The Role of β -Amyloid Protein in Synaptic Function: Implications for Alzheimer's Disease Therapy

F. Peña^{1,*}, A.I. Gutiérrez-Lerma¹, R. Quiroz-Baez² and C. Arias²

¹Departamento de Farmacobiología, Cinvestav-Coapa, México D.F. 14330, México; ²Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, UNAM, México D.F. 04510, México

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive and irreversible loss of memory and other cognitive functions. Substantial evidence based on genetic, neuropathological and biochemical data has established the central role of β -amyloid protein (β AP) in this pathology. Although the precise etiology of AD is not well understood yet, strong evidence for some of the molecular events that lead to progressive brain dysfunction and neurodegeneration in AD has been afforded by identification of biochemical pathways implicated in the generation of β AP, development of transgenic models exhibiting progressive disease pathology and by data on the effects of β AP at the neuronal network level. However, the mechanisms by which β AP causes cognitive decline have not been determined, nor is it clear if the degree of dementia correlates in time with the degree of neuronal loss. Hence, it is of interest to understand the biochemical processes involved in the mechanisms of β AP-induced neurotoxicity and the mechanisms involved in electrophysiological effects of this protein on different parameters of synaptic transmission and on neuronal firing properties. In this review we analyze recent evidence suggesting a complex role of β AP in the molecular events that lead to progressive loss of function and eventually to neurodegeneration in AD as well as the therapeutic implications based on β AP metabolism inhibition.

Key Words: Alzheimer disease, β -amyloid protein, cognitive impairment, synaptic dysfunction, synaptic plasticity.

I. INTRODUCTION

Alzheimer Disease (AD) is a progressive neurodegenerative disorder and the most common of the late-life dementias. The sporadic form of AD frequently begins after the age of 60 years and its prevalence rises steadily with age, affecting less than 3% of individuals between 60 and 70 years of age, up to 12% of those between 70 and 80, and more than 40% of people over 85 [78]. It is expected that the number of individuals with AD will increase dramatically as the world population gets older [78]. AD is characterized by synaptic and neuronal loss, amyloid β protein (β AP) deposition, and the presence of neuro-fibrillary tangles. A central role of β AP in AD has been established by substantial genetic, neuropathological and biochemical evidence [28, 39, 52, 76, 82, 99, 101, 102, 143, 147, 153, 171, 183, 185, 201]. Although the precise etiology of AD still remains poorly understood, the identification of biochemical pathways implicated in β AP generation, and the development of β AP transgenic models exhibiting progressive disease pathology provide a strong correlation between β AP generation and the progressive neurodegeneration characteristic of AD. However, up to now the precise mechanism by which β AP causes cognitive decline has not been determined, nor if the degree of dementia correlates in time with the degree of neuronal loss.

There is growing interest in understanding the biochemical processes involved in the mechanisms of β AP-induced neurotoxicity and, more recently, in the mechanisms

involved in the electrophysiological effects of this protein on different parameters of synaptic function. Here we review how β AP is produced, and the putative effects of this protein once it has been released to the extracellular space, in order to identify therapeutic targets to prevent β AP-induced neurotoxicity.

II. β AP METABOLISM

The β AP is a 39-43 amino acid peptide cleavage product derived from the amyloid precursor protein (APP) [67, 125] a type I integral membrane glycoprotein. The APP gene is located in chromosome 21, widely expressed in cells throughout the body and is also highly conserved in evolution [68, 173]. There are 10 isoforms of this protein ranging in size from 563 to 770 amino acids. Neurons mainly express the 695 amino acid-long form (APP695) that lacks a Kunitz-type protease inhibitor sequence [172].

The proteolytic pathway by which β AP is generated has been well characterized in a number of cell lines [159]. β AP is generated by the sequential processing of two proteases, β -secretase and γ -secretase, which produce the N and the C termini of β AP, respectively, through the amyloidogenic pathway. Alternatively APP can be processed by α -secretase, which precludes the formation of β AP in the non-amyloidogenic pathway. Although cleavage of APP by α -secretase is the major proteolytic pathway, the exact identity of α -secretase has not been confirmed; however, its activity has been associated with regions with low cholesterol content [103]. Pharmacologic studies suggest that α -secretase could be a zinc-dependent metalloprotease [138]. This enzymatic activity may be constitutive or inducible through activation of protein kinase C (PKC) [109]. Preliminary data suggest that TACE (TNF- α converting enzyme), a metalloprotease

*Address correspondence to this author at Departamento de Farmacobiología, Cinvestav-Coapa, Calz. de los Tenorios 235; Col. Granjas Coapa, 14330, México D.F., México; Tel: +52(55)5061-2852; Fax: +52(55)5061-2863; E-mail: jfpena@cinvestav.mx

that belongs to the ADAM (a disintegrin and metalloprotease) family (also called ADAM17), may have α -secretase-inducible activity [139]. On the other hand, ADAM10 also appears to process APP through the α -secretase pathway. The expression of a dominant-negative form of ADAM10 inhibits endogenous α -secretase activity, whereas its overexpression increases both constitutive and inducible activities [191]. Some studies suggest that ADAM9 could be another candidate protein with α -secretase activity [11].

Under normal metabolic conditions about 10% of APP molecules fail to be cleaved by α -secretase, so APP can be internalized into endocytic compartments and subsequently cleaved by β -secretase and γ -secretase, to generate β AP as mentioned above. The β -site APP-cleaving enzyme (BACE) has been identified as the protein that contains the β -secretase activity; BACE is a protein with homology to the pepsin family of aspartyl proteases [180]. The BACE-1 protein is highly expressed in neurons and appears to be the major enzyme in the amyloidogenic pathway [60]. Moreover, antisense inhibition of BACE-1 reduces the generation of β AP in cell cultures [180, 196]. BACE-1-mediated cleavage occurs at the Asp-1 of the β AP domain; interestingly, the homologous protein BACE-2 has a distinct APP-cleavage specificity. It has been demonstrated in cell cultures that BACE-2 cleavage occurs in the middle of the β AP domain between phenylalanines 19 and 20 [60].

