

Modulation of ionotropic glutamate receptors and acid- sensing ion channels by nit...

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Introduction

Ionotropic glutamate receptors (iGluR) are ligand-gated cation ion channels. They are classified into *N*-methyl-*D*-aspartate receptors (NMDAR), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA), and kainate receptors ([Dingledine et al., 1999](#)). These receptors are densely distributed in broad regions of the mammalian central nervous system (CNS). Functional iGluRs are assembled by distinct subunits. Activation of iGluRs by an endogenous ligand, i. e., neurotransmitter glutamate, opens the channel for the Na^+ flow into cells, resulting in depolarization. NMDARs and GluR2-lacking AMPARs also allow Ca^{2+} influx for triggering multifunctional Ca^{2+} -associated signaling pathways. Compared to NMDARs, AMPARs open and close more quickly, and thus mediate most of the fast excitatory synaptic transmission in the CNS. As a major group of excitatory receptors, iGluRs are critical for normal operations of cellular and synaptic activity and plasticity. Malfunction of these ion channels is thus frequently linked to the pathogenesis of a wide range of neurological disorders ([Dingledine et al., 1999](#)).

Neuronal cells are sensitive to changing extracellular proton (acid) concentrations. In sensory neurons, an acid-triggered inward ion current was first observed in 1980 ([Krishtal and Pidoplichko, 1980](#)). This current was then found to be mediated through the membrane-bound acid-sensing ion channel (ASIC; [Waldmann et al., 1997b](#)). ASICs are a distinct family of proton (H^+)-gated, voltage-independent, and cation (Na^+)-selective channels. They are broadly expressed in peripheral sensory neurons and CNS

neurons ([Waldmann et al., 1997a](#) , [b](#) ; [Alvarez de la Rosa et al., 2003](#)). More specifically, among all ASIC subunits so far identified, ASIC1a, 2a, and 2b are expressed in CNS neurons at a high level, while all other ASICs are expressed in peripheral sensory neurons. In addition, ASICs are seen in non-neuronal cells, such as vascular smooth muscles and bone ([Jahr et al., 2005](#) ; [Grifoni et al., 2008](#)). ASICs are important for maintaining cell homeostasis in response to normal changes in pH signals and are involved in discrete disorders where a dramatic drop in extracellular pH values (acidosis) occurs, such as seen in inflammation, ischemic stroke, traumatic brain injury, and acid nociception ([Wemmie et al., 2006](#) ; [Chu et al., 2011](#)).

Like many other ion channels, iGluRs and ASICs are subject to the modulation by various extracellular and intracellular signals. This modulation is essential for normal channel operations and for adjusting the efficacy and strength of channels to properly respond to a given stimulus. Among important modulators is nitric oxide (NO), a short-lived and plasma membrane diffusible gasotransmitter. Increasing evidence shows that NO can modulate iGluRs and ASICs through a direct (cGMP-independent) or an indirect (cGMP-dependent) pathway ([Ahern et al., 2002](#)). The direct pathway involves a NO-based post-translational modification of iGluR and ASIC proteins, i. e., S-nitrosylation. This biochemical reaction occurs when a nitrosyl group is added to the thiol side-chain of cysteine residues to form S-nitrosothiols, leading to changes in tertiary structure and function of modified iGluRs and ASICs ([Sen and Snyder, 2010](#)). The indirect pathway starts with NO stimulation of soluble guanylyl cyclase, leading to an increase in the second messenger cGMP production and activation of cGMP-

dependent downstream protein kinases ([Bredt and Snyder, 1989](#)). This review will discuss current progress in understanding the modulation of iGluRs and ASICs by NO. We reviewed these two types of channels together because (1) they are co-localized in the confined postsynaptic density microdomain ([Zha et al., 2006](#)), (2) they are functionally coupled to each other to contribute to neurological disorders involving excessive glutamate release and acidosis ([Gao et al., 2005](#)), and (3) they show some common properties in the regulation by NO.

Modulation of iGluRs by NO

NMDARs

The NMDAR is a unique ion channel that is both ligand-gated and voltage-dependent. Co-activation of NMDARs by the endogenous transmitters (glutamate and glycine) and the release of voltage-dependent Mg^{2+} block trigger the opening of ion channels, allowing the inward flow of Na^{+} and small amounts of Ca^{2+} into cells ([Dingledine et al., 1999](#)). The Ca^{2+} influx is critical for a variety of NMDAR signaling and function. Functional NMDARs are an assembly of obligatory NR1 and the modulatory NR2 subunits. Among all of the modulatory subunits (A-D), NR2A and NR2B are predominant NMDAR components and are mostly enriched in neurons ([Stephenson, 2001](#)).

