NMDA receptor subunits: function and pharmacology
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N-methyl-D-aspartate receptors (NMDARs) are glutamate-gated ion channels widely expressed in the central nervous system that play key roles in excitatory synaptic transmission. Because of their involvement in numerous neurological disorders, NMDARs are also targets of therapeutic interest. NMDARs occur as multiple subtypes which differ in their subunit composition and in their biophysical and pharmacological properties. In particular, NMDARs contain a diversity of sites at which endogenous ligands or pharmacological agents can act to modulate receptor activity in a subunit-selective manner, and recent structural and functional data have started to reveal the molecular determinants for this subunit selectivity. These include the binding sites for glutamate, the ion-channel pore and the recently identified allosteric sites on the N-terminal domain. Other potential sites yet unexplored by medicinal chemistry programs are also considered, in particular at the interface between subunits. Given the growing body of evidence that diverse brain disorders implicate different NMDAR subtypes, such as NR2B in pain or NR3A in white matter injury, there is a growing interest in exploiting the pharmacological heterogeneity of NMDARs for the development of novel NMDAR subtype-selective compounds.

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Introduction
Within the large family of excitatory ionotropic glutamate receptors (iGluRs), N-methyl-D-aspartate receptors (NMDARs) constitute a subfamily identified by specific molecular composition and unique pharmacological and functional properties [1,2]. Of particular importance is the high permeability to calcium ions, which confers on NMDARs a central role in both synaptic plasticity under physiological conditions and neuronal death under excitotoxic pathological conditions. Because they are built by heteromeric assembly from a relatively large pool of homologous subunits, NMDARs exist as diverse subtypes endowed with distinctive functional properties and patterns of expression [3]. Since the cloning of the different subunit isoforms, relating particular functions to NMDAR subtypes has been a continuous challenge [2]. In this review, we concentrate on recent structural and pharmacological data that could help in revealing detailed NMDAR functions.

Molecular organization and operation of NMDARs
NMDARs are heteromeric complexes incorporating different subunits within a repertoire of three subtypes: NR1, NR2 and NR3. There are eight different NR1 subunits generated by alternative splicing from a single gene, four different NR2 subunits (A, B, C and D) and two NR3 subunits (A and B); the NR2 and NR3 subunits are encoded by six separate genes [1]. Expression of functional recombinant NMDARs in mammalian cells requires the co-expression of at least one NR1 and one NR2 subtype. The stoichiometry of NMDARs has not yet been established definitely, but the consensus is that NMDARs are tetramers that most often incorporate two NR1 and two NR2 subunits of the same or different subtypes [1]. In cells expressing NR3, it is thought that this subunit co-assembles with NR1 and NR2 to form ternary NR1/NR2/NR3 tetrameric complexes [4].

Functional domains in NMDAR subunits
NMDAR subunits all share a common membrane topology (Figure 1) characterized by a large extracellular N-terminus, a membrane region comprising three transmembrane segments (TM1, 3 and 4) plus a re-entrant pore loop (M2), an extracellular loop between TM3 and TM4, and a cytoplasmic C-terminus, which varies in size depending upon the subunit and provides multiple sites of interaction with numerous intracellular proteins [1,5*].

The extracellular region of NMDAR subunits (like that of other eukaryotic iGluR subunits) is organized as a tandem of two domains that share structural and functional homologies with two families of bacterial periplasmic proteins (Figure 1). The N-terminal domain (NTD; first 350 amino acids) shows sequence homology with the bacterial protein leucine/isoleucine/valine-binding protein (LIVBP) [6,7]. This domain plays an important role in subunit assembly [8]. In NR2A and NR2B, the NTD also contains binding sites for allosteric inhibitors such as Zn²⁺ and ifenprodil (see below). The second domain comprises the pre-TM1 region and the TM3–TM4 loop (~150 amino acids each). It shows sequence homology...
The presence of a re-entrant loop in the transmembrane region of iGluR subunits, together with a probable tetrameric quaternary structure, has favoured the hypothesis that iGluR ionic pores are homologous to an inverted potassium channel [11]. The sequences of the regions lining the pore are highly conserved in NR2 subunits and, accordingly, permeation properties (i.e. single-channel conductance, ionic selectivity), as well as affinity for the pore blocker Mg$^{2+}$, vary little among the different NR1/NR2 receptor subtypes. By contrast, incorporating the NR3 subunit markedly decreases single-channel conductance, Ca$^{2+}$ permeability and Mg$^{2+}$ block [4]. The NR3 pore loop significantly diverges from that of other subunits, most prominently around the Q/R/N site that forms the selectivity filter of iGluRs. The sequence at this locus is Asn–Ser in NR1, Asn–Asn in NR2 and Gly–Arg in NR3. The presence of a positively charged amino acid in NR3 is likely to be responsible for the specific permeation properties of NR3-containing receptors [12].

