

NEUROSCIENCE FOREFRONT REVIEW

THE KEYSTONE OF ALZHEIMER PATHOGENESIS MIGHT BE SOUGHT IN A β PHYSIOLOGY

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Abstract—For several years Amyloid-beta peptide (A β) has been considered the main pathogenetic factor of Alzheimer's disease (AD). According to the so called Amyloid Cascade Hypothesis the increase of A β triggers a series of events leading to synaptic dysfunction and memory loss as well as to the structural brain damage in the later stage of the disease. However, several evidences suggest that this hypothesis is not sufficient to explain AD pathogenesis, especially considering that most of the clinical trials aimed to decrease A β levels have been unsuccessful. Moreover, A β is physiologically produced in the healthy brain during neuronal activity and it is needed for synaptic plasticity and memory. Here we propose a model interpreting AD pathogenesis as an alteration of the negative feedback loop between A β and its physiological receptors, focusing on alpha7 nicotinic acetylcholine receptors (α 7-nAChRs). According to this vision, when A β cannot exert its physiological function a negative feedback mechanism would induce a compensatory increase of its production leading to an abnormal accumulation that reduces α 7-nAChR function, leading to synaptic dysfunction and memory loss. In this perspective, the indiscriminate A β removal might worsen neuronal homeostasis, causing a further impoverishment of learning and memory. Even if further studies are needed to better understand and validate these mechanisms, we believe that to deepen the role of A β in physiological conditions might represent the keystone to elucidate important aspects of AD pathogenesis. © 2015 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: Amyloid-beta peptide, Alzheimer's disease; nAChRs; synaptic plasticity; memory.

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INTRODUCTION

Dementia is a term describing a constellation of symptoms of cognitive decline that impairs the ability of a patient to perform a normal life. The main characteristics are represented by a complete or partial loss of memory and reasoning, as well as emotional, language and personality changes leading, ultimately, to death. Several metabolic, vascular and neurological disorders might induce a dementia state, but Alzheimer's disease (AD) is the most common cause responsible for the 60–80% of cases in North America and Europe, followed by vascular dementia. Since AD prevalence is age-related and the aging population is progressively growing up, a dramatic increase of the disease is expected in the coming decades, making urgent to find valid diagnostic tools and therapeutic strategies. Although basic and clinical research has made considerable progresses, an effective AD treatment is not yet available.

The first description of the clinical and neuropathological features of AD dates back to the early 1900s when the German psychiatrist Alois Alzheimer met a 51-year-old woman, Auguste Deter, suffering of cognitive and psychosocial impairment, hallucinations and disorientation (Maurer et al., 1997). Her post-mortem brain investigation showed thinning of the cerebral cortex together with two characteristic lesions, neurofibrillary tangles and extracellular deposits later named senile plaques. First validated by epidemiological, clinical and neuroanatomical studies, and then supported by genetic and biochemical evidences, tangles and plaques have dominated the AD research scene for more

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Abbreviations: α 7-nAChRs, alpha7 nicotinic acetylcholine receptors; AA, aminoacids; A β , Amyloid-beta peptide; AD, Alzheimer's disease; ADDLs, A β -derived diffusible ligands; AICD, amyloid precursor protein intracellular domain; AID, amyloid intracellular domain; APP, Amyloid Precursor Protein; APOE, apolipoprotein E; BACE, beta-site amyloid precursor protein cleaving enzyme; CBP, CREB-binding protein; CREB, cAMP response element-binding protein; CTF, carboxy-terminal fragments; FAD, Familial Alzheimer's disease; ISF, interstitial fluid; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate receptor; PS, presenilin proteins.

