Neurosci Bull December 1, 2013, 29(6): 752–760. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1383-2

·Review·

Dysregulation of synaptic and extrasynaptic N-methyl-*D*-aspartate receptors induced by amyloid-β

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The toxicity of amyloid-beta (Aβ) is strongly associated with Alzheimer's disease (AD), which has a high incidence in the elderly worldwide. Recent evidence showed that alteration in the activity of N-methyl-*D*-aspartate receptors (NMDARs) plays a key role in Aβ-induced neurotoxicity. However, the activation of synaptic and extrasynaptic NMDARs has distinct consequences for plasticity, gene regulation, neuronal death, and Aβ production. This review focuses on the dysregulation of synaptic and extrasynaptic NMDARs induced by Aβ. On one hand, Aβ downregulates the synaptic NMDAR response by promoting NMDAR endocytosis, leading to either neurotoxicity or neuroprotection. On the other hand, Aβ enhances the activation of extrasynaptic NMDARs by decreasing neuronal glutamate uptake and inducing glutamate spillover, subsequently causing neurotoxicity. In addition, selective enhancement of synaptic activity by low doses of NMDA, or reduction of extrasynaptic activity by memantine, a non-competitive NMDAR antagonist, halts Aβ-induced neurotoxicity. Therefore, future neuroprotective drugs for AD should aim at both the enhancement of synaptic activity and the disruption of extrasynaptic NMDAR-dependent death signaling.

Keywords: amyloid-β; synaptic NMDA receptor; extrasynaptic NMDA receptor; neurotoxicity

Introduction

Alzheimer's disease (AD) is the most common form of dementia and is pathologically characterized by senile plaques, neurofibrillary tangles, and synaptic loss. Although the pathogenesis of the disease is still not well understood, amyloid-beta (Aβ) is widely recognized to be neurotoxic. To date, the downstream signaling pathways of N-methyl-*D*-aspartate receptors (NMDARs) are thought to be involved in Aβ-induced neurotoxicity. For example, Aβ induces synaptic loss[1-3] and postsynaptic density-95 (PSD-95) degradation[4-6], stimulates the production of reactive oxygen species (ROS)[7-10], disrupts axonal transport[11], and causes microtubule deregulation[12] through an NMDAR-dependent mechanism. Furthermore, Aβ not only binds to domains within or near NMDARs *in vitro* and *in vivo*[3, 7, 9, 13], but also directly activates NMDARs[14-16].

NMDARs are the major subtype of ligand-gated ionotropic glutamate receptors expressed widely in the central nervous system. Based on their localization on the cell membrane, NMDARs are distinguished as synaptic or extrasynaptic. Synaptic NMDARs are classically defined as functional receptors that are activated by glutamate released during low-frequency synaptic events, whereas extrasynaptic NMDARs, which are not activated by synaptically-released glutamate from presynaptic vesicles, are found at various locations such as the cell body, the dendritic shaft, and the neck of the dendritic spine. For many years it has been thought that the degree of Ca^{2+} influx through NMDARs is solely responsible for differences in cellular outcome: moderate levels of NMDAR activity are beneficial for neurons, while excessive activation of NMDARs is deleterious due to Ca^{2+} overload. However, synaptic and extrasynaptic NMDARs are known to play opposing roles in some signaling pathways: synaptic NMDARs play a protective role by promoting nuclear

signaling to cAMP response element binding protein (CREB), inducing gene expression of brain-derived neurotrophic factor (BDNF), activating extracellular signal-regulated kinases (ERK) and an anti-apoptotic pathway, whereas extrasynaptic NMDARs antagonize signaling to CREB, block BDNF expression, and cause mitochondrial membrane potential loss and cell death[17-23]. Also, selective stimulation of extrasynaptic NMDARs triggers excitotoxicity, but Ca^{2+} overload through synaptic NMDARs is not neurotoxic[19, 21, 24]. This review aims to summarize recent studies on the dysregulation of synaptic and extrasynaptic NMDARs induced by Aβ, and provide new insights into the development of AD therapies based on the balance between synaptic and extrasynaptic NMDARs.

Activation of Synaptic or Extrasynaptic NMDARs Influences Aβ Production

NMDAR stimulation has been reported to increase the levels of α-C-terminal fragments (C83) of amyloid precursor protein (APP) and release soluble APP (sAPP), as well as decrease the production and release of $Aβ_{1-40}$, all of which are blocked by NMDAR antagonists or α-secretase inhibitors[25]. However, chronic NMDA exposure increases the expression of neuronal Kunitz protease inhibitory domain-containing APPs (KPI-APPs; isoforms exhibiting important amyloidogenic potential), which subsequently inhibit the α-secretase candidate tumor necrosis factor-α converting enzyme, and increase the production of Aβ[26].

