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Recent insights into the mode of action of memantine and ketamine

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Abstract

The clinical benefits of the glutamate receptor antagonists memantine and ketamine have helped sustain optimism that glutamate receptors represent viable targets for development of therapeutic drugs. Both memantine and ketamine antagonize *N*-methyl-D-aspartate receptors (NMDARs), a glutamate receptor subfamily, by blocking the receptor-associated ion channel. Although many of the basic characteristics of NMDAR inhibition by memantine and ketamine appear similar, their effects on humans and to a lesser extent on rodents are strongly divergent. Some recent research suggests that preferential inhibition by memantine and ketamine of distinct NMDAR subpopulations may contribute to the drugs' differential clinical effects. Here we review studies that shed light on possible explanations for differences between the effects of memantine and ketamine.

Introduction

The strikingly broad involvement of *N*-methyl-D-aspartate receptors (NMDARs) in nervous system disorders has led to persistent hope that pharmacological NMDAR modulators will provide a rich source of pharmaceuticals. However, many NMDAR-focused drug development efforts have ended with failed clinical trials. Although the failures resulted in part from weaknesses in trial design [1-3], an important implication is that nonspecific NMDAR inhibition is unlikely to yield successful treatments, probably because NMDARs play many fundamental physiological roles. Optimism endures that NMDARs may be a fruitful pharmaceutical target using drugs that select for receptor subpopulations based on NMDAR subtype, location, and/or mechanism of activation. The encouraging but divergent clinical effects of the NMDAR antagonists memantine and ketamine have helped motivate continuing efforts to develop new drugs based on NMDAR modulation. Understanding the mechanistic bases of the beneficial effects of these drugs may help guide development of

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more effective therapies based on NMDAR modulation. Here we review research that sheds light on the similarities and differences in memantine and ketamine actions, focusing where possible on research that compares memantine and ketamine directly.

NMDARs and their inhibition by memantine and ketamine

NMDARs are tetrameric ionotropic glutamate receptors found at nearly all vertebrate excitatory synapses. NMDARs are centrally involved in fundamental nervous system functions including learning and memory [3,4]. NMDAR dysfunction has been implicated in nervous system disorders including Alzheimer's disease, Huntington's disease, depression, schizophrenia, chronic and neuropathic pain, epilepsy, and neuron death following stroke [5-7]. NMDARs are obligate heterotetramers composed of GluN1 subunits in combination with GluN2 and/or GluN3 subunits [3,4,8]. The GluN1 subunit is encoded by a single gene; four genes encode the GluN2 subunits (GluN2A, GluN2B, GluN2C, and GluN2D); two genes encode the GluN3 subunits (GluN3A and GluN3B). Most NMDARs are composed of two GluN1 subunits and two GluN2 subunits, and their activation requires binding of agonists to all four subunits. The principal endogenous agonists that bind to the GluN1 subunit are glycine and D-serine, whereas the principal endogenous agonist that binds to GluN2 subunits is glutamate. The open channel of NMDARs mediates permeation predominantly of Na^+, K^+, and Ca^{2+}; the influx of Ca^{2+} ions through NMDAR channels is critical to both the physiological and the pathological effects of receptor activation. Many endogenous substances modulate NMDAR activity, including Mg^{2+}, Zn^{2+}, H^+, polyamines, neurosteroids, and fatty acids [3]. Mg^{2+} is a physiologically crucial modulator that blocks the channel of NMDARs, conferring strong voltage dependence to NMDAR-mediated conductance.

