Symposium

Unconventional NMDA Receptor Signaling

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In the classical view, NMDA receptors (NMDARs) are stably expressed at the postsynaptic membrane, where they act via Ca^{2+} to signal coincidence detection in Hebbian plasticity. More recently, it has been established that NMDAR-mediated transmission can be dynamically regulated by neural activity. In addition, NMDARs have been found presynaptically, where they cannot act as conventional coincidence detectors. Unexpectedly, NMDARs have also been shown to signal metabotropically, without the need for Ca^{2+}. This review highlights novel findings concerning these unconventional modes of NMDAR action.

Key words: **Alzheimer's disease; LTD; LTP; metabotropic NMDA receptor; presynaptic NMDA receptor; short-term plasticity**

Introduction

The *N*-methyl-D-aspartate (NMDA) receptor (NMDAR), a member of the glutamate-gated cation channel family, is ubiquitously expressed in the brain (Moriyoshi et al., 1991), where it plays numerous roles, most notably in neurodevelopment, synaptic transmission and plasticity, and learning and memory (Traynelis et al., 2010; Paoletti et al., 2013; Iacobucci and Popescu, 2017). NMDARs consist of a tetrameric subunit structure, conventionally comprised of two GluN1 and two GluN2 subunits that confer Ca^{2+} permeability and Mg^{2+} sensitivity (Traynelis et al., 2010; Paoletti et al., 2013; Iacobucci and Popescu, 2017). However, NMDARs can also include other subunits and alternative splice variants, which greatly affect receptor kinetics, trafficking, and signaling properties. For example, GluN3 is typically expressed early in development and confers unconventional properties, such as Mg^{2+} insensitivity and low Ca^{2+} conductance, with important implications for synapse maturation and plasticity (Pérez-Otaño et al., 2016). Until recently, NMDAR functions have generally been attributed to their ability to conduct Ca^{2+} ions at the postsynapse, where their stability and function were thought to be unperturbed by neural activity.

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Here, we start by discussing several independent studies demonstrating that NMDAR-mediated transmission can be modified in an activity-dependent manner (Lau and Zukin, 2007; Rebola et al., 2011; Hunt and Castillo, 2012). Next, we describe how presynaptic NMDARs (preNMDAR), which have been found at several synapse types in the brain (Duguid and Sjöström, 2006; Banerjee et al., 2016), signal differentially to control evoked and spontaneous release independently. Finally, we highlight emerging evidence that NMDARs can signal independent of ion flow, focusing on recent findings demonstrating that glutamate binding to the NMDAR is sufficient to induce LTD of synaptic transmission (Nabavi et al., 2013) and shrinkage of dendritic spines (Stein et al., 2015), likely through conformational change in the NMDAR intracellular domain (Aow et al., 2015; Dore et al., 2015). We end with a discussion of potential roles of unconventional NMDAR signaling in synaptic diseases, such as Alzheimer's disease, ischemia, and schizophrenia (Lau and Zukin, 2007; Paoletti et al., 2013), highlighting evidence that metabotropic NMDAR signaling may contribute to Alzheimer's disease (Kessels et al., 2013; Tamburri et al., 2013; Birnbaum et al., 2015). Even though NMDARs feature prominently in textbooks on cellular learning and information storage in the brain, these novel unconventional modes of NMDAR signaling are still hotly debated. The complete elucidation of the many different modes of NMDAR signaling is therefore of utmost importance for understanding and treating these diseases.

