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New developments on the role of NMDA receptors in Alzheimer's disease

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Abstract

Since the initial findings that NMDA receptors play important roles in cellular models of learning as well as neurotoxicity, abnormal function of this receptor has been considered a potential mechanism in the pathophysiology underlying Alzheimer's disease. Treatment of Alzheimer's disease with an NMDA receptor antagonist began several years ago, with some limited success. More recent mechanistic studies have examined the role of NMDA receptors in the synaptic effects of beta amyloid.

Introduction

The NMDA receptor has played a dominant role for many years in studies focusing on learning and memory [1] as well as neurotoxicity [2]. This dual role has naturally led to the question of its potential role in the pathophysiology underlying Alzheimer's disease [3]. Recently, a number of studies (discussed below) have examined the relation between NMDA receptors and beta amyloid (Aβ). Notably, a Pubmed search of "Aβ" and "NMDA" produced 354 entries, only a small fraction of which will be discussed.

The amyloid hypothesis [4], proposing that an excessive amount of Aβ is responsible for the cognitive impairment in Alzheimer's disease, is the most widely accepted model for the pathophysiology underlying the disease. In theory, there are several potential roles for the NMDA receptor in Aβ-related mechanisms. 1) the NMDA receptor may be a receptor for Aβ – or it may associate indirectly, by interacting with molecules that bind Aβ; 2) NMDA receptors may be necessary, either by mediating or acting permissively, in the actions of Aβ on synaptic transmission and plasticity; 3) NMDA receptor function may be an important downstream target of Aβ, i.e. Aβ may cause a reduced or enhanced function of NMDA receptors; and 4) NMDA receptor activity may control the formation of Aβ.

How to define the Aβ receptor

A number of molecules have been proposed to act as Aβ receptors [5–10]. The key question is not if some molecule binds to Aβ (as Aβ is quite sticky, it may bind to many innocent bystanders, including plastic), but if an interaction between Aβ and molecule X plays a key role in the deleterious effects of Aβ. Thus, the question of receptors for Aβ is inextricably linked to the toxic effects of Aβ. What are the toxic effects of Aβ? This question is also

complex, as it may rely on many factors. The mode of exposure in the temporal domain – minutes, hours, days, weeks, months, years is potentially important; while the disease requires years to progress, it may still be that the actions of Aβ in minutes gives key clues as to the pathophysiological mechanisms. There may be a series of effects that could be triggered by the actions of Aβ at minutes leading to compensatory effects which have manifestations after years. Alternatively, for each time domain Aβ may produce different independent effects and very likely each time domain must be studied in different preparations, which makes comparisons difficult. The mode of exposure in the concentration domain – the concentration(s) of Aβ that are relevant to the disease are not known – certainly may produce different effects. It should be kept in mind that there is considerable inhomogeneity in concentrations of Aβ in the Alzheimer's brain, with sites of release/production (such as neurons) or potential sources like amyloid plaques, being higher than distant sites. Sites of origin and sites of action of Aβ will be important to delineate. A recent study from our laboratory examined potential neuronal subcellular sources of Aβ release [11]. We acutely overexpressed APP in either presynaptic or postsynaptic neurons in organotypic hippocampal slices. We observed an effect on dendritic spine density and plasticity in dendritic segments of non-overexpressing neurons that were close (<10 um) to dendritic segments or (<3 um) presynaptic terminals overexpressing APP. These studies indicate that both presynaptic and postsynaptic sites can release Aβ, and the target of action may be quite near to the source of Aβ production. Similar distance-dependent findings have been observed in studies using calcium imaging to measure neuronal activity. In this case, neurons within ~60 um of amyloid plaques showed abnormal activity[12]. It is notable that Aβ may have different effects on different brain regions or different neurons. For instance, different effects on dentate granule cells and CA1 neurons have been documented [13]. Thus, to find the receptor for Aβ, one must first identify effects of Aβ on neuronal function that are relevant to the disease.