The γ -secretase is a protein complex that cleaves within one of the transmembranal regions of the APP, and it is formed by presenilin (PS) (which contains the protease activity of the complex), nicastrin, Aph-1 and Pen-2 [202, 61]. These components are critical to the γ -secretase function because each one may modify the activity and response to physiological stimuli (for review see [26]). The participation of PS in the pathogenesis of AD has been demonstrated in most cases of familial AD (FAD), with clear genetic causes (for review see [145]).

Some studies have found that a small fraction of β AP peptides could be generated in the Golgi apparatus and, to a lesser extent, in the endoplasmic reticulum. β AP peptides generated in intracellular organelles can be secreted into the extracellular space [73]. The major species of secreted β AP are the soluble 40 amino acid-long peptides (β AP₁₋₄₀), found in the CSF at low nanomolar concentrations [181]. However, the minor species of 42 amino acids length (β AP₁₋₄₂) is more fibrillogenic and is highly enriched in amyloid plaque cores from AD patients and from the brain of transgenic mice models [84, 106].

III. β AP INDUCES SYNAPTIC TOXICITY

The possibility that β AP plays a physiological role throughout life is suggested by reports that show that β AP is routinely produced by many cell types [159]. In neuronal cultures, β AP is generated at high picomolar to low nanomolar concentrations [161]. Similarly, it has been postulated that secreted β AP possibly interacts with extracellular substrate molecules in the nervous system and exerts neurotrophic actions [197].

Some studies have shown that neuronal electrical activity can modulate the APP secretory products [136] and, more recently, Kamenetz *et al.*, [89], in an acute model of overexpressed APP, reported that neuronal electrical activity modulates APP processing, possibly by promoting the endocytosis of surface APP, which becomes more accessible to BACE in endosomal/recycling compartments. Moreover, the authors suggest that β AP may have a physiological negative feedback function: increased neuronal activity produces more β AP and, in turn, β AP depresses synaptic function. Consistent with these findings it has been recently demonstrated that β AP is capable of regulating the surface expression and endocytosis of NMDA receptors [164]. Conceivably, prolonged depression of NMDA receptor-mediated transmission may initiate the pathological changes observed in AD.

The data described above may have therapeutic implications because benzodiazepines have been found to protect against AD [58] and NMDA antagonists like memantine have been shown to be effective in mild to severe AD patients [192].

In AD, loss of synapses exceeds neuronal loss and seems to underlie the cognitive deficits that characterize this degenerative dementia [47]. Some data suggest that synapses may be sites where the neurodegenerative cascade may initiate, and, in fact, the loss of the synaptic-associated protein synaptophysin has been taken as an early marker of neurodegeneration [123]. Moreover, in plaque-forming APP transgenic mice, the developed markers of active loss of synapses have been observed [38].

The loss of synaptophysin in synaptic terminals in specific brain regions [50, 79, 123, 170, 175] correlates well with the cognitive decline in AD. In contrast, the relationship between amyloid plaques and clinical manifestations of neurodegenerative changes remains controversial [16, 42, 43, 45, 69, 118, 127, 174]. Interestingly, in some APP transgenic mouse lines, the numbers of synaptophysin-positive presynaptic terminals and microtubule-associated protein (MAP2)-positive neurons are around 30% less than in nontransgenic controls at age 2 to 3 months old, well before any β AP plaque formation [81]. Comparisons of transgenic lines with variable levels of APP expression suggest that decreases in presynaptic terminals are critically dependent on cortical β AP levels, but not on the β AP plaque burden or APP levels [133]. In accordance with this finding, presynaptic terminals are significantly depleted in 2 to 4 month-old transgenic APP mice, in correlation with an increase of soluble β AP before plaque formation. These data nicely show that memory and cognitive deficits in AD correlate far better with cortical β AP levels than with plaque numbers [135]. Even in very mildly impaired cognitive patients, soluble β AP levels in the cortex show a significant correlation with the degree of synaptic loss [118]. In the transgenic mice Tg2576, the reduction in synaptic terminals is also observed in the hippocampus; in this case the presynaptic protein SNAP-25 (synaptosomal-associated protein 25) is greatly reduced prior to the formation of plaques, and the intracerebroventricular injection of anti- β AP antibodies reverts the synaptic protein lost at the age of 11 months [31].

Recent evidence has shown that the Fyn-kinase pathway seems to be involved in β AP synaptotoxicity, since on a Fyn^{+/+} background, β AP decreased hippocampal synaptophysin levels, but on a Fyn^{-/-} background this decrease was not observed [34]. Furthermore, the overexpression of Fyn exacerbated the reduction of synaptophysin-immunoreactive presynaptic terminals in transgenic mice [34]. Dysregulation of the ERK/CREB signaling in an AD mouse model displaying extracellular β AP accumulation has also been demonstrated [51], and in rats expressing AD transgenes that accumulate β AP intraneuronally, the presence of β AP is sufficient to induce up-regulation of the phosphorylated form of ERK-2 [54]. Given that these signaling pathways are involved in synaptic plasticity [1], similar biochemical changes may contribute to the mild cognitive impairment observed in the preclinical stages of AD.

In addition to the evidence discussed above, other biochemical and morphological indicators suggest that an attack on synapses may underlie the cognitive decline in AD [163]. A quantitative morphometric study from Alzheimer's brains revealed a 25%–35% decrease in the density of synapses in cerebral cortex and a 15%–35% decrease in the number of synapses per cortical neuron [44]. The neurochemical consequences of this synaptic terminal decrease must be expressed at several levels of synaptic function (for electrophysiological evidence, see below). For example, it has been observed that in hippocampal slices, β AP_{25–35} induces an increase in the release of excitatory amino acids after depolarization [5]. Consistent with this result, it has been reported that in cortical synaptosomes, β AP_{25–35} profoundly affects synaptosomal morphology as well as the levels of synaptophysin and actin proteins. Electron microscopic analysis of synaptosomes incubated with β AP shows a depletion in the content of synaptic vesicles as well as recruitment to and docking at the active zone, in addition to the appearance of pleomorphic vesicles, suggesting that β AP is capable of activating the mechanism of vesicular exocytosis [134]. Interestingly, microarray analysis of transgenic APP₆₉₅-SWE mice showed that the transcript levels for some of the synaptic vesicles, trafficking-related genes are decreased [198].

