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Amyloid-β Peptide: Dr. Jekyll or Mr. Hyde?

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Abstract

Amyloid-β peptide (Aβ) is considered a key protein in the pathogenesis of Alzheimer's disease (AD) because of its neurotoxicity and capacity to form characteristic insoluble deposits known as senile plaques. Aβ derives from amyloid-β protein precursor (AβPP), whose proteolytic processing generates several fragments including Aβ peptides of various lengths. The normal function of AβPP and its fragments remains poorly understood. While some fragments has been suggested to have a function in normal physiological cellular processes, Aβ has been widely considered as a "garbage" fragment that becomes toxic when it accumulates in the brain, resulting in impaired synaptic function and memory. Aβ is produced and released physiologically in the healthy brain during neuronal activity. In the last 10 years, we have been investigating whether Aβ plays a physiological role in the brain. We first demonstrated that picomolar concentrations of a human $A\beta_{42}$ preparation enhanced synaptic plasticity and memory in mice. Next, we investigated the role of endogenous Aβ in healthy murine brains and found that treatment with a specific antirodent Aβ antibody and an siRNA against murine AβPP impaired synaptic plasticity and memory. The concurrent addition of human $A\beta_{42}$ rescued these deficits, suggesting that in the healthy brain, physiological Aβ concentrations are necessary for normal synaptic plasticity and memory to occur. Furthermore, the effect of both exogenous and endogenous Aβ was seen to be mediated by modulation of neurotransmitter release and α7-nicotinic receptors. These findings need to be taken into consideration when designing novel therapeutic strategies for AD.

Keywords

Amyloid-β peptide; hippocampus; memory; nicotinic receptor; synaptic plasticity

GREAT IS THE POWER OF MEMORY

> Great is the power of memory, a fearful thing, O my God, a deep and boundless manifoldness; and this thing is the mind, and this am I myself. […] So great is the force of memory, so great the force of life, even in the mortal life of man.
>
> from "The Confessions of St. Augustine"

Memory has a central role in life: our experiences contribute to making us who we are and give us an identity, a history, a culture. What would we be without our past, without a story

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to tell, without people to remember? Our existence would be like a leaky bucket that, though filled with new memories every day, lets them flow away, erasing the past and threatening the future. It is this intriguing, perfectly designed and harmonically constructed mechanism that we have set out to explore: to clarify how memory works helps avoid the dreadful notion of forgetfulness. A greater understanding of the physiological basis of memory formation is therefore required if we are to gain deeper insights into the impairment of cognitive functions related to neurodegenerative disorders such as Alzheimer's disease (AD).

THE AMYLOID HYPOTHESIS OF ALZHEIMER'S DISEASE

Amyloid-β peptide (Aβ), a protein found in large amounts in AD brains, has been the focus of AD research for the last 30 years. We owe to Glenner and Wong in 1984 the "initial report of the purification and characterization of a novel cerebrovascular amyloid protein" associated with AD [1]. Subsequent discoveries led to an explosion of studies on the toxic effects of Aβ as the main pathogenic factor in AD. Milestones in Aβ-AD research have been the demonstration that: i) the characteristic senile plaques in AD brains consist of Aβ aggregates [2]; ii) amyloid-β protein precursor (AβPP) is located on chromosome 21 (21q21.2-3) [3, 4], the same chromosome is involved in Down syndrome, which is characterized by Aβ deposition and AD-like neurodegeneration [5]; and iii) AβPP genetic mutations are involved in familial AD [6–10].