Neuronal impact of Aβ

While neuronal death is a clear deleterious effect in Alzheimer's disease, there is growing evidence that synapses are initial targets of the disease [14]. One robust effect of Aβ on synapses is to produce depression of glutamatergic synaptic transmission when overexpressed in hippocampal CA1 pyramidal neurons. This effect is observed for virally overexpressed APP [15](producing effects within 16 hours) as well as transgenically overexpressed (where it has been observed in 3 week old animals, [16]). The effect is seen both electrophysiologically (by a decrease in both AMPA-R and NMDA-R mediated transmission in CA1 region, with a selective reduction in NMDA-R mediated transmission in the dentate gyrus [13,15]) as well as structurally (by a reduction in dendritic spine density [17–22]). The reduction in surface glutamate receptors and other synaptic components produced by Aβ has been seen in dissociated cultured hippocampal neurons[23–25]. It is notable that the cellular phenotype produced by acute (~16 hr) application or overexpression of Aβ is similar to what is observed in transgenic mice overexpressing APP for months. This gives credence to the view that identifying mechanisms produced by transient overexpression or exposure to Aβ will give insight into mechanisms observed following chronic exposure to Aβ.

The depressive effect of Aβ on excitatory transmission appears to use signaling pathways used by long-term depression (LTD)[19,20,26]; for instance the activity of calcineurin, a calcium-activated phosphatase, is required for LTD and Aβ–induced synaptic depression. Recent studies have also found that caspase-3, an element of the apoptotic pathway, participates in both Aβ–induced synaptic depression and LTD [27,28]. The effects of Aβ on synapses are similar to those seen during LTD: loss of glutamate receptors and dendritic spines. A recent study showed that LTD can be facilitated by Aβ [29], suggesting that

normal synaptic activity patterns in the brain may lead to an LTD-like synaptic weakening in the presence of Aβ. Effects of Aβ on long-term potentiation (LTP) have also been widely documented [15,26,30–35]. Nevertheless, it is somewhat perplexing as to why no decrement of LTP is observed in CA1 hippocampus from one strain of APP transgenic mice [16]. These mice do show a decrement in excitatory transmission in in CA1 hippocampus [16]). Perhaps the intact LTP this is due to lower levels of Aβ reached in these transgenic mice or some issue related to genetic background of these mice; e.g. the genetic background rescues the effects of Aβ on LTP in these mice (although it is notable that LTP in the dentate gyrus appears not to be rescued in these mice). In general, these studies provide the impression that an important link exists between Aβ, glutamatergic transmission and synaptic plasticity.

NMDA-R mediating effects of Aβ

The Aβ–induced depression of glutamatergic transmission was first shown to be blocked by the NMDA-R antagonist D-APV [15]. Subsequently, NMDA-R antagonists were shown to block the structural effects of Aβ [19,20] in organotypic slices. Using NMDA-R antagonists to rescue LTP (from the effects of Aβ) is somewhat counterintuitive, since LTP itself requires the function of NMDA-Rs. However, this has been achieved in two different manipulations. In one, organotypic slices overexpressing APP were exposed to an NMDA-R antagonist for 60 min prior to the induction of LTP and quickly washed out before LTP induction. Such a protocol rescued LTP, as measured by an increase in spine size [11]. In a separate strategy, selective blockade of NMDA-Rs containing NR2B rescued the block of LTP by Aβ [36–38].

