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The NMDA receptor as a target for cognitive enhancement

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Abstract

NMDA receptors (NMDAR) 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.

Keywords

Synaptic plasticity; NMDA receptor; cognitive enhancement; LTP; synaptic transmission; hippocampus; positive allosteric modulators

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

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(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 over-simplification. 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 & 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 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 (AMPA 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 deactivation (Partin et al., 1996). Such AMPAR PAMs were shown to potentiate LTP presumably by indirect enhancement of NMDARs (Staubli 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., 1985). GABA_ARs are activated rapidly whereas GABA_BRs 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_AR 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_AR antagonist enables a noticeable activation of NMDARs (Herron et al., 1985; Dingledine et al., 1985) 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_BRs provide a more complex regulation of NMDARs. The postsynaptic GABA_BR 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_BRs 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 GABA_R-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_BR 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_BRs are no longer required to suppress GABA_R-IPSPs and so GABA_BR antagonists no longer inhibit the induction of LTP. Whether the regulation of GABA_BRs can be exploited to enhance cognition is not known. The prediction from these LTP experiments is that the selective antagonism of postsynaptic GABA_BRs might have the desired effect. This might be possible since a greater occupancy of postsynaptic GABA_BRs is required to elicit a response and so this response is the more sensitive to antagonism (Seabrook et al., 1990).

2.3. Acetylcholine receptors

The crucial role of acetylcholine in cognition has long been recognized (Sarter and Parikh, 2005). There is good evidence that some of its actions might be mediated via the regulation of NMDARs. In particular, the stimulation of muscarinic AChRs (mAChRs) is known to facilitate the activation of NMDARs (Markram and Segal, 1990). This probably occurs via multiple mechanisms. Activation of mAChRs leads to depolarization of neurons and so would be expected to facilitate the Hebbian depolarization. Since mAChRs depolarize neurons via the inhibition of K⁺ channels, the associated increase in membrane resistance will also facilitate the Hebbian depolarization. A particularly interesting regulation is via the inhibition of SK channels that are located at synapses and activated by Ca²⁺ entry during the synaptic activation of NMDARs (Buchanan et al., 2010). In addition, it is likely that the activation of mAChRs facilitates the activation of NMDARs via mechanisms independent of K⁺ channels. Low concentrations of a mAChR agonist, carbachol, below those that

appreciably affect K^+ channels, can exert a powerful regulation of NMDARs, via a pathway that has not been fully delineated but seems to be independent of PKC and the release of Ca^{2+} from stores (Harvey et al., 1993). Activation of mAChRs can also lead to a long-lasting depression of NMDAR mediated synaptic transmission, via the induction of a form of synaptic plasticity. This effect is due to the internalization of NMDARs and is triggered by IP_3 receptor-mediated Ca^{2+} release from stores (Jo et al., 2010). Clearly, the mAChR regulation of NMDARs is multifaceted and the direction of the regulation (enhancement or depression) depends on a variety of factors.

2.4. Metabotropic glutamate receptors

Group I mGluRs (mGlu1 and mGlu5), which like muscarinic M1 receptors couple to Gq11, are also able to regulate the activation of NMDARs in multiple ways. For example, it was found that activation of group I mGluRs, using 3,5-dihydroxyphenylglycine (DHPG) (Fitzjohn et al., 1996), or more specifically mGlu5 receptors, using 2-chloro-5-hydroxyphenylglycine (CHPG) (Doherty et al., 1997; Fig. 2), is able to directly potentiate the depolarization of CA1 neurons induced by NMDA. This effect is very robust and has been exploited in attempts to boost NMDAR function, though again its mechanism has not been fully elucidated. The mGlu5 receptor and NMDARs can work in concert for induction of LTP (Bortolotto et al., 2005; Lante et al., 2006) with mGlu5 playing an increasing role with age (Lante et al., 2006). An mGlu5 receptor antagonist blocked LTP in the dentate gyrus and reduced performance on a radial maze task (Manahan-Vaughan et al., 2004). A series of positive allosteric modulators (PAMs) of mGlu5 receptors have been developed and shown to facilitate the activation of NMDARs (see Vinson and Conn 2011 for review) and enhance LTP (Ayala et al., 2009; Kroker et al., 2011). These compounds have been found to increase behavioural flexibility in a set-shifting paradigm (Darrah et al., 2008) to enhance novel object recognition and to reduce impulsivity in a five choice serial reaction time test (Liu et al., 2008), to reverse cognitive deficits induced by MK-801 (Vales et al., 2010) and to improve learning deficits in the methylazoxymethanol acetate (MAM) model of schizophrenia (Gastambide et al., 2012; and see Vinson and Conn, 2011 for a review).

2.5. Other modulators

There are numerous modulators that can regulate NMDAR function via depolarization (to relieve the Mg^{2+} block and thereby facilitate the Hebbian depolarization). Regulation can also be via intracellular signaling pathways, as exemplified by mGluRs and mAChRs. The former is a regulation that can, in principle, occur during the synaptic release of L-glutamate and, as such, can contribute to the property of cooperativity. Acetylcholine represents one of potentially many neurotransmitters and neuronal regulators that may regulate NMDAR function in an associative manner. As discussed later (see 3.6.1), other G-protein-coupled receptors (GPCRs; e.g. pituitary adenylate cyclase activated peptide 1 receptors, PAC1Rs) and dopamine 1 receptors (D1Rs) have also been implicated in the subtype-specific modulation of NMDARs via Src family kinases (Yang et al., 2012). These properties may therefore be exploited physiologically during the execution of cognitive processes.

