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Invited review

NMDA receptors in nervous system diseases☆

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ABSTRACT

NMDA receptor (NMDAR) dysfunction has emerged as a common theme in several major nervous system disorders, including ischemic brain injury, chronic neurodegenerative diseases, pain, depression and schizophrenia. Either hyperactivity or hypofunction of NMDARs could contribute to disease pathophysiology. It is likely that distinct subtypes of NMDARs (as defined by subunit composition and/or subsynaptic location) are differentially involved in central nervous system diseases. Here we focus on a few examples of nervous system diseases where the contribution of NMDARs is relatively well characterized and discuss the implications for potential treatment of these illnesses.

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NMDA (*N*-methyl-D-aspartate) receptors (NMDARs) are a subclass of glutamate receptors that requires both binding of glutamate and postsynaptic depolarization for their activation, and that mediates Ca^{2+} entry when they are activated. NMDAR dysfunction – arising from altered receptor-channel activity, subunit expression, trafficking, or localization – may contribute to a variety of neurological and psychiatric conditions. In fact, many nervous system diseases are now considered to be associated with, or even caused by, synaptic dysfunction. It has become increasingly clear that detrimental effects can arise from either hyperactivity or hypofunction of NMDARs.

Altered NMDAR presence/functions can contribute to central nervous system (CNS) disease in different ways: their excessive activation could cause neuronal death, as in stroke and perhaps in Huntington's disease, or their reduced activity could alter the balance of excitation and inhibition in neural circuitry to affect CNS functions, as likely occurs in schizophrenia. NMDARs are present at glutamatergic synapses on both excitatory and inhibitory neurons. Given the differential and often opposite functions of excitatory versus inhibitory neurons, the functional contributions of these NMDARs are likely to be different or even opposite. For example, enhanced NMDAR function on excitatory neurons could lead to enhanced synaptic plasticity of excitatory neurons, whereas enhancing NMDARs on inhibitory neurons is likely to boost inhibition (reducing excitation as a consequence) and hence reduce synaptic plasticity of excitatory neurons. Thus, depending on their locus, altered expression/activity of NMDARs can influence the balance between excitation and inhibition and affect circuit and brain function. At excitatory synapses, the contributions of NMDARs to CNS diseases may also depend on the subunit composition and/or the subsynaptic location of these receptors.

This review is not intended to cover the involvement of NMDARs in every disease of the CNS, but rather to focus on examples where the contribution of NMDARs is relatively well characterized, and which might offer insights into treatment of these illnesses.

1. Subunit composition and synaptic location of NMDA receptors

NMDARs are heterotetramers composed of two GluN1 subunits (previously called NR1) plus two GluN2 subunits (previously known as NR2encoded by four different genes GluN2A-D). NMDARs containing different GluN2A-D subunits exhibit distinct electrophysiological and pharmacological properties and somewhat different distribution and expression profiles (Cull-Candy and Leszkiewicz, 2004; Paoletti and Neyton, 2007; Traynelis et al., 2010). For example, NMDARs containing GluN2A or GluN2B have larger single channel conductance, higher sensitivity to blockade by extracellular Mg^{2+} and greater Ca^{2+} permeability than NMDARs containing GluN2C or GluN2D (Paoletti, 2011). In this review, GluN2A-NMDARs refer to NMDARs that contain two GluN2A subunits while GluN2B-NMDARs are those that contain two GluN2B subunits. A significant portion of synaptic NMDARs, however, contain one GluN2A and one GluN2B subunit (the so-called triheteromeric NMDARs; Sheng et al., 1994; Luo et al., 1997;

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Al-Hallaq et al., 2007). Although these triheteromeric NMDARs appear to have properties distinct from the GluN2A-NMDARs and GluN2B-NMDARs (Neyton and Paoletti, 2006; Rauner and Köhr, 2011), their contribution to physiological and pathological processes is poorly defined due to the lack of inhibitors that specifically block this subset of NMDARs (Neyton and Paoletti, 2006).

