NMDA Receptor Function and Physiological Modulation

K Zito, University of California at Davis, Davis, CA, USA
V Scheuss, Max-Planck-Institute for Neurobiology, Martinsried, Germany

Introduction

With key roles in essential brain functions ranging from the basics of excitatory neurotransmission to the complexities of learning and memory, the N-methyl-D-aspartate (NMDA) receptor can be considered one of the fundamental neurotransmitter receptors in the brain. Named for its most potent exogenous agonist, the NMDA receptor has been thoroughly characterized via electrophysiological and pharmacological techniques, as well as through molecular manipulations and transgenic knockout strategies. The NMDA receptor belongs to a family of ionotropic receptors for the excitatory amino acid glutamate and is characterized by high affinity for glutamate, a high unitary conductance, high calcium permeability, and a voltage-dependent block by magnesium ions. this article focuses on the basic biophysical properties and physiological functions of NMDA receptors and how these are modulated by various signaling molecules and biochemical cascades under physiological conditions.

Biophysical Properties of NMDA Receptors

During excitatory neurotransmission, presynaptic release of glutamate activates glutamate receptors in the postsynaptic membrane, resulting in the generation of an excitatory postsynaptic potential (EPSP). Contributing to the EPSP are two classes of glutamate receptors, the non-NMDA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors) and the NMDA receptors (Figure 1). The rise times for NMDA receptor currents (10–50 ms) are much slower than those of non-NMDA receptors (0.2–0.4 ms). NMDA receptors also deactivate with a slower time course ($\sim$50–500 ms vs. $\sim$2 ms for non-NMDA glutamate receptors), much longer than the time course of glutamate in most synaptic clefts ($\sim$1.2 ms). Therefore, during synaptic transmission, the non-NMDA glutamate receptors provide rapid depolarization in response to neurotransmitter release, and the NMDA receptor kinetics determine the duration of the synaptic current.

Activation of NMDA receptors by the neurotransmitter glutamate requires glycine as an essential coagonist. Glutamate and glycine molecules bind different subunits of the receptor; two of each are thought to be required for maximum activation of the receptor. Recent experiments have shown that D-serine can also bind at the glycine site and might represent another physiological coagonist. Compared with glutamate receptors of the non-NMDA type, which have low-affinity binding sites for glutamate (EC_{50} $\sim$500 μM), NMDA receptors bind glutamate with high affinity (EC_{50} $\sim$1 μmol l^{-1}). Despite this high affinity for glutamate, NMDA receptors are not saturated during synaptic transmission at synapses of cortical pyramidal neurons.

NMDA receptor activation leads to opening of an ion channel that is selective for cations, resulting in the influx of Na^+ and Ca^{2+} ions and efflux of K^+ ions. Although most glutamate receptors are cation selective, few are permeable to calcium ions. Its exceptional calcium permeability is the first of two key properties of the NMDA receptor that form the basis for its regulatory role in synaptic plasticity. Entry of calcium into the postsynapse via the NMDA receptor (Figure 2) permits coupling of electrical synaptic activity to biochemical signaling via activation of Ca^{2+}-dependent enzymes and downstream signaling pathways. In this way, calcium influx through the NMDA receptor can lead to long-term changes in synaptic strength and other cellular modifications, including alterations in synaptic structure or connectivity.

The NMDA receptor has a high single channel conductance ($\sim$30–50 pS) compared with that of other glutamate receptor types ($\sim$4–15 pS). The open probability of agonist-bound receptors has been estimated to range between 0.04 and 0.3, and open times can vary from 0.1 to 8 ms. The molecular events that underlie the opening of NMDA receptors are predicted to include two independent agonist-binding steps preceding a single, concerted conformational change that results in channel opening. Channel closing is thought to be controlled both by the unbinding rate of glutamate and by receptor desensitization. In fact, NMDA receptors can enter long-lived desensitized conformations in which glutamate is bound but the channel remains closed.

