Minireview

NMDA Receptor as a Newly Identified Member of the Metabotropic Glutamate Receptor Family: Clinical Implications for Neurodegenerative Diseases

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Recent reports have proposed a novel function for the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR), a well-known excitatory, ionotropic receptor. A series of observations employing pharmacological techniques has proposed that upon ligand binding, this ionotropic receptor can actually function via signaling cascades independent of traditional ionotropic action. Moreover, the “metabotropic” action of NMDARs is suggested to mediate a form of synaptic plasticity, namely long-term synaptic depression (LTD), which shares cellular mechanisms with the synaptic deficits observed in Alzheimer’s disease. Given that a growing body of clinical and preclinical evidence strongly recommends NMDAR antagonists for their therapeutic potentials and advantages in a variety of diseases, further investigation into their molecular and cellular mechanisms is required to better understand the “metabotropic” action of NMDARs.

INTRODUCTION

The *N*-methyl-D-aspartate (NMDA) receptor is probably one of the most extensively studied ionotropic glutamate receptors. Recent studies have proposed that the NMDA receptor (NMDAR) actually exerts long-lasting changes in synaptic transmission via initiation of intracellular signaling pathways, even in the absence of ion flux. In other words, NMDAR can also function as a *metabotropic* receptor (Kessels et al., 2013; Nabavi et al., 2013). This proposal is quite striking, and urges researchers to take a fresh look at the working principles of the central synapse as well as at the accumulated observations from the past decades.

TRADITIONAL UNDERSTANDING OF NMDA RECEPTORS

It is well known that glutamate exerts its excitatory action upon binding to ionotropic or metabotropic partners in the postsynaptic density (PSD) of the central nervous system. These receptors have been studied extensively for decades. Once released,

glutamate activates its receptors that, in turn, either causes immediate ion influx (“*ionotropic*”) or initiates signaling cascades upon ligand binding (“*metabotropic*”). It has been well documented that ionotropic receptors for glutamate include the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor (AMPA), NMDAR, and kainate receptor (Collingridge and Lester, 1989). Metabotropic receptors include 8 isoforms of G-protein coupled receptors, namely mGluR1-8 (Conn and Pin, 1997). Ionotropic receptors mediate fast, immediate responses, whereas metabotropic receptors mediate relatively slower synaptic responses (Traynelis et al., 2010).

In general, ionotropic glutamate receptors are tetrameric, ligand-gated cation channels. Among these, NMDAR has been the center of attention predominantly due to its unique features: 1) it allows Ca^{2+} influx upon activation, in addition to other cation-mediated currents, and 2) it requires additional conditions for activation (specifically, the Mg^{2+} block has to be released for opening) (MacDermott et al., 1986; McBain and Mayer, 1994; Regehr and Tank, 1990). The combination of 2 duplicated subunits (generally, GluN1 subunits with co-activator, glycine binding sites, and regulatory GluN2 subunits with glutamate binding sites) consist of NMDARs, and the subunit composition (particularly among GluN2 isoforms) is known to determine ion conductance through the receptor and be developmentally regulated (Al-Hallaq et al., 2007; Collingridge et al., 2009; Monyer et al., 1994; Rauner and Kohr, 2011; Sheng et al., 1994; Stocca and Vicini, 1998). The mature human brain is known to express mainly GluN1 and GluN2A (Petrulia et al., 1994). Each NMDAR subunit exhibits an extracellular N-terminal domain for tetramerization, a ligand-binding domain for glutamate or co-activator glycine, a transmembrane domain for pore-formation, and a C-terminal domain for receptor localization and modulation (Traynelis et al., 2010). The size of the C-terminal domain differs depending on the subunits. A number of postsynaptic proteins are known to interact with NMDARs through the C-terminal domain, including postsynaptic density protein 95 (PSD-95), synaptic scaffolding molecule (S-SCAM), Homer, and collapsing response mediator protein 2 (CRMP2) (Al-Hallaq et al., 2007; Kim

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and Sheng, 2004).

