



Review

Presynaptic NMDA receptors: Are they dendritic receptors in disguise?

Ian C. Duguid*

Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh EH8 9XD, Scotland, UK

ARTICLE INFO

Article history:

Received 7 November 2012

Received in revised form

19 December 2012

Accepted 20 December 2012

Available online 29 December 2012

Keywords:

Presynaptic

NMDA receptor

Release probability

Synapse-specific

ABSTRACT

The N-methyl-D-aspartate (NMDA) receptor plays an essential role in excitatory transmission, synaptic integration, and learning and memory. In the classical view, postsynaptic NMDA receptors act as canonical coincidence detectors providing a 'molecular switch' for the induction of various forms of short- and long-term synaptic plasticity. Over the past twenty years there has been accumulating evidence to suggest that NMDA receptors are also expressed presynaptically and are involved in the regulation of synaptic transmission and specific forms of activity-dependent plasticity in developing neural circuits. However, the existence of presynaptic NMDA receptors remains a contentious issue. In this review, I will discuss the criteria required for identifying functional presynaptic receptors, novel methods for probing NMDA receptor function, and recent evidence to suggest that NMDA receptors are expressed at presynaptic sites in a target-specific manner.

© 2013 Elsevier Inc. All rights reserved.

Contents

1. Introduction	4
2. Criteria for defining presynaptic receptors	5
3. Controversy surrounding locus of NMDA receptor expression	5
4. Novel methods for probing NMDA receptor function	6
4.1. Caged MK-801	6
4.2. Caged NMDA and bouton calcium imaging	6
5. Target-specific expression of presynaptic NMDA receptors	6
6. Functional role of presynaptic NMDA receptors	7
7. Future directions	7
References	8

1. Introduction

The activity-dependent modulation of synaptic efficacy is an important mechanism for enhancing the computational power of neural circuits in the brain. The strength of communication between individual neurons can be regulated by modifying the: postsynaptic receptor number or responsiveness; number of synaptic release sites or contacts; or the release probability at individual synapses. Classically, presynaptic metabotropic receptors such as GABA_B, endocannabinoid and metabotropic glutamate receptors are thought to regulate the probability of neurotransmission through G-protein-coupled signalling pathways that affect presynaptic ion channel function or the presynaptic release machinery (Kandel and Schwartz, 1982; Schlicker and Kathmann,

2001). Over the past two decades there has been growing evidence to suggest that ionotropic glutamate receptors are also expressed at presynaptic loci and may be involved in the regulation of synaptic transmission and activity-dependent synaptic plasticity (Khakh and Henderson, 2000; Langer, 2008; MacDermott et al., 1999). One such example is the N-methyl-D-aspartate (NMDA)-sensitive glutamate receptor, which was first proposed to have a presynaptic locus of expression after exogenous application of NMDA facilitated the release of tritiated neurotransmitter from synaptosomes prepared from noradrenergic terminals in the hippocampus (Pittaluga and Raiteri, 1992), cerebral cortex (Fink et al., 1990) and from dopaminergic terminals in the striatum (Johnson and Jeng, 1991; Krebs et al., 1991; Wang, 1991). Further evidence for the existence of presynaptic NMDA receptors came from pioneering immunohistochemical studies that identified GluN1 and GluN2 subunit expression on axon terminals in the spinal cord (Liu et al., 1994), cerebral cortex (Petralia et al., 1994a,b) and at mossy fibre-CA3 synapses in monkey hippocampus (Siegel et al., 1994). Although

* Tel.: +44 131 650 3113; fax: +44 131 650 2872.

E-mail address: Ian.Duguid@ed.ac.uk

these studies provided an important step towards the identification of presynaptic NMDA receptors, they failed to determine their exact locus of expression or functional significance. These preliminary findings paved the way for a plethora of studies focused on establishing the existence of presynaptic NMDA receptors and their role in regulating synaptic transmission and plasticity throughout the CNS (Duguid and Sjöström, 2006; Corlew et al., 2008; Duguid and Smart, 2009). However, even after twenty years of rigorous research the existence of ‘presynaptic’ NMDA receptors remains a contentious issue generating fierce debate.

In this review, I will discuss the different criteria required to define presynaptic receptors and recent contradictory results that have fuelled the debate over the presence of NMDA receptors at presynaptic sites. I will then discuss how the combined use of patch clamp electrophysiology, multi-photon imaging and uncaging techniques has provided important new insights into the synapse-specific expression of presynaptic NMDA receptors and their role in activity-dependent modulation of synaptic transmission.

