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MINIREVIEW

ANTAGONISTS OF THE NMDA RECEPTOR-CHANNEL COMPLEX AND MOTOR COORDINATION

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Summary

Many structurally different, centrally active antagonists of the NMDA receptor-channel complex induce phencyclidine-like side effects in mammals which include head weaving, body rolling, sniffing and disturbances of motor coordination. The ability of these compounds to cause disturbances of motor coordination correlates directly with their ability to antagonize the NMDA receptor-channel complex *in vivo*. Although noncompetitive antagonists increase motility in rodents, whereas competitive antagonists do not, both classes of compounds appear to induce schizophrenia-like psychosis in human beings, and cause similar changes in a variety of different biogenic amine neurotransmitter systems in the limbic and motoric areas of the brain. The complex spectrum of behavioural effects observed after the administration of antagonists of the NMDA receptor-channel complex probably reflects the intricate nature of the interaction with positive and negative feedback loops of the motor circuit. Recent research indicates that the site of integration of this interaction could be the striatal medium spiny GABAergic neuron.

Key Words: NMDA, NMDA antagonists, phencyclidine, ketamine, MK-801, motor coordination, ataxia, psychosis, motility, locomotion

> Now, *here*, you see, it takes all the running *you* can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!
>
> Lewis Carroll (1832-1898)
> *Through the Looking-Glass*

Ketamine is a powerful anaesthetic which is popular because of its good safety profile, especially in children and young healthy adults (1). The drug can, however, also be abused (2,3). A recent report outlined how four young men described symptoms of paralysis resembling catalepsy after illicitly taking ketamine: they could not move or speak although their eyes remained open (4). This example underlines the dangers of the abuse of ketamine because the drug can induce a state of virtual helplessness to a far greater extent than most other substances of abuse (2). Ketamine induces a characteristic state of sedation, immobility, amnesia and marked analgesia (1); indeed, the term dissociative anaesthesia has been used to convey the strong feeling of dissociation from

the environment experienced by the individual taking these drugs. It differs from other anaesthetics such as barbiturates by producing a state of catalepsy in animals and human beings without hypnosis at subanaesthetic doses (5). The catalepsy is characterized by an akinetic state in which the extremeties of the body appear to be paralyzed by motor deprivation and there is a loss of the body righting reflex (6).

Ketamine belongs to a class of compounds known as arylcyclohexylamines which also includes phencyclidine (PCP). Although PCP was originally developed as a general anaesthetic agent, the frequent occurrence of hallucinations and psychological problems soon led to it being abandoned (5). Some patients can even experience a psychotic phase which lasts for several days after ingestion of a single dose of PCP and constitutes, at least in the initial phase, a psychiatric emergency (7). PCP has also been abused. Indeed, the extent of abuse of PCP over the past ten years has meant that it had become a serious problem in the USA involving significant numbers of users (7). Interestingly, a major cause of PCP-induced deaths in California was reported to have been drowning (7), a fact which also implies dissociation from the environment and interference with motor coordination. Recent work in healthy volunteers has shown that ketamine can also produce a broad range of symptoms, behaviours and cognitive deficits reminiscent of endogeous psychoses and schizophrenia (8).

Ketamine and PCP have been shown to antagonize the effects of glutamate at one particular subtype of ionotropic receptor channel, the N-methyl-D-asparate (NMDA) receptor-channel complex (9). And there is now a good case to be made that ketamine exerts its anaesthetic effects by inhibiting the NMDA receptor (10,11). For instance, the stereoselectivity of the anaesthetic and analgesic effects of ketamine in humans (12,13) is mirrored by the stereoselectivity for antagonizing the effects of NMDA *in vitro* (14,15). Glutamate and aspartate are the major excitatory neurotransmitters in the mammalian central nervous system (16). It is therefore perhaps not surprising that antagonists of the NMDA receptor-channel complex cause a variety of centrally mediated side effects. The aim of this review is to summarize the results obtained from experiments with NMDA antagonists in order to begin to understand the role of the NMDA receptor-channel complex in intricate behaviours such as motor coordination.

