THE KEYSTONE OF ALZHEIMER PATHOGENESIS MIGHT BE SOUGHT IN Aβ PHYSIOLOGY

Daniela Puzzo[a,*], **Walter Gulisano**[a], **Ottavio Arancio**[b], and **Agostino Palmeri**[a]

[a]Department of Biomedical and Biotechnological Sciences, Section of Physiology, Viale A. Doria 6 (ed. 2), University of Catania, Catania, 95125 Italy

[b]Department of Pathology and Cell Biology and Taub Institute for Research on Alzheimer's Disease and the Aging Brain, 630 W 168th St., Columbia University, New York (NY), 10032 USA

Abstract

For several years Amyloid-beta peptide (Aβ) has been considered the main pathogenetic factor of Alzheimer's disease (AD). According to the so called Amyloid Cascade Hypothesis the increase of Aβ 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 Aβ levels have been unsuccessful. Moreover, Aβ 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 Aβ and its physiological receptors, focusing on α7-nAchRs. According to this vision, when Aβ cannot exert its physiological function a negative feedback mechanism would induce a compensatory increase of its production leading to an abnormal accumulation that reduces α7-nAchR function, leading to synaptic dysfunction and memory loss. In this perspective, the indiscriminate Aβ 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 Aβ in physiological conditions might represent the keystone to elucidate important aspects of AD pathogenesis.

Keywords

Amyloid-beta peptide; Alzheimer's disease; nAchRs; synaptic plasticity; memory

> We have to remember that what we observe is not nature in itself but nature exposed to our method of questioning.

*Corresponding author. Address: [a]Department of Biomedical and Biotechnological Sciences, Section of Physiology, University of Catania, Viale A. Doria 6 (ed. 2), Catania, 95125 Italy Tel. +39-095-7384033/4053; Fax: +39-095-7384217. danypuzzo@yahoo.it.

Werner Heisenberg, Physics and Philosophy: The Revolution in Modern Science

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 of 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 psychiatrists Alois Alzheimer met a 51 years 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 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 than one century. In particular, a great deal of attention has been focused on Amyloid-beta peptide (Aβ) 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 Aβ 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 Aβ , involved in plaque formation, to soluble Aβ, 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 Aβ 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 Aβ 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 Aβ 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 Aβ in physiological conditions, aiming to find the mechanisms underlying the switch towards

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, sAPPα, and a carboxyterminal 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 intracellular domain) (Passer et al. 2000) and a small p3 peptide. When APP is cleaved by β-secretase, it generates a soluble extracellular fragment, sAPPβ, and a carboxyterminal fragment of 99 AA, CTF99. The latter is further cut by γ-secretase generating AICD/AID and generally a 40 to 42 AA fragment called Aβ. Thus, formation of Aβ 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 Aβ research. Indeed, mutations in the genes for APP, PS1 and PS2 were observed in AD families, and all these mutations induced an increase of Aβ 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-ε4 allele had a more than 10-fold higher risk of dementia (Corder et al., 1993; Slooter et al., 1998); iv) studies on animal models have demonstrated that if mutations of APP, PS or secretases leading to an increase of Aβ burden might be responsible of 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 t 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). Gain or lack of function studies have also pointed out an important role for sAPPα, 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 cleavage 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; Willem et al., 2006; Hu et al., 2008; 2010), 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 APPswe;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 Aβ40 al 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 sAPPβ, 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), Aβ (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 NMDA receptor-mediated responses, synaptic levels of NMDA receptors, αCaMKII, expression of CBP and CREB/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 been also 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 Aβ-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.

Aβ BETWEEN PATHOLOGY AND PHYSIOLOGY

Aβ 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. Aβ peptides are usually 39–43 amino acids long, but a variety of APP fragments have been found in the brain (Portelius et al., 2009). The major part of Aβ is secreted as Aβ40, 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, Aβ42 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 Aβ 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; Herrupp, 2015), suggesting that deposits of Aβ 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 overexpression 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 to the increase of Aβ production (Xia et al., 2015). Reasonably, Aβ 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 Aβ even if, lately, the attention has been shifted from plaques towards soluble forms of Aβ, such as Aβ derived diffusible ligands (ADDLs, Lambert et al., 1998). The involvement of soluble Aβ in AD has been showed by several approaches on animal models or humans (Walsh and Selkoe, 2007). The observations that i) low-weight Aβ 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 Aβ oligomers (synthetic, derived from AD brains or naturally-secreted from AD cells) impairs hippocampal synaptic plasticity and memory (for a review see Selkoe, 2008; 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; 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, Aβ is present also inside neurons. The main issue in detecting Aβ 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 Aβ is present inside neurons (for a review see Cuello et al., 2012): i) a specific antibody recognizing the N-terminal end of Aβ that does not cross-react with APP allowed to detect intraneuronal Aβ in 3×Tg and 5×FAD mice brains (Youmans et al., 2012); ii) conformation-specific antibodies have been used to detect intraneuronal Aβ in 3×Tg (Wirths and Bayer, 2012; Wirths et al., 2012); iii) a multi-dimentional study using high-resolution microscopy, mass spectrometry analysis, and ELISAs has shown that Aβ accumulates inside neurons of an AD-like transgenic rat (Iulita et al., 2014). Recently, it has been demonstrated that intraneuronal injections of Aβ caused an impairment of basal synaptic transmission and LTP. Aβ internalization from the extracellular space and its intraneuronal accumulation might be responsible for synaptic dysfunction independently of Aβ interaction with plasma membrane receptors (Ripoli et al., 2014).

Intracellular Aβ 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 Aβ in pyramidal neurons of healthy people with no difference in gender, postmortem interval, or age, further supporting a physiological role for intracellular Aβ (Blair et al., 2014). Intriguingly, Aβ 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 Aβ-immunopositive. In adulthood, Aβ 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 Aβ immunoreactivity, especially at hippocampal level. Also in this case, it is questionable whether APP rather than Aβ is detected inside neurons (Aho et al., 2010). Aβ reduction of Aβ levels has been also found in the CSF of AD patients (Andreasen et al., 1999; 2001; Blennow and Hampel, 2003; Blenow, 2004; Giedraitis et al., 2007; Shaw et al., 2009). On the other hand, recent studies have demonstrated that pan-Aβ 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 Aβ species present in healthy versus diseased brains.

In any case, the concentration of soluble Aβ 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 physiological low Aβ levels have been suggested to play a role in synaptic function, even if the kind of Aβ species responsible for such physiological function is unknown. While a great effort has been made to identify the different aggregation forms of soluble Aβ 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 Aβ, 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 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 Aβ the main culprit of AD pathogenesis. In this view, most of the approaches attempting to target Aβ by the use of anti-amyloid antibodies failed because they did not specifically target oligomers but all Aβ 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 Aβ aggregates, including plaques, but sparing monomers (Patel, 2015). Nevertheless, other studies have revised the role of oligomers, finding that blocking new production of APP/Aβ ameliorated the AD phenotype in animal models despite persistent levels of previously formed soluble and insoluble Aβ assemblies (Melnikova et al., 2013).