2. Criteria for defining presynaptic receptors

To classify a receptor as having a presynaptic locus of expression and role in modulating synaptic efficacy, it is imperative that several criteria should be satisfied:

- (1) *Immunohistological or electron microscopic (EM) evidence of receptor subunit expression* – the minimum requirement for NMDA receptor cell surface expression is for a single GluN1 subunit and at least one GluN2 subunit isoform expressed in close proximity (hundreds of nanometers – several micrometres) to the active zone.
- (2) *Exogenous agonist application should mimic physiological activation* – focal pressure application, iontophoresis or uncaging of NMDA receptor agonists should mimic activity-dependent activation of the receptor.
- (3) *Selective genetic or pharmacological manipulations should block receptor activation* – cell-selective knockdown of NMDA receptor subunits using small interfering RNAs (siRNAs) or dialysing the presynaptic cell with selective blockers such as MK-801 should block presynaptic NMDA receptor activation.
- (4) *Activation of the receptor should directly affect release probability* – NMDA receptor-dependent modulation of synaptic efficacy can be measured as a change in the: frequency, but not amplitude, of spontaneous miniature synaptic events; paired-pulse ratio (PPR) of the amplitudes of two consecutively evoked synaptic currents; and coefficient of variation (CV) of evoked synaptic current amplitudes.
- (5) *Presynaptic bouton recordings should reveal ionotropic receptor activity* – patch clamp recordings from excised patches of presynaptic boutons should reveal single-channel activity in the presence of NMDA.
- (6) *Receptor activation alters presynaptic terminal calcium dynamics* – activation of NMDA receptors located on, or close to, the presynaptic terminal may increase cytosolic calcium *via* direct entry through the NMDA receptor, recruitment of local voltage-gated calcium channels, or enhanced release of calcium from presynaptic intracellular calcium stores.

Previous studies focusing on the role of presynaptic NMDA receptors in modulating synaptic transmission have successfully satisfied some, but not all, of the criteria listed above. This has led to ambiguity and considerable debate over whether NMDA receptors are truly presynaptic or whether they are dendritic receptors that influence release probability from afar (Christie and Jahr, 2008).

3. Controversy surrounding locus of NMDA receptor expression

The identification of presynaptic NMDA receptors has been hindered by the fact that experimental manipulations designed to perturb the activity of presynaptic receptors also affect receptors expressed in the somatodendritic compartments of neurons. This is an important consideration given that the electrotonic spread of somatodendritic depolarisation influences release probability in the axon, with a space constant of many hundreds of microns (Alle and Geiger, 2006; Shu et al., 2006; Glitsch and Marty, 1999). In the cerebellum, bath application of NMDA significantly increased the rate of miniature inhibitory postsynaptic currents (mIPSCs) recorded in Purkinje cells and molecular layer interneurons, suggesting the presence of presynaptic NMDA receptors on inhibitory axon terminals (Glitsch and Marty, 1999; Duguid and Smart, 2004; Glitsch, 2008). Although bath application of NMDA resulted in significant somatodendritic depolarisation even in the presence of TTX, the electrotonic spread of depolarisation along the axon appeared insufficient to account for the large increase in mIPSC rate observed (Glitsch and Marty, 1999). The most parsimonious explanation for these findings is that presynaptic NMDA receptor activation facilitates synaptic transmission at inhibitory synapses in the cerebellum. However, this view has recently been challenged by a study suggesting that dendritic NMDA receptor activation is sufficient to influence presynaptic release *via* electrotonic spread of depolarisation from the dendrite to the axon (Christie and Jahr, 2008). In this study, the authors were unable to detect direct activation of axonal NMDA receptors using two-photon laser-scanning microscopy, axonal iontophoresis of L-aspartate and calcium imaging in molecular layer interneurons. Importantly, focal activation of dendritic NMDA receptors elicited small calcium transients in interneuron axon varicosities. These local transients resulted from calcium entry *via* voltage-gated calcium channels (VGCCs), opened as a result of the passive spread of depolarisation generated by activation of dendritic NMDA receptors (Christie and Jahr, 2008). These findings indicate that dendritic glutamate receptors can influence the release probability at proximal and distal release sites along the axon and that interneuron axons are devoid of functional NMDA receptors. However, these findings are in direct contrast to previous reports demonstrating NMDA receptor single-channel currents in excised patches of molecular layer interneuron axon varicosities (Fiszman et al., 2005a) and NMDA receptor-mediated facilitation of synaptic transmission in dissociated Purkinje cell-interneuron bouton preparations (Duguid et al., 2007).

The dispute over the existence of presynaptic NMDA receptors has not been confined to the cerebellar cortex. In pyramidal cells of the developing visual cortex, presynaptic NMDA receptors are thought to play a pivotal role in the regulation of spontaneous neurotransmission and induction of timing-dependent long-term depression (tLTD) at pyramidal cell-to-pyramidal cell synapses in layer 5 (Sjöström et al., 2003, 2004; Corlew et al., 2007). This plasticity mechanism requires the activation of endocannabinoid receptors and presynaptic NMDA receptors to facilitate a long-term reduction in release probability, which can be blocked by bath application of the non-selective NMDA receptor antagonist D-APV (Duguid and Sjöström, 2006; Sjöström et al., 2003; Min and Nevian, 2012). Interestingly, there appears to be a developmental switch in the contribution of pre- and postsynaptic NMDA receptors in the induction of tLTD in more superficial cortical layers, suggesting that presynaptic NMDA receptors may be required for cortical network development before the onset of the critical period (Corlew et al., 2007). These findings, together with evidence from studies investigating spike-timing dependent plasticity at layer 4-to-layer 2/3 (Duguid and Sjöström, 2006; Corlew et al., 2008, 2007; Brasier and Feldman, 2008; Rodriguez-Moreno and Paulsen, 2008; Bender