3. Direct modulation

3.1. Antagonists

Consistent with the idea that NMDAR-LTP is important for learning and memory, NMDAR antagonists have been found, in numerous investigations, to impair these processes. However, NMDAR antagonists can also be cognitively enhancing under certain circumstances. The most notable example of this is memantine, a substance that is used in the treatment of Alzheimer's disease where it has a modest effect in delaying the decline in cognitive function (Danysz and Parsons, 2003).

One way in which NMDAR antagonists may be able to enhance cognition is by selectively inhibiting the “pathological activation” while preserving the “physiological activation” of NMDARs. This principle was first demonstrated in a simple slice experiment in which Mg^{2+} was removed from the perfusing solution (Coan et al., 1989). This treatment led to the inhibition of LTP. Under these conditions, addition of the specific competitive NMDAR antagonist AP5 was able to fully restore the ability to induce LTP. This was because AP5 was able to block the aberrant activation of NMDARs caused by the removal of Mg^{2+} but during tetanic stimulation sufficient glutamate release occurred to outcompete the AP5 to activate NMDARs appropriately to enable the induction of LTP. These results are re-plotted and represented schematically in Fig. 3.

This mechanism (block of pathological but not physiological NMDAR activation) is the rationale behind the cognitive enhancing effects of memantine. Indeed, it was shown that memantine could, like AP5, restore the loss of LTP resulting from treatment with a low Mg^{2+} solution (Frankiewicz and Parsons, 1999). With memantine the mechanism is slightly different since it is a fast, voltage-dependent channel blocker (Bresink et al., 1996; Frankiewicz et al., 1996). Therefore memantine suppresses the pathological activation of NMDARs by occupying the channel but its block is relieved by the Hebbian depolarization during the induction of LTP (Fitzjohn et al., 2008).

Along the same lines, the pathological activation of NMDARs may be limited, without greatly affecting its physiological activation, by increasing the Mg^{2+} concentration. This strategy has also proven effective and so Mg^{2+} can be considered a cognitive enhancing agent (Slutsky et al., 2010). This principle can, of course, be extended to other types of NMDAR antagonists and compounds that regulate NMDAR function indirectly, such as mGlu5 receptor negative allosteric modulators. With respect to NMDAR antagonists, there is evidence to suggest that compounds selective for GluN2B may enhance cognitive and their possible use in Alzheimer's disease is under investigation (see Mony et al, 2009).

3.2. Glycine site

The co-agonist role of glycine or a glycine-like substance, such as D-serine, for the NMDAR channel complex was discovered by Johnson and Ascher (1987) who initially hypothesized an allosteric site that positively modulates the probability of channel opening. This initial observation was quickly followed by demonstrations of selective functional antagonists at the glycine site (HA-966: Fletcher and Lodge, 1988; Foster and Kemp, 1989), (7-chlorokynurenic acid: Kemp et al., 1988) and (1-aminocyclobutane-1-carboxylate: Hood

et al., 1989). The absolute requirement for occupation of the glycine-site was confirmed by Kleckner and Dingledine (1988) by meticulous elimination of glycine from the extracellular medium. Full activation of NMDARs requires agonist binding at two glycine and two glutamate receptors on the tetrameric complex (Benevise and Mayer, 1991; Clements and Westbrook, 1991). Site directed mutagenesis of the GluN1 subunit determined GluN1 as the site of glycine's action (Kuryatov et al., 1994; Wafford et al., 1995). Interestingly, the GluN3 subunits are also activated by glycine rather than by glutamate so that tetrameric GluN1/GluN3 receptors are putative excitatory glycine receptors, not requiring the presence of glutamate (Chatterton et al., 2002; Madry et al., 2007)

The apparent high affinity of glycine for this site (Johnson and Ascher, 1987; Kleckner and Dingledine, 1988) and several experimental studies at the time (Fletcher and Lodge, 1988; Kemp et al., 1988; but see Thomson et al., 1989) indicated that the glycine site was likely to be fully occupied *in vivo* either by glycine itself or by D-serine which had been originally described as mimicking the actions of glycine (Johnson and Ascher, 1987). Further studies (e.g. Berger et al., 1998) suggested that at some locations in the central nervous system (CNS) at least and, as a result of the activity of high affinity glycine transporters (GlyT-1; Supplison and Bergman, 1997), the glycine site is not fully saturated by glycine.

As a result of this incomplete occupancy, several potential strategies for enhancing NMDAR function, and hence putatively improving cognition, via the glycine site have emerged (Fig. 2). Most obvious is exogenous administration of agonists and partial agonists. Access of exogenous glycine to synapses utilising NMDARs is, however, limited by GlyT-1 and inhibition of this transporter is, therefore, more likely to be successful in increasing glycine levels at the NMDAR (Supplison and Bergman, 1997; Berger et al., 1998; Chen et al., 2003; Bergeron et al., 1998; Martina et al., 2004; Stevens et al., 2010). GlyT-1 inhibition has been shown to enhance LTP (Martina et al., 2004; Manahan-Vaughan et al., 2008) and cognition in both a social recognition test (Shimazaki et al., 2010) and an attentional set-shifting task (Nikifurik et al., 2011). Some preliminary studies in schizophrenics indicate improved cognitive performance (Tsai et al., 1998, 2004; Lane et al., 2005; Heresco-Levy et al., 1996) but the danger of side effects due to activation of strychnine-sensitive inhibitory glycine receptors needs attention (Kopac et al., 2010).