To determine whether this contradiction is explainable in terms of the activation of synaptic or extrasynaptic NMDARs, they were separately activated in a series of experiments. Activation of synaptic NMDARs alone inhibits Aβ release and increases C83 production and ERK phosphorylation[25] (Fig. 1). Aβ is produced primarily within neurons and secreted into the interstitial fluid (ISF). Using a micro-dialysis technique to specifically measure dynamic changes in ISF Aβ levels *in vivo*, Verges *et al.* revealed that high doses of NMDA or NMDAR agonist activate ERK and reduce the processing of APP into Aβ, while NMDAR antagonists increase ISF Aβ levels, suggesting that basal activity of these receptors normally suppresses Aβ levels[27]. Similar to these reports, after synaptic NMDAR activation, Bordji *et al.* failed to detect any KPI-APPs, and Aβ levels were not modified[19]. Mechanistically, stimulation of NMDARs up-regulates the genes encoding a disintegrin and metalloproteinase 10 (ADAM10), the constitutive α-secretase that governs the non-amyloidogenic pathway of APP processing, and increases the trafficking of ADAM10 to the postsynaptic membrane[28, 29]. On the other hand, selectively activating extrasynaptic NMDARs does not stimulate C83 production and ERK phosphorylation[25], but induces a significant increase in KPI-APP mRNA and Aβ production, with no change in total APP mRNA expression, implying that a shift from normal APP to KPI-APP expression causes the higher production of Aβ[19] (Fig. 1).

Dysregulation of Synaptic NMDARs Induced by Aβ

Aβ Promotes Synaptic NMDAR Endocytosis

To determine the effect of Aβ on cell surface (both synaptic and extrasynaptic) NMDAR expression, Snyder *et al.* treated cultured cortical neurons with Aβ for 1 h and found that Aβ reduces the surface expression of the NR2B and NR1 subunits of NMDARs, but does not change the total levels (including internalized surface receptors) of NR2B, which is observed in the neurons from APP_{Swe} mice that over-express human APP with the familial Swedish mutation. And the effect of Aβ is completely inhibited by a γ-secretase inhibitor, which substantially reduces the Aβ level[30]. Consistent with these data, Aβ-mediated NMDAR endocytosis also occurs in other mouse cortical or hippocampal neurons that are exposed to Aβ[3, 13, 31-33], and neurons or retinal membrane from transgenic animals with AD[13, 33, 34].

Specifically, Aβ significantly reduces NR1 at synaptic sites, further supporting the selective action of Aβ on synaptic NMDARs[30]. In neurons from APP [V717I] transgenic mice, a model that mimics the early cognitive impairment in AD, the amounts of postsynaptic NR2B are also decreased[13]. In addition, Li *et al.* used a biochemical approach to separate synaptic and extrasynaptic fractions from acute hippocampal slices after incubation with 7PA2 CM (medium from cells stably over-expressing a human APP mutation and secreting Aβ). They found a significant decrease of synaptic NR2B at 6 and 16 h, but no change of the NR2B levels in either the synaptic or extrasynaptic fractions at 30 min[35].