et al., 2006) neocortical synapses, provides strong evidence to support a role for non-postsynaptic, putatively presynaptic NMDA receptors in cortical information processing and long-term synaptic plasticity. However, this view has also been challenged by a recent study in which focal iontophoretic stimulation of pyramidal cell axons with an NMDA receptor agonist failed to depolarise the axon, modulate axonal excitability, or evoke NMDA receptor-mediated calcium entry in axonal varicosities – suggesting NMDA receptors are excluded from pyramidal cell axons (Christie and Jahr, 2009).

These apparently contradictory and conflicting results leave us in somewhat of a quandary. On the one hand, there is strong anatomical, electrophysiological and functional evidence to suggest that NMDA receptors are expressed at presynaptic sites in the cerebellum (Glitsch and Marty, 1999; Duguid and Smart, 2004; Casado et al., 2000; Fiszman et al., 2005b; Huang and Bordey, 2004), neocortex (Duguid and Sjöström, 2006; Corlew et al., 2008, 2007; Brasier and Feldman, 2008; Rodriguez-Moreno and Paulsen, 2008; Bender et al., 2006; Aoki et al., 1994; Conti et al., 1997), entorhinal cortex (Berretta and Jones, 1996; Woodhall et al., 2001; Yang et al., 2006) and hippocampus (Madara and Levine, 2008; McGuinness et al., 2010), while on the other hand, direct attempts to visualise functional NMDA receptors on axon terminals in the cerebellum (Christie and Jahr, 2008; Shin and Linden, 2005) or neocortex (Christie and Jahr, 2009) have failed. This leaves us with the question: *are presynaptic NMDA receptors just dendritic receptors in disguise?*

4. Novel methods for probing NMDA receptor function

The main pitfall of using conventional pharmacological manipulations to investigate the functional role of presynaptic NMDA receptors is their inability to differentiate between dendritic and axonal receptors on the presynaptic neuron. To address this issue it has been necessary to develop and employ sophisticated uncaging techniques to selectively manipulate NMDA receptor activity in subcompartments of the presynaptic neuron, thus providing an opportunity to confirm or disprove the existence of NMDA receptors in axon terminals.

4.1. Caged MK-801

NMDA receptors have been shown to be important for synaptic plasticity induction in the developing neocortex, with timing-dependent long-term depression (tLTD) and long-term potentiation (tLTP) mediated by non-postsynaptic, putatively presynaptic (Bender et al., 2006; Bi and Poo, 1998; Feldman, 2000) and postsynaptic (Sjöström et al., 2003; Rodriguez-Moreno and Paulsen, 2008; Bender et al., 2006) NMDA receptors, respectively. To investigate the precise location of the NMDA receptors involved in spike timing-dependent synaptic plasticity at layer 4-to-layer 2/3 pyramidal cell synapses, Rodriguez-Moreno and colleagues synthesised a novel caged form of the use-dependent NMDA receptor antagonist MK-801 that could be dialysed into individual neurons *in vitro* (Rodriguez-Moreno et al., 2011). The authors found that somatodendritic uncaging of MK-801 in the postsynaptic neuron resulted in a use-dependent block of synaptic NMDA receptor-mediated currents and the induction of tLTP. In contrast, compartment-specific uncaging of MK-801 in the presynaptic neuron revealed that axonal, but not somatodendritic NMDA receptors, are required for the induction of tLTD at layer 4-to-layer 2/3 pyramidal cell synapses in the developing neocortex. This method for precise spatial and temporal uncaging of NMDA receptor blockers provides strong evidence in support of functional presynaptic NMDA receptors in the induction of long-term cortical plasticity.