The second key biophysical property of the NMDA receptor, and the one that bestows its proposed role in learning and memory, is that it is blocked by magnesium ions in a voltage-dependent manner. At resting membrane potential, NMDA receptors are blocked by magnesium ions; however, if excitation by synaptic inputs causes sufficient depolarization of the neuron, the Mg^{2+} block is relieved and those NMDA receptors which have glutamate bound will open (Figure 3).
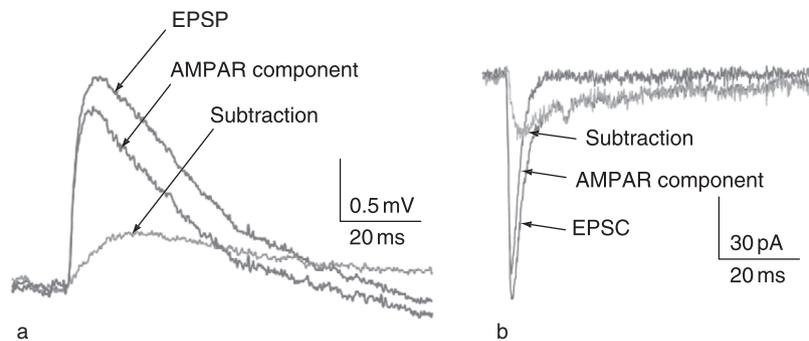
Figure 1 NMDA receptor component of excitatory postsynaptic potentials (EPSPs) and excitatory postsynaptic currents (EPSCs). (a) Unitary EPSP ('EPSC') recorded in a L2/3 cortical pyramidal neuron. The NMDA receptor-mediated component (subtraction) was obtained by subtracting the non-NMDA receptor-mediated component (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAR) component) when NMDA receptors were blocked with the NMDA receptor antagonist AP5. (b) Unitary EPSC ('EPSC') recorded in a L2/3 cortical pyramidal neuron. The NMDA receptor-mediated component (subtraction) and the non-NMDA receptor mediated component (AMPAR component) were determined as in (a). Reproduced from Blackwell Publishing: figure 6A and B in Feldmeyer D, Lübke J, Silver RA, et al. (2002) Synaptic connections between layer 4 spiny neuron-layer 2/3 pyramidal cell pairs in juvenile rat barrel cortex: Physiology and anatomy of interlaminar signaling within a cortical column. *Journal of Physiology* 538(3): 803–822.
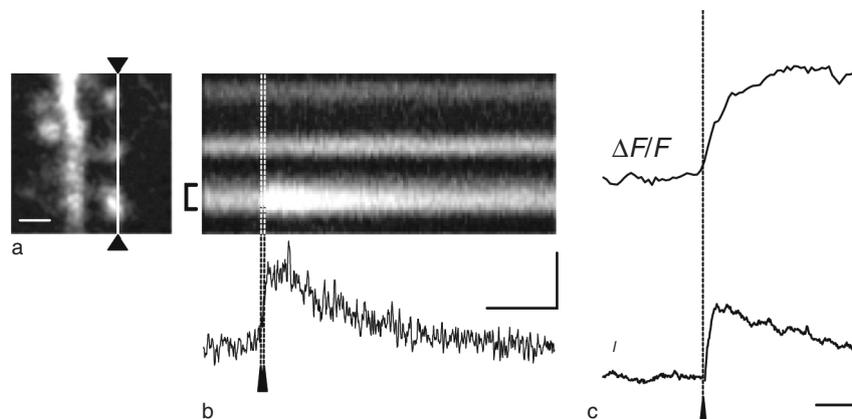
Figure 2 Synaptic activation of NMDA receptors causes calcium entry into spines. (a) Two-photon fluorescence image of a dendritic branch of a hippocampal CA1 pyramidal neuron loaded with the calcium indicator Oregon Green BAPTA. Scale bar $= 1\,\mu m$. (b) Sequences of line scans in which the vertical dimension corresponds to the line indicated in (a) and the horizontal dimension represents time. Below: Relative change in fluorescence ($\Delta F/F(t)$) at the bottom spine (averaged over window indicated by bracket) during calcium entry evoked by synaptic stimulation (time indicated by arrowhead). The neuron was voltage clamped at positive potential to isolate NMDA receptor-mediated Ca^{2+} influx. Scale bars $= 250\,ms$, 50% $\Delta F/F_{max}$. (c) Average EPSC (bottom) and corresponding $\Delta F/F(t)$ (top) at the same spine as in (b). Scale bars $= 25\%$ $\Delta F/F_{max}$, 100 pA, 25 ms. Reprinted by permission from MacMillan Publishers Ltd.: *Nature* (Mainen ZF, Malinow R, and Svoboda K (1999) Synaptic calcium transients in single spines indicate that NMDA receptors are not saturated. *Nature* 399: 151–155) copyright 1999.

Since opening of the NMDA receptor requires simultaneous activation by glutamate and depolarization to relieve the magnesium block, the NMDA receptor can act as a coincidence detector for pre- and postsynaptic activity.

Glutamate and glycine affinities, calcium permeability, ion conductance, channel kinetics, and sensitivity to Mg^{2+} block of the NMDA receptor are all determined in part molecularly, by alternative splicing and subunit composition. Most of these biophysical properties of NMDA receptors can also be modulated by various ionic and molecular interactions and signaling pathways (described below).