Activity-dependent synaptic plasticity of NMDARs

NMDARs are traditionally thought to act postsynaptically as coincidence detectors of presynaptic glutamate release and postsynaptic depolarization for the induction of LTP and LTD of AMPAR-mediated transmission, during which NMDAR-mediated transmission was thought to remain stable (Lüscher and Malenka, 2012). Postsynaptic NMDARs also have well-established roles in synaptic transmission (Daw et al., 1993) and neuronal integra-

tion (Larkum and Nevian, 2008; Major et al., 2013) via their slow kinetics, Mg^{2+}-dependent nonlinear amplification at resting potential, and high Ca^{2+} permeability (McBain and Mayer, 1994; Traynelis et al., 2010; Iacobucci and Popescu, 2017). Growing evidence, however, demonstrates that postsynaptic NMDARs themselves can be regulated in an activity-dependent manner; indeed, both LTP and LTD of NMDAR-mediated transmission have been reported throughout the brain (Lau and Zukin, 2007; Rebola et al., 2011; Hunt and Castillo, 2012). Furthermore, pioneering studies have revealed that GluN2 subunit trafficking is influenced by NMDAR agonists (Vissel et al., 2001; Barria and Malinow, 2002) and coagonists (Nong et al., 2003; Ferreira et al., 2017). Changes in NMDAR function or expression would modify the induction threshold of AMPAR-mediated plasticity, thereby mediating metaplasticity (Abraham, 2008), and also would alter NMDAR-mediated functions in homeostatic plasticity (Pérez-Otaño and Ehlers, 2005). Thus, NMDAR plasticity is expected to play important roles in normal brain function.

Synaptic plasticity of NMDARs has been reported by several groups using diverse stimulation paradigms in several different brain areas. NMDAR-LTP can be coinduced with AMPAR plasticity, and develops more slowly both in neocortex (Watt et al., 2004) and hippocampus (Muller and Lynch, 1988; Xiao et al., 1995; Peng et al., 2010). Similarly, AMPAR and NMDAR LTD can coinduce at a number of synapses (Hunt and Castillo, 2012). Remarkably, NMDAR plasticity can also occur independently of AMPAR plasticity. For example, brief bursts of synaptic activity elicit NMDAR-LTP at the mossy fiber to CA3 pyramidal cell synapse (Hunt et al., 2013). Some synapses can also undergo bidirectional NMDAR plasticity, for example, mossy fiber synapses (Hunt et al., 2013) and glutamatergic synapses onto midbrain dopaminergic neurons (Harnett et al., 2009).

Mechanistically, the induction and expression of NMDAR plasticity share common properties across synapses (Hunt and Castillo, 2012). For example, induction typically requires coactivation of NMDARs and mGluR1/5 (Kotecha et al., 2003; Lau and Zukin, 2007). Whereas mGluR5 is essential for NMDAR-LTP, mGluR1 is essential for NMDAR-LTD (Hunt et al., 2013; Bhouri et al., 2014). Chemical NMDAR-LTD can be induced by exogenous activation of mGluR1/5 (Ireland and Abraham, 2009) and other Gq-coupled receptors, such as mAChRs (Jo et al., 2010), and orexin-2 receptors (Perin et al., 2014). Induction of NMDAR-LTP and LTD also requires postsynaptic NMDAR-mediated Ca^{2+} influx and Ca^{2+} release from internal stores. The sign of NMDAR plasticity appears to depend on the free Ca^{2+} concentration during the induction (Harney et al., 2006). While PKC, PKA, and Src kinases are involved in NMDAR-LTP induction, the Ca^{2+} targets that mediate NMDAR-LTD are less clear. Protein phosphatase-1 (PP1)/protein phosphatase-2A (PP2A) are required for NMDAR-LTD (Morishita et al., 2005), whereas the Ca^{2+} sensor hippocalcin has been implicated in mAChR-mediated LTD (Jo et al., 2010). Expression of NMDAR-LTP relies on increased synaptic NMDAR surface expression (Grosshans et al., 2002; Kwon and Castillo, 2008) and synaptic recruitment of extrasynaptic NMDARs (Harney et al., 2008). NMDAR-LTD may involve dynamin-dependent endocytosis of NMDARs (Montgomery and Madison, 2002; Montgomery et al., 2005; Jo et al., 2010; Hunt et al., 2013) as well as Ca^{2+}-dependent actin depolymerization, which likely promotes cytoskeletal destabilization and lateral NMDARs diffusion to extrasynaptic sites (Morishita et al., 2005; Ireland and Abraham, 2009; Peng et al., 2010). Last, in addition to strengthening or weakening of NMDAR transmission, NMDAR plasticity may involve changes in receptor properties as a result of an activity-dependent shift in receptor subunit composition (Bellone and Nicoll, 2007; Harney et al., 2008; Peng et al., 2010; Matta et al., 2011).