These controversial results might be understandable in light of the complexity of Aβ aggregation and the continuous dynamic rearrangement of oligomers (Bemporad and Chiti, 2012). Aβ is secreted in monomeric form and this has lead to ascribe the physiologic effects of Aβ to monomers. However a certain degree of oligomerization is likely to occur whenever Aβ 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 Aβ 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 Aβ species so that a clear picture in terms of monomers/ oligomers balance may not be possible. However, it is intriguing to hypothesize that Aβ40 and Aβ42, 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 Aβ binding to a particular target, or might let Aβ interact with different receptors resulting in an additive or synergistic effect. For example, it has been demonstrated that: i) Aβ40 or Aβ42 compete for insulin binding to the insulin receptor in a concentration-dependent manner (Xie et al., 2002); ii) different Aβ species bind to hippocampal neurons and affect neurotransmission at different concentrations (Moreth et al., 2013); iii) Aβ40 acts specifically on α7-nAChRs when at low picomolar concentrations, whereas high nM levels involved both α7- and α4β2-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 Aβ binds to different targets. This is an issue that needs further studies but, in any case, it is undeniable that low soluble Aβ species exert a physiological function at synaptic level. Indeed, in the last few years, several studies have provided solid evidences for a role of Aβ in the healthy brain. First, the production and release of Aβ is regulated by neuronal activity. In rat hippocampal slices electrical depolarization caused an increase in both neurotransmitters release and release of APP fragments including Aβ (Nitsch et al., 1993). Secretion of Aβ is also

enhanced by spontaneous neuronal activity through an enhanced APP cleavage by BACE in hippocampal neurons overexpressing APP (Kamenetz et al., 2003). Other studies have shown that ISF Aβ levels are dynamically regulated by synaptic activity, probably by a presynaptic mechanism related to vesicle exocytosis (Cirrito et al., 2005). Also, the increase of Aβ 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 Aβ acts as a positive modulator of release probability in hippocampal synapses (Abramov et al., 2009) and with our data indicating that hippocampal Aβ production is enhanced during memory induction for contextual fear learning (Puzzo et al., 2011). Aβ 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 Aβ is physiologically produced in an activity-dependent fashion.

Based on these findings, it has been proposed an interesting model according to which Aβ acts as a negative feedback regulator of synaptic plasticity (Kamenetz et al., 2003), i.e. the increase of neuronal activity induces an increase of Aβ secretion that in turn, decreases neuronal activity. The dose-dependent effect of Aβ are 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). Aβ 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 Aβ 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 Aβ 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 Aβ (Puzzo et al., 2011). The absence of endogenous Aβ (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 Aβ. The mechanisms underlying the physiological role of Aβ involved K^+ and Ca^{2+} 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 et al., 2013; 2014); ii) the cholinergic deficit is closely related to the pathogenesis of AD (Levey, 1996; Clader and Wang, 2005; Oddo and La Ferla, 2006; Yakel, 2013); iii) Aβ has a picomolar affinity for α7-nAChRs (Wang et al., 2000); iv) Aβ modulate α7-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 Aβ-nAChR interaction in health and disease]. In our works (Puzzo et al., 2008; 2011) we have shown that a pharmacological or genetic blockage of α7-nAChRs resulted in inhibition of the Aβ-induced increase of post-tetanic potentiation, LTP and memory; moreover the inhibition of endogenous Aβ did not affect synaptic plasticity in α7-nAChR-KO, supporting the hypothesis that the physiological effect of low Aβ concentrations is mediated by α7-nAChRs. A recent paper (Lawrence et al., 2014) has shown that an Aβ 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 Aβ release which, in turn, modulates α7-nAchRs leading to an enhancement of neurotransmitter release with a consequent increase of synaptic plasticity and memory. Conversely, one can speculate that when Aβ 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 α7-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 overcome the ability to the organism to respond and adapt. Overall, neurodegenerative, metabolic, cardiovascular disease and aging itself 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 Aβ 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 Aβ levels have mostly been unsuccessful (see Reitz, 2012; Castello et al., 2014; Herrup, 2015). In our opinion, the indiscriminate Aβ removal would interfere with neuronal homeostasis, causing a further impoverishment of learning and memory.

In conclusion, we do not believe that Aβ should disappear from the AD scene, but a different vision is needed to build the bridge between its physiological and pathological role.

ACKNOWLEDGEMENTS

REFERENCES

Abramov E, Dolev I, Fogel H, Ciccotosto GD, Ruff E, Slutsky I. Amyloid-beta as a positive endogenous regulator of release probability at hippocampal synapses. Nat Neurosci. 2009; 12:1567–76. [PubMed: 19935655]

Aho L, Pikkarainen M, Hiltunen M, Leinonen V, Alafuzoff I. Immunohistochemical visualization of amyloid-beta protein precursor and amyloid-beta in extra-and intracellular compartments in the human brain. J Alzheimers Dis. 2010; 20:1015–28. [PubMed: 20413866]

Albuquerque EX, Pereira EF, Alkondon M, Rogers SW. Mammalian nicotinic acetylcholine receptors: From structure to function. Physiol Rev. 2009; 89:73–120. [PubMed: 19126755]

Allinquant B, Hantraye P, Mailleux P, Moya K, Bouillot C, Prochiantz A. Downregulation of amyloid precursor protein inhibits neurite outgrowth in vitro. J Cell Biol. 1995; 128:919–27. [PubMed: 7876315]

Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early-and late-onset Alzheimer disease and stability during the course of disease. Arch Neurol. 1999; 56:673–80. [PubMed: 10369305]

Andreasen N, Minthon L, Davidsson P, Vanmechelen E, Vanderstichele H, Winblad B, Blennow K. Evaluation of CSF-tau and CSF Abeta42 as diagnostic markers for Alzheimer disease in clinical practice. Arch Neurol. 2001; 58:373–379. [PubMed: 11255440]

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992; 42:631–9. [PubMed: 1549228]

Balducci C, Beeg M, Stravalaci M, Bastone A, Sclip A, Biasini E, Tapella L, Colombo L, Manzoni C, Borsello T, Chiesa R, Gobbi M, Salmona M, Forloni G. Synthetic amyloid-β oligomers impair long-term memory independently of cellular prion protein. Proc Natl Acad Sci U S A. 2010; 107:2295–300. [PubMed: 20133875]

Bemporad F, Chiti F. Protein misfolded oligomers: experimental approaches, mechanism of formation, and structure-toxicity relationships. Chem Biol. 2012; 19:315–27. [PubMed: 22444587]

Blair JA, Siedlak SL, Wolfram JA, Nunomura A, Castellani RJ, Ferreira ST, Klein WL, Wang Y, Casadesus G, Smith MA, Perry G, Zhu X, Lee HG. Accumulation of intraneuronal amyloid-β is common in normal brain. Curr Alzheimer Res. 2014; 11:317–24. [PubMed: 24597504]

Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2003; 2:605–613. [PubMed: 14505582]

Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's diasease. NeuroRx. 2004; 1:213–25. [PubMed: 15717022]

