Sigma-1 and N-Methyl-D-Aspartate Receptors: A Partnership with Beneficial Outcomes

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Abstract

Sigma-1 receptors (σ -1R) are interorganelle signaling molecules, which have been implicated in synaptic plasticity, primarily by enhancing the function of N-methyl-D-aspartate receptors (NMDARs). On the other hand, excessive influx of calcium via activated NMDAR can cause excitotoxicity. Yet, despite their NMDAR-enhancing role, multiple lines of evidence suggest that σ -1Rs are involved in neuroprotection. The mechanism underlying these intriguing opposing effects is not known. Recent studies now suggest the possibility that σ -1Rs could exert neuroprotective effects via targeted disruption of protein-protein interactions between NMDARs and their associated intracellular signaling machinery, specifically the neuronal nitric oxide synthase (nNOS). This targeted disruption of protein-protein interactions between NMDARs and nNOS results in lower levels of nitric oxide generation, thus having a neuroprotective effect. Here, we briefly summarize aspects of σ -1R-mediated enhancement of NMDAR function and possible neuroprotection. In-depth mechanistic understanding of σ -1R modulation of

NMDAR function, which preserves Ca^{2+} homeostasis while limiting excitotoxicity would provide valuable information for designing novel as well as improving prevailing therapeutic strategies.

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A remarkable number of intra- and extracellular components in a highly organized and intricate manner mediate neurons' health and spatiotemporal communication. Among many components, calcium ion (Ca^{2+}) has a prominent role and, in fact, stands at the crossroads of having either beneficial (e.g., synaptic plasticity) or toxic (e.g., excitotoxicity) effects on the neuron [1–3]. An optimal and regulated intracellular influx of Ca^{2+} into the neuron elicits signaling cascades that strengthen the communication between synapses (i.e., underlying synaptic plasticity) [3]. However, an excess influx of Ca^{2+} can also elicit signaling cascades, which in this case may result in a toxic insult to neurons and glia [1]. While the overarching mechanisms underlying the dichotomous effects of Ca^{2+} are not fully understood, several seminal discoveries have demonstrated a predominant role for N-methyl-D-aspartate receptors (NMDARs), more specifically the NMDAR-associated intracellular signaling machinery, in

mediating the dichotomous effects of Ca^{2+} [4, 5]. Not surprisingly, neurons employ a number of specialized mechanisms to govern and tailor the function of NMDARs and/or the NMDAR-associated intracellular signaling machinery. These include mainly, but are not limited to, engaging modulators. The sigma-1 receptor (σ -1R) is one such modulator, which is known to enhance the function of NMDARs (i.e., heightened Ca^{2+} influx via NMDARs); however, σ -1Rs can also prevent the Ca^{2+} -induced toxicity by modulating the function of a specific NMDAR-associated intracellular signaling component (neuronal nitric oxide synthase, nNOS), which generates toxic species (nitric oxide, NO). These intriguing opposing effects are discussed here. We provide a brief overview on NMDARs and σ -1Rs and then summarize mechanistic aspects of σ -1R modulatory action on the function of NMDARs and its association with nNOS.

NMDARs are glutamate-gated Ca^{2+} -permeable ion channels [6]. They are heterotetrameric assemblies of two compulsory GluN1 subunits together with either two GluN2 (A-D) subunits or a combination of GluN2 or GluN3 (A and B) subunits. These glutamatergic receptors display a characteristic subunit- and age-dependent temporal and spatial distribution throughout the central nervous system. At the synapse, NMDARs exist as large macromolecular complexes that contain numerous types of molecules, including scaffold/signaling proteins, e.g., postsynaptic density-95 (PSD-95). The Ca^{2+} conductance through NMDARs at synapses acts as a regulator of excitatory synaptic transmission, and any sort of deregulation in NMDAR function leads to neurological disorders, including schizophrenia and stroke [7].