4.2. Caged NMDA and bouton calcium imaging

To elucidate the functional role of presynaptic NMDA receptors it is necessary to identify their exact locus of expression by visualising activity- or agonist-dependent receptor activation at presynaptic release sites. However, in the past this has proven difficult, resulting in contradictory results and intense debate as to whether functional NMDA receptors actually exist (Duguid and Sjöström, 2006; Duguid and Smart, 2009; Christie and Jahr, 2008, 2009; Pugh and Jahr, 2011). The recent synthesis of a caged form of NMDA (MNI-caged-NMDA) has to some extent addressed this issue, providing a unique method to focally activate NMDA receptors with exquisite spatial and temporal resolution (Palma-Cerda et al., 2012). By combining precise NMDA uncaging (~1 µm diameter uncaging spot), calcium imaging and *in vitro* patch clamp electrophysiology it has been possible to demonstrate agonist-induced bouton calcium transients in the axons of cerebellar molecular layer interneurons (Rossi et al., 2012) and layer 5 pyramidal cells in the neocortex (Buchanan et al., 2012). In layer 5 pyramidal cells, uncaging NMDA at discrete sites along the axon generated supra-linear calcium signals when paired with 30 Hz trains of action potentials, suggesting that presynaptic NMDA receptors in the neocortex function as glutamate autoreceptors during high frequency presynaptic firing (Fig. 1A) (Duguid and Sjöström, 2006; Sjöström et al., 2003; Buchanan et al., 2012). In contrast, focal uncaging of NMDA at specific locations along the axons of cerebellar molecular layer interneurons evoked robust bouton calcium transients and axonal current responses in the absence of presynaptic spiking, suggesting that coincident presynaptic activity is not a prerequisite for NMDA receptor activation (Fig. 1B) (Rossi et al., 2012). Interestingly, these findings are in direct contrast to previous studies that employed focal iontophoresis of L-aspartate or glutamate uncaging and found no evidence for functional presynaptic NMDA receptors in the neocortex or cerebellum (Christie and Jahr, 2008, 2009; Pugh and Jahr, 2011). The reason for this discrepancy remains unclear but may be due to the heterogeneity of presynaptic NMDA receptor expression, as discussed below.

5. Target-specific expression of presynaptic NMDA receptors

Over the past decade there has been growing evidence to suggest that presynaptic NMDA receptor expression may not be random but instead is synapse-specific, implying they serve dedicated network functions *in vivo*. The first indication that NMDA receptor expression may be synapse-specific came from a study by Brasier and Feldman (2008) who demonstrated that presynaptic NMDA receptors were expressed in only a subset of pyramidal neuron terminals in the developing somatosensory cortex. The expression of presynaptic NMDA receptors at feedforward layer 4-to-layer 2/3 pyramidal cell synapses, but not at layer 2/3-to-layer 2/3 or layer 4-to-layer 4 connections, suggested that synaptic terminals along the same axon may differentially express presynaptic NMDA receptors depending on the postsynaptic target. The target-specific expression of presynaptic NMDA receptors may preferentially enhance the transfer of ascending, feedforward information within a single column in primary somatosensory cortex, relative to the lateral spread across adjacent cortical columns (Brasier and Feldman, 2008). The concept that NMDA receptor expression may be non-random has been strengthened by a recent study investigating target-specific expression of presynaptic NMDA receptors in layer 5 of the developing visual cortex. By employing: targeted paired recordings; two-photon calcium imaging; neurotransmitter uncaging; and computer simulations, Buchanan and colleagues found that pyramidal cell-to-pyramidal cell connections

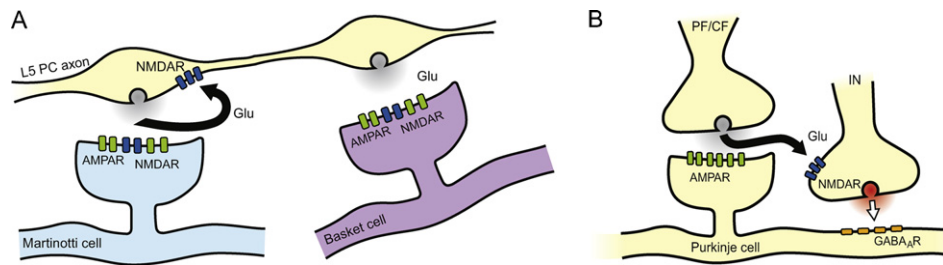


Fig. 1. (A) Target-specific expression of presynaptic NMDA receptors in neocortical circuits. High-frequency stimulation of layer 5 pyramidal neurons generates glutamate pooling, presynaptic autoreceptor activation and modulation of the release probability. The target-specific expression of presynaptic NMDA receptors is governed by the identity of the postsynaptic cell type. (B) Spillover-dependent NMDA receptor activation. High-frequency activity of climbing fibres (CF) or parallel fibres (PF) in the cerebellum results in glutamate pooling, spillover to adjacent interneuron axon terminals and activation of presynaptic NMDA receptors. This leads to an increase in synaptic efficacy at selected inhibitory synapses.

Adapted with permission from Duguid and Smart (2009).

in layer 5 and layer 5 pyramidal cell-to-Martinotti cell connections express functional presynaptic NMDA receptors, while layer 5 pyramidal cell-to-basket cells synapses do not (Buchanan et al., 2012). Importantly, synaptic terminals that originated from the same pyramidal cell but targeted different postsynaptic cell types differentially expressed NMDA receptors, thus strengthening the view that postsynaptic cell identity regulates the expression of functional presynaptic NMDA receptors in developing neocortical circuits (Fig. 1A) (Brasier and Feldman, 2008; Buchanan et al., 2012).

