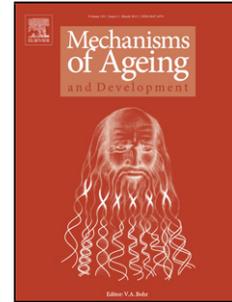


Accepted Manuscript

Title: Amyloid β : Walking on the dark side of the moon

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PII: S0047-6374(15)30012-9
DOI: <http://dx.doi.org/doi:10.1016/j.mad.2015.09.001>
Reference: MAD 10789

To appear in: *Mechanisms of Ageing and Development*

Received date: 31-7-2015
Revised date: 31-8-2015
Accepted date: 3-9-2015

Please cite this article as: Fedele, Ernesto, Rivera, Daniela, Marengo, Barbara, Pronzato, Maria A., Ricciarelli, Roberta, Amyloid β : Walking on the dark side of the moon. *Mechanisms of Ageing and Development* <http://dx.doi.org/10.1016/j.mad.2015.09.001>

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Amyloid β : Walking on the dark side of the moon

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Highlights

- A β is physiologically produced in the brain
- A β is necessary for the expression of LTP and for memory formation
- cAMP is required for LTP and memory
- cAMP stimulates A β production that is needed for LTP and memory
- A β physiological functions need to be unravelled to better understand Alzheimer's disease

ABSTRACT

For some decades, amyloid β (A β) has only been considered as a cytotoxic peptide, putative cause and marker of Alzheimer's disease (AD). Today, however, a considerable amount of evidence goes against the classical amyloid hypothesis and illustrates a new picture in which the A β loss of function, rather than its accumulation, has a pathogenic role in AD. In this concise review, we

summarize some highlights of a collection of research pointing to the physiological function of A β and its role in the mechanisms of memory formation.

1. Introduction

Since its discovery in 1984 (Glennner and Wong, 1984), amyloid β (A β) has been considered the main culprit of Alzheimer's disease (AD) and even if a direct relationship between A β and neurodegeneration has not yet been established, the concept that A β is the disease-causing factor has assumed the value of a dogma within the field. Undeniably, the amyloid hypothesis, which states that accumulation of A β peptides triggers a pathogenic cascade leading to synaptic loss and neuronal death (Hardy and Higgins, 1992), has been strongly supported by four conceptually important observations. Firstly, mutations in three genes directly involved in the production of A β (*APP*, *PS1* and *PS2*) were shown to be causative of familial AD. Secondly, *APP* gene is located on chromosome 21, and a considerable portion of patients with Down syndrome develops AD early in life. Thirdly, A β is known to exert cytotoxic effects on *in vitro* cell systems. Finally, based on established diagnostic criteria, A β accumulation in senile plaques is an obligate feature for the diagnosis of AD. In the last two decades, however, a large and diffused body of evidence has revealed the other side of the coin, demonstrating that A β should not only be considered a pathogenic factor that requires eradication, as recently confirmed by the failure of clinical trials designed to lower A β brain levels (Doody et al., 2014). As a matter of fact, the presence of this peptide in the cerebrospinal fluid (CSF) of healthy individuals (Tamaoka et al., 1997), in neuronal cell cultures (Haass et al., 1992), and in the extracellular compartment of normal brains (Cirrito et al., 2003), has led to the idea that A β may play a functional role in the physiology of the central nervous system (CNS) (Pearson and Peers, 2006). Interestingly, in humans and rodents, interstitial concentration of A β positively correlates with the brain's state of wakefulness, and direct

manipulation of sleep and A β production in rodents has established the bidirectional relationship between these two factors (Kang et al., 2009; Mander et al., 2015; Xie et al., 2013). Furthermore, a very recent genetic study has reported that a substantial fraction of genes related to the production of A β has not only been highly conserved during evolution, but may have contributed to define the cognitive abilities of anatomically modern humans (Zhou et al., 2015).

This brief review summarizes some highlights of a collection of research pointing to the physiological function of A β and its role in the mechanisms of memory formation.

2. How A β is produced

A β peptides range in length from 38 to 43 amino acid residues with two prevalent forms in human, A β ₁₋₄₀ and A β ₁₋₄₂. They all derive from the amyloid precursor protein (APP), whose gene maps to chromosome 21 and contains 19 exons. Alternate splicing of the APP transcript generates different isoforms of which the most common are the 695 amino acid form, mainly expressed in the brain, and the 751 and 770 amino acid forms, more ubiquitously expressed throughout the body (De Strooper and Annaert, 2000). APP is structurally related to the APP-like proteins, APLP1 and APLP2, which are type-I integral membrane proteins with a relatively large extracellular domain and a short intracellular motif. The A β sequence, however, is unique to APP.

