**Calcium-Dependent Desensitization of NMDA Receptors**

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**Abstract**—Glutamate receptors play the key role in excitatory synaptic transmission in the central nervous system (CNS). N-methyl-D-aspartate-activated glutamate receptors (NMDARs) are ion channels permeable to sodium, potassium, and calcium ions that localize to the pre- and postsynaptic nmdar, as well as extrasynaptic neuronal membrane. Calcium entry into dendritic spines is essential for long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission. Both LTP and LTD represent morphological and functional changes occurring in the process of memory formation. NMDAR dysfunction is associated with epilepsy, schizophrenia, migraine, dementia, and neurodegenerative diseases. Prolonged activation of extrasynaptic NMDARs causes calcium overload and apoptosis of neurons. Here, we review recent findings on the molecular mechanisms of calcium-dependent NMDAR desensitization that ensures fast modulation of NMDAR conductance in the CNS and limits calcium entry into the cells under pathological conditions. We present the data on molecular determinants related to calcium-dependent NMDAR desensitization and functional interaction of NMDARs with other ion channels and transporters. We also describe association of NMDARs with lipid membrane microdomains.

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**NMERA RECEPTORS: GENERAL INFORMATION**

Ionotropic glutamate receptors are ligand-activated ion channels that include N-methyl-D-aspartate (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid (AMPAR), and kainate receptor subtypes. NMDARs have the highest permeability for calcium among the ionotropic glutamate receptors. They consist of two GluN1 subunits and two GluN2 subunits; one of the GluN2 subunits may be replaced with GluN3. The diheteromeric NMDARs are assembled from two GluN1 molecules and two GluN2 subunits of the same type (GluN2A, B, C, or D), while triheteromeric NMDARs consist of two GluN1 and two different GluN2 subunits [1-3]. The existence of numerous NMDAR molecular variants ensures the diversity of their functional and pharmacological characteristics [4, 5]. NMDAR activation requires simultaneous binding of glycine [6] (or D-serine [7]) to the GluN1 subunit and glutamate (or aspartate) to the GluN2 subunit [8] and results in the opening of channel pore permeable to sodium, potassium, and calcium [9].

Calcium is one of the most important intracellular messengers controlling the processes of synaptic plasticity, differentiation, and excitotoxicity. Calcium entry into dendritic spines through NMDARs is essential for long-term potentiation (LTP) and long-term depression (LTD) of the synaptic transmission [10, 11]. LTP is induced by a high-frequency synaptic activity resulting in the postsynaptic membrane depolarization, decrease of voltage-dependent magnesium block of the NMDAR channels, and massive Ca²⁺ entry into dendritic spines leading to calmodulin (CaM) activation. Activated Ca/CaM binds to the CaM-dependent kinase II (CaMKII) and causes its autophosphorylation and activation, which leads to phosphorylation of AMPA receptors (AMPARs) and their mobilization to the membrane. Incorporation of additional AMPARs receptors into the dendritic spine membrane increases the postsynaptic response amplitude [12, 13]. The NMDAR-dependent form of LTD is induced by a low-frequency stimulation (<3 Hz) and causes an increase in the concentration of postsynaptic Ca²⁺, as

**Abbreviations:** AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid receptor; CaM, calmodulin; NCX, sodium-calcium exchanger; LTD, long-term depression; LTP, long-term potentiation; NMDAR, N-methyl-D-aspartate receptor; PMCA, plasma membrane calcium pump; VGCC, voltage-gated calcium channel.

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well as activation of the serine/threonine signaling cascade [14, 15]. It is interesting that the NMDAR-dependent induction of LTD can occur in the absence of ion currents through the receptor channel due to the metabotropic effect of ligand binding to the GluN2 subunit. The resulting conformational changes in the receptor intracellular domain reduce receptor association with the serine/threonine phosphatase PP1 and CaMKII, which causes p38 MAPK phosphorylation, AMPAR internalization, and dendritic spine shrinkage [16].

NMDA receptors are essential for memory formation [10, 12]. However, excessive calcium entry through NMDARs in the extrasynaptic membrane of neurons (e.g., in ischemia and stroke) can cause cell death [17, 18].

