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REVIEW

SURFACE TRAFFICKING OF *N*-METHYL-D-ASPARTATE RECEPTORS: PHYSIOLOGICAL AND PATHOLOGICAL PERSPECTIVES

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Abstract—The *N*-methyl-D-aspartate receptor (NMDAR) plays a crucial role in shaping the strength of synaptic connections. Over the last decades, extensive studies have defined the cellular and molecular mechanisms by which synaptic NMDARs control the maturation and plasticity of synaptic transmission, and how altered synaptic NMDAR signaling is implicated in neurodegenerative and psychiatric disorders. It is now clear that activation of synaptic or extrasynaptic NMDARs produces different signaling cascades and thus neuronal functions. Our current understanding of NMDAR surface distribution and trafficking is only emerging. Exchange of NMDARs between synaptic and extrasynaptic areas through surface diffusion is a highly dynamic and regulated process. The aim of this review is to describe the identified mechanisms that regulate surface NMDAR behaviors and discuss the impact of this new trafficking pathway on the well-established NMDAR-dependent physiological and pathophysiological processes.

Key words: synapse, glutamate, plasticity, development.

Contents

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Abbreviations: CAMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CK2, casein kinase 2; D1R, D1 receptor; ECM, extracellular matrix; EphBR, EphrinB receptor; ER, endoplasmic reticulum; FRAP, fluorescent recovery after photobleaching; MAGUK, membrane-associated guanylate kinase; NMDAR, *N*-methyl-D-aspartate receptor; PKC, protein kinase C; PP, perforant path; PSD, postsynaptic density; SAP-102, synapse-associated protein 102; Sch, Schaffer collateral.

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The understanding of *N*-methyl-D-aspartate receptor (NMDAR) cellular trafficking has captured a lot of attention over the last decades, providing a substantial knowledge on their synthesis and intracellular traffickings. The key role of NMDARs in the induction of some forms of synaptic plasticity has further stimulated studies on the molecular and biophysical properties of NMDARs during changes of synaptic transmission. Such knowledge has recently been summarized in several excellent reviews (Lau and Zukin, 2007; Chen and Roche, 2007; Cull-Candy and Leszkiewicz, 2004; Kohr, 2006; Perez-Otano and Ehlers, 2005; Wenthold et al., 2003) and will thus not be discussed in the present review. Of interest, it recently appeared that NMDARs diffuse at the surface of neurons and, more generally, that the heterogeneous surface distribution of NMDARs may play pivotal roles in the complexity of NMDAR signaling. The aim of this review is to delineate our current knowledge on the distribution and trafficking of surface NMDARs and how this may relate to their function. In addition, some of the numerous questions that remain to be addressed in this field are highlighted and discussed.

NMDAR STRUCTURE AND INTRACELLULAR TRAFFICKING: OVERVIEW

Over the last decades, the NMDAR has emerged as one key regulator of the glutamatergic synaptic transmission. The glutamatergic synapses undergo various forms of NMDAR-dependent long-lasting changes in strength, a process thought to underlie some forms of learning and

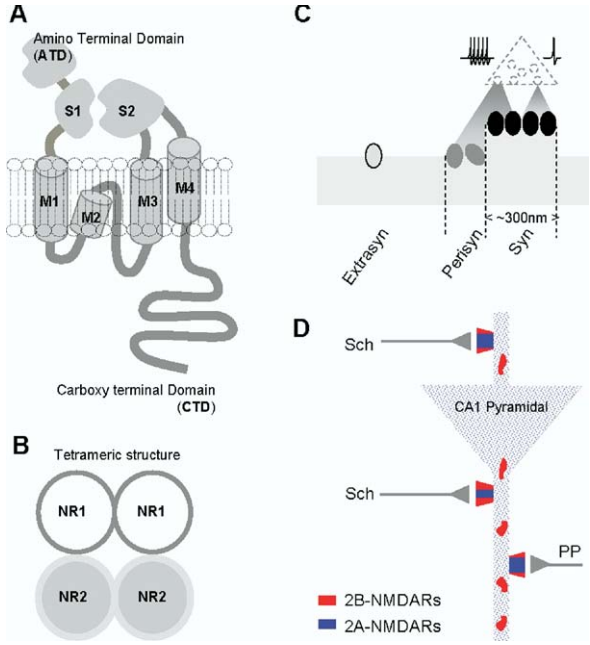

Fig. 1. Surface distribution of NMDARs. (A) Schematic structure of a NR subunit that is composed of an amino terminal domain (ATD), transmembrane domains (M1 to M4), and a carboxy terminal domain (CTD). The glutamate binding pocket is constituted by the two S domains (S1 and S2). (B) Most of the NMDARs contain two NR1 subunits and two NR2 subunits (a dimer of dimer). (C) Depending on their surface localization, NMDARs can be sorted as either synaptic, perisynaptic (several hundreds of nanometers around the PSD), or extrasynaptic. (D) Example of the heterogeneous content of synaptic surface NMDARs from individual CA1 pyramidal neuron. Inputs from the Sch in the radians layer exhibit a low 2A/2B ratio whereas inputs from the Sch in the oriens layer or inputs from the PP exhibit a high 2A/2B ratio.

