

REVIEW

Ketamine and phencyclidine: the good, the bad and the unexpected

D Lodge and M S Mercier

Centre for Synaptic Plasticity, School of Physiology and Pharmacology, University of Bristol, Bristol, UK

Correspondence

D. Lodge, Centre for Synaptic Plasticity, School of Physiology and Pharmacology, Dorothy Hodgkin Building, University of Bristol, Bristol BS1 3NY, UK.
E-mail: david.lodge@bristol.ac.uk

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The history of ketamine and phencyclidine from their development as potential clinical anaesthetics through drugs of abuse and animal models of schizophrenia to potential rapidly acting antidepressants is reviewed. The discovery in 1983 of the NMDA receptor antagonist property of ketamine and phencyclidine was a key step to understanding their pharmacology, including their psychotomimetic effects in man. This review describes the historical context and the course of that discovery and its expansion into other hallucinatory drugs. The relevance of these findings to modern hypotheses of schizophrenia and the implications for drug discovery are reviewed. The findings of the rapidly acting antidepressant effects of ketamine in man are discussed in relation to other glutamatergic mechanisms.

Abbreviations

2-MDP, 2-methyl-3,3-diphenyl-3-propanolamine; D-AP5/D-APV, D-2-amino-5-phosphonovalerate; GAD67, glutamic acid dehydrogenase; LTP, long-term potentiation; MK-801, dizocilpine; PV, parvalbumin; SKF10,047, N-allyl-normetazocine

Tables of Links

TARGETS	
GPCRs^a	Ligand-gated ion channels^b
κ receptor	AMPA receptors
μ receptor	GluN2A
ACh receptors (muscarinic)	GluN2B
Cannabinoid receptors	GluN2C
D ₂ receptor	GluN2D
Metabotropic glutamate receptors	Kainate receptors
Enzymes^d	NMDA receptors
Cholinesterases	Nicotinic ACh receptors
GAD-67	
GSK-3	Ion channel^c
mTOR	HCN1
PKB (Akt)	

LIGANDS		
5-HT	Dopamine	Morphine
ACh	Ethylketocyclazocine	Naloxone
AMPA	HA-966	NMDA
Amphetamine	Ifenprodil	Noradrenaline
Bicuculline	Kainate	Pentazocine
Chlorpromazine	Ketamine (CI-581)	Phencyclidine
Cyclazocine	Levorphanol	Pregnenolone
D-AP5	LSD	Quisqualate
Dextromethorphan	Memantine	U50488H
Dizocilpine (MK-801)		

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (^{a,b,c,d}Alexander *et al.*, 2013a,b,c,d).

Preamble

In April 1981, Nabil Anis and David Lodge showed for the first time that ketamine was a selective antagonist of the NMDA subtype of glutamate receptor. Unlike the discovery of bicuculline as a GABA antagonist, reported by Graham Johnston in an earlier publication in this series of historical reviews (Johnston, 2013), the editors of *Nature* were not impressed, the finding 'not being of sufficient general interest'. Fortunately, the *British Journal of Pharmacology* took a different view and the resulting paper has now over 1000 citations (Anis *et al.*, 1983). Both before and since this discovery, ketamine and its congener, phencyclidine, have captured the interest of clinicians, basic scientists and sections of the general public. This review will attempt to describe some of this history and bring the reader up to date with the latest twists of this fascinating story in the context of these drugs as NMDA receptor antagonists.

Discovery of phencyclidine and ketamine: early observations

About 27 years earlier, phencyclidine had been synthesized by chemists at Parke Davis Company but not published for some 10 years (Maddox *et al.*, 1965). Initial pharmacology, however, was described by Chen *et al.* (1959) who noted lack of sensation, hyperlocomotion, ataxia and catalepsy in rats and pigeons. They ascribed these to monoaminergic mechanisms and showed partial reversal by the neuroleptic chlorpromazine (Chen *et al.*, 1959). At about the same time, Ed Domino commenced a fuller study of the neuropharmacology of phencyclidine (Domino, 1964). In rats, he described a 'drunken state' with increased locomotor activity leading to ataxia and catatonia at higher doses. Dogs also showed a similar state called 'canine delirium, although in monkeys a more satisfactory anaesthetic state was achieved but with some catatonia' (Domino, 1964). Such catatonia had been observed by one of the present authors in the mid-1960s, as a veterinarian using phencyclidine to 'immobilise' monkeys for chest radiography for tuberculosis (D. Lodge, unpublished).