The functional consequences of NMDAR plasticity are profound and may include not only metaplasticity but also changes in neuronal integrative properties. At hippocampal mossy fibers, where NMDAR-LTP can occur in the absence of AMPAR-LTP (Kwon and Castillo, 2008; Rebola et al., 2008), NMDAR-LTP is a prerequisite for induction of NMDAR-dependent AMPAR-LTP (Rebola et al., 2011). Bidirectional NMDAR plasticity contributes to fidelity of mossy fiber-driven CA3 pyramidal cell spiking, and also modulates LTP at neighboring synapses (Hunt et al., 2013). These forms of plasticity may thus determine memory encoding and retrieval by the dentate-CA3 circuit (Rebola et al., 2017). In hippocampal cultures, prolonged suppression of spontaneous glutamate release upregulates AMPARs via postsynaptic store-driven Ca^{2+} signaling (Reese and Kavalali, 2015) but also NMDARs, thereby augmenting spine Ca^{2+} to facilitate AMPAR-LTP induction (Lee et al., 2010), indicating that NMDAR plasticity can act homeostatically over longer timescales. In addition to acting as triggers of AMPAR-LTP/LTD, NMDARs also mediate inhibitory synaptic plasticity (Castillo et al., 2011). NMDAR plasticity could therefore modulate neural circuits via inhibition. Although NMDAR plasticity has been extensively studied *in vitro*, a future challenge is to determine the precise contribution of this form of plasticity *in vivo*.

PreNMDAR-mediated regulation of neurotransmitter release

In the canonical view, NMDARs induce Hebbian LTP by fluxing Ca^{2+} when simultaneously glutamate bound and depolarized, and also contribute to dendritic integration (Maheux et al., 2015), which requires NMDARs be located postsynaptically (Duguid and Sjöström, 2006). Yet, presynaptically located NMDARs (preNMDARs) have been reported for decades: cortex (Berretta and Jones, 1996; Sjöström et al., 2003), spinal cord (Liu et al., 1994), hippocampus (Siegel et al., 1994; McGuinness et al., 2010), and cerebellum (Casado et al., 2000; Bidoret et al., 2009). Curiously, these Mg^{2+}-sensitive preNMDARs are opened by glutamate and depolarization of presynaptic origin (but see Larsen et al., 2011), which means they cannot act in classical Hebbian plasticity, suggesting that these mysterious receptors play other roles (Duguid and Sjöström, 2006; Banerjee et al., 2016). For example, preNMDARs have been shown to modulate neurotransmitter release, affecting spontaneous (Berretta and Jones, 1996; Sjöström et al., 2003; Kunz et al., 2013) as well as evoked release, both short- and long-term (Sjöström et al., 2003; Duguid and Smart, 2004; Bidoret et al., 2009; McGuinness et al., 2010; Buchanan et al., 2012).

Adding further to the mystery, Mg^{2+}-blocked preNMDARs should only be activated at sufficiently high presynaptic frequencies, yet this is not always the case. These presumed autoreceptors should require high presynaptic firing rates to activate because by the time they are glutamate bound, the presynaptic spike should be gone, thus requiring depolarization from the next spike (Duguid and Sjöström, 2006; Banerjee et al., 2016). In agreement, several studies have found frequency dependencies (Sjöström et al., 2003; Bidoret et al., 2009; McGuinness et al., 2010). However, preNMDARs also regulate spontaneous release, which generally occurs at very low frequencies, resulting in a long-standing conundrum in the field (Sjöström et al., 2003; Brasier and Feldman, 2008; Banerjee et al., 2016). Some resolution was provided by the discovery that GluN3A-containing preNMDAR types are insensitive to Mg^{2+} (Larsen et al., 2011; but see Pérez-Otaño et al., 2016), and that preNMDAR control of spontaneous release is

not Ca^{2+}-sensitive (Kunz et al., 2013) (Fig. 1), suggesting a dichotomy in preNMDAR regulation of evoked and spontaneous release. Indeed, differential regulation of spontaneous and evoked release is likely a general principle in the brain (Kavalali, 2015).