**Structural aspects of NMDAR activation**

The crystallographic studies of Gouaux and colleagues [13] on the ABD of GluR2 (an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR] subunit) have markedly improved our understanding of the initial steps in iGluR activation. The available structures, which now include NR1 and NR2A ABDs, have fully confirmed the predicted structural and functional homologies between bacterial glutamine-binding protein and iGluR ABDs.
[9,14]. These latter domains show the typical two-lobed fold with ligand binding in the central interlobe cleft. Agonists stabilize a closed conformation of the cleft, whereas competitive antagonists prevent its closure [5]. Within this overall conserved mechanism, the crystallographic structures allow identification of interesting subunit specificities. Whereas coordination of the α-carboxylate moiety of the agonist is very much conserved in all iGluR ABDs, coordination of the α-amino group differs between NR2A and all other crystallized iGluR ABDs [9]. In NR1 and GluR2, the α-amino group makes a salt bridge with a conserved carboxylate from lobe 2 (E705 in GluR2, D732 in NR1). In NR2A, the lateral chain of the homologous carboxylate (D731) has flipped away from the α-amino group and the salt bridge is replaced by a H-bond network that includes residues from both lobes. This structural rearrangement has an important pharmacological consequence: it provides space in the NR2A binding pocket for the NMDA molecule to fit. Another substitution one residue upstream in NR1 explains why glutamate does not bind the NR1 ABD. In that subunit, a bulkier tryptophan replaces a tyrosine (NR2) or leucine (GluR2) and prevents glutamate binding by steric hindrance [14]. Comparison of ligand-bound GluR2 and NR1 ABDs shows yet another difference: there are more direct inter-lobe interactions in the ligand-bound NR1 ABD than in the GluR2 ABD [15]. This could explain why the NMDAR affinity for glycine (EC50 0.1–2 μM) is significantly higher than that of AMPARs for glutamate (EC50 10–100 μM). It would be interesting to explore whether a high number of inter-lobe interactions also controls the high affinity of NR2 ABDs for glutamate (EC50 0.5–5 μM).

In iGluRs, the mechanism that links agonist binding to channel gating is partly known and relies upon subunit dimerization. The ABDs form dimers through back-to-back apposition of lobes 1, burying a large surface area (Figure 1) [5,9]. Because lobes 1 are ‘glued’ together by this domain interface within a dimer, closure of the ABDs upon agonist binding increases the distance between lobes 2. This, in turn, exerts some tension on the linkers connecting the ABDs to the pore domain, leading to channel opening (activation). The tension can be relaxed by breaking the ABD dimer interface. This is the core of the mechanism of desensitization in AMPARs [16].

In the heteromeric NMDAR complex, the quaternary arrangement of the subunits around the central symmetry axis will govern the dimerization possibilities. Alternating NR1 and NR2 subunits would prevent the formation of homodimers, whereas an NR1/NR1/NR2/NR2 arrangement would allow homo- as well as hetero-dimer formation. Experiments using concatenated subunits favour the homodimer hypothesis and thus the second type of arrangement [17]. Crystallized NR1 ABD homodimers have been observed under particular conditions [15]. However, upon co-crystallization of NR1 and NR2A ABDs, only heterodimers were obtained, and functional data using engineered intersubunit disulfide bridges indicate that such NR1–NR2A heterodimers are present in the intact receptor [9]. Similar results have not yet been obtained with other NR2 subunits. The possibility remains that the functional dimerization and possibly the quaternary arrangement depend upon the type of NR2 (or NR3) present in the receptor.