Increasing extracellular levels of D-serine, which does not activate the glycine inhibitory receptor, offers several approaches. Exogenous D-serine has been shown to enable LTP, when the glycine site is not fully occupied by glycine (Oliver et al., 1990; Bashir et al., 1990; Watanabe et al., 1992; Duffy et al., 2008). Endogenous D-serine, produced in astrocytes by serine racemase from L-serine and glycine, has been shown to be necessary for both LTP and LTD (Yang et al., 2003; Yang et al., 2005; Mothet et al., 2006; Henneberger et al., 2010; Fossat et al., 2012). Age-related or genetic deficiencies in serine racemase lead to reduced LTP and memory disruption which can be reversed by exogenous D-serine administration (Mothet et al., 2006; DeVito et al., 2011).

A further potential means of enhancing D-serine levels is by inhibition of its catabolising enzyme, D-amino acid oxidase (DAAO). This strategy has received a boost from the finding that mutant mice lacking DAAO show enhanced hippocampal LTP and improved Morris

water maze performance compared with normal mice (Maekawa et al., 2005). Furthermore there are growing genetic associations between DAAO and schizophrenia, (for example Chumakov et al., 2002). Several DAAO inhibitors have been synthesised and assessed in models of schizophrenia (see Ferraris and Tsukamoto, 2011) but it seems that DAAO inhibition alone does not raise D-serine levels as efficiently as exogenous administration of D-serine (see Smith et al. 2010). In support of this, Strick et al. (2011) found that DAAO inhibition did not significantly affect either brain levels of D-serine, except in the cerebellum, or performance in cognitive behavioural assays although there was an increase in hippocampal theta rhythm.

Enhancement of NMDA activity via the glycine site remains an attractive therapeutic possibility. As occupancy of this site decreases with old age, some combination of exogenous administration of D-serine, inhibition of GlyT-1 and inhibition of DAAO may prove therapeutically successful.

3.3 Polyamines

Endogenous polyamines, such as spermine, have been shown to potentiate the activity of agonists on NMDARs (Williams et al., 1994). This potentiation is thought to be mediated by (i) a glycine-dependent, (ii) a voltage-dependent and (iii) a glycine-and voltage-independent effects of spermine. The glycine-dependent effect is observed in GluN2A or GluN2B containing NMDARs and is thought to be due to an increase in the affinity of glycine for the receptor. The presence of exon 5 in the N-terminal domain (NTD) of GluN1 does not affect the glycine-dependent effect nor does extracellular pH (Williams, 1997). The glycine-independent effect refers to the ability of spermine to enhance NMDAR currents evoked by saturating concentrations of glycine and glutamate. Tonic inhibition of NMDARs by protons can be relieved by stimulation by spermine (Traynelis et al., 1995). This effect is only observed in GluN1/GluN2B containing NMDARs and only if the NTD of the GluN1 subunit does not contain the exon-5 insert. Spermine has a weaker potentiating effect at subsaturating concentrations of glutamate due its effect of lowering sensitivity of GluN1/GluN2B-containing NMDARs to glutamate (Williams, 1994a).

3.4. Neurosteroids

Endogenous neurosteroids have numerous actions in the brain including modulation of GABARs and NMDARs (Korinek et al., 2011). Pregnanolone and allopregnanolone, like progesterone, potentiate the actions of GABARs with minimal inhibitory effects on NMDAR function, which may underlie their anaesthetic actions (Selye, 1941). Pregnanolone sulfate weakly inhibits both GABAR and NMDAR actions whereas pregnenolone sulfate (PS) strongly potentiates NMDAR function (Fig. 2) and weakly inhibits GABAergic activity. Other neurosteroids related to pregnenolone have similar but in general less efficacious profiles.

PS, which is synthesized in brain tissue (Corpechot et al., 1983), is then the neurosteroid of interest for potentiating NMDAR function. PS, first described as a positive and selective allosteric modulator of NMDARs on chick spinal neurons (Wu et al., 1991) and hippocampal neurons (Bowlby et al., 1993) was shown to enhance learning and memory

(Flood et al., 1992; Mayo et al., 1993). It now appears that its actions are quite complex with both inhibitory and facilitatory sites on NMDARs (Park-Chung et al., 1997; Horak et al., 2006; Kotsakis et al., 2011). In GluN2A or GluN2B subunit containing NMDARs, the facilitatory site predominates whereas, on those with GluN2C or GluN2D, inhibition by PS predominates (Kotsakis et al., 2011). An earlier study suggested selective effects of PS and other neurosteroids (but not anabolic androgenic steroids) on GluN2B rather than GluN2A containing receptors (see Elfverson et al., 2011). These PS binding sites are likely to be in the M3-M4 extracellular loop (S2 domain) of the GluN2 subunits, close to the proton site (Kotsakis et al., 2011). A further complication is that positive modulation of NMDARs by PS has been reported to be phosphorylation state dependent (Petrovic et al., 2009).

Enhanced NMDAR function underlies enhanced LTP at CA1 synapses in the presence of PS (Sliwinski et al., 2004; Sabeti et al., 2007) and PS alone is able to induce long lasting potentiation (LLP) of synaptic efficacy at granule cell synapses (Chen et al., 2007). In this PS-induced LLP, the LTD-LTP induction curve is shifted to the left so that lower stimulus frequencies are needed to induce these two forms of plasticity (Chen et al., 2010). Levels of this endogenous neurosteroid declines with age in parallel with cognitive decline (Flood et al., 1995; Vallee et al., 1997). This decline in performance in the water maze task can be reversed by exogenous administration of PS (Vallee et al., 1997). PS has also been claimed to reduce the amnesic effects of stress (Reddy et al., 1998; Urani et al., 2002).