AβPP and its processing have been intensively investigated. AβPP is a type-1 transmembrane glycoprotein expressed in several cells (e.g., neurons, glia, endothelial cells, fibroblasts) that undergoes a complex cleavage process by secretases. AβPP is initially cleaved into α- and β-fragments, generating two soluble extracellular domains (sAβPPα and sAβPPβ) that differ only by a 17AA at the COOH terminus. The remaining AβPP portion, the carboxy-terminal fragment (CTF), contains 83AA (C83) after cleavage by α-secretase, or 99AA (C99) after cleavage by β-secretase. Then, γ-secretase generates a p3 fragment and a 57-59AA CTF from C83 and generally a 40 to 42 AA fragment called $Aβ_{40}$, or 42 together with AβPP intracellular domain (AICD) fragment from C99. Aβ generation thus requires the action of β- and γ-secretase on AβPP. Based on the knowledge of AβPP processing, a number of therapeutic strategies aimed at reducing Aβ production in the AD brain have been developed. At the same time, several genetically-modified animals have been generated carrying AβPP or secretase mutations [11]. In particular, amyloid-depositing mice overexpressing human AβPP or proteins belonging to the γ-secretase complex, known as presenilins (PS1 and PS2), have been widely used to study AD features. For example, AβPP/PS1 mice [12] show impaired long-term potentiation (LTP)—a form of synaptic plasticity underlying memory [13]—as early as 3 months of age and a decline of reference memory at approximately 6 months of age, in parallel to increased Aβ production and deposition [14]. Synaptic plasticity and memory are also impaired after administration of high Aβ concentrations [15–29]. A large body of data suggests that, at least in the early stages of AD, synaptic disorders underlying memory impairment could be due to raised Aβ levels [30, 31].

Aβ accumulation would lead to oligomerization followed by peptide deposition in senile plaques, resulting in irreversible structural damage. Based on these findings, several therapeutic approaches to AD have been developed using strategies such as specific anti-Aβ antibodies, drugs aimed to shift AβPP processing, block Aβ accumulation, and/or act on Aβ downstream pathways. However, none of the approaches aimed at reducing amyloid load has been successful so far because, even when these drugs effectively clear the brain from Aβ deposits, they do not improve cognition and have several side effects [32–37]. Indeed, whereas a large number of findings support the amyloid hypothesis, there are important

aspects that need to be clarified. First of all, a direct correlation between amyloid deposits and dementia severity has not been demonstrated, since some patients without amyloid deposition show severe memory deficits while other patients with cortical Aβ deposits have no dementia symptoms. Second, it is very difficult to study the pathophysiological role of each Aβ species and their aggregation status (e.g., $A\beta_{42}/A\beta_{40}$ and monomers/oligomers/fibrils), because the very composition of Aβ solutions and, their molarities used in *in vitro* and *in vivo* conditions, are hard to establish precisely. This is due to the fact that Aβ can easily change conformation after preparation, not to mention that it sticks to the tubes, altering the final concentration of the solution. Finally, it should be stressed that the results found in experimental models using a single Aβ species are not easily transposable *in vivo*, mainly because the brain normally produces a variety of Aβ peptides and we do not clearly know how and why.

THE STRANGE CASE OF Aβ PEPTIDE: DR. JEKYLL OR MR. HYDE?

As reported in numerous manuscripts, high Aβ levels are involved in AD synaptic dysfunction and memory loss. However, a number of issues remain to be solved before clinical trials aiming to decrease the Aβ load can be undertaken, especially if they are directed at disease “prevention” in healthy subjects. Low Aβ levels are found in the brain throughout life, and the possibility of a physiological role for it is increasingly being investigated by the neuroscience community.

Whereas 20 years ago studies of the physiological function of Aβ peptides were quite limited, the interest has progressively increased in the following two decades. In 1990, Yankner and co-workers emphasized the dual role of Aβ, demonstrating that it could exert a neurotrophic action in differentiating neurons, whereas high concentrations caused neuronal degeneration in mature neurons [38]. Other studies highlighted its neuroprotective role, suggesting that Aβ promotes neuronal growth and survival [39, 40], also protecting against excitotoxic death by activating the phosphatidylinositol-3-kinase pathway [41, 42]. Aβ was shown to serve a double prooxidant/antioxidant role [43–46] and to bind and remove harmful substances by blocking them in plaques [47, 48]. Aβ has also been implicated in neurogenesis and has been suggested to increase the total number of neurons *in vitro* in a dose-dependent manner [49]. Finally, interesting findings suggest that Aβ is a molecule of innate immunity system because of its antimicrobial activity against common microorganisms [50] and the vulnerability to infections founded in mice lacking β-secretases and in AD patients treated with Aβ-lowering drugs [51, 36]. Aβ is normally found in the brain and in blood. In rodents, normal brain concentrations have been estimated to be in the picomolar range [52, 53]. In humans, the concentrations of $A\beta_{40}$ and $A\beta_{42}$ in cerebrospinal fluid (CSF) are around 1,500 pM and 200 pM, respectively; in plasma they are 60 pM and 20 pM, respectively [54]. CSF and plasma concentrations have been used as markers to determine AD prognosis and treatment. However, research outcomes are contradictory, especially when human and animal findings are compared. Notably, Aβ concentrations are higher in the young and decline with age [55]. Moreover, increased CSF levels have been seen in patients with mild cognitive impairment who progressed to AD [56], whereas low levels have been found in AD patients [57, 54]. Aβ concentrations in brain interstitial fluid (ISF) thus seem to correlate with neurological status, and it has been demonstrated that concentrations increase when the neurological status improves, and that they decrease when the cognitive status declines [58]. Aβ levels in brain ISF have been seen to be dynamically influenced by synaptic activity [59], and synaptic transmission has been found to induce more AβPP endocytosis and a consequent increase in Aβ release [60]. In a paper using Sindbis virus to overexpress AβPP, it was shown that neuronal activity stimulates Aβ secretion in hippocampal slice neurons and, in turn, Aβ depresses excitatory synaptic transmission in the same neurons [61]. The endogenously released Aβ seems also to exert a