Pharmacology of NMDAR subtypes

Ever since the pioneering work of Watkins and colleagues showing that NMDA selectively activates a subclass of glutamate receptors (hence coined NMDARs), extensive efforts have been made to discover potent and selective NMDAR antagonists. The 1980s saw the development of the first broad-spectrum competitive antagonists and high-affinity channel blockers. The cloning of NMDAR subunits in the early 1990s and the subsequent finding that NMDARs occur in vivo as multiple subtypes with distinct subunit composition renewed this initial effort and triggered an intense campaign in the pharmaceutical industry to identify receptor subtype-selective compounds. This led to the identification of a new class of compounds, exemplified by ifenprodil, which selectively inhibit receptors containing the NR2B subunit [18]. More recently, zinc, an ion naturally occurring in the brain, has also been shown to be a selective antagonist of NR2A-containing receptors when applied at low (nanomolar) concentrations [19,20]. However, almost 30 years after the discovery of the first NMDAR antagonist, the pharmacological tools available for discriminating between receptor subtypes remain surprisingly limited, and organic compounds highly selective for NR2A-, NR2C-, NR2D or NR3-containing receptors are still lacking.

Compounds acting at the agonist binding domains

The first NMDAR antagonists were competitive antagonists acting at the glutamate binding site on the NR2 subunits. They are usually conformationally constrained amino acid derivatives containing an ω-phosphonic group [21]. One of the first compounds discovered, (R)-2-amino-5-phosphono pentanoate (R-AP5), remains widely used because it displays strong preference for NMDARs over all other iGluRs. These compounds show some selectivity between the different NR2 subunits (affinity ranking typically NR2A > NR2B > NR2C > NR2D), but the variations of affinity are modest (<10-fold; Table 1) and do not allow selective inhibition of a particular receptor subtype. The lack of subunit selectivity probably originates from the high degree of conservation in the NR2 glutamate binding pockets. All 10 residues that directly contact the glutamate molecule in NR2A are strictly conserved in the other NR2 subunits [9]. However, a detailed comparison of the various NR2 ABDs using three-dimensional models reveals a few subunit-specific amino acids exposed to the ligand binding cavity [22]. They are located on the
edge of the glutamate binding pocket, suggesting that small antagonists which only probe the immediate vicinity of the glutamate-binding site are not likely to display significant NR2-subtype selectivity, whereas larger molecules can acquire subunit selectivity through steric effects. Accordingly, the two antagonists (R)-CPP and (R)-AP7 display greater subunit selectivity (NR2A/C29 NR2D) than do their shorter homologues PMPA and (R)-AP5 (Table 1) [23]. The Novartis compound NVP-AAM077 is another competitive antagonist with enhanced selectivity for NR2A- over NR2B-containing receptors. However, its selectivity, originally reported to be >100-fold [24], had been over-estimated and is actually an order of magnitude lower (~10-fold) [25]. In addition, it is also a powerful antagonist of NR2C- and NR2D-containing receptors [26].

In summary, recent years have seen promising progress towards the discovery of NMDAR subtype-selective competitive antagonists. However, none of the available compounds are truly selective yet. The recent discovery of competitive antagonists highly selective for GluR5 kainate receptors, despite strong sequence conservation with other iGluR members [27], should nevertheless encourage further efforts to develop novel, more selective NMDAR competitive antagonists. Finally, numerous glycine binding site competitive antagonists have been described but they show little receptor subtype selectivity (Table 1), as expected for compounds targeting a binding site located on NR1, a subunit present in all receptor subtypes.

**Compounds acting in the pore**

A large number of organic compounds inhibit NMDARs by occluding the ion channel pore [21]. These compounds are uncompetitive antagonists because their action requires prior activation of the receptor (i.e. pore opening). Moreover, although structurally diverse, they are all positively charged and act in a voltage-dependent manner. NMDAR pore blockers usually discriminate poorly between NMDAR subtypes. This is indeed the case for the dissociative anaesthetics phenycyclidine (PCP), thiencyclohexylpiperidine (TCP) and ketamine, and of the clinically used drugs memantine and amantadine (Table 2). The highly selective NMDAR channel blocker dizocilpine (MK-801) is more potent at inhibiting NR1/NR2A and NR1/NR2B receptors than NR1/NR2C and NR1/NR2D receptors, but the difference in affinity is relatively small (~10-fold; Table 2). A similar pattern of selectivity is seen for bulky polyamine derivatives such as the spider toxin argiotoxin-636 or N1-dansyl-spermine. Interestingly, however, these channel blockers display over 50-fold ‘preference’ for NR1/NR2A or NR1/NR2B receptors compared with NR1/NR2C or NR1/NR2D receptors [28,29]. The structural determinants underlying this selectivity are not fully understood, but hydrophobic interactions between aromatic cycles of the blockers and hydrophobic residues lining the outer vestibule of the pore are likely to play an important role [28,30]. Channel blockers with a large head group might thus be useful antagonists, at least to differentiate NR2A- and NR2B- versus NR2C- and NR2D-containing receptors.