Excitatory amino acid receptors

As the name suggests, the history of excitatory amino acids began with the discovery of their excitatory nature. The amino acids, glutamate and aspartate, were shown to produce convulsions when injected into the cortex of dogs or monkeys (17). Later, the toxic effects of these amino acids were documented when they were administered subcutaneously to mice and damage was observed in the inner layers of the retina (18). In an elegant series of electrophysiological experiments with spinal neurons, Curtis and Watkins (19) were able to dissociate excitatory from inhibitory actions of different amino acids, and to carefully define the structure-activity relationships involved. They also postulated the existence of receptors located on neurons which are specific for excitatory amino acids.

The existence of more than one type of glutamate receptor was suggested as long ago as 1968 by McLennan and coworkers (20): they demonstrated that the sensitivity of neurons to glutamate varied widely from one region to another, whereas the sensitivity to another amino acid homocysteate varied to a lesser extent and in the opposite direction. Later work showed that glutamate and aspartate possessed different relative potencies depending on their site of action in the spinal cord (21). McCulloch *et al.* (22) proposed the existence of two different subtypes of receptor, and suggested that glutamate is an excitatory transmitter at primary afferent synapses in the spinal cord.

Although several electrophysiological experiments had pointed to the presence of different glutamate receptor subtypes, it was not until the advent of antagonists that this hypothesis could be tested. One of the first compounds discovered was glutamic acid diethylester; this compound was shown to reversibly antagonize the excitatory effects of glutamate (23). This work was later extended to show that the diethylester was more effective at antagonizing the responses induced by glutamate than by other amino acids (24). Another compound, 3-amino-1-hydroxy-3-pyrrolidone-2 (HA-966), was also shown to selectively antagonize glutamate- and aspartate-evoked excitation of single neurons (25). An important observation was made by Evans and colleagues (26): they demonstrated that low concentrations of Mg^{2+} markedly depressed neuronal depolarizations in spinal cord preparations produced by some amino acids (NMDA and homocysteate), but not by others (kainate and quisqualate). The selective antagonism of certain amino acid responses by Mg^{2+} and other longer chain glutamate analogues, e.g. D-α-aminoadipate, prompted the proposal that there were at least two main types of excitatory amino acid receptor: NMDA and non-NMDA (27,28).

Antagonists of excitatory amino acids have attracted a great deal attention because of their great therapeutic potential. Originally, Olney and colleagues (29) proposed that naturally occurring excitatory amino acids might be involved in certain neurodegenerative diseases. Olney expanded this theory later by combining both the excitatory and toxic nature of these amino acids in the word *excitoxicity* (30). This work was extended subsequently by Rothman (31,32) who proposed that synaptic release of excitatory amino acids caused the death of cultured neurons which had been deprived of oxygen. *In vivo* experiments demonstrated that high levels of excitatory amino acids are released during transient forebrain ischaemia, and that blockade of one particular subtype, the NMDA receptor-channel complex protects the neurons from ischaemic damage (33,34). These results provoked Olney and Rothman (35,36) to postulate that excitatory amino acids play a key role in ischaemic damage, and that drugs which antagonize their effects may be a suitable therapy for stroke. Ensuing research has also implicated excitatory amino acids in traumatic brain injury (37) and epilepsy (38).

The NMDA receptor-channel complex

In 1982, it was reported that aspartate and certain other related amino acids caused a voltage-dependent membrane conductance in cultured spinal cord neurons (39,40). Later, several groups established that it was in fact Mg^{2+} which, at resting membrane potential, blocked the channel conductance, and that this blockade was voltage dependent (41-43). Furthermore, the channel of the receptor complex was found to have a very high Ca^{2+} permeability compared to other excitatory amino acid receptors (42,44,45). Thus the receptor is in many respects unique, and is often referred to as the NMDA receptor-channel complex. Functionally, it consists of a voltage-dependent channel, which is permeable to both Ca^{2+} and Na^{+}, and at least three different regulatory domains (46). The first site, by definition, is the neurotransmitter recognition site to which compounds such as glutamate, aspartate or NMDA bind (47,48); this site can be blocked by competitive antagonists such as D-CPPene and CGP 37849 (48). The second site is in the receptor channel itself and can be blocked by Mg^{2+} or by various noncompetitive antagonists such as the arylcyclohexylamines or certain benzomorphans (49). The strychnine-insensitive glycine constitutes the third regulatory domain of the receptor-channel complex (50). There is also speculation that there are sites for zinc (51,52) and polyamines (53,54) which can influence the activity of the complex.