Moreover, physiologically relevant concentrations of β AP-related peptides have acute, negative effects on multiple aspects of acetylcholine (ACh) synthesis and release, without inducing toxicity. These data suggest a neuromodulatory influence of the β AP peptides on central cholinergic functions (for review see [92]). The amyloid pathology seems to progress in time and affect neurotransmitter release in a specific manner, first in the cholinergic system which appears to be the most vulnerable, followed by the glutamatergic presynaptic boutons and finally by the somewhat more resilient GABAergic terminals, as has been shown in a transgenic mouse model [19].

Some studies in hippocampal slices and synaptic nerve endings have indicated that β AP is capable of inhibiting choline uptake and the release of ACh [91]. In transgenic APP-SWE mice the degeneration of ChAT-immunoreactive fibers in the environment of amyloid plaques suggests a role for β AP and/or inflammation in the specific degeneration of

cholinergic synaptic structures [119]. Recently, other groups have reported an increase in the activity of the enzyme acetylcholinesterase (AChE), and specific high-affinity binding of β AP_{1–42} to the neuronal $\alpha 7$ AChR, and low-affinity binding to the receptor $\alpha 4\beta 2$, concomitant with a regulatory function on NMDA-R throughout the modification of the NR2A subunit [71].

Synaptic vulnerability to β AP may also be increased by other factors associated with the aging brain in AD. Epidemiological evidence suggests a strong correlation between vascular disorders, which can predispose to cerebrovascular disease or stroke, and AD, implicating vascular disease as a risk factor for AD [88]. Some results indicate that coadministration of β AP with low concentrations of the metabolic toxins 3-NP and iodoacetate produces a drastic inhibition of the synaptosomal redox function [6]. Interestingly, synaptosomes isolated from the hippocampal region appear to be more vulnerable to β AP toxicity in the presence of metabolic inhibitors than synaptosomes obtained from the neocortex, and in all conditions, the metabolic substrate pyruvate served as an excellent substrate to restore synaptosomal mitochondrial redox function altered by metabolic inhibition and β AP toxicity [6].

Many of the mentioned abnormalities induced by the presence of β AP in the brain would be expected to play a role in interfering with memory function. In this context, some very interesting studies report that β AP deposition modifies the shape and length of pyramidal and dentate granular cells dendrites [100, 178, 193], which has been suggested is sufficient to modify the relative timing of pre- and post-synaptic action potentials. Computational studies indicate that the effects of β AP on dendritic remodeling could be of considerable importance in AD [163]. In cultured neurons from Tg2576 mice, selective alterations have been found in pre- and post-synaptic compartments compared to wild-type neurons. While pre-synaptic sites appear fewer and enlarged, post-synaptic compartments appear fewer and shortened. Among the earliest changes is the reduction in the post-synaptic protein PSD-95 accompanied by reduction of the glutamate receptor subunit GluR1 [3]. On the other hand, in living Tg2576 mice, an altered pattern of disrupted neurite trajectories and a 25% reduction in dendritic spines density compared with age-matched control mice have been recently reported [165].

Interestingly, it has been suggested that β AP and not amyloid plaques play the major role in the damaging effect on dendrites. In two transgenic mouse strains (J20 and APP/PS1) that express mutant forms of the APP, swollen bulbous dystrophic neurites have been found with loss of spines as early as 3 months after birth, and not associated with amyloid plaques [132]. All these data suggest the importance of the synapto-dendritic complex in the pathophysiology of AD.

The fundamental mechanisms underlying the neuronal toxicity of β AP are complex and not well understood yet. It has been proposed that this peptide produces an early disruption of Ca^{2+} homeostasis [63, 65], and also increases reactive oxygen species (ROS), which in turn may alter several neuronal functions [27, 94].

It is generally accepted that β AP is neurotoxic in micromolar concentrations depending on its conformational state [117, 142]. β AP toxicity may be induced by two pathways: the first implies direct injury to the cell by membrane damage [121], and in the second, β AP acts indirectly by enhancing neuronal vulnerability to neurotoxic insults, such as excitotoxicity, hypoglycemia, oxidative stress or metabolic impairment [6, 126].

Current data show that β AP oligomers are stable molecules that can exist for long periods in the brain prior to conversion to fibrillar structures [35]. Target sites for oligomers are dendritic arbors; in fact, oligomers extracted from AD brain were found to attach selectively to dendrites in culture [70]. Recently, Lacor *et al.*, [107] reported that β AP oligomers extracted from AD brain or prepared *in vitro*, bind to neuronal surfaces in small punctate clusters that colocalize almost exclusively with a subpopulation of synaptic terminals in cultured hippocampal neurons. Binding is accompanied by ectopic induction of Arc, a synaptic immediate-early gene involved in long-term memory formation [74].

Other synaptic signal transduction pathways are also affected by β AP oligomers in culture models. In cortical cultures, low doses of β AP oligomers inhibit the glutamate-stimulated phosphorylation of cAMP response element-binding protein [177], a signaling pathway associated with synaptic plasticity [169].

The action of β AP oligomers as pathogenic synaptic ligands provides an interesting hypothesis to explain the failure of synapse in AD. All data taken together show that β AP seems to be an instrument of synaptic attack and that synapses may be targets of therapeutic intervention in AD. We will now review evidence showing that β AP may have detrimental effects on neuronal network function through its effects on the two major components of a neuronal circuit, its intrinsic and its synaptic properties [148].

