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NMDA and AMPA receptors dysregulation in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by cognitive dysfunction and synaptic failure. The current therapeutic approaches are mainly focused on symptomatic treatment and possess limited effectiveness in addressing the pathophysiology of AD.

It is known that neurodegeneration is negatively correlated with synaptic plasticity. This negative correlation highlights glutamatergic neurotransmission via N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors and (AMPA) receptors as a critical mediator of synaptic plasticity. Despite this favorable role, extensive extracellular glutamate concentration induces excitotoxicity and neurodegeneration.

NMDA receptors containing GluN2A subunits are located at synaptic sites, implicated in the protective pathways. In comparison, GluN2B containing receptors are located mainly at extrasynaptic sites and increase neuronal vulnerability. AMPA receptors are consistently endocytosed and recycled back to the membrane. An increase in the rate of endocytosis has been implicated as a part of AD pathophysiology through inducing long-term depression (LTD) and synaptic disintegration.

In the present review, we focused on the mechanisms of glutamatergic system dysregulation in AD, particularly on its interaction with amyloid-beta. We concluded that assigning a specific role to an individual subtype of either NMDA receptors or AMPA receptors might be an oversimplification as they are not static receptors. Therefore, any imbalance between synaptic and extrasynaptic NMDA receptors and a reduced number of surface AMPA receptors will lead to synaptopathy.

1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder identified by memory impairment and cognition deficit. More than 50 million people are currently affected by AD worldwide, and it is predicted to grow to 150 million by 2050 (Amakiri et al., 2019).

Alzheimer's disease exists in two forms based on family history: early-onset familial, which is mainly related to genetic factors and affects middle-aged individuals, and late-onset or sporadic (over 65 years old). The etiology of late-onset AD has not been understood, and it is thought to be much more multifactorial than anticipated. Besides genetic predisposition, other factors, including aging, female gender, diabetes mellitus, cardiovascular disturbances, depression, insomnia, head trauma, and vitamin B deficiency, should be concerned (Silva et al., 2019).

1.1. Pathophysiology of Alzheimer's disease

Currently, the pathophysiology of AD has been designated by the presence of two types of abnormal protein deposition in the brain: extracellular plaques of β-amyloid (Aβ) and intracellular neurofibrillary tangles (NFTs) (Querfurth and LaFerla, 2010; Singh et al., 2018; Walsh and Selkoe, 2004). Amyloid-β monomers are derived from a neural membrane amyloid precursor protein (APP) following cleavage by β-secretase and γ-secretase enzymes (Sastre et al., 2006). Aβ 1–42 is a toxic peptide, which is capable of inhibiting long-term hippocampal potentiation (LTP), produce reactive oxygen species (ROS) (Ma et al., 2011), promote apoptosis, and disrupt synaptic integrity (Kim et al., 2014).

On the other hand, tangles are the second pathological marker comprised of the phosphorylated microtubule-associated protein tau, capable of being aggregated intra-cellularly and disturb the normal

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function of microtubules and neurons (Mudher and Lovestone, 2002).

Below we review the glutamate system pharmacology, then explain their dysregulation in AD considering molecular signaling pathways.

2. Glutamate buffering system

Normally, glutamatergic neurons are involved in different functions of the CNS such as learning, memory, and synaptic plasticity (Butterfield and Pocernich, 2003; Paoletti et al., 2013; Sullivan et al., 2013). It seems an optimum level of glutamate is required for normal functions of the brain, and the elevated concentration of glutamate leads to synaptic dysregulation and memory impairment (Palop et al., 2006).

Glutamatergic neurotransmission is mainly mediated by ionotropic and metabotropic glutamate receptors. The ionotropic glutamate receptors belong to the ligand-gated ion channel families and are permeable to Na+, K+, and Ca2+. They are divided into three groups: α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid receptors (AMPA receptors), kainate receptors, and N-methyl-D-aspartate receptors (NMDA receptors) (Paoletti et al., 2013; Traynelis et al., 2010).

Glutamate synapses are composed of a presynaptic neuron, a postsynaptic spine, and, in cases of tripartite synapses, an astrocyte, as well (Rudy et al., 2015) (Fig. 1). When presynaptic neuron is depolarized, Ca^{2+}channels open and cause influx of Ca^{2+} and result in exocytosis of glutamatergic vesicles (Südhof, 2004). Then released glutamate activates both pre and postsynaptic ionotropic and metabotropic receptors on neurons and glial cells. Glia cells either clear the extra glutamates via astrocytic excitatory amino acid transporters (EAAT1/2) or reuptake it by presynaptic EAAT2/5 to restore into the vesicles (Corlew et al., 2008). In astrocytes, glutamine synthetase converts glutamate into glutamine which is transported back into the glutamatergic neuron, where it is hydrolyzed into glutamate (Schousboe et al., 2014). When glutamate accumulates next to the extrasynaptic receptors, it leads to excitatory signaling and cytotoxicity (O'Donovan et al., 2017), and results in neuronal damage and death (Soni et al., 2014).