**Compounds acting at the NR2 N-terminal domains**

The only known organic compounds that display a high NMDAR subtype selectivity are ifenprodil and derivatives, which are selective antagonists of NR2B-containing receptors [18]. Because of the important therapeutic promise of these antagonists (see below), significant efforts to identify novel derivatives have been made during the past decade [31], and some compounds with affinities and selectivities greater than that of ifenprodil have been found.
However, it is only recently that the binding site for this class of molecules has been identified. As suggested by their voltage-independent and non-competitive mechanism of action, these compounds bind neither the ABDs nor the pore but the large NTD of NR2B [32,33]. As all NMDAR subunits possess an N-terminal LIVBP-like domain, it is tempting to hypothesize that other molecules bind to other NMDAR NTDs and constitute new subunit-specific allosteric inhibitors. Such a compound has already been identified: the Zn$^{2+}$ ion, which binds to the NR2A NTD with nanomolar affinity [7,34]. Zn$^{2+}$ also binds to the NR2B NTD but with >100-fold lower affinity and does not bind NR2C or NR2D NTDs [20,35]. Because it is concentrated and released at many glutamatergic synapses [36], Zn$^{2+}$ is likely to be an endogenous allosteric modulator of NMDARs.

There are some limitations to the use of NTD-targeted allosteric inhibitors to eliminate selectively a specific NMDAR subtype (Table 3). In particular, they all act as partial antagonists (the inhibition is not total at saturating inhibitor concentrations). This phenomenon is particularly pronounced for Zn$^{2+}$ acting on NR1/NR2A receptors (~70% maximal inhibition) but is also present for ifenprodil-like compounds on NR1/NR2B receptors (~90% maximal inhibition) [19,37]. This pharmacological ‘defect’ might turn into a therapeutic advantage if a minimal level of NMDAR activation is required for proper brain function.

### Other potential sites for ligand binding

There are other hypothetical sites where extracellular ligands could act to modulate NMDAR activity. Besides the NR1 NTD (Figure 1, site 2), the ABD dimer interface might provide another site for new allosteric modulators (Figure 1, site 3). In AMPARs, this interface binds positive allosteric modulators such as cyclothiazide and aniracetam [16,38]. These agents reduce AMPAR desensitization and slow channel deactivation by stabilizing the ABD interface and the closed-cleft active conformation of each ABD, respectively. Given the strong conservation in...
the architecture of the ABD dimer between NMDARs and AMPARs [9*], it is tempting to speculate that the NMDAR ABD dimer interface could also be a locus for allosteric modulation. As NMDARs show only little desensitization, a screening protocol looking at possible changes in deactivation kinetics might be required to identify NMDAR ABD dimer interface modulators. Another candidate site is the linker region connecting the ABDs to the transmembrane segments (Figure 1, site 4). In AMPARs, this region forms a binding site for AMPAR-selective non-competitive antagonists of the GYKI family [39]. It remains to be explored whether the homologous region in NMDARs could also bind antagonists.

**Triheteromeric NMDARs complicate native NMDAR pharmacology**

There is compelling evidence that NMDARs are not always simple binary assemblies of NR1 with only one type of NR2 subunit, and that some receptors can incorporate two types of NR2 subunits [1,2]. Such triheteromeric assemblies have been observed in many brain regions, such as NR1/NR2A/NR2B in the forebrain and NR1/NR2A/NR2C in the cerebellum (see [40*]). In *vivo*, the NR3 subunit is believed to form ternary complexes by co-assembling with NR1 and NR2 subunits [4]. The heterogeneity of recombinant NMDAR populations obtained when expressing three types of subunits has hampered the study of the functional properties of triheteromeric NMDARs. Recently, however, Hatton and Paoletti [40*] have been able to overcome this difficulty and isolate recombinant triheteromeric receptors using an approach combining mutagenesis and pharmacology. They showed that receptors formed by co-assembly of NR1, NR2A and NR2B retain sensitivity for submicromolar concentrations of zinc or ifenprodil, but the inhibition saturates at ~20%. Similarly, NR1/NR2A/NR2C receptors containing a single zine-binding NTD are inhibited by zinc with high potency but low efficacy [40*]. The fact that triheteromeric receptors show an ‘intermediate’ sensitivity to subunit-selective modulators means that it is not possible, with currently available pharmacological tools, to fully eliminate NR2A- or NR2B-containing receptors using zinc or ifenprodil. This is a serious limitation in attempts to relate NMDAR function to individual subunits, and it is unclear whether it will be possible to discover antagonists that differentiate between di- and tri-heteromeric receptors.