than one century. In particular, a great deal of attention has been focused on Amyloid-beta peptide ($A\beta$) which is thought to be responsible for synaptic dysfunction and memory loss as well as of the structural damage of the brain in the later stages of the disease. According to the so called Amyloid Cascade Hypothesis (Hardy and Allsop, 1991), the increase of $A\beta$ leads to a series of events consisting in formation of plaques, neurofibrillary tangles of hyperphosphorylated tau, neuronal death and the concomitant inflammatory response. Notwithstanding attention has recently shifted from fibrillar $A\beta$, involved in plaque formation, to soluble $A\beta$, whose accumulation is thought to be responsible for the early synaptic dysfunction (Selkoe, 2002), the protein is still considered the *primum movens* of AD. However, there are many other evidences indicating that this hypothesis is not sufficient to explain the multifaceted features of the disease (Herrup, 2015). Moreover, as of now, most of the clinical trials aimed to decrease $A\beta$ levels have been unsuccessful, even if many researchers argue that the difficulty to make an early diagnosis has prevented to start an early “anti-amyloid” therapy, thus justifying the failure of this approach. In any case, the complex AD etiopathogenesis together with the crystallization of our studies around the vision of $A\beta$ exclusively as a “bad” protein have probably prevented us to focus on other important aspects of the disease. Among these, we believe that it is essential to understand why a protein physiologically produced in the healthy brain, at some point, increases, and why several individuals present an increase of $A\beta$ levels or plaque deposits without any sign of clinical dementia. In other words, based on the assumption that to comprehend how a system works is crucial to unravel its failure, we and other research groups have sought to deepen the study of $A\beta$ in physiological conditions, aiming to find the mechanisms underlying the switch toward pathology and providing a new vision of how the Amyloid Cascade Hypothesis should be revised and resized.

APP AND ITS FRAGMENTS

Amyloid Precursor Protein (APP) is a type-1 transmembrane glycoprotein formed by 365–770 aminoacids (AA), with the isoform APP695 highly expressed in human neuronal tissues. APP undergoes a complex cleavage by α - or β -secretases that initiate two different pathways. When APP is cleaved by α -secretase, a soluble extracellular fragment, sAPP α , and a carboxy-terminal fragment of 83 AA, CTF83, are generated. The latter is further cut by a complex of proteins named γ -secretase whose catalytic subunit is represented by presenilin proteins (PS1 and PS2). CTF83 origins the intracellular peptide AICD/AID (amyloid precursor protein intracellular domain/amyloid intracellular domain) (Passer et al. 2000) and a small p3 peptide. When APP is cleaved by β -secretase, it generates a soluble extracellular fragment, sAPP β , and a carboxy-terminal fragment of 99 AA, CTF99. The latter is further cut by γ -secretase generating AICD/AID and generally a 40–42 AA fragment called $A\beta$. Thus, formation of $A\beta$ requires β - and γ -secretases.

The discovery of this pathway together with the discovery of rare forms of early onset Familial Alzheimer’s disease (FAD), inherited in an autosomal dominant fashion, has been one of the main pillars in $A\beta$ research. Indeed, mutations in the genes for APP, PS1 and PS2 were observed in AD families, and all these mutations induced an increase of $A\beta$ production; on the other hand, a mutation in the APP gene that results in a reduction in the formation of amyloidogenic peptides protects against cognitive decline in the elderly (Jonsson et al., 2012). FAD mutations also gave the opportunity to create animal models of the disease that have been studied in the last 20 years to investigate the pathogenetic mechanisms, the progression of the disease, and the efficacy of new drugs in preclinical studies (Puzzo et al., 2015).

However, it is interesting to notice that: (i) AD is primarily a sporadic disorder, even if a genetic susceptibility is suggested by the fact that first-degree relatives of patients with AD have an increased risk of developing the disease (Reitz, 2012); (ii) no α - or β -secretases mutations have been associated with FAD or sporadic AD; (iii) the major genetic risk factor for sporadic AD is not represented by APP or PS genes, but apolipoprotein E (APOE) gene, since subjects with the APOE- ϵ 4 allele had a more than 10-fold higher risk of dementia (Corder et al., 1993; Slioter et al., 1998); (iv) studies on animal models have demonstrated that if mutations of APP, PS or secretases leading to an increase of $A\beta$ burden might be responsible for synaptic and memory loss, on the other hand, the inhibition or genetic deletion of these proteins might also be deleterious because they exert a physiological function.