Both memantine and ketamine inhibit NMDARs by occupying the NMDAR's ion channel and occluding current flow. Both drugs are open channel blockers: when the channel is closed, the drugs have little or no ability to enter an unblocked channel or to unbind after blocking the channel. Both drugs exhibit voltage dependence, entering the channel more quickly, leaving the channel more slowly, and inhibiting more effectively as a cell's membrane potential is hyperpolarized. The basic characteristics of NMDAR inhibition by memantine and ketamine, including IC_{50}, kinetics, and voltage dependence, do not differ strongly [9-12]. Many studies report that ketamine inhibits NMDAR channels with slightly lower IC_{50} and slower kinetics than memantine; however, the differences are small (generally less than a factor of 2). However, ketamine is used in most experiments as a racemic mixture of two enantiomers, S- and R-ketamine; each enantiomer has somewhat different pharmacological properties [13,14]. Voltage dependence of memantine and ketamine are similar, although memantine's has been reported to be slightly greater [15]. Because both memantine's and ketamine's binding site in the NMDAR channel (Figure 1) overlaps with the Mg^{2+} binding site, Mg^{2+} competes with both drugs for binding to NMDAR channels. As a result, physiological concentrations of Mg^{2+} ($\sim$1 mM) substantially increase the IC_{50}, modify the voltage dependence, and alter the NMDAR subtype-selectivity of both memantine and ketamine [16-18].

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Despite their many similarities, the clinical effects of memantine and ketamine, and to a lesser extent the behavioral effects in rodents, are surprisingly distinct.

Clinical, behavioral, and circuit effects of memantine and ketamine

Human studies

There are clear differences between the clinical effects of memantine and ketamine. Memantine is the only glutamate receptor ligand that is approved for treatment of Alzheimer's disease (AD). The clinical benefits of memantine in AD patients are modest but broad, and include positive effects on communication, comprehension, memory, and activities of daily living. Memantine is very well tolerated and appears to have no abuse potential [19-21]. Ketamine, in contrast, is a drug of abuse that produces schizophrenia-like symptoms in healthy adults and exacerbates symptoms in schizophrenics [11,22,23].

Ketamine also has demonstrated impressive beneficial effects in clinical studies. Along with its well-established utility as a general anesthetic, ketamine has been found useful in the treatment of several disorders, including depression and pain. A single ketamine infusion has been found to alleviate rapidly and for an extended period the symptoms of major depressive disorder [6,24]. Ketamine also is effective in pain management [25,26]. Memantine, however, does not appear to be effective in treating either depression [27,28] or pain [29]. Thus, the differences between the effects of memantine and ketamine in humans appear robust and consistent.

Rodent studies

Based in part on the ability of ketamine to produce schizophrenia-like symptoms in humans, ketamine administration has been widely used to produce rodent models of schizophrenia [30,31]. Although memantine generally is not used to model schizophrenia, comparisons of the behavioral effects of memantine and ketamine in rodents reveal similarities as well as differences, with differences weaker than in human studies. Especially at lower doses (very approximately, and depending on route of administration, below 20 mg/kg), memantine and ketamine have broadly similar effects on locomotor and exploratory activity, stereotypic behavior, impulsive choice, and attention [32-37]. Several of those studies also found similar tendencies for memantine and ketamine to impair memory function, although low doses of memantine can improve memory [38-40], an observation not reported for ketamine. Both memantine and ketamine decrease ethanol ingestion by alcohol-preferring rats, but only the effect of ketamine is blocked by mTOR (mammalian target of rapamycin) inhibition [41]. Differences at low doses between the effects of memantine and ketamine were reported for aggressive behavior when combined with alcohol ingestion [42], and striking differences in antidepressant-like effects were observed [43]. At higher doses, a wide variety of differences between the locomotor and cognitive effects of memantine and ketamine emerged [33,36]. When memantine and ketamine were compared in drug discrimination studies, ketamine displayed complete substitution for PCP or MK-801, and memantine displayed complete [44] or partial [11,45] substitution.

Many NMDAR channel blockers have been found to exhibit properties thought to be associated with activation of brain circuits. Ketamine powerfully increases gamma (~30 –