NMDARs are closely linked to the NO system. Activation of NMDARs consistently increases activity of neuronal nitric oxide synthase (nNOS) in the cytoplasm of neurons. Active nNOS then catalyzes the production of endogenous NO from L-arginine, leading to an increased release of NO from

neurons ([Garthwaite et al., 1988](#) ; [Shibuki and Okada, 1991](#) ; [Bredt and Snyder, 1992](#)). A number of studies *in vitro* and *in vivo* have demonstrated a significant role of NO in the regulation of normal NMDAR function. In cultured neurons, the NO-producing agent 3-morpholino-sydnonimine (SIN-1) inhibited NMDA-induced currents and associated increases in Ca²⁺ influx ([Manzoni et al., 1992](#)). Similar results were observed with 1-nitrosopyrrolidine (an NO-containing agent) and NaNO₂ (a released form of NO), while NO scavenging by hemoglobin reversed the effect of these agents ([Manzoni et al., 1992](#)). Endogenous NOS activity in cultured striatal neurons is also closely linked to NMDAR activity. The natural substrate of NOS, L-arginine, diminished NMDAR activity, which was reversed by the NOS inhibitor L-nitroarginine ([Manzoni and Bockaer, 1993](#)). In channel recordings from rat cortical neurons or *Xenopus oocytes* , the NO-generating agent S-nitrosocysteine (SNOC) decreased NMDAR channel opening ([Lei et al., 1992](#) ; [Lipton et al., 1998](#)) or NMDA-evoked currents ([Omerovic et al., 1995](#) ; [Choi et al., 2000](#)). Similar to the *in vitro* results, an *in vivo* microdialysis study showed that the NO donor S-nitroso- N -acetylpenicillamine (SNAP) suppressed the NMDA-stimulated NO release in the rat striatum ([Kendrick et al., 1996](#)). Together, *in vitro* and *in vivo* data support an inhibitory modulation of NMDARs by NO under normal conditions. Given that NMDAR stimulation increases NO synthesis, NO and NO-related species serve as key regulators in a use-dependent negative feedback mechanism to prevent excessive NMDAR activation and to maintain the receptor activity at the physiological level ([Choi et al., 2000](#)).

The mechanism underlying the NO modulation of NMDARs seems to involve a direct and cGMP-independent pathway. It has been found that NMDARs can be directly modified by a biochemical reaction, S-nitrosylation. S-nitrosylation is an important biological reaction of NO and is a key post-translational modification for multiple ion channels ([Hess et al., 2005](#)). Such modification adds a nitrosyl group (NO^+) to the thiol side-chain of cysteine residues to form S-nitrosothiols, leading to a reversible change in tertiary structure and function of modified proteins ([Sen and Snyder, 2010](#)). In dissecting a molecular mechanism for the NO-NMDAR coupling, a single cysteine residue (C399) in the extracellular N terminus of NR2A was found to account for the predominant effect of NO. This cysteine can be physiologically S-nitrosylated after NO^+ transfer, and site-directed mutation of it to alanine abolished the NO-mediated inhibition of NR1/NR2A receptors ([Choi et al., 2000](#)). Thus, C399 S-nitrosylation serves as an important pathway linking NO to NMDARs. Additionally, two pairs of cysteine residues on NR1 (C744, C789) and NR2A (C87, C322) could undergo S-nitrosylation and thereby inhibit NMDARs if they are in the free thiol form ([Choi et al., 2000](#), [2001](#); [Lipton et al., 2002](#)). Of note, nNOS forms a complex with NR1 via a scaffolding protein PSD-95 in the postsynaptic density microdomain ([Brenman et al., 1996](#)). Co-localization of these proteins at defined synaptic sites facilitates their direct interactions and enables rapid feedback inhibition of NMDARs via a NO-sensitive mechanism.

