholesterol affects

the structural and functional properties of the muscle-type AChR protein, its trafficking from the site of synthesis to the cell surface, its spatio-temporal distribution and organization – including clustering – at the plasmalemma, its rate of endocytosis, and even single-channel behavior [29]. The most important message that emerges from two decades of research on the effect of the sterol on the muscle-type AChR is that cholesterol effects on the receptor protein are multiple, are exerted at various levels of organization – ranging from the molecular to the cellular level – and occur within multiple time windows, covering the millisecond (single-channel properties) to the minute and hour (endocytic/exocytic trafficking) time scales, during ontogenetic development and adulthood [30].

The neuronal α7 AChR was the first to be suggested to occur in lipid "*rafts*" at the surface of the somatic spines in chick ciliary ganglion sympathetic neurons [31]. The association of AChR with lipid "*rafts*" was postulated on the basis of biochemical criteria: cold detergent extraction procedures combined with subcellular fractionation techniques resulting in detergent-resistant (DRM) and detergent-soluble fractions. The DRMs are thought to represent liquid order (l_o) domains, which coexist in the same membrane with liquid disorder (l_d) domains [32]. The resistance of l_o domains to detergent solubilization is ascribed to the close packing of lipids in the l_o phase, which prevents detergent incorporation into the bilayer [33]. When the peripheral, muscle-type AChR was overexpressed in COS-7 cells the receptor protein was found to be present in the DRM fraction obtained by cold 1% Triton X-100 extraction followed by gradient centrifugation [34]. In the muscle cell line C2C12, the stability of AChR aggregates was found to depend on cholesterol content [35]. Using CHO-K1/A5 cells, a clonal cell line that expresses adult muscular AChR [36,37], it was demonstrated that chronic cholesterol depletion by treatment with the drug Mevinolin decreases cell-surface AChRs by inhibition of receptor exocytosis and retention of the protein at the Golgi complex. Acute cholesterol depletion of CHO-K1/A5 cells with methyl-β-cyclodextrin reduced the amount of muscle type cell-surface AChR by accelerating receptor endocytosis [22]. Stimulated emission depletion superresolution microscopy [38] reported changes in the distribution of AChR particles after cholesterol depletion. We also found that cholesterol depletion affects AChR mobility at the plasma membrane as measured by fluorescence recovery after photobleaching and fluorescence correlation spectroscopy [39]. More recently, we investigated whether the paradigm *Torpedo* AChR protein favors lipid ordered domains: the AChR was found not to display any preference for a liquid-ordered or disordered lipid domain. In fact, *Torpedo* AChR behaves in vitro as a DRM-disruptor [40]. This extensive series of studies strongly supports the notion of a close correlation between AChR and cholesterol, but the occurrence of the protein and the sterol within a "*raft*" domain is still a contentious issue: the effects of detergents on biological membranes are much too complex and in many cases "*raft*" markers are spatially segregated in the membrane into physically distinct compartments, their association upon subcellular fractionation and detergent extraction being man-tailored rather than reflecting the nanoscale organization in situ [41].

4. Cholesterol in AD

Cholesterol biosynthesis and catabolism are affected in AD, mainly because APP processing and Aβ production depend on membrane cholesterol content and on levels of isoprenoid intermediates in cholesterol biosynthesis (Fig. 2). The role of cholesterol as a risk factor for AD remains controversial [42,43]. Several studies have sought an association between hypercholesterolemia, mainly in mid age, and increased susceptibility to sporadic late-onset AD [42]. It is also well known that the brain is one of the tissues with the highest levels of cholesterol. This endogenous sterol is very important in the CNS because of its capacity to modulate synaptic plasticity, membrane fluidity, and the function of various membrane proteins, including ion channels [29]. The first connection between a defect in cholesterol metabolism and AD came with the observation that the heritage of the ε4 allele of the ApoE, the principal cholesterol transport protein in the brain, constituted a risk factor for the disease, a subject that will be developed in a separate section of this review.

Genetic studies of the risk of AD have reported association with polymorphisms in three other cholesterol related genes: cholesterol 24-hydroxylase, ATP-binding cassette transporter A1 (ABCA1) and lipoprotein receptor-related protein [44–46]. The possible link between abnormal cholesterol homeostasis and AD is currently viewed as a major physiopathological relationship. The mechanisms underlying such link are far from being understood and seem to be a complex network affecting diverse aspects of the disease. There is evidence suggesting the involvement of cholesterol in APP metabolism, in the susceptibility of neurons to Aβ toxicity, in the progression of tau pathology and in the correct function of synapses [20,47]. Thus, many steps in the development of AD may be affected by altered levels of cholesterol (Fig. 3).