**Renaissance of NMDARs as targets of therapeutic interest**

NMDARs have always triggered an intense interest as potential therapeutic drug targets because they are involved in many brain disorders [41]. Traditionally, NMDARs are best known for their role in excitotoxicity, a process during which excessive glutamate release causes overactivation of NMDARs, accumulation of intracellular calcium and, eventually, neuronal death. Excitotoxicity occurs during cerebral ischemia (following stroke or brain trauma) and in neurodegenerative disorders such as Parkinson’s and Huntington’s diseases. Overactivity of excitatory pathways is also observed in epilepsy and neuropathic pain. Most NMDAR antagonists developed in the 1980s and 1990s to treat these disorders failed in clinical trials because of unacceptable side effects (e.g. hallucinations, and memory and motor deficits). Considered too risky, the development of NMDAR-based therapies was abandoned. Recently, however, there has been growing evidence that subunit-selective NMDAR antagonists have a much improved side effect profile compared with broad-spectrum antagonists. Moreover, novel functions of NMDARs have been uncovered, triggering a renewed interest in drugs targeting NMDARs.

**NR2B-selective antagonists**

One explanation for the failures of first-generation NMDAR antagonists is their lack of subunit specificity. By targeting the ABD (competitive antagonists) or the channel pore (channel blockers), these compounds do not discriminate between the various NMDAR subtypes. NMDAR antagonists with improved tolerability have now been identified. The most promising compounds are ifenprodil derivatives, which selectively inhibit NR2B-containing NMDARs by binding to the NR2B N-terminal domain (see above) [18,32,33]. Several highly potent NR2B-selective antagonists show good efficacy as neuroprotectors and/or pain killers in a variety of animal models [42]. These NR2B-selective antagonists are also effective in rodent and primate models of Parkinson’s disease, either alone or in combination with L-dopa treatment [41]. Encouragingly, in humans, NR2B-selective antagonists do not induce the side effects usually seen with non-selective NMDAR antagonists, even at maximally neuroprotective doses [41,42]. The reasons for their better tolerability are twofold: firstly, they spare NMDARs that do not contain NR2B (e.g. most NMDARs of the cerebellum, a region important for motor coordinate); secondly, they are maximally effective at persistently activated NMDARs and at acidic pH, conditions encountered during excitotoxicity [37,43]. Whereas the first NR2B-selective antagonists displayed off-target activity (particularly at adrenergic α1 receptors), second-generation compounds with substantially improved safety profiles have been reported. However, NR2B-selective antagonists have not yet developed into approved drugs because of hERG K+ channel-mediated cardiotoxicity and poor oral bioavailability [21]. The situation is changing rapidly as recent screenings of large chemical libraries have yielded novel NR2B-selective antagonists, structurally unrelated to ifenprodil, which could overcome these limitations [44,45].
NR3A subunit and the myelin sheath

It was generally assumed that NMDAR expression in the central nervous system was restricted to neurons, with no (or very little) expression in glial cells. Several recent studies, however, indicate that NMDARs are present on both astrocytes and oligodendrocytes. Oligodendrocytes — cells in the white matter that produce the myelin sheath surrounding axons — are damaged by an excess of glutamate, and loss of the myelin sheath is observed in multiple neurological disorders including cerebral palsy, spinal cord injury, stroke and multiple sclerosis. This excitotoxicity was thought to proceed through activation of AMPA/kainate receptors, as oligodendrocyte somata are not protected against glutamate-mediated injury by NMDAR antagonists. Three new studies now reveal that oligodendrocytes do express functional NMDARs, but only on their processes [46–48]. Myelin NMDARs are only weakly blocked by extracellular Mg²⁺ and mediate calcium accumulation in myelin during ischemia. NMDAR antagonists prevent this accumulation and protect against ischemia-induced myelin damage. Interestingly, all three studies suggest that myelin NMDARs have an unusual subunit composition, with high levels of NR2C and NR3A subunits, two subunits that are known to decrease Mg²⁺ block. NMDARs containing NR3A (or NR2C) subunits are thus potentially major therapeutic targets for preventing white matter damage. There is currently no known pharmacology for NR3A, but this subunit has a ligand binding profile substantially different from that for NR1 (despite the fact that both bind glycine), suggesting that it should be possible to develop NR3A-selective antagonists [10]. However, one should keep in mind that NR3A (expressed in isolation) has an exceptionally high affinity for glycine (650-fold higher than NR1), such that, in vivo, NR3A subunits are likely to be tonically occupied by ambient glycine [10]. Therefore, only highly potent NR3A-selective competitive antagonists, capable of displacing endogenous glycine, would be therapeutically valuable. The alternative would be to develop NR3A-selective allosteric inhibitors. Intriguingly, cortical astrocytes also express NMDAR-mediated currents with low Mg²⁺ sensitivity [49], suggesting that incorporation of NR3A subunits might be a distinctive feature of glial NMDARs.

