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Invited review

The NMDA receptor as a target for cognitive enhancement

Graham L. Collingridge [a,b,*], Arturas Volianskis [a], Neil Bannister [a], Grace France [a], Lydia Hanna [a], Marion Mercier [a], Patrick Tidball [a], Guangyu Fang [a], Mark W. Irvine [a], Blaise M. Costa [c], Daniel T. Monaghan [c], Zuner A. Bortolotto [a], Elek Molnár [a], David Lodge [a], David E. Jane [a]

[a] MRC Centre for Synaptic Plasticity, School of Physiology and Pharmacology, University of Bristol, Bristol BS1 3NY, UK
[b] Department of Brain and Cognitive Sciences, Seoul National University, Seoul, Republic of Korea
[c] Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-6260, USA

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ABSTRACT

NMDA receptors (NMDARs) play an important role in neural plasticity including long-term potentiation and long-term depression, which are likely to explain their importance for learning and memory. Cognitive decline is a major problem facing an ageing human population, so much so that its reversal has become an important goal for scientific research and pharmaceutical development. Enhancement of NMDAR function is a core strategy toward this goal. In this review we indicate some of the major ways of potentiating NMDAR function by both direct and indirect modulation. There is good evidence that both positive and negative modulation can enhance function suggesting that a subtle approach correcting imbalances in particular clinical situations will be required. Excessive activation and the resultant deleterious effects will need to be carefully avoided. Finally we describe some novel positive allosteric modulators of NMDARs, with some subunit selectivity, and show initial evidence of their ability to affect NMDAR mediated events.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

The NMDA receptor (NMDAR) is a prime target for cognitive enhancement since it is centrally involved in cognitive processes. Approximately 30 years ago, it was shown that the transient activation of NMDARs is the trigger for the induction of long-term potentiation (LTP) at synapses made between CA3 and CA1 pyramidal neurons in the hippocampus (Collingridge et al., 1983). Shortly afterwards direct evidence was provided that NMDARs are also required for forms of hippocampus dependent learning and memory (Morris et al., 1986). These findings have led to numerous studies into the role of NMDARs in synaptic plasticity, learning and memory and have placed the NMDAR at the heart of cognition. Since NMDARs are required for these processes the simple notion is that boosting NMDAR function should enhance cognition and, indeed, there is evidence that this may be true under certain circumstances (Tang et al., 1999). We will commence our discussion on this assumption: that NMDAR activation leads to LTP and that this equates with learning and memory and consequently enhancing NMDAR function is good for cognition. This is, of course, a gross oversimplification. Most importantly, NMDAR activation can result in pathological conditions, such as epilepsy (Croucher et al., 1982), neuronal cell death (Simon et al., 1984) and hyperalgesia (Davies and Lodge, 1987). Therefore, too much activation of the NMDAR is detrimental. The key is to boost the physiological function without promoting the tendency for pathological consequences.

NMDARs are obligate heterotetramers formed from assemblies of GluN1 subunits with GluN2A-D and GluN3A/B. In addition, GluN3A can assemble with GluN1 (without other GluN2 subunits) to form excitatory, Ca^{2+}-impermeant glycine receptors. Eight

Abbreviations: AChR, acetylcholine receptor; AKAP79/150, A-kinase anchoring proteins; AMPAR, AMPA receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase; CK2, casein kinase II; D1R, dopamine 1 receptor; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; fEPSP, field excitatory postsynaptic potentials; $GABA_AR$, $GABA_A$ receptor; $GABA_BR$, $GABA_B$ receptor; GPCR, G-protein-coupled receptors; iGluR, ionotropic glutamate receptor; IPSP, inhibitory postsynaptic potential; LTP, long-term potentiation; mAChR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; NMDAR, NMDA receptor; NMDAR-LTP, NMDA receptor dependent long-term potentiation; PAC1R, pituitary adenylate cyclase activated peptide 1 receptor; PKA, protein kinase A; PKC, protein kinase C; PSD95, postsynaptic density protein 95; STEP, striatal-enriched tyrosine phosphatase.

* Corresponding author. MRC Centre for Synaptic Plasticity, School of Physiology and Pharmacology, University of Bristol, Bristol BS1 3NY, UK. Tel.: +44 (0) 117 33 11913.
E-mail address: G.L.Collingridge@bristol.ac.uk (G.L. Collingridge).

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possible variations of the GluN1 subunit arise by alternative splicing of a single gene transcript. The presence of one splice cassette at the N-terminal region of GluN1 and two independent consecutive splice variants at the C terminus have been identified. Therefore, a large number of different NMDARs with differing functional and pharmacological properties exist in different parts of the brain or at different stages in development (Molnár, 2008). Unusually for the ionotropic glutamate receptors (iGluRs), L-glutamate is not the only agonist for the NMDAR. Glycine and D-serine, two neutral endogenous amino acids, are co-agonists and the presence of one or other along with glutamate are needed for the receptor to function. The binding sites for glutamate and glycine/D-serine are found on different subunits – glycine binds to the GluN1 (and GluN3) subunits while glutamate binds to the GluN2 subunits. Consequently, both subunit types are required to generate a fully functioning NMDAR.

The NMDAR has several unique properties that are important for its function. Foremost, it is sensitive to block by low micromolar concentrations of magnesium ions (Mg^{2+}) (Ault et al., 1980) in a manner that is highly voltage-dependent (Nowak et al., 1984; Mayer et al., 1984). The consequence of this block is such that at normal resting membrane potentials (typically between −50 and −75 mV) the NMDAR is largely blocked by Mg^{2+} from the synaptic cleft. Depolarization greatly reduces the Mg^{2+} block so that the participation of NMDARs in the synaptic response becomes substantially greater (Collingridge et al., 1988). This property explains the "Hebbian" nature of synaptic plasticity, whereby the NMDAR senses the co-incidence between presynaptic activity (which releases L-glutamate to bind to the NMDAR) and postsynaptic activity (defined as enough depolarization to reduce the Mg^{2+} block sufficiently to trigger the induction of plasticity). We shall refer to this depolarization as "Hebbian depolarization". The NMDAR is also directly permeable to Ca^{2+} and this is extremely relevant for both its physiological and pathological actions.

