Alzheimer's Disease Research Journal ISSN: 1935-2514
Volume 3, Number 1

AMYLOID PRECURSOR PROTEIN IN CENTRAL AND PERIPHERAL CHOLINERGIC SYNAPTOPATHIES

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ABSTRACT

Alzheimer´s disease is the most widespread form of dementia in the elderly. One of the characteristics of this disease is the profound functional deficit of the cholinergic system as a consequence of synaptic loss. Amyloid precursor protein (APP) is a type-I transmembrane protein present in brain synapses and at the neuromuscular junction in the peripheral nervous system. It is developmentally regulated and affects synapse formation and cholinergic transmission. Misprocessing of APP leads to the generation of a highly fibrillogenic peptide, amyloid beta (Aβ), which aggregates and forms amyloid plaques, one of the histological hallmarks of Alzheimer's disease. Aβ can also aggregate at a peripheral synapse, the neuromuscular junction, in the form of intracellular lesions characteristic of the degenerative muscle disease termed sporadic inclusion body myositis. The relationship between the increased production and aggregation of Aβ and the synaptic dysfunction observed in the two disorders is not clear, but the similarities point to the important role of APP in cholinergic synapses. Here we review the biological functions of APP under normal conditions and their dysfunctional counterparts in an attempt to explain the involvement of this protein in cholinergic synaptopathies in general.

INTRODUCTION

Alzheimer's disease, the most widespread form of senile dementia, is a neurodegenerative disease with progressive decline in cognition and memory. Sporadic inclusion body myositis is considered the most common acquired myopathy in patients older than 50 years. It is also a degenerative disorder exhibiting a progressive and rather slow evolution, from muscle weakness to severe disability of the patient. In addition to affecting

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the same age-group, the two diseases also share the pathogenesis of amyloid peptide (Aβ) accumulation in amyloid plaques generated by amyloidogenic processing of the amyloid precursor protein (APP). This short overview discusses recent evidence of the common biochemistry, metabolism and physiopathology of APP and derived peptides in the two disorders.

FUNCTIONAL ROLE AND METABOLISM OF APP AND DERIVED FRAGMENTS

Amyloid precursor protein (APP) is a type-I integral membrane protein with a bulky domain exposed to the extracellular space, one transmembrane domain and a rather small moiety in the cytoplasmic compartment (Figure 1A). APP belongs to a gene family that in mammals also includes the APP-like proteins (APLPs), APLP1 and ALPL2. Mutants of APP are linked to some cases of early onset in familial Alzheimer's disease [28,36,56,110] and the principal proteolysis product of APP, the amyloid peptide (Aβ), is the main component of amyloid plaques [33], histopathological hallmarks of Alzheimer's disease and inclusion body myositis [9,37,46]. The study of the physiological properties of APP is complicated by the occurrence of APP-like proteins APLP1 and APLP2, which display structural and functional similarities [5]. It is interesting to note that the Aβ peptide domain (Figure 1A) is unique to APP [115].

APP exhibits a complex metabolism, involving phosphorylation as well as proteolytic cleavage of the protein. Phosphorylation occurs at multiple sites and regulates APP processing and its interaction with other proteins [4,80,82]. It was suggested that full-length APP is initially targeted to the plasma membrane in the cell soma, then internalized by endocytosis and processed in cell body endosomes [42,52,93]. The rate of APP endocytosis is therefore intimately linked to and a critical regulatory factor of APP cleavage. The segregation of cleaved fragments to different destinations is probably a reflection of the multiple functions displayed by APP [67].

Two pathways have been described for the proteolytic processing of APP: amyloidogenic and non-amyloidogenic (Figure 1B). In the former, the enzyme BACE1 (β site APP-cleaving enzyme/ β-secretase) cleaves APP after residue 671, releasing a fragment named sAPP-β and retaining in the membrane a 99-residue long C-terminal fragment, C99. This fragment is further cleaved by γ-secretase to release a 40- or 42-amino acid-long Aβ fragment and the APP intracellular domain, AICD, into the cytoplasm (Figure 1B). In the non-amyloidogenic pathway, APP is first cleaved by ADAM (α secretase) which results in the production of the soluble ectodomain sAPP-α, and a C-terminal fragment of 83 amino acids, C83. Cleavage of C83 by γ-secretase generates a small peptide, p3, and AICD (Figure 1B). Under physiological conditions the majority of APP is processed by the non-amyloidogenic pathway, whereas in Alzheimer's disease the balance is shifted towards the amyloidogenic pathway. Both pathways are regulated and inhibition of one often increases the activity of the other, in a typical homeostatic equilibrium. Inhibition of BACE1, for example, decreases brain levels of sAPP-β while increasing that of sAPP-α [31]. This mechanism is analogous to that operating in the case of Notch receptors, an important signalling pathway that regulates cell differentiation events. These similarities have been used to support the hypothesis that APP