NO can also indirectly modulate NMDARs through S-nitrosylating the prime regulators of NMDARs. Serine racemase (SR) is an enzyme which converts L-serine to D-serine, a co-agonist with glutamate at NMDARs. It has been <https://assignbuster.com/modulation-of-ionotropic-glutamate-receptors-and-acid-sensing-ion-channels-by-nitric-oxide/>

shown that SR is physiologically S-nitrosylated for marked inhibition of the enzyme ([Mustafa et al., 2007](#)). This S-nitrosylation was enhanced by NMDAR-activated nNOS. Thus, postsynaptic stimulation of NO formation possibly feeds back to presynaptic cells to S-nitrosylate SR and decrease D-serine availability. This contributes to inhibiting excitatory synaptic transmission and preventing overstimulation of postsynaptic NMDARs. PSD-95 is a principal scaffolding protein at synaptic sites where it determines the number of NMDARs and thus efficiency and strength of the receptor. It also couples NMDARs to nNOS to form signalosomes for local NO production. Like SR, PSD-95 is physiologically S-nitrosylated ([Ho et al., 2011](#)). S-nitrosylation occurs at two specific cysteines (C3 and C5). Interestingly, these sites are also subject to palmitoylation, another reversible and cysteine-based post-translational modification which covalently attaches a fatty acid (palmitic acid) to cysteine ([Ho et al., 2011](#)). In cerebellar neurons, NO inhibited PSD-95 palmitoylation and decreased synaptic delivery of PSD-95. In heterologous cells, decreased palmitoylation resulted in increased PSD-95 S-nitrosylation ([Ho et al., 2011](#)). These data support a model in which NMDARs stimulate NO to regulate PSD-95 via mutually competitive cysteine modifications. Regulated PSD-95 then reciprocally controls expression and activity of NMDARs.

Normal NMDAR activity is important for cell signaling and synaptic plasticity. Excessive activation of the receptor, however, results in excitotoxicity and cell death. To this end, NMDARs are crucial for neuronal survival in various neurodegenerative disorders ([Lipton and Rosenberg, 1994](#)). Since NO inhibits excessive stimulation of NMDARs, it could consequently ameliorate

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NMDAR-mediated neurotoxicity. Of note, both NMDAR and NO activities are upregulated in parallel during neurological disorders such as ischemia, trauma, and inflammation. As such, they both are actively involved in resultant neuronal death under these neurodegenerative conditions ([Dawson et al., 1993](#) ; [Bonfoco et al., 1995](#)). Indeed, hypoxia renders NMDARs exquisitely sensitive to NO-induced S-nitrosylation and inhibition of NMDARs in cortical neurons and *oocytes* ([Takahashi et al., 2007](#)). Such enhanced NO inhibition of NMDARs is thought to be neuroprotective and serves as a mechanism to counteract NMDAR-mediated cytotoxicity in hypoxia insults ([Lei et al., 1992](#) ; [Lipton et al., 1993](#) ; [Choi et al., 2000](#) ; [Takahashi et al., 2007](#)). In addition, a large increase in NO levels in rat brains was discovered immediately after middle cerebral artery occlusion ([Malinski et al., 1993](#)). A higher level of NO, through the NO-mediated vasodilation, can increase cerebral blood flow and oxygen delivery ([Toda et al., 2009](#)). This, in concert with the NO inhibition of NMDARs, protects brain tissue during focal ischemia, although neuronal overproduction of NO may elicit neurotoxicity ([Dalkara et al., 1994](#)). The inhibitory control of NMDARs by NO has potential clinical implications. Pharmacotherapies targeting nitrosylatable cysteine residues can be developed to prevent NMDAR-mediated neurotoxicity during stroke ([Takahashi et al., 2007](#)).

AMPARs

AMPARs are another important glutamate ion channel. Like NMDARs, AMPARs become functional upon a heterotetrameric assembly of four subunits (GluR1–4 or GluRA–D; [Dingledine et al., 1999](#)). Most AMPARs contain symmetric “ dimer of dimers” of GluR2 and either GluR1, GluR3, or

GluR4 ([Greger et al., 2007](#)). Activation of these receptors promotes Na⁺ influx and induces rapid depolarization. AMPARs open and close quickly and thus carry out the most of fast excitatory synaptic transmission in the CNS.

