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New advances in NMDA receptor pharmacology

Kevin K. Ogden and Stephen F. Traynelis

Department of Pharmacology, Emory University School of Medicine 5025 Rollins Research Center, 1510 Clifton Road, Atlanta, GA 30322

Abstract

N-Methyl-D-aspartate (NMDA) receptors are tetrameric ion channels containing two of four possible GluN2 subunits. These receptors have been implicated for decades in neurological diseases such as stroke, traumatic brain injury, dementia, and schizophrenia. The GluN2 subunits contribute substantially to functional diversity of NMDA receptors and are distinctly expressed in development and among brain regions. Thus, subunit-selective antagonists and modulators that differentially target the GluN2 subunit might provide an opportunity to pharmacologically modify the function of select groups of neurons for therapeutic gain. A flurry of clinical, functional, and chemical studies have together reinvigorated efforts to identify subunit-selective modulators of NMDA receptor function, resulting in a handful of new compounds that appear to act at novel sites. Here we review the properties of new emerging classes of subunit-selective NMDA receptor modulators, which we predict will mark the beginning of a productive period of progress for NMDA receptor pharmacology.

Historical overview of NMDA receptor pharmacology

Nearly three decades ago, pharmacological advances in subtype-selective glutamate receptor antagonists fueled an explosive increase in our understanding of NMDA receptor function in the central nervous system. D-APV and MK-801 (Box 1, Table 1) showed strong selectivity for NMDA receptors over AMPA and kainate receptors, providing neuroscientists studying physiology, behavior, development, and neurological disease tools with which to dissect the role NMDA receptors play in a myriad of processes. Use of both competitive antagonists and NMDA receptor channel blockers provided key insights about the receptor composition of the excitatory postsynaptic current, and the role of various glutamate receptors in synaptic plasticity, neuronal death during CNS injury, and developmental biology. This stimulating period in excitatory amino acid research was closely followed by the cloning of cDNAs that revealed NMDA receptors consist of a glycine-binding GluN1 subunit and glutamate-binding GluN2 subunits [1], providing even deeper insight into NMDA receptor function, and ushering in a molecular era for those working on glutamate receptors. The identification of four different GluN2 gene products as integral components of NMDA receptors (Figure 1) offered the promise that subunit-selective agonists, antagonists, and modulators could be found that would allow NMDA receptor function to be regulated in region-specific manner. This hope initially seemed to be well-founded, as extensive pharmacology was developed around the GluN2B subunit, triggered by the discovery that the antihypertensive agent ifenprodil was a subunit-selective antagonist for NMDA receptors containing the GluN2B

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Corresponding author: Traynelis, S.F. (strayne@emory.edu).

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subunit [2]. However, shortly after this period of sustained progress, discovery of new ligands and pharmacological tools stalled. For over ten years there seemed to be little advance in development of subunit-selective antagonists and modulators for NMDA receptors comprised of subunits other than GluN2B (Figure 1). Moreover, this pause in discovery coincided with the realization that the clinical utility of NMDA receptor antagonists in neurological diseases such as stroke, traumatic brain injury, and dementia was more complex than initially appreciated, as a multitude of clinical trials involving a wide range of mechanistically distinct NMDA receptor antagonists repeatedly failed [3,4]. With the gradual realization that NMDA receptor on-target actions often constitute dose-limiting side effects for many indications, reports on the development of new ligands by the pharmaceutical industry diminished. Nevertheless, academic interest in subunit-selective NMDA receptor antagonists persisted, as a need for tools to dissect subunit contribution to region-specific processes was acutely appreciated by those working on systems involving excitatory amino acids. This sustained need motivated multiple laboratories to search for subunit-selective compounds with which to answer important questions about the role of NMDA receptors in normal and neuropathological functions.