The search for the NMDA subtype of glutamate receptor was for many years the Holy Grail of neurotransmitter receptor molecular biology (55). In a major breakthrough, the receptor was first cloned and sequenced from rat brain by Nakanishi and coworkers (56). Since then, there has been intense activity in this area which has resulted in the cloning and sequencing of two families of NMDA receptor subunits, NR1(or NMDAR1)A-G and NR2A-D, from rat (56-58) and mouse (59-62). The receptor is predicted from the cDNA sequence to be a polypeptide of 938 amino acids, with 5 hydrophobic sequences which are thought to represent 4 transmembrane domains, and has a molecular mass of 103 kDa (63). It is therefore similar in size to the non-NMDA receptor subunits and twice as large as the subunits encoding acetylcholine (ACh), γ-aminobutyric acid (GABA), glycine and serotonin (5-HT). Eight different isoforms with distinct functional properties can be generated from alternative splicing of a single NR1 gene (64-68). Heterogeneity is generated within the NR2 subunit family by the expression of four closely related genes (57,58,60). Although the single polypeptide encoded by the NR1 subunit is enough to form a functional homo-oligomeric NMDA receptor-channel complex that displays most of the physiological and pharmacological characteristics of the native receptor, NMDA receptors are believed to be heteromeric complexes *in vivo*. Coexpression of NR1 with NR2A, NR2B, or NR2C greatly enhances responses to NMDA *in vitro* (57,58,60,61). Indeed, recent work has shown that four previously identified native NMDA receptor subtypes differ in their NR2 subunit composition, and that these subunits significantly contribute to the anatomical and pharmacological diversity of NMDA receptor subtypes *in vivo* (69).

Disturbances of motor coordination

Antagonists of the NMDA receptor-channel complex can profoundly affect animal behaviour. Systemic administration of the noncompetitive NMDA antagonists, (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine (MK-801), PCP, ketamine, *N*-allylnormetazocine and dextrorphan to rodents causes a complex series of behaviours called PCP-like effects which include enhanced locomotion, head weaving, body rolling, sniffing and disturbances of motor coordination (70-76). In pigeons, MK-801 and PCP produce catalepsy, defined as the loss of righting without eye closure and muscle relaxation (73,77,78). Noncompetitive antagonists of the NMDA receptor-channel complex cause ataxia and nystagmus at low doses and ketamine-like anaesthesia at higher doses in rhesus monkeys (73). A variety of competitive antagonists, AP5, NPC 17742, CGS 19755, CGP 37849 and CGP 39551 also appear to exhibit similar properties in rodents, pigeons and monkeys (70,74,78-83). The first studies with systemically active antagonists of the strychnine-insensitive glycine site indicate that these compounds are likewise able to cause disturbances in motor coordination (84).

Selective blockade of the NMDA receptor-channel complex inhibits the convulsions and death caused by the systemic administration of NMDA to mice (71,74,75,84,85). The ability of these compounds to antagonize the effects of NMDA correlates well with their ability to cause disturbances of motor coordination as measured by the rotarod technique (75,84,85). Although Koek and Colpaert initially claimed that competitive antagonists and antagonists of the glycine site are not as potent as noncompetitive antagonists at producing PCP-like effects, recent work indicates that this is not the case when equipotent doses are used (84,86). All systemically active antagonists of the NMDA receptor-channel complex thus far, irrespective of whether they are noncompetitive, competitive or glycine site antagonists, cause disturbances of motor coordination. Nevertheless, the variety of behavioural effects observed with antagonists of the NMDA receptor-channel is still perplexing and requires more detailed study with a variety of techniques.

Do low affinity noncompetitive antagonists offer the best therapeutic window?