2.1. NMDA receptors

NMDA receptors are ligand-gated ion channels that play a pivotal role in memory formation (Paoletti et al., 2013). NMDA receptors include seven subunits of GluN1, four various GluN2 (GluN2A-D), and two GluN3 (GluN3A-B) (Paoletti et al., 2013; Traynelis et al., 2010). Subunits assemble differently and perform various subtypes with distinct physiological functions (Al-Hallaq et al., 2007).

NMDA receptors opening requires binding of glutamate to the GluA2 subunit of AMPA receptors, and depolarization eliminates Mg^{2+} blockade of NMDA receptors. Postsynaptic NMDA receptors allow Ca^{2+} entry and propagation of the action potential (Dore et al., 2017).

Recently it has been shown that activation of NMDA GluN2A receptors exerts pro-survival effects, while NMDA GluN2B receptors, which are mainly segregated to extrasynaptic sites, exhibit deleterious effects (Akashi et al., 2009; McQuail et al., 2016; Sachser et al., 2016; Soltani, 2014; Triller and Choquet, 2005), (Fig. 2). In addition, there are two more subunits of GluN2C and GluN2D, which are positively involved in synaptic transmission and working memory (Suryavanshi et al., 2014).

The second group of NMDA receptors is metabotropic receptors, including eight isoforms of G-protein coupled receptors, mGluR1-8, and exhibit slower synaptic responses (Traynelis et al., 2010). Interestingly, NMDA receptors can transfer signals metabotropically, without the need for Ca^{2+} influx through the channel (Dore et al., 2017). While activating ionotropic NMDA receptors induces LTP, metabotropic receptors induce LTD, triggering p38 mitogen-activated protein kinases (p38MAPK) signaling cascades (Nabavi et al., 2013) and synaptic deficits similar to circumstances in AD (Chung, 2013).

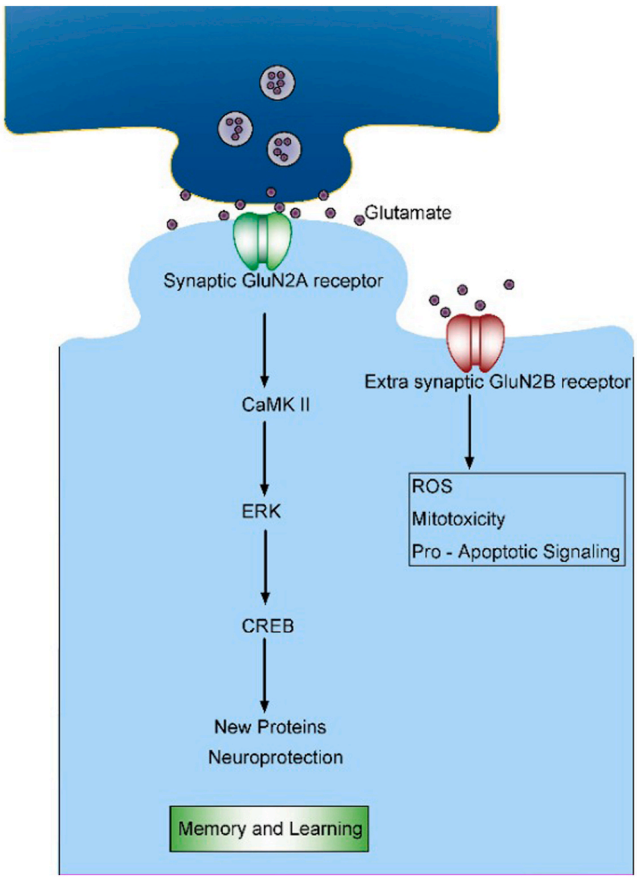

Fig. 1. The glutamate synapse
Pre and post synaptic (N-Methyl-D-aspartic acid) NMDA receptors together with an astrocyte are shown. Glutamate is released into the synaptic cleft, binds to synaptic or extra-synaptic receptors. Then glutamate is taken up by astrocytes through EAAT1/2 (excitatory amino acid) to store into vesicles. Ca^{++} influx through synaptic NMDA receptors triggers the activation of neural survival, while Ca^{++} influx via extra synaptic receptors couples to cell death.
Signaling pathways regulating CAM/ERK/CREB-dependent transcription in neurons. CREB elevation leads in neural protection and memory improvement. Activation of extrasynaptic NMDA NR2B receptors shuts off CREB-regulated pathway and elevates ROS, induces mitotoxicity and apoptosis.
CAMK Ca2+/calmodulin-dependent protein kinases, CREB: cAMP-response element-binding protein ERK, extracellular signal-related kinase; EAAT2, excitatory amino acid,ROS: reactive oxygen specious.