Box 1

Discovery of NMDA Receptor Ligands

An active period for discovery of new ligands as well as new sites and mechanisms of action on the NMDA receptor occurred following the description of D-APV as a highly selective competitive NMDA receptor antagonist [68]. During the following dozen or so years, antagonists acting at the glycine binding site, the glutamate binding site, the channel pore, the amino terminal domain, and a region of the ligand binding domain encoded by the S2 region of the cDNA (e.g. neurosteroids) were described. The pace of discovery slowed over the next dozen years, with relatively few new prototypical compounds being described between 1995 and 2009, even though significant advances in medicinal chemistry continued to refine and embellish existing classes of compounds (such as GluN2B antagonists), as well as identify new scaffolds acting at known sites. In 2010, however, discovery of new ligands accelerated as a number of new compounds acting on the receptor with unique structural determinants were reported. These included a novel GluN2A-selective antagonist (TCN 201 [7]), a highly selective GluN2C/D potentiator with unique structural determinants of action in the M1 transmembrane region (CIQ [6]), GluN2C/D inhibitors with structural determinants of action in the lower lobe of the GluN2 ligand binding domain (QNZ46 [5,37]; DQP-1105 [9]), as well as a host of intriguing naphthyl and phenanthryl antagonists (e.g. UBP618, UBP710, see [8] for additional analogues). These new advances in understanding the pharmacology and structure of this receptor class bodes well for future availability of subunit-selective pharmacological tools with which to elucidate the role of NMDA receptor subtypes in normal and neuropathological processes. Moreover, testing of these new compounds and the forthcoming analogues in animal models of disease may lead to new therapeutic strategies to address unmet clinical needs.

The figure provides a time line illustrating several different ligand classes acting by different mechanisms to inhibit or potentiate NMDA receptor function; a more comprehensive list of antagonists with K_i and IC_{50} values can be found elsewhere (see Tables 11, 13, and 15 in [4]). Identification of a new site of action is marked by the red circles within the time line. Representative examples for competitive antagonists (including both glycine site antagonists and glutamate site antagonists), channel blockers (acting at the ion channel pore), and negative allosteric modulators (acting at the amino terminal domain of GluN2B-containing receptors) are shown, and include D-aminophosphonovaleric acid (APV [68]), the low efficacy agonist HA-966 [69],

phencyclidine (PCP [70]), ketamine [70], dextrorphan [71], CPP [72], MK801 [73], 7-chlorokynurenic acid (7CK [74]), ifenprodil [75,76], eliprodil [75], memantine [77], argiotoxin [59], selfotel [78], CPPene [79], polyamines[12,80], arcaine [14], conoantokins-G and -T (Con, [81,82]), aptiganel (CNS-1102, [83]), neurosteroids [84], CP101,606 [85], Ro25-6981 [62], Conantokin-R [86], NVP-AAM077 [42], UBP141 [56]. In addition, representative members of the few known classes of positive allosteric potentiators are shown, including polyamines [13,87] and neurosteroids [25]. Some of these ligands were exceptionally potent, highly-selective for NMDA receptors over kainate and AMPA receptors, and in some cases (ifenprodil and analogues acting at GluN2B) highly subunit-selective.

In the last few years, there has been an acceleration in our understanding of the pharmacology of the NMDA receptor (Box 1), as the discovery of a handful of new binding sites on the receptor for positive and negative allosteric modulators has stimulated new thinking about NMDA receptor regulation and function [5–9]. This advance, fueled both by translational programs at the USA National Institutes of Health (NIH) and other funding agencies, as well as cross-cutting academic collaborations between neuropharmacologists and medicinal chemists, correlates with renewed clinical interest in NMDA receptor pharmacology driven by several intriguing clinical trials (e.g. [10,11]). Thus, it appears that the glutamate receptor field may again be poised to witness a rapid set of advances as proof-of-concept compounds acting at new sites are refined through medicinal chemistry into potent compounds with high degrees of subunit-selectivity that can serve as reliable new subunit-selective probes. Here we review the recent advances in identifying new NMDA receptor potentiators and inhibitors.

Positive modulators

Throughout the early 1990s, several endogenous compounds including polyamines and other biogenic amines were recognized as NMDA receptor positive modulators, i.e. compounds that bind to the receptor and cause an increase in its maximal response or agonist affinity (or both), but do not act as agonists[12–19]. Spermine can enhance the response of GluN2B-containing neurons through interactions with an extracellular site on the receptor [12–17] and has been suggested to bind at the GluN1-GluN2B amino terminal domain dimer interface, potentially shielding ionic interactions between residues that influence receptor function [20]. Polyamine binding to NMDA receptors enhances the sensitivity of the receptors to glycine [16] and relieves tonic proton inhibition of the receptors [21]. However, the potency with which polyamines potentiate native NMDA receptor responses (EC_{50} of 10–125 μ M) is higher than estimates of the basal extracellular spermine concentrations (4 μ M; [22]).