IV. β AP-INDUCED ALTERATIONS OF THE SYNAPTIC FUNCTION

We have mentioned that synapses are a chief target for β AP-induced pathology [50, 79, 124, 122, 170, 175] and that the decrease in synapse number is a major feature of AD [20, 44, 46]. Although initial studies suggested that only aggregated forms of β AP were neurotoxic [117], overwhelming evidence [56, 153] suggests that the soluble oligomeric form may also be neurotoxic at the functional level. But how does soluble β AP impair cognitive functions?

The precise mechanism that explains the link between β AP and the progressive loss of cognitive functions is still unresolved. Perturbations of proper neuronal network functioning may constitute the missing link. As we mentioned before, it is well known that the interplay between intrinsic and synaptic properties defines the functional properties of a given neuronal circuit and that alterations in one or in both components may be responsible for neuronal network dysfunction (for review see [148]). Two major neuronal network processes have been proposed to be associated with cognition, one involves synchronous activities of neuronal ensembles, such as theta and gamma

rhythms [176] (for review see [17, 18]) and the other involves a diversity of effects on synaptic plasticity [2, 24, 53, 104], particularly on Long Term Potentiation (LTP), and Long Term Depression (LTD, for review see [23, 116]).

IV.A. Electrophysiological Studies

Some questions arise from the above considerations: what are the neurophysiological consequences of the β AP-induced synaptotoxicity on neuronal networks? Are the neurophysiological consequences related with cognitive dysfunction? So far, the answers remain elusive, and the results of several studies involving these issues are controversial. For example, some reports show that β AP applied *in vivo* or *in vitro*, or overproduced by transgenic mice, is capable of reducing, or alternatively having no effect on basal synaptic transmission; and the same applies for LTP. The variety of effects observed over the past years correlates with the variety of *in vivo* and/or *in vitro* models. However, in all reports, regardless of the approach used, there is always an effect of β AP either on basal synaptic transmission, on LTP or on both. There are some exceptions where no effects of β AP on basal synaptic transmission or on LTP have been shown, but in those cases, alterations in other neuronal network properties, such as the ability to induce network oscillations, have been described (see below).

IV.A.1. Effects of β AP on Basal Synaptic Transmission

There are two lines of evidence regarding the effect of β AP on basal synaptic transmission: one shows no effect of β AP on basal synaptic transmission and the other shows a β AP-induced decrease of basal synaptic transmission. In general, no significant effect on the baseline transmission amplitude was detected in the CA1 area of the hippocampus *in vivo* in the PDAPP transgenic mice (which expresses the human APP with the V717F mutation) both at ages 3–4.5 and 24–27 months; no changes were detected in neurons from the dentate gyrus of the hippocampus either [66]. Studies on transgenic mice overexpressing mutated human amyloid precursor protein (APP695-SWE) exhibited normal fast synaptic transmission and normal paired pulse facilitation in both the CA1 and dentate gyrus regions of the hippocampus when assessed both *in vitro* and *in vivo* at ages 2 to 8 months (without β AP deposits) or at ages 15 to 17 months (with many β AP deposits) [30]. In the same transgenic mice, also named APP-SWE Tg2576, the overall level of spontaneous cortical activity is indistinguishable from that observed in control non-transgenic mice [167]. In the prefrontal cortex of APP23 transgenic mice *in vitro*, no alterations in synaptic transmission were observed whereas in the hippocampus a reduction was detected at 12 and 18 months of age [152]. When β AP was intracerebroventricularly injected, no effect was observed on single-pulse-evoked glutamatergic and GABAergic synaptic transmission onto the hippocampal CA1 pyramidal cells assessed in hippocampal slices [168]. The same approach showed no effect on basal synaptic transmission tested *in vivo* [40]. In *in vitro* preparations, brief perfusion of slices with low concentrations (200 nM or 1 μ M) of β AP_{1–42}, β AP_{1–40} or the active fragment β AP_{25–35} did not affect the basal synaptic transmission in the Schaffer collateral-CA1 pathway [32]. On the other hand, slices pre-incubated for 60 minutes in the presence of β AP-derived diffusible ligands, showed no

differences in threshold intensity to evoke a synaptic response, in the slope of field excitatory post-synaptic potentials or in the input/output function [187]. Since β AP administration has no effect on paired-pulse facilitation, [64, 187], or on glutamate evoked currents [141], it has been proposed that β AP does not alter the presynaptic and postsynaptic sites.

In contrast to the evidence showing no effect of β AP on basal synaptic transmission, there is another body of evidence that shows that β AP has a strong effect on it. For example, Hsia *et al.*, [81] showed a 40% loss of basal synaptic transmission in hippocampal slices in PDAPP transgenic mice. Synaptic impairment appeared to be due to a significant reduction in synaptic number, not to the synaptic strength. In the same report, a second mouse line to which they added the Swedish mutation was analyzed and an even worse deficit in synaptic transmission at age 2 to 4 months was observed, attributable to the accumulation of diffusible forms of β AP before plaque formation [81]. In another study with PDAPP mice, a reduction in basal synaptic transmission was confirmed in the CA1 area of the hippocampus *in vitro*. This reduction was accompanied by an increase in paired-pulse facilitation [110]. We previously mentioned that the basal synaptic function in the hippocampus was reduced in the homozygous APP23 mice compared with their wild type littermates at 12 and 18 months of age [152]. Finally, slices taken from 12-month-old APP695-SWE transgenic animals, displayed reduced levels of synaptic transmission in the CA1 region of the hippocampus when compared with wild-type littermate controls, but in this case paired-pulse facilitation was normal [59]. When β AP was injected intracerebroventricularly, a deficit in basal synaptic transmission was observed [41, 166].

In an *in vitro* study it was reported that bath and intracellular application of 200 nM β AP₁₋₄₀ to rat dentate gyrus slices resulted in rapid enhancement of NMDA receptor-mediated currents in granule cells [194]. Furthermore, a higher dose of β AP₂₅₋₃₅ (1 μ M) amplified NMDA receptor-mediated depolarization of guinea pig lateral septal neurons [29]. A recent study observed a mild reversible inhibition of NMDA receptor-mediated field potentials by 200 nM β AP₁₋₄₀ [151]. Low doses of β AP₁₋₄₂ were also found to inhibit NMDA receptor-mediated synaptic currents in dentate granule cells [33], in contrast to the finding by Wu *et al.*, [194].