Earlier, Greifenstein and co-workers had examined the anaesthetic utility of phencyclidine in man (Greifenstein *et al.*, 1958; Meyer *et al.*, 1959); it proved to be safe with good analgesia but with alarming signs of delirium or psychosis in the recovery stage including a state of centrally mediated sensory deprivation, investigated later in detail by Domino and colleagues (see Domino and Luby, 2012). Although phencyclidine continued to be used as a veterinary anaesthetic particularly for primates, the severe emergence phenomena prevented its further use in man. Parke Davis chemists made many analogues of phencyclidine using rats, dogs and monkeys to find compounds with shorter duration and less potential for delirium; this culminated in ketamine (CI-581; McCarthy *et al.*, 1965), which became a successful human and veterinary anaesthetic. Its properties differed from the standard barbiturate and gaseous anaesthetics of the time, ketamine being a good analgesic, poor muscle relaxant and weak sympathomimetic with a good margin of safety (White and Holtzman, 1982; White *et al.*, 1982; personal observations). Although emergence phenomena were less severe

than with phencyclidine (Domino *et al.*, 1965), they have nevertheless limited its use mostly to paediatric and geriatric anaesthesia where safety is the prime consideration (but see Rappaport *et al.*, 2015 for current discussion). It also maintains a particular place on the battlefield where analgesia and safety are paramount. Interestingly in 1982, ketamine became difficult to obtain for our own electrophysiological studies, as all supplies were prioritized to the Falkland Islands!

Psychotomimetic effects: early observations

The schizophrenia-like effects of phencyclidine, and later of ketamine, were known from the outset and indeed phencyclidine was called 'a new schizophrenomimetic drug' in the title of Luby's first study in 1959 (Luby *et al.*, 1959). These effects of phencyclidine and ketamine were a focus of research from the early 1960s. From comparisons made with other psychogens, such as lysergic acid diethylamide (LSD) and mescaline, and from procedures such as sensory isolation and sleep deprivation, it was concluded that phencyclidine-induced psychosis was most akin to schizophrenia (Luby *et al.*, 1959; Domino *et al.*, 1965); a conclusion that has been reiterated with further supportive evidence for both phencyclidine and ketamine over the subsequent half century (e.g. Javitt and Zukin, 1991; Krystal *et al.*, 1994; Olney and Farber, 1995; Malhotra *et al.*, 1996; Newcomer *et al.*, 1999; Jentsch and Roth, 1999; Geyer *et al.*, 2001; Lahti *et al.*, 2001; Tsai and Coyle, 2002; Morris *et al.*, 2005; Ehrlichman *et al.*, 2009; Saunders *et al.*, 2012; Moghaddam and Krystal, 2012; Gil-da-Costa *et al.*, 2013); this is particularly so following repeated abuse (Javitt and Zukin, 1991; Jentsch and Roth, 1999). Negative, positive, cognitive and electrophysiological signs of schizophrenia are all reported to be replicated to some extent by phencyclidine and ketamine (Javitt and Zukin, 1991; Krystal *et al.*, 1994). Indeed, so much so that in the late 1970s and early 1980s, pharmaceutical companies and academics, hoping for antipsychotic agents as therapy for schizophrenia, invested heavily in searching for antagonists of phencyclidine (Kamenka *et al.*, 1983).

Underlying these overt behavioural effects of phencyclidine and ketamine were changes in the CNS both in the EEG and in glucose metabolism.