2.2. Synaptic and extrasynaptic localization of NMDA receptors

Generally, NMDA receptors are located at postsynaptic sites in dendritic spines, within the postsynaptic density proteins (PSD), and are involved in various forms of synaptic plasticity such as LTP (Köhr, 2006). During LTP, the presynaptic release of glutamate activates AMPA receptors, and the subsequent depolarization removes the Mg^{2+}blockade of the NMDA channel and allows the influx of Ca^{2+}. The strong activation of NMDA receptors triggers a Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII) signaling cascade that leads to LTP, Brain derived neurotrophic factor (BDNF) secretion, and synaptic amplification (Kullmann and Lamsa, 2007), (Fig. 2).

NMDA receptors have also been found on presynaptic and perisynaptic sites (Hardingham and Bading, 2010). Presynaptic NMDA receptors regulate glutamate release and modulate synaptic plasticity (Dore et al., 2017). They may control spontaneous release independently of $Mg^{2+}$and Ca^{2+} in contrast to evoked release, which is Mg^{2+}-dependent (Bouvier et al., 2018). These receptors promote transmitter release partly via protein kinase C signaling (Kunz et al.,

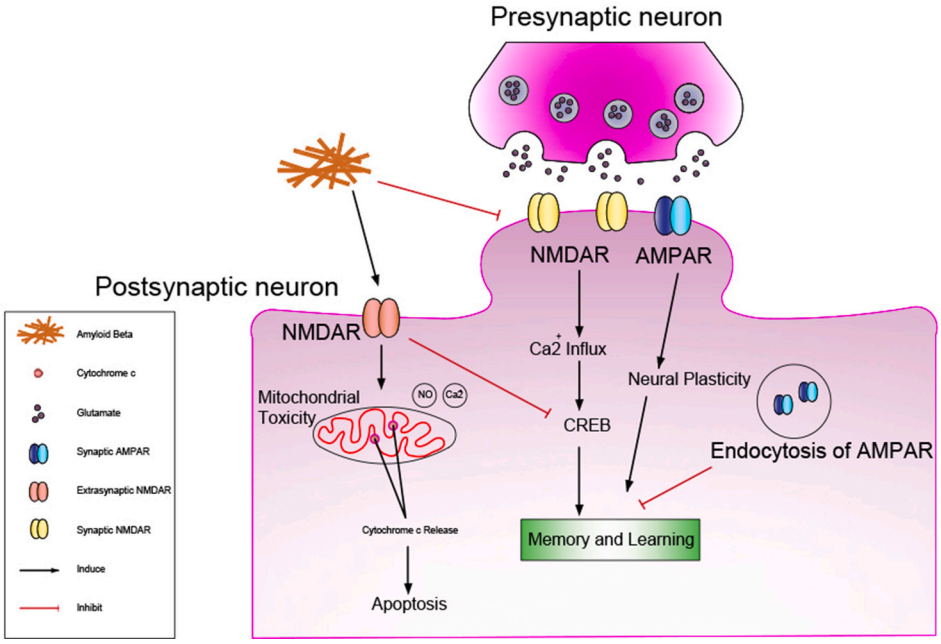

Fig 2. Represents the signaling pathways from NMDA and AMPA receptors.
AMPA receptors endocytosis impairs learning and memory. Amyloid-beta binding to extrasynaptic NR2B NMDA receptors leads to memory impairment via inhibiting CREB. Also, they cause mitochondrial toxicity, release of caspace 3 and induces apoptosis. However, synaptic NR2A NMDA receptors facilitate LTP and enhances memory via activation in CREB. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acids. LTP (Long term potentiation), CREB (cAMP-response element-binding protein

2013), indicating metabotropic function (Dore et al., 2017). However, activation of perisynaptic NMDA receptors and a lower increase in intracellular Ca^{2+} lead to LTD, spine shrinkage, and synaptic loss (Kullmann and Lamsa, 2007).

Extrasynaptic NMDA receptors are localized at sites further from the PSD, on the spine neck, the dendritic shaft, or soma close to the mitochondria. Therefore, when they are activated, leads in loss of mitochondrial membrane potential and induce Ca^{2+}neurotoxicity (Hardingham and Bading, 2010) (Fig. 2).