NMDAR enhancers against NMDAR hypofunction in schizophrenia

Several lines of evidence indicate that hypofunction of NMDARs may be a key feature in major human cognitive disorders, particularly schizophrenia. Non-selective NMDAR channel blockers (e.g. PCP or ketamine) disrupt memory formation and cause a schizophrenia-like syndrome in humans, recapitulating both positive and negative symptoms and cognitive impairments [50]. Transgenic mice with reduced NMDAR expression or impaired NMDAR function display behaviours related to schizophrenia [51,52]. Finally, recent genetic linkage and postmortem studies point to the direct involvement of NMDAR dysfunctions in the pathogenesis of human psychoses [53,54]. All of this evidence indicates that increasing NMDAR activity should be beneficial for treating cognitive disorders. Direct activation of the receptors by glutamate site agonists, if conceivable in theory, raises immediate concerns regarding excitotoxicity. Increasing the activity at the co-agonist glycine site is a possible alternative and has shown some clinical benefit [55]. Another promising strategy might reside in developing molecules capable of enhancing NMDAR activity through binding to modulatory sites (NMDAR enhancers or positive allosteric modulators). There are two potential mechanisms through which NMDAR activity could be enhanced: firstly, by preventing NR2 NTD closure with compounds that would displace the endogenous ligand Zn²⁺ and maintain the NTD cleft in a more open configuration (Figure 1, site 1); secondly, by stabilizing the channel open state (slowing of deactivation) or blocking the entry into a desensitized state with compounds that bind the ABD dimer interface (Figure 1, site 3). There are thus varied opportunities to enhance NMDAR activity and the coming years should tell us if NMDARs are a viable target for the development of novel antipsychotic agents.

Conclusions

The NMDAR complex contains several potential binding sites for extracellular modulators. In this review, we have advertised the choice of the NTDs of NMDAR subunits as an interesting therapeutic target. These domains indeed bind allosteric modulators in two NMDAR subunits (NR2A and NR2B) with strong subunit selectivity, and it is tempting to speculate that other selective modulators may be found that bind NTDs of other NMDAR subunits (and more generally those of other iGluRs). More knowledge on the three-dimensional structure could help in the search for new active molecules. No iGluR NTD has yet been crystallized, and even the source of the selectivity of NR2A and NR2B NTDs for Zn²⁺ and ifenprodil remains unclear. Eagerly awaited three-dimensional structures will not only help in understanding the selectivity and the mechanism of action of the available allosteric inhibitors, but might also enable the design of new inhibitors for orphan NTDs.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


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10. Yao Y, Mayer ML: Characterization of a soluble ligand binding domain of the NMDA receptor regulatory subunit NR3A. *J Neurosci* 2006, 26:2993-2996. This paper presents biochemical evidence showing that the ABDs of the NR3A and NR1 subunits have a distinct pharmacological profile, despite the fact that both bind glycine.


In this study, the authors combine mutagenesis and pharmacology 'tricks' to isolate recombinant NR1/NR2A/NR2B or NR1/NR2A/NR2C triheteromeric NMDARs and characterize their sensitivity to the subunit-selective allosteric modulators Zn²⁺ and ifenprodil.


One of three back-to-back papers (together with [47,48]) which show that NMDARs are expressed in the myelinating processes of oligodendrocytes and are activated under ischemic conditions. Myelin NMDARs have an unusual subunit composition with high levels of NR2C and NR3A subunits. These studies strongly suggest that oligodendrocyte NMDARs, in particular those containing NR3A, are promoting therapeutic targets for preventing white matter damage.


See annotation [46]


See annotation [46]


This study demonstrates that cortical astrocytes express functional NMDARs. Similar to oligodendrocyte NMDARs, astrocyte NMDARs have a low Mg²⁺ sensitivity, indicating that this might be a distinctive property of glial NMDARs.