TYPES OF NMDAR DESENSITIZATION

All glutamate receptors are subjected to desensitization. Desensitization is a decreased receptor responsiveness that occurs with long-term exposure to the agonist. It is most rapid in AMPA and kainate receptors: the amplitude of ion currents through these receptors can decrease by almost 90% within ~20 ms. NMDAR desensitization is much slower and less pronounced or even absent in receptors containing GluN2C and GluN2D subunits.

Desensitization of AMPA and kainate receptors [4] is associated with conformational changes induced by ligand binding and causing receptor transition into one of the desensitized states [19]. However, desensitization of NMDA receptors is more complicated, being a result of several different concurrent processes. The following two types of desensitization develop after NMDAR activation by agonists.

1) Glutamate binding to GluN2 reduces the affinity of GluN1 to glycine via negative allosteric modulation; this results in gradual reduction of the ion current through the NMDAR in the presence of agonists. An increase in glycine concentration abolishes this effect [20, 21]. Since the affinity of glycine binding to NMDAR largely depends on the GluN2 subunit subtype [22, 23], the negative feedback between glutamate and glycine binding also depends on the receptor subunit composition.

2) Calcium-dependent desensitization, which is also referred to as calcium-dependent inactivation, results from calcium binding to the intracellular portion of the GluN1 subunit after its entrance to the cell through the NMDAR pore [24-27]. The kinetics of NMDAR desensitization depends on the receptor subunit composition (Fig. 1) [28-35]. For example, in the presence of 2 mM extracellular calcium, glutamate-induced ion currents through the recombinant GluN1/GluN2A and GluN1/GluN2B receptors, gradually decrease by 42 and 24%, respectively [36]. Calcium-dependent desensitization is most pronounced for NMDARs that include GluN2A subunits and almost absent in the GluN2C- and GluN2D-containing receptors [36, 37]. The functional properties of NMDAR subtypes determine their different roles in synaptic plasticity [18]. Diheteromeric GluN1/GluN2A NMDARs in the CNS are found mainly in the post-synapse, while GluN1/GluN2B receptors perform both synaptic and extrasynaptic functions [18, 38]. Slow deactivation and desensitization of GluN2C- and GluN2D-containing receptors facilitate summation of postsynaptic currents, e.g., in the cerebellum [39] and the spinal cord [40].

A unique property of diheteromeric GluN1/GluN2A NMDARs that determines the key role of these

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**Fig. 1.** The kinetics of calcium-dependent desensitization of recombinant NMDARs with different subunit composition. a) Inward currents normalized by the maximum amplitude during NMDAR activation by glutamate/glycine at physiological values of extracellular calcium. b) Parameters of NMDAR desensitization: extent of desensitization (residual current) [29], open state probability ($P_{\text{open}}$) [4, 30, 31], deactivation time ($\tau$) constant [30, 33], and the domain of calcium current in the total current through the channel ($C_{\text{Ca}} / C_{\text{Na}}$) [18, 35].
receptors in LTP is rapid deactivation that is most pronounced in the calcium-dependent, glycine-dependent, and glycine-independent types of desensitization [18]. The disturbances in the kinetics of GluN1/GluN2A receptor desensitization (e.g., as a result of mutations) lead to the development of different types of epilepsy [41-43]. GluN1/GluN2B NMDARs are less susceptible to the calcium-dependent desensitization than GluN1/GluN2A receptors but display a high conductance for sodium and calcium ions [28], which determines their involvement in the LTD development [18], as well as their contribution to calcium overload of neurons in excitotoxicity.

MOLECULAR MECHANISMS OF CALCIUM-DEPENDENT INACTIVATION

It is well known that intracellular calcium suppresses NMDAR currents [25, 27, 37, 44, 45]. In neurons, calcium entry through NMDAR channels inactivates these receptors more efficiently than calcium entry through the voltage-gated calcium channels (VGCCs) [25], which suggests that the calcium-binding site is located near the cytoplasmic part of NMDAR.

The multifunctional calcium-binding protein calmodulin 1 (CaM) acts as a universal intracellular sensor for free cytoplasmic calcium. CaM contains four EF hand motifs connected by short (12-amino acid) loops. An increase in the cytoplasmic calcium concentration to low micromolar values results in calcium binding by all four EF hands. The resulting conformational changes make CaM capable of binding to different target proteins [46-48]. In the absence of bound calcium, α-helices of the EF hands are in the closed (parallel) conformation. In the presence of calcium, the EF hands acquire the open conformation (almost orthogonal) and can bind target proteins.