Besides the location of NMDA receptors, the subunit composition of NMDA receptors also determines the effect of these receptors by glutamate (Liu et al., 2007). For instance, GluN2A- and GluN2B-containing NMDA receptors are predominantly found synaptically and extrasynaptically, respectively, with opposing effects on neurons (Vizi et al., 2013). Calcium entry through synaptic GluN2A-containing receptors increases cAMP response element binding protein (CREB) and BDNF, which are involved in the neuroprotective action. In contrast, Ca^{2+}entry through extrasynaptic GluN2B-containing NMDA receptors shuts off the CREB pathway (Leveille et al., 2008),(Fig. 2). Therefore, considering the finding that NMDA receptors, particularly the NMDA GluN2B receptors, are mobile between synaptic and extrasynaptic sites (McQuate and Barria, 2020), it can be speculated different responses relative to the zone of activity. Moreover, glutamate spillover from synapses or astrocytes activates extrasynaptic NMDA receptors. Astrocytic NMDA receptors exert dynamic intracellular Ca^{2+} rise and regulate synaptic function (Hogan-Cann and Anderson, 2016). Astrocytic NMDA receptors are assumed to be involved in neuroinflammatory processes and contribute to reactive astrogliosis and exacerbate the release of proinflammatory cytokines (Gérard and Hansson, 2012). Taken all together, the sensitivity of NMDA receptors to detect physiological signals depends on various factors such as numbers, concentration, subunit varieties, location of receptors, and presence of other modulators (Iacobucci and Popescu, 2017). It is suggested that synaptic NMDA GluN2A receptors are pro-survival (Lee et al., 2005; Papadia et al., 2005). By contrast, extrasynaptic GluN2B (located on the peri- and extrasynaptic sites of dendrites, axons, axon terminals, or glia) contribute to neurotoxicity (Li and Zhou, 2015; Papouin and Oliet, 2014) and LTP impairment (Findley et al., 2019; Li et al., 2011).

2.3. NMDA receptors and Alzheimer' disease

Activation of the NMDA GluN2B extrasynaptic receptors leads to LTD, spine shrinkage, and synaptic loss (Kullmann and Lamsa, 2007) and contribute to AD due to glutamate excitotoxicity (Liu et al., 2019). These receptors, which are very close to the mitochondria, might shift Ca^{2+} ions toward the mitochondrial membranes (Nikseresht et al., 2021) and increase reactive oxygen species (ROS) (Zhang et al., 2016) and nitric oxide (NO) production, which reach mitochondria and cooperate with death-associated protein kinase 1 and contribute in cell death (Bading, 2017).

Indeed, extracellular glutamate concentration is increased as the result of Aβ functions on both neurons and glial cells, but the expression of NMDA GluN2A receptors is reduced (Lewerenz and Maher, 2015; Lim et al., 2014; Magi et al., 2016; Zhang et al., 2016). More molecular mechanisms are given in the following section. Therefore, the glutamate system, particularly NMDA GluN2B receptors widely involved in the pathology of AD.

2.4. NMDA receptors– amyloid-beta interaction

There is a complex relationship between NMDA receptors activation and Aβ. In a way that, the production of Aβ requires activation of extrasynaptic NMDA receptors, and vice versa, Aβ accumulation activates extrasynaptic NMDA receptors (Varga et al., 2014). Indeed, some types of neuronal activity mediated by NMDA receptors increase b-secretase activity rather than α secretase, leading to an increased Aβ production, similar to the early stages of AD (Liu et al., 2019). Additionally, activation of extrasynaptic NMDA receptors induces tau overexpression and phosphorylation (Shi et al., 2016), forming neurofibrillary tangles (Shi et al., 2016). On the other hand, Aβ interaction with NMDA GluN2B receptors immediately enhances Ca^{2+} (Ferreira et al., 2015), and then downregulates the GluN1 mRNA levels (Mayordomo-Cava et al., 2015). Thus, Aβ appears to shift the balance between synaptic and extrasynaptic NMDA receptors signaling towards the extrasynaptic receptors and mediate neurotoxicity. It has been reported that elevated Aβ dysregulates NMDA receptors, Ca^{2+} homeostasis, and causes early cognitive deficits, which could be exacerbated after treatment with antagonists of GluN2A (Li and Zhou, 2015). Therefore, taken all together, glutamate receptors are dysregulated by Aβ

oligomers, resulting in disruption of glutamatergic synaptic transmission, which parallels early cognitive deficits (Nabavi et al., 2013).