To help resolve this conundrum (Sjöström et al., 2003; Brasier and Feldman, 2008; Banerjee et al., 2016), the P.J.S. laboratory explored how preNMDARs signal to regulate evoked and spontaneous release in visual cortex layer 5 pyramidal cells. They found that preNMDAR regulation of evoked release was sensitive to Mg^{2+} and presynaptic firing frequency, whereas preNMDAR control of spontaneous release was Mg^{2+} independent (Abrahamsson et al., 2017), suggesting that preNMDARs might signal metabotropically (Nabavi et al., 2013; see below) to control spontaneous release (Abrahamsson et al., 2017). Consistent with differential preNMDAR signaling in evoked versus spontaneous release, preNMDAR regulation of evoked neurotransmission maintained release probability during high-frequency firing by increasing the replenishment rate of the readily releasable pool, instead of directly affecting release probability, as might be expected from the regulation of spontaneous release (Fig. 1) (Abrahamsson et al., 2017).

Moreover, two proteins, Rab3-interacting molecule 1 (RIM1) (Südhof, 2012) and c-Jun-N-terminal kinase 2 (JNK2) (Nisticò et al., 2015), were differentially required for preNMDAR control of evoked and spontaneous neurotransmission, respectively, in a nonoverlapping manner (Fig. 1) (Abrahamsson et al., 2017). Conditional RIM1$\alpha\beta$ deletion thus abolished preNMDAR control of evoked release without impacting that of spontaneous release (Fig. 1). Conversely, pharmacological JNK2 blockade abolished preNMDAR control of spontaneous release (as previously shown in entorhinal cortex) (Nisticò et al., 2015) without having an effect on preNMDAR regulation of evoked release (Fig. 1). These findings thus revealed a double dissociation in preNMDAR signaling (Fig. 1), providing resolution to the conundrum of how preNMDARs may control evoked release at high frequencies while still affecting spontaneous release at low rates (Sjöström et al., 2003; Brasier and Feldman, 2008; Banerjee et al., 2016).

In summary, preNMDARs may control spontaneous release independently of Mg^{2+} and Ca^{2+} (Kunz et al., 2013; Abrahamsson et al., 2017) while regulating evoked release in a frequency-dependent manner by relying on the more conventional Mg^{2+}-dependent pathway (Fig. 1). These findings provide a foundation for further exploration of preNMDAR signaling (Abrahamsson et al., 2017), which is presently poorly understood.