NMDA Receptor Physiological Function

The outstanding physiological function of NMDA receptors is the coupling of electrical to biochemical signaling in neurons by mediating calcium influx in response to synaptic activity. However, NMDA receptors also serve important functions in electrical neurotransmission alone. Despite the voltage-dependent magnesium block, NMDA receptors can contribute significantly to the amplitude of unitary evoked postsynaptic potentials. The slow kinetics of NMDA receptor-mediated excitatory postsynaptic currents (EPSCs) facilitates temporal summation and reduces
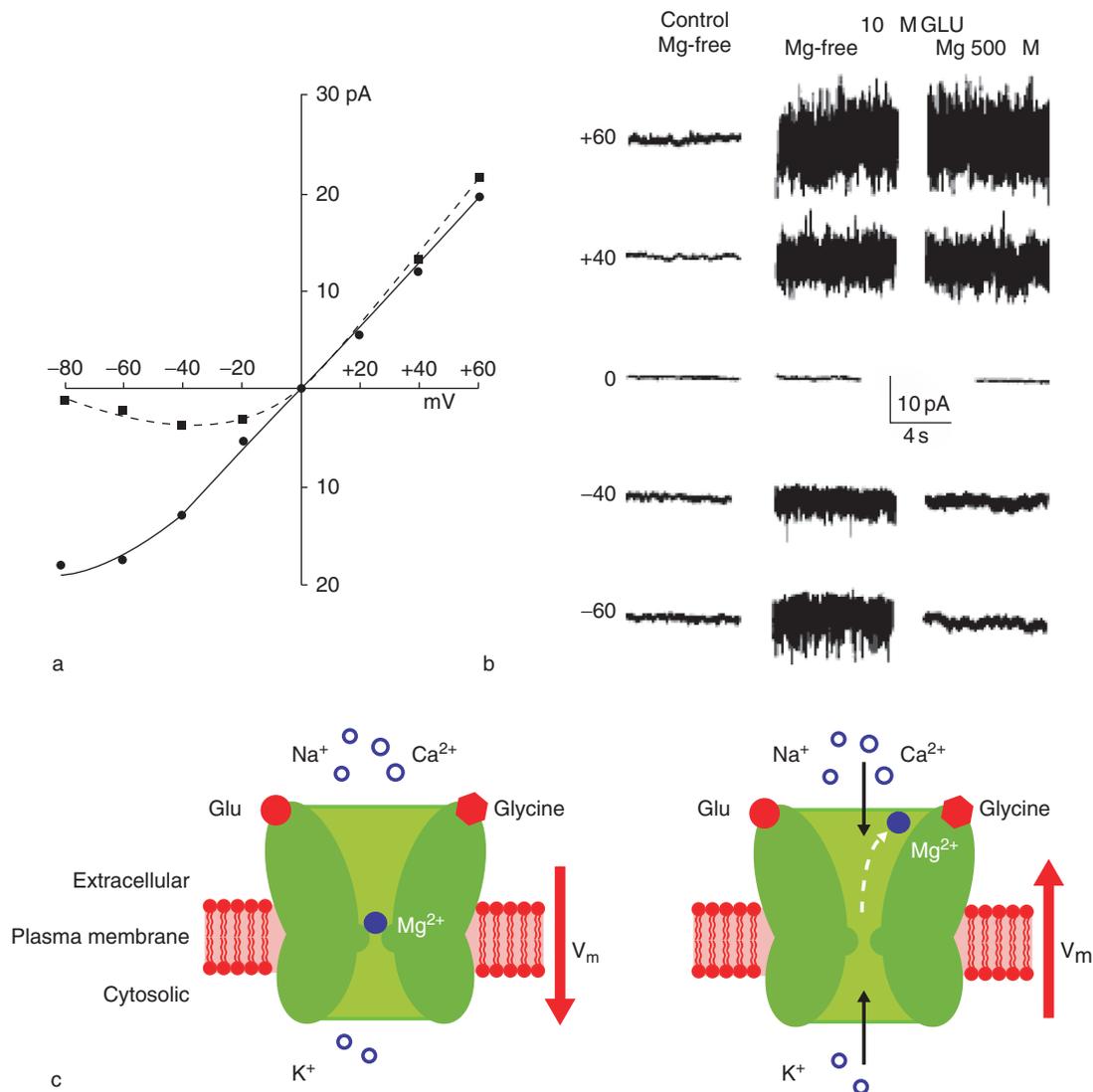
Figure 3 Magnesium block of NMDA receptors. (a) Voltage dependence of glutamate-induced currents in Mg^{2+}-free (circles) and Mg^{2+}-containing solution (500 μM; squares). (b) Voltage and Mg^{2+}-dependence of NMDA receptor current noise. Reprinted by permission from MacMillan Publishers Ltd: *Nature* (Nowak L, Bregestovski P, Ascher P, et al. (1984) Magnesium gates glutamate-activated channels in mouse central neurons. *Nature* 307: 462–465) copyright 1984. (c) Schematic of the mechanism of the magnesium block. At resting potential, the pore of the NMDA receptor channel is blocked by magnesium ions. Upon depolarization, the magnesium ions are removed from the pore, and the channel can pass current.

dendritic filtering of synaptic inputs. In addition, coactivation of multiple synapses can trigger NMDA receptor-dependent dendritic spikes by generating sufficient depolarization to overcome the magnesium block. Such dendritic spikes cause nonlinear synaptic integration, which enhances the computational power of neurons and may allow neurons to detect the synchrony of inputs (**Figure 4**).

The NMDA receptor plays an essential role in brain plasticity, that is, the ability of the brain to change in response to external stimuli, such as during learning and memory. First investigated pharmacologically, chronic blockade of the NMDA receptor by

infusion of an antagonist into the ventricles of rats was shown to impair spatial learning. Since that time, similar behavioral experiments have been performed using knockout mice lacking NMDA receptor subunits from specific subregions of the hippocampus. These experiments have repeatedly provided evidence for the importance of the NMDA receptor in learning and memory processes.