There are extensive reports documenting interactions of dynorphin and the NMDA receptor system. Interestingly, dynorphin can both inhibit NMDA receptor-mediated currents, as well as potentiate responses in low glycine with an EC_{50} value for dynorphin A(1–13) of 2.8 μ M [23] (Table 1). Arachidonic acid can also enhance native NMDA receptor responses, presumably through direct interactions with a fatty acid binding domain on the receptor [24]. Furthermore, certain neurosteroids potentiate NMDA receptor function with some subunit selectivity [25]. Pregnenolone sulfate (PS), for example, potentiates GluN1/GluN2A and GluN1/GluN2B, but inhibits GluN1/GluN2C and GluN1/GluN2D [26,27] (Table 1). PS acts by increasing the peak open probability [28] in a manner controlled by phosphorylation [29]. Moreover, portions of the S2 region between the third and fourth transmembrane helices are critical for PS activity [30, 27]. Although some neurosteroids are likely to have important roles in regulating receptor function in tissue, the neurosteroid scaffold has yet to be

exploited for the development of potent and highly subunit-selective molecules that can discriminate between NMDA receptors that contain different GluN2 subunits.

Recent evaluation of a series of tetrahydroisoquinoline analogues lead to the identification of (3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1 H)-yl)methanone), or CIQ, which is a small drug-like molecule that is a highly selective allosteric potentiator of recombinant and native NMDA receptors that contain the GluN2C or GluN2D subunits [6]. This compound has no detectable potentiating activity on AMPA or kainate receptors or on GluN2A- or GluN2B-containing NMDA receptors, but can enhance by over 2-fold the response amplitude of GluN2C- and GluN2D-containing NMDA receptors. Potentiation of GluN2D-containing receptors occurs with an EC₅₀ value of 3 μM, whereas this compound is inactive at GluN2A- and GluN2B-containing receptors at 20 μM. CIQ has no agonist activity, does not alter agonist EC₅₀ values, and is uninfluenced by agonist concentration [6]. Single channel analysis demonstrates that CIQ enhances channel opening frequency without impacting lifetime of the open state, suggesting that CIQ reduces the activation energy for channel opening.

A chimeric strategy using GluN2A and GluN2D revealed that the structural determinants of action involve membrane spanning elements as well as extracellular linker regions, and ensuing site-directed mutagenesis identified a single residue residing in the first transmembrane helix that can control CIQ function [6]. This residue (Thr592 in GluN2D) is conserved between GluN2C and GluN2D but divergent in GluN2A and GluN2B, suggesting it may interact directly with CIQ, although further experiments are needed to verify this (see [31] for an example where a crystal structure revealed a ligand binding site that was not predicted by chimera and mutagenesis data). Nevertheless, Thr592 and the nearby pre-M1 helix, a short helix running almost parallel to the membrane and acting as a ‘cuff’ at the extracellular region of the ion channel pore [32], are ideally positioned to influence the gating process [33] and an interaction between CIQ and Thr592 would be consistent with the effects of CIQ at the single channel level. It is noteworthy that this region of the NMDA receptor has not previously been implicated in either gating or pharmacology, suggesting tetrahydroisoquinolines such as CIQ influence function in a manner that involves novel structural elements. Figure 1 illustrates the position of the residues that can control the actions of CIQ in homology model of GluN1/GluN2D. The discovery of a subunit-selective NMDA receptor potentiator and identification of its molecular determinants of action provides new opportunities to investigate mechanisms of NMDA receptor allosteric regulation as well as to explore the nature of channel gating at the single channel level.

CIQ can enhance the response of native NMDA receptors to exogenous application of NMDA in neurons in the subthalamic nuclei [6], which has been suggested to express GluN2D [34]. By contrast, CIQ appears to have little effect on the response to NMDA of CA1 pyramidal cells, which have typically been thought to express GluN2A and GluN2B. Thus, CIQ can be used to probe the subunit composition of native NMDA receptors. Moreover, the existence of a small molecule allosteric potentiation provides an opportunity to test a number of hypotheses about the effects that enhancement of NMDA receptor function might have on circuits, behaviors, and in disease models.