Ca/CaM binds to the NMDAR intracellular site and inactivates it in a dose-dependent manner [49]. Ca/CaM binds to two separate sites in the C-terminal fragment of the GluN1 subunit. Ca/CaM binding to the NMDAR decreases the probability of channel opening and shortens the open state duration. Taking into account the permeability of NMDAR to calcium, this ion entry into the cells after channel opening by glutamate activates CaM and enables Ca/CaM binding to two sites in the C-terminal domain of GluN1 (Fig. 2). However, neither the exact mechanism of this process, nor the degree of cooperativity between the two Ca/CaM-binding sites have been studied.

Structurally similar Ca/CaM-binding sites are present in other types of ionotropic receptors. Thus, Ca/CaM binding to the N-terminal domain of the cyclic nucleotide receptor decreases the activity of the receptor cationic channel [50, 51]. VGCCs are susceptible to the Ca/CaM-dependent inactivation [52-54]. It is possible that CaM binding is a widespread mechanism for the regulation of ion channel permeability.

The molecular determinants of calcium-dependent desensitization of NMDARs are shown in Fig. 3 [36, 55-58]. The CaM-binding fragment of 37 amino acid residues at the C-terminus of the GluN1 subunit is of great significance for the regulation of channel functions. This fragment (region C1) (Fig. 3, a and b) is phosphorylated by protein kinase C [59] and protein kinase A [60]. The C1 fragment also provides receptor interaction with the cytoskeleton and formation of receptor clusters [61]. Ehlers et al. [49, 62] identified two CaM-binding regions in the C-terminal domain of GluN1 (C0 and C2). Deletion of the GluN1 C-terminal domain or mutations of specific CaM-binding sites in the C0 region abolish calcium-dependent desensitization of NMDARs, while intracellular infusion of the CaM inhibitory peptide reduces calcium-dependent desensitization of NMDARs [57].

Rosenmund and Westbrook [26] showed that association between NMDARs and actin cytoskeleton regulates calcium-dependent desensitization via competition between Ca/CaM and cytoskeletal elements for the binding sites in the C1 region. Calcium directly decreases the affinity of α-actin to GluN1 via the interaction between EF hands and α-actin calcium-sensitive form [36, 63, 64] (Fig. 2). Overexpression of α-actin reduces calcium-dependent desensitization of NMDARs. This fact confirms the competition between CaM and α-actin for the binding site in the GluN1 C-terminal domain after calcium entry into the cell [36, 57].

Therefore, the mechanism of calcium-dependent desensitization is realized via the GluN1 subunit present in all NMDARs. However, the extent of desensitization significantly depends on the GluN2 subtype (Fig. 1). Thus, calcium-dependent desensitization is almost absent in NMDARs containing GluN2C and GluN2D subunits [58, 65, 66]. Structural determinants that determine the insensitivity of these receptors to desensitization were found in the N-terminal fragments of GluN2C and GluN2D [36, 67] (Fig. 3c), including amino acid residues at positions 555 and 556 between the S1 and M1 domains [64] and the 190-a.a. fragment homologous to the leucine/isoleucine/valine-binding protein (LIVBP) in the S1 domain [4] (Fig. 3a). Both structural determinants act cooperatively, because removal of only one of them has no substantial effect on desensitization. It is interesting that Ala555 and Ser556 are essential for desensitization of not only GluN2A-containing NMDARs but also determine desensitization of AMPA receptors [68]. Amino acid substitutions at positions 552 [55] and 557 [56] (Fig. 3a) and in the sequences between the M1/M2 and M2/M3 domains also modulate calcium-dependent desensitization [67].
Fig. 2. The molecular mechanism of calcium-dependent desensitization of NMDARs and the effect of GluN1 binding with actin and CaM on NMDAR channel conductance. During receptor activation by glutamate (Glu) and glycine (Gly), the intracellular domain is initially bound to $\alpha$-actin (a), which is accompanied by a high probability of the receptor open state ($P_{open}$). An increase in the intracellular calcium concentration during neuron excitation (b) leads to $\alpha$-actin dissociation and CaM association (c) causing a decrease in $P_{open}$, which reflects calcium-dependent inactivation of NMDAR (d) observed as a decrease in the whole-cell and synaptic currents, which provides dynamic regulation of NMDAR activity during synaptic transmission.