Because the opening of NMDARs requires both glutamate binding to its GluN2 subunits and depolarization to eliminate the voltage-dependent Mg^{2+} block, conventional fast synaptic transmission has been depicted as follows: AMPAR will be opened immediately by the released glutamate, causing depolarization of postsynaptic neurons, which in combination with the released glutamate, activates NMDARs. The opening of NMDARs allows cation influx with additional Ca^{2+} influx. This series of events has been extensively investigated (McBain and Mayer, 1994; Traynelis et al., 2010).

ROLE OF NMDARS IN SYNAPTIC PLASTICITY

NMDAR is often referred as the “coincidence detector” due to its concurrent requirement for ligand binding and depolarization induced by AMPARs for opening. Together with its ability to allow Ca^{2+} influx, its dual opening requirement suggests that NMDARs might play an essential role in basal transmission as well as in synaptic plasticity (Malenka and Nicoll, 1993). Synaptic plasticity, a well-established cellular model of learning and memory, occurs in 2 forms, depending on the electrical stimulation patterns: long-term potentiation (LTP; long-lasting enhancement of synaptic efficacy after certain patterns of stimulation) and long-term depression (LTD; long-lasting depression of synaptic transmission after a pattern of stimulation) (Bliss and Collingridge, 1993; Kandel, 2001; Malenka and Bear, 2004; Morris et al., 2003). Currently, textbooks explain that the level of Ca^{2+} influx resulting from a given pattern of stimulation determines whether to produce LTP or LTD by inserting or removing AMPARs from the surface, respectively (Kessels and Malinow, 2009; Neveu and Zucker, 1996). Multiple forms of LTP and LTD have been characterized in various brain structures. LTP and LTD occur in an NMDAR-dependent manner in the hippocampus, a structure deeply implicated for learning and memory. The electrical stimulation pattern, such as brief, high frequency stimulation (HFS; for example, 100 Hz for 0.2–2 s) or theta burst stimulation (TBS; for example, 4–5 pulses at 100 Hz, repeated 5–10 times at 5 Hz), induces an immediate but brief increase in Ca^{2+} levels, thus resulting in LTP (Bashir et al., 1991; Berretta et al., 1991; Lee et al., 2000). However, low frequency stimulation (LFS; for example, 1 Hz for 5–15 min in the hippocampus) induces a slower and lower Ca^{2+} rise, which contributes to AMPAR internalization and thus to LTD induction (Gean and Lin, 1993; Man et al., 2000; Montgomery and Madison, 2002; Montgomery et al., 2005). Ca^{2+} influx is thought to activate a group of kinases and/or phosphatases, including Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), protein kinase A (PKA), the tyrosine kinase Src, and the protein phosphatases PP1/PP2A, within the cell to eventually modulate the number of surface AMPARs as well as the number of spines, thus leading to LTP or LTD (Berridge et al., 2003; Harnett et al., 2009; Lee et al., 2000; Li et al., 2011; Liu and Zukin, 2007; Morishita et al., 2005). Therefore, NMDARs have been proposed to be hallmarks of synaptic plasticity due to their instrumental role in long-lasting changes in synaptic efficacy (Malenka and Bear, 2004; Malenka and Nicoll, 1993).

The role of Ca^{2+} through NMDARs has been extensively investigated in long-term synaptic potentiation. Classical studies using NMDAR antagonists failed to induce LTP (Harris et al., 1984; Morris et al., 1986), as did experiments with Ca^{2+} chelators to block Ca^{2+} elevation within the cell (Lynch et al., 1983). Another line of evidence came from additional electrical stimulation patterns developed to induce LTP. In addition to HFS, the

pairing moderate stimulation (1–2 Hz) with depolarization (holding at 0 mV) induces robust potentiation in synaptic responses, suggesting that release of the Mg^{2+} block during moderate activity is sufficient to activate NMDARs, thereby causing LTP (Chen et al., 1999; Malinow and Tsien, 1990). Similar observations have been obtained for LTD. Treatment with Ca^{2+} chelators or NMDAR antagonists successfully blocked LTD induction in given synapses (Cummings et al., 1996; Dudek and Bear, 1992), supporting the idea that elevated Ca^{2+} , presumably through NMDAR together with voltage-gated Ca^{2+} channels, is instrumental for synaptic plasticity, and for learning and memory.