In addition to CIQ, several structurally unrelated molecules (e.g. UBP710 and UBP646) have recently been reported to potentiate NMDA receptors [8] without agonist activity. At concentrations above 30 μM, UBP646 potentiated responses from GluN2A, 2B, 2C, and 2D. By contrast, UBP710 only potentiated GluN2A- and GluN2B-containing receptors. Recordings from chimeras of GluN2A and GluN2C suggest the entire S2 region between the third and fourth transmembrane helices is important for potentiation by UBP710. The existence of at least two structurally unrelated classes of subunit-selective NMDA receptor

potentiators in addition to other potentiators with intriguing patterns of subunit-selectivity [8] suggests that either multiple potentiating sites exist or a single site can accommodate a variety of different scaffolds.

Non-competitive antagonists

The structure-activity relationship of GluN2B-selective antagonists that interact with the amino terminal domain has been extensively studied (for reviews see [35, 36]). An X-ray crystal structure of the GluN1/GluN2B amino terminal domain dimer has revealed the binding site for the GluN2B- selective antagonists ifenprodil and Ro 25-6891 [31], which will no doubt aid in development of a clinically well-tolerated GluN2B-selective antagonist. In contrast to the abundant GluN2B-selective antagonists, no other highly subunit-selective non-competitive antagonists have been described. However, novel non-competitive antagonists of both GluN2A and GluN2C/D have been recently reported. Bettini *et al.* [7] described a series of sulfonamides with high selectivity for GluN2A- containing receptors. For example, 3-chloro-4-fluoro-*N*-[(4-{[2-(phenylcarbonyl)hydrazino]carbonyl}phenyl)methyl]benzenesulfonamide (compound 1, referred to as TCN 201) is an apparent non- competitive antagonist whose actions cannot be surmounted by glutamate. It does partially displace glutamate site antagonists in radioligand binding assays in a manner similar to displacement of glutamate site ligands by glycine site antagonists. In contrast to glutamate, glycine can surmount the inhibition by TCN 201 in functional Ca²⁺ imaging assays, even though TCN 201 is minimally effective in displacing glycine site antagonists in radiolabelled binding studies. These data lead to the hypothesis that TCN 201 acts at a site allosterically modulated by glycine as well as the prediction that TCN 201 may act at the GluN1/GluN2A ligand binding domain interface [7]. A recent study by Costa *et al.* [8] has identified several phenanthrene and naphthyl analogues that act as non-competitive antagonists of GluN2C- and GluN2D-containing receptors. UBP618 shows robust inhibition with IC₅₀ values of 1.8–2.4 μM (Table 1) that are minimally influence by glutamate and glycine concentration [8]. These compounds suggest a new negative modulatory site exists that could be exploited for the development of novel probes.

Another series of novel non-competitive antagonists were recently discovered through medicinal chemistry efforts to increase the potency of a quinazolin-4-one that was identified as an NMDA receptor inhibitor through a fluorescence-based multi-well screen [5]. These antagonists had IC₅₀ values ranging from 600 nM to 3 μM. A gain-of-function chimeric strategy utilizing one analogue (QNZ46) with greater than 50-fold selectivity for recombinant GluN2D over GluN2A identified unique structural determinants of action of these compounds [37]. The selectivity of QNZ46 for GluN2D can be transferred to GluN2A by residues within a loop region on the lower lobe of the ligand-binding bilobed clamshell (Figure 1). Subsequently, a handful of individual residues were identified that control the actions of these compounds. Interestingly, this class of antagonist shows a unique mechanism of action, with an unusual use-dependence that involves a 20-fold enhancement of IC₅₀ when glutamate (but not glycine) binds to its recognition site. This enhancement suggests a simple mechanism of action that leads to an inhibition of opening frequency upon binding of inhibitors after glutamate binding. The dependence on glutamate (but not glycine) binding is consistent with the modular nature of glutamate receptor structure, as well as previous suggestions that different subunits may control independent conformational changes [38].