Deletion of APP induced an impairment of neuronal viability in vitro and synaptic activity in vivo (Perez et al., 1997), neurite outgrowth and branching (Allinquant et al., 1995; Perez et al., 1997; Young-Pearse et al., 2008), long-term potentiation (LTP) and memory (Hérard et al., 2006; Puzzo et al., 2011). Moreover, the lack of APP increases cortical and hippocampal gliosis (Müller et al., 1994; Zheng et al., 1995; Dawson et al., 1999; Phinney et al., 1999; Seabrook et al., 1999; Ring et al., 2007) and induces several other alterations (low body weight, agenesis of the corpus callosum, hypersensitivity to seizures, defects in copper and lipid homeostasis, impaired grip strength, locomotor, exploratory activity, and cognition).

Also acute injections of siRNA against murine APP reduced LTP as well as contextual fear memory and reference memory (Puzzo et al., 2011). The gain or lack of function studies has also pointed out an important role for sAPP α , which origins from the “good” cleavage of APP, in neurogenesis, synaptic plasticity and memory (Turner et al., 2003; Han et al., 2005; Taylor et al., 2008; Gakhar-Koppole et al., 2008). Although the deleterious effect of the inhibition of full-length APP or α -secretases (Hick et al., 2015; for a review see Müller and Zheng, 2012) has been widely studied and accepted by the neuroscience community, the deletion of β - or γ -secretases activity is equally harmful and should be taken into major consideration, especially when

considering the failure of several secretases-based clinical trials against AD.

The main neuronal β -secretase is BACE1 (an aspartic protease, β -site APP cleaving enzyme 1) (Hussain et al., 1999; Sinha et al., 1999) which, besides APP and its homologs APLP1 and APLP2, acts on other important substrates involved in brain function and development, such as neuregulin and the voltage-gated sodium channel (for a review see Prox et al., 2012). In BACE1 KO mice, the suppression of neuregulin function seems to be related to hypomyelination in the central and peripheral nervous system (Hu et al., 2006, 2008, 2010; Willem et al., 2006), and the onset of a schizophrenia-like phenotype (Savonenko et al., 2008), whereas seizures and altered Na^+ current found in Purkinje cells are due to the lack of action on voltage-gated sodium channel (Hu et al., 2010). BACE1 KO mice present dysfunctions in synaptic transmission and plasticity in CA1 and CA3 hippocampal area (Laird et al., 2005; Wang et al., 2008) as well as several cognitive and emotional behavioral deficits (Harrison et al., 2003; Laird et al., 2005; Savonenko et al., 2008). Interestingly, cognitive deficits in BACE1 KO mice were rescued by concomitant expression of APP_{swe}; PS1DeltaE9 transgenes (Laird et al., 2005), whereas reduction in cell viability in rat neuronal cells induced by secretase inhibitors was rescued by co-incubation with A β 40 at low picomolar concentrations (Plant et al., 2003).

Despite these studies have pointed out the importance of β -secretases, there are still few studies supporting the physiological function of sAPP β , which seems to be involved in cell adhesion, axonal outgrowth (Chasseigneaux et al., 2011) and neural differentiation (Freude et al., 2011), even if there are no evidences of a role for this fragment in neuroprotection and synaptic plasticity.

After α - or β -secretases cleavage, remaining CTFs undergo a further cleavage by γ -secretases to generate p83 (from CTF83), A β (from CTF99) and AICD/AID (from both pathways). γ -secretase is a member of the aspartyl protease family able to regulate intramembrane proteolysis for several type 1 integral membrane proteins, including APP, APLPs, Notch, E-Cadherin and many others (for a review see Krishnaswamy et al., 2009). Four main components of the γ -secretase complex have been identified: PS, nicastrin, anterior pharynx defective homolog 1, and presenilin enhancer 2 (Krishnaswamy et al., 2009). PS are responsible for γ -secretase catalytic activity (Edbauer et al., 2003; Hayashi et al., 2004; Zhang et al., 2005). Because of PS action on Notch is critical for development (for a review see Vetrivel et al., 2006), loss of PS function determined deficits during development and in adult brain. PS1 controls neuronal differentiation (Handler et al., 2000) in association with the down-regulation of Notch signaling during embryonic (Sarkar and Das, 2003) and adult (Gadadhar et al., 2011) neurogenesis. PS plays an important role also in synaptic plasticity and memory. Loss of PS function induced LTP and memory deficits associated with reductions in N-methyl-D-aspartate receptor (NMDA) receptor-mediated responses, synaptic levels of NMDA receptors, α CaMKII, expression of CREB-binding protein