The sparse, non-random expression of presynaptic NMDA receptors is not unique to the cortex and can be found in molecular layer interneurons in the cerebellum. Focal stimulation of axon terminals using glutamate or NMDA uncaging resulted in robust calcium transients or NMDA-receptor-evoked currents in ~30% of locations along single axons (Rossi et al., 2012), consistent with data from cultured molecular layer interneurons showing that ~40% of excised patches from axon terminals expressed functional NMDA receptors (Fizman et al., 2005a). The sparse nature of axonal NMDA signalling in cerebellar interneurons may, in part, account for the failure of previous studies to detect NMDA receptor activation using iontophoretic agonist applications (Christie and Jahr, 2008; Pugh and Jahr, 2011; Clark and Cull-Candy, 2002) or glutamate uncaging (Pugh and Jahr, 2011). The next step will be to investigate whether presynaptic NMDA receptors are expressed in the cerebellum in a target-specific manner, similar to that observed in the developing neocortex.

Together, these studies provide compelling evidence to suggest that presynaptic NMDA receptor expression is not random but may be governed by the identity of the postsynaptic cell type. How the postsynaptic cell identity is communicated to the presynaptic bouton to regulate expression remains to be established, but may be *via* extracellular leucine-rich repeat (LRR) proteins (Sylwestrak and Ghosh, 2012).

6. Functional role of presynaptic NMDA receptors

In the central nervous system, NMDA receptors are typically seen as canonical coincidence detectors, requiring glutamate binding and depolarisation to open (Ascher and Nowak, 1988; MacDermott et al., 1986). This classical view places the NMDA receptor in the postsynaptic membrane directly opposing glutamatergic afferent inputs, where high frequency pre- and postsynaptic activity results in glutamate-bound NMDA receptors being relieved from magnesium block. This coincidence detection mechanism provides a 'molecular switch' for the induction of various forms of short- and long-term synaptic plasticity. Over the past decade, this view has been revised due to the growing body of evidence demonstrating presynaptic, target-specific expression of NMDA receptors. Although presynaptic

NMDA receptors are not ideally located for traditional coincidence detection, they are perfectly situated to act as autoreceptors. In the cerebellum, hippocampus and developing neocortex, presynaptic NMDA autoreceptors appear to implement a high-pass filter that selectively regulates the release probability at synapses undergoing high frequency bursts of activity (Sjöström et al., 2003; Corlew et al., 2007; Casado et al., 2000, 2002; McGuinness et al., 2010; Rodriguez-Moreno et al., 2011; Buchanan et al., 2012; Bidoret et al., 2009) (see also Shin and Linden, 2005). Moreover, synapse-specific presynaptic NMDA receptor activation could provide an important mechanism for re-routing information flow in the developing visual cortex during high-frequency firing (Buchanan et al., 2012). In contrast, presynaptic NMDA receptors expressed on interneuron axon terminals appear to act as spillover detectors "sensing" glutamate release from adjacent excitatory terminals (Huang and Bordey, 2004; Shin and Linden, 2005; Liu and Lachamp, 2006; Lien et al., 2006; Humeau et al., 2003). The spillover activation of presynaptic NMDA receptors promotes synaptic crosstalk, regulates the activity of local interneuronal networks, and ultimately modulates the level of feedforward inhibition to downstream principal cells. In addition, presynaptic NMDA receptors may play a 'housekeeping' role by regulating spontaneous transmitter release (Glitsch and Marty, 1999; Duguid and Smart, 2004; Sjöström et al., 2003), although the extent to which presynaptic NMDA receptors are activated by ambient glutamate remains unclear. There is now a wealth of information to suggest that presynaptic NMDA receptors play a critical role in regulating synaptic transmission and plasticity induction. However, we are only just beginning to understand the possible physiological functions of these receptors and it will be important for future studies to identify not only their exact locus of expression but also how they regulate information processing and network dynamics *in vivo*.

7. Future directions

The expression of NMDA receptors at presynaptic release sites provides a direct signalling pathway to modulate the strength of synaptic transmission in an activity-dependent manner. Although the existence of presynaptic NMDA receptors remains a contentious issue, the use of advanced pharmacological tools, neurotransmitter uncaging, two-photon calcium imaging and patch clamp electrophysiology has provided fresh new insights into the role of presynaptic NMDA receptors in regulating release probability, circuit function and synaptic plasticity induction. The development of new technologies heralds a new era in the study of presynaptic inotropic receptor function, giving us the possibility to address specific and fundamentally important questions. What are the signals that generate target-specific expression of

presynaptic NMDA receptors? What are the molecular mechanisms that traffic and target NMDA receptors to the axon and to distinct axonal varicosities along the same axon? Is the synapse-specific expression of presynaptic NMDA receptors a general principle of developing circuits in the brain? Importantly, given that presynaptic NMDA receptors exist early in development in the visual cortex (Corlew et al., 2007), hippocampus (Mameli et al., 2005) and entorhinal cortex (Yang et al., 2006) and have been shown to be important for the onset of the critical period for receptive field plasticity (Corlew et al., 2007), this suggests that the developmental regulation of presynaptic NMDA receptor expression may be a fundamentally important hallmark of early circuit formation. Although this remains to be established, we are entering an exciting time where the development of novel pharmacological, molecular genetic and imaging tools will provide us with the unique opportunity to investigate the subunit composition, synapse-specific expression and functional role of presynaptic NMDA receptors in information processing *in vivo*.