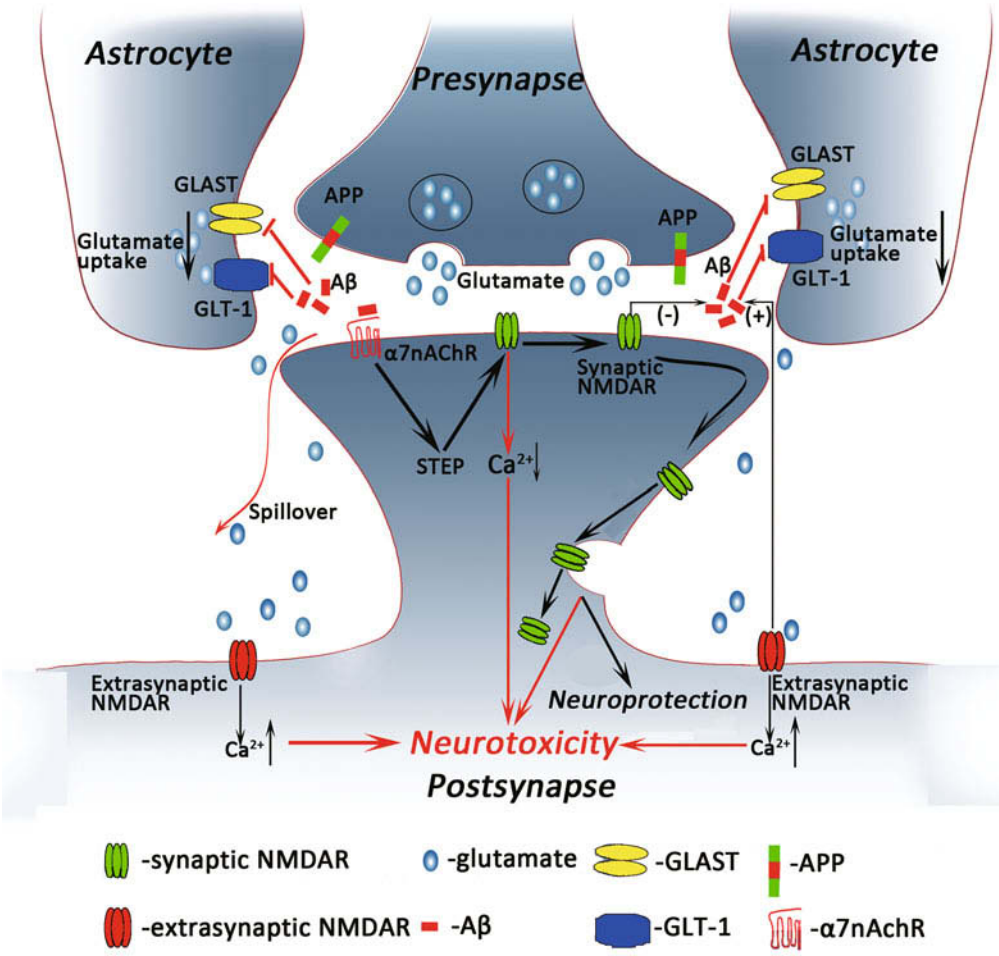

Fig. 1. Schematic of the dysregulation of synaptic and extrasynaptic NMDARs by Aβ. Aβ downregulates the synaptic NMDAR response by promoting NMDAR endocytosis, and leads to neurotoxicity or neuroprotection. On the other hand, Aβ enhances the activation of extrasynaptic NMDARs by decreasing neuronal glutamate uptake and inducing glutamate spillover, subsequently causing neurotoxicity. Moreover, synaptic NMDAR activation inhibits the production of Aβ, while extrasynaptic NMDAR activation increases it.

Although NMDARs can be redistributed from synaptic to extrasynaptic sites, Snyder *et al.* failed to find an increase in extrasynaptic staining of NMDARs after Aβ treatment[30]. Incubating neurons with Aβ does not change extrasynaptic NR2B clusters at 30 min, 6 h, and 16 h[35], indicating that Aβ does not promote extrasynaptic NR2B endocytosis.

Mechanistically, Aβ-mediated NMDAR endocytosis requires α-7 nicotinic acetylcholine receptors (α7nAChRs) and striatal-enriched protein tyrosine phosphatase (STEP)[30]. Wang *et al.* reported that Aβ binding to neuronal α7nAChRs promotes the aggregation of intraneuronal Aβ and the formation of neurofibrillary tangles (NFTs)[36, 37]. S24795, a novel α7nAChR agonist, reduces the Aβ-α7nAChR interaction, decreases Aβ-induced NFTs and Aβ accumulation, and reverses the attenuation of Ca^{2+} influx through NMDARs in the Aβ-infused mouse brain[38]. Similarly, a study on a transgenic mouse model of AD over-expressing APP and lacking the α7nAChR gene showed that these mice are better able to solve a cognitive challenge such as the Morris water maze test, and α7nAChR deletion protects the loss of synapses and preserves the capacity to elicit long-term potentiation (LTP)[39]. STEP61 levels are progressively increased in the prefrontal cortex of AD patients and transgenic mouse models of AD[33]. Using genetic manipulations to

reduce STEP activity in transgenic AD mice increases the expression of NR2B, leads to significantly improved cognitive function, and facilitates LTP[40, 41] (Fig. 1). Moderate ethanol consumption has been associated with a reduced risk of AD in several epidemiological studies. Recently, ethanol preconditioning-dependent neuroprotection was found to be associated with early enhancement of synaptic NR2B localization and NMDAR activity[42]. Also, chronic ethanol exposure increases synaptic NR2B clusters and synaptic NMDA currents, but does not change extrasynaptic NMDAR clusters[43].