The C-terminal cytoplasmic domains of GluN2A and GluN2B contain numerous protein interaction and phosphorylation sites that can affect receptor activity and trafficking (Salter and Kalia, 2004). Although both GluN2A-NMDARs and GluN2B-NMDARs share some common binding partners (such as postsynaptic density protein 95 (PSD-95), Sheng and Kim, 2011), they bind differentially to some other proteins. For example, GluN2A-NMDARs interact with Homer and β-Catenin (Al-Hallaq et al., 2007), whereas GluN2B-NMDARs bind to Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII) and synaptic Ras GTPase activating protein (SynGAP) (Leonard et al., 1999; Kim et al., 2005). The C-terminal tails of GluN2A and GluN2B may also determine the apparent differential roles of GluN2A and GluN2B in excitotoxicity and neuronal survival (see below).

Activation of NMDARs can be either toxic to neurons or promote their survival and plasticity. Prolonged exposure of neurons to glutamate leads to cell death, which is mediated by Ca^{2+} entry through NMDARs (Choi, 1987; Rothman and Olney, 1995), in other words, NMDARs can cause excitotoxicity. On the other hand, activity of synaptic NMDARs is crucial for the survival of neurons, and blocking NMDAR activity in vivo, especially during development, results in neuronal apoptosis (Ikonomidou et al., 1999; Hetman and Kharebava, 2006). How can these apparently paradoxical actions of NMDARs be explained? There are two models – localization vs. subunit composition – to explain the differential contribution of NMDARs to excitotoxicity and neuronal survival. The "localization model" (Fig. 1a) posits that activation of extrasynaptic NMDARs is neurotoxic, whereas activation of synaptic NMDARs is neuroprotective (Hardingham et al., 2002; Hardingham and Bading, 2010). Stimulating synaptic NMDARs activates cAMP response element-binding protein (CREB) signaling and promotes survival, while activation of extrasynaptic NMDARs attenuates CREB signaling and promotes cell death (Hardingham and Bading, 2010). The localization model relies largely on an operational definition of extrasynaptic vs. synaptic location of NMDARs (i.e., extrasynaptic receptors are those not activated by synaptically released glutamate but are stimulated by bath-applied glutamate or NMDA) (Hardingham et al., 2002; Hardingham and Bading, 2010). Due to technical limitations, most studies on differential roles of synaptic vs. extrasynaptic NMDARs have been performed in dissociated cultured neurons. For these reasons, the conclusions reached are not completely satisfying. This situation could be changed by the recent work of Papouin et al. (2012) that showed that synaptic and extrasynaptic NMDARs use D-serine and glycine as their coagonists, respectively. Thus, by reducing the level of D-serine or glycine with enzymes that selectively degrade D-amino acids (including D-serine) or free extracellular glycine, it might be possible to specifically control the activation of synaptic or extrasynaptic NMDARs in neural preparations that more resembles the in vivo network (such as brain slices). There is some evidence that D-serine levels are reduced in certain CNS diseases (e.g., schizophrenia, Labrie et al., 2012). By selectively reducing the levels of D-serine and/or glycine, it might then be possible to determine whether alterations in synaptic or extrasynaptic NMDAR activity could contribute to the pathophysiology of the CNS diseases.

In the "subunit composition model" (Fig. 1b), it is the subunit make-up of NMDARs that determines whether their activation has neurotoxic or neuroprotective consequences – activation of GluN2B-NMDARs is excitotoxic, while activation of GluN2A-NMDARs is neurotrophic (Lai et al., 2011). Activation of pro-survival signaling pathways, such as CREB and phosphatidylinositol 3-kinase (PI3K), has been linked to GluN2A-NMDAR activation, whereas cell death signaling is more associated with activation of GluN2B-NMDARs (Liu et al., 2007; Terasaki et al., 2010). By