The role of the NMDA receptor in learning and memory is attributed to its ability to regulate excitatory synaptic transmission. The NMDA receptor has been shown to play an essential role in both the strengthening of synapses, through long-term

Paired-pulse stimulation

a

b
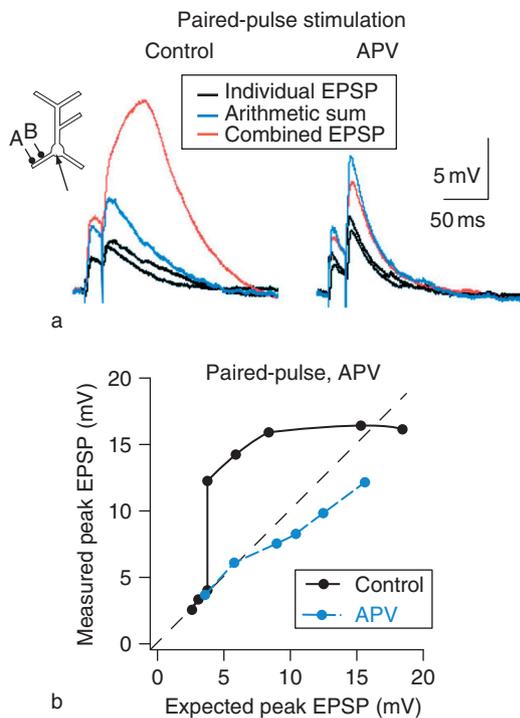
Figure 4 NMDA receptors in nonlinear synaptic integration. (a) Somatic voltage responses of a layer 5 pyramidal neuron to stimuli from two electrodes (A and B) placed 30 μm apart on a single dendritic branch display nonlinear summation (left panel). With application of the NMDA receptor antagonist, APV, the summation is linear. EPSP, excitatory postsynaptic potential. (b) Expected vs. actual peak somatic responses plotted for different stimulus intensities before (black) and after (blue) application of APV. NMDA receptor blockade linearizes synaptic summation. Reprinted by permission from MacMillan Publishers Ltd: *Nature Neuroscience* (Polsky A, Mel BW, and Schiller J (1994) Computational subunits in thin dendrites of pyramidal cells. *Nature Neuroscience* 7: 621–627), copyright 1994.

potentiation (LTP), and the weakening of synapses, through long-term depression (LTD). LTP and LTD are proposed to be cellular mechanisms underlying learning and memory. Via its role as a coincidence detector, the NMDA receptor is capable of signaling coincident pre- and postsynaptic activity. Detailed studies of the relationship between the temporal correlation of pre- and postsynaptic activity and the resulting type of plasticity have led to the discovery of spike-timing dependent plasticity. If the presynaptic action potential (AP; and thus synaptic activity) repetitively precedes the generation of the postsynaptic AP by less than ∼50 ms, the synapse is potentiated; however, if the postsynaptic AP occurs within ∼50 ms before the presynaptic AP (and thus independently of presynaptic activity), the synapse is depressed (Figure 5). With respect to the more complex and irregular patterns of neuronal activity that are likely found *in vivo*, it has been suggested that both rate and timing determine the direction of neuronal plasticity.
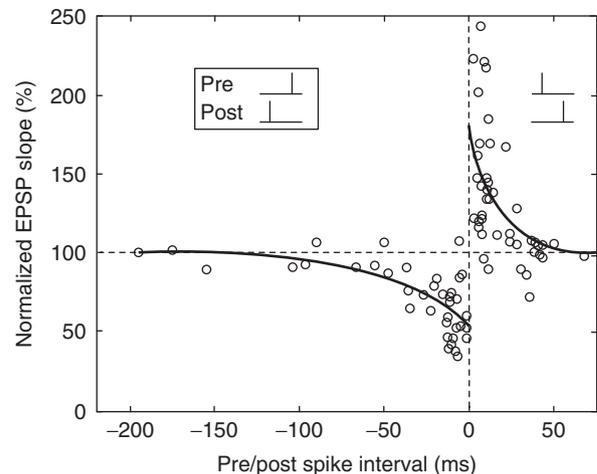
Figure 5 Spike-timing-dependent synaptic plasticity. Change in excitatory postsynaptic potential (EPSP) slope induced by repetitively paired pre- and postsynaptic spikes in layer 2/3 of rat visual cortex. Insets depict the sequence of spiking. Pre before postsynaptic spiking leads to potentiation while post before presynaptic spiking leads to depression. Used from The American Physiological Society: figure 1 in Dan Y and Poo MM (2006) Spike timing-dependent plasticity: From synapse to perception. *Physiological Reviews* 86: 1033–1048.

The NMDA receptor also acts as a coincidence detector during development, where it plays a critical role in the maturation of synapses and the activity-dependent establishment of topographic maps in the brain. By acting to strengthen neighboring connections of similar activity patterns, the NMDA receptor enforces the principle that 'cells that fire together, wire together.' In addition, early in development, many excitatory synapses appear to contain only NMDA receptors, and therefore these synapses are thought to be at first silent (no EPSP in response to synaptic stimulation). It is hypothesized that only through coincident activity sufficiently robust to depolarize the postsynaptic cell and relieve the voltage-dependent Mg^{2+} block of the NMDA receptors does the insertion of non-NMDA receptors at these synapses occur.