Dehydroepiandrosterone sulfate (DHEAS), itself synthesized from PS, also potentiates NMDARs and enhances LTP (Randall et al., 1995; Chen et al., 2006; for review see, Dubrovsky, 2005). Interestingly, inhibition of the synthesis of PS and DHEAS in hippocampal slices reduces NMDAR function and LTP induction, suggesting a local ongoing synthesis of these neurosteroids (Tanaka and Sokabe, 2012).

3.5. Histamine and ATP

Histamine has been shown to potentiate agonist stimulated effects on recombinant NMDARs containing GluN1/GluN2B but not those containing GluN2A or GluN2C subunits (Williams, 1994). The effect was dependent on high agonist concentrations and did not occur in NMDARs containing GluN1 subunits with the exon 5 insert in the NTD.

Adenosine triphosphate (ATP) inhibits recombinant NMDARs containing GluN1/GluN2A or GluN1/GluN2B subunits at low agonist concentrations but at saturating agonist concentrations acts as a potentiator (Kloda et al., 2004). In contrast, ATP potentiates NMDARs containing GluN1/GluN2C even at nonsaturating agonist concentrations. ATP has been proposed to compete with glutamate for its binding site and this may explain why high agonist concentrations are required to reveal the potentiating effect of ATP on GluN1/GluN2A or GluN1/GluN2B.

3.6. Intracellular modulation of NMDARs

The function of NMDARs, like other iGluRs, is also regulated by posttranslational modifications (e.g. phosphorylation, palmitoylation, ubiquitination, proteolytic cleavage by calpain) and by protein binding partners. Here we overview some of the complex

intracellular pathways that are key modulators of NMDAR function. These regulatory mechanisms could in principle be targeted pharmacologically.

3.6.1. Functionally significant key phosphorylation sites of NMDAR subunits

—The function and subcellular distribution of NMDARs are differentially regulated by phosphorylation of specific serine (S) / threonine (T) and tyrosine (Y) amino acid residues in the intracellular C-terminal domains of various subunit proteins (Salter et al., 2009; Traynelis et al., 2010). Protein kinases that catalyze phosphorylation and phosphoprotein phosphatases that catalyze dephosphorylation are recruited to NMDARs via interactions with postsynaptic density protein 95 (PSD95), A-kinase anchoring proteins (AKAP79/150) and yotiao (Colledge et al., 2000; Klauck et al., 1996; Salter et al., 2009; Westphal et al., 1999). This compartmentalisation is likely to increase the selectivity, efficiency and speed of phosphorylation and dephosphorylation events. In this section, we highlight some of the main functional changes produced by the phosphorylation of key sites in core NMDAR subunit proteins. See recent reviews for a more extensive list of possible, but not fully verified NMDAR phosphorylation sites (Salter et al., 2009; Traynelis et al., 2010).

In the alternatively spliced C-terminal C1-cassette of GluN1, protein kinase C (PKC) phosphorylates serine residues GluN1-S₈₉₀ and GluN1-S₈₉₆ (Tingley et al., 1997) (Fig. 4). In contrast, the neighbouring GluN1-S₈₉₇ is phosphorylated by cyclic AMP-dependent protein kinase A (PKA; Tingley et al., 1997) (Fig. 4). Phosphorylation of these sites regulates cell surface expression and clustering of NMDARs (Crump et al., 2001; Ehlers et al., 1995; Fong et al., 2002; Scott et al., 2003; Tingley et al., 1997) and may affect channel function by modulating the inhibitory interaction between GluN1 and calmodulin (Ehlers et al., 1996; Hisatsune et al., 1997). GluN1-S₈₉₀ and GluN1-S₈₉₆ are preferentially phosphorylated by PKC γ and PKC α , respectively (Sánchez-Pérez and Felipo, 2005) (Fig. 4). Phosphorylation of the GluN1-S₈₉₀ but not GluN1-S₈₉₆ or GluN1-S₈₉₇ residues facilitates rapid dispersal of synaptic NMDARs (Tingley et al., 1997). Activation of group I mGluRs by DHPG increases GluN1-S₈₉₀ but not GluN1-S₈₉₆ phosphorylation. Surface expressed GluN1 proteins are phosphorylated at S₈₉₀ but not at S₈₉₆ (Sánchez-Pérez and Felipo, 2005). The dual PKC/PKA phosphorylation of GluN1-S₈₉₆/GluN1-S₈₉₇ promotes NMDARs trafficking from the endoplasmic reticulum to the cell surface (Scott et al., 2001, 2003).

The C-terminal domains of GluN2A and GluN2B are substrates for Ca²⁺/calmodulin-dependent protein kinase (CaMKII; Omkumar et al., 1996), PKC and PKA (Leonard and Hell, 1997; Liao et al., 2001; Fig 4). NMDAR-PSD95/SAP102 interactions are disrupted by casein kinase II (CK2)-mediated GluN2B-S₁₄₈₀ phosphorylation (Chung et al., 2004). This activity-dependent process is thought to be an important component of the developmental switch from GluN2B- to GluN2A-containing NMDARs at synapses (Sanz-Clemente et al., 2010). Phosphorylation of GluN2B-S₁₃₀₃ and GluN2B-S₁₃₂₃ by PKC potentiates GluN2B-containing NMDAR current (Liao et al., 2001; Fig 4). GluN2B-S₁₃₀₃ may also be phosphorylated by CaMKII, which affects the receptor-kinase interaction (Liu et al., 2006). In GluN2C, S₁₂₃₀ is phosphorylated by both PKA and PKC (Chen et al., 2006). Phosphomimetic mutation of GluN2C-S₁₂₃₀ accelerates channel kinetics by increasing the speed of both the rise and decay of NMDA-evoked currents (Chen et al., 2006). Increased

PKA activity can facilitate the induction of LTP by increasing the Ca^{2+} permeability of NMDARs in dendritic spines (Skeberdis et al., 2006).