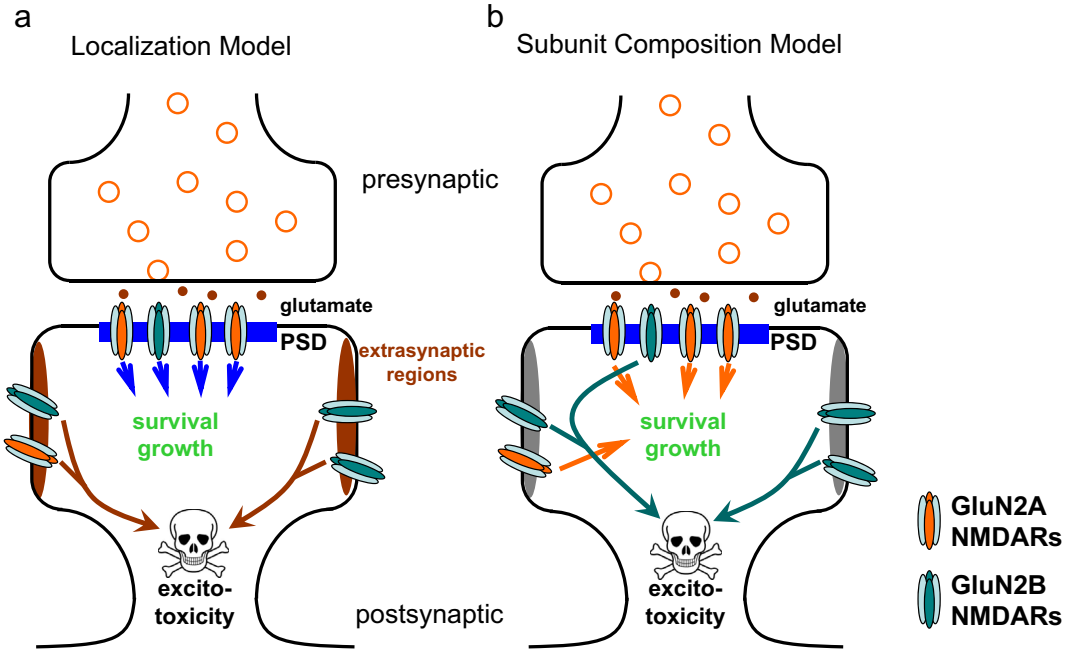

Fig. 1. The localization model vs. subunit composition model to account for the differential contributions of NMDARs to neuronal survival and excitotoxicity/death. a. The localization model proposes that activation of NMDARs in the extrasynaptic regions (areas outside the PSDs, brown) leads to activation of cell death signaling pathways, while activation of synaptic NMDARs (in the PSDs, blue) is neuroprotective. b. The subunit composition model proposes that activation of GluN2B-NMDARs (green) is excitotoxic, while activation of GluN2A-NMDARs (orange) is neurotrophic. Note that GluN2A-NMDARs are more preferentially localized to the synapse, whereas GluN2B-NMDARs are preferentially distributed in the extrasynaptic regions.

swapping the C-terminal regions between GluN2A and GluN2B in knock-in mice, it was shown that the cytoplasmic tail of GluN2B is preferentially coupled to excitotoxicity in neurons, both in vitro and in vivo (Martel et al., 2012). Studies supporting the subunit composition model are based on genetic manipulations and pharmacological tools (which can be applied in in vivo experiments). However, they suffer from caveats such as confounding secondary effects of GluN2 gene disruptions (e.g., lethality of GluN2B knockout) and problematic specificity of GluN2A-NMDAR antagonists. For example, the widely used GluN2A-NMDAR antagonist NVP-AAM077 has only 10 fold selectivity for GluN2A- over GluN2B-NMDARs in rodents, and the concentrations used in many studies inhibit both GluN2A- and GluN2B-NMDARs significantly (Berberich et al., 2005; Weitlauf et al., 2005; Frizelle et al., 2006; Neyton and Paoletti, 2006).

It should be emphasized that the localization and subunit composition models are not mutually exclusive since GluN2A and GluN2B are differentially distributed in neurons. In the adult brain, GluN2A-NMDARs are largely concentrated within synapses while GluN2B-NMDARs are largely extrasynaptic (Tovar and Westbrook, 1999; Traynelis et al., 2010). Therefore the localization and subunit composition models are largely overlapping in practice. It is thus our view that these two models cannot be experimentally distinguished at this time.