IV.A.2. Effects of β AP on Long-Term Plasticity

It has been proposed that long-term plasticity (specifically LTP and LTD) is intimately related with learning and memory (for review see [23, 53, 116]). For this reason it has been of great interest to study the effects of β AP on long-term plasticity, trying to find a correlation of these effects with cognitive impairment in AD. Similarly as with the diversity of effects of β AP on basal synaptic transmission, there are also controversial findings with respect to the effects of β AP on long-term plasticity.

IV.A.3. β AP may Reduce LTP

In the APP-SWE Tg2576 mice that showed no major disruption of synaptic markers, of cell viability, and no change in basal synaptic transmission, there was an

impairment of LTP both *in vivo* and *in vitro* [30]. In the PDAPP mouse line, at 3 months of age (long before plaque formation) a decrease in LTP was observed which correlated temporarily with cognitive impairment [131]. In the same transgenic mice at age 4–5 months (prior to the deposition of β AP), a slight reduction in basal synaptic transmission was found in the CA1 area *in vitro*, which was associated with a reduction in theta-induced LTP. In aged mice (27 months), which had amyloid plaque formation, baseline transmission was reduced by 70%, but LTP was normal [110]. On the other hand, complete inhibition of LTP of the population spike with no significant effect on baseline amplitude was detected in the CA1 area of the hippocampus *in vivo* in PDAPP mice both at ages 3–4.5 and 24–27 months. Interestingly, no changes were detected in the dentate gyrus [66]. Another mutant hAPP line (V642I, London mutation, termed TgAPP/Ld/2 mice) had a deficit in the persistence of LTP of the postsynaptic potential induced by strong high frequency stimulation in the CA1 region of the hippocampus at age 5–7 months, even though amyloid plaque formation was only detected in animals older than 12 months [131]. The inhibition of LTP was confirmed in similar mice (V717I, London mutation) but was absent in double transgenic mice that also had a conditional knockout of PS1. Since β AP production might be blocked in the double transgenic, the inhibition of LTP in V717I mice was attributed to β AP [49]. When conditioned cell medium containing naturally secreted human β AP oligomers, at low concentrations, was microinjected intracerebroventricularly in rats, failure to maintain LTP in the hippocampus was observed [184]. When synthetic β AP is applied *in vivo*, a reduction in LTP without changes in basal synaptic transmission both in CA1 and the dentate gyrus was reported [32, 41, 64, 83, 108, 166, 182]. *In vitro*, brief perfusion of slices with low concentrations (200 nM or 1 mM) of β AP₁₋₄₂, β AP₁₋₄₀ or β AP₂₅₋₃₅, significantly inhibited LTP induction without affecting basal synaptic transmission and post-tetanic potentiation in the dentate medial perforant pathway. Interestingly, the cell-secreted oligomeric forms of the amyloid protein used *in vivo*, were able to inhibit LTP in hippocampal slices from rats [188]. Furthermore, in hippocampal slices prepared from 20–30-day-old rats, soluble β AP₁₋₄₂ (500 nM) was found to inhibit LTP induction by strong high frequency stimulation of the medial perforant pathway in the dentate gyrus in both population spikes [108], and postsynaptic potentials [187]. This study also showed that early- and late-phase LTP were strongly inhibited whereas basal AMPA receptor mediated synaptic transmission was not altered, although a reduction in paired-pulse depression at a short (20 ms) inter-pulse interval was found. Similarly, LTP of field EPSPs in rat CA1 and the medial perforant pathway of the dentate gyrus was inhibited by β AP₁₋₄₂, β AP₁₋₄₀ or by the active sequence form of β AP₂₅₋₃₅. In fact it was shown that this sequence is necessary for inhibition of LTP induction [32]. Moreover, truncated β AP variants that were not lethal to cultured neurons also blocked LTP induction [32]. A more recent work confirmed that β AP oligomers, but not monomers, are responsible for LTP blockade [186].

The mechanisms by which β AP inhibits LTP are not well understood. Inhibition of NMDA receptor-mediated depo-

larization does not appear to be a key mechanism, since NMDA receptor antagonists at doses that inhibit NMDA receptor-mediated potentials to the same extent as β AP, failed to modify LTP [151, 200]. β AP effects appear to be independent of GABA_A receptor-mediated synaptic inhibition, since LTP remains inhibited by the amyloid peptide even in the presence of a high dose of the GABA_A receptor antagonist picrotoxin [151]. These findings suggest that β AP interferes with hippocampal LTP mechanisms downstream from NMDA receptor activation, probably by modulating a non-glutamatergic pathway.

A proposed mechanism through which β AP inhibits LTP is by up-regulation of the p38 mitogen-activated protein kinase. Thus, administration of the p38 MAPK inhibitor SB203580 blocked the effect of β AP-induced inhibition of LTP in the dentate gyrus [155]. β AP is also capable of inhibiting protein kinase A (PKA) activity, and consequently the phosphorylation of CREB [182]. These proteins play key roles in both the induction and maintenance of LTP; indeed, elevation of cAMP levels and the resultant PKA activation protects against β AP-induced inhibition of LTP [182].

IV.A.4. β AP may Increase or have no Effect on LTP

In addition to the abundant data reviewed above showing that β AP produces a strong LTP inhibition, there is another body of evidence, albeit smaller, that shows that β AP has no effect on LTP, using transgenic mice and the *in vivo* approach as well. In the APP23 mice, LTP in the hippocampus and the prefrontal cortex was similar, compared with their wild-type littermates [152]. As mentioned before, despite the change in basal synaptic transmission observed in 12 and 18-month old APP695SWE transgenic mice, no change in LTP was observed [59]. In another study performed on the PDAPP transgenic line, LTP induction in response to strong high frequency stimulation remained unchanged [81]. Regarding *in vivo* approaches, acute single intracerebroventricular injection of synthetic β AP₁₋₄₀ (0.4 or 3.5 but not 0.1 nmol) caused a reduction in baseline transmission and no change in LTP in the dentate gyrus 48 hours later [41]. Another report showed no change, neither in basal synaptic transmission nor in LTP [168].