Brody DL, Magnoni S, Schwetye KE, Spinner ML, Esparza TJ, Stocchetti N, Zipfel GJ, Holtzman DM. Amyloid-beta dynamics correlate with neurological status in the injured human brain. Science. 2008; 321:1221–4. [PubMed: 18755980]

Cao X, Südhof TC. A transcriptionally active complex of APP with Fe65 and histone acetyltransferase Tip60. Science. 2001; 293:115–20. [PubMed: 11441186]

Castello MA, Jeppson JD, Soriano S. Moving beyond anti-amyloid therapy for the prevention and treatment of Alzheimer's disease. BMC Neurol. 2014; 14:169. [PubMed: 25179671]

Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT, Younkin SG, Hsiao KK. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat Neurosci. 1999; 2:271–276. [PubMed: 10195221]

Chasseigneaux S, Dinc L, Rose C, Chabret C, Coulpier F, Topilko P, Mauger G, Allinquant B. Secreted amyloid precursor protein and secreted amyloid precursor protein β induce axon outgrowth in vitro through Egr1 signaling pathway. PLoS One. 2011; 6:e16301. [PubMed: 21298006]

Cheng IH, Scearce-Levie K, Legleiter J, Palop JJ, Gerstein H, Bien-Ly N, Puoliväli J, Lesné S, Ashe KH, Muchowski PJ, Mucke L. Accelerating amyloid-β fibrillization reduces oligomer levels and

functional deficits in Alzheimer disease mouse models. J Biol Chem. 2007; 282:23818–23828. [PubMed: 17548355]

Chow VW, Mattson MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. Neuromolecular Med. 2010; 12:1–12. [PubMed: 20232515]

Cirrito JR, Kang JE, Lee J, Stewart FR, Verges DK, Silverio LM, Bu G, Mennerick S, Holtzman DM. Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. Neuron. 2008; 58:42–51. [PubMed: 18400162]

Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, Holtzman DM. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron. 2005; 48:913–22. [PubMed: 16364896]

Clader JW, Wang Y. Muscarinic receptor agonists and antagonists in the treatment of Alzheimer's disease. Curr Pharm Des. 2005; 11:3353–3361. [PubMed: 16250841]

Cleary JP, Walsh D, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, Ashe KH. Natural oligomers of the amyloid β-protein specifically disrupt cognitive function. Nature Neurosci. 2005; 8:79–84. [PubMed: 15608634]

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921–3. [PubMed: 8346443]

Cuello AC, Allard S, Ferretti MT. Evidence for the accumulation of Abeta immunoreactive material in the human brain and in transgenic animal models. Life Sci. 2012; 91:1141–7. [PubMed: 22705309]

Cullen WK, Suh YH, Anwyl R, Rowan MJ. Block of LTP in rat hippocampus in vivo by beta-amyloid precursor protein fragments. NeuroReport. 1997; 8:3213–3217. [PubMed: 9351645]

Dawson GR, Seabrook GR, Zheng H, Smith DW, Graham S, O'Dowd G, Bowery BJ, Boyce S, Trumbauer ME, Chen HY, Van der Ploeg LH, Sirinathsinghji DJ. Agerelated cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the beta-amyloid precursor protein. Neuroscience. 1999; 90:1–13. [PubMed: 10188929]

Delaère P, Duyckaerts C, Masters C, Beyreuther K, Piette F, Hauw JJ. Large amounts of neocortical beta A4 deposits without neuritic plaques nor tangles in a psychometrically assessed, non-demented person. Neurosci Lett. 1990; 116:87–93. [PubMed: 2259457]

Dickson DW, Crystal HA, Bevona C, Honer W, Vincent I, Davies P. Correlations of synaptic and pathological markers with cognition of the elderly. Neurobiol Aging. 1995; 16:285–298. [PubMed: 7566338]

Dineley KT. Beta-amyloid peptide--nicotinic acetylcholine receptor interaction: the two faces of health and disease. Front Biosci. 2007; 12:5030–8. [PubMed: 17569627]

Dineley KT, Bell KA, Bui D, Sweatt JD. Beta-amyloid peptide activates alpha 7 nicotinic acetylcholine receptors expressed in Xenopus oocytes. J Biol Chem. 2002; 277:25056–25061. [PubMed: 11983690]

Donald JMM, Savva GM, Brayne C, Welzel AT, Forster G, Shankar GM, Selkoe DJ, Ince PG, Walsh DM, Medical Research Council Cognitive Function and Ageing Study. The presence of sodium dodecyl sulphate-stable Aβ dimers is strongly associated with Alzheimer-type dementia. Brain. 2010; 133:1328–1341. [PubMed: 20403962]

Dougherty JJ, Wu J, Nichols RA. Beta-amyloid regulation of presynaptic nicotinic receptors in rat hippocampus and neocortex. J Neurosci. 2003; 23:6740–6747. [PubMed: 12890766]

Edbauer D, Winkler E, Regula JT, Pesold B, Steiner H, Haass C. Reconstitution of gamma-secretase activity. Nat Cell Biol. 2003; 5:486–488. [PubMed: 12679784]

Enya M, Morishima-Kawashima M, Yoshimura M, Shinkai Y, Kusui K, Khan K, Games D, Schenk D, Sugihara S, Yamaguchi H, Ihara Y. Appearance of sodium dodecyl sulfate-stable amyloid beta-protein (Abeta) dimer in the cortex during aging. Am J Pathol. 1999; 154:271–9. [PubMed: 9916941]

Fodero LR, Mok SS, Losic D, Martin LL, Aguilar MI, Barrow CJ, Livett BG, Small DH. Alpha7-nicotinic acetylcholine receptors mediate an Abeta(1-42)-induced increase in the level of acetylcholinesterase in primary cortical neurones. J Neurochem. 2004; 88:1186–1193. [PubMed: 15009674]

Freude KK, Penjwini M, Davis JL, LaFerla FM, Blurton-Jones M. Soluble amyloid precursor protein induces rapid neural differentiation of human embryonic stem cells. J Biol Chem. 2011; 286:24264–24274. [PubMed: 21606494]

Fukumoto H, Tokuda T, Kasai T, Ishigami N, Hidaka H, Kondo M, Allsop D, Nakagawa M. High-molecular-weight β-amyloid oligomers are elevated in cerebrospinal fluid of Alzheimer patients. FASEB J. 2010; 24:2716–2726. [PubMed: 20339023]

Funato H, Yoshimura M, Kusui K, Tamaoka A, Ishikawa K, Ohkoshi N, Namekata K, Okeda R, Ihara Y. Quantitation of amyloid beta-protein (Abeta) in the cortex during aging and in alzheimers-disease. Am J Path. 1998; 152:1633–1640. [PubMed: 9626067]

Gadadhar A, Marr R, Lazarov O. Presenilin-1 regulates neural progenitor cell differentiation in the adult brain. J Neurosci. 2011; 31:2615–23. [PubMed: 21325529]