Due to the complex molecular organization, functional and pharmacological properties of NMDARs, the design of agents to boost cognition via the regulation of NMDAR function needs to take account of many factors. In the present article, we discuss ways in which NMDAR function can be regulated. Broadly speaking, compounds that regulate NMDAR function do so in one of two ways. First, they may interact with other proteins that then regulate NMDAR function indirectly. Second, they may bind directly to the NMDAR to regulate its function. In the present article we discuss some of the ways in which NMDAR function may be regulated and describe some recently reported NMDAR positive allosteric modulators (PAMs).

2. Indirect modulation

The properties of the NMDAR enables many forms of indirect modulation, many of which are probably utilized physiologically for cognitive purposes and can be exploited, in principle, for the design of cognitive enhancing compounds. Some of the more important indirect modulators are described below and illustrated schematically in Fig. 1.

2.1. AMPARs

During the induction of LTP, Hebbian depolarization is provided in part by the temporal summation of AMPAR-mediated EPSPs (Collingridge, 1985). Therefore one way, in theory, of boosting NMDAR function is to enhance the depolarization provided by the synaptic activation of AMPARs. This is one of the ideas behind the use of positive allosteric modulators of AMPARs (AMPAR PAMs), compounds that bind to the AMPAR itself to enhance its function. Following the initial descriptions of aniracetam (Ito et al., 1990), diazoxides and thiazides (Yamada and Rothman, 1992), including cyclothiazide (Palmer and Lodge, 1993; Patneau et al., 1993) and benzamides (Arai et al., 1994), AMPAR potentiators were found to limit receptor desensitization and slow deactivation (Partin et al., 1996). Such AMPAR PAMs were shown to potentiate LTP presumably by indirect enhancement of NMDARs (Stäubli et al., 1994b), as demonstrated in vivo (Vandergriff et al., 2001). In parallel with these electrophysiological studies, AMPAR PAMs were soon shown to enhance learning and memory (Staubli et al., 1994a). Since then, many other structural classes have been described (Ward and Harries, 2010; Pirotte et al., 2010) and their positive effects on cognition in laboratory animals and human patients have been extensively reported and reviewed (Morrow et al., 2006; Arai and Kessler, 2007; O'Neill and Dix, 2007; Cleva et al., 2010; Lynch et al., 2011). The potential site of action of AMPAR PAMs, together with other cognitive enhancing agents that may act at the glutamatergic synapse, is shown schematically in Fig. 2.

2.2. GABARs

GABA receptors (GABARs) provide a powerful physiological regulation of NMDARs. During low frequency transmission the synaptic activation of GABARs prevents NMDARs from contributing appreciably to the synaptic response by hyperpolarizing the neuron and thereby intensifying the Mg^{2+} block (Herron et al., 1985; Dingledine et al., 1986). $GABA_A$Rs are activated rapidly whereas $GABA_B$Rs are activated after a delay of around 20 ms but provide a longer lasting hyperpolarization (Davies et al., 1990). Together, these two inhibitory synaptic responses effectively limit the synaptic activation of NMDARs throughout its time-course. Consequently, blocking either $GABA_A$ or $GABA_B$ receptors may lead to the enhanced synaptic activation of NMDARs (Davies and Collingridge, 1996). Since the $GABA_A$R mediated inhibitory postsynaptic potential (IPSP) coincides with the peak NMDAR synaptic conductance, this is likely to have the most dramatic effect. During low frequency synaptic transmission, a $GABA_A$R antagonist enables a noticeable activation of NMDARs (Herron et al., 1985; Dingledine et al., 1986) and the effect is magnified during high frequency transmission, since it facilitates the temporal summation of NMDAR-EPSPs to generate a larger Hebbian depolarization. This effect can be sufficient to enhance the induction of LTP (Abraham et al., 1986).

$GABA_B$Rs provide a more complex regulation of NMDARs. The postsynaptic $GABA_B$R IPSPs helps limit the synaptic activation of NMDARs and so its selective blockade is able to enhance the induction of LTP (Olpe et al., 1993). However, $GABA_B$Rs are also located presynaptically where they function as both autoreceptors, inhibiting GABA release (Davies et al., 1990), and heteroreceptors, inhibiting glutamate release (Davies et al., 1993; Isaacson et al., 1993). The autoreceptor function is important for the induction of LTP by theta/priming patterns of activity (Davies et al., 1991), which are a more physiologically relevant pattern of activation than a conventional tetanus (Larson et al., 1986; Diamond et al., 1988). This is because theta frequencies are optimally tuned for the suppression of GABAR-mediated IPSPs, via the autoreceptor mechanism, and this promotes the synaptic activation of NMDARs by facilitating the Hebbian depolarization (Davies and Collingridge, 1993). Antagonism of $GABA_B$R autoreceptors therefore inhibits the induction of LTP when theta patterns of activity are used, by limiting the synaptic activation of NMDARs. However, when longer trains are used to induce LTP (i.e, a tetanus) $GABA_B$Rs are no longer required to suppress GABAR-IPSPs and so $GABA_B$R antagonists no longer inhibit the induction of LTP. Whether the regulation of $GABA_B$Rs can be exploited to enhance cognition is not known. The