2.5. Pro survival and excitotoxic signaling pathways of NMDA receptors

As mentioned above, glutamate overflow in neurons activates extrasynaptic NMDA GluN2B receptors, resulting in complex deleterious downstream events, including LTP impairment and cell apoptosis (Rudy et al., 2015). Recent evidence indicates that the administration of NMDA GluN2B receptors antagonists ameliorates molecular and behavioral presentations of AD (Ashourpour et al., 2020; Nimmrich and Eckert, 2013; Saravanaraman et al., 2014).

Different molecular signaling pathways mediate the deleterious effects of Aβ, such as extracellular signal-related kinase (ERK), CREB, and mitogen-activated protein kinase (MAPK) (Hardingham and Bading, 2010; Navarrete et al., 2019). NMDA GluN2B receptors exert a bidirectional role in the regulation of ERK based on their localization. While synaptic NMDA GluN2A receptors elevate ERK/CREB to facilitate synaptic plasticity, the extrasynaptic receptors reduce it and impair synaptic strange (Hardingham and Bading, 2010). Phosphorylated CREB has been known as a universal transcription factor playing an essential role in maintaining LTP and synaptic plasticity (Briand et al., 2015).

In our previous studies, we showed that simultaneous intracerebroventricular (ICV) injection of an agonist of NMDA GluN2A receptors (D-cycloserine) and antagonist of NMDA GluN2B receptors (Ifenprodil) successfully ameliorate spatial memory impairment via an elevation in hippocampal phosphorylated CREB (Ashourpour et al., 2021; Nikseresht et al., 2021). Meanwhile, increased NMDA GluN2A receptors activity elevates the nuclear accumulation of Jacob, a caldendrin binding protein in the brain (Dieterich et al., 2008). Then phosphorylated Jacob is translocated to the nucleus and plays a neuroprotective role by expressing various target genes. On the other hand, non-phosphorylated Jacob is associated with decreased CREB activity, and reduced synaptic density following NMDA GluN2B receptors activation (Karpova et al., 2013).

Another signaling pathway mediating excitotoxicity following the increase in extrasynaptic NMDA receptor activity is the forkhead transcription factor (FoxO3a). FoxO3a is downregulated in the presence of NMDA GluN2A receptors activity and upregulated after NMDA GluN2B receptors activity (Hu et al., 2017). Meanwhile, Aβ mediated synaptic depression also shares signaling pathways with extrasynaptic NMDA GluN2B receptors via calcineurin; a calcium-activated phosphatase, caspase-3, and apoptosis (Xu et al., 2009).

In addition, Calcium/calmodulin-dependent protein kinase II **(CaMKII)** contributes to a downstream pathway of NMDAR-dependent synaptotoxicity. While, basal activity of NMDA receptors and formation of LTP require CaMKIIα, the absence of CaMKIIα leads in abolished LTP (Incontro et al., 2018). On the other hand, overactivation of extrasynaptic receptors induced by Aβ leads to astrocytic MAPK/CaMKIIα activity and LTD formation, which can be ameliorated by blocking p38MAPK (Navarrete et al., 2019; Li et al., 2011).

Besides the molecular signaling pathway mentioned above, Aβ oligomers could interact with synaptic Ephrin Type-B receptor 2 (EphB2) that is crucial for maintaining the integrity of NMDA receptors. Thus, loss of EphB2 by Aβ results in decreased surface localization of NMDA GluN2B receptors (Shi et al., 2016). On the other hand, overexpression of EphB2 in the hippocampus rescues impaired NMDA receptors trafficking and cognitive dysfunction in the AD model (Hu et al., 2017).

Similarly, synaptic NMDA GluN2A receptors are phosphorylated by the tyrosine kinase Fyn and form a complex with the postsynaptic density protein 95 (PSD95), and this interaction is required for normal morphology of synapse and spines (Amico-Ruvio et al., 2012; Ittner et al., 2010). However, the complex of tau-Fyn PSD95-NMDA receptors is assumed to be required for the toxic effect of Aβ peptide (Avila et al., 2017).

Finally, the excitotoxicity mediated by glutamate may end in apoptosis mechanisms via calcimycin. Calcimycin is a Ca^{2+} mobilizer that cooperates with p53, which in turn promotes Bax expression, release of cytochrome *c* from mitochondria, activation of caspase-3, and then subsequent execution of apoptosis in neurons (Giorgi et al., 2012; Li et al., 2005; Smaili et al., 2003). All these events end in cell death and synaptic disintegration (Fig. 2).

Altogether, these findings provide a molecular link between glutamate-mediated excitotoxicity and morphological abnormalities that underlie memory dysfunctions in AD.

Despite the numerous signaling pathways that have been reported on the interaction of NMDA receptors and Aβ, there is still much confusion that warrants future studies to clarify whether the benefits of targeting one type of receptors surpass the other.