Gakhar-Koppole N, Hundeshagen P, Mandl C, Weyer SW, Allinquant B, Müller U, Ciccolini F. Activity requires soluble amyloid precursor protein alpha to promote neurite outgrowth in neural stem cell-derived neurons via activation of the MAPK pathway. Eur J Neurosci. 2008; 28:871–82. [PubMed: 18717733]

Garcia-Osta A, Alberini CM. Amyloid beta mediates memory formation. Learn Mem. 2009; 16:267–72. [PubMed: 19318468]

Gentleman SM, Nash MJ, Sweeting CJ, Graham DI, Roberts GW. Beta-amyloid precursor protein (beta APP) as a marker for axonal injury after head injury. Neurosci Lett. 1993; 160:139–44. [PubMed: 8247344]

Ghosal K, Vogt DL, Liang M, Shen Y, Lamb BT, Pimplikar SW. Alzheimer's disease-like pathological features in transgenic mice expressing the APP intracellular domain. Proc Natl Acad Sci U S A. 2009; 106:18367–72. [PubMed: 19837693]

Giedraitis V, Sundelöf J, Irizarry MC, Gårevik N, Hyman BT, Wahlund LO, Ingelsson M, Lannfelt L. The normal equilibrium between CSF and plasma amyloid beta levels is disrupted in Alzheimer's disease. Neurosci Lett. 2007; 427:127–31. [PubMed: 17936506]

Giuffrida ML, Caraci F, De Bona P, Pappalardo G, Nicoletti F, Rizzarelli E, Copani A. The monomer state of beta-amyloid: where the Alzheimer's disease protein meets physiology. Rev Neurosci. 2010; 21:83–93. [PubMed: 20614800]

Grassi F, Palma E, Tonini R, Amici M, Ballivet M, Eusebi F. Amyloid beta(1-42) peptide alters the gating of human and mouse alpha-bungarotoxin-sensitive nicotinic receptors. J Physiol. 2003; 547:147–157. [PubMed: 12562926]

Greenfield JP, Tsai J, Gouras GK, Hai B, Thinakaran G, Checler F, Sisodia SS, Greengard P, Xu H. Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer b-amyloid peptides. Proc Natl Acad Sci USA. 1999; 96:742–747. [PubMed: 9892704]

Gu L, Guo Z. Alzheimer's Aβ42 and Aβ40 peptides form interlaced amyloid fibrils. J Neurochem. 2013; 126:305–11. [PubMed: 23406382]

Hamid R, Kilger E, Willem M, Vassallo N, Kostka M, Bornhövd C, Reichert AS, Kretzschmar HA, Haass C, Herms J. Amyloid precursor protein intracellular domain modulates cellular calcium homeostasis and ATP content. J Neurochem. 2007; 102:1264–75. [PubMed: 17763532]

Han P, Dou F, Li F, Zhang X, Zhang YW, Zheng H, Lipton SA, Xu H, Liao FF. Suppression of cyclin-dependent kinase 5 activation by amyloid precursor protein: a novel excitoprotective mechanism involving modulation of tau phosphorylation. J Neurosci. 2005; 25:11542–52. [PubMed: 16354912]

Handler M, Yang X, Shen J. Presenilin-1 regulates neuronal differentiation during neurogenesis. Development. 2000; 127:2593–606. [PubMed: 10821758]

Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci. 1991; 12:383–8. [PubMed: 1763432]

Harrison SM, Harper AJ, Hawkins J, Duddy G, Grau E, Pugh PL, Winter PH, Shilliam CS, Hughes ZA, Dawson LA, Gonzalez MI, Upton N, Pangalos MN, Dingwall C. BACE1 (beta-secretase) transgenic and knockout mice: identification of neurochemical deficits and behavioral changes. Mol Cell Neurosci. 2003; 24:646–55. [PubMed: 14664815]

Hayashi I, Urano Y, Fukuda R, Isoo N, Kodama T, Hamakubo T, Tomita T, Iwatsubo T. Selective reconstitution and recovery of functional gamma-secretase complex on budded baculovirus particles. J Biol Chem. 2004; 279:38040–38046. [PubMed: 15215237]

Hayden EY, Teplow DB. Amyloid β-protein oligomers and Alzheimer's disease. Alzheimers Res Ther. 2013; 5:60. [PubMed: 24289820]

Hérard AS, Besret L, Dubois A, Dauguet J, Delzescaux T, Hantraye P, Bonvento G, Moya KL. siRNA targeted against amyloid precursor protein impairs synaptic activity in vivo. Neurobiol Aging. 2006; 27:1740–50. [PubMed: 16337035]

Herrup K. The case for rejecting the amyloid cascade hypothesis. Nat Neurosci. 2015; 18:794–9. [PubMed: 26007212]

Hick M, Herrmann U, Weyer SW, Mallm JP, Tschäpe JA, Borgers M, Mercken M, Roth FC, Draguhn A, Slomianka L, Wolfer DP, Korte M, Müller UC. Acute function of secreted amyloid precursor protein fragment APPsα in synaptic plasticity. Acta Neuropathol. 2015; 129:21–37. [PubMed: 25432317]

Hsia AY, Masliah E, McConlogue L, Yu GQ, Tatsuno G, Hu K, Kholodenko D, Malenka RC, Nicoll RA, Mucke L. Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. Proc Natl Acad Sci U S A. 1999; 96:3228–33. [PubMed: 10077666]

Hu X, He W, Diaconu C, Tang X, Kidd GJ, Macklin WB, Trapp BD, Yan R. Genetic deletion of BACE1 in mice affects remyelination of sciatic nerves. FASEB J. 2008; 22:2970–2980. [PubMed: 18413858]

Hu X, Hicks CW, He W, Wong P, Macklin WB, Trapp BD, Yan R. Bace1 modulates myelination in the central and peripheral nervous system. Nat Neurosci. 2006; 9:1520–1525. [PubMed: 17099708]

Hu X, Zhou X, He W, Yang J, Xiong W, Wong P, Wilson CG, Yan R. BACE1 deficiency causes altered neuronal activity and neurodegeneration. J Neurosci. 2010; 30:8819–8829. [PubMed: 20592204]

Hussain I, Powell D, Howlett DR, Tew DG, Meek TD, Chapman C, Gloger IS, Murphy KE, Southan CD, Ryan DM, Smith TS, Simmons DL, Walsh FS, Dingwall C, Christie G. Identification of a novel aspartic protease (Asp 2) as betasecretase. Mol Cell Neurosci. 1999; 14:419–427. [PubMed: 10656250]

Itoh A, Akaike T, Sokabe M, Nitta A, Iida R, Olariu A, Yamada K, Nabeshima T. Impairments of long-term potentiation in hippocampal slices of beta-amyloid-infused rats. Eur J Pharmacol. 1999; 382:167–175. [PubMed: 10556667]

Iulita MF, Allard S, Richter L, Munter LM, Ducatenzeiler A, Weise C, Do Carmo S, Klein WL, Multhaup G, Cuello AC. Intracellular Aβ pathology and early cognitive impairments in a transgenic rat overexpressing human amyloid precursor protein: a multidimensional study. Acta Neuropathol Commun. 2014; 2:61. [PubMed: 24903713]