In the following sections of the review, we will summarize the contributions of NMDARs to the pathophysiology of CNS diseases, and where appropriate, we will discuss the differential involvement of GluN2A- versus GluN2B-NMDARs, or synaptic versus extrasynaptic NMDARs. Selective and potent antagonists of GluN2B-NMDARs allow their contribution to be studied in detail while the lack of highly selective GluN2A-NMDAR antagonists has created controversy and contradictory results in the functional dissection of GluN2A-NMDARs' roles. In addition, subunit-selective or -preferring NMDAR antagonists can also inhibit triheteromeric NMDARs, although likely to a lesser extent than their homomeric counterparts (Hatton and Paoletti, 2005). These caveats need to be kept in mind when interpreting the results obtained with NMDAR antagonists. We will also identify the critical issues that need to be resolved to advance our understanding of NMDAR involvement in a particular CNS disease.

2. Stroke and traumatic brain injury (TBI) – excitotoxicity by NMDARs

It is long known that sustained elevation of extracellular glutamate results in neuronal death (Lucas and Newhouse, 1957; Choi, 1987; Rothman and Olney, 1995) and this excitotoxicity contributes to the acute neuronal death seen in stroke and TBI (Bullock et al., 1998). NMDAR-mediated excitotoxicity may also contribute to neuronal death in some chronic neurodegenerative diseases, such as Huntington's disease (Milnerwood and Raymond, 2010). In stroke and TBI, NMDAR-dependent excitotoxicity appears to be a primary cause of neuronal death occurring acutely after ischemia or injury, and NMDAR blockers protect neurons against ischemic cell death in vitro and in vivo (Simon et al., 1984; Chen et al., 1991, 2008; Liu et al., 2007). Interestingly, NMDAR excitotoxicity seems to be subunit-dependent, since selective GluN2B antagonists blocked, whereas GluN2A-preferring antagonists exacerbated, ischemic cell death (Liu et al., 2007; Chen et al., 2008). Thus it is possible that excessive activation of GluN2B-NMDARs underlies ischemic cell death whereas activity of GluN2A-NMDARs may promote recovery after the ischemic insult.

Although results from preclinical studies were promising, clinical trials with NMDAR antagonists in stroke all ended in disappointment (Lai et al., 2011). Among many contributing factors to failure are intolerable side effects of NMDAR antagonists and the short therapeutic window for their efficacy – the elevated extracellular glutamate level due to reverse operation of glutamate transporters during ischemia appears to last less than an hour (Lai et al., 2011). Consistently, NMDAR antagonists are protective against ischemic cell death when they were administered in animal models prior to (Margaill et al., 1996; Liu et al., 2007; Chen et al., 2008), but not 30 min (Margaill et al., 1996) or 3 h (Liu et al., 2007) after the onset of stroke. However, another study showed that GluN2B antagonist was effective in reducing brain infarct volume when given 2 h after stroke onset (Yang et al., 2003). Rather than inhibiting the NMDARs themselves, it has also been shown that disrupting the interactions between NMDARs and their scaffolding proteins and associated signaling molecules is also effective in reducing cell death in stroke models. Binding to GluN2B-NMDARs by PSD-95, phosphatase and tensin homolog (PTEN) or death-associated protein kinase 1 (DAPK1) can enhance the activity of GluN2B-NMDARs and their coupling to downstream cell death pathways (Aarts et al., 2002; Soriano et al., 2008; Jurado et al., 2010; Tu et al., 2010). Attempts to disrupt these protein interactions of NMDARs using synthetic peptides have been reported to reduce ischemic brain damage in animals (Aarts et al., 2002; Tu et al., 2010; Cook et al., 2012) and even in humans (Hill et al., 2012).

As in stroke, NMDAR antagonists (including selective GluN2B antagonists) have failed so far to show any benefit in TBI (Beauchamp et al., 2008). Although there is clear evidence of elevated extracellular glutamate level in TBI as in stroke, it is likely that the elevation of extracellular glutamate (and hence the period of excitotoxicity) is short-lived and this may contribute to the failure of NMDAR antagonists in clinical trials. In addition, although excessive activation of NMDARs is toxic, physiological activation of NMDARs after TBI may be required for improving functional recovery (Biegon et al., 2004). In summary, the involvement of NMDARs in stroke and TBI is likely to be two-fold – an initial short period of excessive activation which contributes to cell death and tissue damage, and a subsequent much longer phase during which adequate activation of NMDAR is critical for functional recovery. The critical issue that needs to be resolved is whether GluN2B antagonists or GluN2B-PSD-95 interaction inhibitors can work in human cases if treatment is applied early enough after ischemia/TBI. In addition, it will be of great interest to test whether enhancing NMDAR function/activity during the recovery phase will reduce neuronal loss and promote functional recovery.

