N-Methyl D-Aspartate (NMDA) Receptors

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1. N-Methyl D-Aspartate (NMDA) Receptors

N-methyl-d-aspartate receptor (NMDAR) is a ligand-gated ionotropic glutamate receptor that selectively binds with NMDA for neurotransmission. This glutamatergic receptor consists of two glycine-binding subunits (i.e., GluN1), two glutamate-binding subunits (i.e., GluN2A, GluN2B, GluN2C, and GluN2D), a combination of a GluN2 subunit and glycine-binding GluN3 subunit (i.e., GluN3A or GluN3B), or two GluN3 subunits. Thus, in NMDR, the binding of two different neurotransmitters, glutamate and glycine, is essential for the activation of glutamate-gated ion channel [1]. In addition, the activation for NMDAR is also largely dependent on the removal of the extracellular Mg^{2+} block (voltage dependent) through a strong membrane depolarization, that subsequently allows an influx of Ca^{2+} to initiate synaptic signaling that is essential for learning and memory functions [2]. NMDAR are expressed in the CNS where they are responsible for transmitting the Ca^{2+} permeable excitatory neuronal signals and are considered to have a significant role in synaptic plasticity and memory functions. NMDAR dysfunction, including receptor inactivation and Ca^{2+}flux of, is associated with learning and memory impairments, which are characteristic features of age-related neurodegenerative disease such as AD [3]. Understanding NMDAR's role at the central synapses may prove beneficial for determining therapeutic targets for reversing the memory disorders and synaptic functioning associated with AD pathology.

2. Specifics

In the mammalian CNS, the excitatory glutamate neurotransmitter is predominant and acts on a number of glutamate neurotransmitters, including NMDARs. While synaptic NMDARs are crucial for normal brain functioning, extra-synaptic NMDARs and over activation of these excitatory receptors leading to excess Ca^{2+} influx in the cells, is responsible for neuronal excitotoxicity [4]. Similarly, dysfunctional glutamatergic signaling, involving Ca^{2+} homeostasis via NMDAR, has a direct link to AD pathology. Aβ plaques and hyper phosphorylated tau proteins are considered responsible for disrupting glutamatergic tripartite synapse functioning. The tripartite synapse consists of presynaptic and postsynaptic terminals along with the glial cells. The synapse receptor proteins modulate the extracellular glutamate levels and are considered deregulated in AD pathology [5].

Amyloid-β peptide (Aβ), one component of the extracellular amyloid plaque, is a hallmark of Alzheimer's disease (AD). Proponents of the amyloid hypothesis argue that the accumulation of Aβ in the brain is AD's driving factor [6]. An increase of Aβ accumulation leads to NMDA-induced synaptic dysfunction via the activation of NMDAR's extra synaptic NR2B subunit, fostering NMDAR endocytosis at the synapse while also shrinking glutamate reuptake and promoting glutamate spillover [7]. The aftermath of NMDAR endocytosis is attenuation of NMDAR mediated Ca^{2+} influx at the synapse and spine head. In addition, Aβ is also shown to hinder the supply of AMPA receptors to post synaptic neurons [7]. Paradoxically, Aβ excitotoxicity is actuated by over activation of extracellular NR2B due to inhibition of intracellular glutamate reuptake. Further, it has been shown that Aβ promotes release of glutamate from astrocytes. All these phenomena promote the sustained influx of Ca^{2+} through NMDAR rendering an excitotoxic effect [8]. Interestingly, amyloid precursor protein (APP) processing is expedited upon NMDA receptor activation at the synapse, whereas Aβ is synthesized by beta-secretase cleavage of APP on extra-synaptic activation.

NMDA receptor activation occurs when endogenous agonist glutamate NR2 family subunits bind at the NR1 subunit. Simultaneously, it co activates glycine, and releases the magnesium block by membrane depolarization. D-Serine, the other endogenous ligand, found abundantly in astrocytes, shares the same glycine binding site with somewhat similar potency. Interestingly, D-serine seems to be the dominant coactivator of NMDA induced neurotoxicity compared to glycine.

The magnesium and S-nitrosylation sites are two prominent modulatory sites located inside the ion channel and extracellular amino-acid terminal domain (ATD), respectively. ATD offers allosteric regulation of ion channel open probability, receptor deactivation speed. Selective calcium permeability and the magnesium blockade are mediated by arginine residue present in the pore lining of the transmembrane loop (M2). S1 and S2, the two discontinuous ligand binding domain, constitute ligand binding location. Upon ligand binding and subsequent receptor activation, the Mg^{2+} block is released, the channel opens and the influx of Ca^{2+}, Na^{+} and K+ occurs inside the neuron [9][10].

Harnessing the neuroprotective effect of the NMDAR blockade has long been pursued as a target to address various neurological diseases, including Alzheimer's disease; however, harsh side effects have resulted in failed clinical trials. Envisioning future NMDAR drug discovery targets, Lipton put forward a conceptual framework for tolerated antagonists, explicitly negating the possibility of competitive antagonists and arguing that the competitive blockade may also affect healthy brain function involving glutamate or glycine activation of NMDA [8]. In fact, high extracellular glutamate or glycine accumulation over time displaces antagonists, thus preferentially altering healthy brain rather than pathological physiology. An uncompetitive open channel blockade emphasizing on-off rate was presented as an alternative. Succinctly, an uncompetitive antagonist offers greater inhibition to agonists at higher concentrations than lower concentrations. In addition, an optimal off rate that is slower than Mg^{2+} yet faster than MK-801′s off rate enables the ligand to achieve an excessively open state, compared to the receptor, under normal transmission. One exception, Memantine, has a proven clinical safety profile [9], is well tolerated, is an effective treatment of moderate to severe AD [11], and fits well in this paradigm. Memantine's success may be due to the drug's selectivity to extra synaptic NMDAR [8], its low-affinity/rapid off rate, and uncompetitive channel blockade [11].

An uncompetitive NMDAR antagonist, memantine is thought to slow neuronal cell death observed in AD by blocking the action of the NMDA-receptor ultimately inhibiting the over activation of glutamatergic neurotransmission, particularly in relation to calcium influx resulting from excessive NMDAR stimulation [12][13]. Memantine is an amantadine derived compound and the amino group in the adamantane ring binds at or in the vicinity of the Mg^{2+} binding site in the NMDA-gated channel [14]. Besides this major binding site, another memantine binding site has also been reported. This superficial site has low affinity at the channel vestibule and also serves as a memantine blocking site [15].

Memantine is used along with acetylcholine esterase inhibitors for treating moderate to severe AD cases. It has the ability to block the action of excessive NMDAR; however, due to its low affinity binding power it can be easily replaced, subsequently releasing the NMDAR blocking action [16]. This scenario demonstrates the importance of identifying molecular devices that mimic the action of NMDAR blocking tools and their ability to modulate and fine tune the NMDA-receptor function. As NMDAR serves as the key factor in controlling synaptic plasticity and memory performances, such process anticipates as an effective therapeutic approach for the improvement of cognitive and learning functions in AD pathology and other brain disorders.

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