Jarrett JT, Berger EP, Lansbury PT Jr. The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease. Biochemistry. 1993; 32:4693–7. [PubMed: 8490014]

Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, Stefansson H, Sulem P, Gudbjartsson D, Maloney J, Hoyte K, Gustafson A, Liu Y, Lu Y, Bhangale T, Graham RR, Huttenlocher J, Bjornsdottir G, Andreassen OA, Jönsson EG, Palotie A, Behrens TW, Magnusson OT, Kong A, Thorsteinsdottir U, Watts RJ, Stefansson K. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature. 2012; 488:96–9. [PubMed: 22801501]

Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. Neuron. 2003; 37:925–37. [PubMed: 12670422]

Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol. 1988; 23:138–44. [PubMed: 2897823]

Kawarabayashi T, Shoji M, Younkin LH, WenLang L, Dickson DW, Murakami T, Matsubara E, Abe K, Ashe KH, Younkin SG. Dimeric amyloid beta protein rapidly accumulates in lipid rafts

followed by apolipoprotein E and phosphorylated tau accumulation in the Tg2576 mouse model of Alzheimer's disease. J Neurosci. 2004; 24:3801–9. [PubMed: 15084661]

Khan GM, Tong M, Jhun M, Arora K, Nichols RA. Beta-Amyloid activates presynaptic alpha7 nicotinic acetylcholine receptors reconstituted into a model nerve cell system: Involvement of lipid rafts. Eur J Neurosci. 2010; 31:788–796. [PubMed: 20374280]

Kinoshita A, Shah T, Tangredi MM, Strickland DK, Hyman BT. The intracellular domain of the low density lipoprotein receptor-related protein modulates transactivation mediated by amyloid precursor protein and Fe65. J Biol Chem. 2003; 278:41182–8. [PubMed: 12888553]

Krishnaswamy S1, Verdile G, Groth D, Kanyenda L, Martins RN. The structure and function of Alzheimer's gamma secretase enzyme complex. Crit Rev Clin Lab Sci. 2009; 46:282–301. [PubMed: 19958215]

Laird FM, Cai H, Savonenko AV, Farah MH, He K, Melnikova T, Wen H, Chiang HC, Xu G, Koliatsos VE, Borchelt DR, Price DL, Lee HK, Wong PC. BACE1, a major determinant of selective vulnerability of the brain to amyloidbeta amyloidogenesis, is essential for cognitive, emotional, and synaptic functions. J Neurosci. 2005; 25:11693–11709. [PubMed: 16354928]

Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE, Rozovsky I, Trommer B, Viola KL, Wals P, Zhang C, Finch CE, Krafft GA, Klein WL. Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci U S A. 1998; 95:6448–53. [PubMed: 9600986]

Lawrence JL, Tong M, Alfulaij N, Sherrin T, Contarino M, White MM, Bellinger FP, Todorovic C, Nichols RA. Regulation of presynaptic Ca2+, synaptic plasticity and contextual fear conditioning by a N-terminalβ-amyloid fragment. J Neurosci. 2014; 34:14210–8. [PubMed: 25339735]

Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006; 440:352357.

Lesné SE, Sherman MA, Grant M, Kuskowski M, Schneider JA, Bennett DA, Ashe KH. Brain amyloid-β oligomers in ageing and Alzheimer's disease. Brain. 2013; 136:1383–1398. [PubMed: 23576130]

Levey AI. Muscarinic acetylcholine receptor expression in memory circuits: Implications for treatment of Alzheimer disease. Proc Natl Acad Sci U S A. 1996; 93:13541–13546. [PubMed: 8942969]

Levin ED. Nicotinic receptor subtypes and cognitive function. J Neurobiol. 2002; 53:633–640. [PubMed: 12436426]

Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet. 1997; 349:1546–9. [PubMed: 9167474]

McDonald MP, Dahl EE, Overmier JB, Mantyh P, Cleary J. Effects of an exogenous betaamyloid peptide on retention for spatial learning. Behav Neural Biol. 1994; 62:60–67. [PubMed: 7945146]

McKenzie JE, Gentleman SM, Roberts GW, Graham DI, Royston MC. Increased numbers of βAPPimmunoreactive neurones in the entorhinal cortex after head injury. NeuroReport. 1994; 6:161–164. [PubMed: 7703405]

McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, Bush AI, Masters CL. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999; 46:860–866. [PubMed: 10589538]

Melnikova T, Fromholt S, Kim H, Lee D, Xu G, Price A, Moore BD, Golde TE, Felsenstein KM, Savonenko A, Borchelt DR. Reversible pathologic and cognitive phenotypes in an inducible model of Alzheimer-amyloidosis. J Neurosci. 2013; 33:3765–79. [PubMed: 23447589]

Moechars D, Dewachter I, Lorent K, Reversé D, Baekelandt V, Naidu A, Tesseur I, Spittaels K, Haute CV, Checler F, Godaux E, Cordell B, Van Leuven F. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. J Biol Chem. 1999; 274:6483–6492. [PubMed: 10037741]

Moreth J, Kroker KS, Schwanzar D, Schnack C, von Arnim CAF, Hengerer B, Rosenbrock H, Kussmaul L. Globular and protofibrillar Aβ aggregates impair neurotransmission by different mechanism. Biochem. 2013; 52:1466–1476. [PubMed: 23374097]

Morley JE, Farr SA, Banks WA, Johnson SN, Yamada KA, Xu L. A physiological role for amyloid-beta protein: enhancement of learning and memory. J Alzheimers Dis. 2010; 19:441–9. [PubMed: 19749407]

Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, McConlogue L. High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci. 2000; 20:4050–4058. [PubMed: 10818140]

Müller T, Concannon CG, Ward MW, Walsh CM, Tirniceriu AL, Tribl F, Kögel D, Prehn JH, Egensperger R. Modulation of gene expression and cytoskeletal dynamics by the amyloid precursor protein intracellular domain (AICD). Mol Biol Cell. 2007; 18:201–210. [PubMed: 17093061]

Müller T, Meyer HE, Egensperger R, Marcus K. The amyloid precursor protein intracellular domain (AICD) as modulator of gene expression, apoptosis, and cytoskeletal dynamics-relevance for Alzheimer's disease. Prog Neurobiol. 2008; 85:393–406. [PubMed: 18603345]

Müller U, Cristina N, Li ZW, Wolfer DP, Lipp HP, Rülicke T, Brandner S, Aguzzi A, Weissmann C. Behavioral and anatomical deficits in mice homozygous for a modified beta-amyloid precursor protein gene. Cell. 1994; 79:755–65. [PubMed: 8001115]

Müller UC, Zheng H. Physiological functions of APP family proteins. Cold Spring Harb Perspect Med. 2012; 2:a006288. [PubMed: 22355794]

Mura E, Zappettini S, Preda S, Biundo F, Lanni C, Grilli M, Cavallero A, Olivero G, Salamone A, Govoni S, Marchi M. Dual effect of beta-amyloid on α7 and α4β2 nicotinic receptors controlling the release of glutamate, aspartate and GABA in rat hippocampus. PLoS One. 2012; 7:e29661. [PubMed: 22253754]