Some statins (atorvastatin, simvastatin, lovastatin), used for the treatment of hypercholesterolemia, can cross the BBB and have been proposed as possible pharmacological agents in the treatment of AD. This is supported by clinical studies indicating that individuals chronically treated with these drugs display lower risk of developing late-onset AD [48]. Furthermore, cultured hippocampal cells as well as neuroblastoma cells that express the amyloidogenic Swedish mutation of APP reduced the production of Aβ when treated with statins, possibly as a combination of lowered geranylgeranyl isoprenoids synthesis [49], increased α-secretase activity [50] and decreased inflammatory response when exposed to Aβ aggregates [51]. In conclusion, statins may contribute to the homeostasis of cholesterol distribution in cell membranes and provide an anti-inflammatory effect, beneficial for AD patients. Similarly, increased consumption of polyunsaturated fatty acids (notably the omega-3 family) associated with a low intake of hydrogenated fats has been reported to reduce the risk of developing AD and other dementias, particularly those associated with vascular alterations [42]. In addition, vascular injury has been shown to affect the translocation of cholesterol-carrying lipoproteins in the CNS, leading to increases in membrane cholesterol. This in turn can affect the regulation of secretase activity and the generation of Aβ peptides [52]. The latter can enhance vasoconstriction, reduce cerebral blood flow [53] and increase ROS production [54]. These chains of events worsen vascular endothelial damage and reduce brain parenchyma perfusion with more atheromatous plaques [55]. The data could explain, at least in part, why age and high blood cholesterol constitute main risk factors for sporadic AD.

5. Apolipoproteins and AChR

ApoE is the main apolipoprotein in cerebrospinal fluid and is essential for the normal catabolism of triglyceride-rich lipoprotein constituents and the transport of fat-soluble vitamins and cholesterol. ApoE is also involved in neuronal development and regeneration. The ApoE is a polymorphic gene mapped to chromosome 19 and encodes a 299 amino acid long class of apolipoprotein. There are three isoforms of ApoE: ApoE2 (Cys112, Cys158; ε_2), ApoE3 (Cys112, Arg158; ε_3), and ApoE4 (Arg112, Arg158; ε_4), which differ from one another only by a single amino acid substitution [56,57] and exhibit different conformation and lipid-binding properties. ApoE binds to the seven identified mammalian members of the highly conserved low-density lipoprotein receptor (LDLR) family