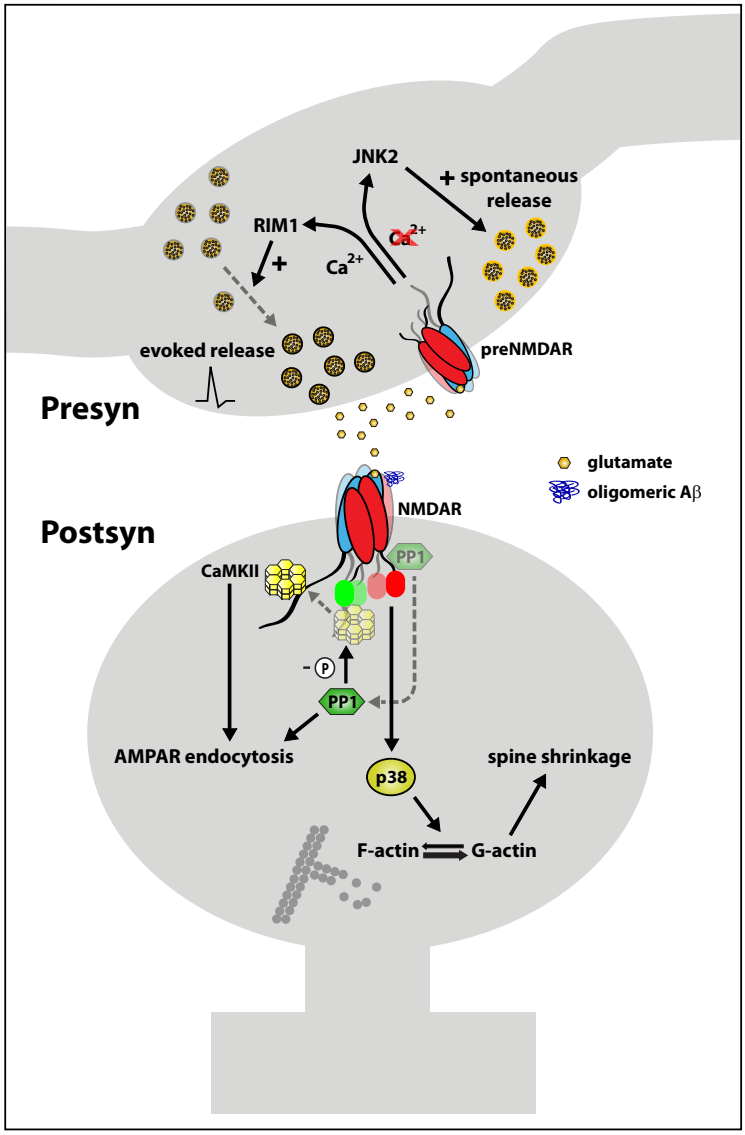

Figure 1. Recent discoveries of novel unconventional NMDAR signaling modes indicate that our view of this receptor type may need to be expanded. Mg^{2+}-blocked presynaptic NMDARs (preNMDAR) rely on RIM1 to control, in a frequency-dependent manner, the replenishment rate of the readily releasable pool of vesicles. Control of spontaneous release by preNMDARs, however, is not sensitive to Mg^{2+} or Ca^{2+} and relies on JNK2. Postsynaptic NMDARs can act as coincidence detectors for Hebbian plasticity of AMPARs, but plasticity of NMDARs can also be coinduced and likely plays important roles. Moreover, several studies suggest that, if ion flux is blocked through postsynaptic NMDARs, they can still signal metabotropically. Upon glutamate binding, movement in the NMDAR cytoplasmic domain may permit PP1 catalytic access to phospho-CaMKII-T286 and, in parallel, activation of p38 MAPK. These (and other) signaling molecules can eventually lead to LTD: AMPAR removal and spine shrinkage. Furthermore, elevated amyloid-β can depress synaptic transmission and cause spine elimination in a manner that is dependent on glutamate binding to, but not ion flux through, NMDARs. All signaling modes need not coexist at the same synapse type.

Metabotropic NMDAR signaling in LTD

The complex pharmacology of NMDARs suggests that their function can be regulated in many different ways. Classically, it was thought that the presence of several binding sites provided the coincidence detection properties of NMDARs (ion-flux is only permitted when neurotransmitters are bound and the cell is depolarized to remove the Mg^{2+} block). However, several studies have revealed that binding of NMDAR agonists (Vissel et al., 2001; Barria and Malinow, 2002) or coagonists (Nong et al., 2003; Ferreira et al., 2017) can affect trafficking of GluN2 subunits without ion-flux. Furthermore, growing evidence supports the view that glutamate binding alone can induce LTD of AMPAR-mediated transmission, suggesting that the NMDAR has a

metabotropic function, distinct from its ion channel role. Interestingly, early reports of non-ionotropic NMDAR signaling came >20 years ago, when two different groups showed that MK-801, which blocks the NMDAR channel pore, abolished LTP but not LTD (Mayford et al., 1995; Scanziani et al., 1996). These surprising observations were not discussed in either study, probably because a model suggesting that LTD required moderate increases in intracellular Ca^{2+} was already proposed (Bröcher et al., 1992; Malenka, 1994).