Besides findings showing no effect on LTP in the presence of β AP, there is the report of Wu *et al.*, [194], showing that synthetic β AP₁₋₄₀ (200 nM) could enhance LTP induction in the associational–commissural pathway of the dentate gyrus of 30–50-day-old rats [195], and another report showing that β AP may rescue CA1 LTP in slices maintained 21 hours *ex-vivo* [105]. Moreover, in the transgenic mice that express a familial AD-linked mutation in PS-1 (A246E), in which an increase in amyloid accumulation is expected at the age of 5–6 months, facilitation of LTP was observed [137].

IV.A.5. Other Possibilities Besides LTP

Another possibility, besides the changes in LTP produced by β AP, may be the other form of long-term plasticity, which is long-term depression (LTD). Unfortunately, there are also controversial reports with respect to this issue. The fronto-striatal LTD induced by tetanic stimulation of the cortico-striatal input was similar in the transgenic mice Tg2576 and in wild-type control mice [130]. Two studies

reported no effect of soluble β AP on LTD in hippocampal slices from either CA1 area [151] or the dentate gyrus [187]. In contrast, intracerebroventricular injection of β AP₁₋₄₂ has been reported to facilitate the induction of LTD in the CA1 region of anesthetized animals [96]. These controversial data, along with the ones obtained from LTP, open the possibility of exploring other processes that may be underlying the β AP effects in neuronal network dysfunction, which are probably associated with cognitive impairment. One of the mechanisms that may be worthwhile to explore are neuronal network oscillations, the induction and maintenance of which have also been related to cognition [176]; (for review see [17, 18]). In fact, there are a couple of reports suggesting the β AP may disturb such oscillations. Sun and Alkon [168] reported that single intracerebroventricular injection of β AP produced cognitive impairment that was not related with changes in basal synaptic activity or in LTP, but, interestingly, the authors found that the ability of the hippocampus to generate carbachol-induced theta rhythm was abolished [115]. Theta activity is believed to gate or facilitate memory information processing in the hippocampus [176], and disruption of this kind of rhythms may also be involved in β AP-induced cognitive deficits. On the other hand, in Tg2576 transgenic mice it was found that despite no alterations observed in normal “bistable” activity produced by cortical neurons, these mice had dramatic alterations in the synaptically-induced transitions from the up-state to the down-state and *viceversa*; the authors suggest that this failure may be due to a β AP-induced disruption in synaptic synchronization [167]. This possibility has been suggested in other transgenic as well [25].

So, reports regarding the effect of β AP applied *in vivo*, *in vitro* or produced in transgenic mice on basic neuronal mechanisms necessary for proper network functioning and plasticity are controversial. β AP either reduces or has no effect on basal synaptic transmission, LTP or LTD. In general, we can conclude that β AP may produce very complex effects on neuronal network activity that lead to disruption of the normal neurophysiological state involving synaptic transmission, synaptic plasticity or both. The challenge is to determine the conditions in which these electrical alterations may occur in order to find ways to prevent this from happening. It is clear that β AP always produce an inhibitory effect either on basal synaptic transmission or on long-term plasticity, with some exceptions reviewed as well. It is conceivable that β AP-induced alterations of just one of the neuronal processes may be enough to induce neuronal network dysfunction and, consequently, cognitive impairment if the dysfunction occurs preferentially in those circuits related to cognition.

IV.A.6. Molecular Bases of the Differential Effects of β AP on Synaptic Function

There are several molecular aspects to be considered with respect to the reported differences elicited by β AP on synaptic or neuronal function. The diversity of models used for testing different aspects of β AP effects should be considered. They include *in vivo* transgenic mice and *in vivo* intracerebral injections of β AP in non-transgenic rodents [30, 41, 66]. There are also reports with an *ex-vivo* approach using brain slices obtained from transgenic mice or from

non-transgenic rodents after treatment with β AP *in vivo* [30, 152, 168]. On the other hand, in *in vitro* experiments, the procedures to obtain brain slices and the conditions of recording may also contribute to the variable effects of β AP on synaptic and intrinsic neuronal properties [13, 32, 187]. Another source of discrepancy may be the variability in length of β AP peptides with different biological activity and their state of aggregation. In fact, it was originally proposed that the neurotoxic effects of β AP required micromolar concentrations and highly aggregated states [117, 118, 144]. However, recent evidence suggests a role of soluble monomer or oligomer forms of β AP that alter neuronal activity and remodeling at the functional level (long before neurodegeneration). For example structural changes as well as behavioral abnormalities are observed long before plaques are formed [34, 81, 133]. In addition, protofibrils, an intermediary form between soluble and aggregated β AP, are toxic to primary neuronal cultures and alter their electrophysiological properties [77, 199, 200, 189]. It has also been shown that oligomers but not fibrils or monomers are responsible for the inhibition of LTP *in vivo* [184, 186]. Furthermore, a recent report showed that, among the naturally secreted oligomers, there is a set that includes dimers and trimers, necessary and sufficient to produce cognitive deficit in rats [37]. Interestingly, it has also been found that β AP may undergo an aggregation process *in vitro* [112, 189]. In fact the fibrils obtained *in vitro* are quite similar to those observed in patients [97, 98, 129, 160]. This opens the possibility that the β AP solutions prepared to study the effects of exogenous added β AP may have mixed forms of β AP in different states of aggregation. The coexistence of several states of aggregation in the same preparation can be applied to *in vivo* experiments with non-transgenic and transgenic rodents since it has been shown that different forms of β AP in different states of aggregation can coexist in these animals as well as in humans with the disease [75, 144, 42, 127, 135]. A different proportion of β AP in different states of aggregation may then be an explanation of the discrepancy observed in the literature. Finally, another source of discrepancy is that distinct β AP sequences may have different effects, for instance it has been reported that oligomeric β AP₂₅₋₃₅ increases L-type Ca^{2+} currents whereas β AP₁₋₄₀ does not [154]. In contrast β AP₁₋₄₀ may increase N- and P-types Ca^{2+} currents [120, 149].