The EEG showed bizarre and complex changes in rhythmic activity, reduced evoked potentials and inhibition of some pathways in a dose-dependent manner (Domino, 1964). The EEG was dominated by increased delta and reduced alpha waves in the thalamo-neocortical pathways, accompanied by theta bursts in the hippocampal formation, suggesting a dissociation of sensory and limbic systems (Miyasaka and Domino, 1968). For example, in one of the earliest studies, Rodin *et al.* (1959), cited by Domino and Luby (2012), reported 'rather profound slowing of the EEG with pronounced theta activity'. With ketamine, 'abolishing of the alpha waves and induction of theta activity were the most consistent and typical EEG effects' (Domino *et al.*, 1965). These complex disruptions of the EEG signal by ketamine and phencyclidine and their relationship to desynchronization seen in schizophrenia has remained a subject of research for the ensuing 50 years (see Table 1).

Desynchronization was also implied from brain metabolism studies using the 2-deoxyglucose method which showed increases in limbic areas, particularly hippocampus, cingulate

Table 1

Some shared GABAergic features between schizophrenia and the effect of arylcyclohexylamines

Feature	Schizophrenia	Phencyclidine/ketamine
Reduction in markers of cortical GABAergic interneurons (e.g. PV, GAD-67)	Akbarian <i>et al.</i> , 1995; Beasley and Reynolds, 1997; Woo <i>et al.</i> , 1998; Guidotti <i>et al.</i> , 2000; Hashimoto <i>et al.</i> , 2003; Reynolds <i>et al.</i> , 2004	Cochran <i>et al.</i> , 2003; Keilhoff <i>et al.</i> , 2004; Reynolds <i>et al.</i> , 2004; Cunningham <i>et al.</i> , 2006; Behrens <i>et al.</i> , 2007; Morrow <i>et al.</i> , 2007; Broberg <i>et al.</i> , 2008; Wang <i>et al.</i> , 2008
Decreased chandelier synapses and up-regulation of GABA receptors	Woo <i>et al.</i> , 1998; Volk <i>et al.</i> , 2002	Pierri <i>et al.</i> , 1999; Abe <i>et al.</i> , 2000; Wang <i>et al.</i> , 2008; du Bois <i>et al.</i> , 2009; Beninger <i>et al.</i> , 2010
Disinhibition increasing glutamate release with risk of excitotoxicity via AMPA receptors	Harrison and Weinberger, 2005; Coyle, 2012; Kraguljac <i>et al.</i> , 2013; Poels <i>et al.</i> , 2014	Olney and Farber, 1995; Moghaddam <i>et al.</i> , 1997; Lorrain <i>et al.</i> , 2003
EEG changes, including desynchronization and alterations in gamma and lower frequencies	Friston, 1998; Cho <i>et al.</i> , 2006; Roopun <i>et al.</i> , 2008; Minzenberg <i>et al.</i> , 2010; Uhlhaas and Singer, 2010	Cunningham <i>et al.</i> , 2006; Ehrlichman <i>et al.</i> , 2009; McNally <i>et al.</i> , 2011; Troyano-Rodriguez <i>et al.</i> , 2014; Moran <i>et al.</i> , 2015
Deficit in mismatch negativity and pre-pulse inhibition	Javitt <i>et al.</i> , 1996; Umbricht and Krljes, 2005; Braff <i>et al.</i> , 2007	Javitt <i>et al.</i> , 1996; Heekeren <i>et al.</i> , 2008; Amann <i>et al.</i> , 2010; Gil-da-Costa <i>et al.</i> , 2013

gyrus and entorhinal cortex, but decreases in more afferent-related areas, including inferior colliculus and sensory motor cortex (Nelson *et al.*, 1980; Crosby *et al.*, 1982; Hammer *et al.*, 1982).