Our recent unpublished studies suggest an unusual mechanistic role of NMDA-Rs in the actions of Aβ. We examined the effects of various NMDA-R antagonists on Aβ-induced depression of glutamatergic synaptic transmission. Antagonists at the glutamate binding site (which lies in the NR2 subunit) block the effects of Aβ. However, antagonists at the NMDA-R channel pore or at the glycine binding site, which lies in the NR1 subunit, have no effect on Aβ-induced synaptic depression. The most efficacious drugs in blocking the effects of Aβ are those acting on the NR2B subunit. These findings suggest that conformational changes in NR2B, but not calcium flux through the NMDA-R channel pore are important in the actions of Aβ. Two such ligand-dependent, ion-flux independent functions of NMDA-Rs have been previously reported: ligand-driven endocytosis of NMDA-Rs, mediated by dephosphorylation of tyrosine residues close to the transmembrane domain [39] and ligand-driven exchange of NR2B-containing- to NR2A-containing NMDA-Rs [40]. It will be important to determine if mechanisms participating in these previously described ligand-driven NMDA-R functions participate in Aβ-induced synaptic depression. Other important questions: are conformational changes in NR2B necessary for the NMDA-R to bind to other molecules that participate in Aβ-induced synaptic depression? Or do such conformational changes trigger intracellular signaling that leads to synaptic depression? Does Aβ activate ion-flux through native NMDA-R in neurons, as recently reported[41] for recombinant receptors expressed in oocytes?

NMDA-Rs have also been suggested to mediate the effects of tau, a protein implicated in Alzheimer's disease and thought to be a downstream effector of elevated Aβ [42]. In one study, tau, which has traditionally been considered as an axonal protein, is driven into dendritic spines once it becomes hyperphosphorylated [43]. In this location tau perturbs synaptic function by removing AMPA-R and NMDA-R from synapses. In another study [44] tau is proposed to transport the tyrosine kinase fyn to dendritic spines where it can phosphorylate the NR2 subunit of NMDA-Rs. Such phosphorylation increases the association with PSD-95 which increases the excitotoxic effects of NMDA-Rs. It is notable that this increased toxicity occurs in the absence of increase NMDA-R synaptic currents,

again suggesting that conformational changes in NMDA-R, or association with other molecules is important for the mechanism by which NMDA-R cause Aβ-induced deleterious effects.

The Aβ receptor

But is the NMDA-R 'the' Aβ receptor? One prominent recent study [10] has provided evidence that the EphB2 protein, a surface tyrosine kinase that binds the NMDA-R [45], is 'the' Aβ receptor. This study provides evidence that Aβ binds to EphB2, leads to EphB2 degradation, leading to loss of NMDA-R function and reduced LTP. It is notable that Aβ has been observed to bind to synapses (in dissociated cultured neurons); although curiously Aβ does not bind to all excitatory synapses [46]. Since all excitatory synapses appear to have NMDA-Rs [47], perhaps Aβ binds to synapses that have EphB2 associated with NMDA-Rs. It will be important to determine if blockade of NMDA-R prevents the Aβ-induced loss of EphB2. Also, these studies were conducted in dentate gyrus granule cells, which appear to respond differently to Aβ as compared to other brain regions (e.g. CA1 hippocampus); it will thus be important to determine if the EphB2 receptor acts as the Aβ receptor in all brain regions. In short, this study suggests that the NMDA-R downregulation is a key downstream effect of Aβ.

Neuronal activity and Aβ production: role of NMDA-Rs

Several years ago our laboratory found that increased neuronal activity in cultured organotypic hippocampal slices made from mice overexpressing APP led to increased amount of Aβ detected in the media [15]. This increase in Aβ was found not to depend on basal levels of NMDA-R activity; the effect of increased levels of NMDA-R activation on Aβ secretion was not examined. The neuronal activity-dependence of Aβ secretion was demonstrated using in vivo microdialysis techniques in a subsequent study [48]. These studies have argued that the activity dependence lies in the presynaptic compartment [48] suggesting no NMDA-R dependence. However, more recent studies present a more conflicting picture of the role of NMDA receptors in the production of Aβ. Some studies suggest that NMDA-R activation lowers Aβ production[49,50]. A study in dissociated cultured neurons suggests that activation of extra-synaptic NMDA-Rs contribute to the release of Aβ [51], while an in vivo study indicates that the level of NMNDA-R activation may control the effect on Aβ production: low levels of NMDA-R activation increase while higher levels reduce Aβ production[52]. The role of NMDA-R in production of Aβ is likely complex and requires more investigation.