and its fragments act as signalling molecules in a physiological context and that disturbance of these signalling mechanisms may be causally linked to APP-related diseases such as Alzheimer's disease and inclusion body myositis.

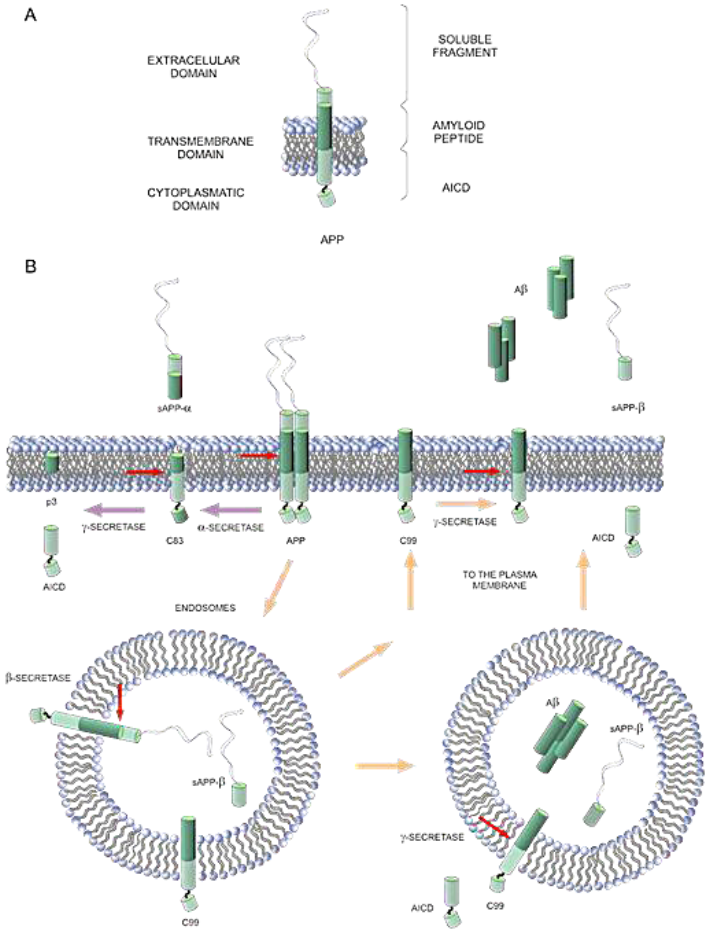

Figure 1. Structure, trafficking and proteolytic processing of APP in the amyloidogenic and non-amyloidogenic pathways. A) Overall architecture of the amyloid precursor protein. APP is an integral membrane protein with a large extracellular domain (ribbon), a single transmembrane domain and a short cytoplasmic tail. In the sequence of this protein are the precursors of three active fragments: soluble APP (sAPP), amyloid peptide (Aβ) and APP intracellular domain (AICD). B) APP at the plasma membrane is cleaved by three different enzymes at three different loci along its sequence: β secretase cleaves APP at position 1 or 11 of the Aβ region; α secretase digestion site is at position 17, and γ secretase cleaves a transmembrane site at position 40-42. The enzyme α-secretase operates within the region corresponding to the Aβ sequence, generating a soluble fragment, the ectodomain sAPP-α, and a C-terminal fragment of 83 amino acids, C83. The latter is further cleaved by a γ-secretase, thus releasing the APP intracellular domain (AICD) into the cytoplasmic compartment. The remaining membrane fragment, p3, is subsequently degraded. In the amyloidogenic pathway APP is internalized by a clathrin-dependent endocytic mechanism and cleaved in endosomes by β-secretase, generating a soluble fragment, sAPP-β, and a C-terminal fragment of 99 amino acids, C99. Cleavage of C99 by γ-secretase can occur either in endosomes or at the cell surface, to release the amyloid-β peptide and AICD. Internalization of APP is thus an essential requisite for APP processing by the amyloidogenic pathway.