Nakaya T, Suzuki T. Role of APP phosphorylation in Fe65-dependent gene transactivation mediated by AICD. Genes Cells. 2006; 11:633–645. [PubMed: 16716194]

Nitsch RM, Farber SA, Growdon JH, Wurtman RJ. Release of amyloid beta-protein precursor derivatives by electrical depolarization of rat hippocampal slices. Proc Natl Acad Sci U S A. 1993; 90:5191–3. [PubMed: 8506366]

Oddo S, LaFerla FM. The role of nicotinic acetylcholine receptors in Alzheimer's disease. J Physiol Paris. 2006; 99:172–179. [PubMed: 16448808]

Ohkawara T, Nagase H, Koh CS, Nakayama K. The amyloid precursor protein intracellular domain alters gene expression and induces neuron-specific apoptosis. Gene. 2011; 475:1–9. [PubMed: 21145952]

Pardossi-Piquard R, Checler F. The physiology of the β-amyloid precursor protein intracellular domain AICD. J Neurochem. 2012; 120:109–24. [PubMed: 22122663]

Pardossi-Piquard R, Petit A, Kawarai T, Sunyach C, Alves da Costa C, Vincent B, Ring S, D'Adamio L, Shen J, Müller U, St George Hyslop P, Checler F. Presenilin-dependent transcriptional control of the Abeta-degrading enzyme neprilysin by intracellular domains of betaAPP and APLP. Neuron. 2005; 46:541–54. [PubMed: 15944124]

Passer B, Pellegrini L, Russo C, Siegel RM, Lenardo MJ, Schettini G, Bachmann M, Tabaton M, D'Adamio L. Generation of an apoptotic intracellular peptide by gamma-secretase cleavage of Alzheimer's amyloid beta protein precursor. J Alzheimers Dis. 2000; 2:289–301. [PubMed: 12214090]

Patel KR. Biogen's aducanumab raises hope that Alzheimer's can be treated at its source. Manag Care. 2015; 24:19.

Perez RG, Zheng H, Van der Ploeg LH, Koo EH. The beta-amyloid precursor protein of Alzheimer's disease enhances neuron viability and modulates neuronal polarity. J Neurosci. 1997; 17:9407–14. [PubMed: 9390996]

Phinney AL, Calhoun ME, Wolfer DP, Lipp HP, Zheng H, Jucker M. No hippocampal neuron or synaptic bouton loss in learning-impaired aged beta-amyloid precursor protein-null mice. Neuroscience. 1999; 90:1207–1216. [PubMed: 10338291]

Plant LD, Boyle JP, Smith IF, Peers C, Pearson HA. The production of amyloid beta peptide is a critical requirement for the viability of central neurons. J Neurosci. 2003; 23:5531–5535. [PubMed: 12843253]

Podlisny MB, Ostaszewski BL, Squazzo SL, Koo EH, Rydell RE, Teplow DB, Selkoe DJ. Aggregation of secreted amyloid betaprotein into sodium dodecyl sulfate stable oligomers in cell culture. J Biol Chem. 1995; 270:9564–9570. [PubMed: 7721886]

Portelius E, Brinkmalm G, Tran AJ, Zetterberg H, Westman-Brinkmalm A, Blennow K. Identification of Novel APP/Aβ Isoforms in Human Cerebrospinal Fluid. Neurodegenerative Dis. 2009; 6:87–94.

Prox J, Rittger A, Saftig P. Physiological functions of the amyloid precursor protein secretases ADAM10, BACE1, and presenilin. Exp Brain Res. 2012; 217:331–41. [PubMed: 22120156]

Puzzo D, Arancio O. Amyloid-β peptide: Dr. Jekyll or Mr. Hyde? J Alzheimers Dis. 2013; 33:S111–20. [PubMed: 22735675]

Puzzo D, Gulisano W, Palmeri A, Arancio O. Rodent models for Alzheimer's disease drug discovery. Expert Opin Drug Discov. 2015; 30:1–9.

Puzzo D, Privitera L, Fa' M, Staniszewski A, Hashimoto G, Aziz F, Sakurai M, Ribe EM, Troy CM, Mercken M, Jung SS, Palmeri A, Arancio O. Endogenous amyloid-β is necessary for hippocampal synaptic plasticity and memory. Ann Neurol. 2011; 69:819–30. [PubMed: 21472769]

Puzzo D, Privitera L, Leznik E, Fa' M, Staniszewski A, Palmeri A, Arancio O. Picomolar amyloid-beta positively modulates synaptic plasticity and memory in hippocampus. J Neurosci. 2008; 28:14537–14545. [PubMed: 19118188]

Puzzo D, Privitera L, Palmeri A. Hormetic effect of amyloid-β peptide in synaptic plasticity and memory. Neurobiol Aging. 2012; 33:1484, e15–24. [PubMed: 22284988]

Puzzo D, Vitolo O, Trinchese F, Jacob JP, Palmeri A, Arancio O. Amyloid-beta peptide inhibits activation of the nitric oxide/cGMP/cAMP-responsive element-binding protein pathway during hippocampal synaptic plasticity. J Neurosci. 2005; 25:6887–97. [PubMed: 16033898]

Regland B, Gottfries CG. The role of amyloid beta-protein in Alzheimer's disease. Lancet. 1992; 340:467–9. [PubMed: 1354793]

Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. Int J Alzheimers Dis. 2012; 2012:369808. [PubMed: 22506132]

Ring S, Weyer SW, Kilian SB, Waldron E, Pietrzik CU, Filippov MA, Herms J, Buchholz C, Eckman CB, Korte M, Wolfer DP, Müller UC. The secreted beta-amyloid precursor protein ectodomain APPs alpha is sufficient to rescue the anatomical, behavioral, and electrophysiological abnormalities of APP-deficient mice. J Neurosci. 2007; 27:7817–7826. [PubMed: 17634375]

Ripoli C, Cocco S, Li Puma DD, Piacentini R, Mastrodonato A, Scala F, Puzzo D, D'Ascenzo M, Grassi C. Intracellular accumulation of amyloid-β (Aβ) protein plays a major role in Aβ-induced alterations of glutamatergic synaptic transmission and plasticity. J Neurosci. 2014; 34:12893–903. [PubMed: 25232124]

Roberts GW, Gentleman SM, Lynch A, Murray L, Landon M, Graham DI. β Amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1994; 57:419–25. [PubMed: 8163989]

Roher AE, Chaney MO, Kuo YM, Webster SD, Stine WB, Haverkamp LJ, Woods AS, Cotter RJ, Tuohy JM, Krafft GA, Bonnell BS, Emmerling MR. Morphology and toxicity of Abeta(1-42) dimer derived from neuritic and vascular amyloid deposits of Alzheimer's disease. J Biol Chem. 1996; 271:20631–20635. [PubMed: 8702810]