While presynaptic NMDA receptors have been detected by immuno-electron microscopy, their function remains far less established compared with their postsynaptic counterparts. As autoreceptors, presynaptic NMDA receptors have been shown to modulate synaptic transmission in the spinal cord, cerebellum, and entorhinal cortex and to play a role in cerebellar and cortical LTD.

Calcium influx through the NMDA receptor is thought to be responsible for its roles in LTP and LTD and for both neuroprotective and neurotoxic effects. Although these various effects may at first seem contradictory, the explanation lies in the spatial

and temporal patterns of calcium influx. Calcium influx at synaptic sites is thought to activate signaling pathways that lead to LTP or LTD, depending on the temporal pattern and amplitude of the calcium transient. Synaptic calcium influx also leads to activation of cyclic adenosine monophosphate response element binding protein (CREB), a transcription factor, resulting in activation of gene expression. One of the genes upregulated in response to activated CREB is brain-derived neurotrophic factor (BDNF), which acts to promote prosurvival programs. In contrast, calcium influx through extrasynaptic NMDA receptors is thought to lead to CREB deactivation and inhibition of BDNF expression, which can have deleterious effects on cell health. In fact, overstimulation of NMDA receptors results in neuronal excitotoxicity, which has been implicated in the loss of neurons associated with ischemic stroke; Alzheimer's, Parkinson's, and Huntington's disease; and amyotrophic lateral sclerosis.

Physiological Modulation of NMDA Receptors

Although glycine and/or D-serine are essential co-agonists of the NMDA receptor, and thus, strictly speaking, not modulators, their cytosolic levels nevertheless regulate NMDA receptor activation. One of two amino acids appears to predominate, dependent on the brain region. The cytosolic concentrations are controlled by release and uptake by both neurons and glia. Stimulated release of glycine and D-serine can be induced by depolarization or non-NMDA glutamate receptor activation. In the spinal cord, glycine spillover from inhibitory synapses has been shown to enhance NMDA receptor currents.

Desensitization

As the NMDA receptor is a ligand-gated ion channel, it can display a decrease in conductance despite the continuous presence of agonist, a process referred to as desensitization. Three different types of desensitization have been reported for NMDA receptors, a glycine-sensitive, a glycine-insensitive, and a calcium-dependent type. The glycine-sensitive desensitization refers to the transition of the NMDA receptor into a glutamate-bound closed state, reflecting a negative allosteric interaction between the glutamate and the glycine binding sites, which results in a reduced glycine affinity in the presence of high glutamate concentrations. High glycine concentrations can overcome this type of desensitization. Glycine-insensitive desensitization has been observed only in dialyzed cells and excised membrane patches and thus does not appear to be physiologically relevant. The calcium-dependent desensitization (also referred to as calcium-dependent inactivation) provides a negative feedback loop by which calcium entering the cell via NMDA receptors in turn leads to the desensitization of the receptor (Figure 6), although calcium from other sources (voltage-gated calcium channels or release from intracellular stores activated by second messenger cascades) has the same effect. In a current model, calcium influx activates calmodulin to displace α-actinin2 from the NMDA receptor. The resulting dissociation of the NMDA receptor from the cytoskeleton is proposed to cause a conformational change in the receptor, which reduces its open probability.

Endogenous Allosteric Modulators

NMDA receptor function is fine-tuned by various forms of allosteric modulation involving endogenous extracellular substances such as zinc ions, protons, polyamines,
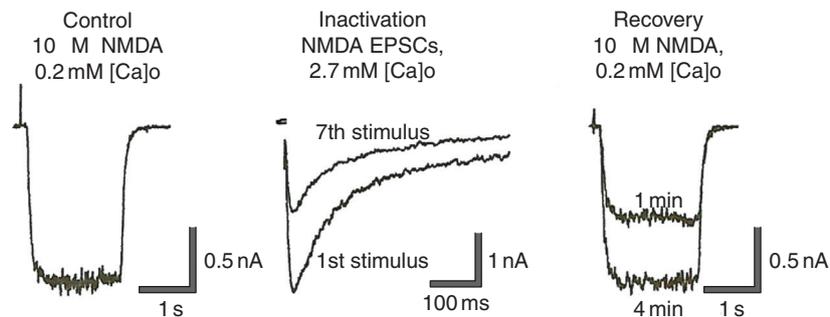
Figure 6 Calcium-dependent desensitization of NMDA receptors. Whole cell currents of cultured rat hippocampal neurons (left and right panels) were evoked in low calcium (0.5 μM) solutions by application of NMDA. During a train of seven excitatory postsynaptic currents (EPSCs) evoked in 2.7 μM calcium, the NMDA receptor mediated EPSC was inactivated to ∼50% of control (middle). The whole cell current was inactivated to a similar degree and recovered within 4 min. Used from The American Physiological Society: figure 3 in Rosenmund C, Feltz A, and Westbrook GL (1995) Calcium-dependent inactivation of synaptic NMDA receptors in hippocampal neurons. *Journal of Neurophysiology* 73: 427–430.