σ -1Rs are intracellular proteins which primarily reside on membranes of the endoplasmic reticulum that are in juxtaposition to mitochondria [8]. They are also present on the plasma membrane and are ubiquitous in neuronal and non-neuronal cells. It is predicted that σ -1Rs possess two transmembrane units along with short N- and long C-terminus tails. Recent investigations have disclosed σ -1R as an interorganelle 'modulator' that has chaperone-like activity and also acts as an intracellular sensor in regulating Ca^{2+} homeostasis [8, 9]. Furthermore, σ -1Rs have been implicated in several physiological functions, including shaping neuronal excitability and long-term potentiation, mainly through functional modulation of ion channels (e.g., NMDARs) [10].

Electrophysiology-based investigations demonstrated that activated σ -1R enhances the frequency and amplitude of various NMDAR-mediated responses as well as NMDAR-dependent long-term potentiation [11–13].

Additionally, concurrent behaviour-based studies demonstrated improvements in learning and memory behaviour of animals after the activation of σ -1Rs that are experiencing NMDAR antagonism-induced amnesia [14, 15]. Two important features can be inferred from these multimodal studies: first, low doses of σ -1R agonists enhance NMDAR function, while high doses ($\geq 10 \mu\text{M}$) of σ -1R agonists do not enhance NMDAR function [12, 13]. At the moment, it is unclear why high doses of σ -1R agonists do not promote NMDAR function, but it is proposed that at high doses σ -1R agonists can cross-react with NMDARs at their pore sites and eventually block ion channel conductance [16]. Second, the ameliorative effect on NMDAR function by σ -1R agonists can be observed in minutes and sustained for hours [11]. This time scale window reflects the possibility that σ -1Rs may accomplish the functional enhancement of NMDARs through both direct and indirect (i.e., engagement of multiple cellular components) mechanisms (fig. 1). Indeed, σ -1Rs were shown to directly interact with GluN1 subunit of NMDARs [17], and this interaction may explain some of the facilitatory effects of σ -1R agonists on NMDARs. On the other hand, electrophysiology-based examinations have revealed σ -1R-mediated recruitment of small-conductance K^{+} -activated Ca^{2+} channels (SK channels) [11], G proteins [18], and intracellular kinases (e.g., members of the Src family of kinases [19]) for increasing the function of NMDARs, but with the shortcomings that many aspects remain untested, such as, for instance, the effect of σ -1R agonists on NMDAR subunit-dependent biophysical properties (e.g., gating, single-channel conductance, and open probability). This is especially important in lieu of changes in phosphorylation status – a posttranslational modification that influences the biophysical properties of an ion channel – of NMDAR GluN2B subunits following treatment with σ -1R agonists [19]. Several other reports also demonstrate an increased phosphorylation of GluN1 subunits of NMDAR by kinases such as protein kinases A and C [20, 21] after ligand activation of σ -1Rs. Furthermore, a recent biochemistry-based study showed σ -1R-mediated augmentation in expression, trafficking, and surface levels of NMDARs [22]. Equally, another recent report, although through a different viewpoint, demonstrated σ -1R-mediated suppression of NMDAR internalization and obstruction of NMDAR hypofunction [23]. An additional mechanistic modality likely to contribute is the indirect action of σ -1R on NMDAR function through σ -1R-mediated Ca^{2+} mobilization from the internal stores [e.g., via inositol 1,4,5-trisphosphate receptors (IP3Rs) on ER membranes] [9]. A

Fig. 1. σ -1R enhancement of NMDAR function. σ -1Rs adapt a multi-component approach to promote NMDAR function, including the inhibition of SK channels (a), G proteins (identity is unclear; b), and intracellular kinases (c) alongside with an increase in the expression, trafficking, and surface levels (d) of NMDARs. In addition, σ -1R-mediated Ca^{2+} mobilization from ER via IP3 receptors may contribute to functional enhancement of NMDARs (e). The resultant increase in the influx of Ca^{2+} (blue arrow) further promotes synaptic plasticity [9, 11, 18–22].

role for σ -1R-mediated Ca^{2+} mobilization in NMDAR functional augmentation seems plausible, but it remains to be directly tested. Early evidence in support of such a mechanism shows that activation of σ -1Rs in the presence of BAPTA [1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid], a Ca^{2+} chelating agent, does not induce a functional enhancement of NMDARs [11].