References

- Alle, H., Geiger, J.R., 2006. Combined analog and action potential coding in hippocampal mossy fibers. *Science* 311, 1290–1293.
- Aoki, C., Venkatesan, C., Go, C.G., Mong, J.A., Dawson, T.M., 1994. Cellular and subcellular localization of NMDA-R1 subunit immunoreactivity in the visual cortex of adult and neonatal rats. *Journal of Neuroscience* 14, 5202–5222.
- Ascher, P., Nowak, L., 1988. The role of divalent cations in the N-methyl-D-aspartate responses of mouse central neurones in culture. *The Journal of Physiology* 399, 247–266.
- Bender, V.A., Bender, K.J., Brasier, D.J., Feldman, D.E., 2006. Two coincidence detectors for spike timing-dependent plasticity in somatosensory cortex. *Journal of Neuroscience* 26, 4166–4177.
- Berretta, N., Jones, R.S., 1996. Tonic facilitation of glutamate release by presynaptic N-methyl-D-aspartate autoreceptors in the entorhinal cortex. *Neuroscience* 75, 339–344.
- Bi, G.Q., Poo, M.M., 1998. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *The Journal of Neuroscience* 18, 10464–10472.
- Bidoret, C., Ayon, A., Barbour, B., Casado, M., 2009. Presynaptic NR2A-containing NMDA receptors implement a high-pass filter synaptic plasticity rule. *Proceedings of the National Academy of Sciences of the United States of America* 106, 14126–14131.
- Brasier, D.J., Feldman, D.E., 2008. Synapse-specific expression of functional presynaptic NMDA receptors in rat somatosensory cortex. *The Journal of Neuroscience* 28, 2199–2211.
- Buchanan, K.A., Blackman, A.V., Moreau, A.W., Elgar, D., Costa, R.P., Lalanne, T., Tudor Jones, A.A., Oyrer, J., Sjöström, P.J., 2012. Target-specific expression of presynaptic NMDA receptors in neocortical microcircuits. *Neuron* 75, 451–466.
- Casado, M., Dieudonné, S., Ascher, P., 2000. Presynaptic N-methyl-D-aspartate receptors at the parallel fiber-Purkinje cell synapse. *Proceedings of the National Academy of Sciences of the United States of America* 97, 11593–11597.
- Casado, M., Isope, P., Ascher, P., 2002. Involvement of presynaptic N-methyl-D-aspartate receptors in cerebellar long-term depression. *Neuron* 33, 123–130.
- Christie, J.M., Jahr, C.E., 2008. Dendritic NMDA receptors activate axonal calcium channels. *Neuron* 60, 298–307.
- Christie, J.M., Jahr, C.E., 2009. Selective expression of ligand-gated ion channels in L5 pyramidal cell axons. *The Journal of Neuroscience* 29, 11441–11450.
- Clark, B.A., Cull-Candy, S.G., 2002. Activity-dependent recruitment of extrasynaptic NMDA receptor activation at an AMPA receptor-only synapse. *Journal of Neuroscience* 22, 4428–4436.
- Conti, F., Minelli, A., DeBiasi, S., Melone, M., 1997. Neuronal and glial localization of NMDA receptors in the cerebral cortex. *Molecular Neurobiology* 14, 1–18.
- Corlew, R., Wang, Y., Ghermazien, H., Erisir, A., Philpot, B.D., 2007. Developmental switch in the contribution of presynaptic and postsynaptic NMDA receptors to long-term depression. *The Journal of Neuroscience* 27, 9835–9845.
- Corlew, R., Brasier, D.J., Feldman, D.E., Philpot, B.D., 2008. Presynaptic NMDA receptors: newly appreciated roles in cortical synaptic function and plasticity. *The Neuroscientist* 14, 609–625.
- Duguid, I., Sjöström, P.J., 2006. Novel presynaptic mechanisms for coincidence detection in synaptic plasticity. *Current Opinion Neurobiology* 16, 312–322.
- Duguid, I.C., Smart, T.G., 2004. Retrograde activation of presynaptic NMDA receptors enhances GABA release at cerebellar interneuron-Purkinje cell synapses. *Nature Neuroscience* 7, 525–533.
- Duguid, I., Smart, T., 2009. Presynaptic NMDA receptors. In: Van Dongen, A. (Ed.), *Biology of the NMDA Receptor*. CRC Press, pp. 313–328.
- Duguid, I.C., Pankratov, Y., Moss, G.W., Smart, T.G., 2007. Somatodendritic release of glutamate regulates synaptic inhibition in cerebellar Purkinje cells via autocrine mGluR1 activation. *Journal of Neuroscience* 27, 12464–12474.
- Feldman, D.E., 2000. Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. *Neuron* 27, 45–56.
- Fink, K., Bonisch, H., Gothert, M., 1990. Presynaptic NMDA receptors stimulate noradrenaline release in the cerebral cortex. *European Journal of Pharmacology* 185, 115–117.
- Fizman, M.L., Barberis, A., Lu, C., Fu, Z., Erdélyi, F., Szabó, G., Vicini, S., 2005a. NMDA receptors increase the size of GABAergic terminals and enhance GABA release. *Journal of Neuroscience* 25, 2024–2031.
- Fizman, M.L., Barberis, A., Lu, C., Fu, Z., Erdelyi, F., Szabo, G., Vicini, S., 2005b. NMDA receptors increase the size of GABAergic terminals and enhance GABA release. *Journal of Neuroscience* 25, 2024–2031.
- Glitsch, M.D., 2008. Calcium influx through N-methyl-D-aspartate receptors triggers GABA release at interneuron-Purkinje cell synapse in rat cerebellum. *Neuroscience* 151, 403–409.
- Glitsch, M., Marty, A., 1999. Presynaptic effects of NMDA in cerebellar Purkinje cells and interneurons. *Journal of Neuroscience* 19, 511–519.