Abuse of phencyclidine and ketamine: early observations

Despite apparently unpleasant sensory changes described above, both phencyclidine and ketamine soon became substances of abuse. Commonly known as 'Angel Dust' or 'Pea-CePill', phencyclidine appeared on the streets of West Coast USA by 1965, reaching epidemic proportions, such that in Washington, DC, there were more psychiatric admissions due to its overdose than for alcohol abuse and schizophrenia combined (Luisada and Reddick, 1975; Petersen and Stillman, 1978), symptoms often being mistaken for schizophrenia. Such psychotomimetic episodes may persist for several weeks following its last use (Luby *et al.*, 1959; Domino *et al.*, 1965), and even after long abstinence, some abusers progressed to schizophrenia (Luisada, 1978). Fortunately, phencyclidine is no longer so widely abused (Moeller *et al.*, 2008). Ketamine, however, has become a common recreational drug, particularly prevalent at rave parties and music venues throughout the world, where it appears as Special K, Kit Kat, Cat Valium, etc. (Nutt *et al.*, 2007; Morris and Wallach, 2014). Presumably in human endophenotypes that encompass the 'Special K' abusers, the 'out-of-body', 'dissociative' experiences and hallucinations, possibly related to facilitation of dopaminergic systems (Wise, 1996), outweigh the drug-induced disabilities and risks of near-death experiences in the 'K-hole'.

Putative mechanisms of action: early considerations

Because dopamine is implicated in the aetiology of schizophrenia and in drug abuse, the interaction of phencyclidine with dopaminergic and other neurotransmitter systems was widely investigated (see Johnson, 1983). Phencyclidine inhibits dopamine uptake and enhances dopamine release (Garey

and Heath, 1976; Smith *et al.*, 1977; Vickroy and Johnson, 1980; 1982), and the behavioural actions of phencyclidine could be reversed by functional antagonists of dopaminergic transmission (Freeman and Bunney, 1984). Similar effects of phencyclidine on noradrenaline and 5-hydroxytryptamine (5-HT) transport were also reported (Taube *et al.*, 1975; Garey and Heath, 1976; Smith *et al.*, 1977). The cholinergic system also provided potential targets for phencyclidine, which has modest affinity for nicotinic and muscarinic receptors as well as for cholinesterases (Kloog *et al.*, 1977; Vincent *et al.*, 1978; Albuquerque *et al.*, 1980). Other proposed mechanisms for the action of phencyclidine included block of potassium channels (Albuquerque *et al.*, 1981; Blaustein and Ickowicz, 1983) and μ -opioid receptors (Vincent *et al.*, 1978). These somewhat confusing multifarious putative mechanisms received two new challenges between 1979 and 1983.

Firstly, the description of specific sub-micromolar binding of tritiated phencyclidine to brain membranes (Vincent *et al.*, 1979; Zukin and Zukin, 1979) gave a new impetus to the field but also a major challenge; binding of phencyclidine was displaced by other arylcyclohexylamines with a rank order similar to their behavioural potencies. However, although more than 40 compounds were examined, including monoamines, acetylcholine, amino acid neurotransmitters, analogues and antagonists including neuroleptic and other centrally active drugs, there was no clear link to the above-mentioned putative mechanisms. The one chemically unrelated compound that displaced phencyclidine binding was the benzomorphan, SKF10 047 or N-allyl-normetazocine (Zukin and Zukin, 1979), a prototypical sigma opiate (Martin *et al.*, 1976). In the following few years, cross displacement in binding studies in rat and human tissue between arylcyclohexylamines, sigma opiates (e.g. SKF10 047 and cyclazocine), dioxolanes (e.g. dexoxadrol) and morphinans (e.g. dextrorphan) suggested a common site of action of these psychotomimetics (Quirion *et al.*, 1981; Zukin and Zukin, 1981; Hampton *et al.*, 1982; Zukin, 1982; Sircar and Zukin, 1983; Murray and Leid, 1984; Zukin *et al.*, 1984).

Secondly, drug discrimination tests for phencyclidine showed that other arylcyclohexylamines, and many of the above benzomorphans, generalized to the subjective phencyclidine cue (Holtzman, 1980). In the following few years, cross generalization within the arylcyclohexylamines, sigma opiates, dioxolanes and morphinans in rats, pigeons and monkeys was well documented (Holtzman, 1980; 1982; Brady and Balster, 1981; Herling *et al.*, 1981; Shannon, 1981; 1982a,b; 1983; Brady *et al.*, 1982a,b; White and Holtzman, 1982). There was a good correlation between displacement of phencyclidine binding and generalization to the phencyclidine cue (Javitt and Zukin, 1991). Importantly, other classes of psychoactive drugs not displacing phencyclidine binding did not generalize to the phencyclidine cue.