Little is known about whether AMPAR subunits are direct targets of NO. However, several key AMPAR-interacting proteins that actively control AMPAR trafficking, expression, and function are S-nitrosylated and regulated by NO. *N*-ethylmaleimide sensitive factor (NSF) is an ATPase enriched in neurons. It binds to GluR2 ([Nishimune et al., 1998](#) ; [Osten et al., 1998](#) ; [Song et al., 1998](#)), stabilizing or recycling AMPARs into postsynaptic membranes ([Braithwaite et al., 2002](#) ; [Lee et al., 2002](#)). It was found that synaptic NSF was physiologically S-nitrosylated by endogenous, neuronally derived NO in mouse brain ([Huang et al., 2005](#)). NMDAR activation enhanced NSF S-nitrosylation and thereby augmented NSF binding to GluR2 and surface insertion of GluR2. These data reveal a NO-sensitive pathway linking NMDARs to AMPARs. Specifically, NMDARs, through activating associated nNOS, trigger NO formation, which upregulates NSF S-nitrosylation to promote its associations with GluR2 and increase surface expression of GluR2-containing AMPARs ([Huang et al., 2005](#)). In this process, PICK1 (protein interacting with C kinase 1), a synaptic anchoring protein binding and retaining GluR2 in intracellular pools, seems to mediate the NSF regulation of GluR2. S-nitrosylated NSF can disassemble the PICK1-GluR2 complex, leading to a release of GluR2 from PICK retention and subsequent surface delivery of GluR2/AMPARs ([Hanley et al., 2002](#) ; [Sossa et al., 2007](#)).

Stargazin is another synaptic protein that links NO to AMPARs. As a founding member of the transmembrane AMPAR regulatory protein (TARP) family, stargazin serves as an auxiliary subunit of all AMPAR subtypes and directly interacts with a large part of AMPARs. As such, stargazin is thought to be a principal determinant of AMPAR surface expression. Indeed, Snyder and co-workers showed that stargazin, like NSF, is physiologically S-nitrosylated at C302 in primary neurons and heterologous cells ([Selvakumar et al., 2009](#)). S-nitrosylation of stargazin was positively linked to surface expression of this small tetraspanning membrane protein. S-nitrosylation also increased binding of stargazin to the AMPAR subunit GluR1, causing upregulated surface expression of the AMPAR. NMDAR stimulation increased S-nitrosylation of stargazin and binding of stargazin to AMPARs. Apparently, stargazin, like NSF, is a physiological regulator of AMPARs and a linker between NMDARs and AMPARs. Through a NO-sensitive mechanism, stargazin transmits NMDAR signals to the level of surface expression of AMPARs.

In addition to S-nitrosylation, NO stimulates soluble guanylyl cyclase to form the second messenger cGMP ([Bredt and Snyder, 1989](#)). Thus, cGMP and downstream protein kinases could constitute an indirect pathway to regulate AMPARs. A recent study supports this notion ([Serulle et al., 2007](#)). In this study, the cGMP-dependent kinase type II (cGKII), a distinct GK isoform located in cellular membranes and broadly expressed in the brain ([Francis and Corbin, 1999](#)), was found to directly bind to GluR1. This binding was sensitive to nNOS activity and cGMP. Moreover, the binding enables the kinase to phosphorylate GluR1 at an intracellular serine site (S845). In

cultured hippocampal neurons, active cGKII accumulated GluR1 on the plasma membrane at extrasynaptic sites. Blockade of cGKII prevented this accumulation and also an increase in mEPSC frequency and amplitude. Of note, S845 was also phosphorylated by protein kinase A (PKA), which was required for GluR1 synaptic insertion ([Esteban et al., 2003](#)). Thus, both cGKII and PKA pathways converge on S845 to regulate its phosphorylation and the phosphorylation-dependent GluR1 insertion into the surface membrane. It is believed that the two pathways operate in concert and in distinct temporospatial manners to modulate synaptic plasticity.

Modulation of ASICs by NO

In addition to glutamate receptor channels, ASICs represent another family of ion channels subjected to the modulation by NO. Seven subunits of ASICs (1a, 1b1, 1b2, 2a, 2b, 3, and 4) have been identified to date, which are encoded by four genes ([Price et al., 1996](#) ; [Lingueglia et al., 1997](#) ; [Waldmann et al., 1997a](#) , [b](#) ; [Chen et al., 1998](#) ; [Akopian et al., 2000](#)). A major function of ASICs is to maintain normal cellular activity in response to changing pH signals. Given the fact that a variety of neurological disorders, including inflammation, ischemic stroke, traumatic brain injury and acid nociception, cause severe acidosis, ASICs are deemed to be activated and play a role in cell death and in the pathogenesis or progression of these diseases ([Wemmie et al., 2006](#) ; [Chu et al., 2011](#)). As a result, ASICs are emerging as new pharmacotherapeutic targets for these illnesses ([Wemmie et al., 2006](#) ; [Xiong et al., 2008](#) ; [Sluka et al., 2009](#) ; [Xu and Duan, 2009](#)).