3. AMPA receptors

AMPA receptors are a class of ionotropic glutamate receptors mediating the fast excitatory neurotransmission. AMPA receptors are comprised of different combinations of GluA1–GluA4. The GluA2 subunit is subject to RNA editing process by which glutamine is converted to arginine. While most AMPA receptors in the brain contain the edited GluA2 subunit, and they are Ca^{2+}-impermeable, the unedited AMPA GluA2 receptors are Ca^{2+}-permeable and contribute in excitotoxicity (Wright and Vissel, 2012).

AMPA GluA1 receptors are inserted into synapses upon the induction of LTP in brain slices (O'Donovan et al., 2017), and play a prominent role in memory formation (Al-Hallaq et al., 2007; Soni et al., 2014). In contrast, AMPA GluA2/3 receptors participate in the homeostatic scaling of synapse strength (Sachser et al., 2016; Suryavanshi et al., 2014).

Synaptic AMPA receptors, which consist of GluA1 and GluA2 combination (Lu et al., 2009), are essential for neural plasticity. They are rapidly recycled in the postsynaptic area, thus their number on the plasma membrane reflects the balance between exocytosis and endocytosis (Ahmadian et al., 2004; Bassani et al., 2009). It has been evident that defects in AMPA receptors trafficking and synaptic assembly processes are related to cognitive decline (Henley and Wilkinson, 2016). AMPA GluA1 receptors are delivered to the synapses in an activity-dependent manner (Henley and Wilkinson, 2013), however, GluA2/3 are continuously delivered into synapses independently of synaptic activity (Esteban et al., 2003). Therefore, the process of trafficking has been known as an essential mechanism underlying synaptic plasticity, since the recruitment of AMPA receptors to the postsynaptic membrane is positively correlated with LTP, and their endocytosis is negatively correlated with LTP (Bassani et al., 2009; Esteban et al., 2003).

Different molecules, mainly protein kinase Mζ (PKMζ) regulates AMPA GluA2 receptors trafficking, increasing the number of postsynaptic AMPA receptors (Yao et al., 2008). As a result, PKMζ maintains long-term memory and acquired aversive memory by constantly inhibiting AMPA receptors removal from postsynaptic sites (Amirshabani et al., 2017; Migues et al., 2010). Thus, LTP is controlled by changes in the properties, localization, and the number of AMPA receptors, provided proteins interactions and phosphorylation. During LTP, Ca^{2+} influx through NMDA receptors activates CaMKII, then activated CaMKII phosphorylates the AMPA GluA1 receptors, and enhances their conductance (Lee et al., 2000). Therefore, mobile pools of AMPA receptors are recruited and trapped at activated synapses when NMDA receptors are activated due to Ca^{2+} influx and elevated CaMKII (Opazo et al., 2010). Moreover, CaMKII activation leads to phosphorylation of a protein named "stargazing" and its binding to postsynaptic scaffold proteins and thus trapping AMPA receptors at the synapse (Opazo et al., 2010). Besides, NMDA receptors influence on synaptic stabilization of AMPA receptors via protein kinase C (Hsieh et al., 2006) and protein kinase A (Oh et al., 2006).

3.1. AMPA receptors and Aβ interaction

AMPA receptors dysfunction correlates with the presence of soluble Aβ, and it might be prevented by Aβ immunotherapy (Baglietto-Vargas et al., 2018). Aβ has been known to bind to GluA2 C-tail of the Ca^{2+-}impermeable type II AMPA receptors and leads to internalization of these receptors (Lacor et al., 2004; Snyder et al., 2005; Zhao et al., 2004, 2010), and induces synaptic modifications (Passafaro et al., 2003) via increase in ubiquitination, internalization, and degradation of AMPA receptors (Zhang et al., 2018). These processes are dose-dependent so that, under normal conditions, most internalized AMPA receptors are recycled back to the plasma membrane by PKA-dependent phosphorylation of the GluA1. However, in the presence of high concentrations of soluble oligomeric Aβ, AMPA receptors are constantly endocytosed and removed (Guntupalli et al., 2017). Our latest study showed that the administration of TAT-GluA23Y peptide, an inhibitor of GluA2/r-eceptors endocytosis, successfully ameliorates Aβ induced cognitive dysfunctions in the rat model of AD (Ashourpour et al., 2020).

AMPA GluA3 receptors are also important for Aβ-mediated synaptic and cognitive deficits. It has been reported that hippocampal neurons lacking GluA3 are resistant to Aβ-mediated synaptic depression and spine loss (Reinders et al., 2016). Molecular pathways of AMPA GluA3 receptors involvement need further investigation.