In common with arylcyclohexylamines, the drugs that displaced phencyclidine binding and that generalized to the phencyclidine cue had known psychotomimetic properties in man. These included the sigma opiates (e.g. cyclazocine and SKF10.047) (Keats and Telford, 1964; Haertzen, 1970; Martin *et al.*, 1976), dioxolanes (e.g. etoxadrol) (Wilson *et al.*, 1970; Frederickson *et al.*, 1976) and morphinans (e.g. dextrorphan and dextromethorphan) (Isbell and Fraser, 1953; Jasinski, 1979).

The above, and much more, was detailed at an excellent meeting in Montpellier in 1983 organized by Ed Domino, a pioneering leader in all matters related to phencyclidine (Kamenka *et al.*, 1983).

So by the early 1980s, it seemed likely that this phencyclidine binding site mediated the psychotomimetic effects in man of arylcyclohexylamines and the above structurally diverse drugs. The challenge was to find the central synaptic correlate.

Ketamine and spinal reflexes

In 1981, Lodge and Anis were studying the effects on synaptic transmission of short acting i.v. anaesthetics (e.g. methohexitone, alphaxolone/alphadolone and ketamine) on spinal reflexes (Lodge and Anis, 1982; 1984). To their surprise, ketamine (2.5–10 mg·kg⁻¹, i.v.) preferentially reduced polysynaptic, rather than monosynaptic, reflexes but was without effects on synaptic inhibition and dorsal root potentials. By contrast and as expected, barbiturate and steroid anaesthetics reduced both mono- and polysynaptic reflexes by enhancing GABAergic inhibition (Lodge and Anis, 1984). Not known to these authors at the outset, this sensitivity of spinal polysynaptic reflexes to ketamine had been reported some 10 years earlier (Tang and Schroeder, 1973; Chen and Chow, 1975). Subsequently, when ketamine was administered directly into the region of single neurones in the spinal cord, polysynaptic excitations were selectively reduced (Anis *et al.*, 1983). This was a key experiment because it demonstrated that the action of ketamine was close to the soma and dendrites of the postsynaptic cell and most likely at the excitatory synapse itself. It had been recently demonstrated that ketamine did not affect the uptake or release of amino acids (Minchin, 1981), leaving the possibility that it acted on the postsynaptic receptors.

At this time it had just been established that, in the mammalian CNS, glutamate acted on three subtypes of

ionotropic receptor, namely NMDA, quisqualate and kainate receptors (Davies and Watkins, 1979; McLennan and Lodge, 1979; Watkins and Evans, 1981). Because quisqualate also acts at metabotropic glutamate receptors and because AMPA is a selective ionotropic receptor agonist (Krogsgaard-Larsen *et al.*, 1980), the name quisqualate was replaced by AMPA (Watkins and Evans, 1981). Importantly, in relation to the effects of ketamine, studies with competitive antagonists had already demonstrated that postsynaptic NMDA receptors mediated spinal polysynaptic excitation (Biscoe *et al.*, 1977; Lodge *et al.*, 1978; Davies and Watkins, 1979).

The NMDA receptor, ketamine and phencyclidine

To determine whether the action of ketamine was on postsynaptic receptors, a series of experiments were commenced using the microelectrophoresis technique to eject ketamine and some of the above excitatory amino acid agonists into the vicinity of single spinal neurones. Local application of ketamine reduced or abolished responses to N-methyl-DL-aspartate (NMDA) and left responses to quisqualate and kainate largely unchanged (Figure 1; Anis *et al.*, 1983). This exciting discovery was quickly followed by the same experiment with intravenous ketamine (2.5–10 mg·kg⁻¹). In parallel with the reduction of polysynaptic reflexes, responses induced by exogenous activation of the NMDA receptor were reduced within 5 min of injection and recovered slowly over the next 30–120 min. Interestingly, nicotinic responses of Renshaw cells were also reduced but to a lesser extent (Anis *et al.*, 1983). Ketamine is a racemic mixture, the ((S)+) enantiomer being approximately two to four times more potent than the ((R)-) enantiomer as an anaesthetic (Ryder *et al.*, 1978; Franks and Lieb, 1994), as an analgesic (Klepstad *et al.*, 1990), as an inhibitor of phencyclidine binding (Zukin, 1982; Murray and Leid, 1984) and in drug discrimination studies (Brady and Balster, 1982). The (+) rather than the (–) enantiomer is psychotomimetic in man (Vollenweider *et al.*, 1997). As an NMDA receptor antagonist, (+)-ketamine was about 3 times more potent than the (–) enantiomer but only 1.5 times more potent as a nicotinic antagonist (Lodge and Anis, 1982; Lodge *et al.*, 1982).