(CBP) and CREB (cAMP response element-binding protein)/CBP target genes, such as c-fos and BDNF (Saura et al., 2004). Conditional inactivation of PS in either hippocampal CA3 or CA1 neurons induced a decrease of LTP and a modification of short-term plasticity and synaptic facilitation after presynaptic deletion of PS (Zhang et al., 2009, 2010), indicating a role for PS in regulation of neurotransmitter release and LTP. In other studies, PS1 conditional KO mice showed normal synaptic transmission and plasticity but significant deficits in long-term spatial memory (Yu et al., 2001). In addition to synaptic and memory deficits, PS conditional double KO mice present an age-related and progressive neurodegeneration by 4 months of age, together with mitochondrial defects (Wines-Samuelson et al., 2010). Recently, it has also been shown that a FAD mutation in PSEN1 can cause the impairment of memory through a loss-of-function mechanism (Xia et al., 2015).

γ -Secretase also produces AICD/AID (Passer et al., 2000) that exerts several physiological functions (for a review see Pardossi-Piquard and Checler, 2012). More than 20 proteins have been reported to interact with AICD/AID (Müller et al., 2007, 2008). Its interaction with the nuclear adaptor protein Fe65 and the histone acetyltransferase Tip60 forms a multimeric complex that stimulates transcription of different genes (Cao and Südhof, 2001) known to affect development, synaptic plasticity and cytoskeletal dynamics. AICD/AID has also been demonstrated to modulate intracellular homeostasis of calcium and ATP (Hamid et al., 2007), to control neuronal networks, microtubule stabilization and cell death (Kinoshita et al., 2003; Nakaya and Suzuki, 2006; Ghosal et al., 2009; Vogt et al., 2011; Ohkawara et al., 2011), to regulate transcriptional activation of A β -degrading enzyme neprilysin (Pardossi-Piquard et al., 2005).

In summary, these studies suggest that an inhibition of the APP pathway, including β - and γ -secretases, could interfere with important physiological functions related to neuronal development, neurogenesis, synaptic plasticity and memory.

A β BETWEEN PATHOLOGY AND PHYSIOLOGY

A β is produced by the cleavage of APP by β - and γ -secretases in the endoplasmic reticulum, trans-Golgi and endosomal-lysosomal systems (Xu et al., 1997; Greenfield et al., 1999), and it is then secreted through exocytosis in the extracellular space where it targets several receptors. A β peptides are usually 39–43 AA long, but a variety of APP fragments have been found in the brain (Portelius et al., 2009). The major part of A β is secreted as A β 40, a form thought to have neurotrophic properties (Yankner et al., 1990; Zou et al., 2002, 2003) and a fewer tendency to aggregate (Zou et al., 2002). Conversely, A β 42 is produced in low quantities but it is more prone to the formation of oligomers, protofibrils and fibrils and represents the main form contained in AD brain plaques (Jarrett et al., 1993; Gu and Guo, 2013).

The study of A β aggregation state has been crucial in AD research in the attempt to unravel the correlation between the severity of dementia and the presence of