However, downregulation of NMDARs can also be neuroprotective. Pretreating cultured neurons with Aβ promotes NMDAR endocytosis, decreases Ca^{2+} influx, and protects neurons from NMDA- and glutamate-induced excitotoxicity[31, 44]. Likewise, the retinas of transgenic mice over-expressing Aβ have reduced NR2B, and present with less NMDA-induced retinal damage than wild-type mice[34]. Moreover, donepezil, an acetylcholinesterase inhibitor, decreases glutamate toxicity *via* promoting NMDAR endocytosis and attenuating glutamate-mediated Ca^{2+} entry[45].

Aβ Reduces Postsynaptic NMDA Currents

To investigate the effect of Aβ on synaptic transmission, excitatory postsynaptic currents (EPSCs) were recorded in neurons from mice over-expressing APP. Li *et al.* reported a significant decrease of NMDA-EPSCs in slices treated with 7PA2 CM. Moreover, they suggested that an Aβ-mediated rise in glutamate levels leads to receptor desensitization and then causes NMDA-EPSC reduction[46]. Also, it has been reported that Aβ reduces NMDA postsynaptic currents[47]. A decrease in evoked-response amplitude could result from negative modulation of the presynaptic release machinery, yet Aβ does not alter the synaptic release probability and presynaptic vesicle release at presynaptic sites[2, 47, 48].

Since Aβ promotes synaptic NMDAR endocytosis and reduces NMDA-evoked currents, Aβ may attenuate Ca^{2+} influx at synapses. Using two-photon uncaging of glutamate to stimulate individual dendritic spines while monitoring spine head Ca^{2+} transients, Shankar *et al.* showed that Aβ reduces NMDAR-dependent Ca^{2+} influx into the spine head[1]. Pre-incubation of cortical and hippocampal neurons with a low (100 nmol/L) or a high concentration (1 μmol/L) of Aβ for 30 min or 3 h inhibits the NMDA or glutamate-mediated increase of cytosolic Ca^{2+}[13, 16, 31, 44]. Also, prolonged exposure (16 h) of cortical neurons to Aβ causes an attenuation of NMDAR-mediated Ca^{2+} influx[8].

Dysregulation of Extrasynaptic NMDARs Induced by Aβ

Aβ Enhances the Activation of Extrasynaptic NMDARs by Reducing Excitatory Amino-acid Transporters

The glutamate-aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1) are the main proteins responsible for removing excess glutamate from the synaptic cleft. Considerable evidence supports the hypothesis that Aβ downregulates the uptake of glutamate by decreasing these glutamate transporters in both the cortex and fibroblasts of AD patients or animal models of AD[49-52], as well as astrocytes both *in vitro* and *in vivo*[53, 54]. Recently, Bicca *et al.* revealed decreases in GLT-1 and GLAST expression and glutamate uptake in the hippocampus of Aβ-treated mice, which could be prevented by a selective and competitive NMDAR antagonist[10]. Interestingly, disturbance of cholesterol metabolism or aging may contribute to a reduction in glutamate transporters[55, 56]. Moreover, Aβ promotes extracellular glutamate release from hippocampal neurons[57], and increases the hippocampal levels of extracellular glutamate[58]. After selectively blocking synaptic NMDARs, perfusing 7PA2 CM markedly increases NMDA-EPSCs, and a selective NR2B inhibitor strongly inhibits NMDA-EPSCs, suggesting that Aβ enhances the activation of extrasynaptic NR2B[35, 46] (Fig. 1). Also, inhibition of glutamate transporters causes glutamate spillover from the synapse and increases extrasynaptic NMDA-EPSCs[35, 59].

As discussed above, Aβ can decrease the NMDAR-mediated intracellular Ca^{2+} concentration[13, 16, 31, 44], but triggers a sustained Ca^{2+} influx mediated by NMDARs[7, 15, 60]. This paradox may be explained by the activation of extrasynaptic NMDARs. Li *et al.* showed that the change in extrasynaptic NMDAR-mediated cytosolic Ca^{2+} in response to NMDA is significantly greater in 7PA2 CM-treated neurons[35], and this is significantly attenuated by memantine[7, 16, 60], consistent with the notion that memantine predominantly blocks extrasynaptic NMDARs[21, 61, 62].