3.1.1. AMPA receptors trafficking mechanisms

One of the first signs of AD is cognitive impairment, which has been shown to correlate with synapse loss (Penzes and VanLeeuwen, 2011). The addition of Aβ to neurons induces loss of synapses, impairs LTP, enhances LTD, and increases AMPA receptor internalization to depress transmission (Hsieh et al., 2006). AMPA receptors are clustered at the PSD, a postsynaptic disk-like membrane specialization approximately 200–800 nm wide and 30–50 nm thick, directly opposed to the active zone (Carlin et al., 1980; Hsieh et al., 2006). The PSD is a specialized megaorganelle composed of many cytoplasmic scaffold proteins, signaling enzymes, and cytoskeletal elements, which anchor glutamate receptors and cell adhesion molecules, recruit intracellular signaling molecules, and provide a structural link cytoskeletal network of the spine (Jeyifous et al., 2009; Sheng and Hoogenraad, 2007). Among the many PSD proteins, two important families are membrane-associated guanylate kinases (MAGUKs) and src homology 3 (SH3) domain and ankyrin repeat proteins (SHANKs), which are known as key organizers of excitatory glutamatergic synapses. MAGUKs interact with glutamate receptors and regulate their trafficking, targeting, and insertion at the synapse (Schnell et al., 2002; Waites et al., 2009). Another protein, Stargazin, links surface AMPA receptors to the intracellular scaffold (Schnell et al., 2002) and modulates surface AMPA receptors properties by slowing channel deactivation and desensitization (Tomita et al., 2005). Other major scaffolding proteins, including Homer1c, Synapse-associated protein 97 SAP97, and guanylate kinase-associated protein (GKAP) that binds directly to the guanylate kinase domain of PSD-95 family, also participate in receptor trafficking. SAP97 interacts directly with the GluA1 AMPAR and contributes to sorting and trafficking them from the soma to the synaptic membrane (MacGillavry et al., 2013). GKAP interact with certain ion channels (NMDA receptors and K+ channels), thereby promoting the clustering of these proteins, and Shank, as “master regulators” of the glutamatergic excitatory postsynapse provide a virtual platform for structural and functional formation, maturation, and maintenance of excitatory synapses (Berkel et al., 2012).

During LTD, clathrin-mediated endocytosis via adaptor protein Apetala 2 (AP2) and N-ethylmaleimide-sensitive factor (NSF) is assumed to be a possible mechanism for regulating AMPA receptor (Man et al., 2000). This endocytosis is mediated by several proteins, including hippocalcin, which translocates to the plasma membrane upon a slight rise in Ca^{2+} (Palmer et al., 2005). AMPA receptors exocytosis has been observed directly at synapses, perisynaptic to the PSD, on the dendritic spine, spine shaft, and soma. AMPA GluA2 receptors continually exchange with existing synaptic AMPA receptors under basal conditions by mediating different scaffolding proteins. In contrast, AMPA GluA1 receptors are inserted into the membrane via recycling endosomes outside of the PSD and diffuse laterally into the synapse, where PSD95 proteins scaffold them. AMPA receptors incorporation is upregulated in response to synaptic activity and involves phosphorylation of GluA1.

Meanwhile, different modulators such as Arc (activity-regulated cytoskeletal gene) interact with endophilin and dynamin and contribute to AMPA receptors modulation by enhancing receptor endocytosis (Chowdhury et al., 2006). When Arc expression is low, the steady-state of AMPA receptors trafficking will shift to increase the distribution of them to the membrane (Shepherd et al., 2006). The inverse is valid under conditions of high Arc expression. As outlined above, it appears that Arc controls surface expression of AMPA receptors in a homeostatic manner and acts to keep surface levels and subunit composition optimal for Hebbian plasticity in normal physiology(Gao et al., 2010). If Arc-mediated endocytosis remains unchecked, excessive modifications of synaptic strength might generate instability or altered synchrony in neuronal networks, leading to disease states characterized by network imbalances, as observed in AD (Bragin et al., 2009; Palop and Mucke, 2009).

3.1.2. AMPA receptors and synaptopathy

There is a positive correlation between the number of synaptic AMPA receptors and synapse size (Hsieh et al., 2006; Passafaro et al., 2003). More notably, the N-terminal domain of the GluA2 subunit is essential for spines and synapse components, such that removal of surface AMPA GluA2 receptors leads to spine loss (Bassani et al., 2009; Hsieh et al., 2006) similar to that observed in AD (Li et al., 2010). Therefore, different mechanisms regulating AMPA receptors activity, including those affecting the number of receptors and those influencing up and down-regulation of receptors determine synaptic strength. As we discussed above, the number of AMPA receptors is positively associated with LTP, spine type, and synaptic maturity (Matsuzaki et al., 2004). Conversely, synaptic strength can be decreased by a decrease in the AMPA receptor-mediated synaptic currents (Larson and Munkácsy, 2015).