fundamental role in the regulation of neurotransmitter release by modulating vesicle cycling. Indeed, the acute endogenously-released Aβ induced an increase in the number of synapses and in neurotransmitter release whereas a chronic persistence of Aβ, due to a inhibition of its clearance, induced the opposite effect [62]. Other studies suggest that Aβ may stimulate or inhibit the pre-synaptic release of excitatory neurotransmitters such as aspartate and glutamate depending upon the dose [63]. Taken together, these studies suggest that Aβ and neuronal function are closely related. Dependent upon the concentration of Aβ, the peptide might have a positive regulation upon excitatory synaptic transmission from low physiologic concentrations, or a negative regulation from high pathologic concentrations.

Some researchers have explored the possible physiological effect of Aβ by blocking its production *via* inhibition of secretases or AβPP. Inhibition of β-or γ-secretase activity induced neuronal death that was rescued by preincubation with picomolar concentrations of Aβ [64]. Loss of presenilin function determined LTP and memory deficits [65] and, interestingly, changes in hippocampal synaptic plasticity and cognition in β-secretase-null mice [66] have been prevented by co-expression of AβPP and PS1 transgenes [67]. Interestingly, both the overexpression and the deletion of the β-AβPP cleavage enzyme 1 (BACE1) determined behavioral changes [68]. Even AβPP-deficient mice present impaired LTP and hippocampal memory and marked cortical and hippocampal gliosis [69–74]. However, the complex phenotype of AβPP knock-out (KO) mice (characterized by low body weight, agenesis of the corpus callosum, hypersensitivity to seizures, defects in copper and lipid homeostasis, and impaired grip strength, locomotor and exploratory activity, and cognition) makes them difficult to study, especially where behavioral aspects are concerned. Moreover, use of AβPP-KO animals does not exclude the possibility that other AβPP fragments or AβPP itself other than Aβ might be biologically important. For instance, sAβPP fragments have neurotrophic properties and are required for synaptic plasticity and memory [75–83], and intracellular CTF may regulate gene transcription, calcium signaling, synaptic plasticity, and memory [84–88].

PHYSIOLOGICAL ROLE OF Aβ IN SYNAPTIC PLASTICITY AND MEMORY: OUR FINDINGS

Because of the problems linked to the complexity of the AβPP processing, we decided to use a different approach starting from the use of exogenous application of different concentrations of $A\beta_{42}$ preparations containing both monomers and oligomers [53]. In particular, we found that picomolar concentrations of $A\beta_{42}$ enhanced LTP and hippocampal-dependent memory as tested by the Morris water maze and by fear conditioning. A dose/response curve for the effect of Aβ on LTP showed that perfusion with 200 nM $A\beta_{42}$ for 20 min impaired LTP at the synapses between Schaeffer collateral fibers and CA1 neurons, whereas lower concentrations enhanced it, with a maximal effect around 200 pM. This effect was not found with scrambled $A\beta_{42}$, or when the peptide was administered after tetanization. We next investigated the effect of low doses of $A\beta_{42}$ on memory by injecting 200 pM $A\beta_{42}$, 200 pM scrambled $A\beta_{42}$, or vehicle into the hippocampus, and found that low Aβ concentrations improved both reference and contextual memory. Interestingly, a dose-response curve for memory showed a similar biphasic effect of $A\beta_{42}$, with low doses stimulating and high doses inhibiting reference memory [29]. Our next goal was to inquire into the mechanism by which Aβ improved LTP and memory. We first studied the possible role of NMDA and AMPA receptors, given their involvement in LTP [89]. However, low doses of Aβ did not change current-voltage (I/V) relationships for NMDA and AMPA receptor currents, nor did they alter the amplitude of AMPA receptor-mediated excitatory postsynaptic potentials (EPSCs) or their amplitude distribution. In our experimental conditions, NMDA and AMPA receptors were therefore not involved in Aβ-induced improvement of synaptic function. We also assessed whether Aβ might affect spontaneous