3. Huntington's disease (HD)

NMDARs are highly expressed in striatal medium spiny neurons (MSNs), the major neuronal population in the striatum that degenerates in HD. Increased levels of extrasynaptic NMDARs in MSNs are seen in an HD mouse model (YAC128) and their activation appears to contribute to the vulnerability of MSNs to excitotoxicity caused by mutant Huntingtin protein (mtHTT; Okamoto et al., 2009; Milnerwood et al., 2010). Interestingly, activation of synaptic NMDARs enhances the formation of non-toxic mtHTT inclusions and reduces mtHTT-induced toxicity (Okamoto et al., 2009). Inhibiting NMDARs with a low dose of the non-selective NMDAR antagonist memantine at ages prior to onset of motor dysfunction reversed deficits in phosphorylated CREB in the striatum and rescued performance in a rotarod assay (Okamoto et al., 2009; Milnerwood et al., 2010). These effects are consistent with the observation that memantine at low doses preferentially inhibits extrasynaptic NMDARs (Xia et al., 2010). However, another study points to a different mode of action for memantine (preferential inhibition of GluN2C/2D-containing NMDARs than GluN2A/2B-NMDARs) (Kotermanski and Johnson, 2009).

The extrasynaptic NMDARs are GluN2B-containing and GluN2B-NMDARs contribute more to total NMDA-evoked current in D2 dopamine receptor-containing MSNs than in D1-containing MSNs in a HD mouse model, consistent with the earlier degeneration of D2 MSNs in HD (Jocoy et al., 2011); and crossing GluN2B-overexpressing mice with HD model mice exacerbates the death of MSNs (Heng et al., 2009). Thus, extrasynaptic GluN2B-NMDARs could play an important role in neuronal cell death in HD. However, in an R6/2 HD mouse model of HD, high doses of GluN2B antagonists did not show significant benefits on either motor behavior or animal survival (Tallaksen-Greene et al., 2010). The lack of efficacy of GluN2B antagonists could be due to antagonists being administered too late (i.e., after the onset of motor dysfunctions), or alternatively, antagonists may also block the beneficial effects mediated by the synaptic GluN2B-NMDARs. Thus, it is important to determine whether GluN2B antagonists are effective in the YAC128 model, or memantine is effective in the R6/2 model. Besides memantine (for which there is still debate about whether it selectively inhibits extrasynaptic NMDARs at low doses), there appears to be no pharmacologic way to specifically block extrasynaptic NMDARs without affecting synaptic NMDARs. Thus, it remains to be established whether GluN2B-NMDARs or extrasynaptic NMDARs have critical contributions to Huntington disease pathogenesis.