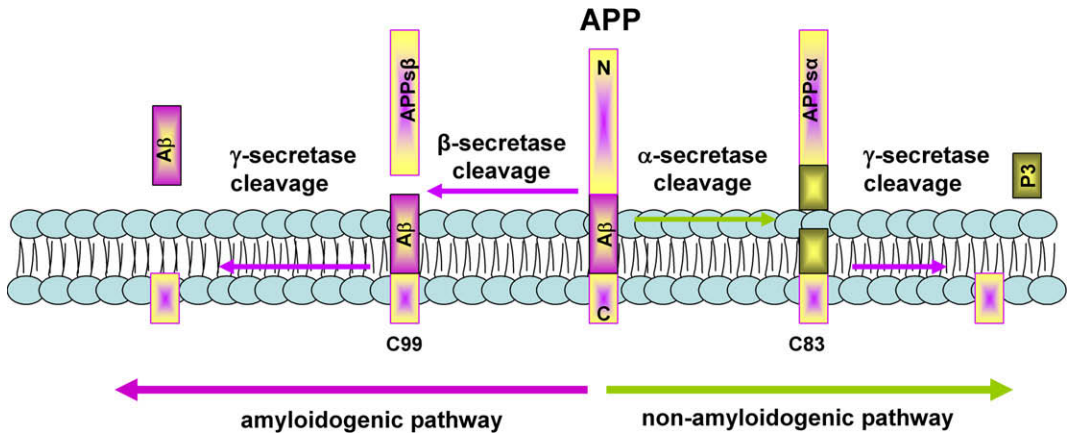

Fig. 2. APP metabolism by the secretase enzymes. APP can be sequentially cleaved by β-secretase and γ-secretase, to generate Aβ in an amyloidogenic pathway, or be hydrolyzed by α-secretase and γ-secretase to follow the non-amyloidogenic pathway. In the *amyloidogenic* pathway, β-secretase cleavage of APP releases APPsβ, an ectodomain secreted to the extrasynaptic space, and C99, a membrane-bound fragment. C99 is a substrate for γ-secretase, and its cleavage generates the APP intracellular domain together with the C-terminus of Aβ. In the *non-amyloidogenic* pathway, α-secretase cleaves APP to generate the secreted ectodomain, APPs α and membrane-bound fragment C83. The latter is subsequently cleaved by the γ-secretase complex to yield the 3 kDa fragment, P3, and the APP intracellular domain.

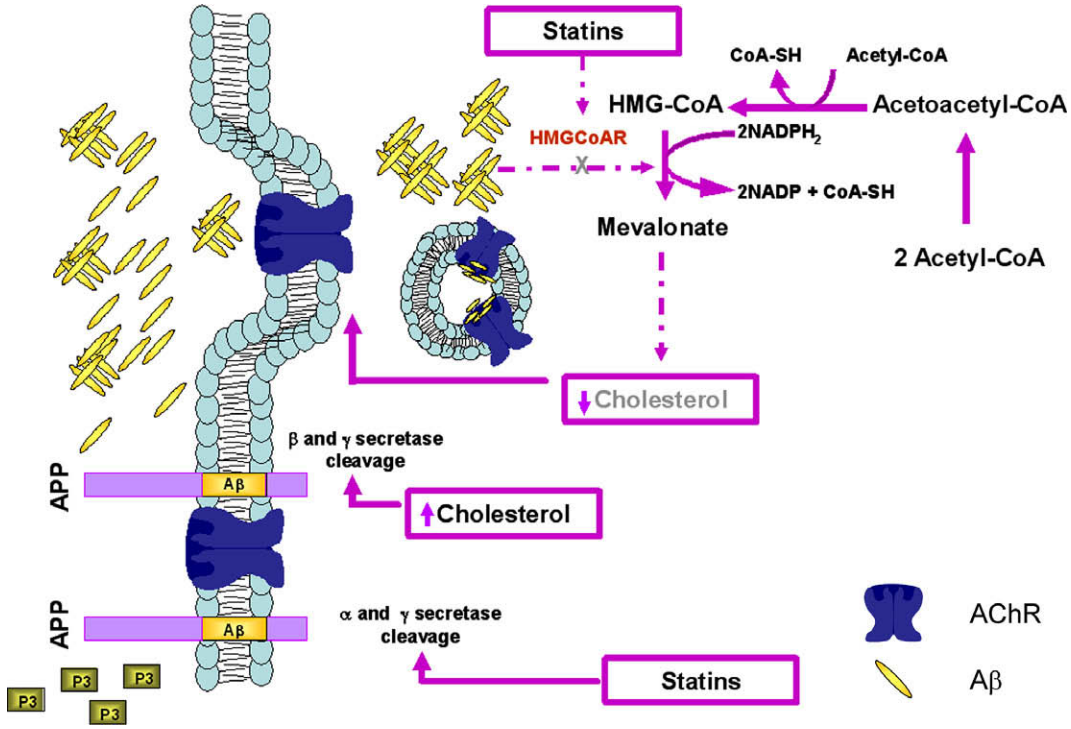

Fig. 3. Cholesterol, Aβ and AChR. Cholesterol exerts a homeostatic fine tuning of muscle-type AChR function, number and distribution at the cell surface: cholesterol depletion lengthens the AChR channel mean open time and reduces receptor cell-surface levels by increasing the rate of endocytosis, and increases the size of AChR nanoclusters and their "social" supramolecular organization [29]. In the CNS cholesterol also modulates secretase activities: increased levels of cholesterol augment β and γ secretase activities with a consequent rise in Aβ production. Aβ interacts with α7 AChR and promotes receptor internalization. Aβ aggregation can in turn reduce cellular cholesterol content by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis [77]. Decreased levels of cholesterol have been reported to promote AChR endocytosis [22] therefore worsening this scenario. This sequence of events leads to a cycle that regulates cholesterol levels. Although statins inhibit HMGCoA reductase activity, resulting in lower cholesterol levels, these drugs can also increase α-secretase activity [50], thus rescuing the cell from certain death.