Several potential sites of tyrosine kinase phosphorylation have been identified in GluN1, GluN2A and GluN2B (Moon et al., 1994; Lau and Huganir 1995; Fig. 4). Disruption of GluN1-Y₈₃₇ and GluN2A-Y₈₄₂, by site-directed mutagenesis, prevented use-dependent desensitization of GluN1/GluN2A NMDARs (Vissel et al., 2001). However, the GluN1 intracellular C-terminus does not appear to be tyrosine phosphorylated in neurons (Lau and Huganir, 1995). GluN2A-Y₁₃₈₇ and GluN2B-Y₁₄₇₂ are major sites of phosphorylation by Src-family kinases (Nakazawa et al., 2001; Yang and Leonard, 2001; Fig 4). Tyrosine phosphorylation potentiates the NMDAR ion channel resulting in increased Ca^{2+} currents (Ali and Salter, 2001) and has been implicated in the regulation of the internalization of NMDARs (Vissel et al., 2001; Li et al., 2002). Increased GluN2B-Y₁₄₇₂ phosphorylation promotes the synaptic targeting of NMDARs (Prybylowski et al., 2005). Furthermore, Src-mediated upregulation of NMDARs is thought to play an important role in LTP of CA1 neurons (Groveman et al., 2012; Ohnishi et al., 2011; Trepanier et al., 2012). This is supported by the finding that the level of GluN2B-Y₁₄₇₂ phosphorylation increases following tetanic stimulation in the CA1 region of the hippocampus (Nakazawa et al., 2001). The striatal-enriched tyrosine phosphatase (STEP) dephosphorylates GluN2B-Y₁₄₇₂ (Braithwaite et al., 2006; Pelkey et al., 2002; Snyder et al., 2005) and also inactivates Fyn (Nguyen et al., 2002), therefore both directly and indirectly downregulates synaptic NMDAR expression. Furthermore, synaptic and extrasynaptic NMDARs are differentially phosphorylated at GluN2B-Y₁₄₇₂ and GluN2B-Y₁₃₃₆, respectively (Goebel-Goody et al., 2009), suggesting that modulation of NMDAR tyrosine phosphorylation affects receptor retention and translocation between synaptic and extrasynaptic sites (Gladding and Raymond, 2011).

A recent study raised the intriguing possibility that the direction of synaptic plasticity in CA1 neurons is determined by different classes of GPCRs that differentially target tyrosine phosphorylation sites in GluN2A and GluN2B NMDAR subunits (Fig. 4) via selective activation of Src and Fyn kinases (Yang et al., 2012). The Gαq-coupled pituitary adenylate cyclase activating peptide 1 receptors (PAC1Rs) selectively enhanced the activity of GluN2A-containing NMDARs through the activation of Src kinase. In contrast, the Gαs-coupled dopamine 1 receptors (D1R) enhanced GluN2B-containing NMDARs via selective activation of Fyn (Yang et al., 2012). While PAC1R lowered the threshold for LTP, D1R enhanced LTD indicating that NMDAR-mediated metaplasticity is gated by GPCRs (Yang et al., 2012). These findings are consistent with the notion that the balance between the activities of GluN2A- and GluN2B-containing NMDARs is a key determinant of the direction of synaptic plasticity (Cho et al., 2009; Fox et al., 2006; Liu et al., 2004; Massey et al, 2004) and GPCRs can provide a mechanism by which other neuromodulators affect NMDAR function (section 2. Indirect modulation). Compounds acting via GPCRs to alter the tyrosine phosphorylation status of NMDARs, offer a wide spectrum of possibilities for modulating cognitive function.

3.6.2. Palmitoylation of NMDARs—Palmitic acid is a saturated fatty acid that is highly abundant in the CNS. Palmitate forms a covalent attachment to proteins via thioester

bonds at cysteine (C) residues. This modification is labile, reversible and dynamically regulated by neuronal activity (Hayashi et al., 2009). GluN2A and GluN2B have two potential palmitoylation sites in their C-terminal domains (Cys clusters I and II; Fig 4, Hayashi et al., 2009). Palmitoylation of Cys cluster I controls stable synaptic expression and constitutive internalization of surface NMDARs. De-palmitoylation of Cys cluster II regulates surface delivery of NMDARs (Hayashi et al., 2009). Decreased GluN2B palmitoylation at both clusters is likely to reduce synaptic NMDAR population and increase extrasynaptic NMDAR numbers (Gladding and Raymond, 2011). Therefore, palmitoylation of GluN2 subunits also contributes to regulation of NMDAR trafficking and affects brain function.

3.6.3. Ubiquitination of NMDARs—Ubiquitin is a small (76 amino acid containing) protein that covalently attaches to specific lysine (K) residues in substrate proteins in an ATP-dependent, sequential action of three classes of enzymes, E1-3 (Mabb and Ehlers, 2010). The number and subunit composition of synaptic NMDARs are regulated by activity-dependent protein degradation through the ubiquitin-proteasome system (Ehlers, 2003). Increased synaptic activity leads to upregulation of GluN2A, PSD95 and Homer protein expression and downregulation of GluN1, GluN2B and Shank (Ehlers, 2003). These changes are blocked by proteosomal inhibitors (Ehlers, 2003). Mind bomb-2 (Mib2) E3 ubiquitin ligase interacts with and ubiquitinates the GluN2B NMDAR subunit in a Fyn phosphorylation-dependent manner (Jurd et al., 2008). These findings indicate that ubiquitination is an important mechanism for the removal and degradation of NMDARs that results in dynamic regulation of synaptic strength in response to activity.