APP is sequentially cleaved by enzymes termed β - and γ -secretase. The β -site APP cleavage enzyme (BACE) has been identified as a membrane-bound aspartyl-protease (Vassar et al., 1999) which cleaves APP at the N-terminus of the A β sequence, the first prerequisite for the generation of A β peptides. An additional cleavage in the transmembrane domain by γ -secretase produces the C-terminal end of A β and its consequent release into the extracellular compartment (Fig. 1). Gamma-secretase is a multiprotease complex consisting of at least four components (Presenilins, Nicastrin, Aph-1 and Pen-2), all necessary for the full proteolytic activity (De Strooper, 2003). Given that the

γ -cleavage occurs in the transmembrane domain of APP, it was basically unclear how water, needed to perform hydrolysis, could be provided for this reaction. Only in 2006, the studies performed by Tolia and colleagues gave experimental evidence for the existence of a water-filled cavity in the catalytic core of Presenilin (Tolia et al., 2006).

In an alternative and non-amyloidogenic pathway, APP is proteolytically cleaved by a third secretase, named α -secretase. This processing precludes $A\beta$ production because α -secretase cleaves APP within the $A\beta$ sequence, generating a soluble fragment (sAPP α) endowed with neurotrophic and neuroprotective properties [reviewed by (Postina, 2012)]. For this reason, the α -secretase-mediated cleavage has initially been considered the physiological processing of APP, whereas the amyloidogenic proteolysis operated by BACE was regarded as pathogenic. It should be noted, however, that as α - and β -secretase compete for the same substrate APP, it is likely that an imbalance between these two pathways plays a role in the pathogenesis of AD. Unfortunately, the real identity of α -secretase is still to be established, although it would appear to be a metalloprotease of the ADAM family (Hooper and Turner, 2002; Kuhn et al., 2010).

3. Neuroprotective functions of $A\beta$

The clear evidence that $A\beta$ is physiologically produced by neurons emerged in 1997, when Tamaoka and collaborators demonstrated that the CSF levels of $A\beta_{1-40}$ were comparable between AD and control subjects, and that, unexpectedly, $A\beta_{1-42}$ was significantly lower in the CSF from AD patients (Tamaoka et al., 1997). However, despite this and other evidence, most of the molecular and cellular studies continued focusing on the neurotoxic concentrations of $A\beta$, which are generally much higher than those found in CSF (< 10 nM).

In 2003, treatments to abolish $A\beta$ production in primary neuronal cultures were shown to cause cell death and, even most importantly, such a cytotoxic effect could be prevented by

picomolar concentrations of exogenous A β peptides (Plant et al., 2003). The following year, the conditional double knockout of Presenilin-1 and -2 in postnatal mice proved that, with increasing age, neurodegeneration accompanied by hyperphosphorylation of tau, a hallmark of AD, still occurs in the absence of A β production (Saura et al., 2004). In line with these results, in 2008, it was shown that wild-type Presenilin, but not the mutant form found in familial AD, prevents neurodegeneration by stimulating protective signaling mechanisms (Baki et al., 2008).

Moreover, basic and clinical research on the etiopathogenesis of AD have recently revealed that diverse stimuli, such as head injury, inhaled anesthetics and stimulant drugs, can trigger the production of A β and hyperphosphorylated tau without necessarily leading to neurodegeneration. In fact, these studies contributed to developing the attractive hypothesis that A β and tau may represent the potential physiological mechanism of neuronal repairing or a kind of defense after transient stress and trauma (reviewed by (Bisette, 2009)). In the light of this, A β upregulation has also been proposed as a cellular response to oxidative damage, another hallmark of AD, due to its ability to bind metal ions (Baruch-Suchodolsky and Fischer, 2009) and quench hydroxyl radicals (Nadal et al., 2008). Consequently, a reduction of stress has been shown to lower A β levels in both cellular and animal models (Lim et al., 2001; Veurink et al., 2003).

Finally, it has been hypothesized that even insoluble A β aggregates (i.e. senile plaques) may represent a sort of neuroprotective device able to clear the extracellular fluid of toxic solutes (reviewed by (Robinson and Bishop, 2002)).

Thus, evidence has been accumulated which clearly indicates that the scientific community must look beyond the pathological role of A β and try to unravel its diverse physiological functions.