and reducing and oxidizing agents (Figure 7). Zinc and polyamines mediate a voltage-dependent block of NMDA receptors, which is weaker but appears to involve the same intrapore residues as block by magnesium. Some of the voltage-independent effects of allosteric modulators are mutually interdependent, and structural evidence suggests convergence by overlapping binding sites or common downstream structural modifications. Zinc, protons, and oxidizing agents inhibit NMDA receptor function, while polyamines and reducing agents cause potentiation by modifying channel open frequency and time or agonist or modulator affinities. These modulations are considered to be physiologically relevant during synaptic transmission, when synaptic activity can cause shifts in pH, co-release of Zn^{2+} occurs at certain synaptic terminals (e.g., mossy fiber-CA3), and the amine histamine is released from modulatory afferents (e.g., those arising from the anterior hypothalamus). An important aspect of the negative regulation of NMDA receptor function by pH and oxidizing agents is that it can limit or delay cell damage under pathological conditions such as stroke and ischemia.

Phosphorylation

NMDA receptors can be phosphorylated by the serine/threonine kinases protein kinase C (PKC), protein kinase A (PKA) and calcium/calmodulin-dependent protein kinase II (CaMKII), as well as by the tyrosine kinases Src and Fyn. In general, phosphorylation enhances NMDA receptor function (Figure 7).

A significant percentage of NMDA receptor subunits in the brain are estimated to be phosphorylated by PKC or PKA at one or more sites (10–70%, depending on the region of the brain). Phosphorylation by PKC reduces the affinity for extracellular magnesium ions and increases the open probability. Calcium influx through the NMDA receptor itself can enhance the potentiation mediated by PKC. However, in some preparations, phosphorylation by PKC reduced NMDA receptor-mediated responses by preventing NMDA receptor subunit clustering. Less is known about the regulation of NMDA receptors by PKA and CaMKII. Active CaMKII directly associates with the NMDA receptor, and this association is required for some forms of activity-driven synaptic potentiation. PKA activation has been shown to increase the fractional Ca^{2+} influx through the NMDA receptor; however, some of the effects of PKA activation on NMDA function appear to be indirect.

In contrast, fewer NMDA receptor subunits on neural membranes are phosphorylated on tyrosine residues (2–4%). Phosphorylation by Src enhances NMDA receptor function (Figure 8) by reducing the potency of Zn^{2+} block of recombinant NMDA receptors expressed heterologously; however, evidence is lacking for this mechanism in hippocampal or spinal cord neurons. An alternative view proposes that phosphorylation of NMDA receptor subunits by Src-family kinases could affect downstream signaling proteins, either by recruiting them to the NMDA receptor, by
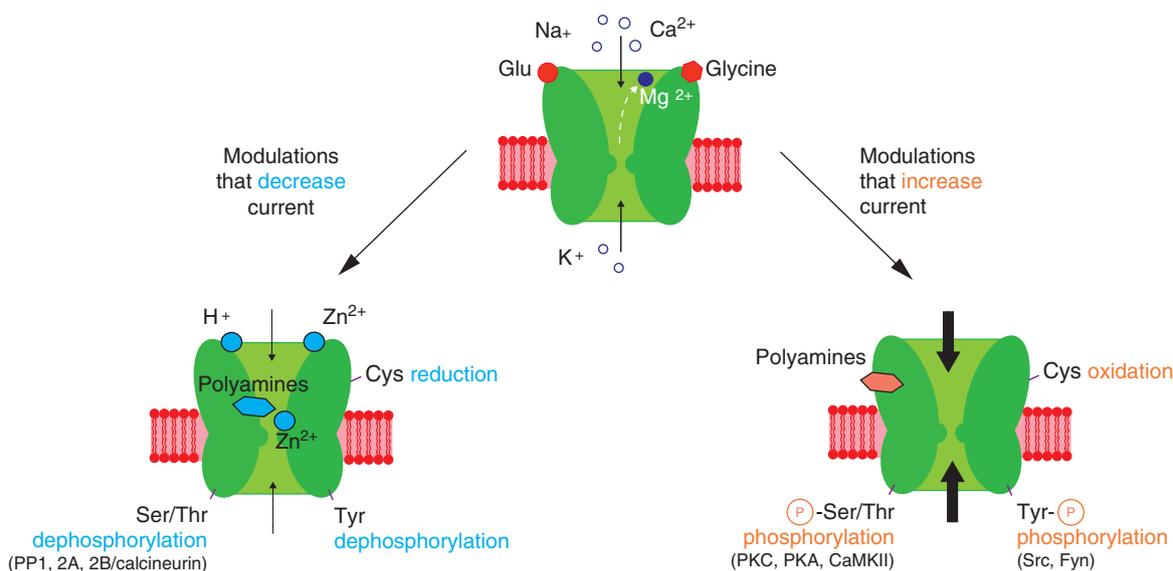
Figure 7 Schematic overview of modulators of NMDA receptor functions. Activation of the NMDA receptor requires binding of glutamate (Glu) and glycine (or serine) together with membrane depolarization to release the magnesium block (center). Modulators causing depression of NMDA receptor currents (left) include H^+, Zn^{2+}, polyamines, reducing agents, and the protein phosphatases PP1, PP2A, and PP2B/calcineurin. Polyamines and Zn^{2+} cause a voltage-dependent block similar to that caused by Mg^{2+}. Modulators causing potentiation of NMDA receptor currents (right) include external polyamines, oxidizing agents, and the protein kinases PKC, PKA, CaMKII, Src, and Fyn. For details see text.

protecting them against degradation, or through blocking the assembly of signaling complexes. Src-mediated phosphorylation appears to play a role in LTP induction and seems to be modulated by BDNF. Phosphorylation by Fyn may target the NMDA receptor to the plasma membrane by antagonizing its interaction with spectrin.