3.6.4. Proteolytic cleavage of NMDAR subunits by calpain—The Ca^{2+} -activated protease calpain cleaves the C-terminal domains of GluN2A-C subunits, but not GluN1 (Dong et al., 2006; Guttman et al., 2001; Simpkins et al., 2003; Doshi and Lynch, 2009; Fig. 4). While the proteolytic truncation of NMDAR subunits removes regulatory and protein-protein interaction sites and reduces synaptic activity, basic ion channel gating and key pharmacological properties are not affected (Guttman et al., 2001; Simpkins et al., 2003). Therefore, it is plausible that calpain cleaved NMDARs remain functional on the cell surface at extrasynaptic sites (Gladding and Raymond, 2011).

3.6.5. Protein binding partners of NMDARs—Like other iGluRs, NMDARs also interact with a wide range of cytoskeletal, scaffolding and signalling proteins (e.g. α -actin-2, AP2, calmodulin, CaMKII, CARPI, COPII, GPS2, LIN7, MAP1S, PACSIN1, plectin, PSD95, RACK1, SALM1, SAP97, SAP102, S-SCAM; Traynelis et al. 2010). An auxiliary subunit, Neto1, has also been described for NMDARs (Ng et al., 2009). Neto1 interacts with an extracellular domain of GluN2 as well as through an intracellular interaction with PSD95. Loss of Neto1 in transgenic mice preferentially results in a loss of synaptic GluN2A expression, with only a modest impact on GluN2B expression, which leads to impaired hippocampal LTP and hippocampal-dependent learning and memory (Ng et al., 2009).

At synapses, NMDARs are stabilised by interaction with PSD95 (Roche et al., 2001; Li et al., 2003). The association of NMDARs with PSD95 and their subsequent endocytosis is regulated by tyrosine phosphorylation. Phosphorylation of GluN2B-Y₁₄₇₂ interferes with

binding to PSD95 and promotes clathrin-dependent endocytosis by promoting the binding of AP2 to GluN2B. Dephosphorylation of GluN1-Y₈₃₇ and GluN2A-Y₈₄₂ might affect AP2 binding, promoting clathrin-dependent endocytosis in a similar way (Vissel et al., 2001). There is evidence that the synaptic activation of mAChRs leads to a reduction in the surface expression of synaptic NMDARs via the recruitment of hippocalcin, which triggers the exchange of PSD-95 for AP2 to promote endocytosis (Jo et al, 2010).

Intradendritic trafficking of GluN2B subunits requires them to associate with the motor protein KIF17 through LIN10 (Guillaud et al., 2003). Within the PSD, NMDARs are linked by α -actin and spectrin to f-actin, which associates with myosin and might be dynamically regulated by MLCK (myosin light chain kinase; Lei et al., 2001). Synaptic GluN2A containing NMDARs seem to be important for LTP and extrasynaptic GluN2B-containing receptors are involved in LTD (Cull-Candy et al., 2001). In adult neocortical slices de novo LTD induction is enhanced by blockage of glutamate uptake, indicating that the diffusion of glutamate to extrasynaptic GluN2B containing NMDARs triggers LTD (Massey et al., 2004). Furthermore, LTD can be induced after blockade of synaptic NMDARs (Massey et al., 2004). Therefore, NMDAR interactions, localisation and targeting are crucial determinants of synaptic plasticity and consequently cognition.

4. Recently discovered NMDAR PAMs

4.1 Phenanthrene derivatives

A series of 9-substituted phenanthrene-3-carboxylic acid derivatives has been reported to potentiate NMDAR activity with different patterns of GluN2 subunit selectivity (Costa et al., 2010). In an electrophysiological assay on GluN1/GluN2 NMDAR subtypes expressed in *Xenopus oocytes*, the 9-iodo derivative, UBP512, weakly potentiated GluN2A, had little or no effect on GluN2B and inhibited GluN2C- and GluN2D-containing NMDARs. When tested in the presence of 30-fold higher concentrations of glycine and glutamate UBP512 displayed an enhanced potentiating effect on GluN2A. Potentiation of GluN1/GluN2A by UBP512 due to chelation of Zn²⁺, resulting in reversal of Zn²⁺ inhibition, was ruled out in this study (Costa et al., 2010). The 9-cyclopropyl derivative, UBP710 (Fig. 2), potentiated GluN2A and GluN2B but had inhibitory activity on GluN2C or GluN2D-containing NMDARs, when tested at higher concentrations. The 9-i-hexyl derivative, UBP646, however, acted as a universal potentiator on recombinant NMDARs containing GluN2A-D, displaying the greatest potentiating effect on GluN2D.

The NTD is not necessary for the potentiating effect of UBP512 or UBP710, as these compounds still caused potentiation when tested on GluN1/GluN2A receptors without NTDs (Costa et al., 2010). Chimeric receptor studies were used to investigate whether the S1 and S2 regions of the ligand binding domain (LBD) of GluN2A were involved in the NMDAR potentiating activity of UBP512 and UBP710 (Costa et al., 2010). These studies relied on the different modes of action of UBP512 and UBP710 on GluN2 subunits, i.e. the potentiation of GluN2A and inhibition of GluN2C. Swapping the S1 domain of GluN2A with the S1 domain of GluN2C did not affect the potentiating effect of UBP512 and UBP710. However, swapping the S2 domain of GluN2A with the S2 domain of GluN2C

converted the compounds to inhibitors, suggesting that they may be binding to the S2 domain or that the S2 domain is involved in the transduction of the potentiating effect.