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90 Hz) oscillations in cortex (for review, see [46]) and delta (~0.5 – 4 Hz) oscillations in multiple brain regions [47]. Although the effects of memantine on oscillations have been less extensively studied, a recent article showed that memantine as well as ketamine increased gamma oscillations in rat cortex, whereas ketamine but not memantine increased delta oscillations [48]. Both memantine and ketamine increased 2-deoxyglucose (2-DG) uptake, a marker of neuronal activation [49]. Ketamine has been hypothesized to disinhibit cortical circuits [12,50,51], a process that may underlie increases in gamma oscillations and 2-DG uptake. Similarly, memantine inhibition of NMDARs was proposed to produce cognitive improvements in AD patients through disinhibition [52], although memantine's ability to mediate disinhibition has not been directly assessed. Ketamine reduces expression of the important GABAergic interneuron markers parvalbumin (a Ca^{2+} binding protein) and GAD67 (a GABA synthetic enzyme) in rodents, thereby compromising inhibitory neuron function [53-55]. The relation of decreased interneuron function to increased oscillations, however, has been questioned [56,57]. Memantine and ketamine also have been proposed to inhibit a subpopulation of interneurons (but see [58]) as a result of the drugs' selectivity in physiological Mg^{2+} for GluN2C and GluN2D subunit-containing NMDARs [16]. Because GluN2D subunits are expressed predominantly by inhibitory neurons in mature cortex and hippocampus [59,60], preferential inhibition of GluN2D-containing receptors could mediate disinhibition.

Both memantine and ketamine have been shown to be neuroprotective using many in vivo and in vitro paradigms, and their neuroprotective actions are thought to contribute to their clinical benefits (for reviews, see [10,61,62]). There has been very limited comparison of the neuroprotective properties of memantine and ketamine. In one direct comparison of their ability to reduce the effects of oxygen-glucose deprivation in cultured hippocampal slices at equal concentrations, ketamine was found to be slightly more effective than memantine [63].

Thus, the effects of memantine and ketamine in rodent studies demonstrate both strong similarities and clear differences; in human studies, the drugs' effects differ conspicuously.

Mechanistic bases for differential effects of memantine and ketamine

Pharmacological differences between memantine and ketamine

We will consider several possible explanations for the differential effects of memantine and ketamine noted above.

Drugs with the same site of action can differ in their clinical and behavioral effects because of pharmacokinetic differences. The increase in serum and brain concentration, and subsequent elimination, is much faster for ketamine than memantine in both humans and rodents, a difference that could be responsible for the drugs' differential effects (see [9,10,36,64,65]). Several lines of evidence argue against the hypothesis that pharmacokinetic differences between memantine and ketamine are the principal explanation for their differential clinical and behavioral effects. First, numerous studies of ketamine action in humans have involved drug infusion protocols (e.g., [66,67]), some of which have been demonstrated to maintain a steady serum concentration [68]. Nevertheless, the effects of infused ketamine differed strongly from the effects of memantine, which is maintained at

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stable levels in patients treated by oral administration due to its slow pharmacokinetics [10]. Second, phencyclidine, an analog of ketamine, has much slower pharmacokinetics than ketamine [69], but greater psychotomimetic effects [70]. Third, a recent study compared in rats the behavioral effects of memantine and ketamine at two time points: 15 min after i.p. injection, when ketamine concentration should be near peak but memantine concentration rising, and 45 min after i.p. injection, when ketamine but not memantine concentration should have substantially decreased. The behavioral effects of memantine and ketamine at low doses were similar at both time points, and differences in the drugs' effects at higher doses were similar at both time points [36]. The results suggested that the pharmacokinetic differences between the drugs do not make a major contribution to their differential behavioral effects in rodents. It appears likely that some of the observed differences between the effects of memantine and ketamine, for example sensitivity to transient inhibition of downstream effectors [41], could result from pharmacokinetic differences. However, it appears unlikely that the clinical and behavioral effects of memantine and ketamine differ predominantly because of the faster pharmacokinetics of ketamine.

A second possibility is that the differential clinical and behavioral effects of memantine and ketamine result from differences in their action at sites other than NMDARs. Multiple other sites of action have been reported for each drug (e.g., [26,71,72]). For example, memantine inhibits multiple acetylcholine receptors subtypes [73-76] and 5-HT_3 serotonin receptors [10,77], whereas ketamine binds to dopamine D2 and 5-HT_2 serotonin receptors [12,78] and to HCN1 channels [79]. Although multiple lines of evidence support the hypothesis that the actions of memantine and ketamine depend predominantly on NMDAR binding [10,70,80,81], there also is strong evidence supporting the importance of other sites of action [79]. It seems likely that some of the differences in the drugs' effects, especially at higher doses, depend on action at targets other than NMDARs.