V. β AP EFFECTS ON NEURONAL EXCITABILITY

Since de 1990's extensive research has revealed that β AP affects neuronal excitability through its effects on a wide array of ionic currents [4, 14, 36, 55, 72, 85, 113, 120, 149, 150, 154, 157, 162, 179, 199, 203, 204, 205] and on ionic channels formed by the β AP itself [7, 8, 9, 10, 62, 86, 87, 95, 115, 128]. From these works emerges the proposal that β AP can alter cellular homeostasis and neuronal network communication through the modulation of ion channel function. The modulating effects of β AP on potassium and calcium channels are listed in Table 1.

V.A. β AP-formed Cationic Channels

Arispe *et al.*, [10] showed that β AP is capable of forming pores in lipid bilayers, and suggested that these channels may directly alter cellular homeostasis and produce cell

death. This proposal has since been supported by several studies, including those conducted in natural cell membranes [7, 8, 9, 10, 62, 86, 87, 95, 115, 128]. β AP is certainly capable of producing cation-selective ion channels in cellular membranes. The original study reports that β AP₁₋₄₀ forms current-conducting channels across bilayer membranes, which allows the passage of different cations with selective permeability: $P_{\text{Cs}} > P_{\text{Li}} > P_{\text{Ca}} \geq P_{\text{K}} > P_{\text{Na}}$. The β AP₁₋₄₀-induced channel current was reversibly blocked by tromethamine and by Al^{3+} [8]. The precise conformation of these channels in membranes is still unknown; however, there are models that suggest that a transmembrane annular polymeric structure is responsible for the ion channel properties of the membrane-bound β AP [7]. By the use of atomic force microscopy, it can be seen that globular, non-fibrillar β AP₁₋₄₂ reconstituted in a planar lipid bilayer, forms multimeric channel-like structures [115].

But how do the β AP-induced alterations on ion channel activity translate to the firing properties of neurons, and of neuronal networks? Generally, suppression or reduction of K^+ currents augment neural excitability and hence can alter the precise timing of neuronal firing, which is fundamental for the adequate processing of information through the nervous system. All studies that have found β AP-induced reduction of K^+ channel activity [85, 199] support this motion. Indeed, it has been shown that β AP protofibrils, but presumably not fibrils, produce a rapid increase in EPSPs, action potentials, and membrane depolarizations in cultured neurons [77]. In differentiated human hNT neuronal cells, β AP induces a significant and lasting calcium-independent membrane depolarization in a concentration-dependent manner through a glutamate mediated system [22]. Of possible therapeutic interest, compounds that can inhibit the β AP-mediated membrane depolarization in this model, include specific tyrosine kinase inhibitors and inhibitors of certain chloride channels [21]. The increase in calcium conductance through specific L-VSCC can also add to abnormal neuronal hyperexcitability [14, 113, 154, 179], as β AP can induce bursts of excitatory potentials and action potential firing in individual neurons, which would affect the neuronal network communication.

VI. THERAPEUTIC APPROACHES

To date, there are no therapeutic interventions available yet capable of halting or reversing AD. The factors implicated in the chronic imbalance between production and clearance of β AP are unknown, but numerous researchers have proposed the inhibition of the proteases implicated in the generation of β AP as a therapeutic strategy.

Acetylcholinesterase inhibitors (AChEIs) are the only drugs currently available for AD treatment. Some authors have suggested that AChEIs do not only function by inhibiting ACh degradation, but also through a possible role in β AP metabolism beyond their well-known symptomatic effects. For example, donepezil increases ADAM10 levels in membrane compartments and significantly decreases the soluble APP α -form levels suggesting a role in the processing of key proteins related with AD pathogenesis [206].

In the case of β -secretase, the chemical compounds under evaluation should be small molecules, capable of binding to