- Huang, H., Bordey, A., 2004. Glial glutamate transporters limit spillover activation of presynaptic NMDA receptors and influence synaptic inhibition of Purkinje neurons. *Journal of Neuroscience* 24, 5659–5669.
- Humeau, Y., Shaban, H., Bissière, S., Lüthi, A., 2003. Presynaptic induction of heterosynaptic associative plasticity in the mammalian brain. *Nature* 426, 841–845.
- Johnson, K.M., Jeng, Y.J., 1991. Pharmacological evidence for N-methyl-D-aspartate receptors on nigrostriatal dopaminergic nerve terminals. *Canadian Journal of Physiology and Pharmacology* 69, 1416–1421.
- Kandel, E.R., Schwartz, J.H., 1982. *Molecular biology of learning: modulation of transmitter release*. *Science* 218, 433–443.
- Khakh, B.S., Henderson, G., 2000. Modulation of fast synaptic transmission by presynaptic ligand-gated cation channels. *Journal of the Autonomic Nervous System* 81, 110–121.
- Krebs, M.O., Desce, J.M., Kemel, M.L., Gauchy, C., Godeheu, G., Chéramy, A., Glowinski, J., 1991. Glutamatergic control of dopamine release in the rat striatum: evidence for presynaptic N-methyl-D-aspartate receptors on dopaminergic nerve terminals. *Journal of Neurochemistry* 56, 81–85.
- Langer, S.Z., 2008. Presynaptic autoreceptors regulating transmitter release. *Neurochemistry International* 52, 26–30.
- Lien, C.C., Mu, Y., Vargas-Caballero, M., Poo, M.M., 2006. Visual stimuli-induced LTD of GABAergic synapses mediated by presynaptic NMDA receptors. *Nature Neuroscience* 9, 372–380.
- Liu, S.J., Lachamp, P., 2006. The activation of excitatory glutamate receptors evokes a long-lasting increase in the release of GABA from cerebellar stellate cells. *Journal of Neuroscience* 26, 9332–9339.
- Liu, H., Wang, H., Sheng, M., Jan, L.Y., Jan, Y.N., Basbaum, A.I., 1994. Evidence for presynaptic N-methyl-D-aspartate autoreceptors in the spinal cord dorsal horn. *Proceedings of the National Academy of Sciences of the United States of America* 91, 8383–8387.
- MacDermott, A.B., Mayer, M.L., Westbrook, G.L., Smith, S.J., Barker, J.L., 1986. NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones. *Nature* 321, 519–522.
- MacDermott, A.B., Role, L.W., Siegelbaum, S.A., 1999. Presynaptic ionotropic receptors and the control of transmitter release. *Annual Review of Neuroscience* 22, 443–485.
- Madara, J.C., Levine, E.S., 2008. Presynaptic and postsynaptic NMDA receptors mediate distinct effects of brain-derived neurotrophic factor on synaptic transmission. *Journal of Neurophysiology* 100, 3175–3184.
- Mameli, M., Carta, M., Partridge, L.D., Valenzuela, C.F., 2005. Neurosteroid-induced plasticity of immature synapses via retrograde modulation of presynaptic NMDA receptors. *Journal of Neuroscience* 25, 2285–2294.
- McGuinness, L., Taylor, C., Taylor, R.D., Yau, C., Langenhan, T., Hart, M.L., Christian, H., Tynan, P.W., Donnelly, P., Emptage, N.J., 2010. Presynaptic NMDARs in the hippocampus facilitate transmitter release at theta frequency. *Neuron* 68, 1109–1127.
- Min, R., Nevian, T., 2012. Astrocyte signaling controls spike timing-dependent depression at neocortical synapses. *Nature Neuroscience* 15, 746–753.
- Palma-Cerda, F., Auger, C., Crawford, D.J., Hodgson, A.C., Reynolds, S.J., Cowell, J.K., Swift, K.A., Cais, O., Vyklícký, L., Corrie, J.E., Ogden, D., 2012. New caged neurotransmitter analogs selective for glutamate receptor sub-types based on methoxynitroindoline and nitrophenylethoxycarbonyl caging groups. *Neuropharmacology* 63, 624–634.
- Petralia, R.S., Wang, Y.X., Wenthold, R.J., 1994a. The NMDA receptor subunits NR2A and NR2B show histological and ultrastructural localization patterns similar to those of NR1. *The Journal of Neuroscience* 14, 6102–6120.
- Petralia, R.S., Yokotani, N., Wenthold, R.J., 1994b. Light and electron microscope distribution of the NMDA receptor subunit NMDAR1 in the rat nervous system using a selective anti-peptide antibody. *The Journal of Neuroscience* 14, 667–696.
- Pittaluga, A., Raiteri, M., 1992. N-methyl-D-aspartic acid (NMDA) and non-NMDA receptors regulating hippocampal norepinephrine release. I. Location on axon terminals and pharmacological characterization. *The Journal of Pharmacology and Experimental Therapeutics* 260, 232–237.
- Pugh, J.R., Jahr, C.E., 2011. NMDA receptor agonists fail to alter release from cerebellar basket cells. *The Journal of Neuroscience* 31, 16550–16555.
- Rodríguez-Moreno, A., Paulsen, O., 2008. Spike timing-dependent long-term depression requires presynaptic NMDA receptors. *Nature Neuroscience* 11, 744–745.
- Rodríguez-Moreno, A., Kohl, M.M., Reeve, J.E., Eaton, T.R., Collins, H.A., Anderson, H.L., Paulsen, O., 2011. Presynaptic induction and expression of timing-dependent long-term depression demonstrated by compartment-specific photorelease of a use-dependent NMDA receptor antagonist. *The Journal of Neuroscience* 31, 8564–8569.

