

Amyloid Beta and the Brain: Where Are We Now?

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Alzheimer's disease (AD) is certainly the most devastating and common form of dementia afflicting more than 40 million people worldwide today, with an expected escalation up to 130 million by 2050. The early sign of dementia is represented by the difficulty in remembering recent events but more symptoms emerge as AD inexorably progresses, including confusion, disorientation, severe memory loss and cognitive alterations, mood and behavioural changes, difficulties in reading, writing, speaking, swallowing and walking. These increasing disabilities dramatically affect the daily life of patients but also of their relatives, and have a highly relevant socioeconomic impact, taking into account direct, indirect and intangible costs [1].

Certainly, in the last 30 years a milestone of AD research has been the discovery of the amyloid β peptide ($A\beta$) that, since then, has been considered the main cause of the pathology. Thus, the "amyloid hypothesis" soon became the prevailing theoretical model of AD pathophysiology that is still driving the development of pharmacological treatments.

$A\beta$ peptides originate from the cleavage of a transmembrane precursor protein called APP (Amyloid Precursor Protein) that is first processed by a β -secretase (BACE, beta-site APP-cleaving enzyme) and then by a γ -secretase. Among the different fragments produced by this processing, $A\beta_{1-42}$ is more self-aggregating than $A\beta_{1-40}$ that, on the other hand, has been shown to prevent $A\beta_{1-42}$ deposition [2].

At present, it is quite clear that neurotoxicity is not initiated by aggregation of amyloid peptides into senile plaques, as originally thought, but rather by formation of soluble β -amyloid dimers/oligomers that have been shown to impair long-term potentiation (LTP), to enhance long-term depression (LTD), to alter synaptic structures and, consequently, to deteriorate memory [3].

Indeed, it has been hypothesized that $A\beta$ plaques could represent a defence mechanism to sequester soluble synaptotoxic $A\beta$ species [4]. In line with this view, amyloid plaque cores, directly isolated from AD patients, are not able to affect LTP that, on the contrary, is impaired by soluble oligomers released from plaques using strong denaturants [3]. Interestingly, a recent study has found that the oligomer/plaque ratio was significantly higher in mildly demented patients than in non-demented control subjects with the same amyloid plaque burden [5].

Although $A\beta_{1-40}$ and $A\beta_{1-42}$ are the most common forms, increasing evidence demonstrate that there are far more peptide species that accumulate in AD brains (e.g. $A\beta_{1-37,38,43,56}$, $A\beta pE$), which can be modified over time and that could play a pathogenic role in the development of the disease [6]. To further complicate $A\beta$ peptide heterogeneity, it has been recently shown that novel, N-terminally extended $A\beta$ -containing monomers (NTE- $A\beta$), produced in cells expressing mutant human APP, can impair hippocampal LTP *in vivo* [7]. These fragments are distinct from classical $A\beta_{1-40/42}$ oligomers and, unexpectedly, their levels increase upon inhibition of β -secretase, suggesting that they could originate from a protease cleavage different from that of BACE.

As for the mechanisms through which $A\beta$ can exert its toxic effects, several lines of evidence have identified a plethora of proteins

which monomers, dimers and oligomers can bind to, such as $\alpha 7$ -nAChR, NMDA receptor, RAGE, insulin receptor, PrP^c and others [8,9]. However, the role of many of these proteins is still a matter of controversy and the use of different, often poorly characterized, $A\beta$ oligomers to target them in different *in vitro* or *in vivo* models has led to a rather confusing scenario.

In any case, although we have certainly increased our knowledge on APP processing and $A\beta$ toxicity, it has become evident that the amyloid hypothesis is not sufficient to explain the pathophysiology of AD, the living proof being the almost complete failure of clinical trials aimed at reducing the brain levels of this peptide in AD patients.

But should we really aim at clearing $A\beta$ from the brain?

Over the last decade or so, a growing body of data has provided incontrovertible evidence for a key role of this peptide in the biological functions of the brain.

First of all, it has to be borne in mind that $A\beta$ is present not only in the brain of AD patients but also in healthy individuals and it is produced physiologically at low (picomolar) concentrations throughout lifetime.

One of the first evidence suggesting that $A\beta$ could participate in normal central functions came from studies on APP knockout mice, which showed memory deficits in the conditioned avoidance test and in the Morris water maze. In addition, hippocampal LTP in these animals was significantly impaired and was associated with abnormal neuronal morphology [10,11]. Similar results were successively obtained in BACE KO mice [12]. However, the decisive evidence of $A\beta$ involvement in memory formation has been provided by the finding that clearing the peptide from the hippocampus, using selective antibodies, resulted in the impairment of LTP that led to contextual fear and reference memory deficits; moreover, all these antibody-induced alterations were indeed rescued by the addition of exogenous $A\beta_{1-42}$ [13]. In this context, we have recently demonstrated that APP expression and $A\beta$ production are controlled by the second messenger cAMP through activation of PKA, and that endogenous $A\beta$ is necessary for cAMP-mediated expression of LTP [14,15].

Also in this case, $A\beta$ classical fragments do not seem the only species able to modulate memory formation. In fact, it has been recently reported that a monomeric N-terminal $A\beta_{1-15}$ fragment, present in the

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Received April 18, 2016; Accepted April 19, 2016; Published April 22, 2016

Citation: Fedele E, Rebosio C, Pronzato MA, Ricciarelli R (2016) Amyloid Beta and the Brain: Where Are We Now? J Biomol Res Ther 5: e147. doi:10.4172/2167-7956.1000e147

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CSF of healthy individuals as well as of AD patients, is able to potently enhance hippocampal LTP (50 fM) and to improve memory in the contextual fear conditioning paradigm [16]. Intriguingly enough, the hippocampal LTP impairment caused by high concentrations of exogenous $A\beta_{1-42}$ (slices from wild type mice) or by endogenous $A\beta$ (slices from APP_{SWE} transgenic mice) was rescued by pre-treatment with $A\beta_{1-15}$.

Apart from memory formation, $A\beta$ has been shown to play also critical roles in neuronal survival, since its reduction by β - or γ -secretase inhibitors, as well as its immunodepletion, caused neuronal death in cortical cultures that could be prevented by addition of physiological concentrations of $A\beta$ [17]. At variance with this result, however, APP KO mice showed marked reactive gliosis, loss of presynaptic and dendritic markers, but not neuronal death [10], probably because of compensatory mechanisms operating during development.

It has also been proposed that $A\beta$ is involved in the physiological control of neuronal activity by depressing synaptic functions through a negative feedback mechanism, once increased synaptic activity enhances the production of $A\beta$ itself [18].

Finally, up regulation of $A\beta$ production could also represent a protective cellular response to oxidative stress, as it can sequester metal ions and can act as an antioxidant scavenging free radicals [19].

Thus, although an enormous progress has been done in elucidating the various pathological aspects of APP processing and $A\beta$ formation, we have just commenced to unravel the physiological roles of this peptide in the brain. Such aspect is of fundamental importance if we intend to understand Alzheimer's disease and develop successful therapeutic interventions.

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