different forms of the peptide in the brain. In this regard, one of the main criticisms raised against the Amyloid Cascade Hypothesis has been the poor correlation between plaques and the degree of cognitive impairment in AD patients (Terry et al., 1991; Arriagada et al., 1992; Dickson et al., 1995; Sloane et al., 1997). It is even more peculiar that there have been reports of brain plaques in the brains of healthy individuals without any sign of dementia (Katzman et al., 1988; Delaère et al., 1990; Dickson et al., 1995; Herrup, 2015), suggesting that deposits of A β are not sufficient to determine AD. According to some researchers, the formation of plaques and tangles might be the result of a reactive process (Reitz, 2012) in which APP and its products would increase to help maintaining cell functions in response to different kinds of injuries, such as head trauma or denervation (Wallace et al., 1991; Gentleman et al., 1993; McKenzie et al., 1994; Roberts et al., 1994; Torack and Miller, 1994). Thus, in contrast with the conventional dogma, an insufficient APP function rather than its over-expression would be responsible for the disease (Regland and Gottfries, 1992). Interestingly, a recent work has demonstrated that the impairment of synaptic plasticity and memory induced by PS mutations is due to the loss of physiological PS function rather than due to the increase of A β production (Xia et al., 2015). Reasonably, A β overproduction might be interpreted as a compensatory mechanism (see later for details). Although this interesting hypothesis was proposed more than 20 years ago (Regland and Gottfries, 1992), the major part of the studies have continued to focus on the neurotoxic role of A β even if, lately, the attention has been shifted from plaques toward soluble forms of A β , such as A β -derived diffusible ligands (ADDLs, Lambert et al., 1998). The involvement of soluble A β in AD has been shown by several approaches on animal models or humans (Walsh and Selkoe, 2007). The observations that (i) low-weight A β oligomers (monomers, dimers and trimers) (Vigo-Pelfrey et al., 1993; McLean et al., 1999) have been found in soluble fractions and in extracts of plaques in AD brains and CSF (Podlisny et al., 1995; Roher et al., 1996; Funato et al., 1998; Enya et al., 1999; McLean et al., 1999; Kawarabayashi et al., 2004; Lesne et al., 2006); (ii) administration of A β oligomers (synthetic, derived from AD brains or naturally secreted from AD cells) impairs hippocampal synaptic plasticity and memory (for a review see McDonald et al., 1994; Cullen et al., 1997; Sweeney et al., 1997; Itoh et al., 1999; Vitolo et al., 2002; Walsh et al., 2002; Cleary et al., 2005; Puzzo et al., 2005; Townsend et al., 2006; Shankar et al., 2007, 2008; Selkoe, 2008; Balducci et al., 2010); (iii) APP transgenic mice present the cognitive impairment before amyloid deposition (Chapman et al., 1999; Hsia et al., 1999; Moechars et al., 1999; Mucke et al., 2000; Westerman et al., 2002; Wu et al. 2004), suggest that soluble forms might mediate neuronal dysfunction at the early stages of the disease (Selkoe, 2002).

Another critical point is whether in addition to its extracellular localization, A β is also present inside neurons. The main issue in detecting A β inside cells is represented by the method used to unravel it, which is

not considered sensitive enough because of the variety of staining protocols and the use of antibodies such as 6E10 and 4G8 that cross-react with APP (Aho et al., 2010). However, different methods have been used to demonstrate that A β is present inside neurons (for a review see Cuellar et al., 2012): (i) a specific antibody recognizing the N-terminal end of A β that does not cross-react with APP allowed to detect intraneuronal A β in 3 \times Tg and 5 \times FAD mice brains (Youmans et al., 2012); (ii) conformation-specific antibodies have been used to detect intraneuronal A β in 3 \times Tg (Wirhth and Bayer, 2012; Wirhth et al., 2012); (iii) a multi-dimensional study using high-resolution microscopy, mass spectrometry analysis, and ELISAs has shown that A β accumulates inside neurons of an AD-like transgenic rat (Iulita et al., 2014). Recently, it has been demonstrated that intraneuronal injections of A β caused an impairment of basal synaptic transmission and LTP. A β internalization from the extracellular space and its intraneuronal accumulation might be responsible for synaptic dysfunction independently of A β interaction with plasma membrane receptors (Ripoli et al., 2014).