In addition to quinazoline-4-ones, structurally unrelated compounds that possess a pyrazoline scaffold appear to act at a similar site, as determined by the coordinated study of GluN2A-GluN2D chimeric receptors together with site-directed mutagenesis [9]. These compounds, exemplified by DQP-1105, show an unusual property in that their potencies at

the GluN2A subunit may be enhanced by desensitization that occurs following dialysis of the intracellular solution. Thus, in conventional patch mode, these antagonists do not appear as selective as they do in perforated patch recording mode. The mechanistic basis of this observation remains to be determined.

Competitive antagonists and channel blockers

The identification of D-APV as a competitive antagonist that is highly selective for NMDA receptors over AMPA and kainate receptors led to significant advances in our understanding of the role of NMDA receptors in numerous biological phenomena. D-APV has for years been the definitive antagonist to show NMDA receptor involvement in a neurological process or disease state [39–41]. However, D-APV shows K_i values that vary less than ten-fold among NMDA receptors comprised of different GluN2 subunits, a level of selectivity generally considered too low to provide trustworthy dissection of subunit contribution, particularly in native tissue. Moreover, efforts to identify competitive antagonists with GluN2 subunit-selectivity have yet to improve much on D-APV (e.g. see table 11 in [4]). Considerable enthusiasm around NVP-AAM077, a proposed GluN2A-selective competitive antagonist [42], was short-lived as estimates of K_i values from IC_{50} values [43] and later determination of the K_i values by Schild analysis [44,45] revealed that selectivity was less than 10-fold. Similarly, a handful of phenanthrene derivatives show 7- to 10-fold differences in estimated K_i values [46], favoring inhibition of GluN2D over GluN2A.

Crystal structures of the ligand binding domain among glutamate receptors offer an explanation for the difficulty in obtaining subunit-selective competitive antagonists. The key agonist contact residues are conserved almost universally across the glutamate receptor family and strongly conserved within the glutamate binding pocket across GluN2 subunits [47–49], although the hinge region in the GluN2 ligand binding domain shows agonist-dependent diversity [50]. Whereas the glutamate binding pockets show some differences [51] that can be exploited to develop agonists with limited preference for different GluN2 subunits [52], in general, the highly conserved nature of the agonist binding domain diminishes the prospect that strong subunit selectivity can be achieved through conventional modifications of competitive antagonist structure.

Uncompetitive antagonists, which are typically channel blockers, target perhaps the most highly conserved portion of the NMDA receptor, and thus there is little selectivity (<10 fold) for various channel blockers across NMDA receptor subunits [53]. The lone exception is a class of synthetic polyamines that contain a long chain with various aromatic headgroups [54]. Some of these compounds can achieve up to 50-fold selectivity between GluN2A and GluN2D, raising the possibility that these scaffolds could be modified in a manner that allows interaction with less conserved portions of the receptor. This may occur as the length of the blocker engages atomic interactions beyond the conserved ion permeation pore, potentially sensing more distinctive elements of the receptor. In addition, given the unusually large and diverse collection of molecules that can act as NMDA receptor blockers, it seems possible that some subunit selectivity might yet be encountered through extensive screening among GluN2 subunits; however, this awaits further study.

Concluding remarks

Our knowledge of NMDA receptor biology has been inextricably linked to the diverse array of small molecules acting on the receptors. For example, identification of NMDA receptors as a mediator of excitatory neurotransmission and some forms of synaptic plasticity relied heavily upon agonists and antagonists that were selective for NMDA over AMPA and kainate receptors. These pharmacological tools have been used extensively to test important hypotheses about the contribution of the NMDA receptor family to neurological diseases

including stroke, traumatic brain injury, dementia, epilepsy, and neuropathic pain. However, the numerous roles of NMDA receptors in normal brain function make it difficult to selectively target this receptor class in a disease state while preserving normal function in patients, which has limited the utility of NMDA receptor antagonists as therapeutics.