A few years ago, this model was challenged by a study where the ion-flux dependence of LTD was examined more closely (Nabavi et al., 2013). Low-frequency stimulation produced LTD in the presence of either MK-801 or 7-chlorokynurenate (7-CK), two antagonists abolishing NMDAR ion flux without affecting the glutamate binding site, but not APV, which is a competitive GluN2 antagonist blocking the glutamate binding site. This surprising finding was subsequently challenged by some recent studies (Babiec et al., 2014; Volianskis et al., 2015; Sanderson et al., 2016) but confirmed by others (Kim et al., 2015; Stein et al., 2015). It was proposed that these discrepancies were due to differences in methodology (Nabavi et al., 2014). Moreover, LTD was observed in experiments in which intracellular Ca^{2+} was clamped to basal levels (Nabavi et al., 2013), in contrast to those earlier studies in which intracellular Ca^{2+} was completely depleted (Bröcher et al., 1992), suggesting that a rise in intracellular Ca^{2+} is not required for LTD. It was thus proposed that glutamate binding to the NMDAR could induce a conformational change in the cytoplasmic domain of the NMDAR that triggers downstream signaling resulting in LTD.

To explore the metabotropic function of NMDARs in LTD, FRET-FLIM (Förster resonance energy transfer measured by fluorescence lifetime imaging of the FRET donor) (Wallrabe and Periasamy, 2005; Yasuda, 2006) was used (Dore et al., 2015). Recombinant GluN1 subunits of NMDARs were tagged with GFP or mCherry at their carboxyl(c)-terminus and coexpressed in neurons. A transient change in FRET consistent with conformational movement of the NMDAR cytoplasmic domain was measured during NMDA bath application or glutamate uncaging in the presence of MK801 and 7CK, but not APV (Dore et al., 2015; independently replicated by Ferreira et al., 2017) (Fig. 1). Infusing neurons with a GluN1 c terminus antibody through a patch pipette blocked changes in FRET and LTD. Together, these findings suggest that conformational changes in the NMDAR, without its ionotropic function, are necessary for LTD induction (Aow et al., 2015).

PP1 may signal downstream of NMDARs as it was shown to be necessary for LTD induction (Mulkey et al., 1993) and coimmunoprecipitated with NMDAR complexes (Husi et al., 2000). LTD induction transiently reduced FRET between GluN1-GFP and PP1-mCherry in a manner that required NMDAR conformational movement but not PP1 activity (Aow et al., 2015). The transient movement of PP1 relative to the NMDAR cytoplasmic domain may expose the catalytic active site of PP1 to an otherwise unreachable target. CaMKII, one potential target, is required for both LTP and LTD. Changes in FRET between CaMKII and GluN1 was observed in ion-flux independent LTD in a PP1-dependent fashion; a phosphomimetic form of CaMKII suggested that dephosphorylation of the Thr-286 residue was required to modify the CaMKII-NMDAR interaction (Fig. 1; Aow et al., 2015). These findings provide evidence for NMDAR-mediated ion-flux-independent LTD that is mediated by PP1-driven dephosphorylation of CaMKII, leading to changes in CaMKII position within the NMDAR complex (Aow et al., 2015). This may allow CaMKII to act on a novel site of the GluA1 subunit (Ser-567) that undergoes phosphorylation during LTD (Coultrap et al., 2014). Consistent with this model, CaMKII phosphorylation of GluA1-Ser-567 did not require Ca^{2+} or calmodulin (Coultrap et al., 2014), and may result in increased AMPAR endocytosis and decreased synaptic transmission (Lüscher et al., 1999; Lin et al., 2000; Kim et al., 2001; Shi et al., 2001).