EVIDENCE FOR THE IONOTROPIC GLUTAMATE RECEPTOR AS A METABOTROPIC RECEPTOR

The provocative idea that NMDAR, the most traditional ionotropic glutamate receptor, may work as a *metabotropic* receptor arises from observations on synaptic depression induced by LFS, which employed a series of NMDAR antagonists. LFS-induced synaptic depression has been well characterized in acute hippocampal slice preparations and is referred to as NMDAR-dependent LTD (Thiels et al., 1996). Blockade of NMDAR function by using APV [D-(–)-2-amino-5-phosphonopentanoic acid], a widely used antagonist, completely blocked LTD induction in the hippocampus, consistent with previous observations. Striking differences were observed upon application of other antagonists, namely, MK-801 and 7CK (7-chlorokynurenate). Unlike APV, these NMDAR antagonists failed to block NMDAR-dependent LTD in given synapses (Nabavi et al., 2013).

Pharmacologically inconsistent action of antagonists sometimes reveals a novel function of given receptors or uncovers the involvement of unknown pathways, including unexpected receptors. For example, in a previous study on long-term synaptic depression of excitatory synapses onto interneurons in the hippocampus, the possible involvement of endocannabinoid receptors (CB1R) was investigated using two different antagonists (Gibson et al., 2008). Blockade of CB1R using its antagonist SR141716A abolished interneuron LTD, whereas blockade by another antagonist AM251 failed to do so. As AM251 exhibited no deficits as the CB1R antagonist when applied with a CB1R agonist, unknown receptors were sought that were possibly blocked by SR141716A but not by AM251. It was previously known that this type of interneuron LTD is independent of NMDAR activation so the authors examined the possible involvement of unknown receptors. Upon careful examination, it was determined that SR141716A also inhibits the function of transient receptor potential V1 (TRPV1) receptors in addition to CB1Rs (De Petrocellis et al., 2001). It turns out that extrasynaptic TRPV1 contributes to the interneuron LTD in the hippocampus. This view is now widely accepted in the field and led to further studies (for review, see Kullmann et al., 2012). Similarly, in the NMDAR-dependent LTD study discussed above, all three antagonists effectively blocked NMDAR-mediated currents. Instead, the pharmacological sites of action of these antagonists differ. MK-801 blocks NMDAR by clogging the pore for ion flux, and so does 7CK. 7CK competitively binds to a co-activator (such as glycine) binding site. However, APV binds to glutamate binding sites on GluN2 subunits, while leaving the pore open (Traynelis et al., 2010). Therefore, the glutamate binding itself appears to be important for successful induction of NMDAR-dependent synaptic depression, thereby dissociating NMDAR function into ionotropic and metabotropic (Nabavi et al., 2013) (Fig. 1).

More striking observations come from experiments where

Fig. 1. Schematic diagram of a new model that depicts ionotropic and metabotropic actions of NMDARs. (A) NMDARs are tetramers, composed of 2 GluN1 subunits and 2 GluN2 subunits. The GluN1 subunit contains glycine-binding sites that can be antagonized by 7CK. The GluN2 subunit contains glutamate-binding sites that can be antagonized by APV and R-CPP. MK-801 is a pore blocker that eliminates ion flux through NMDARs in a use-dependent manner as ketamine. The new model proposes that upon glutamate binding and release of the Mg^{2+} block, NMDARs allow ion flux and initiate signaling cascades, presumably via the C-terminal domain (CTD). (B) When ionotropic action is selectively inhibited by antagonists such as 7CK, MK-801, and ketamine, NMDAR-dependent LTD in the hippocampus is expected to be intact. (C) When the metabotropic action of NMDAR is selectively inhibited using competitive antagonists such as APV and R-CPP, NMDAR-dependent LTD is anticipated to be eliminated due to blockade of the necessary signaling cascades.