A promising approach to achieve the selective modulation of aberrant NMDA receptor function is to target the specific GluN2 subtypes, which are differentially expressed in the CNS. Additionally, there has been a growing appreciation that various NMDA receptor subtypes are likely to play unique roles in the neurophysiology of different brain regions. However, apart from the GluN2B subunit, it has been impossible to assess contribution of specific NMDA receptor subtypes to brain function or evaluate the potential therapeutic utility of targeting particular NMDA receptor subtypes because potent, subunit-selective antagonists that distinguish between NMDA receptors comprised of different GluN2 subunits simply have been unavailable. This mismatch finally is being resolved, as a handful of novel subunit-selective NMDA receptor modulators have been described recently. It is no accident that the newly discovered GluN2 subunit-selective molecules are largely allosteric modulators. Linker regions, the amino terminal domain, and portions of the ligand binding domain distal to the residues that contact the agonist are not well conserved among NMDA receptor subunits. Moreover, the highly modular arrangement of extracellular domains creates numerous potential regulatory sites at various protein-protein interfaces, and provides an opportunity to inhibit specific conformational changes that might take place within individual subunits en route to channel opening. We predict that new subunit-selective compounds acting at sites distinct from agonist binding pocket or the channel pore will continue to be found for the NMDA receptor. Almost certainly, medicinal chemistry efforts applied to the initial proof-of-concept molecules will improve the potency and selectivity of these new families of modulators. Availability of the resulting new pharmacological tools will stimulate experimental work that dissects the contribution of the different GluN2 subunits to various neurological processes and disease states, with potential for addressing unmet clinical need. Thus, our understanding of NMDA receptors seems poised again for explosive growth, triggered by the discovery of pharmacological tools.