APP Intracellular C-Terminal Domain (AICD)

AICD can modulate gene expression in a manner similar to the effect exerted by the Notch intracellular domain (NICD), although some controversy remains around the identification of AICD target genes [3,41,43,83]. AICD interacts with and is stabilized by the nuclear adaptor protein Fe65 [38,51,62,83]. This complex seems to act as a point of membrane recruitment for Tip60, a histone acetyltransferase (19,97). At the membrane, Tip60 is phosphorylated and subsequently translocated to the nucleus together with Fe65, where it activates gene transcription [18]. This occurs only when AICD is bound to the membrane [18]. Besides its participation in gene transcription, interaction between APP and Fe65 may be involved in the regulation of neuronal actin-based membrane motility and neuronal growth cone formation [64]. Both processes are important for neurite growth and synapse modification. Activity of the AICD generating enzyme, γ-secretase, was shown to be higher in embryonic than in adult rat brains [30]. These changes in AICD generation along ontogeny and aging suggest a possible physiological action of AICD in synapse development. In support of this hypothesis is the observation that APP intracellular sequences are required for APP-mediated survival and neuromuscular synapse assembly in vivo [58].

As is the case with other proteins, the C-terminal domain of APP also serves as an anchor for the endocytic machinery responsible for APP internalization, a structural feature with functional implications in APP processing (Figure 1B) [93]. In fact, when APP lacks its cytoplasmic internalization motif it accumulates at the plasma membrane and undergoes increased α-secretase, but reduced β-secretase, cleavage [92]. Since the AICD fragment is generated by both the amyloidogenic and non-amyloidogenic pathways, the level and functions of AICD may not be affected even in pathologies when there is a misbalance between the two routes. This is corroborated by recent findings showing that the production of AICD was not decreased by genetic manipulation of BACE1 activity [89] . However, it was suggested that nuclear signalling is predominantly mediated by AICD generated from amyloidogenic cleavage [34] (Figure 1B).

APP Extracellular Domain

The extracellular domain of APP and its derived soluble fragments (sAPP) have also been studied in the search for the physiological function of this intriguing molecule. They have been implicated in various cellular processes including neuroprotection, memory enhancement, regulation of neuronal excitability and synaptic plasticity [23,85,101,115]. sAPP-α can also rescue anatomical and behavioral defects present in APP knock-out mice, although it does not completely revert the phenotype, highlighting the importance of the integrity of the APP molecule or relevant fragments thereof for the correct function of the synapse [58,87].

Overexpression of APP has been reported to increase the number of dendritic spines, whereas the opposite is observed when APP levels decrease in cultured hippocampal neurons and in transgenic mice *in vivo* [57]. This effect requires both the extracellular and intracellular domains of APP and is accompanied by specific up-regulation of GluR2, a subunit of the AMPA-type glutamate receptor, the principal excitatory neurotransmitter system in brain

[57]. As shown in Figure 2, sAPP-α has also been reported to increase neurite outgrowth by an integrin-mediated signalling pathway, but *only* in the presence of complete APP [112]**.** Interestingly, secreted APP is also necessary for epidermal growth factor-induced proliferation of progenitor cells in the adult subventricular zone [17]. Since this area is one of the two sites in the adult that contributes with neural progenitor cells capable of producing neurons in the adult brain, the endogenous function of secreted APP may be related to adult neurogenesis [24].

APP has also been suggested to function as a cell-surface receptor. Ligands shown to bind APP include Aβ, integrins, the glycoprotein F-spondin and extracellular matrix proteins [44,61,95]. sAPP-α could then act by competing with full-length APP for the same binding sites [112]. Another suggested mechanism includes disruption of cell-surface organization of APP. Almost all APP present at the membrane is organized as homodimers, and direct binding of sAPP-α to APP disturbs this organization. The rupture of APP homodimers was shown to be required for the neuroprotective effects of sAPP-α to occur [35]. sAPP-α mediated signaling could therefore occur via two modalities: autocrine and paracrine.