Metabotropic NMDAR signaling in structural plasticity

Independent support for a non-ionotropic NMDAR signaling mechanism in driving synaptic depression came from the identification that such a mechanism also can regulate the structural plasticity of dendritic spines. Synaptic function and dendritic spine size are closely coupled (Matsuzaki et al., 2001), and the induction of synaptic depression has been shown to be tightly correlated with decreased spine size (Okamoto et al., 2004; Zhou et al., 2004; Hayama et al., 2013; Oh et al., 2013). Notably, a recent report demonstrated that input-specific NMDAR-dependent shrinkage of individual dendritic spines in response to low-frequency glutamate uncaging (Oh et al., 2013) persisted even in the presence of the NMDAR glycine/D-serine binding site antagonist 7-CK (Stein et al., 2015), supporting a non-ionotropic mechanism for spine shrinkage. Furthermore, block of ion flow through the NMDAR by application of 7CK or MK-801 during high-frequency uncaging, converted high-frequency uncaging-induced spine enlargement into spine shrinkage (Stein et al., 2015), consistent with the finding that high-frequency stimulation in the presence of MK-801 induced LTD instead of LTP (Nabavi et al., 2013). Importantly, the direct stimulation of individual spiny synapses through glutamate uncaging bypassed the requirement of presynaptic glutamate release and avoided effects of the pharmacological inhibitors on preNMDARs. Uncaging-induced spine shrinkage in the presence of 7-CK was independent of Group I mGluR (Stein et al., 2015) and AMPAR activation (I.S.S., unpublished observation). Inhibition of p38 MAPK signaling, which has been implicated in both NMDAR- and mGluR-dependent LTD (Bolshakov et al., 2000; Zhu et al., 2002; Huang et al., 2004; Nabavi et al., 2013) and has been recently reported to be necessary for the cofilin-dependent reorganization of the actin cytoskeleton during mGluR-dependent LTD (Eales et al., 2014), blocked non-ionotropic NMDAR-mediated spine shrinkage (Stein et al., 2015). Thus, p38 MAPK signaling is essential for non-ionotropic NMDAR signaling in structural and functional plasticity. These results clearly demonstrate that non-ionotropic NMDAR signaling is sufficient to drive both functional and structural synaptic depression.

Unconventional NMDAR signaling and disease

The dysregulation of NMDAR-dependent plasticity mechanisms has been associated with neuropsychiatric and neurodegenerative diseases (Lau and Zukin, 2007; Paoletti et al., 2013), and recent findings implicated unconventional NMDAR signaling. In Alzheimer's disease, early synaptic dysfunction is associated with increased levels of oligomeric amyloid-β (Aβ) protein, which causes a rapid NMDAR-dependent synaptic depression and spine elimination in model systems (Hsieh et al., 2006; Shankar et al., 2007, 2008; Wei et al., 2010). Indeed, dendritic spine loss in the cerebral cortex is one of the first structural changes that can be observed in the early stages of Alzheimer's disease, and the amount of spine loss is correlated with cognitive decline (DeKosky and Scheff, 1990; Terry et al., 1991; Selkoe, 2002). Notably, this NMDAR-dependent, Aβ-induced synaptic depression and spine elimination are also independent of ion flow through the NMDAR

(Kessels et al., 2013; Tamburri et al., 2013; Birnbaum et al., 2015). Although Aβ-induced spine elimination was blocked in the presence of the NMDAR glutamate binding site antagonist APV, it was unaffected by the channel pore blockers MK-801 or memantine. Interestingly, the conformation of the NMDAR cytoplasmic domain was also affected by Aβ, in a similar manner as during LTD induction (K.D., unpublished observation). Consistent with the idea that LTD and Aβ-induced depression share common signaling mechanisms (Hsieh et al., 2006), p38 MAPK signaling is also involved in Aβ-induced spine elimination, as phosphorylation of p38 MAPK increased with Aβ treatment and block of p38 activity prevented Aβ-induced spine elimination (Birnbaum et al., 2015). Together, these findings strongly implicate unconventional, ion-flow-independent NMDAR signaling in the etiology of Alzheimer's disease.