Intracellular A β has been found in normal human brains during development, adulthood, and aging, with different patterns of distribution compared to AD or Down's syndrome brains (Wegiel et al., 2007). Recently, an analysis of hippocampal sections identified the presence of intracellular A β in pyramidal neurons of healthy people with no difference in gender, postmortem interval, or age, further supporting a physiological role for intracellular A β (Blair et al., 2014). Intriguingly, A β is already present inside neurons in infant brains, and it increases at 4–8 years, a period of high brain plasticity, when about half of the neurons are A β -immunopositive. In adulthood, A β is present in the major part of the neurons whereas in aged people there is a 20% reduction. Surprisingly, patients with sporadic AD present a further reduction of intraneuronal A β immunoreactivity, especially at the hippocampal level. Also in this case, it is questionable whether APP rather than A β is detected inside neurons (Aho et al., 2010). A reduction of A β levels has also been found in the CSF of AD patients (Andreasen et al., 1999, 2001; Blennow and Hampel, 2003; Blennow, 2004; Giedraitis et al., 2007; Shaw et al., 2009). On the other hand, recent studies have demonstrated that pan-A β immunoreactivity did not discriminate between age and cognitive status in post-mortem brain analyses, whereas immunodetection with an oligomer-sensitive antibody specifically showed immunoreactivity in AD brains (Blair et al., 2014), suggesting a possible difference between the A β species present in healthy versus diseased brains.

In any case, the concentration of soluble A β in the normal healthy brain has been estimated in the picomolar range with species ranging from monomers to higher oligomers (Schmidt et al., 2005; Giedraitis et al., 2007; Puzzo et al., 2008). These physiologically low A β levels have been suggested to play a role in synaptic function, even if the kind of A β species responsible for such physiological function is unknown. While a great effort has been made to identify the different aggregation forms of soluble A β responsible for its toxic actions, studies

aimed at unraveling form/s involved in normal physiology are restricted to monomers (Giuffrida et al., 2010).

With respect to the toxic action of A β , different types of oligomers (i.e. ADDLs, globulomers, oligomers of different size, amylospheroids, protofibrils; for a review see Roychaudhuri et al., 2009) have been taken into consideration because they correlate better than plaques with cognitive decline in AD (McLean et al., 1999; Donald et al., 2010) and are present in the human brain or CSF decades prior to AD onset (Fukumoto et al., 2010; Lesné et al., 2013). Lately, it has also been proposed that the acceleration of fibril formation might be even beneficial because it can decrease oligomers' level (Cheng et al., 2007). This has led to substitute the Amyloid Cascade Hypothesis, mostly based on brain deposition of amyloid fibrils, with the "Oligomer Hypothesis", considering oligomeric forms of A β the main culprit of AD pathogenesis. In this view, most of the approaches attempting to target A β by the use of anti-amyloid antibodies failed because they did not specifically target oligomers but all A β species, including monomers and fibrils. Thus, the use of specific anti-oligomers therapies has been suggested. In this regard, it is interesting the on-going phase III clinical trial of Aducanumab, reported to target A β aggregates, including plaques, but sparing monomers (Patel, 2015). Nevertheless, other studies have revised the role of oligomers, finding that blocking new production of APP/A β ameliorated the AD phenotype in animal models despite persistent levels of previously formed soluble and insoluble A β assemblies (Melnikova et al., 2013).

These controversial results might be understandable in light of the complexity of A β aggregation and the continuous dynamic rearrangement of oligomers (Bemporad and Chiti, 2012). A β is secreted in monomeric form and this has led to ascribe the physiologic effects of A β to monomers. However a certain degree of oligomerization is likely to occur whenever A β is present, and therefore the native state characteristics of the peptide might be impossible to determine (for a review see Hayden and Teplow, 2013). This is even more complex considering that several factors such as concentration, temperature and pH play a fundamental role in the aggregation process. Moreover, synthetic peptides, such as those used in most of the experiments, might also behave differently than A β oligomers extracted from biological material and a further heterogeneity might be found between extracts from humans and animal models, and between extracts from wild type and Tg animal models. Thus, too many features can affect A β species so that a clear picture in terms of monomers/oligomers balance may not be possible. However, it is intriguing to hypothesize that A β 40 and A β 42, released as monomers, undergo a certain degree of oligomerization that, if does not exceed a critical point, might have a role in the physiology of neuronal transmission. Finally, another important point is whether the oligomerization level might influence the A β binding to a particular target, or might let A β interact with different receptors resulting in an additive or synergistic effect. For example, it has been demonstrated that: (i) A β 40 or A β 42 compete for insulin binding to the insulin receptor in a concentration-dependent manner