The therapeutic index (TI) has been used to compare the effects of antiepileptic compounds.TI is defined as the ratio between the dose which impairs motor performance in 50% of animals (ED_{50}) and the effective dose for protecting against tonic hindlimb extension in the maximal electroshock test in 50% (MID_{50}) of the animals (87). The maximal electroshock test is commonly used for drug screening because it predicts clinical activity against generalized tonic-clonic seizures (88). Potent noncompetitive antagonists of the NMDA receptor-channel complex, such as PCP and MK-801, typically have TI values of less than 1 (87-89), thus making it unlikely that they will ever be useful for the chronic treatment of seizure disorders (88). The TI values for competitive antagonists were in the range of two to three, and therefore not far removed from the values for the noncompetitive antagonists (88). Moderate separation of TI values is probably not sufficient to allow these compounds to be used clinically for the treatment of seizures.

Noncompetitive antagonists have a theoretical advantage over competitive antagonists in epilepsy and ischaemia because the noncompetitive blocking action cannot be overcome by excess glutamate, despite them having relatively poor TI values. Recently however, certain weaker binding noncompetitive antagonists, e.g. dextrorphan, memantine and remacemide, have been shown to produce substantially less motor impairment than would be predicted on the basis of the results from the maximal electroshock test (89-93). These observations have prompted Rogawski (94) to postulate that low-affinity antagonists at equieffective concentrations exhibit faster apparent rates of block and unblock, and that this could contribute, in part, to their lower toxicity. Although this is an interesting theory, there may be other explanations.

One possibility which Rogawski himself suggested is that synergistic effects at other molecular targets such as voltage-dependent cation channels may also increase the therapeutic window (94). This latter explanation is more plausible because weaker binding noncompetitive antagonists tend not to be selective for NMDA channels: e.g. dextrorphan and dextromethorphan also block a variety of different voltage-sensitive Ca^{2+} channels (95-98), a fact which could explain their extra anticonvulsive effects in the maximal electroshock model. Moreover, the excellent correlation between the ability of various antagonists of the NMDA receptor-channel complex, including compounds with only a low affinity such as ketamine and dextrorphan, to cause disturbances of motor coordination and their ability to antagonize the effects of NMDA (84) also argues against the theory of Rogawski. Carefully conducted *in vivo* experiments with a variety of different drugs, whose spectrum of effects on different ion channels are known, should resolve this issue.

An apparent excitation/inhibition incongruity?

Although there are many similarities in the behavioural effects of systemically active competitive, noncompetitive and glycine site antagonists, Willets and her colleagues (99) have proposed that there may also be differences such as the poor cross-generalization in drug discrimination studies (74,100-102). They postulated that competitive antagonists may be less likely to exhibit PCP-like psychotomimetic effects or abuse potential (99). Indeed, there do appear at first glance to be differences between the ability of competitive and noncompetitive antagonists to produce excitation in rodents. Noncompetitive antagonists cause marked stimulation of locomotor activity, whereas competitive antagonists either had no effect or decreased it (103-109). I have called this an apparent excitation/inhibition incongruity because there appears at first sight to be key qualitative differences in behaviour which depend on the nature of antagonism at receptor level. Moreover, one would perhaps normally have expected antagonists of excitatory amino acid transmission to have sedative rather than excitatory effects.

Attempts have also been made to quantify the excitation observed after the administration of noncompetitive antagonists in ways other than simple measures of motility. These experiments have yielded similar results. Evoniuk and colleagues (110) developed a tower apparatus consisting of a circular arena mounted on a platform. Mice treated with MK-801, ketamine or PCP sprang from the arena, whereas those treated with competitive or glycine antagonists failed to do so. Alternatively, discrete episodes of explosive jumping behaviour, designated as "popping", exhibited by mice after administration of MK-801 or PCP have been quantified (111). Given the fact that PCP and ketamine have been shown to precipitate schizophrenia-like psychosis in human beings (7,8), some researchers have predicted that competitive antagonists should not cause such effects because they lack excitatory effects in rodents (99,111,112).

