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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 (Aβ) 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.

Aβ 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, $Aβ_{1–42}$ is more self-aggregating than $Aβ_{1–40}$ that, on the other hand, has been shown to prevent $Aβ_{1–42}$ 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 Aβ plaques could represent a defence mechanism to sequester soluble synaptotoxic Aβ 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 $Aβ_{1–40}$ and $Aβ_{1–42}$ are the most common forms, increasing evidence demonstrate that there are far more peptide species that accumulate in AD brains (e.g. $Aβ_{1–37,38,43,56}$, AβpE), which can be modified over time and that could play a pathogenic role in the development of the disease [6]. To further complicate Aβ peptide heterogeneity, it has been recently shown that novel, N-terminally extended Aβ– containing monomers (NTE-Aβ), produced in cells expressing mutant human APP, can impair hippocampal LTP *in vivo* [7]. These fragments are distinct from classical $Aβ_{1–40/42}$ 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 Aβ 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 α7-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, Aβ 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 Aβ 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 Aβ 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 Aβ 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 Aβ 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 Aβ 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 $Aβ_{1–42}$ [13]. In this context, we have recently demonstrated that APP expression and Aβ production are controlled by the second messenger cAMP through activation of PKA, and that endogenous Aβ is necessary for cAMP-mediated expression of LTP [14,15].

Also in this case, Aβ 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 $Aβ_{1–15}$ fragment, present in the

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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 Aβ (slices from APP_{SWE} transgenic mice) was rescued by pre-treatment with $A\beta_{1-15.}$

Apart from memory formation, Aβ 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 Aβ [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 Aβ 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 Aβ itself [18].

Finally, up regulation of Aβ 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 Aβ 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.

References

1. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, et al. (2016) Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 15: 455-532.
2. Kim J, Onstead L, Randle S, Price R, Smithson L, et al. (2007) Aβ-40 inhibits amyloid deposition *in vivo*. J Neurosci 27: 627-633.
3. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, et al. (2008) Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 14: 837-842.
4. Robinson SR, Bishop GM (2002) Abeta as a bioflocculant: implications for the amyloid hypothesis of Alzheimer's disease. Aging 23: 1051-1072.
5. Esparza TJ, Zhao H, Cirrito JR, Cairns NJ, Bateman RJ, et al. (2013) Amyloid-β oligomerization in Alzheimer dementia versus high-pathology controls. Ann Neurol 73: 104-119.
6. Forloni G, Artuso V, La Vitola P, Balducci C (2016) Oligomeropathies and pathogenesis of Alzheimer's and Parkinson's diseases. Mov Dis.
7. Welzel AT, Maggio JE, Shankar GM, Walker DE, Ostaszewski BL, et al. (2014) Secreted amyloid β-proteins in a cell culture model include N-terminally extended peptides that impair synaptic plasticity. Biochemistry 53: 3908-3921.
8. Govoni S, Mura E, Preda S, Racchi M, Lanni C, et al. (2014) Dangerous liaisons between beta-amyloid and cholinergic neurotransmission. Curr Pharm Des 20: 2525-2538.
9. Jarosz-Griffiths HH, Noble E, Rushwoth JV, Hooper NM (2016) Amyloid-β receptors: the good, the bad and the prion protein. J Biol Chem 291: 3174-3183.
10. Dawson GR, Seabrook GR, Zheng H, Smith DW, Graham S, et al. (1999) Age-related cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the β-amyloid precursor protein. Neuroscience 90: 1-13.
11. Seabrook GR, Smith DW, Bowery BJ, Easter A, Reynolds T, et al. (1999) Mechanisms contributing to the deficits in hippocampal synaptic plasticity in mice lacking amyloid precursor protein. Neuropharmacology 38: 349-359.
12. Laird FM, Cai H, Savonenko AV, Farah MH, He K, et al. (2005) BACE1, a major determinant of selective vulnerability of the brain to amyloid-beta amyloidogenesis, is essential for cognitive, emotional, and synaptic functions. J Neurosci 25: 11693-11709.
13. Puzzo D, Privitera L, Fa' M, Staniszewski A, Hashimoto G, et al. (2011) Endogenous amyloid-β is necessary for hippocampal synaptic plasticity and memory. Ann Neurol 69: 819-830.
14. Canepa E, Domenicotti C, Marengo B, Passalacqua M, Marinari UM, et al. (2013) Cyclic adenosine monophosphate as an endogenous modulator of the amyloid-β precursor protein metabolism. IUBMB Life 65: 127-133.
15. Ricciarelli R, Puzzo D, Bruno O, Canepa E, Gardella E, et al. (2014) A novel mechanism for cyclic adenosine monophosphate-mediated memory formation: Role of amyloid beta. Ann Neurol 75: 602-607.
16. Lawrence JL, Tong M, Alfulaij N, Sherrin T, Contarino M, et al. (2014) Regulation of presynaptic Ca^{2+}, synaptic plasticity and contextual fear conditioning by a N-terminal β-amyloid fragment. J Neurosci 34: 14210-14218.
17. Plant LD, Boyle JP, Smith IF, Peers C, Pearson HA (2003) The production of amyloid beta peptide is a critical requirement for the viability of central neurons. J Neurosci 23: 5531-5535.
18. Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, et al. (2003) APP processing and synaptic function. Neuron 37: 925-937.
19. Nadal RC, Rigby SE, Viles JH (2008) Amyloid beta-Cu^{2+} complexes in both monomeric and fibrillar forms do not generate H_2O_2 catalytically but quench hydroxyl radicals. Biochemistry 47: 11653-11664.