As previously stated, soluble fragments of APP are generated by both the amyloidogenic and non-amyloidogenic pathways. The difference lies in the end-product: 16 amino acids that are present in sAPP-α and absent in sAPP-β. Initial reports have indicated that sAPP-α is approximately 100-fold more potent than sAPP-β in protecting hippocampal neurons against various forms of injury [32]. Whether the differences in sequence account for such functional differences between the soluble fragments has not yet been fully investigated.

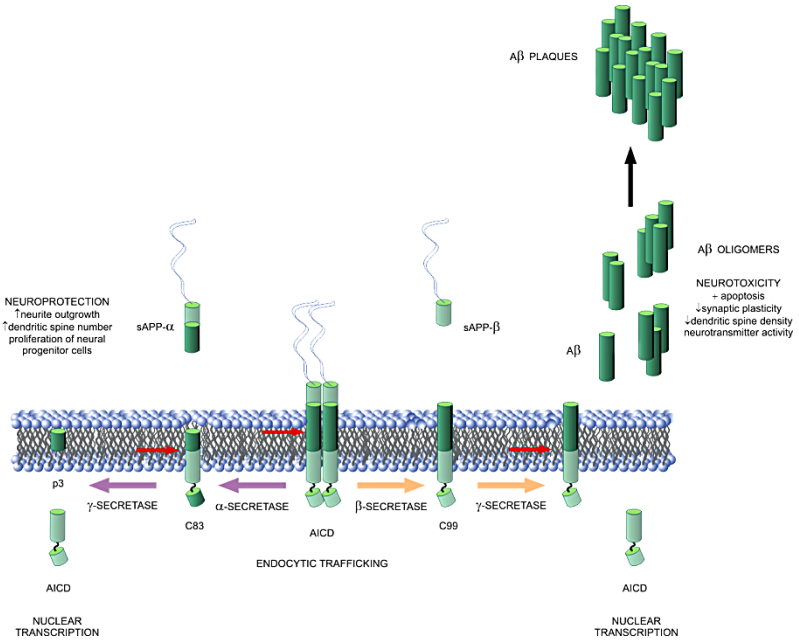

Figure 2. Function of different fragments of APP. The soluble fragment derived from the non-amyloidogenic pathway (sAPP-α) has neurotrophic activity, whereas the amyloid peptide (Aβ) derived from the amyloidogenic pathway aggregates to form oligomers that are neurotoxic. AICD can act as a transcriptional activator of different genes. It also contains the internalization motif that couples APP with the clathrin-endocytic machinery. The correct balance between amyloidogenic and non-amyloidogenic pathways determines synaptic fate.

Most studies rely on the function of sAPP-α; however, under pathological conditions the secretase enzymic activity switches from α to the β modality, implying not only an increase in Aβ but also in sAPP-β levels. The increase in Aβ and the decrease in sAPP-α could thus counterbalance the beneficial effect of sAPP-α on synapses. In addition, it is also possible that sAPP-β may function as a dominant negative mutant of sAPP-α, thus competing for the same binding sites.

Amyloid Peptide

The main structural and probably functional difference between APLP1, APLP2 and APP is that the latter includes in its sequence the Aβ peptide. As stated before, Aβ can only be generated by amyloidogenic processing of APP by the sequential cleavage by β and γ secretases, and is the major component of the amyloid plaques found in the brain of patients suffering Alzheimer's disease and in the muscle of patients with inclusion body myositis. In normal individuals the 40 amino acid-long peptide (Aβ40) accounts for most of the total Aβ population in brain, the rest corresponding to the 42-mer peptide, Aβ42. In contrast, in brains of patients suffering from Alzheimer's disease this ratio is altered and the levels of Aβ42 are much higher, reaching local concentrations in the pico- to nanomolar range [6]. Aβ42 is also the predominant species accumulated in inclusion body myositis muscle fibers [74]. Aβ42 is more toxic than Aβ40 and this toxicity is attributed to the increased ability of Aβ42 to aggregate and form soluble oligomers [29,114]. Deposition of Aβ in plaques is now being considered as a possible mechanism of temporal clearance of this toxic form of the peptide instead of the direct cause of the cytotoxicity [39]. Aβ is a minor product of APP cleavage in normal individuals and the physiological significance of the amyloidogenic pathway, if any, is poorly understood. Furthermore, effects of Aβ on the cell may depend on the state of aggregation of the peptide and this is not clearly consigned in all studies, thus precluding proper comparison between them. It appears, however, that Aβ is related to signaling pathways such as TrkA, MAPK and JNK [15,63,78,79,111] and that Aβ can induce apoptosis by activation of p53 [77]. Aβ was also shown to act as a ligand for different neurotransmitter receptors *in vitro* [49,59,76,96]**.** It has also been suggested that Aβ can act as a modulator of synaptic activity and prevent excito-toxicity (Figure 3) [21,22,48,71,72]**.** Thus the correct balance between amyloidogenic and non-amyloidogenic cleavage of APP may be another homeostatic modulatory mechanism required for synaptic *health*, synaptic activity being the determinant positive factor [45].