4. Alzheimer's disease (AD)

It is widely believed that soluble oligomeric forms of amyloid-β (Aβ) perturb synaptic function and plasticity (Sheng et al., 2012). Long-term potentiation (LTP) is impaired while long-term depression (LTD) is facilitated by Aβ (Ondrejcak et al., 2010). Downstream mediators of Aβ-induced deficits in LTP may include caspase-3 and GSK-3β (Jo et al., 2011). Recent studies indicate that Aβ-induced alterations in synaptic function and plasticity require the activation of GluN2B-NMDARs, as GluN2B antagonists rescued Aβ-induced impairment of LTP (Rönicke et al., 2011; Li et al., 2011b), Aβ-induced loss of synapses and synaptic proteins (Rönicke et al., 2011) (Liu et al., 2010), Aβ-induced facilitation of LTD (Li et al., 2009), and targeting of Aβ to synapses (Deshpande et al., 2009). Further evidence suggests that Aβ affects predominantly the extrasynaptic NMDARs (Li et al., 2009, 2011b), which are largely GluN2B-containing. However, other studies showed that non-selective NMDAR antagonists could also block Aβ-induced spine loss (Shankar et al., 2007) and Aβ-induced deficits in LTP (Rammes et al., 2011), leaving open the possibility that activation of NMDARs in general, rather than GluN2B-NMDARs exclusively, are required for Aβ-induced synaptic dysfunction. Interestingly, the localization of NMDARs appears to determine their contribution to the production of Aβ. For example, stimulation of synaptic NMDARs increased non-amyloidgenic processing of APP by alpha-secretase and inhibited the release of Aβ (Hoey et al., 2009); while activation of extrasynaptic rather than synaptic NMDARs increased neuronal production of Aβ (Bordji et al., 2010). It needs to be emphasized that the above evidence supporting NMDAR/GluN2B-NMDARs' role in Aβ-induced excitotoxicity have largely been obtained using in vitro preparations and synthetic Aβ.

Tau has been shown to be required for localization of fyn tyrosine kinase to dendritic spines, where it phosphorylates GluN2B-NMDARs, thereby enhancing GluN2B-NMDAR association with PSD-95 and coupling to downstream neurotoxic effects (Ittner et al., 2010). One intriguing possibility is that conformational changes in GluN2B-NMDARs, rather than Ca^{2+} influx through these receptors mediate the toxic effects of Aβ (Malinow, 2012; Ittner et al., 2010). Furthermore blocking the interaction between GluN2B and PSD-95 with a synthetic peptide in vivo improved memory functions and reduced premature death in AD mice (Ittner et al., 2010). It is interesting that the same peptide was effective in reducing neuronal death in stroke models (Aarts et al., 2002). It will be important to resolve the contribution of GluN2B-NMDARs to AD by testing whether long-term dosing of GluN2B antagonists is beneficial in animal models of AD.

5. Pain

Neuropathic pain is a type of chronic pain that occurs following injury or damage to neurons or nerves in the nervous system. NMDARs are known to be present in neurons/synapses of the nociceptive pathway, where NMDARs containing distinct subunit compositions show differential expression patterns. GluN2B-NMDARs, but not GluN2A-NMDARs, are present in C-and A-fibers of the dorsal root ganglia (Marvizón et al., 2002). At the spinal cord level, GluN2A-NMDARs are present throughout dorsal horn except in lamina II, while GluN2B-NMDARs appear to be largely absent from lamina II and restricted to certain areas in the superficial dorsal horn (Watanabe et al., 1992; Boyce et al., 1999). Both GluN2A- and GluN2B-NMDARs are widely distributed in the cortex. NMDARs appear to play an important role in neuropathic pain since non-selective NMDAR and GluN2B-selective antagonists have been reported to alleviate neuropathic pain in animals (Wu and Zhuo, 2009; Niesters and Dahan, 2012).

A few key questions need to be resolved regarding the contribution of NMDARs to the development and/or maintenance of neuropathic pain. The first question is subunit composition – which subtype of NMDARs is involved, GluN2B- or GluN2A-NMDARs? As discussed above, the distribution of GluN2A-NMDARs and GluN2B-NMDARs along the nociceptive pathway appears to be different, suggesting potentially differential contributions from these receptors. In neuropathic pain models, reduced GluN2A expression (Karlsson et al., 2002) and increased GluN2B expression (Wilson et al., 2005) in dorsal horn neurons was seen after nerve injury. Does this mean a shift in the balance between GluN2A- and GluN2B-NMDARs (toward elevated GluN2B-NMDARs) could underlie the development of neuropathic pain? Enhanced phosphorylation of GluN2B at the Tyr1472 site was observed after induction of neuropathic pain (Abe et al., 2005), while diminished neuropathic pain was seen in knock-in mice with a mutation preventing phosphorylation of Tyr1472 on GluN2B, which is essential to their synaptic targeting (Matsumura et al., 2010). Neuropathic pain is enhanced in knock-in mice with a mutation of GluN2A that reduces Zn^{2+} inhibition, thereby elevating GluN2A-NMDAR function (Nozaki et al., 2011), suggesting that enhanced GluN2A-NMDAR function could contribute to neuropathic pain. Nevertheless, a different study showed that GluN2A knockout mice can still exhibit neuropathic pain (Abe et al., 2005).