A third possibility is that the effects of drug metabolites contribute to the differential pharmacological effects of memantine and ketamine. The (S)- and (R)-enantiomers of norketamine are major metabolites of ketamine, and inhibit NMDARs, although with lower potency than (S)- and (R)-ketamine [14,82,83]. Similar to ketamine, (R,S)-norketamine and (2S,6S)-hydroxynorketamine, another ketamine metabolite [83], can increase mTOR function [84]. Several ketamine metabolites potently inhibit α7-nicotinic acetylcholine receptor-mediated currents [85]. Although, to our knowledge, no active memantine metabolites have been reported, differences in the activity of metabolites of ketamine and potentially memantine at NMDARs or at non-NMDAR sites could underlie some of their differential clinical and behavioral effects.

A fourth possibility is that memantine and ketamine block overlapping but distinct populations of NMDARs. NMDARs play diverse roles in nervous system function, and differential inhibition of receptors involved in distinct functions could lead to divergent clinical and behavioral effects. Although memantine and ketamine bind to overlapping sites on NMDARs, there are multiple mechanisms by which they might inhibit distinct receptor subpopulations. In the next section we will focus on studies that address the hypothesis that memantine and ketamine inhibit distinct subpopulations of NMDARs.

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Differential inhibition of NMDAR subpopulations by memantine and ketamine

Current understanding of the mechanisms of action of memantine and ketamine do not permit a confident determination of whether, and if so how, they inhibit distinct subpopulations of NMDARs. However, data pointing to an important dichotomy in the NMDAR subpopulations inhibited by memantine and ketamine have emerged.

Many recent studies suggest that the important NMDARs inhibited by memantine are predominantly extrasynaptic, whereas the important NMDARs inhibited by ketamine are synaptic. The significance of differential relative inhibition of synaptic and extrasynaptic NMDARs derives from a hypothesis particularly relevant to neurodegenerative diseases: that synaptic NMDAR stimulation activates cell survival pathways, whereas extrasynaptic NMDAR stimulation activates cell death pathways [86-88]. Activation of extrasynaptic NMDARs by ambient glutamate mediates tonic NMDAR current [89-91], and augmented extrasynaptic receptor activation has been hypothesized to compromise neuron health in nervous system disorders [86-88]. However, it is important to note that there is no consensus on the differential implications of synaptic and extrasynaptic NMDAR activation [6,24,92-95].

Memantine has been found to inhibit extrasynaptic NMDARs more potently than synaptic NMDARs ([96-102]; but see [63,93,94]). However, memantine inhibition of synaptic NMDARs can increase with increasing intensity of synaptic stimulation [93,103]. Memantine can restore long term potentiation impaired by tonic NMDAR activation following reduction of Mg^{2+} in hippocampal slices [104]; since tonic NMDAR current depends mainly on extrasynaptic NMDARs [89], these data are generally consistent with the idea that memantine preferentially inhibits extrasynaptic NMDARs. In Huntington's disease model mice, memantine reduced functional extrasynaptic NMDAR expression, reversed aberrant activation of cell death pathways by suppressing p38 MAPK activation and increasing nuclear CREB signaling, and reversed disease-associated deficits [98,100,102].

In contrast, the NMDAR subpopulation of central importance to the rapid anti-depressant effects of ketamine was proposed to be synaptic, and possibly a subgroup of NMDARs predominantly activated by spontaneous synaptic vesicle release [6,43,105,106]. Acute inhibition of synaptic NMDARs by ketamine at doses sufficient to produce antidepressant behavioral effects in rodents deactivated eukaryotic elongation factor 2 (eEF2) kinase, reducing eEF2 phosphorylation, relieved block of BDNF translation, and increased surface expression of AMPARs [105,106]. A recent study found that in the presence of physiological Mg^{2+}, ketamine inhibited synaptic NMDARs in hippocampal pyramidal neurons much more effectively than memantine [43]. The same study showed that in the absence of Mg^{2+}, inhibition of synaptic NMDARs by memantine and ketamine was indistinguishable, consistent with previous findings [63]. These results suggest that Mg^{2+}, which has been excluded in many basic studies of memantine and ketamine action on NMDARs, could play a key role by influencing relative inhibition of NMDAR subpopulations by memantine and ketamine.