APP AND CHOLINERGIC TRANSMISSION

Cholinergic transmission is mediated by the neurotransmitter acetylcholine (ACh). Upon synthesis by the enzyme choline acetyltransferase (ChaT) the natural neurotransmitter is accumulated in synaptic vesicles by the vesicular acetylcholine transporter (VAChT). ACh released from presynaptic terminals binds to acetylcholine receptors (AChRs) to elicit pre- or post-synaptic responses. Most of the ACh is rapidly hydrolyzed by acetylcholinesterase

(AChE) to choline. The rate-limiting step in cholinergic transmission is the recycling of choline by the high-affinity choline transporter (ChT) located in the presynaptic terminals. Regulation of ChT at the synaptic membrane depends on synaptic activity and is attained by trafficking of ChT from and to the plasma membrane (Figure 4A) [27,86].

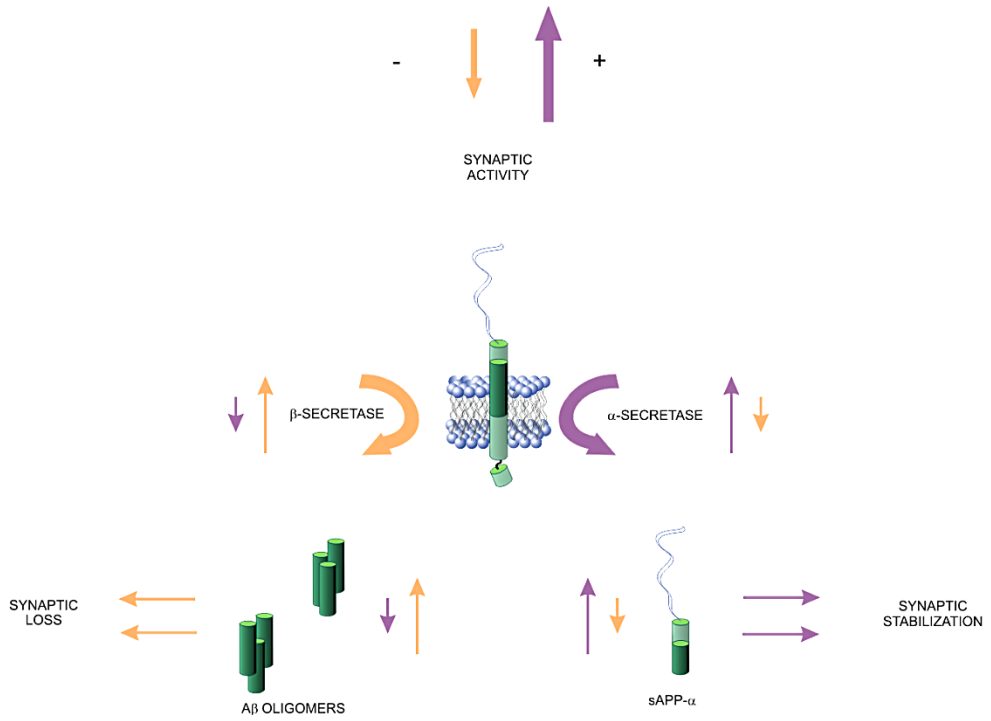

Figure 3. Synaptic activity regulates APP metabolism. Synaptic activity (blue arrows) stimulates the non amyloidogenic pathway and increases the concentration of sAPP-α, which in turn promotes synaptic stabilization. Concomitantly, the amyloidogenic pathway is inhibited. When synaptic activity does not reach certain levels the amyloidogenic processing of APP predominates and the increase in Aβ induces synaptic loss. This mechanism may serve during development to rescue active synapses from the elimination process.