- Rossi, B., Ogden, D., Llano, I., Tan, Y.P., Marty, A., Collin, T., 2012. Current and calcium responses to local activation of axonal NMDA receptors in developing cerebellar molecular layer interneurons. *PLoS ONE* 7, e39983.
- Schlicker, E., Kathmann, M., 2001. Modulation of transmitter release via presynaptic cannabinoid receptors. *Trends in Pharmacological Sciences* 22, 565–572.
- Shin, J.H., Linden, D.J., 2005. An NMDA receptor/nitric oxide cascade is involved in cerebellar LTD but is not localized to the parallel fiber terminal. *Journal of Neurophysiology* 94, 4281–4289.
- Shu, Y., Hasenstaub, A., Duque, A., Yu, Y., McCormick, D.A., 2006. Modulation of intracortical synaptic potentials by presynaptic somatic membrane potential. *Nature* 441, 761–765.
- Siegel, S.J., Brose, N., Janssen, W.G., Gasic, G.P., Jahn, R., Heinemann, S.F., Morrison, J.H., 1994. Regional, cellular, and ultrastructural distribution of N-methyl-D-aspartate receptor subunit 1 in monkey hippocampus. *Proceedings of the National Academy of Sciences of the United States of America* 91, 564–568.
- Sjöström, P.J., Turrigiano, G.G., Nelson, S.B., 2003. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. *Neuron* 39, 641–654.
- Sjöström, P.J., Turrigiano, G.G., Nelson, S.B., 2004. Endocannabinoid-dependent neocortical layer-5 LTD in the absence of postsynaptic spiking. *Journal of Neurophysiology* 92, 3338–3343.
- Sylwestrak, E.L., Ghosh, A., 2012. Elfn1 regulates target-specific release probability at CA1-interneuron synapses. *Science* 338, 536–540.
- Wang, J.K., 1991. Presynaptic glutamate receptors modulate dopamine release from striatal synaptosomes. *Journal of Neurochemistry* 57, 819–822.
- Woodhall, G., Evans, D.I., Cunningham, M.O., Jones, R.S., NR2B-containing, 2001. NMDA autoreceptors at synapses on entorhinal cortical neurons. *Journal of Neurophysiology* 86, 1644–1651.
- Yang, J., Woodhall, G.L., Jones, R.S., 2006. Tonic facilitation of glutamate release by presynaptic NR2B-containing NMDA receptors is increased in the entorhinal cortex of chronically epileptic rats. *Journal of Neuroscience* 26, 406–410.