Fig. 3. Structural determinants of GluN1 and GluN2 subunits influencing the parameters of calcium-dependent desensitization. a) The structure of NMDAR consisting of GluN1 and GluN2 subunits. b) C0 and C2 regions in the GluN1 C-terminal fragment, that are critically important for the receptor desensitization and binding of actin (C0) and CaM (C0, C2). c) The differences in the amino acid sequence of GluN2A and GluN2C subunits in the region between the transmembrane hydrophobic domains M1 and M3. Asterisks indicate GluN2A residues whose substitution results in disappearance or considerable suppression of calcium-dependent desensitization of the receptor [36, 55-58]. NTD, N-terminal domain; LBD, ligand-binding domain including S1 and S2 domains; TMD, transmembrane domain including M1-M4 domains; CTD, C-terminal domain.
THE MECHANISMS OF CALCIUM ENTRY TO THE INTRACELLULAR PRE-MEMBRANE REGION

CaM-dependent inactivation of NMDAR channels provides a negative feedback that limits the calcium entry into the spines during excessive synaptic activation and protects neurons from excitotoxicity. During synaptic activity, calcium also enters the cytoplasm through VGCCs and calcium-permeable AMPARs and via other pathways. Because of co-expression of NMDARs and calcium-permeable AMPARs in the synapse, calcium entering through AMPARs during synaptic activation facilitates calcium-dependent desensitization of NMDARs [69-71].

VGCCs transport less calcium than NMDARs during neuronal excitation. However, VGCCs are also undergo calcium-dependent inactivation governed by their intracellular Ca/CaM-binding site [52-54], which limits the voltage-gated calcium entry into the neurons. TRPV1 receptors are widely expressed in the CNS and participate in LTD, in particular, in the hippocampus [72]. As calcium-permeable receptors, TRPV1 are prone to Ca/CaM-dependent desensitization [73].

In addition to calcium entry through ionotropic receptors, synaptic activity can induce calcium release from the intracellular depots [74, 75]; however, such calcium does not contribute much to the increase in the cytoplasmic calcium concentration caused by short-term application of glutamate [76].

CALCIUM REMOVAL FROM THE CYTOPLASM

The plasma membrane contains numerous types of channels, through which calcium ions penetrate into the cytoplasm by the concentration gradient. Calcium homeostasis is maintained differently in different parts of the neuron. In the cell processes, most of calcium is captured by calcium-binding proteins [77, 78] and removed from the cytoplasm by the sodium/calcium exchanger [77]. In the soma, calcium is sequestered in the intracellular depots [77]. The differences in the mechanisms of calcium removal might be due to the fact that dendrites, compared to the soma, are lacking intracellular structures, such as mitochondria and endoplasmic reticulum.

There are two mechanisms of active calcium removal. The first one involves sodium/calcium exchanger (NCX) which has low affinity to calcium but high transport capacity; the second one uses calcium pump (PMCA), an ATPase with a high affinity to calcium and low transport capacity [79]. The NCX/PMCA ratio in the membrane depends on the cell type. The affinity of PMCA to calcium ($K_d < 0.5 \mu M$) allows efficient pumping of calcium from the cell even in the resting state, when the level of free calcium in the cytoplasm varies within 0.05-0.1 \mu M. At the same time, PMCA interaction with CaM determines the low $K_d$ values of PMCA (<1 \mu M), allowing PMCA to finely adjust calcium levels inside the cell.

NCX, on the contrary, needs high calcium concentrations for its saturation ($K_d \sim 1-20 \mu M$) [79]. Despite the fact that the transport capacity of NCX is high (2000-5000 cycles/s), the Michaelis constant ($K_m(Ca)$) measured for the inner side of the membrane substantially exceeds 1 \mu M [80, 81], i.e., NCX cannot decrease calcium concentration below $K_m$. It cannot be excluded that NCX phosphorylation by kinases or interaction with other factors can decrease its $K_m$; however, it is most probable that the concentration of free calcium observed in the narrow pre-membrane region exceeds many times calcium concentration on the rest of the cytoplasm [79]. Therefore, calcium removal from the pre-membrane region with NCX and PMCA should limit the degree and duration of calcium-dependent desensitization of NMDARs.