In contrast to the above predictions, Löscher and Hönack (113) have shown that the systemically active, competitive agonist CGP 37849 can preferentially induce PCP-like behavioural effects in kindled rats. The authors concluded that epileptogenesis in humans may alter their susceptibility to the adverse effects of NMDA antagonists (114). Recent clinical work has substantiated these predictions. For example, the competitive antagonist D-CPPene has been reported to cause severe adverse advents in epileptic patients, including confusion, disorientation, ataxia and impaired concentration (115). Furthermore, CGS 19755 caused a disturbing incidence of psychotomimetic adverse reactions, including agitation, confusion and hallucination, in patients with stroke (116). Thus with respect to the clinical profile, the excitation/inhibition incongruity appears not to be one after all. Perhaps neurochemical studies can help us to understand this better.

Interactions with biogenic amine systems

MK-801 was originally described in 1982 as a potent anticonvulsant that exhibited both anxiolytic and sympathomimetic properties (117,118). It was not until four years later that MK-801 was shown to be a potent NMDA antagonist (119). The ability to antagonize the NMDA receptor-channel explains the anticonvulsive effects. Could it also explain the sympathomimetic properties? The sympathomimetic effects were recognized as being indirect in the original work, and were thought to be mediated by a catecholamine-dependent process because they could be blocked by reserpine and haloperidol (117). Subsequent research with classical biochemical techniques has extended these original findings to show the general involvement of several biogenic amines: MK-801 and the related compounds PCP and ketamine increase dopamine, noradrenaline and 5-HT turnover in several regions of the brain, including the cortex, striatum and limbic areas (86,103-105,120-127).

Until recently, results from similar studies with competitive antagonists have yielded equivocal results. Many groups have failed to observe changes in dopamine turnover with classical neurochemical techniques after the administration of various competitive antagonists (104,105,124,128). Many of the compounds used, however, exhibit poor brain bioavailability. Latest results with a more potent competitive antagonist, CGP 37849, show that the compound can indeed produce activation of dopaminergic and serotonergic pathways similar to that caused by uncompetitive antagonists provided that behaviourally equipotent doses are used (86).

Brain microdialysis studies have confirmed and extended many of the above observations. Systemic administration of PCP or MK-801 causes an increase in the extracellular levels of dopamine and 5-HT in the striatum (129-132), frontal cortex (125), and hippocampus (130). MK-801 was also shown to increase acetylcholine (ACh) levels in the parietal cortex (133) and decrease them in the striatum (134). The changes in ACh levels in the parietal cortex did not coincide with behavioural changes such as hypermotility (133), whereas the changes in the striatum did (134). The technique of microdialysis may also help to clear up some of the

contradictions which have arisen from classical neurochemical studies because compounds can be perfused directly through the microdialysis probe to obviate problems of brain bioavailability. Perfusion of MK-801 through a microdialysis probe implanted in either the striatum or the nucleus accumbens caused increases in the extracellular concentrations of dopamine (135). In the same study, perfusion of a weak competitive antagonist, CPPene, also caused similar changes in the concentrations of dopamine. More recent work has confirmed that competitive antagonists are indeed able to cause increases in the extracellular concentrations of dopamine in the striatum and frontal cortex of rats (136, 137). These results demonstrate that there are no qualitative differences between competitive and noncompetitive antagonists on dopaminergic systems when equipotent concentrations are delivered directly to the tissues in question. Thus, the neurochemical evidence supports the clinical findings.

Excitatory effects of MK-801 and PCP have also been recorded electrophysiologically on dopaminergic neurons in the ventral tegmental area (112,138,139). The inhibition of the effects of MK-801 and PCP on motility by dopamine antagonists such as haloperidol has also been confirmed by several groups (127,140-142). The hypermotility induced by either MK-801 or PCP could also be attenuated by 5-HT antagonists (140,143-145). Indeed, many of the behavioural alterations observed after the administration of antagonists of the NMDA receptor-channel complex have been likened to those caused by 5-HT_{1A} agonists (145). Interestingly, the hypermotility can also be blocked by α_1-adrenoceptor antagonists (145), muscarinic antagonists (146) and GABA transferase inhibitors (147). Overall, these results indicate that the effects of NMDA antagonists on brain neurochemistry are very complex. How can we hope to make sense of them?

