*Neuroscience* 311 (2015) 322–340

# NEUROSCIENCE FOREFRONT REVIEW

# PRESYNAPTIC NMDA RECEPTORS: ROLES AND RULES

**G. BOUVIER,[a] C. BIDORET,[b] M. CASADO[a]* AND P. PAOLETTI[a]***

[a] *Institut de Biologie de l'Ecole Normale Supérieure (IBENS), CNRS UMR8197, INSERM U1024, Ecole Normale Supérieure, Paris F-75005, France*

[b] *Laboratoire de Neurophysiologie et Nouvelles Microscopies, INSERM U1128, Université Paris Descartes, Paris F-75006, France*

**Abstract—NMDA receptors (NMDARs) are glutamate-gated ion channels widely expressed in the central nervous system (CNS) and endowed with unique biophysical, pharmacological and signaling properties. These receptors are best known for their critical roles in synaptic plasticity and their implications in a variety of neurological and psychiatric disorders. Since their discovery three decades ago, NMDARs have been thoroughly studied as components of postsynaptic excitatory potentials. Early on, however, both anatomical and physiological evidence pointed out to the existence of NMDARs away from the postsynaptic density. Some were found to be extrasynaptic, while others seemed to be specifically present at presynaptic (i.e. axonal) elements. Although presynaptic NMDARs (preNMDARs) were at first thought to be exceptional, there is now strong evidence that these receptors are relatively widespread in the CNS and regulate synaptic strength in specific sets of synapses. In this review, we compile our current knowledge on preNMDARs, presenting their anatomical distribution, developmental regulation, subunit composition, activation mechanisms as well as their downstream effects on synapse function. Contentious issues that animate the field are also discussed. Finally, particular emphasis is put on the molecular and cellular diversity of preNMDARs which translates into a variety of effects, both short- and long-term, on synaptic efficacy. Overshadowed by their postsynaptic counterparts, preNMDARs are progressively emerging as important regulators of neuronal signaling.**


**Key words: glutamate, synapse, NMDA receptor, presynaptic regulation, synaptic plasticity.**

*Corresponding authors.
E-mail addresses: casado@biologie.ens.fr (M. Casado), pierre.paoletti@ens.fr (P. Paoletti).

*Abbreviations:* APV, 2-amino-5-phosphonopentanoic acid; BDNF, brain-derived neurotrophic factor; EPSC, excitatory postsynaptic current; mIPSC, miniature inhibitory postsynaptic current; MK-801, dizocilpine; MLI, molecular layer interneuron; NMDARs, NMDA receptors; nNOS, neuronal NO synthase; NO, nitric oxide; NST, nucleus of the solitary tract; PC, Purkinje cell; PF, parallel fiber; PP, perforant path; preNMDARs, presynaptic NMDARs; SCs, Schaffer collaterals; SP, substance P.

http://dx.doi.org/10.1016/j.neuroscience.2015.10.033
0306-4522/

Contents



## INTRODUCTION

NMDARs were first proposed to have a presynaptic locus of expression in the early 90's after it was discovered that exogenous applications of NMDA enhanced the release of neurotransmitter from synaptosomes prepared from monoaminergic terminals (Fink et al., 1990; Johnson and Jeng, 1991; Krebs et al., 1991; Wang, 1991; Pittaluga and Raiteri, 1992). Concomitant observations at excitatory synapses also provided the first evidence that glutamate could modulate its own release through activation of presynaptic glutamate receptors displaying a typical NMDAR signature (Martin et al., 1991; Bustos et al., 1992). Since then, accumulating evidence has emerged both from anatomical and functional studies that presynaptic NMDARs (preNMDARs) are in fact widespread in the CNS (Fig. 1; for previous reviews on the topic see Corlew et al., 2008; Duguid and Smart, 2009; Rodriguez-Moreno et al., 2010). It is now well established that preNMDARs can be found both at excitatory (i.e. glutamatergic) and inhibitory (i.e. GABAergic) synapses, acting as auto- or hetero-receptors. Although present in