Concluding remarks

NMDA-Rs appear to mediate several Aβ-induced effects. Delineating the exact mechanistic role of NMDA receptors in such effects will be important if a therapeutic target is sought. Since NMDA-Rs are necessary for normal neuronal function, blockade of NMDA-Rs using standard inhibitors is unlikely to have beneficial effects. However, Aβ may drive some abnormal conformation of the NMDA-R, or deleteriously enhance the association of the NMDA-R with some molecule. Such events may be potential targets that do not disrupt normal NMDA-R function.

Highlights

>The multiple potential roles of NMDA receptors in the actions of beta amyloid on synapses are considered. >Specific examples of the impact of beta amyloid on synapses

are discussed. > Several mechanisms by which the NMDA receptor may mediate the actions of beta amyloid on synapses are proposed.

Refs

1. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993; 361:31–39. [PubMed: 8421494]
2. Olney JW. Excitotoxin-mediated neuron death in youth and old age. Prog Brain Res. 1990; 86:37–51. [PubMed: 1982368]
3. Greenamyre JT, Young AB. Excitatory amino acids and Alzheimer's disease. Neurobiol Aging. 1989; 10:593–602. [PubMed: 2554168]
4. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297:353–356. [PubMed: 12130773]
5. Yan SD, Chen X, Fu J, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Morser J, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature. 1996; 382:685–691. [PubMed: 8751438]
6. Parri RH, Dineley TK. Nicotinic acetylcholine receptor interaction with beta-amyloid: molecular, cellular, and physiological consequences. Curr Alzheimer Res. 7:27–39. [PubMed: 20205670]
7. Lee CY, Landreth GE. The role of microglia in amyloid clearance from the AD brain. J Neural Transm. 117:949–960. [PubMed: 20552234]
8. Diarra A, Geetha T, Potter P, Babu JR. Signaling of the neurotrophin receptor p75 in relation to Alzheimer's disease. Biochem Biophys Res Commun. 2009; 390:352–356. [PubMed: 19818333]
9. Lauren J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature. 2009; 457:1128–1132. [PubMed: 19242475]
10. Cisse M, Halabisky B, Harris J, Devidze N, Dubal DB, Sun B, Orr A, Lotz G, Kim DH, Hamto P, et al. Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. Nature. 469:47–52. [PubMed: 21113149] Provides remarkable results indicating that reintroduction of the putative Ab receptor into neurons in a small region of the brain reverses the deleterious phenotype in an AD model.
11. Wei W, Nguyen LN, Kessels HW, Hagiwara H, Sisodia S, Malinow R. Amyloid beta from axons and dendrites reduces local spine number and plasticity. Nat Neurosci. 13:190–196. [PubMed: 20037574]
12. Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Wiederhold KH, Haass C, Staufenbiel M, Konnerth A, Garaschuk O. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. Science. 2008; 321:1686–1689. [PubMed: 18802001]
13. Harris JA, Devidze N, Halabisky B, Lo I, Thwin MT, Yu GQ, Bredesen DE, Masliah E, Mucke L. Many neuronal and behavioral impairments in transgenic mouse models of Alzheimer's disease are independent of caspase cleavage of the amyloid precursor protein. J Neurosci. 30:372–381. [PubMed: 20053918]
14. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002; 298:789–791. [PubMed: 12399581]
15. Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. Neuron. 2003; 37:925–937. [PubMed: 12670422]
16. Hsia AY, Masliah E, McConlogue L, Yu GQ, Tatsuno G, Hu K, Kholodenko D, Malenka RC, Nicoll RA, Mucke L. Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. Proc Natl Acad Sci U S A. 1999; 96:3228–3233. [PubMed: 10077666]
17. Shrestha BR, Vitolo OV, Joshi P, Lordkipanidze T, Shelanski M, Dunaevsky A. Amyloid beta peptide adversely affects spine number and motility in hippocampal neurons. Mol Cell Neurosci. 2006; 33:274–282. [PubMed: 16962789]
18. Lanz TA, Carter DB, Merchant KM. Dendritic spine loss in the hippocampus of young PDAPP and Tg2576 mice and its prevention by the ApoE2 genotype. Neurobiol Dis. 2003; 13:246–253. [PubMed: 12901839]

19. Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron. 2006; 52:831–843. [PubMed: 17145504] One of several studies that link effects of Ab with signaling underling LTD.
20. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci. 2007; 27:2866–2875. [PubMed: 17360908] One of several studies that link effects of Ab with signaling underling LTD.
21. Calabrese B, Shaked GM, Tabarean IV, Braga J, Koo EH, Halpain S. Rapid, concurrent alterations in pre- and postsynaptic structure induced by naturally-secreted amyloid-beta protein. Mol Cell Neurosci. 2007; 35:183–193. [PubMed: 17368908]
22. Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, Viola KL, Klein WL. Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J Neurosci. 2007; 27:796–807. [PubMed: 17251419]
23. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, et al. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci. 2005; 8:1051–1058. [PubMed: 16025111] Identify surface removal of NMDA-R as an important downstream effect of Ab.
24. Liu J, Chang L, Roselli F, Almeida OF, Gao X, Wang X, Yew DT, Wu Y. Amyloid-beta induces caspase-dependent loss of PSD-95 and synaptophysin through NMDA receptors. J Alzheimers Dis. 22:541–556. [PubMed: 20847396]
25. Almeida CG, Tampellini D, Takahashi RH, Greengard P, Lin MT, Snyder EM, Gouras GK. Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. Neurobiol Dis. 2005; 20:187–198. [PubMed: 16242627]
26. Jo J, Whitcomb DJ, Olsen KM, Kerrigan TL, Lo SC, Bru-Mercier G, Dickinson B, Scullion S, Sheng M, Collingridge G, et al. Abeta(1-42) inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt1 and GSK-3beta. Nat Neurosci. 14:545–547. [PubMed: 21441921] One of several studies that link effects of Ab with signaling underling LTD.
27. Li Z, Jo J, Jia JM, Lo SC, Whitcomb DJ, Jiao S, Cho K, Sheng M. Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. Cell. 141:859–871. [PubMed: 20510932] One of several studies that link effects of Ab with signaling underling LTD.
28. D'Amelio M, Cavallucci V, Middei S, Marchetti C, Pacioni S, Ferri A, Diamantini A, De Zio D, Carrara P, Battistini L, et al. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease. Nat Neurosci. 14:69–76. [PubMed: 21151119] One of several studies that link effects of Ab with signaling underling LTD.
29. Li S, Hong S, Shepardson NE, Walsh DM, Shankar GM, Selkoe D. Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. Neuron. 2009; 62:788–801. [PubMed: 19555648] One of several studies that link effects of Ab with signaling underling LTD.
30. Cullen WK, Suh YH, Anwyl R, Rowan MJ. Block of LTP in rat hippocampus in vivo by beta-amyloid precursor protein fragments. Neuroreport. 1997; 8:3213–3217. [PubMed: 9351645]
31. Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE, Rozovsky I, Trommer B, Viola KL, et al. Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci U S A. 1998; 95:6448–6453. [PubMed: 9600986]
32. Chen QS, Wei WZ, Shimahara T, Xie CW. Alzheimer amyloid beta-peptide inhibits the late phase of long-term potentiation through calcineurin-dependent mechanisms in the hippocampal dentate gyrus. Neurobiol Learn Mem. 2002; 77:354–371. [PubMed: 11991763]
33. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature. 2002; 416:535–539. [PubMed: 11932745]
34. Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT, et al. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat Neurosci. 1999; 2:271–276. [PubMed: 10195221]