neurotransmitter release, but average miniature EPSC frequency and amplitude were not affected by treatment with 200 pM Aβ. Given that mechanisms regulating basal neurotransmission were not affected, we turned our attention toward mechanisms that are involved in synaptic plasticity. In particular, we investigated a presynaptic phenomenon, the transmitter release occurring during the tetanus. We recorded post-tetanic potentiation (PTP), a form of short-term plasticity that reflects the increase in glutamate release from presynaptic terminals due to brief periods of high-frequency stimulation [90]. PTP was increased by perfusion with low Aβ concentrations, suggesting that its favorable effect on synaptic plasticity is exerted through enhancement of transmitter release during the tetanus.

Our next question was: how do picomolar levels of $A\beta_{42}$ enhance PTP? Aβ might have several targets. We chose to focus onto acetylcholine receptors (AChRs). Indeed, both nicotinic (nAChRs) and muscarinic receptors (mAChRs) play a fundamental role in learning and memory in physiological and pathological conditions such as AD [91–93]. Because of their impaired cholinergic activity pharmacological strategies to improve cholinergic transmission (i.e., cholinesterase inhibitors) have been used in AD patients [94, 95]. Moreover, nAChRs are involved in multiple brain functions including learning and memory. In particular, we concentrated on the central α7-nAChRs, which boost synaptic plasticity and memory [96–98] and enhance transmitter release in several brain structures including hippocampus [99, 100], spinal cord dorsal horn [101], and amygdala [102]. We reasoned that targeting the α7-nAChR subtype might reduce AD symptoms [for a review, see 103], and an association between a genetic variant of the α7-nAChR subunit and AD had recently been documented [104]. Moreover, Aβ has a picomolar affinity for α7-nAChRs [105], may regulate nAChR function by binding with membrane lipids [106] such as lipid rafts [107], or may activate α7-nAchRs at presynaptic nerve endings of synaptosomes [108]. Intriguingly, Aβ might act either as an α7-nAChR agonist [109] or an α7-nAChRs inhibitor [110], with low concentrations activating and high concentrations inhibiting α7-nAChRs [111]. We tried to establish whether α7-nAchRs were involved in Aβ-induced improvement of synaptic plasticity. To do so, we studied the effect of Aβ after pharmacological or genetic blockage of nAChRs. First, blocking them with mecamylamine (MCL) or with the selective α7-nAchR blocker α-bungarotoxin resulted in inhibition of the Aβ-induced increase of PTP. Importantly, MCL or α-bungarotoxin alone did not affect PTP. Finally, perfusion of hippocampal slices with picomolar concentrations of Aβ did not enhance LTP or memory in α7-nAchR-KO mice, providing genetic evidence for the involvement of α7-nAchRs in the enhancing effect of Aβ. Taken all together, these results support the hypothesis that the enhancement of synaptic plasticity and memory by picomolar concentrations of $A\beta_{42}$ involves neurotransmitter release and α7-nAChRs.