In the presence of extracellular calcium, NCX inhibition significantly promotes calcium-dependent desensitization of NMDARs, manifested as a reduction in the ion currents in response to NMDA application [82]. The level of NMDAR desensitization in neurons caused by short-term NMDA application is limited by the NCX activity. In turn, NCX inhibition increases many times the Ca/CaM-dependent desensitization of NMDARs [82]. The forward-mode functioning of NCX thereby facilitates ion entry through NMDARs but, due to the high transport capacity of the exchanger, limits the diffusion of calcium from the pre-membrane space to other cytoplasmic regions. The gradient of sodium ions necessary for NCX function is maintained by the Na/K-ATPase; the potentiation of this enzyme by subnanomolar concentrations of the cardiotonic steroid ouabain increases the efficiency of NCX function and calcium removal from neurons during the long-term exposure to agonists of NMDARs [83], AMPARs, and kainate receptors [84].

In general, the level of free intracellular calcium in the narrow pre-membrane region of the post-synapse is controlled by the functional interactions between NMDARs, AMPARs, VGCCs, and NCX (Fig. 4). At the same time, calcium entry through NMDARs, calcium-permeable AMPARs, and VGCCs enhances NMDAR desensitization, while calcium removal by NCX driven by the sodium gradient generated by Na/K-ATPase, on the contrary, suppresses NMDARs desensitization. The involvement of a large number of participants in the regulation of intracellular calcium concentration in the postsynaptic zones brings up the question about the absolute values of ion concentrations required for calcium-dependent functional interactions, as well as about the physical size of compartments where they are concentrated. Lipid microdomains (nanoclusters), or lipid rafts, are
natural structural elements ensuring close functional coupling between protein molecules in the cell membrane.

INTERACTION BETWEEN ION CHANNELS AND TRANSPORTERS IN LIPID RAFTS

It has been established that agents interacting with plasma membrane cholesterol, e.g., filipin and methyl-β-cyclodextrin, suppress the NMDA-induced entry of calcium into neurons [85] due to the 7-fold increase in NMDAR desensitization and reduction of NMDA-mediated ion currents [86]. At the same time, NMDAR surface expression, affinity to agonists, channel conductance, and the open-state time are not affected by the extraction of membrane cholesterol [84]. In particular, many GluN2B subunits in neurons are associated with membrane microdomains and insoluble in Triton X-100. Destruction of lipid domains by cholesterol extraction makes these subunits soluble in Triton X-100 [87]. Therefore, NMDARs are located in cholesterol-enriched lipid rafts, and their dynamic characteristics depend on the integrity of these lipid microdomains.

The presence of NMDARs in lipid rafts has been demonstrated by several research groups [88, 89]. The use of Forster resonance energy transfer (FRET) for detecting colocalized fluorescence labels has shown the association of NMDARs with L-VGCCs in lipid rafts [90]. At the same time, the distance between NMDARs and PMCA or NCX was found to be several nanometers greater than between NMDARs and L-VGCCs [91].

Lipid rafts have dynamically varying size (10-200 nm) and contain high concentrations of sterols and sphingolipids. Lipid rafts are composed mostly of saturated fatty acids surrounded with more “fluid” unsaturated fatty acids [92]. Signal proteins with the affinity to lipid rafts accumulate in the rafts with the formation of protein complexes with specific functional activities [93]. Formation of actin-dependent lipid nanoclusters in the membrane requires lipids with long saturated acyl chains that make it possible for the lipids in the outer membrane leaflet to bind sphingolipids and gangliosides of the inner membrane leaflet [94]. Cholesterol stabilizes the liquid-crystal structure of lipid rafts and provides recruitment of more components into the clusters via a positive feedback mechanism [95].

The approximation of neuronal currents recorded in patch clamp experiments using computer modeling of diffusion processes has shown that CaM is sensitive to calcium entry through NMDARs, on the assumption of their tight spatial colocalization within tens of nanometers [96]. The modeling showed that the kinetics of CaM