APP is highly expressed in neurons and muscle where it is located at synaptic sites (1,99). At the NMJ, APP is found at pre- and postsynaptic sites. Interaction between pre- and postsynaptic APP promotes adhesion and hence APP is involved in synaptogenesis [107]. Indeed APP/APLP null NMJs exhibit abnormal apposition of presynaptic proteins with postsynaptic AChR clusters [106]**.** In mammals, APP expression peaks around the second postnatal week, i.e. at the developmental period in which the most rapid cortical synaptogenesis occurs [57]. In muscle, the APP protein becomes progressively concentrated at NMJs as development proceeds and this profile of APP localization correlates with the time of polyneuronal synapse elimination (1) . Since synaptic activity can be involved in the non-amyloidogenic cleavage of APP and sAPP-α can act as a stabilizer of synaptic function [65,72], APP processing can thus modulate survival of active synapses. When activity is reduced, the increase in amyloidogenic and/or the fall in non-amyloidogenic processing could result in loss of synapses (Figure 3). In hippocampal neurons in culture, lack of APP is accompanied by an increase in the number of functional synapses in young but not in old

mice, and this phenotype can be mimicked by inhibition of γ-secretase, suggesting the involvement of the Aβ peptide [81]. This reinforces the idea that Aβ generation may be part of a negative feedback mechanism that controls neuronal excitability.