Examination of the crystal structure of the LBDs of GluN1/GluN2A suggested that Y535 in GluN1 can play a positive allosteric modulatory role by interacting with hydrophobic residues in the dimer interface, thereby stabilizing the dimer interface and slowing deactivation (Furukawa et al., 2005). In support of a role for Y535 in controlling deactivation, the Y535L mutant showed a modest increase in the rates of glycine and glutamate deactivation, whereas the Y535F mutant showed slightly slower deactivation rates (Furukawa et al., 2005). Given that the S2 domain of GluN2A is required for the potentiating effect of UBP512 and UBP710 on GluN2A, it is reasonable to suggest that these compounds are binding at the GluN1/GluN2A dimer interface to block desensitization and/or slow deactivation, perhaps by stabilizing the interaction of Y535 with the hydrophobic site in the dimer interface or by contributing additional stabilization to that provided by Y535. However, it is also possible that these compounds are binding within or in close proximity to the transmembrane region leading to stabilization of the open channel conformation. More work is required to identify the precise binding site(s) and mechanism of action of the UBP compounds.

4.2 Naphthalene derivatives

A naphthalene derivative, 3,5-dihydroxynaphthalene-2-carboxylic acid, UBP551 showed a selective potentiating effect on GluN2D and inhibitory activity on GluN2A-C (Costa et al., 2010). The concentration response curve for the potentiating activity of UBP551 on GluN2D is bell shaped, greatest potentiation was observed at 30 μ M and potentiation was reduced at higher concentrations. UBP551 is unique amongst the recently reported potentiators in that it has differential activity on GluN2C and GluN2D. The mechanism underlying the potentiating effect of UBP551 on GluN2D is unknown but it may differ from that of the structurally dissimilar phenanthrene based potentiators.

4.3 Coumarin derivatives

The coumarin derivative, 6-bromo-4-methylcoumarin-3-carboxylic acid, UBP714 (Fig. 2), has been shown to have a weak potentiating effect on recombinant GluN2A-, GluN2B- and GluN2D-containing NMDARs (Fig. 5 and Irvine et al., 2012). UBP714 potentiated field excitatory postsynaptic potentials (fEPSPs) mediated by NMDARs but not those due to AMPARs in the CA1 region of the hippocampus (Fig. 5 and Irvine et al., 2012). Interestingly, an analogue of UBP714, without the 4-methyl group, 6-bromocoumarin-3-carboxylic acid, UBP608, was a moderately potent inhibitor of GluN1/GluN2A with an IC_{50} value 18.6 μ M, suggesting that the methyl group of UBP714 is necessary for potentiating activity (Costa et al., 2010; Irvine et al., 2012).

4.4 Isoquinoline derivatives

A novel structural class of NMDAR potentiator, CIQ ((3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2-(1H)-yl)methanone, Fig. 2) has been reported to selectively potentiate NMDARs containing GluN2C or GluN2D subunits (Mullasseril et al., 2010). CIQ was found to potentiate recombinant triheteromeric GluN1/

GluN2A/GluN2C or GluN1/GluN2A/GluN2D NMDARs, suggesting that only one GluN2C or GluN2D subunit is required for the potentiating effect. Single channel analysis of the effect of CIQ on GluN1/GluN2D suggested that the potentiating effect was due to an increase in channel opening frequency, without altering mean open time. CIQ also potentiated NMDAR currents mediated by GluN2D expressed in subthalamic neurons. CIQ appears to have different structural requirements for its potentiating effect on NMDARs compared to the UBP compounds and PS. Chimeric receptor and point mutation studies suggest that the linker between the NTD and the LBD and T592 in the M1 region of GluN2D are required for the potentiating effect of CIQ. This, coupled with the minimal effect of CIQ on NMDAR deactivation, suggests that the dimer interface is not a likely site for CIQ binding and that the potentiating effect is occurring by a different mechanism to that observed for UBP compounds.

5. Concluding remarks

This review indicates a number of ways in which NMDAR function could be enhanced. NMDARs are ubiquitously expressed throughout the CNS and as such are involved in all functions of neural circuits of the brain and spinal cord. The complexity and multiplicity of NMDARs, its heteromeric structure with intracellular sites for modulation of function and its subtypes offer numerous opportunities for therapeutic interventions. Because of the widely accepted role of NMDARs in plasticity and memory, the obvious approach for cognitive enhancement is potentiation of NMDAR function. However, given the complex roles of NMDARs in synaptic transmission and bidirectional synaptic plasticity the normalization of function could be a better strategy. Putative compounds for consideration will need to have subtle effects; over-stimulation of NMDARs will *inter alia* likely lead to exacerbation of pain, hyperexcitability and neurodegeneration. Subunit selectivity and limited efficacy may therefore be desirable properties. New compounds with direct but allosteric and specific effects on the NMDAR subunits may offer the most fruitful approach

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Abbreviations

AChR	acetylcholine receptor
AKAP79/150	A-kinase anchoring proteins
AMPA	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

Highlights

- Cognitive decline is a major problem facing an ageing human population.
- NMDA receptors play an important role in neural plasticity and learning and memory.
- Excessive activation of NMDA receptors results in deleterious effects.
- Subtle fine-tuning of NMDAR function is needed for control of cognitive decline.
- Positive allosteric modulators of NMDARs can affect NMDAR mediated events.