memory (Malenka and Nicoll, 1999). NMDARs are heteromeric molecules formed of NR1, NR2, and NR3 subunits, which themselves contain several variants: a single NR1 subunit with eight splice variants, four NR2 subunits (NR2A–D), and two NR3 subunits. A NR subunit is schematically composed of an extracellular N terminus, re-entrant loops that form the pore and an intracellular C terminus (Fig. 1A–B). Schematically, it is proposed that the functional NMDARs contain two NR1 subunits and two NR2 subunits, i.e. a dimer of dimer (NR1 dimer and NR2 dimer) (Kutsuwada et al., 1992; Meguro et al., 1992; Monyer et al., 1992; Ulbrich and Isacoff, 2007). In this review the following abbreviations will be used to designate NMDAR containing some NR1 subunits ("NR1-NMDAR"), NR2A subunits ("2A-NMDAR"), or NR2B subunits ("2B-NMDAR"). Glutamate binds to NR2 subunit while glycine, the co-agonist, binds to NR1 subunit. The selectivity of the NMDAR for Mg^{2+} block and Ca^{2+} permeability is dependent on a critical asparagine residue located within the re-entrant pore loop, similar to the well-known glutamine/arginine (Q/R) site in AMPA receptor that regulates Ca permeability. The NR1 splice variants are critical in influencing NMDAR signaling such as polyamine potentiation, inhibition by Zn^{2+}, inhibition by protons. However, some specific aspects of NR1 splice variants function remain elusive, such as their influence on NMDAR kinetics, whether two distinct variants co-exist within one NMDAR complex, or whether NR1 splice variants are segregated in different surface compartments or synaptic populations. The NR2 subunits are also critical for several key biophysical and pharmacological properties of the NMDAR (Cull-Candy and Leszkiewicz, 2004). This includes sensitivity to Zn^{2+}, protons, polyamines, the high affinity for glutamate, modulation by glycine, fractional Ca^{2+} current, single channel conductance, and channel kinetics (e.g. open probability, deactivation time). For instance, NR1-NR2-NMDARs show deactivation constants that span a 50-fold range: NR2A<NR2C=NR2B≪NR2D. Moreover, the 2A- and 2B-NMDARs exhibit 50 pS openings with high sensitivity to Mg^{2+} block whereas 2C-NMDARs exhibit lower conductance in the range of 30 pS with low sensitivity to Mg^{2+} block (Paoletti and Neyton, 2007). The trafficking toward the membrane has also been extensively studied and it emerges that neither NR1 nor NR2 subunit forms functional receptors when expressed alone remaining within the endoplasmic reticulum (ER). In addition to ER signals, interactions between NR subunit and PDZ proteins occur early in the NMDAR trafficking consistent with an actual model in which there is a large pool of NR1 subunits retained in the ER that await assembly with NR2 subunits to be inserted in the plasma membrane (see for reviews Lau and Zukin, 2007; Wenthold et al., 2003). In addition, intracellular transport of NMDARs along microtubules requires the molecular motor kinesins and the dynamics of NMDAR-kinesin complexes is regulated indicating altogether that the active transport and regulation of various NMDARs by kinesins in living neurons add another layer of complexity in our understanding of NMDAR trafficking (Guillaud et al., 2003, 2008; Nakata and Hirokawa, 2007). The NR3 subunit assembly with other NR subunits is not yet fully understood although NR3-NMDARs emerge as an important player in controlling the NMDAR synaptic signaling during development (Perez-Otano and Ehlers, 2005).

SURFACE DISTRIBUTION OF NMDARS: HETEROGENEOUS WITHIN AND BETWEEN NEURONAL TYPES

As mentioned above, little is known about the surface distribution of NMDARs. An overview of surface NMDARs in different neuronal cell types and synaptic populations reveals clear heterogeneous distributions, with clustered and non-clustered receptors, and a segregation of distinct NMDAR subtypes (e.g. different subunit composition) in certain membrane compartments. First, surface NMDARs can be classified depending on their spatial localization and functional specificities. Schematically, three main categories can be proposed, within which heterogeneous behaviors are likely to occur: i) synaptic, ii) perisynaptic, and iii) extrasynaptic surface NMDARs (Fig. 1C). The synaptic population responds to synaptically-released glutamate from presynaptic vesicles and exhibits the highest density when compared with other membrane compartments. Sec-