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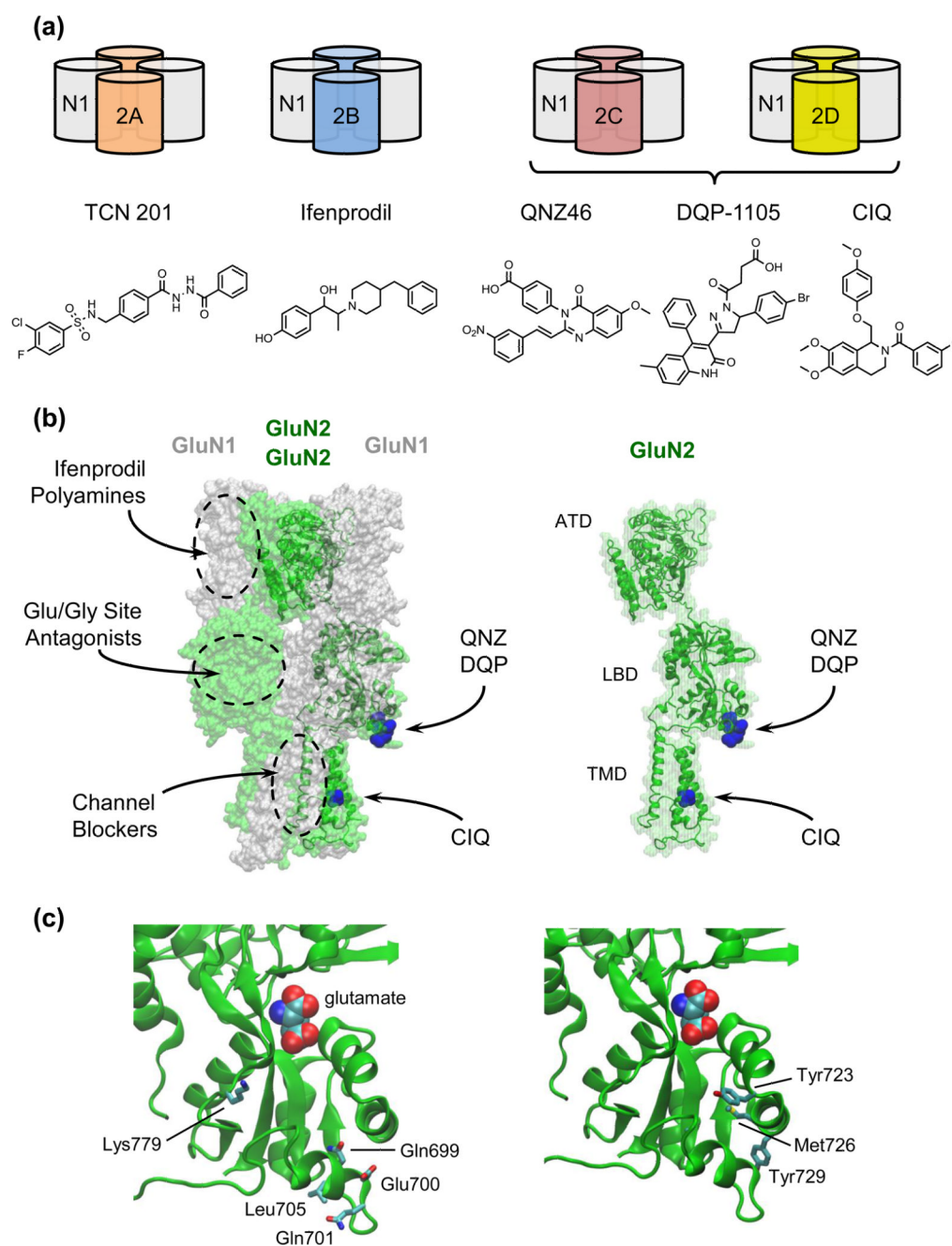
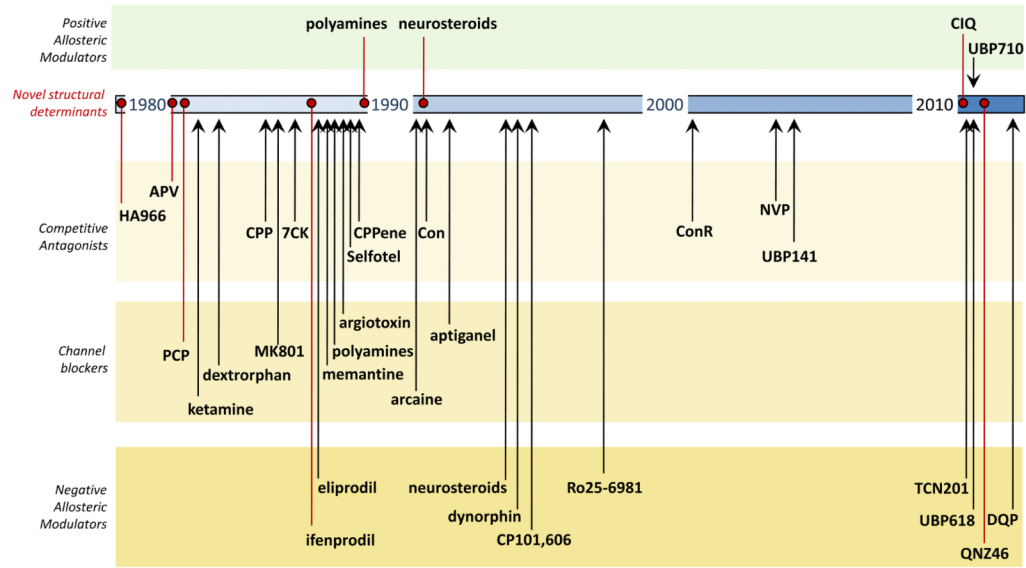


Figure 1. NMDA Receptor Architecture and Ligand Binding Sites

NMDA receptors are tetrameric ion channels canonically comprised of two GluN1 (labeled N1) subunits and two GluN2 subunits (2A, 2B, 2C, or 2D) in a 1-2-1-2 arrangement **(a)**. Receptors containing different GluN1 splice variants and/or a GluN3 subunit have distinct functional properties. Additionally, much of the diversity among receptor subtypes arises from the GluN2 subunits, which are critical in determining biophysical and pharmacological properties of the receptor. Representative compounds acting with greater than 50-fold selectivity at individual GluN2-containing receptors are shown below the receptor subtypes. **(b)** Major ligand binding sites on the NMDA receptor are depicted on a GluN1/GluN2D homology model based on X-ray structures of a GluA2 tetramer (PDB 3KG2), GluN1 amino