35. Moechars D, Dewachter I, Lorent K, Reverse D, Baekelandt V, Naidu A, Tesseur I, Spittaels K, Haute CV, Checler F, et al. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. J Biol Chem. 1999; 274:6483–6492. [PubMed: 10037741]
36. Hu NW, Klyubin I, Anwyl R, Rowan MJ. GluN2B subunit-containing NMDA receptor antagonists prevent Abeta-mediated synaptic plasticity disruption in vivo. Proc Natl Acad Sci U S A. 2009; 106:20504–20509. [PubMed: 19918059] Study shows that blockade of NMDA-R subunit can prevent effects of Ab without blocking LTP.
37. Rammes G, Hasenjager A, Sroka-Saidi K, Deussing JM, Parsons CG. Therapeutic significance of NR2B-containing NMDA receptors and mGluR5 metabotropic glutamate receptors in mediating the synaptotoxic effects of beta-amyloid oligomers on long-term potentiation (LTP) in murine hippocampal slices. Neuropharmacology. 60:982–990. [PubMed: 21310164]
38. Ronicke R, Mikhaylova M, Ronicke S, Meinhardt J, Schroder UH, Fandrich M, Reiser G, Kreutz MR, Reymann KG. Early neuronal dysfunction by amyloid beta oligomers depends on activation of NR2B-containing NMDA receptors. Neurobiol Aging.
39. Vissel B, Krupp JJ, Heinemann SF, Westbrook GL. A use-dependent tyrosine dephosphorylation of NMDA receptors is independent of ion flux. Nat Neurosci. 2001; 4:587–596. [PubMed: 11369939]
40. Barria A, Malinow R. Subunit-specific NMDA receptor trafficking to synapses. Neuron. 2002; 35:345–353. [PubMed: 12160751]
41. Texido L, Martin-Satue M, Alberdi E, Solsona C, Matute C. Amyloid beta peptide oligomers directly activate NMDA receptors. Cell Calcium. 49:184–190. [PubMed: 21349580]
42. Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science. 2007; 316:750–754. [PubMed: 17478722]
43. Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK, Pitstick R, Carlson GA, Lanier LM, Yuan LL, et al. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron. 68:1067–1081. [PubMed: 21172610]
44. Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wolfing H, Chieng BC, Christie MJ, Napier IA, et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell. 142:387–397. [PubMed: 20655099] Identifies a role for NMDA-R in Ab deficits that does not rely on ion-channel flow.
45. Dalva MB, Takasu MA, Lin MZ, Shamah SM, Hu L, Gale NW, Greenberg ME. EphB receptors interact with NMDA receptors and regulate excitatory synapse formation. Cell. 2000; 103:945–956. [PubMed: 11136979]
46. Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, Lambert MP, Velasco PT, Bigio EH, Finch CE, et al. Synaptic targeting by Alzheimer's-related amyloid beta oligomers. J Neurosci. 2004; 24:10191–10200. [PubMed: 15537891]
47. Takumi Y, Ramirez-Leon V, Laake P, Rinvik E, Ottersen OP. Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. Nat Neurosci. 1999; 2:618–624. [PubMed: 10409387]
48. Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, Holtzman DM. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron. 2005; 48:913–922. [PubMed: 16364896]
49. Gordon-Krajcer W, Salinska E, Lazarewicz JW. N-methyl-d-aspartate receptor-mediated processing of beta-amyloid precursor protein in rat hippocampal slices: in vitro--superfusion study. Folia Neuropathol. 2002; 40:13–17. [PubMed: 12121034]
50. Marcello E, Gardoni F, Mauceri D, Romorini S, Jeromin A, Epis R, Borroni B, Cattabeni F, Sala C, Padovani A, et al. Synapse-associated protein-97 mediates alpha-secretase ADAM10 trafficking and promotes its activity. J Neurosci. 2007; 27:1682–1691. [PubMed: 17301176]
51. Bordji K, Becerril-Ortega J, Nicole O, Buisson A. Activation of extrasynaptic, but not synaptic, NMDA receptors modifies amyloid precursor protein expression pattern and increases amyloid-ss production. J Neurosci. 30:15927–15942. [PubMed: 21106831]

52. Verges DK, Restivo JL, Goebel WD, Holtzman DM, Cirrito JR. Opposing Synaptic Regulation of Amyloid-{beta} Metabolism by NMDA Receptors In Vivo. J Neurosci. 2011; 31:11328–11337. [PubMed: 21813692]