In some cases, Src activity is required for PKC-mediated activation of NMDA receptor currents, placing Src downstream of PKC on the same pathway. PKC stimulation leads to the activation of the nonreceptor protein tyrosine kinase, cell adhesion kinase-β, which activates Src by disrupting the intramolecular interactions that maintain Src in a low-activity state. Activation of Src then leads to the potentiation of NMDA receptor currents. The effects of Src on NMDA receptors can be modulated by H-Ras, a small guanosine triphosphate (GTP)-binding protein, which binds Src and inhibits its activity. Hippocampal pyramidal neurons from H-ras homozygous null mice displayed enhanced NMDA receptor synaptic responses.

The activation of NMDA receptors by phosphorylation can be reversed by serine and threonine phosphatases 1, 2A, and 2B (calcineurin) and endogenous tyrosine phosphatases. Inhibition of endogenous protein tyrosine phosphatase activity led to potentiation of NMDA receptor currents, indicating that these phosphatases participate in determining the basal phosphorylation level of the NMDA receptor.
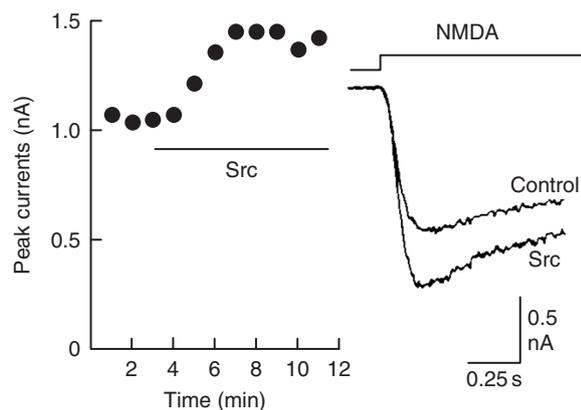
Figure 8 The protein tyrosine kinase pp60^{c-src} potentiates NMDA currents. Whole cell recordings were made from mouse cultured hippocampal neurons. Peak currents evoked by rapid application of NMDA (100 μM) are plotted in the graph on the left. The tyrosine kinase pp60^{c-src} (30 U per milliliter) was actively perfused through the recording electrode. The period of the perfusion is indicated by the horizontal bar on the graph. On the right, representative currents recorded before (Control) and after (Src) intracellular perfusion with pp60^{c-src} are shown. NMDA was applied as indicated by the trace above the currents. Reprinted by permission from MacMillan Publishers Ltd: *Nature* (Wang YT and Salter MW (1994) Regulation of NMDA receptors by tyrosine kinases and phosphatases. *Nature* 369: 233–235), copyright 1994.

Calcineurin can be activated by calcium influx through the NMDA receptor itself.

Modulatory Signaling Receptors

Modulation of NMDA receptors by kinases and phosphatases occurs downstream of a number of membrane receptors, the largest group of which are the G-protein-coupled receptors (GPCRs). GPCRs are integral membrane proteins which transmit extracellular signals to the cytoplasm by coupling to heterotrimeric GTP-binding proteins. Activation of a subset of GPCRs, including metabotropic glutamate receptors (mGluRs), muscarinic acetylcholine receptors, μ opioid receptors, lysophosphatidic acid (LPA) receptors, and the protease-activated receptor PAR1, enhances NMDA receptor currents. Those GPCRs that are coupled to Gq proteins, such as mGluR5, m1 muscarinic receptor, and the LPA receptor, are thought to act through a PKC-Src signaling pathway, and mGluR1 also activates Src, but through a PKC-independent pathway. A second set of GPCRs, those coupled through Gs, are thought to enhance activity of the NMDA receptor through activation of Src-family kinases via PKA and receptor for activated C kinase 1 (RACK1). One such GPCR, the pituitary adenylate cyclase activating polypeptide (PACAP) receptor, is activated by the neuropeptide PACAP(1–38), which has been shown to potentiate NMDA receptor-mediated excitatory postsynaptic field potentials in hippocampal slices. Finally, NMDA receptors have been shown to interact directly with G-protein-coupled dopamine receptors. Depending on the class of dopamine receptor, activation of dopamine receptors has been reported both to enhance and to inhibit NMDA receptor currents.