The second critical unresolved question is functional contribution of NMDARs to pain – are NMDARs enabling the induction of synaptic plasticity? Enhanced synaptic transmission is associated with neuropathic pain (Wu and Zhuo, 2009), and one likely mechanism mediating this enhancement is LTP. LTP of synapses in the nociceptive pathway has been proposed to be involved in pathogenesis of neuropathic pain (Sandkühler, 2007). GluN2B-NMDARs in the spinal cord are required for LTP of C-fiber inputs onto dorsal horn neurons (Pedersen and Gjerstad, 2008; Qu et al., 2009) and GluN2A- and GluN2B-NMDARs are required for LTP of cortical inputs to pyramidal neurons in the cingulate cortex (Zhao et al., 2005). Given that synaptic plasticity is thought to occur during the initial stages of chronic pain development, this rationale would predict that the most effective period for NMDAR antagonists (including GluN2B antagonists) to treat pain is during the early stage of pain, as some studies have suggested (Qu et al., 2009).

Clarifying this issue of whether NMDARs are critically involved in the early pain process via LTP is important since clinical trials with GluN2B antagonists have not yielded conclusive results in treating pain (Niesters and Dahan, 2012). It is also debatable whether LTP is required for neuropathic pain at all. LTP in the insulate cortex requires CaMKIV, and CaMKIV KO mice showed impaired LTP but persistent pain was not altered (Wei et al., 2001), suggesting that LTP, at least in the insulate cortex which is part of the nociceptive pathway, is not required for pain.

The last critical question needs to be resolved is the localization of the NMDARs contributing to pain – are the relevant NMDARs in the spinal cord or cortex? Qu et al. (2009) reported that GluN2B-NMDARs in the spinal cord are required for the development of neuropathic pain while Nakazato et al. (2005) concluded that GluN2B-NMDARs in the brain are involved in neuropathic pain. Both studies examined the effects of injecting GluN2B antagonists into either spinal cord or brain. Resolving the above three questions will lead to better understanding of the roles played by NMDARs in neuropathic pain and shed light on whether they are promising therapeutic targets.

6. Schizophrenia

Traditionally, schizophrenia has been considered a disease of hyperdopaminergic nature. Although targeting the dopamine system is effective in treating positive symptoms, like hallucinations, this classic hypothesis does not provide a satisfactory account of the pathophysiology underlying negative symptoms and cognitive deficits, which are not treated effectively by dopamine receptor antagonists and which are increasingly recognized as the core deficits in schizophrenia (Moghaddam and Javitt, 2012; Lewis et al., 2012). Altered glutamate signaling may provide a better pathophysiologic basis for schizophrenia.

The glutamate hypothesis or NMDAR hypofunction hypothesis states that reduced function of glutamatergic synapses, especially of NMDARs on GABAergic inhibitory interneurons, leads to an imbalance between excitation and inhibition and perturbations in neural circuitry that underlie impaired cognitive and executive functions and ultimately psychosis (Moghaddam and Javitt, 2012). The following findings from humans and animal models are consistent with this hypothesis – (1) NMDAR antagonists cause schizophrenia-like symptoms in healthy humans, and exacerbate symptoms in schizophrenics (Coyle, 2006). (2) Reduced expression of NMDARs (GluN2A subunit in particular) has been observed in a subpopulation of inhibitory neurons (notably those expressing parvalbumin) in postmortem samples of schizophrenia patients (Bitanihirwe et al., 2009). (3) Mice with reduced GluN1 expression showed schizophrenia-like phenotypes (Mohn et al., 1999). More importantly, many of these phenotypes could be reproduced in mice with GluN1 selectively deleted from a sub-population of GABAergic interneurons (the majority of which contain parvalbumin; Belforte et al., 2010), suggesting that deficient NMDAR function in a subclass of inhibitory interneurons may be sufficient to drive the pathophysiology of schizophrenia. Inhibition of NMDAR function led to decreased expression of parvalbumin in parvalbumin-containing inhibitory neurons, with GluN2A-preferring antagonist being more effective than GluN2B antagonist (Kinney et al., 2006). This reduction in parvalbumin is similar to what has been observed in post-mortem schizophrenia brain samples while the density of these parvalbumin-containing neurons is unchanged (Lewis et al., 2005). Thus, enhancing NMDAR functions could potentially boost the decreased activity/function of inhibitory neurons, rebalance neural circuitry and improve cognitive functions in schizophrenia patients.