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**Fig. 4.** Calcium-dependent local functional interactions between NMDARs and other ion channels and transporters within lipid rafts. a) Interactions between NMDARs, AMPARs, VGCCs, NCX, and PMCA. In the absence of receptor activation (1), PMCA maintains the intracellular Ca^{2+} concentration of 30-100 nM. Activation of NMDARs and calcium-permeable AMPARs by glutamate (2) causes calcium and sodium entry, depolarization of neurons, and VGCC activation followed by additional calcium entry. CaM binds calcium with the formation of Ca/CaM. The concentration of intracellular Ca^{2+} becomes sufficient to be transported by NCX. 3) AMPARs undergo ligand-dependent desensitization. Ca/CaM causes desensitization of NMDARs and VGCCs, thereby limiting calcium entry. The equilibrium between calcium entry and removal is achieved. 4) NMDAR deactivation by glutamate removal allows NCX to transport out most of Ca^{2+}, while PMCA brings the concentration of intracellular Ca^{2+} to the basic level. b) The decrease in the amplitude of ion current through NMDARs as a result of calcium-dependent desensitization is facilitated by the AMPAR and VGCC activation but weakens as a result of NCX and PMCA activity.
association with NMDARs most exactly reflects the parameters of calcium-dependent receptor inactivation, which can occur only if CaM molecules localize close to the C-terminal fragments of the GluN1 subunits.

Plasma membrane calcium transporters extruding calcium from the cytosol, such as PMCA and NCX, colocalize within lipid raft-associated microdomains. These proteins co-immunoprecipitate with caveolin-1 after membrane treatment with methyl-β-cyclodextrin that destroys lipid domains. FRET imaging revealed that PMCA and NCX are located at the periphery of microdomains which are usually smaller than 200 nm [92].

Calcium entry through L-VGCCs can create temporary local micromolar concentrations of intracellular calcium at a distance up to 100 nm from the channel (depending on the calcium-buffering capacity of the microenvironment) [97], which approximately corresponds to the size of a dynamic lipid membrane domain of 10-200 nm [92].

At the same time, L-VGCCs and NMDARs colocalize in caveolin-enriched lipid domains within a distance of 200 nm. At such a small distance, L-VGCC activation can temporarily increase the concentration of free calcium near NMDAR up to 10-100 μM. Free calcium concentration can increase to 1 mM within 100 nm from the channel at a low buffering capacity and within 70-80 nm in the presence of 0.1 mM calcium chelator with $K_d \sim 250$ nM [90].

Other factors can also control association between apoCaM (calmodulin not associated with calcium) and its targets. Thus, high amounts of the calcium-binding protein neurogranin in the dendritic spines cause calcium dissociation from Ca/CaM, thereby increasing the content of apoCaM in the microenvironment [98, 99].

It is possible that the binding sites for apoCaM and Ca/CaM in the NMDAR overlap [61] and there is no selectivity in the regulation of calcium-dependent desensitization relative to the source of calcium. Indeed, calcium-dependent desensitization can develop in response to other calcium sources [25, 97]. However, according to the model proposed in [96], all primary channels are inactivated during NMDAR activation, and the contribution of other sources to the calcium concentration increase is minimal. Hence, the initial sensitivity of the receptor to local calcium concentration remains the determining factor, especially in dendritic spines, where the spine geometry and calcium buffering prevent calcium diffusion to a noticeable distance from the primary source.

In inhibitory neurons, the diffusion of calcium entering the dendrites (which carry no spines in this type of neurons) through the ion channels is limited by the calcium-binding protein parvalbumin, which substantially sequesters the postsynaptic calcium responses [100]. Calbindin-D28K is a “slow” calcium chelator, whose kinetics of intracellular calcium binding is close to that of EGTA. Therefore, calbindin probably has no effect on the kinetics of calcium response but limits the maximum distance of free calcium diffusion [101].

In contrast to rapidly internalized AMPARs, NMDARs are stably present in the postsynaptic membrane [66, 102]. Calcium-dependent desensitization of NMDARs ensures rapid modulation of their contribution to synaptic transmission. For example, in glutamatergic synapses, the contribution of NMDARs to the shape of postsynaptic currents depends, in particular, on the calcium entry through calcium-permeable AMPARs and calcium buffering capacity of the postsynaptic microenvironment. Calcium removal from the post-synapse and sequestering of the intracellular calcium, on the contrary, increase the amplitude and duration of NMDAR-mediated postsynaptic currents [103]. The efficiency and the speed of interactions between NMDARs and other modulators of local calcium homeostasis are determined by compartmentalization of ion channels, transporters, and calcium-binding proteins in the lipid membrane microdomains. Impairments in the structure of the latter by statins can exert a neuroprotective effect in ischemia [102] but impairs NMDAR-dependent synaptic plasticity due to the considerable decrease in the membrane cholesterol levels [104].

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