4. A β and memory

Based on the well-recognized role of acetylcholine in learning and memory, acetylcholinesterase inhibitors so far represent the main pharmacological strategy for the symptomatic treatment of AD. Activation of acetylcholine receptors (AChRs) would improve the encoding of new memories through the enhancement of LTP, which is the electrophysiological substrate of memory (Huerta and Lisman, 1995). Interestingly, A β has picomolar affinity for the α 7-nicotinic AChR (α 7-nAChR) (Wang et al., 2000) and directly activates its current in different model systems (Dineley et al., 2002; Puzzo et al., 2008). On the other hand, higher (nanomolar) concentrations of A β inhibit such effects by blocking the postsynaptic α 7-nAChR channels in a way that appears to be peptide- and neuron-specific (Pettit et al., 2001).

The idea that A β might play a positive role in synaptic plasticity and memory came in 1999 from the evident cognitive impairment of APP knockout mice (Dawson et al., 1999; Seabrook et al., 1999). Some years later, it was shown that also β -secretase knockout mice exhibited deficits in hippocampal LTP and memory (Laird et al., 2005; Wang et al., 2008), though a prior study did not report obvious neurological deficits in a similar animal model, probably due to the fact that the production of A β had not completely abolished (Luo et al., 2001). In these studies, however, it was not possible to exclude the involvement of either APP itself or fragments other than A β , such as soluble APP α/β and the APP intracellular domain (AICD). To investigate this, Puzzo and colleagues tested different concentrations of synthetic A β peptides and found that picomolar amounts of A β ₁₋₄₂ were able to enhance LTP and hippocampal-dependent memory in mice, whereas nanomolar concentrations of the peptide gave opposing results. Furthermore, and in line with previous evidence, they also showed that A β failed to increase LTP in a mouse model where the α 7-nAChR had been knocked out (Puzzo et al., 2008). More interestingly, from a physiological point of view, is that the expression of hippocampal LTP and the formation of memory was prevented by A β antibodies, thus demonstrating the key function of the endogenous peptide in synaptic plasticity (Puzzo et al., 2011). Collectively, these studies indicate that A β follows the rule

of hormesis, enhancing memory at physiological concentrations and worsening it at higher levels (Morley and Farr, 2012; Puzzo et al., 2012).

It is now widely accepted that cyclic adenosine monophosphate (cAMP) modulates synaptic plasticity and memory, and that manipulations of the cAMP/protein kinase A (PKA)/cAMP responsive element binding protein (CREB) pathway significantly affect cognitive functions. The impairment of PKA/CREB activity has been observed in the brain of AD patients and AD animal models (Gong et al., 2004; Liang et al., 2007; Yamamoto-Sasaki et al., 1999), thus leading to the hypothesis that cAMP-enhancing strategies may be beneficial for the treatment of memory loss in AD and other neurodegenerative diseases (Bruno et al., 2011, 2014; Burgin et al., 2009, Ricciarelli et al., 2015). Notably, different lines of evidence indicate that cAMP can stimulate both APP synthesis and its amyloidogenic processing (Canepa et al., 2013; Lee et al., 1997; Marambaud et al., 1998). Moreover, the cAMP-mediated induction of LTP has been found to require physiological concentrations of A β (Ricciarelli et al., 2014), supporting the existence of a novel cAMP/PKA/APP/A β molecular cascade with a crucial role in LTP and memory formation.

On the basis of the current knowledge, it is likely to assume that salient stimuli in the hippocampus may activate the cAMP/PKA-mediated production of A β in nerve terminals of the Schaffer-Collateral pathway. The released peptide could then bind to post-synaptic α 7-nAChRs, thus sustaining the expression of LTP (Fig. 2). As a matter of fact, APP processing and extracellular A β levels in the hippocampus are regulated by synaptic activity in an endocytosis-exocytosis manner (Nitsch et al., 1993; Cirrito et al., 2005). Additionally, A β effects on LTP require α 7-nAChRs (Puzzo et al., 2011), which are present on the dendrites of hippocampal neurons (Albuquerque et al., 1997) where they regulate LTP (Soderman et al., 2011; Ma et al., 2014).

5. Conclusions

For some decades A β has played the part of the toxic peptide, killing neurons and devastating the brain to the point of Alzheimer's dementia. Today, however, the demonstration of neuroprotective and cognitive functions of A β , together with the debacle of anti-A β clinical trials, goes against the classical amyloid hypothesis and opens up a new scenario in which the A β loss of function, rather than its accumulation, plays a role in AD. We believe that, in order to obtain a better understanding of AD etiopathogenesis, it is imperative to focus future research on the physiology of A β . We are in fact at the beginning, but we have started to explore the dark side of the moon.