NMDA receptor currents are also influenced by downstream signaling from receptor protein tyrosine kinases, including the EphB receptors, platelet-derived growth factor (PDGF) receptors, and insulin receptors. EphB receptors interact directly with NMDA receptors in cultured neurons, and their activation by ephrinB2 increases NMDA receptor-dependent calcium responses via the activation of Src. Insulin has been shown to enhance NMDA receptor activity in hippocampal slices via a mechanism that requires PKC and tyrosine kinase activity. In contrast, application of PDGF depresses NMDA receptor currents in hippocampal pyramidal neurons via a phospholipase C-IP$_3$ receptor-cyclic AMP-PKA pathway that inhibits Src activity.

Cytokine receptor activation has been shown to enhance NMDA receptor currents. One group of cytokines, leptins, enhances NMDA receptor-mediated EPSCs in hippocampal slices via activation of the leptin receptor Ob-R$_b$. The leptin-mediated potentiation was

reduced by inhibitors of PI3-kinase, mitogen-activated protein kinase, and Src-family kinases. Another cytokine, interleukin (IL)-1β, enhanced the rise in intracellular calcium following application of NMDA to cultured hippocampal neurons, a response mediated by the IL-1RI receptor.

NMDA Receptor Complex

The ability of modulators to influence NMDA receptor currents is dependent on their abundance and proximity to the receptor. Proteomic characterization identified synaptic NMDA receptors as part of a remarkably large macromolecular signaling complex called the NMDA receptor complex. NMDA receptors were found linked to receptors, adhesion molecules, scaffolding proteins, signaling molecules, cytoskeletal proteins, and various novel proteins, in complexes lacking non-NMDA receptors. Among the signaling proteins were kinases, phosphatases, GTPases, and GTPase-activating proteins. Physical linkage of these receptors, signaling molecules, and the cytoskeleton to the NMDA receptor is an important way to facilitate rapid modulation of the receptor in response to synaptic activity.

See also: D-Serine: From its Synthesis in Glial Cell to its Action on Synaptic Transmission and Plasticity; Kainate Receptor Functions; Long-Term Depression (LTD): Metabotropic Glutamate Receptor (mGluR) and NMDAR-Dependent Forms; Long-Term Potentiation (LTP): NMDA Receptor Role; Long-Term Potentiation and Long-Term Depression in Experience-Dependent Plasticity; NMDA Receptors and Development; NMDA Receptors and Disease + C464; NMDA Receptors, Cell Biology and Trafficking.

Further Reading

Cull-Candy SG and Leszkiewicz DN (2004) Role of distinct NMDA receptor subtypes at central synapses. *Science's STKE: Signal Transduction Knowledge Environment* 255: re16.

Dan Y and Poo MM (2006) Spike timing-dependent plasticity: From synapse to perception. *Physiological Reviews* 86: 1033–1048.

Dingledine R, Borges K, Bowie D, et al. (1999) The glutamate receptor ion channels. *Pharmacological Reviews* 51: 7–61.

Edmonds B, Gibb AJ, and Colquhoun D (1995) Mechanisms of activation of glutamate receptors and the time course of excitatory synaptic currents. *Annual Review of Physiology* 57: 495–519.

Feldmeyer D, Lübke J, Silver RA, et al. (2002) Synaptic connections between layer 4 spiny neuron-layer 2/3 pyramidal cell pairs in juvenile rat barrel cortex: Physiology and anatomy of interlaminar signaling within a cortical column. *Journal of Physiology* 538(3): 803–822.

Husi H, Ward MA, Choudhary JS, et al. (2000) Proteomic analysis of NMDA receptor-adhesion protein signaling complexes. *Nature Neuroscience* 3: 661–669.

Kotecha SA and MacDonald JF (2003) Signaling molecules and receptor transduction cascades that regulate NMDA receptor-mediated synaptic transmission. *International Review of Neurobiology* 54: 51–106.

Lester RA and Jahr CE (1992) NMDA channel behavior depends on agonist affinity. *Journal of Neuroscience* 12: 635–643.

Mainen ZF, Malinow R, and Svoboda K (1999) Synaptic calcium transients in single spines indicate that NMDA receptors are not saturated. *Nature* 399: 151–155.

Nowak L, Bregestovski P, Ascher P, et al. (1984) Magnesium gates glutamate-activated channels in mouse central neurons. *Nature* 307: 462–465.

Polsky A, Mel BW, and Schiller J (2004) Computational subunits in thin dendrites of pyramidal cells. *Nature Neuroscience* 7: 621–627.

Rosenmund C, Feltz A, and Westbrook GL (1995) Calcium-dependent inactivation of synaptic NMDA receptors in hippocampal neurons. *Journal of Neurophysiology* 73: 427–430.

Salter MW and Kalia LV (2004) Src kinases: A hub for NMDA receptor regulation. *Nature Reviews Neuroscience* 5: 317–328.

Schneggenburger R, Zhou Z, Konnerth A, et al. (1993) Fractional contribution of calcium to the cation current through glutamate receptor channels. *Neuron* 11: 133–143.

Vanhoutte P and Bading H (2003) Opposing roles of synaptic and extrasynaptic NMDA receptors in neuronal calcium signalling and BDNF gene regulation. *Current Opinion in Neurobiology* 13: 366–371.

Wang YT and Salter MW Regulation of NMDA receptors by tyrosine kinases and phosphatases. *Nature* 369: 233–235.