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Potential mechanisms of differential inhibition

We next will consider mechanisms by which a channel blocker could differentiate NMDAR subpopulations. There are at least three ways inhibitors could distinguish synaptic from extrasynaptic NMDARs: (1) by differential inhibition of NMDAR subtypes expressed synaptically versus extrasynaptically; (2) by differential inhibition based on the concentration of glutamate that activates receptors; (3) by differential inhibition based on the time course of receptor activation.

There is evidence for differential expression of NMDAR subunits by subcellular location. GluN2B-containing NMDARs have been reported to be preferentially localized extrasynaptically, and GluN2A-containing NMDARs to be preferentially localized synaptically in cortical and hippocampal neurons ([107-109]; but see [110,111]). However, neither memantine nor ketamine distinguish strongly between GluN2A- and GluN2B-containing NMDARs [14,16]. A caveat is that memantine and ketamine inhibition of triheteromeric receptors, which are highly expressed in the brain (see [4]), has not been characterized. Newly developed approaches for study of isolated triheteromeric receptors will facilitate determination of possible differential drug selectivity [112]. There also is evidence for preferential extrasynaptic expression of GluN2D-containing NMDARs in multiple brain regions [113,114], including hippocampus [115,116]. Because memantine and ketamine preferentially inhibit GluN2C- and GluN2D-containing NMDARs in physiological Mg^{2+} [16], extrasynaptic localization of GluN2D-containing NMDARs could underlie the drugs' enhanced inhibition of extrasynaptic receptors.

There also is evidence that memantine inhibits NMDARs more effectively at higher agonist concentrations ([117], but see [15,118]). However, this observation would not explain preferential inhibition of extrasynaptic receptors, since extrasynaptic NMDARs are activated by much lower glutamate concentrations than synaptic receptors.

Whether NMDAR inhibition by memantine and/or ketamine depends on the duration of agonist exposure has not been directly investigated. If memantine but not ketamine were to preferentially inhibit NMDARs tonically activated by the extracellular glutamate to which extrasynaptic receptors are exposed, then only memantine would preferentially inhibit extrasynaptic NMDARs. As described above, there are conflicting data on whether memantine distinguishes synaptic and extrasynaptic receptors in 0 Mg^{2+}, but evidence that differential actions of memantine and ketamine appear in the presence of physiological Mg^{2+} [43]. Although initially the powerful effect of Mg^{2+} on inhibition by channel blockers was suggested to affect memantine and ketamine similarly [16], subsequent data suggest that the effect of Mg^{2+} may differ among channel blockers [18]. Further characterization of memantine and ketamine inhibition of NMDAR responses in the presence of physiological Mg^{2+} is warranted.

If memantine and ketamine do inhibit distinct populations of NMDARs, then there must be an underlying difference in the drugs' mechanism of interaction with NMDARs. One difference that has been described is memantine's ability to bind to a superficial site on NMDARs to which ketamine does not bind. Memantine binding to the superficial site contributes to partial trapping of memantine, a phenomenon that has been proposed to

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reduce inhibition of synaptic receptors [15,119-122]. The impact of the superficial memantine binding site on inhibition in the presence of Mg^{2+} is unexplored. Another possibility is that occupation of the channel by memantine or ketamine may differentially affect transition rates between NMDAR states (e.g., between open and closed, agonist-bound and agonist-unbound, and/or desensitized and undesensitized states) of blocked receptors [123-126]. The presence of a blocker in a channel can powerfully influence gating transitions, as suggested by Figure 1(b); the M3 α-helices, which surround the blockers, are centrally involved in channel gating [3]. “Foot-in-the-door” blockers, which do not permit channel closure when bound [127], provide an extreme example of how channel blockers can affect channel gating. Some NMDAR channel blockers act as foot-in-the-door blockers [124,128], but others accelerate channel closure [125] and agonist unbinding [126]. The effect of a channel blocker on transitions between blocked states influences many characteristics of inhibition, including dependence of inhibition on agonist concentration [129] and on duration of agonist presentation (NG Glasgow and JW Johnson, abstract in *Soc Neurosci Abstr* 2014, 501.08). Thus, there are biophysically plausible explanations for why, despite their similarities, memantine and ketamine could inhibit distinct populations of NMDARs.