LTD was induced with HFS (a stimulation pattern generally used to induce LTP) in the presence of MK-801, a pore blocker of NMDARs. This result suggests that as long as no Ca^{2+} enters the neuron, the *metabotropic* activation of NMDARs seems to favor depression of given synapses (Nabavi et al., 2013). Is there any signaling pathway turned on by NMDAR activation upon ligand binding, then? Indeed, binding of glutamate to NMDAR increased the level of activated p38 MAPK in cultured neurons and Ca^{2+} influx was found to play no role in p38 MAPK phosphorylation (Nabavi et al., 2013), which lends further support for this new model of NMDAR action.

Therefore, now what determines whether to induce LTP or LTD does not seem to be the level of Ca^{2+} increase or the pattern of electrical stimulation, but rather the activation modes of NMDARs. The *ionotropic* activation of NMDARs (i.e., massive Ca^{2+} influx) induces LTP, while the *metabotropic* activation of NMDARs (i.e., conformational change of NMDAR, initiating p38 MAPK signaling cascades) induces LTD. Note that Ca^{2+} increase would still induce LTP; however, as long as the Ca^{2+} levels remain at the basal intracellular level, *metabotropic* NMDAR activation will lead to synaptic depression (Fig. 1).

In fact, it has been previously documented that NMDAR could function independent of ion flux. In the hippocampus, phosphorylation of the NMDAR subunit, which is responsible for receptor trafficking was shown to be regulated in an activity-dependent manner regardless of ion influx through the pore (Vissel et al., 2001). In addition, it has been reported that manipulations of the C-terminal domain of NMDARs, without altering synaptic transmission *per se*, could modulate synaptic plasticity (Kohr et al., 2003; Ryan et al., 2013). In hippocampal Schaffer collateral synapses, truncation of the C-terminal domain of an isoform of the GluN2 subunit was shown to have a minimal effect on the amount of Ca^{2+} influx (Kohr et al., 2003). Another recent study took advantage of a line of genetically engineered animals that have swapped C-terminal domains between the GluN2A and 2B subunits and examined the effect of this domain at the cellular as well as behavioral level (Ryan et al., 2013). Synapses prepared from these animals showed no alterations in basal synaptic transmission, which was evaluated by measuring NMDAR-mediated evoked excitatory postsynaptic current (eEPSC) and AMPAR-mediated eEPSC ratio, paired pulse facilitation, and the kinetics of NMDAR-eEPSC. These

data indicate that synaptic transmission, including ion influx, is minimally disrupted. However, swapping C-terminal domains of the GluN2 subunits caused serious defects in various learning or emotional behaviors (Ryan et al., 2013), implying that a distinct mechanism beyond altered synaptic transmission drives synaptic as well as behavioral plasticity, possibly *via metabotropic* signaling cascades induced by the C-terminal domain of GluN2.

CLINICAL IMPLICATIONS OF “METABOTROPIC” NMDARS

The most common progressive neurodegenerative disease, Alzheimer's disease (AD), exhibits neurofibrillary tangles as a distinct pathophysiological hallmark. The tangles are an accumulation of overproduced beta amyloid (A β) proteins and hyperphosphorylated tau protein (Selkoe and Schenk, 2003). One of the currently accepted explanations regarding the pathophysiology of AD is the “amyloid hypothesis”, which proposes that the accumulated hydrophobic A β peptides are the main pathological consequence observed in the brain of patients with AD. A β is generated from amyloid precursor protein (APP) via sequential processing by a series of secretases (Kamenetz et al., 2003; Selkoe and Schenk, 2003).

A β is known to exert detrimental effects at the synaptic level before the onset of behavioral symptoms such as memory loss and cognition deficits (Venkitaramani et al., 2007). It has been reported that preparations obtained from a number of animal models of AD exhibit impaired LTP, thereby recapitulating cognitive dysfunction observed in patients with AD (Shankar et al., 2008; Snyder et al., 2005; Walsh et al., 2002). These studies reported that the type of LTP disrupted in AD model synapses is NMDAR-dependent (Shankar et al., 2007; 2008; Snyder et al., 2005). In addition, it has been well documented that A β -mediated synaptic depression shares signaling pathways with NMDAR-dependent LTD, including major players such as calcineurin, a calcium-activated phosphatase, and caspase-3 (Hsieh et al., 2006; Venkitaramani et al., 2007). Moreover, some reports suggest that blockade of NMDAR alleviates A β -mediated synaptic depression, suggesting NMDAR as a potential drug target (Shankar et al., 2007). However, the detailed action of A β on synaptic depression remains uncertain because the pathological outcomes of A β used in experimental settings differ depending on oligomerization status of A β and/or its location (Gasparini and Dityatev, 2008).