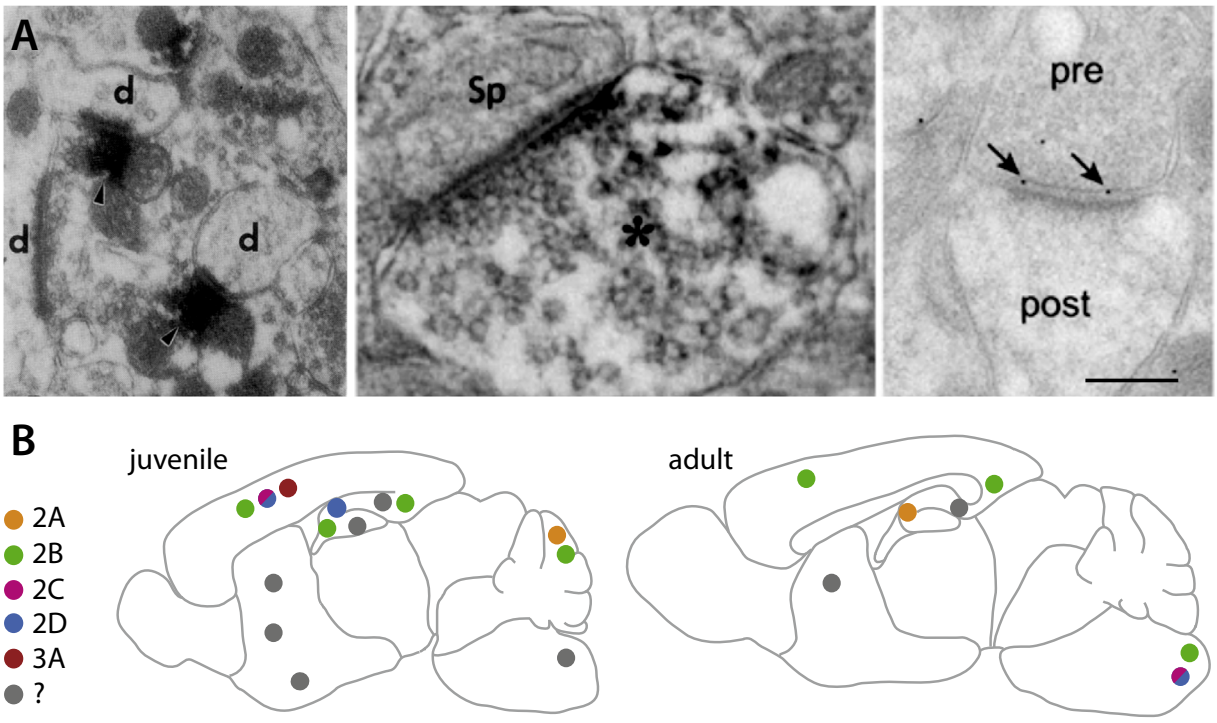


**Fig. 1.** PreNMDAR distribution in the CNS. (A) Electron microscopy evidence for preNMDARs. Left: GluN1 immunoreactivity (arrowheads, peroxydase labeling) at afferent lamina II terminals in the spinal cord dorsal horn of adult rats (from Liu et al., 1994). Middle: GluN2A immunoreactivity (*, peroxydase labeling) at parallel fiber – Purkinje cell synapses in the cerebellum of juvenile rats (from Bidoret et al., 2009). Right: GluN1 immunoreactivity (immunogold beads) at L4–L2/3 synapses in the visual cortex of juvenile mice (from Larsen et al., 2011). Scale bar = 200 nm. (B) Distribution of preNMDAR subunits in the juvenile and adult rodent CNS. GluN2C/D mixed circles indicate preNMDARs that are composed of GluN2C or GluN2D subunits. Gray circles indicate CNS regions where preNMDARs were evidenced but with undefined subunit composition (e.g. dentate gyrus, subiculum, striatum, nucleus accumbens, amygdala, NST, spinal cord).

the adult CNS, their expression is particularly abundant early during development suggesting important roles in synapse and neural network maturation. Yet, contrasting with their postsynaptic counterparts, preNMDARs are not ubiquitous. Rather, they are present in precise sets of neuronal types and display conspicuous input specificity at the single-neuron level pointing to distinctive contributions of preNMDARs in regulating synapse function and information processing. In the following sections, we review our knowledge on the anatomical distribution and molecular composition of preNMDARs, their activation and signaling mechanisms as well as their roles in synaptic transmission and plasticity.

## DISTRIBUTION OF PRENMDARS IN THE CNS AND IMPACT ON SYNAPSE FUNCTION

### Cerebral cortex

One of the brain regions where preNMDARs have been best described is the cerebral cortex (Fig. 1). Light and electron microscopy (EM), together with electrophysiological recordings, revealed that preNMDARs are found in a wide array of cortical synapses and have provided detailed information about their function. GluN1 immunostaining in the rat visual cortex provided the first indication that NMDARs from the cerebral cortex can be expressed in the presynaptic compartment (Aoki et al., 1994). In another pioneering study, Berretta and Jones (1996) showed in principal cells of the entorhinal cortex layer 2 (L2) that the NMDAR antagonist 2-amino-5-phosphonopentanoic acid (APV) acutely reduces the frequency of miniature excitatory postsynaptic currents (mEPSCs), even when postsynaptic NMDARs are silenced (by postsynaptically dialyzing the NMDAR channel blocker MK-801; see Box 1). This result was one of the very first evidence for the presence of functional preNMDARs capable of enhancing spontaneous neurotransmitter release (see also Fig. 2A). It also revealed that preNMDARs can be tonically activated by ambient glutamate. Similar conclusions were reached in L2/3 of the rat somatosensory cortex, where preNMDARs were shown to modify inputs arriving from L4 but not those originating from the same layer (L2/3) (Brasier and Feldman, 2008). Based on the finding that APV decreases evoked EPSCs and modified paired-pulse facilitation at L4–L2/3 synapses, it was again proposed that preNMDARs display basal activation under conditions of modest synaptic activity (Fig. 2B).

The rodent primary visual cortex is particularly well equipped in preNMDARs (Sjostrom et al., 2003; Corlew et al., 2007; Larsen et al., 2011, 2014; Buchanan et al., 2012; Kunz et al., 2013). In this structure, expression of preNMDARs is found in various layers and is under strong