Clinical trials with glycine or D-serine (which target the glycine co-agonist site in NMDARs) aiming to enhance the activity and function of the glutamate system have produced mixed results (Coyle, 2006; Lindsley et al., 2006). There are also ongoing efforts to boost extracellular glycine levels in the brain by inhibiting glycine uptake with glycine transporter-1 (GlyT-1) inhibitors, thereby enhancing NMDAR function (Lindsley et al., 2006). However, it is unknown whether the potential benefits of enhancing NMDAR function (such as by GlyT-1 inhibitors) in schizophrenia is mediated by enhanced activation of inhibitory or excitatory neurons. Excitatory synapses onto interneurons may have a specific composition of NMDAR subtypes (e.g., enriched with GluN2A/2D, Monyer et al., 1994), raising the possibility that inhibitory neurons could be selectively targeted by subunit-selective NMDAR modulators. Regardless of mechanism, one challenge ahead is whether reversing NMDAR hypofunction in the adult schizophrenic brain is sufficient to compensate for the malfunctions that might have accumulated over years during development.

7. Depression

The non-selective NMDAR antagonist ketamine produced rapid (within hours) and sustained reduction (for days) in depressive symptoms in human patients with treatment-resistant depression (Berman et al., 2000; Zarate et al., 2006). The rapid onset is in clear contrast to traditional antidepressants such as selective serotonin reuptake inhibitors (SSRIs). In animals, it was found that low doses of ketamine led to an increase in spine density, enhanced mammalian target of rapamycin (mTOR) signaling and increased protein synthesis in the prefrontal cortex, which accompanied the antidepressant effects (Li et al., 2010). This is consistent with reports of reduced expression of mTOR and its downstream signaling targets in postmortem brain samples from depressed patients (Jernigan et al., 2011). Another study also showed that protein synthesis is required for the fast-acting antidepressant effect of ketamine in animals but the target identified was BDNF rather than mTOR (Autry et al., 2011).

Ketamine reduces the spontaneous activity of GABAergic inhibitory neurons, which leads to a delayed increase in the activity of excitatory neurons in conscious rats (Homayoun and Moghaddam, 2007). Thus one possible target of NMDAR antagonists in depression could again be the GABAergic interneurons. Reducing inhibitory tone could cause immediate effects on the neural circuitry function (such as enhanced neural activity), which could set in motion the cellular signaling events that underlie long-lasting alterations in neural circuitry that mediate antidepressant effects. Interestingly, in the same animal models, GluN2B antagonists triggered similar signaling pathways and also showed antidepressant effects (Li et al., 2010, 2011a), suggesting that inhibiting the activity of GluN2B-NMDARs could account for the majority of the antidepressant effects of ketamine. As an alternative to affecting interneuron functions, GluN2B antagonists could exert their effects by altering the activity of mTOR. In a recent study, Wang et al. (2011) showed that in genetically modified mice by replacing GluN2B with GluN2A, there was an enhanced expression of synaptic AMPARs via activation of mTOR signaling, which resembled ketamine-induced changes. Thus, it remains unclear whether GluN2B antagonists are acting primarily on interneurons or excitatory neurons (or both) to effect their antidepressant action.

8. Concluding remarks

NMDAR dysfunction is emerging as a common theme in several major nervous system disorders. Future studies to elucidate how NMDARs with distinct subunit compositions contribute differentially to nervous system diseases – as well as the specific subsynaptic locations and circuits in which these NMDARs operate –

could inform not only about the pathophysiology but also the potential treatment of ischemic brain injury, chronic neurodegenerative diseases, pain, depression and schizophrenia.

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