Another major question that was tackled in a following work [112] was: does endogenous Aβ have a function throughout life in normal healthy individuals? To address this question we blocked endogenously produced Aβ with a monoclonal antibody, JRF/rAb2, which recognizes a rodent-specific epitope within the first 15 AA of rodent $A\beta_{40}$ and $A\beta_{42}$. Depletion of endogenously produced Aβ caused a reduction of synaptic plasticity (LTP and PTP) and both reference and contextual memory. Interestingly, application of the antibody immediately after the tetanus or training had no effect, suggesting that Aβ is involved in the induction phase of synaptic plasticity and memory, but not in maintenance or consolidation processes. Because the antibody might act on a target other than Aβ (e.g., on other AβPP fragments, or AβPP itself, or other unknown proteins), we next performed rescue experiments with human $A\beta_{42}$, which is not recognized by the antibody. Animals treated with JRF/rAb2 and low doses of Aβ exhibited normal synaptic plasticity and memory, confirming that the antibody acted through Aβ, and that Aβ is required for synaptic plasticity and memory. Moreover, a higher Aβ concentration (300 pM) induced a further increase in synaptic plasticity and memory that resembled the enhancement obtained by 200

pM Aβ alone. These findings were confirmed by an independent approach in which we blocked endogenous Aβ by knocking down AβPP expression in mice using an siRNA specific for murine AβPP (AβPP-siRNA). The LTP and memory impairment by intrahippocampal injections of AβPP-siRNA was rescued by picomolar doses of $A\beta_{42}$. Moreover, neither the antibody nor AβPP-siRNA affected LTP in AβPP-null mice. Consistent with these studies, it was found that low picomolar doses of $A\beta_{42}$ enhanced memory consolidation in tests of inhibitory avoidance in rats [113]. Interestingly, in the same work pre-incubation of human $A\beta_{42}$ with an antibody that recognizes the AA sequence 17–24 of human and rodent Aβ which is also present in AβPP as well as in other fragments of its processing, blocked the impairment of memory by the antibody alone [113]. Moreover, in another study, low doses of Aβ enhanced LTP and memory retention, and acetylecholine production in the hippocampus *in vivo*, and *vice versa* blocking Aβ with an antibody or DFFVG (which blocks Aβ binding) or decreasing Aβ expression with antisense directed at AβPP reduced LTP and memory [114]. Taken all together these data suggest that Aβ is required for hippocampal synaptic plasticity and memory. What is the minimum dose that is necessary for LTP and PTP induction? To address this question, we injected AβPP-siRNA into mouse hippocampus and after 24 h performed electrophysiological recordings by treating slices with different concentrations of vehicle or synthetic human $A\beta_{42}$. Given that complete rescue of potentiation was observed with 300 pM Aβ, and that the levels of endogenous Aβ after siRNA treatment were about 80 pM, we estimated that the $A\beta_{42}$ threshold needed for normal synaptic plasticity is likely to be around 380 pM.

Our finding that Aβ is required for memory induction led us to explore release of Aβ during memory formation. We measured hippocampal $A\beta_{42}$ in mice trained for contextual fear learning and then sacrificed at different intervals after the electric shock. We found that mice sacrificed at 1 min showed a significant increase in hippocampal $A\beta_{42}$, lending support to the hypothesis that hippocampal $A\beta_{42}$ production is enhanced during memory induction.

Another important finding of our work was that a monomer-enriched preparation was unable to rescue LTP in slices that were concomitantly treated with the JRF/rAb2 antibody, suggesting that the “positive” effect of the mixed preparation containing both monomers and oligomers is exerted by oligomeric forms of Aβ.

Next, we studied the involvement of α7-nAChRs in the effect of endogenous Aβ. JRF/rAb2 did not affect PTP or LTP in α7-nAChR-KO mice compared to wild type littermates, confirming that the effect of endogenous Aβ is mediated by α7-nAChRs.

To conclude, our research work demonstrates that picomolar concentrations of Aβ enhance synaptic plasticity and memory, that endogenous Aβ has a critical role in physiological regulation of synaptic plasticity and memory, and that this role is exerted *via* α7-nAChRs (Fig. 1). Aβ can thus be considered as a Dr. Jekyll/Mr. Hyde molecule exhibiting opposite effects at high or low concentrations. These intricate aspects should be taken into consideration when designing therapeutic strategies for AD, especially where Aβ-lowering therapies are concerned. These findings have a broad scope of application, since they span across different fields, including neurodegenerative disorders, synaptic plasticity, memory, and regulation of neurotransmission by nicotinic receptors. Our future work and that of other scientists will hopefully elucidate the questions that are still unanswered.