Roychaudhuri R, Yang M, Hoshi MM, Teplow DB. Amyloid β-protein assembly and Alzheimer disease. J Biol Chem. 2009; 284:4749–4753. [PubMed: 18845536]

Sarkar SN, Das HK. Regulatory roles of presenilin-1 and nicastrin in neuronal differentiation during in vitro neurogenesis. J Neurochem. 2003; 87:333–43. [PubMed: 14511111]

Saura CA, Choi SY, Beglopoulos V, Malkani S, Zhang D, Shankaranarayana Rao BS, Chattarji S, Kelleher RJ 3rd, Kandel ER, Duff K, Kirkwood A, Shen J. Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. Neuron. 2004; 42:23–36. [PubMed: 15066262]

Savonenko AV, Melnikova T, Laird FM, Stewart KA, Price DL, Wong PC. Alteration of BACE1-dependent NRG1/ErbB4 signaling and schizophrenia-like phenotypes in BACE1-null mice. Proc Natl Acad Sci USA. 2008; 105:5585–5590. [PubMed: 18385378]

Schmidt SD, Nixon RA, Mathews PM. ELISA method for measurement of amyloid-beta levels. Methods Mol Biol. 2005; 299:279–297. [PubMed: 15980612]

Seabrook GR, Smith DW, Bowery BJ, Easter A, Reynolds T, Fitzjohn SM, Morton RA, Zheng H, Dawson GR, Sirinathsinghji DJ, Davies CH, Collingridge GL, Hill RG. Mechanisms contributing to the deficits in hippocampal synaptic plasticity in mice lacking amyloid precursor protein. Neuropharmacology. 1999; 38:349–359. [PubMed: 10219973]

Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002; 298:789–91. [PubMed: 12399581]

Selkoe DJ. Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res. 2008; 192:106–13. [PubMed: 18359102]

Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci. 2007; 27:2866–2875. [PubMed: 17360908]

Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med. 2008; 14:837–42. [PubMed: 18568035]

Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ, Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 2009; 65:403–413. [PubMed: 19296504]

Sinha S, Anderson JP, Barbour R, Basi GS, Caccavello R, Davis D, Doan M, Dovey HF, Frigon N, Hong J, Jacobson-Croak K, Jewett N, Keim P, Knops J, Lieberburg I, Power M, Tan H, Tatsuno G, Tung J, Schenk D, Seubert P, Suomensaari SM, Wang S, Walker D, Zhao J, McConlogue L, John V. Purification and cloning of amyloid precursor protein betasecretase from human brain. Nature. 1999; 402:537–540. [PubMed: 10591214]

Sloane JA, Pietropaolo MF, Rosene DL, Moss MB, Peters A, Kemper T, Abraham CR. Lack of correlation between plaque burden and cognition the aged monkey. Acta Neuropathol. 1997; 94:471–8. [PubMed: 9386780]

Slooter AJ, Cruts M, Kalmijn S, Hofman A, Breteler MM, Van Broeckhoven C, van Duijn CM. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. Arch Neurol. 1998; 55:964–8. [PubMed: 9678314]

Small DH, Maksel D, Kerr ML, Ng J, Hou X, Chu C, Mehrani H, Unabia S, Azari MF, Loiacono R, Aguilar MI, Chebib M. The beta-amyloid protein of Alzheimer's disease binds to membrane lipids but does not bind to the alpha7 nicotinic acetylcholine receptor. J Neurochem. 2007; 101:1527–1538. [PubMed: 17286584]

Sweeney WA, Luedtke J, McDonald MP, Overmier JB. Intrahippocampal injections of exogenous beta-amyloid induce postdelay errors in an eight-arm radial maze. Neurobiol Learn Mem. 1997; 68:97–101. [PubMed: 9195595]

Taylor CJ, Ireland DR, Ballagh I, Bourne K, Marechal NM, Turner PR, Bilkey DK, Tate WP, Abraham WC. Endogenous secreted amyloid precursor protein-a regulates hippocampal NMDA receptor function, long-terme potentiation and spatial memory. Neurobiol Dis. 2008; 31:250–260. [PubMed: 18585048]

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991; 30:572–580. [PubMed: 1789684]

Torack RM, Miller JW. Immunoreactive changes resulting from dopaminergic denervation of the dentate gyrus of the rat hippocampal formation. Neurosci Lett. 1994; 169:9–12. [PubMed: 8047299]

Townsend M, Shankar GM, Mehta T, Walsh DM, Selkoe DJ. Effects of secreted oligomers of amyloid beta-protein on hippocampal synaptic plasticity: a potent role for trimers. J Physiol. 2006; 572:477–92. [PubMed: 16469784]

Turner PR, O'Connor K, Tate WP, Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. Prog Neurobiol. 2003; 70:1–32. [PubMed: 12927332]

Vetrivel KS, Zhang YW, Xu H, Thinakaran G. Pathological and physiological functions of presenilins. Mol Neurodegener. 2006; 1:4. [PubMed: 16930451]

Vigo-Pelfrey C, Lee D, Keim PS, Lieberburg I, Schenk D. Characterization of beta-amyloid peptide from human cerebrospinal fluid. J Neurochem. 1993; 61:1965–1968. [PubMed: 8229004]

Vitolo OV, Sant'Angelo A, Costanzo V, Battaglia F, Arancio O, Shelanski M. Amyloid b peptide inhibition of the PKA/CREB pathway and long-term potentiation: reversibility by drugs that enhance cAMP signaling. Proc Natl Acad Sci USA. 2002; 99:13217–13221. [PubMed: 12244210]

Vogt DL, Thomas D, Galvan V, Bredesen DE, Lamb BT, Pimplikar SW. Abnormal neuronal networks and seizure susceptibility in mice overexpressing the APP intracellular domain. Neurobiol Aging. 2011; 32:1725–9. [PubMed: 19828212]

Wallace WC, Bragin V, Robakis NK, Sambamurti K, VanderPutten D, Merril CR, Davis KL, Santucci AC, Haroutunian V. Increased biosynthesis of Alzheimer amyloid precursor protein the in cerebral cortex of rats with lesions of the nucleus basalis of Meynert. Brain Res Mol Brain Res. 1991; 10:173–8. [PubMed: 1649369]

Walsh D, Klyubin I, Fadeeva J, Cullen WK, Anwyl R, Wolfe M, Rowan M, Selkoe D. Naturally secreted oligomers of the Alzheimer amyloid β-protein potently inhibit hippocampal long-term potentiation in vivo. Nature. 2002; 416:535–539. [PubMed: 11932745]

Walsh DM, Selkoe DJ. A beta oligomers - a decade of discovery. J Neurochem. 2007; 101:1172–84. [PubMed: 17286590]

Wang H, Song L, Laird F, Wong PC, Lee HK. BACE1 knock-outs display deficits in activity-dependent potentiation of synaptic transmission at mossy fiber to CA3 synapses in the hippocampus. J Neurosci. 2008; 28:8677–81. [PubMed: 18753368]

Wang HY, Lee DH, D'Andrea MR, Peterson PA, Shank RP, Reitz AB. Beta-Amyloid(1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. J Biol Chem. 2000; 275:5626–5632. [PubMed: 10681545]