It seems clear that functional NMDAR mediates the deleterious effects of A β on synaptic transmission because blockade of NMDARs using APV and R-CPP [3-((R)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid], both of which act on GluN2 subunits, protects synapses from the A β -induced synaptic depression (Kessels et al., 2013; Shankar et al., 2007; Snyder et al., 2005). Organotypic slice preparations sparsely infected with A β precursor proteins were used to allow direct comparison of the synaptic efficacy between control and A β -overexpressed neurons. As suggested previously (Hu et al., 2009), GluN2B-containing NMDARs appear to mediate the deleterious effect of A β on synaptic transmission because the GluN2B-specific antagonists Ro 25-6981 and ifenprodil minimized A β -mediated synaptic deficits (Kessels et al., 2013). Additionally, blockade of GluN1 subunits exhibits no such protective effect, and A β seems to promote the switch between GluN2A and GluN2B, implying that A β has precise target sites on synapses. Differential interaction with various postsynaptic proteins (such as neuronal nitric oxide synthase, Homer, β -catenin, and CRMP2) depending on the subunit composition may help to explain the

specificity of the deleterious effects of A β (Al-Hallaq et al., 2007). Given the similarity in cellular mechanisms shared between NMDAR-dependent LTD and A β -mediated synaptic depression, whether A β -mediated synaptic dysfunction also requires activation of *metabotropic* NMDARs has been examined (Nabavi et al., 2013). Pore blockers of NMDARs, such as ketamine and MK-801, are also unable to abolish A β -induced synaptic depression, strongly suggesting that synaptic defects shown in AD are mediated by “ion flux-independent” actions of NMDARs (Kessels et al., 2013).

CONCLUSION

The new model for NMDAR working principles presents dual action upon activation (*ionotropic* and *metabotropic*) proposing the distinct involvement of each action of one receptor under different physiological as well as pathophysiological conditions. Evidence suggesting that pathological A β accumulation may exert its effects through selective disruption in metabotropic action of NMDARs provides more convincing arguments for this new model, although further examination and careful verification of this model needs to be preceded.

Blockade of NMDAR appears to be one of the favorite target sites for clinical treatment of a number of diseases. For example, a non-competitive NMDAR antagonist ketamine is currently under clinical evaluation for its therapeutic action in depressive disorders (for review, see Chung, 2012; Kavalali and Monteggia, 2012). Ketamine, however, is shown to bind to the allosteric site and blocks Ca²⁺ influx (Anis et al., 1983), thus implying the role of *ionotropic* action of NMDARs in the pathophysiology of depressive disorders. However, this does not suggest that the *metabotropic* action of NMDARs is not involved in depressive disorders because administration of R-CPP, a competitive antagonist for glutamate binding to GluN2 subunits, has been reported to have antidepressant-like effects (Autry et al., 2011). Likewise, the possibility that the ionotropic action of NMDARs also contributes to AD symptoms cannot be ruled out because a previous study using Ca²⁺ imaging approaches reported that A β oligomers reduce Ca²⁺ influx into the spine head (Shankar et al., 2007). In addition, memantine, an effective AD medication, is a fast, voltage-sensitive pore blocker of NMDARs, which hampers Ca²⁺ influx through its pore (Danysz and Parsons, 2003; Frankiewicz et al., 1996; Misztal et al., 1996).

The observations obtained thus far are limited to samples prepared *in vitro*. Therefore, evidence of such metabotropic functions of NMDARs *in vivo* is expected to provide further support for this new member of the metabotropic glutamate receptors. Furthermore, the detailed signaling cascades initiated by NMDARs need to be identified. Thorough investigation of the functional distinction between the *ionotropic* and *metabotropic* actions of NMDARs is anticipated to provide an opportunity to revise our knowledge of the working principles of NMDARs, as well as to contribute for developing possibly more powerful clinical interventions for neurodegenerative diseases.

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