[58]. It has previously been established that the LDLR family is intimately involved in neuronal signal transduction, modulation of ligand-gated ion channels, and control of neurite outgrowth, synapse formation and neuronal migration [59]. The ApoE4 protein isoform has gained importance for its unequivocal role as a genetic risk factor for late-onset AD [60] with a strong gene-dosage effect such that the number of ApoE4 alleles correlates positively with the risk of developing AD and the age of onset [60] and negatively with the number of AChR binding sites in patients with AD, as well as with responsiveness to the therapeutic AChE inhibitor tacrine [61]. The ApoE3 isoform is described as having no effect on AD risk and the ApoE2 isoform expression appears in fact to decrease the risk of disease as compared to ApoE3 [60]. Although the mechanisms underlying the pathogenic effects of the ApoE4 phenotype are not completely understood, there is evidence that ApoE4 promotes toxic Aβ42 production, aggregation, and amyloid plaque

formation [62]. ApoE4 may possibly display weaker affinity for the Aβ peptide than the other ApoE isoforms [63], thus reducing its ability to clear Aβ peptides from neurons favoring Aβ intracellular accumulation and oligomerization [63]. Furthermore, recent observations demonstrate that oligomers, which are the most toxic form of Aβ, are internalized more effectively than the less toxic fibrillar forms [64]. In addition, there is the possibility that multiple pathways may be involved in the pathogenic effects of ApoE4 since there are reports that enhanced proteolytic degradation of ApoE4 is associated with production of toxic fragments [65,66] and with having reduced uptake by the low-density lipoprotein receptor (LDLR) [67].

ApoE has been shown to directly interact with AChRs [68–70]. Experiments using peptides derived from the LDLR binding domain of ApoE resulted in inhibition of the endogenous expression of AChRs in interneurons from rat hippocampal slices, with a submicromolar affinity, and of heterologously expressed α7, α4β2 and α2β2 AChRs. Furthermore, this effect selectively affected members of the Cys-loop family of receptors having permeability to cations, since neither glycine nor GABA receptors were sensitive to block [69]. The latter action is dependent on an arginine-rich segment of the ApoE peptide [68] whereas the degree of the block was greater for the α7 AChRs than that for α4β2 or α2β2 AChRs [69]. Interestingly, ApoE peptides were unable to block functional α-bungarotoxin (α-BTX) binding. This could indicate that the peptides do not interact with α7 AChRs in a competitive fashion, but rather at a site other than the traditional ligand-recognition site or at the interface between subunits at a distinct "microsite" that does not preclude α-BTX binding [69]. ApoE peptides behave, therefore, as non-competitive antagonists of α7 AChRs. Furthermore, the block of α7 AChRs is abolished when Trp55 is mutated to alanine, suggesting that it results from a direct interaction between the peptide and the α7 AChR [70]. From these findings, the inference has been made that ApoE may contribute to cognitive decline by interfering with cholinergic neurotransmission [70].

In summary, several studies suggest that impairment of memory function [71] and synaptic loss [72] is associated with ApoE4 in transgenic mice models. Since α7 AChRs are linked to cognitive function, and dysfunctions in these receptors are thought to be involved in the cognitive decline associated with AD [73], their inhibition by ApoE-derived peptides or ApoE fragments containing the LDLR binding domain could have deleterious consequences for cognition and/or cell viability. It is possible that this adverse interaction is responsible for at least some of the cognitive impairments observed in AD.

6. Lipid metabolism, APP processing and AChR

APP is a conserved type I membrane protein. It is highly expressed in central and peripheral nervous systems, and can be detected in both pre- and postsynaptic compartments [74,75]. The physiological role of APP is still a matter of debate. There is growing evidence that APP and its cleavage products are important modulators of synapse formation and function (Fig. 2). Hippocampal neurons from APP knockout mice show enhanced excitatory synaptic transmission and this effect was attributed to the production of Aβ peptides since it was reproduced in normal neurons treated with presenilin inhibitors and in neurons from presenilin-1 (PS1) knockout mice [76]. Moreover, developmental overexpression of dendritic APP or Aβ increases susceptibility to seizures, and mediates presynaptic localization and activity of the high-affinity choline transporter, consistent with a role of APP in the proper function of synaptic transmission in both the NMJ and central cholinergic neurons.