The number of AMPA receptors is determined by various regulatory proteins and kinases depending on receptors subtypes (Dong et al., 2015; Morishita et al., 2005; Stalnaker and Berridge, 2003). For example, phosphorylation of the GluA1 subunit delivers AMPA receptors to synapses and leads to LTP, whereas dephosphorylation stimulates the internalization of them and formation of LTD. In contrast, phosphorylation of GluA2 by PKC promotes internalization, whereas dephosphorylation is important for synaptic retention (Malinow et al., 1989; Roche et al., 1996; Steinberg et al., 2006). In addition, PSD proteins play pivotal role in stabilizing receptors in the synapse (Shao et al., 2011; Srivastava et al., 1998). On the other hand, addition of Aβ to neurons, increases AMPA receptors internalization, induces loss of synapses, impairs LTP, enhances LTD, and depress neural transmission (Knobloch and Mansuy, 2008). Also Aβ oligomers has been known to bind with GluA2/3 AMPA receptors and remove them from synapses (Ma et al., 2011; Sullivan et al., 2013; Traynelis et al., 2010). GluA2/3 play a role in stabilizing spine structures, through their interaction with N-cadherins (Bading, 2017; Lim et al., 2014). It has been reported that AMPA receptors containing subunit GluA3 to be a critical step in Aβ-driven synapse loss (Reinders et al., 2016), and blockade of GluA3 AMPA receptors endocytosis prevents the loss of spines (Rudy et al., 2015; Südhof, 2004).

Furthermore, any dysfunction in proteins involving in AMPA receptors trafficking such as calcineurin, neural precursor cell expressed, developmentally down-regulated 4–1(Nedd4-1) (Guntupalli et al., 2017), kidney and brain expressed protein (KIBRA) (Makuch et al., 2011) and stargazin (Choi et al., 2002; Opazo et al., 2010) lead to synaptic disintegrity.

4. New therapeutic targets

Recent findings verify the idea that memory decline in AD could be mitigated by drugs aimed at sustaining or augmenting NMDA and AMPA receptors provided considering their different subtypes and signaling pathways. NMDA receptors inhibitors are widely used for AD treatment. However, they represented low efficacy and unexpected side effects (Ellison, 1995) due to the opposing role of the different subtypes of NMDA receptors. Therefore, it is assumed that more selective inhibitors against a particular subunit such as the extrasynaptic NMDA GluN2B receptor might be beneficial because they prevents neuronal cell death but leaves the protective pathways intact (K.M. et al., 2017). In addition, other strategies might be targetting the mediators and proteins involved in NMDA/AMPA receptors anchoring and signaling such as CaMKIIα, PKA (Vizi et al., 2013) or PSD-95 (Morimoto et al., 2018) Fyn (Salter and Kalia, 2004) SHANK and KIBRA (De Bartolomeis et al., 2014; Petr et al., 2015).

Although the window for AMPA/NMDAreceptors -based therapeutics seems to be very narrow, we suggest more investigations on proteins involved in AMPA receptors trafficking in different patterns of neural activities and the presence of different doses of Aβ oligomers.

5. Conclusion

In conclusion, this review emphasizes the importance of both NMDA and AMPA receptors in modulating synaptic plasticity and memory. However, factors determining neurotoxicity or pro-survival outcomes are very complex and include diversity in subunits, receptors allosteric sites, neural activity patterns, and molecular signaling pathways. Therefore, assigning the specific role to individual subunit of glutamatergic receptors might be an oversimplification. As it is evident by literature, not only NMDA receptors hyperactivity is deleterious, but so is their hypo-functionality. Moreover, being located on the extrasynaptic part, makes NMDA receptors toxic and causes synaptopathy, in contrast with synaptic receptors.

On the other hand, AMPA receptors not only are highly dynamic receptors, but they are very complex considering various subtypes, interacting proteins, different regulatory enzymes, trafficking, anchoring, recycling, and signaling pathways. Besides the core components of the AMPA receptors, their physiological and pathological responses significantly depend on the location of the receptors and the intensity of neural activity. Therefore, any imbalance between synaptic and extrasynaptic NMDA receptors and a reduced number of surface AMPA receptors will lead to synaptopathy and should be considered for AD therapy.

Author contribution

Parvin Babaei developed the idea and wrote the manuscript.

Declaration of competing interest

The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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