Abnormalities in NMDAR signaling, specifically a dysregulation or hypofunction of NMDARs, have also been implicated in schizophrenia (Coyle, 2006). Schizophrenia is a complex, heterogeneous neuropsychiatric disorder with deficits in executive and cognitive function. Neuropathological studies have reported an increased dendritic spine loss in specific cortical regions, including the hippocampus (Penzes et al., 2011; Glausier and Lewis, 2013; Konopaske et al., 2014). Notably, reduced levels of the synaptic NMDAR coagonist D-serine and polymorphisms of genes involved in the regulation of endogenous D-serine levels have been found in schizophrenic patients (Hashimoto et al., 2005; Goltsov et al., 2006; Bendikov et al., 2007; Morita et al., 2007; Balu et al., 2013). Furthermore, increased levels of kynurenic acid, an endogenously occurring NMDAR glycine/D-serine binding site antagonist, also have been reported in patients with schizophrenia (Plitman et al., 2017). The consequences of reduced availability or access of the requisite NMDAR coagonist glycine/D-serine are expected to be similar to those found following the experimental application of 7-CK (a derivative of kynurenic acid). Reduced Ca^{2+}-influx through the NMDAR will favor non-ionotropic NMDAR signaling, leading to synaptic depression and spine shrinkage, which could contribute to the observed decrease of dendritic spine number and cognitive deficits in patients with schizophrenia.

Recent work has also revealed a role for metabotropic NMDAR signaling in excitotoxicity and ischemic stroke (Weilinger et al., 2016). In the classical view, ligand-gated Ca^{2+}-permeable NMDARs cause excitotoxicity and neuronal death (Paoletti et al., 2013). However, metabotropic NMDAR signaling together with sarcoma (Src) kinase and pannexin-1 (Panx1) channels have been directly linked to membrane blebbing, mitochondrial dysfunction, and cell death as well as neurological deficits after stroke (Weilinger et al., 2016). This exciting finding may provide novel candidate targets for alleviating ischemic brain damage.

We have provided examples of unorthodox NMDAR signaling in three major neurological pathologies: Alzheimer's, schizophrenia, and stroke. Further investigation of unconventional NMDAR signaling will lead to a deeper understanding of how NMDAR dysregulation contributes to neuropsychiatric and neurodegenerative disease.

Concluding Remarks and Future Directions

In conclusion, we have highlighted here several unorthodox NMDAR signaling modes, metabotropic as well as presynaptic, in the regulation of synaptic structural and functional plasticity that reach beyond the well-described conventional postsynaptic ionotropic roles for NMDAR signaling (Traynelis et al., 2010; Paoletti et al., 2013; Maheux et al., 2015; Iacobucci and Popescu, 2017). Prior studies concluding ionotropic NMDAR function, often based on postsynaptic Ca^{2+} chelation, may need to be revisited in light of new findings supporting metabotropic NMDAR functions (Nabavi et al., 2013; Aow et al., 2015; Dore et al., 2015; Stein et al., 2015; Latif-Hernandez et al., 2016). Furthermore, some findings attributed to postsynaptic NMDAR blockade might be due to preNMDARs (Duguid and Sjöström, 2006; Banerjee et al., 2016), and vice-versa (Carter and Jahr, 2016). In the future, it will be important to elucidate the molecular basis of NMDAR plasticity, and the downstream signaling cascades of preNMDARs and of metabotropic NMDAR signaling, as these may provide novel drug targets for more specific treatments of several devastating neurological disorders. It will also be important to further elucidate the functional roles of different NMDAR subunits, in particular the GluN3 subunit, because it confers resistance to Mg^{2+} blockade (Pérez-Otaño et al., 2016). No matter what the findings are, it is amply clear that a thorough understanding of NMDAR functioning requires increased attention to, and further study of, unconventional modes of NMDAR action.

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