Acknowledgment

This work was partially supported by Genoa University.

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Figure legend

Fig. 1. Amino acid sequence of A β ₁₋₄₂ and schematic structure of its precursor protein APP695. The soluble APP fragment (sAPP) is generated by the β -secretase cleavage of APP, whereas the subsequent γ -secretase cleavage creates the A β peptide along with the APP intracellular domain (AICD).

Fig. 2. Role of A β in memory formation: a theoretical model. At hippocampal presynaptic level, salient stimuli activate the cAMP/PKA/APP pathway with the consequent release of A β peptides which, in turn, bind to and activate postsynaptic AChR, thus boosting LTP and memory.

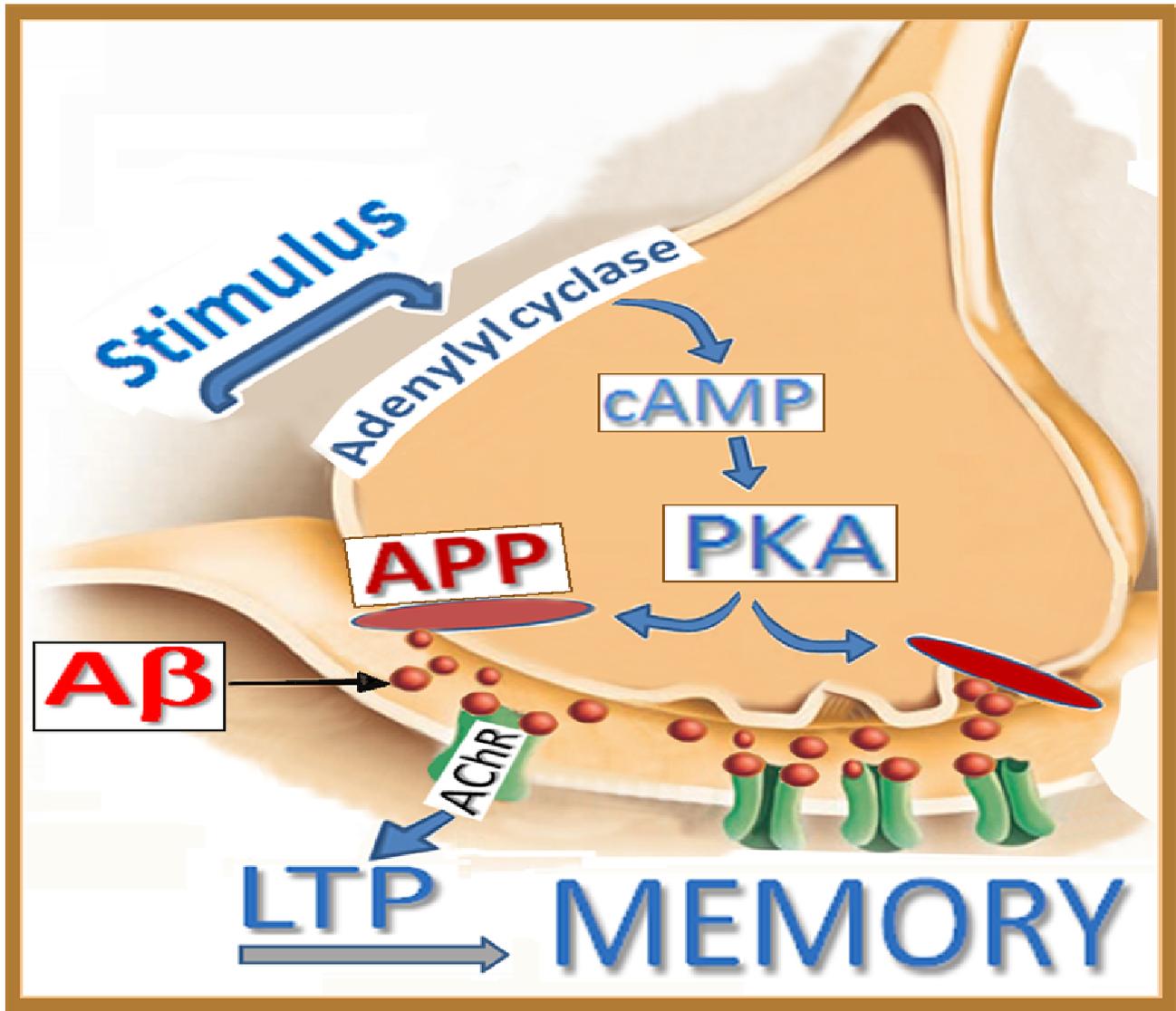


Figure 2 .