Wegiel J, Kuchna I, Nowicki K, Frackowiak J, Mazur-Kolecka B, Imaki H, Wegiel J, Mehta PD, Silverman WP, Reisberg B, Deleon M, Wisniewski T, Pirttilla T, Frey H, Lehtimäki T, Kivimäki T, Visser FE, Kamphorst W, Potempska A, Bolton D, Currie JR, Miller DL. Intraneuronal Abeta immunoreactivity is not a predictor of brain amyloidosis-beta or neurofibrillary degeneration. Acta Neuropathol. 2007; 113:389–402. [PubMed: 17237937]

Westerman MA, Cooper-Blacketer D, Mariash A, Kotilinek L, Kawarabayashi T, Younkin LH, Carlson GA, Younkin SG, Ashe KH. The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease. J Neurosci. 2002; 22:1858–67. [PubMed: 11880515]

Willem M, Garratt AN, Novak B, Citron M, Kaufmann S, Rittger A, DeStrooper B, Saftig P, Birchmeier C, Haass C. Control of peripheral nerve myelination by the beta-secretase BACE1. Science. 2006; 314:664–666. [PubMed: 16990514]

Wines-Samuelson M1, Schulte EC, Smith MJ, Aoki C, Liu X, Kelleher RJ 3rd, Shen J. Characterization of age-dependent and progressive cortical neuronal degeneration in presenilin conditional mutant mice. PLoS One. 2010; 5:e10195. [PubMed: 20419112]

Wirths O, Bayer TA. Intraneuronal Aβ accumulation and neurodegeneration: Lessons from transgenic models. Life Sci. 2012; 91:1148–52. [PubMed: 22401905]

Wirths O, Dins A, Bayer TA. AβPP Accumulation and/or Intraneuronal Amyloid-β Accumulation? The 3×Tg-AD Mouse Model Revisited. J Alzheimers Dis. 2012; 28:897–904. [PubMed: 22112547]

Wu CC, Chawla F, Games D, Rydel RE, Freedman S, Schenk D, Young WG, Morrison JH, Bloom FE. Selective vulnerability of dentate granule cells prior to amyloid deposition in PDAPP mice: digital morphometric analyses. Proc Natl Acad Sci U S A. 2004; 101:7141–6. [PubMed: 15118092]

Xia D, Watanabe H, Wu B, Lee SH, Li Y, Tsvetkov E, Bolshakov VY, Shen J, Kelleher RJ 3rd. Presenilin-1 Knockin Mice Reveal Loss-of-Function Mechanism for Familial Alzheimer's Disease. Neuron. 2015; 85:967–81. [PubMed: 25741723]

Xie L, Helmerhorst E, Taddei K, Plewright B, Van Bronswijk W, Martins R. Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. J Neurosci. 2002; 22:RC221. [PubMed: 12006603]

Xu H, Sweeney D, Wang R, Thinakaran G, Lo ACY, Sisodia SS, Greengard P, Gandy S. Generation of Alzheimer's b-amyloid protein in the trans-Golgi in the apparent absence of vesicle formation. Proc Natl Acad Sci USA. 1997; 94:3748–3752. [PubMed: 9108049]

Yakel JL. Cholinergic receptors: functional role of nicotinic ACh receptors in brain circuits and disease. Pflugers Arch. 2013; 465:441–50. [PubMed: 23307081]

Yakel JL. Nicotinic ACh receptors in the hippocampal circuit; functional expression and role in synaptic plasticity. J Physiol. 2014; 592:4147–53. [PubMed: 24860170]

Yankner BA, Duffy LK, Kirschner DA. Neurotrophic and neurotoxic effects of amyloid b-protein: reversal by tachykinin neuropeptides. Science. 1990; 250:279–282. [PubMed: 2218531]

Youmans KL, Tai LM, Kanekiyo T, Stine WB Jr, Michon SC, Nwabuisi-Heath E, Manelli AM, Fu Y, Riordan S, Eimer WA, Binder L, Bu G, Yu C, Hartley DM, LaDu MJ. Intraneuronal Aβ detection in 5×FAD mice by a new Aβ-specific antibody. Mol Neurodegener. 2012; 7:8. [PubMed: 22423893]

Young-Pearse TL, Chen AC, Chang R, Marquez C, Selkoe DJ. Secreted APP regulates the function of full-length APP in neurite outgrowth through interaction with integrin beta1. Neural Dev. 2008; 3:15. [PubMed: 18573216]

Yu H, Saura CA, Choi SY, Sun LD, Yang X, Handler M, Kawarabayashi T, Younkin L, Fedeles B, Wilson MA, Younkin S, Kandel ER, Kirkwood A, Shen J. APP processing and synaptic plasticity in presenilin-1 conditional knockout mice. Neuron. 2001; 31:713–26. [PubMed: 11567612]

Zhang C, Wu B, Beglopoulos V, Wines-Samuelson M, Zhang D, Dragatsis I, Südhof TC, Shen J. Presenilins are essential for regulating neurotransmitter release. Nature. 2009; 460:632–6. [PubMed: 19641596]

Zhang D, Zhang C, Ho A, Kirkwood A, Südhof TC, Shen J. Inactivation of presenilins causes pre-synaptic impairment prior to post-synaptic dysfunction. J Neurochem. 2010; 115:1215–21. [PubMed: 20854432]

Zhang L, Lee J, Song L, Sun X, Shen J, Terracina G, Parker EM. Characterization of the reconstituted gamma-secretase complex from Sf9 cells co-expressing presenilin 1, nicastrin, aph-1a, and pen-2. Biochemistry. 2005; 44:4450–4457. [PubMed: 15766275]

Zheng H, Jiang M, Trumbauer ME, Sirinathsinghji DJ, Hopkins R, Smith DW, Heavens RP, Dawson GR, Boyce S, Conner MW, Stevens KA, Slunt HH, Sisoda SS, Chen HY, Van der Ploeg LH. Beta-amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity. Cell. 1995; 81:525–531. [PubMed: 7758106]

Zou K, Gong JS, Yanagisawa K, Michikawa M. A novel function of monomeric amyloid b-protein serving as an antioxidant moleculeagainstmetal inducedoxidativedamage. J Neurosci. 2002; 22:4833–4841. [PubMed: 12077180]

Zou K, Kim D, Kakio A, Byun K, Gong JS, Kim J, Kim M, Sawamura N, Nishimoto S, Matsuzaki K, Lee B, Yanagisawa K, Michikawa M. Amyloid beta-protein (Abeta)1-40 protects neurons from damage induced by Abeta1-42 in culture and in rat brain. J Neurochem. 2003; 87:609–19. [PubMed: 14535944]

HIGHLIGHTS

- Physiological concentrations of Aβ are needed for synaptic function

- Alzheimer's disease might be due to a dysregulation of Aβ physiological homeostasis

- The increase of Aβ might be due to an alteration of the feedback loop between Aβ and α7-nAchRs

- Amyloid Cascade Hypothesis should be revisited