Conclusions

The divergent clinical and behavioral effects of memantine and ketamine could be a consequence of multiple differences between the drugs. Their very different pharmacokinetics along with differences in their actions at binding sites other than NMDARs are likely to make some contribution to differences in the drugs' clinical and behavioral effects. There is considerable evidence, however, that the important NMDAR subpopulations inhibited by memantine and ketamine differ: many recent studies have attributed the beneficial effects of memantine to preferential inhibition of extrasynaptic NMDARs, whereas the rapid antidepressant effects of ketamine have been attributed to inhibition of synaptic NMDARs. Although the validity of this dichotomy has been questioned and a mechanistic basis for differential NMDAR inhibition by memantine and ketamine is not established, there are plausible biophysical explanations that remain to be tested. More extensive direct comparison of the effects of memantine and ketamine at multiple experimental levels will provide critical insight into the important mechanisms responsible for the clinical benefits of these NMDAR antagonists.

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* of special interest

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Highlights

- Memantine and ketamine block open NMDAR channels via apparently similar Mechanisms
- Memantine is a very well-tolerated drug approved for treatment of Alzheimer's disease
- Ketamine has rapid antidepressant effects, but replicates symptoms of schizophrenia
- The drugs' differential effects may require inhibition of distinct NMDAR populations

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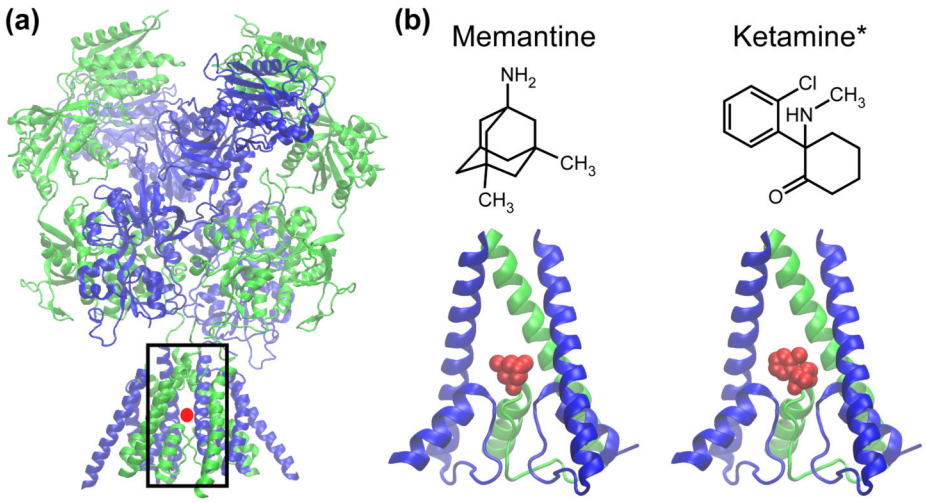

Figure 1.

Images of NMDAR channel blocked by memantine and ketamine. **(a)** Two nearly complete X-ray crystal structures of NMDARs composed of GluN1 and GluN2B subunits recently were published [130,131]. Here, one of the structures (Protein Data Bank (PDB) code 4TLM [131]) is shown with a red dot at the likely approximate location of memantine and ketamine binding sites. The black box indicates the area of the receptor blown up in (b). **(b)** Top, the structure of memantine (left) and ketamine (right). *, ketamine, which has two enantiomers ((S)- and (R)-ketamine), is depicted without chirality in this planar representation. Bottom, a view of the channel region of an NMDAR composed of GluN1 and GluN2A subunits with memantine (left) and with (R)-ketamine (right) blocking the channel. The structure of the NMDAR channel region is based on the homology model of [132]; the memantine structure is from www.edinformatics.com; the (R)-ketamine structure is from PDB code 4F8H [133]. There are no structures of NMDARs with a resolved channel blocker; memantine and ketamine are placed with the charged nitrogen close to the critical NMDAR channel asparagines [121,134,135]. GluN1 subunits are shown in green and GluN2 subunits in blue. Structural images were prepared using the molecular visualization program VMD [136].