Table 1. Effects of β AP over the Activity of Several Ionic Channels

Channel Affected and General Effect	Form and state of β AP used	Particular Effect	Model Used	Ref.
Potassium channels; increase of K^+ -currents.	β AP ₁₋₄₀ (1 μ M).	Increase of I_{K_A} .	Rat cultured cerebellar granule cells.	[150]
	β AP ₁₋₄₀ and β AP ₂₅₋₃₅ .	Increase of I_{K_C} .	Cultured neurons.	[203]
	Presumably, both oligomers and fibrils of β AP ₁₋₄₀ and β AP ₁₋₄₂ .	Up-regulation of the Kv3.4 in late and early stages of AD.	AD brain tissue.	[4]
	Transient transfection of human presenilins 1, 2 and the APP695.	Increase of the delayed I_{K_C} .	Rat hippocampal neurons.	[205]
Potassium channels; suppression or reduction of K^+ -currents.	β AP ₁₋₄₀ and β AP ₂₅₋₃₅ .	Inhibition of $I_{K_{Ca}}$, I_{K_C} and I_{K_A} .	Dissociated cholinergic neurons.	[85]
	β AP ₁₋₄₂ .	Inhibition of I_D and I_{K_A} .	Cortical neurons <i>in vitro</i> .	[199]
Calcium channels; increase in voltage dependent Ca^{2+} -channel current activity.	β AP ₂₅₋₃₅ (40 μ M).	Increase in I_{CaL} associated with a rise in $[Ca^{2+}]_i$.	Human resting microglial cells.	[162]
	Oligomeric forms of β AP ₂₅₋₃₅ (200 nM).	Increase in total I_{Ca} .	CA1 pyramidal neurons.	[154]
	β AP ₂₅₋₃₅ (20 μ M).	Increase in I_{CaL} and induction of cell death.	SK-N-SH cells.	[14]
	(10 μ M)		Rat cultured cortical and hippocampal neurons.	[179]
	β AP ₁₋₄₀ (1 μ M).	Increase in calcium influx through I_{CaN} and I_{CaP} .	Rat cortical synaptosomes and cultured cortical neurons.	[120]
	Unaggregated β AP ₁₋₄₀ (1 μ M).	Increase in I_{CaN} and I_{CaP} .	Cultured rat cortical neurons.	[149]
	Aggregated β AP ₁₋₄₀ (1 μ M).	Increase in total I_{Ca} .	Rat primary hippocampal cell cultures.	[114]
	Aggregated both β AP ₁₋₄₀ and β AP ₂₅₋₃₅ .	Increase in I_{CaL} through MAPK phosphorylation.	Cultured SH-SY-5Y human neuroblastoma cells (22-40 μ M) and mice cultured cortical neurons (10-25 μ M).	[55]
β AP-formed cation-selective channels.	β AP ₁₋₄₀ (about 5 μ g in liposomes).	Formation of cation selective channels.	Synthetic planar bilayers.	[10]
	Soluble β AP ₁₋₄₀ (about 1 μ M).	Formation of cation selective channels; blocked by zinc.	Synthetic planar bilayers.	[8, 9]
	β AP ₁₋₄₀ (about 5 μ g in liposomes).	Reveals that ion channels are probably transmembrane annular polymeric structures.	Synthetic planar bilayers.	[7]
	Soluble β AP ₁₋₄₂ (2 mg / ml in liposomes).	Formation of multimeric channel-like structures.	Synthetic planar bilayers.	[115]
	Soluble β AP ₁₋₄₀	Formation of cation selective channels.	Cell membranes from hypothalamic neurons.	[93]

$I_{K_{Ca}}$, calcium-activated K^+ current; I_{K_C} , delayed rectifier K^+ current; I_D , K^+ current type D (slow activating, inactivating current); I_{K_A} , K^+ current type A (fast activating and inactivating current); I_{CaL} , L-type voltage-dependent Ca^{2+} current; I_{CaN} and I_{CaP} , N and P-type voltage-dependent Ca^{2+} currents.

aspartyl protease and of penetrating the blood-brain barrier. One such compound is P₁₀-P₄statV, a peptidic inhibitor that mimics the transition-state moiety of β -secretase. The inhibitory action is the result of its binding with the two aspartate active-sites [80]. Recently, a new molecular approach has been developed using small interfering RNA (siRNA) as a therapeutic tool; this technique is directed specifically against BACE-1, in order to lower the BACE-1 protein expression levels in primary cortical neurons derived from both wild type and transgenic mice harboring the Swedish APP mutant and in neuroblastoma cells and HEK293 cells [90]. As a result of BACE-1 protein inhibition, the production of APP β -C-terminal fragment (β -CTF) and β AP (1-40 and 1-42) was significantly reduced [90].

The other strategic target to inhibit β AP production, the γ -secretase, could be attacked by drugs that should be potentially membrane-permeable. These compounds are already available, but they are not currently used in humans because they could interfere with Notch signaling. *In vitro* studies in HeLa cells [113], have shown the potent inhibitory action of L-685,458 (IC₅₀ 0.3nM), and of the hydroxyl epimer L-682,679 (IC₅₀ 82nM) over β AP production. The analog L-405,484 has very poor effects on γ -secretase inhibition (IC₅₀ >100 μ M). On the other hand, the biotinylated photoreactive compounds (containing benzophenone moiety), L-852,505 and L-852,646 displayed excellent inhibitory potency (IC₅₀ $\approx$ 1nM). Recently, a group in France has designed a new set of non-peptidic inhibitors of γ -secretase, with the ability to prevent production of β AP₄₀ and β AP₄₂ without deleterious effects on the endoproteolysis of the Notch intracellular domain. These compounds, named JLK1-8, achieved 70-80% inhibition at a concentration of 100 μ M [140].

Because some of the late effects of β AP in neuronal function depend on its aggregation state, the prevention of β AP oligomerization or its clearance may constitute an important avenue of pharmacological intervention. In this respect, many research groups have been developing immunization approaches with the use of β AP-directed antibodies. However, at present immunization has not shown positives results in clinical trials [15, 48, 156].

Another approach that could prevent the early effects of β AP consists in the use of nonsteroidal anti-inflammatory drugs (NSAIDs). It has been noticed that chronically taken NSAIDs appear to delay the onset of AD symptoms. Besides the well-known effects of NSAIDs on COX inhibition, it has been found that some NSAIDs can also reduce nitric oxide (NO) production [53], and exert protective effects on neuronal apoptosis acting as NO scavengers [12]. Moreover, new results indicate that some NSAIDs, like indomethacin and ibuprofen, may control the activity of γ -secretase, and thus reduce the generation of β AP [190].

Recent results obtained in prospective clinical studies of AD subjects with cholesterol-lowering drugs, such as the statins, are much less conclusive. It has been reported that statins do not affect, or slightly reduce plasma or CSF amyloid concentrations [57]. Overall, preliminary results indicate that modulation of brain cholesterol homeostasis

may interfere with disease onset and/or progression in subjects exposed to cholesterol-lowering agents prior to, or following a diagnosis of AD [146]. Taken together, these findings suggest that agents such as statins, which possess both cholesterol-lowering capacity and anti-inflammatory properties, could be useful anti-AD agents.

Recently, a non-pharmacological approach for AD treatment has been proposed [111]. The authors demonstrated that exposure to an enriched environment of male APP/PS1 transgenic mice which carry two distinct, highly penetrant, dominantly acting human disease-causing alleles, results in a remarkable decrease of cerebral β AP and amyloid deposits *in vivo*.

In conclusion, the β AP hypothesis of AD has led and will continue to lead to the development of therapeutic strategies that are likely to either prevent or treat this devastating disease.

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