OUR SCIENTIFIC JOURNEY: OPENING AND ENDING CREDITS

Daniela Puzzo, from the University of Catania, joined Ottavio Arancio at Nathan Kline Institute in Orangeburg and then at Columbia University. At the time, Ottavio’s laboratory was exploring the toxic effect of Aβ on synaptic plasticity and memory; Daniela began her LTP experiments on hippocampal slices using high Aβ concentrations. Surprisingly, slice

perfusion with Aβ induced an improvement in LTP, not the expected impairment. An accurate calculation showed that she was actually using 200 pM, not 200 nM Aβ. What could have been an annoying waste of time turned out to be a serendipitous discovery. Our arduous journey into the physiological role of Aβ started there. Since then several colleagues have helped us delve deeper into this fascinating topic and we would like to thank them all. First, Agostino Palmeri, Professor of Physiology and PI at the Department of Bio-medical Sciences, gave us the intellectual and material support to perform part of these studies at the University of Catania. Lucia Privitera helped with the electrophysiological and behavioral experiments and was in charge of colony maintenance and genotyping; Mauro Fa helped with electrophysiology and siRNA preparation but especially contributed with fruitful scientific discussions; Agnieszka Staniszewski performed the behavioral studies; Elena Leznik performed patch clamp studies; Gakuji Hashimoto and Fahad Aziz carried out ELISA assays; Mikako Sakurai studied siRNA in cell cultures; Elena M. Ribe and Carol Troy helped with siRNA-PEN1 conjugation; and Marc Mercken and Sonia Jung provided and studied the anti-Aβ JRF/rAb2 antibody. We are also grateful to Cristina Alberini, Francesca Bartolini, Rusiko Bourtchouladze, Moses V. Chao, Gilbert Di Paolo, Ana Garcia-Osta, Paul M. Mathews, Ipe Ninan, Filippo Palermo, Marina Picciotto, Lorna Role, and David Talmage for helpful comments and discussions; Paul Mathews for suggestions with the use of antirodent antibody; and Julio Pozueta, Luciano Pellizzoni, and Luciano Saieva for suggestions and siRNA preparation.

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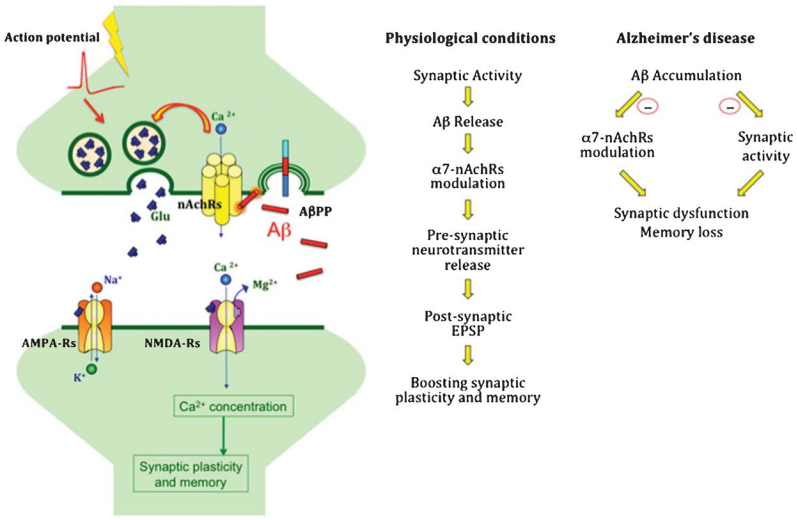

Fig. 1.

Amyloid-β (Aβ) in physiology and pathology. A) Schematic representation of a theoretical model indicating that during neuronal activity the release of Aβ acts on pre-synaptic α7-nAchRs, boosting synaptic plasticity and memory. B) Schematic representation of the role of Aβ in physiology and pathology. In physiologic conditions, synaptic activity triggers Aβ release which, in turn, positively modulates pre-synaptic α7-nAchRs leading to Ca^{2+} entrance into the presynaptic terminal and enhances releases of neurotransmitter boosting synaptic plasticity and memory. In pathologic conditions, Aβ accumulation has a negative feedback onto synaptic activity and reduces α7-nAchR function, leading to synaptic dysfunction and memory loss. (AMPA-Rs, AMPA receptors; NMDA-Rs, NMDA receptors; Glu, glutamate; α7-nAchRs, alpha-7 nicotinic acetylcholine receptors).