(Xie et al., 2002); (ii) different A β species bind to hippocampal neurons and affect neurotransmission at different concentrations (Moreth et al., 2013); (iii) A β 40 acts specifically on α 7 nicotinic acetylcholine receptors (α 7-nAChRs) when at low picomolar concentrations, whereas high nM levels involved both α 7- and α 4 β 2-nAChRs (Mura et al., 2012). This different effect on different targets might be due to the amount of oligomerization: when oligomerization process overruns a certain level, the physiological role is probably broken and A β binds to different targets. This is an issue that needs further studies but, in any case, it is undeniable that low soluble A β species exert a physiological function at synaptic level. Indeed, in the last few years, several studies have provided solid evidences for a role of A β in the healthy brain. First, the production and release of A β is regulated by neuronal activity. In rat hippocampal slices electrical depolarization caused an increase in both neurotransmitters release and release of APP fragments including A β (Nitsch et al., 1993). Secretion of A β is also enhanced by spontaneous neuronal activity through an enhanced APP cleavage by beta-site amyloid precursor protein cleaving enzyme (BACE) in hippocampal neurons overexpressing APP (Kamenetz et al., 2003). Other studies have shown that interstitial fluid (ISF) A β levels are dynamically regulated by synaptic activity, probably by a presynaptic mechanism related to vesicle exocytosis (Cirrito et al., 2005). Also, the increase of A β production and its release in the ISF is mediated by an intensification of APP endocytosis induced by synaptic activity (Cirrito et al., 2008). This is consistent with the finding that endogenously released A β acts as a positive modulator of release probability in hippocampal synapses (Abramov et al., 2009) and with our data indicating that hippocampal A β production is enhanced during memory induction for contextual fear learning (Puzzo et al., 2011). A β levels have been shown to correlate with neurological status, since the increase of the protein parallels an improvement of neurological status, whereas a decrease is present when the neurological status is declined (Brody et al., 2008), further suggesting that A β is physiologically produced in an activity-dependent fashion.

Based on these findings, it has been proposed an interesting model according to which A β acts as a negative feedback regulator of synaptic plasticity (Kamenetz et al., 2003), i.e. the increase of neuronal activity induces an increase of A β secretion that in turn, decreases neuronal activity. The dose-dependent effect of A β is in agreement with data indicating that low concentration of the peptide positively affects synaptic plasticity and memory (Puzzo et al., 2008; Morley et al., 2010), whereas, a pathological accumulation of the peptide exerts the opposite effect causing synaptic failure (Puzzo et al., 2012; for a review see Puzzo and Arancio, 2013). In our study, low picomolar concentrations of a preparation containing both monomers and oligomers of the peptide enhanced LTP and memory (Puzzo et al., 2008) with a mechanism depending upon cholinergic nicotinic receptors (nAChRs). A β also affects neurotransmitter release stimulated by the activation of pre-synaptic nAChRs in a dose-dependent fashion (Mura et al., 2012).