terminal domain (PDB 3Q41), GluN1 ligand binding domain (PDB 2A5T), GluN2B ATD (PDB 3JPY), and GluN2D LBD (PDB 3OEN) (Modeller 9.9). Ifenprodil and related GluN2B-selective molecules bind to the amino terminal domain (ATD) as do polyamines. Competitive antagonists of glycine and glutamate bind to the ligand binding domain (LBD) of GluN1 and GluN2, respectively. Channel blockers bind in the transmembrane domain (TMD). Residues critical for the activity of QNZ46, DQP1105, or CIQ are shown in blue. *Right*, an individual GluN2 subunit from a tetrameric complex is shown with the sites for QNZ46, DQP-1105, and CIQ highlighted in blue. **(c)** The lower portion of the GluN2D LBD harbors residues critical for the actions of QNZ46. Residues Gln699, Glu700, Gln701, Leu705 and Lys779 (*left*) are not conserved between GluN2D and GluN2A, while residues Tyr723, Met726, and Tyr729 (*right*) are conserved. Mutating Gln699, Glu700, Met726 and Tyr729 to the corresponding residue in GluN2A increased QNZ inhibition, while mutating Gln701, Leu705, Lys779, and Tyr729 to the corresponding GluN2A residue reduced QNZ inhibition.



Box Figure.

Table 1

Subunit-selectivity of compounds acting on recombinant NMDA receptors

Compound	GluN2A	GluN2B	GluN2C	GluN2D	Ref
<i>Competitive Antagonists</i>					
APV, (R)-AP5	Ki (μ M)	Ki (μ M)	Ki (μ M)	Ki (μ M)	[55]
	0.28	0.46	1.6	3.7	
Selfotel (CGS-19755)					[55]
	0.15	0.58	0.58	1.1	
(R)-CPP					[55]
	0.041	0.27	0.63	1.99	
NVP-AAAM077					[44]
	0.015	0.078	--	--	
UBP-141					[56]
	14	19	4.2	2.8	
Conantokin-G					[57]
	10	0.1	1	1	
Conantokin-R					[57]
	1	1	7	10	
7-Cl-kynurenatel					[58]
	0.6	0.2	--	--	
<i>Channel blockers</i>					
	IC ₅₀ (μ M)	IC ₅₀ (μ M)	IC ₅₀ (μ M)	IC ₅₀ (μ M)	
Argiotoxin636					[59]
	0.009	0.005	0.46	--	
(+)-MK-801					[53]
	0.015	0.009	0.024	0.038	
Memantine ^b					[60]
	13	10	1.6	1.8	
Ketamine ^b					[60]
	5.4	5.1	1.2	2.9	
Phencyclidine					[53]
	0.82	0.16	0.16	0.22	
Dextrophan					[53]
	1.3	0.33	0.15	0.74	
CNS-1102 (aptiganel)					[53]
	0.13	0.068	0.087	0.14	
<i>Noncompetitive Antagonists</i>					
	IC ₅₀ (μ M)	IC ₅₀ (μ M)	IC ₅₀ (μ M)	IC ₅₀ (μ M)	
Ifenprodil					[61]
	39	0.15	29	76	
Ro 25-6981					[62]
	52	0.0090	--	--	
CP-101,606					[63]
	>100	0.039	>100	>100	
QNZ46					[5]
	229	>300	6	3	
DQP-1105					[9]
	206	121	9	3	
TCN 201					[7]
	0.109	>30	--	>30	
UBP-618					[8]
	1.8	2.4	2.0	2.4	
Dynorphin A (1-13)					[64]
	19	29	228	57	
Pregnanolone sulfate (3 α 5 β S)					[65]
	50	44	26	30	
<i>Allosteric Potentiators</i>					
	EC ₅₀ (μ M)	EC ₅₀ (μ M)	EC ₅₀ (μ M)	EC ₅₀ (μ M)	

Compound	GluN2A	GluN2B	GluN2C	GluN2D	Ref
CIQ	NE	NE	2.8	3	[6]
Spermine	NE ^c	163	NE	NE	[66,67,21]
Pregnenolone sulfate	21	33	NE ^c	NE ^c	[26]
UBP-710	>30	>30	NE ^c	NE ^c	[8]

NE indicates no detectable effect, and -- indicates that data is not available.

^aKB values calculated from Cheng-Prusoff correction of IC₅₀ values.

^bIC₅₀ values determined in extracellular Mg²⁺, which alters subunit selectivity.

^cPartially inhibits with IC₅₀ value of 100 μM or greater.