The ubiquitous presence of APP and its processing enzymes, the presenilins, suggests that their range of action is not restricted to the CNS [77]. In fact, APP may function as a regulator of lipid metabolism. There is a mutual interaction between the generation of Aβ peptide and cholesterol metabolism, hypercholesterolaemia being an early risk factor in the development of AD [78]. In addition, increased levels of cholesterol augment β and γ secretase activities with a consequent rise in Aβ production [47]. Aβ40 may in turn reduce cellular cholesterol content by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis [77]. Since reduced levels of cholesterol diminish the production and secretion of Aβ40 and Aβ42 [47] this sequence of events may function as a cycle to regulate cholesterol levels [79] (Fig. 3). The relationship between Aβ levels and cholesterol appears to be biphasic and to operate within a certain range of cholesterol concentrations [79]. In contrast, Aβ42 activates sphingomyelinase and reduces the levels of sphingomyelin in the cell [77]. The Aβ40/42 ratio can thus modulate the lipid composition of the cell. Interestingly, in AD brains this ratio is altered with an increase in the levels of Aβ42. A change in Aβ40/42 ratio should cause or be the consequence of an altered lipid homeostasis, as occurs in AD [77].

Alterations in the lipid composition of the cell membrane may result in changes in the activity of many membrane-bound proteins. As such, neuronal and muscle AChRs have been shown to be especially sensitive to the lipid environment [80] and this property may contribute to the pathology of AD. Neuronal α7 AChR have been reported to be associated with cholesterol-rich membrane fractions and this association increases during synaptogenesis [31,81]. In contrast, β2 and α5 AChR subunits do not show such an association, pointing to a specific membrane localization of α7 AChRs. Moreover, a reduction in cholesterol levels results in the dispersal of α7 AChR clusters in somatic spines of ciliary ganglion neurons, suggesting that cholesterol is necessary for the localization of α7 AChR at specific sites in the membrane [31]. The same phenomenon occurs with muscle AChR: cholesterol was shown to be required for the formation and maintenance of the large clusters found at the neuromuscular junction [35] and the submicron-sized clusters found in CHO cells [22,38]. Furthermore, chronic, long-term cholesterol depletion attained by metabolic inhibition of its biosynthetic pathways disrupts the cell surface delivery of AChR in CHO cells [37]. It is not only AChR localization and stability in the membrane that are dependent on cholesterol; signal transduction through the α7 AChR is disrupted when cholesterol levels are reduced in PC12 cells [81] and channel properties of muscle AChR are altered too [22,29]. Thus, the disruption of cholesterol homeostasis observed in the AD brain could specifically affect cholinergic synapses and may contribute to the observed decrease in the number of AChRs.

7. Astrocytes, inflammation and Aβ

Whereas the effect of Aβ on neurons has been studied quite thoroughly, less is known about the action of the amyloid peptide on astrocytes. Astrocytes play major roles in both normal and diseased brain [82]. It has been observed that these cells are activated in AD, and Aβ can directly activate cultured astrocytes [83]. Moreover, the astrocytes that accumulate deposits of Aβ can degrade these peptides [84]. Interestingly, the α7 AChR levels in astrocytes of brains with sporadic AD is high [85]. This was also observed in the brains of patients carrying the Swedish APP 670/671 mutation [85]. These high levels of α7 AChR expression may be a consequence of the stimulation of astrocytes by internalized Aβ or be related to the severity of AD pathology [86]. Furthermore, Aβ42 positive astrocytes in the molecular layer of the cortex of AD

patients exhibit intense and specific immunostaining for α7 AChR [87]. The mechanism implicated in the Aβ-induced upregulation of α7 AChRs in astrocytes is still unclear. Interestingly, upregulation of α7 AChRs was also reported in mouse hippocampal slices after chronic exposure to Aβ at concentrations typically found in the brains of AD patients and in animal models of AD [88]. In the latter study, α7 AChR upregulation was a consequence of Aβ activation of the ERK2 MAPK cascade via α7 AChR [88]. Whether this is also the mechanism responsible for α7 AChR upregulation in astrocytes remains to be studied. Alternatively, microglia can exert neuroprotective functions by secreting growth factors or diffusible anti-inflammatory mediators, which help resolve inflammation and restore tissue homeostasis [89]. Since AChRs play an important role in neuroprotection [90], this elevated expression of α7 AChR by astrocytes might thus represent a defense or compensatory mechanism to stimulate the production of suitable amounts of Aβ.

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