The medium spiny GABAergic neuron

MK-801 and PCP cause a pronounced increase in locomotion in mice whose monoamines had been depleted by pretreatment with a combination of reserpine and α-methyl-para-tyrosine (148,149). Interestingly, administration of the competitive antagonists D-CPPene or AP5 also increases locomotion in this model, and the effects were potentiated by the α-adrenoceptor agonist clonidine (149,150). A variety of antagonists of the glycine site of the NMDA receptor-channel complex were also able to increase locomotion in this model (151). Carlsson orginally postulated the existence of a corticostriatothalamocortical negative feedback loop which serves to protect the cortex from an overload of information (152). There is also a direct pathway which forms part of a positive feedback loop. Corticostriatal glutamatergic projections supply both direct and indirect pathways with excitatory input (153). On the basis of their results with various NMDA antagonists, Svenson, Carlsson and Carlsson proposed that corticostriatal glutamatergic pathways exert an inhibitory influence on psychomotor functions (148-150). Thus, suppression of glutamatergic neurotransmission by antagonists of the NMDA receptor-channel complex promotes the locomotor stimulatory potential of biogenic amine systems. The ability of NMDA antagonists to enhance locomotion could even be used therapeutically to treat the paucity of movement associated with Parkinson's disease (154).

The basal ganglia, which include the striatum, are linked to the cerebral cortex and thalamus via a system of parallel feedback loops, and the corticostriatal glutamatergic projections supply these pathways with excitatory input (153). The striatum is comprised mostly of principal neurons which are also called "spiny neurons" because of the large numbers of dendritic spines that cover their dendrites (155). Although several peptides such as dynorphin, substance P and enkephalin have been localized in the medium spiny neuron of the striatum, the most abundant neurotransmitter is GABA (155). The medium spiny GABAergic neuron represents the major input element of the basal ganglia. It receives dopaminergic afferents from the substantia nigra and glutamatergic

afferents from the whole cerebral cortex and intralaminar thalamus (156).The striatal GABAergic neurons also form most of the final ouput of the striatum and comprise two parallel and opposing GABAergic striatonigral and striatopallidonigral pathways which project to the output cells in the substantia nigra. The motor circuit is completed by the GABAergic neurons in the substantia nigra which regulate excitatory thalamocortical drive. Cortical glutamatergic afferents synapse onto the heads of the dendritic spines of the medium spiny neurons, whereas the dopaminergic inputs from the substantia nigra synapse onto the necks of the spines. The medium spiny neuron is therefore in a key position to influence cortical regulation of the thalamus.

The latest results from microdialysis studies are helping to elucidate the pivotal role that the medium spiny GABAergic neuron plays in the cortical circuit. Stimulation of the NMDA receptor-channel complex regulates the extracellular levels of dopamine, GABA and glutamate in the striatum (157), and this can be blocked by antagonizing dopamine D_1 receptors (158). The effects of dopamine are not, however, just inhibitory. In fact, dopamine D_1 and D_2 receptors can differentially modulate NMDA regulation of striatal GABAergic output neurons: D_1 receptors facilitate and D_2 receptors inhibit the NMDA-induced stimulation of striatal GABA release (159). Furthermore, stereotypies induced by MK-801 can also be differentially modulated by dopamine D_1 and D_2 agonists (160). The observation that elevated brain concentrations of GABA can antagonize PCP-induced hyperactivity in mice also supports the fundamental role of GABA in the behavioural responses to NMDA antagonists (147). It will be interesting to see how the other biogenic amine systems fit into the picture.

Conclusions

Research into the effects of antagonists of the NMDA receptor-channel complex is certainly gathering momentum. Such antagonists probably cause hyperactivity and disturbances in motor coordination *in vivo* by interacting with both the direct and indirect feedback loops in the motor circuit. Thus, the characteristic behavioural changes observed, which include both behavioural stimulation and interference, are very likely a complex behavioural manifestation of a very intricate neurochemical interaction, which may well express itself at the level of the medium spiny GABAergic neuron in the striatum. In the words of Lewis Carroll, if we want to get somewhere else, however, and better understand the nature of this interaction, then we must run at least twice as fast in the future.

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