Acid-sensing ion channels are subject to the regulation by various extracellular and intracellular signals ([Chu et al., 2011](#)). Among the known regulators is NO. It has been suggested that ASICs are a potential target for direct modulation by NO-dependent S-nitrosylation ([Cadiou et al., 2007](#)). This is based on the facts that (1) the channel possesses a large number of cysteine residues on their extracellular domains ([Waldmann et al., 1999](#)), and (2) oxidizing agents, 5, 5'-dithio- *bis* -(2-nitrobenzoic acid; DTNB), showed a sizable impact on acid-evoked currents in neurons and heterologous cells ([Andrey et al., 2005](#) ; [Chu et al., 2006](#)). In support of this, [Cadiou et al. \(2007\)](#) reported that the NO donor SNAP potentiated proton-gated currents in rat cultured dorsal root ganglion (DRG) neurons and in CHO cells expressing each of ASIC subunits. The SNAP effect was not due to activation of the cGMP pathway because the cGMP analog db-cGMP did not mimic, and the guanylyl cyclase inhibitor ODQ did not block, the SNAP potentiation. The effect of SNAP was thought to be mediated via a direct mechanism involving NO S-nitrosylation at extracellular cysteines of ASICs ([Cadiou et al., 2007](#)).

Acid-sensing ion channels are known to participate in mediating acid-evoked pain in humans. This process is believed to be regulated by NO, based on the finding that topical application of an NO donor enhanced acid-evoked pain ([Cadiou et al., 2007](#)). Another neurological disorder in which the NO potentiation of ASICs may have a pathophysiological relevance is ischemia. Cerebral ischemia is known to cause metabolic acidosis. This leads to activation of ASICs, especially Ca²⁺ permeable ASIC1a, which increases intracellular Ca²⁺ overload and results in neuronal death ([Xiong et al., 2004](#) <https://assignbuster.com/modulation-of-ionotropic-glutamate-receptors-and-acid-sensing-ion-channels-by-nitric-oxide/>

). NO promoted such neuronal death by potentiating ASICs during mild and moderate acidosis, although in severe acidosis NO synthesis was inhibited and the NO contribution subsided ([Jetti et al., 2010](#)).

Conclusion

Ionotropic glutamate receptors have long been appreciated to be subject to various types of post-translational modifications which determine expression, trafficking, and function of modified receptors. NO-dependent S-nitrosylation is one of these modifications. Available data show that NMDARs are directly modulated by NO-mediated S-nitrosylation. Direct S-nitrosylation occurs at a cysteine site (C399) in an extracellular N-terminal region of NR2A subunits. In addition to NR2A, NO influences other synaptic proteins that are important for NMDAR activity. Serine racemase which generates D-serine, a co-agonist of NMDARs, is S-nitrosylated. The S-nitrosylation inhibits its enzymatic activity. PSD-95, a scaffolding protein stabilizing NMDARs at synaptic sites and linking nNOS to NMDARs, also undergoes physiological S-nitrosylation, which suppresses synaptic delivery of PSD-95. Apparently, the NO regulation of all three elements (NR2A, serine racemase, and PSD-95) can synergistically generate an inhibitory driving force on NMDARs. Given that NMDARs stimulate NO synthesis, NO forms a negative feedback loop to prevent overstimulation of the receptor.

Direct S-nitrosylation of AMPARs has not been reported. Instead, AMPAR-interacting proteins are S-nitrosylated and regulated by NO. NSF binds to AMPAR GluR2, while stargazin binds to GluR1. NMDAR activation enhances S-nitrosylation of both proteins, facilitating their binding to GluR1/2 and

surface expression of AMPARs. In addition to this S-nitrosylation-dependent and cGMP-independent mechanism, the cGMP-dependent pathway also mediates the NO regulation of AMPARs. Like glutamate ion channels, ASICs are modulated by NO. NO is believed to potentiate ASIC activity. This potentiation was not mediated by the cGMP-dependent pathway, but mediated through S-nitrosylation of extracellular cysteines of ASICs. The NO potentiation of ASICs contributes to acid-evoked pain and ischemia-induced neuronal death. It is possible that all NO targets, including NMDARs, AMPARs, ASICs, and their associated proteins, can be co-localized at same subsets of synapses. NO could therefore simultaneously regulate these synaptic proteins and interactions among them to precisely control synaptic transmission. It is anticipated that NO modification biology of ion channels will grow rapidly and more sophisticated NO modification models on glutamate ion channels and ASICs will be characterized *in vivo*. Ultimately, this knowledge will be translated into novel and effective pharmacotherapies for respective neurological disorders.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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