While σ -1R-mediated NMDAR functional enhancement seems semantic and beneficial as it relates to an improvement in the memory behaviour of animals [14, 15],

it could also provoke an excitotoxic insult to the neuron. However, cell culture and behaviour examinations, based primarily on observations of (a) promotion and attenuation in the protein levels of survival and proapoptotic cellular components [24] and (b) reduction in the production of NO [25], suggest that σ -1R ligands can act as neuroprotective agents. The reduction in the production of NO by σ -1R ligands, if at all in doubt, can be due to the blockade of NMDARs by the ligands. However, this may not be the case. Rather, new findings hint that σ -1Rs may

Fig. 2. σ -1R-mediated neuroprotection. **a** In the absence of σ -1R activation, the increased influx of Ca^{2+} through GluN2B-containing NMDARs can trigger neurotoxicity and neurodegeneration by increasing the activation of nNOS (eventually NO species) that is attached to PSD-95. **b** Recent investigations have demonstrated that the activation of σ -1Rs leads to diminution of interactions between GluN2B subunits and PSD-95 as well as PSD-95 and nNOS (represented as a decrease in size). Reducing the interactions between proteins that can generate toxic species may be one of the underlying mechanisms of σ -1R-mediated neuroprotection via reduced neurotoxicity and neurodegeneration [22, 25–27].

adopt an intriguing approach for wielding neuroprotection [22, 26], that is, σ -1R-driven attenuation of targeted protein-protein interactions that mediate neurotoxicity. It has been shown that excessive NMDAR-mediated Ca^{2+} recruits and activates nNOS that is attached to the NMDAR-PSD-95 complex. This tripartite complex is the driving force for neurotoxicity, and a disruption of these interactions between them greatly reduces toxicity-driven neuronal death [27]. Interestingly, agonist activation of σ -1Rs leads to decreased interactions between the NMDAR subunit (GluN2B) and PSD-95 [22] as well as PSD-95 and nNOS [26] (fig. 2), consequently giving rise to reduced neurotoxicity and neurodegeneration.

Why are these recent findings important? Neurons constantly have to recalculate and acclimatize to ever-changing circumstances and perturbations. How such adaptation occurs is not well characterized, especially in cases of perturbation in neuronal Ca^{2+} homeostasis (i.e., too much or too little NMDAR function and Ca^{2+} signaling [4]). Numerous investigations suggest a critical role for Ca^{2+} dyshomeostasis in the pathogenesis of neuropsychiatric and neurodegenerative disorders [28]. On the

other hand, modulation of NMDAR function is beneficial under many circumstances and a current target for therapeutic purposes. Thus, the fact that σ -1R employs a multi-component approach to ensure NMDAR functional enhancement while limiting toxicity-inducible elements may represent a fruitful avenue of further investigation, specifically for gaining further insights into the structural (which domains/sequences of proteins) and time-dependent (acute vs. chronic) aspects of the σ -1R-mediated disruption of targeted protein-protein interactions. Further studies are also needed to determine if σ -1R interaction with NMDAR alone plays a critical role in the σ -1R-mediated increase in NMDAR function. Delving deeper into these alluring aspects – σ -1R-mediated, targeted disruption of interaction between NMDAR and nNOS – using σ -1R knockout mice will validate profiling of σ -1Rs as a neuroprotective target.

In conclusion, obtaining in-depth mechanistic insights into σ -1R modulation of NMDAR function that altogether preserves Ca^{2+} homeostasis would provide valuable information for designing novel as well as improving prevailing therapeutic strategies.

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