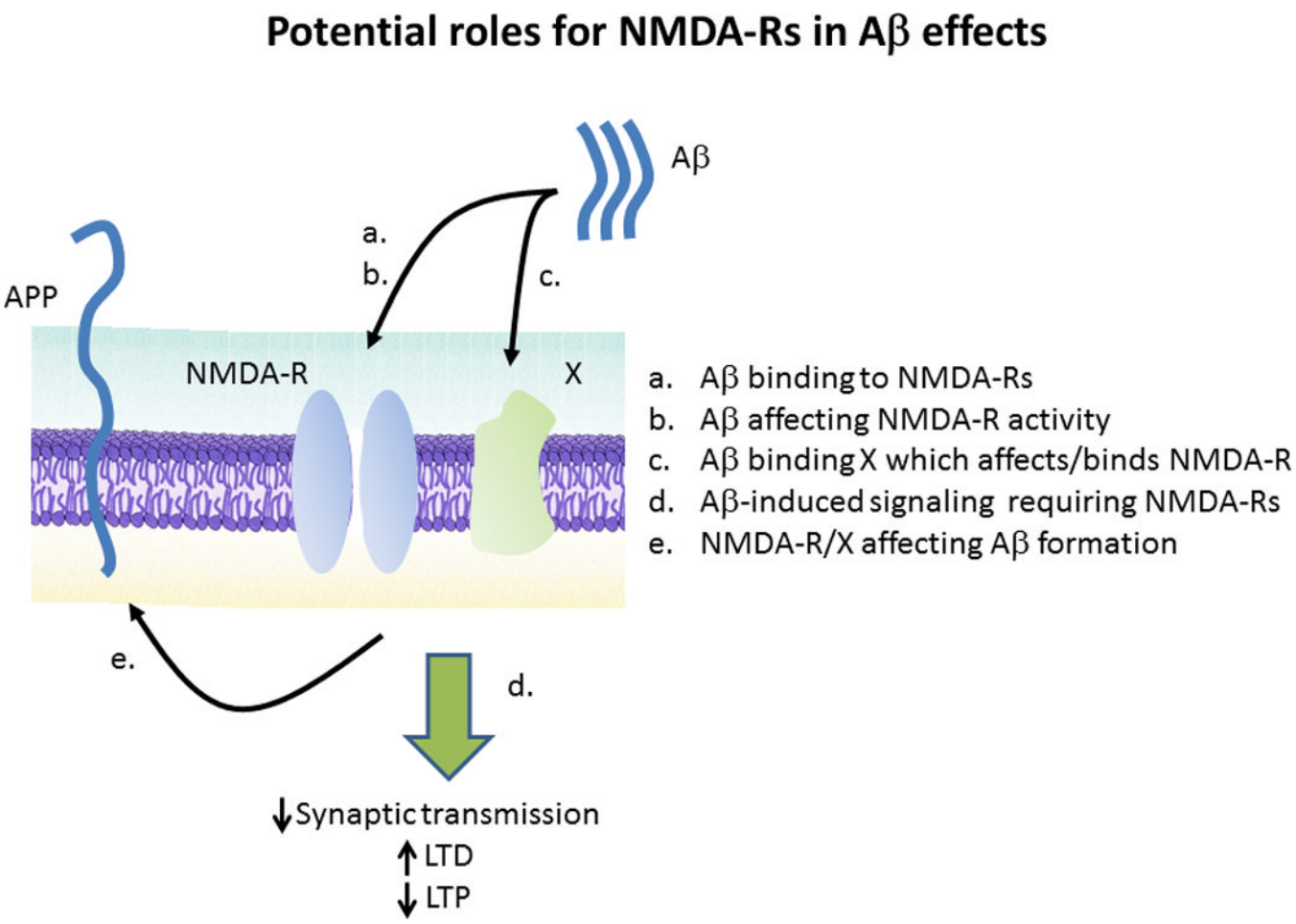

Figure 1.
Several potential roles for NMDA-Rs in the effects of Aβ are depicted.