Fig. 1.

Indirect modulation of NMDARs. (A) Schematic representation of some ways in which NMDAR function can be regulated indirectly. Neurotransmitters, and other neuronal regulators, can facilitate NMDAR function by augmenting the “Hebbian depolarization” and by intracellular regulation. NMDARs are important for (B) synaptic transmission (C) the induction of LTP and (D) the induction of LTD. Note that NMDARs contribute considerably to the synaptic response during high frequency synaptic transmission; in this example the NMDAR-EPSP has summated with the AMPAR-EPSPs (shaded yellow) to fire several action potentials (adapted from Herron et al, 1986). LTP is induced by a brief period of high frequency stimulation whilst LTD is induced by a prolonged period of low frequency stimulation. Key: Different types of receptor populations are shown by a colour-coded symbol. Inward current via AMPARs and NMDARs (carried mainly by Na^+) contributes to the Hebbian depolarization and is shown by a red arrow. Outward current (carried mainly by the movement of K^+ (GABA_B) out of the cell or Cl^- (GABA_A) into the cell) opposes the Hebbian depolarization and is depicted by a blue arrow. Ca^{2+} entry is shown by the grey arrow and Mg^{2+} by a black circle.

Fig. 2.

Potential sites of action of cognitive enhancers at glutamatergic synapses and structures of some compounds that potentiate NMDAR function. The key is the same as in Fig. 1.

Fig. 3.

Inappropriate activation of NMDARs inhibits LTP. The panels show data (left panel; replotted from Coan et al, 1989) and schematics during baseline (centre) and a tetanus (right) under four experimental conditions (from top to bottom): in 1 mM Mg²⁺ (grey shading and black circles), following perfusion with Mg²⁺-free medium, and following the addition of either 20 μ M or 200 μ M D-AP5 in Mg²⁺-free medium (green shading and circles). Calibration bar is 4 mV and 5 min. Optimal conditions for LTP requires minimal activation of NMDARs except during the induction stimulus (time of delivery of the tetanus is indicated by an arrow). By removing Mg²⁺, NMDAR activation is enhanced throughout the recording period and this inhibits the generation of LTP. A low concentration of D-AP5 normalizes the situation by inhibiting spurious NMDAR activation, but is outcompeted by L-glutamate during high frequency stimulation. However, a high concentration of D-AP5 inhibits NMDARs during high frequency stimulation.

Fig. 4.

Sites of intracellular modulation of NMDARs. Schematic representation of the distribution of selected posttranslational regulatory sites on the intracellular C-terminal domains of GluN1, GluN2A and GluN2B NMDAR subunits. Serine (S) phosphorylation sites: GluN1-S₈₉₀, GluN1-S₈₉₆, GluN1-S₈₉₇, GluN2B-S₁₃₀₃, GluN2B-S₁₃₂₃, GluN2B-S₁₄₈₀ (Chung et al., 2004; Leonard and Hell, 1997; Liao et al., 2001; Liu et al., 2006; Sanchez-Perez and Felipe, 2005; Sanz-Clemente et al., 2010; Scott et al., 2001, 2003; Tingley et al., 1997). Tyrosine (Y) phosphorylation sites: GluN1-Y₈₃₇, GluN2A-Y₈₄₂, GluN2A-Y₁₃₃₆, GluN2A-Y₁₃₈₇, GluN2B-Y₁₃₃₆, GluN2B-Y₁₄₇₂ (Lau and Huganir, 1995; Moon et al., 1994; Nakazawa et al., 2001; Vissel et al., 2001; Yang and Leonard, 2001). Cysteine (C) palmitoylation sites: GluN2A-C₈₄₈, GluN2A-C₈₅₃, GluN2A-C₈₇₀, GluN2A-C₁₂₁₄, GluN2A-C₁₂₁₇, GluN2A-C₁₂₃₆, GluN2A-C₁₂₃₉, GluN2B-C₈₄₉, GluN2B-C₈₅₄, GluN2B-C₈₇₁, GluN2B-C₁₂₁₅, GluN2B-C₁₂₁₈, GluN2B-C₁₂₄₂, GluN2B-C₁₂₃₉, GluN2B-C₁₂₄₅ (Hayashi et al., 2009). Calpain cleavage sites: GluN2A-1279, GluN2A-1330, GluN2B~1030 (approximately) (Dong et al., 2006; Guttman et al., 2001; Simpkins et al., 2003; Doshi and Lynch, 2009). See text for further details (3.6. Intracellular modulation of NMDARs).

Fig. 5.

UBP714 potentiates NMDAR responses **A.** Data ($n = 4$, mean $\pm$ S.E.M.), showing that UBP714 potentiates NMDAR-mediated GluN1/GluN2A ($17 \pm 2\%$, 2A), GluN1/GluN2B ($14 \pm 1\%$, 2B) and GluN1/GluN2D ($4 \pm 1\%$, 2D) responses in *Xenopus laevis* oocytes (reprinted from Irvine et al, 2012). The trace to the right shows that 100 μ M UBP714 (gray bar) potentiates GluN1/GluN2A NMDAR response, which was evoked by applying 10 μ M glutamate and 10 μ M glycine (black bar). **B.** Data ($n = 10$) showing that UBP714 potentiates pharmacologically isolated NMDAR-mediated f-EPSPs (inset) in hippocampal slices from adult rat ($19 \pm 2\%$, 1-h after the start of application of 100 μ M UBP714, reprinted from Irvine et al, 2012).