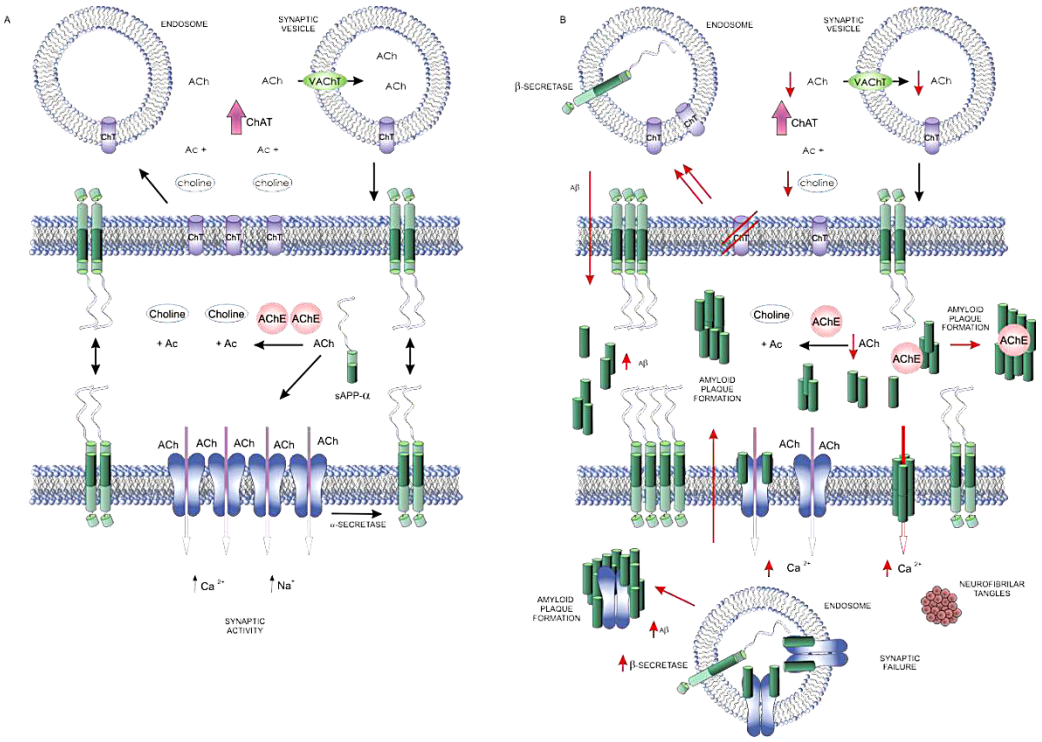

Figure 4. Interaction of APP and its derivatives in a cholinergic synapse. A) Under physiological conditions APP can act as an adhesion molecule that stabilizes the cholinergic synapse and correctly localizes the high affinity choline transporter (ChT). This ensures the formation of the natural neurotransmitter, ACh, and the functionality of the synapse. The α–secretase pathway is the predominantly activated processing pathway under physiological circumstances, and sAPP-α exerts its neuroprotective action ensuring the correct function of the cholinergic system. B) When APP metabolism is not properly regulated as in Alzheimer's disease or inclusion body myositis, the β-secretase pathway is activated and Aβ increases its concentration. This enhances the internalization of ChT, thus reducing the uptake of choline and the amount of ACh synthesized; synapse function is then compromised. Aβ also interacts with AChE and aggregates to form amyloid plaques. AChR bound to Aβ is internalized and this complex can act as a nucleation center that promotes the formation of intracellular amyloid plaques and reduces the levels of AChR at the membrane. Amyloid peptide can also form membrane pores which permeate Ca^{2+}, the concomitant increase in intracellular Ca^{2+} being toxic for the synapse. Aβ signaling also induces the hyper-phosphorylation of the tau protein, leading to the formation of neurofibrilary tangles. In addition, the activity of the α-secretase pathway and its neuroprotective properties are reduced. The combination of these multiple actions leads to the loss of the central and peripheral cholinergic synapse.

The specific link between APP, its derivatives and cholinergic synapses is not clear, but there is mounting evidence showing that many components of the cholinergic system interact with APP or its fragments (Figure 4A). Most of the evidence stems from studies performed in the pathological context of Alzheimer's disease, where APP metabolism is misregulated.

However, the apparent parallelism in the affectation of central and peripheral cholinergic transmissions in APP-related diseases suggests a specific role of APP in the organization of the cholinergic system in general. Thus, the APP family of proteins mediates the post-translational regulation of ChT activity in both the NMJ and in central cholinergic neurons. Loss of APP or APP/APLP2 leads to defective ChT localization in the NMJ and reduced ChT activity in the central nervous system. AChE was shown to enhance Aβ fibril formation in vitro [47], to enhance their neurotoxic effects [2] and to facilitate amyloid plaque formation in vivo [84]. Some of these effects are blocked by the homologous enzyme butyryl-cholinesterase (26). Disruption of cholinergic neurotransmission contributes to the memory impairment characteristically associated with Alzheimer's disease [25,108] and nicotine treatment and drugs that potentiate central cholinergic function have been shown to improve attention and learning and memory performance in patients with mild to moderate Alzheimer's disease [113].

Muscarinic agonists attenuate both Aβ and tau pathologies and delay the development of cognitive impairments in transgenic mice [16]. There is also evidence that Aβ42 binds directly to the nicotinic α7-type homomeric AChR with very high affinity and that this interaction facilitates intraneuronal accumulation of Aβ (Figure 4B) [69]. The Aβ peptide can act as agonist or antagonist of the nicotinic AChR and produce the disregulation of the coupling with cell signaling cascades such as ERK-MAPK and JNK-1 [11,50,60,109,111]. Aβ can also bind and modulate muscle-type nicotinic AChR [100]. Moreover, AChE and neuronal AChR are present in brain amyloid plaques characteristic of Alzheimer’s disease (Figure 4B) [20,105]. A recent study reported that AChR agonists increase αAPPs secretion and reduce Aβ levels [66,70]. These cumulative pieces of evidence support the notion that receptor activity and therefore synaptic activity is in itself a neuroprotective mechanism. This is also illustrated by the fact that inhibition of α7 or α3 AChR subunit expression reduces the level of neurotrophic αAPPs [66].

APP and Cholinergic Synaptopathies

Brain and skeletal muscle are the only known tissues in humans characterized by the pathological accumulation of diverse forms the amyloid peptide (Aβ). This accumulation is associated in both tissues with age-related degenerative diseases such as Alzheimer's disease and inclusion body myositis (Figure 4B). The amyloid pathology in the central neuron system progresses in a neurotransmitter-specific manner, cholinergic neurons being the first and most affected [13]. Disruption of cholinergic neurotransmission contributes to the memory impairment that characterizes Alzheimer's disease [12,25,108]. Increased processing of APP by the amyloidogenic pathway is found in this pathology, with concomitantly higher levels of Aβ. Mutations of APP and of its processing enzymes are found in familiar forms of Alzheimer's disease, highlighting the importance of this pathway in the pathology of cholinergic central synapses [56,110].