Several loss of function studies have suggested that A β is not only involved but needed for normal synaptic plasticity. As stated before, APP KO and BACE KO mice as well as mice treated with inhibitors of β - and γ -secretases or siRNA or antisense against APP show an impairment of synaptic plasticity and memory. However, one can state that this is due to an effect of other APP fragments (for a review on physiological function of APP fragments see [Chow et al., 2010](#)) or other substrates of β - and γ -secretases (see previous paragraph; [Saura et al., 2004](#); [Laird et al., 2005](#)). Nevertheless, the specific block of endogenous A β by antibodies impairs LTP and memory ([Garcia-Osta and Alberini, 2009](#); [Morley et al., 2010](#); [Puzzo et al., 2011](#)) and, more importantly, this impairment is rescued by the administration of picomolar concentrations of A β ([Puzzo et al., 2011](#)). The absence of endogenous A β (induced by inhibitors of β - or γ -secretases or antibodies) also caused neuronal cell death ([Plant et al., 2003](#)) that was restored by picomolar concentrations of A β . The mechanisms underlying the physiological role of A β involved K⁺ and Ca²⁺ ion channels and several key receptors for synaptic function such as glutamatergic and cholinergic receptors. In particular, we have focused on nAChRs because (i) they play a fundamental role in learning and memory in physiological conditions ([Levin, 2002](#); [Albuquerque et al., 2009](#); [Yakel, 2013, 2014](#)); (ii) the cholinergic deficit is closely related to the pathogenesis of AD ([Levey, 1996](#); [Clader and Wang, 2005](#); [Oddo and LaFerla, 2006](#); [Yakel, 2013](#)); (iii) A β has a picomolar affinity for $\alpha 7$ -nAChRs ([Wang et al., 2000](#)); (iv) A β modulates $\alpha 7$ -nAChR function ([Dougherty et al., 2003](#); [Small et al., 2007](#); [Khan et al., 2010](#); [Lawrence et al., 2014](#)) and it is able to act as an agonist or an antagonist depending upon the dose, as previously discussed ([Dineley et al., 2002](#); [Grassi et al., 2003](#); [Fodero et al., 2004](#)). [Please see [Dineley, 2007](#) for a review on A β -nAChR interaction in health and disease]. In our works ([Puzzo et al., 2008, 2011](#)) we have shown that a pharmacological or genetic blockage of $\alpha 7$ -nAChRs resulted in inhibition of the A β -induced increase of post-tetanic potentiation, LTP and memory; moreover the inhibition of endogenous A β did not affect synaptic plasticity in $\alpha 7$ -nAChR-KO, supporting the hypothesis that the physiological effect of low A β concentrations is mediated by $\alpha 7$ -nAChRs. A recent paper ([Lawrence et al., 2014](#)) has shown that an A β N-terminal fragment exerts a highly potent agonist-like action on nicotinic receptors, boosting LTP and contextual fear memory that, in turn, was attenuated by co-administration of a nicotinic antagonist.

A NOVEL VISION OF AD PATHOGENESIS

Based on these data, we hypothesize that in physiological conditions, synaptic activity triggers A β release which, in turn, modulates $\alpha 7$ -nAChRs leading to an enhancement of neurotransmitter release with a consequent increase of synaptic plasticity and memory. Conversely, one can speculate that when A β cannot exert its physiological functions (i.e. for a receptor resistance) a negative feedback mechanism would induce a compensatory

increase of its production leading to an abnormal accumulation that reduces $\alpha 7$ -nAChR function, leading to synaptic dysfunction and memory loss. Overtime, if not brought back to its normal homeostasis, this chronic failure would produce a reduction of the protein levels due to “cellular exhaustion”. This model should not surprise if considering the pathogenetic mechanisms underlying several diseases that result from an alteration of the negative feedback loops (i.e. type 2 diabetes mellitus or thyroid goiter). It is also interesting the similarity with the mechanisms underlying the so called “General Adaptation Syndrome”, already described in 1950 by Hans Selye, and characterized by a phase of alarm, a phase of resistance and a phase of exhaustion during which the chronic stressor overcomes the ability of the organism to respond and adapt. Overall, neurodegenerative, metabolic, cardiovascular diseases and aging themselves might be the result of a homeostatic imbalance that needs therapeutics intervention before the “out of control” irreversible condition. Thus, before finding new therapeutical strategies to eliminate A β tout court from the brain, we should understand why and when the physiological production gives way to the pathological accumulation. This issue is even more critical when considering that clinical trials based on lowering A β levels have mostly been unsuccessful (see [Reitz, 2012](#); [Castello et al., 2014](#); [Herrup, 2015](#)). In our opinion, the indiscriminate A β removal would interfere with neuronal homeostasis, causing a further impoverishment of learning and memory.

CONCLUSION

We do not believe that A β should disappear from the AD scene, but a different vision is needed to build the bridge between its physiological and pathological role.

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We have to remember that what we observe is not nature in itself but nature exposed to our method of questioning.
Werner Heisenberg, Physics and Philosophy: The Revolution in Modern Science.

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