Neurotoxicity Is Mediated by Extrasynaptic NR2B-NMDARs

NR2B-NMDARs are predominantly located at extrasynaptic sites in mature neurons, and their activation promotes cell death through a series of pathways, which have been described in detail elsewhere[63]. Synaptic plasticity such as LTP or long-term depression (LTD) is thought to underlie learning and memory. Depending on the stimulation protocol, Li *et al.* reported that Aβ from several sources (synthetic, cell culture, human brain extracts) facilitates LTD through metabotropic glutamate receptors (300 pulses) or NMDARs (900 pulses). They found that the effect of Aβ is caused by the activation of extrasynaptic NR2B through the inhibition of glutamate uptake, as it can be prevented by an extracellular glutamate scavenger and is closely mimicked by the inhibition of glutamate uptake[46]. Likewise, Aβ-inhibited LTP shares the same mechanism[35, 64]. Moreover, Aβ application impairs early neuronal function before major cytotoxic effects, including LTP, baseline synaptic transmission, spontaneous neuronal network activity, retraction of synaptic contacts, and accumulated Jacob (a messenger that couples extrasynaptic NMDAR activity to CREB) dephosphorylation in the nucleus; all these effects are blocked by extrasynaptic NR2B antagonists[65] (Fig. 1). Consistent with these reports, only NR2B antagonists, but not those of NR2A, protect against NMDA-induced excitotoxicity[16, 66], Aβ-mediated inhibition of plasticity[67], Aβ-induced PSD-95 and synaptophysin loss[5, 6], and Aβ-increased Ca^{2+} influx[16], as well as Aβ-induced ROS production and endoplasmic reticulum stress[68]. In addition, activation of either synaptic or extrasynaptic NR2B results in excitotoxicity and neuronal apoptosis[66].

The Balance between Synaptic and Extrasynaptic NMDARs for Therapeutic Targeting

When glutamate is used to activate both extrasynaptic and synaptic NMDARs, the extrasynaptic receptors shut off synaptic NMDAR signaling[17, 18, 21, 23]. Conversely, enhancement of synaptic NMDAR activity protects against extrasynaptic NMDAR-induced neuronal death[69]. Thus, the selective enhancement of synaptic activity or reduction of extrasynaptic activity may be sufficient to prevent Aβ-induced neurotoxicity.

Aβ downregulates PSD-95 and synaptophysin in an NMDAR-dependent manner, and only extrasynaptic NR2B-NMDAR antagonists abrogate this effect, while blockade of synaptic NMDAR activity does not influence these effects[5, 6]. However, pretreatment with a low dose of NMDA (1 μmol/L) prevents the actions of Aβ, and the protective effect is eliminated only by blockade of synaptic NMDARs. In contrast, a high dose of NMDA (10 μmol/L) potentiates the effect of Aβ, which is only abolished by ifenprodil[5], suggesting that the enhancement of synaptic NMDAR activity can halt the manifestation of early-stage events in AD.

Memantine has received marketing authorization from the European Medicines Agency and the Food and Drug Administration (USA) for the treatment of moderate to severe AD. Recently, accumulating evidence indicates that memantine, at therapeutic concentrations, preferentially blocks extrasynaptic over synaptic NMDARs in hippocampal autapses and cortical neurons[21, 61, 62]. Blocking extrasynaptic NMDARs with memantine inhibits NMDAR-induced KPI-APP expression and decreases Aβ expression and release both in cellular models and transgenic animals[19, 70], reduces tau hyperphosphorylation[71, 72] and microtubule deregulation[12], blocks excessive formation of ROS[7] and intracellular or mitochondrial Ca^{2+} overload[7, 15, 60], and prevents Aβ-inhibited LTP[73] and synaptic deterioration[3]. In addition, memantine inhibits CREB shutoff and rescues neurons from NMDA-mediated toxicity[15, 23].

Conclusions and Perspective

In summary, Aβ differentially affects the activity of synaptic and extrasynaptic NMDARs, resulting in neurotoxicity or neuroprotection. Although most recent evidence supports this notion, some issues still need to be addressed. For example, how Aβ influences NR2A levels and whether there are other potential effects. In addition, it is known that Aβ activates many receptors both on the cellular surface and in the nucleus, and their combined effects as well as the upstream or downstream signaling pathways are yet to be described.

Despite the fact that NMDARs mediate brain damage in AD, clinical trials of NMDAR antagonists are not therapeutically effective due to blockade of synaptic NMDAR activity. Therefore, a sufficient understanding

of NMDAR dysregulation induced by Aβ provides a novel conceptual basis for the future development of neuroprotective therapies for AD. And antagonists designed to selectively target extrasynaptic NMDAR signaling while sparing the physiological and neuroprotective roles of synaptic NMDARs could be promising therapies for AD.

ACKNOWLEDGEMENTS

This review was supported by the National Natural Science Foundation of China (81371223 and 81371437), the Research Fund for the Doctoral Program of Higher Education of China (20122105110010) and the Science and Technology Project of Liaoning Province, China (2011226006).

Received date: 2012-12-09; Accepted date: 2013-02-25

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