Sporadic inclusion body myositis is the most common muscle disease in elderly persons. It is a degenerative disease that progresses from muscle weakness to severe disability. The characteristic histopathological signs of inclusion body myositis are the presence of autophagic vacuoles and protein aggregates inside the muscle fiber. As in Alzheimer's

disease, there is an inflammatory component that in inclusion body myositis is manifested by the presence of cytolytic CD8+ T lymphocytes in the muscle [9]. Vacuoles and protein aggregates distinguish inclusion body myositis from polymyositis. In the former case, the vacuoles are considered to be autophagic, since they often contain lysosomal components.

There are two mayor types of aggregates present in the muscle fibers of patients with inclusion body myositis: dense plaque-like inclusions containing Aβ and more faint inclusions containing phosphorylated tau protein in the form of paired helical filaments. These types of aggregates are also found in postmortem brain of Alzheimer's disease patients. As with Alzheimer's disease, the role of Aβ in inclusion body myositis is still obscure, but there is evidence that it may contribute to the pathogenesis of both diseases. The appearance of Aβ-positive deposits precedes vacuolization of the muscle fibers in inclusion body myositis [7]. APP processing is altered in inclusion body myositis muscle as well as in Alzheimer's disease brain, and this is reflected by increased levels of APP, BACE and two components of the γ-secretase complex [10,102,103]. There is also an increase in APP RNA, thus suggesting that transcriptional activity is altered [90]. Consequently, there is an accumulation of Aβ in affected muscle fibers of patients suffering inclusion body myositis; the predominant species is Aβ42, in the form of the more toxic oligomers [9,75,104] Further evidence supporting the role of Aβ42 in the development of inclusion body myositis is the finding that the muscle weakening phenotype is highly correlated with increasing amounts of this peptide [53]. Aβ oligomers are observed neither in control muscle biopsies [73] nor in neurons in Alzheimer's disease [88]. More importantly, transgenic mice that selectively overexpress full-length human APP develop many of the characteristic pathological findings of inclusion body myositis [98]. The transgenic animals accumulate intracellular Aβ and Aβ-containing fragments in an age-dependent manner, presenting muscle inflammation, centric nuclei, vacuolar changes and motor deficits [98]. Moreover, immunization with Aβ attenuates the observed muscle pathology and motor impairment in a transgenic mouse model of inclusion body myositis [54]. Likewise, early immunization of a mouse transgenic model of Alzheimer's disease prevented the development of amyloid plaques, neuritic dystrophy and astrogliosis. Treatment of the older animals also reduced the extent and progression of these Alzheimer-like neuropathologies [91]. Anti- Aβ immunization was also shown to clear Aβ peptide and to reduce phosphorylated tau from human brain of Alzheimer's disease patients [94].

Despite the similarities, no obvious genetic link exists between inclusion body myositis and Alzheimer's disease-related genes such as apolipoprotein E or APP [8,40]. Moreover, Alzheimer's disease patients exhibit slightly but significantly elevated levels of Aβ42 peptide in their muscle, without any apparent pathological consequences; conversely, during the progression of inclusion body myositis brain function seems to be unaffected [55]. This could imply tissue-specific functions or regulation of APP and its processing machinery. On the other hand it was suggested that if inclusion body myositis developed after dementia, it could pass inadverted [68]. It is interesting to note that muscle strength was associated with a decreased risk of mild cognitive impairment, an early manifestation of Alzheimer's disease [14]. There is also the possibility that central and peripheral cholinergic synapses have different adaptive capacities to absorb the alteration in APP metabolism.

CONCLUSION

Establishment and survival of peripheral and central cholinergic synapses requires a correct balance between the amyloidogenic and non-amyloidogenic processing of APP. Alteration of such balance may result in both central and peripheral synaptophathies that share many molecular manifestations.

ACKNOWLEDGMENTS

Research described in this article was supported in part by PICT 01-12790 and 5-20155 from FONCYT, Ministry of Science and Technology; PIP No. 6367 from the Argentinian Scientific Research Council (CONICET); Philip Morris USA Inc. and Philip Morris International to F.J.B.

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