Was the NMDA receptor antagonism of ketamine also present in 'illegal' phencyclidine? An old veterinary supply of injectable phencyclidine and some phencyclidine powder was obtained from the Metropolitan Police, and checked for purity! Compared with ketamine, phencyclidine proved to be similarly selective as an NMDA receptor antagonist but approximately 10 times more potent and longer lasting following either local or systemic administration (Lodge and Anis, 1982; Anis *et al.*, 1983). Phencyclidine, 0.2–0.5 mg·kg⁻¹ i.v., reduced responses to NMDA for several hours. Interestingly, thienylcyclohexylpiperidine was even more potent than phencyclidine (Lodge *et al.*, 1988c). The enantiomers of both 4- and 5-methyl substituted phencyclidine showed notable stereoselectivity as NMDA receptor antagonists; the (+) enantiomers being 5–10 times more potent and more selective than the (–) enantiomers. By contrast, as antagonists

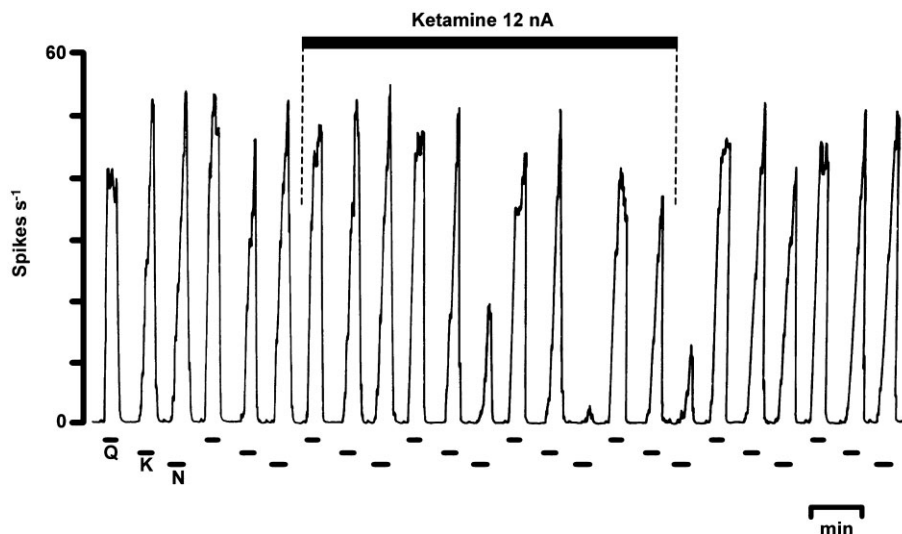


Figure 1

Original record from Anis *et al.* (1983) showing one of the earliest experiments demonstrating the selectivity of ketamine for NMDA. The recording shows the firing rate of a spinal neurone from a pentobarbitone-anaesthetized cat in response to the electrophoretic ejection of quisqualate, kainate and N-methyl-DL-aspartate. The co-ejection of ketamine almost abolishes the latter with only minor effects on responses to the non-NMDA receptor agonists and recovery occurs within 5 min of stopping the ketamine ejection. Other details are in Anis *et al.* (1983).

of acetylcholine on Renshaw cells, there was only minor stereoselectivity (Berry *et al.*, 1983; Lacey and Henderson, 1986).

The NMDA receptor and other psychotomimetics

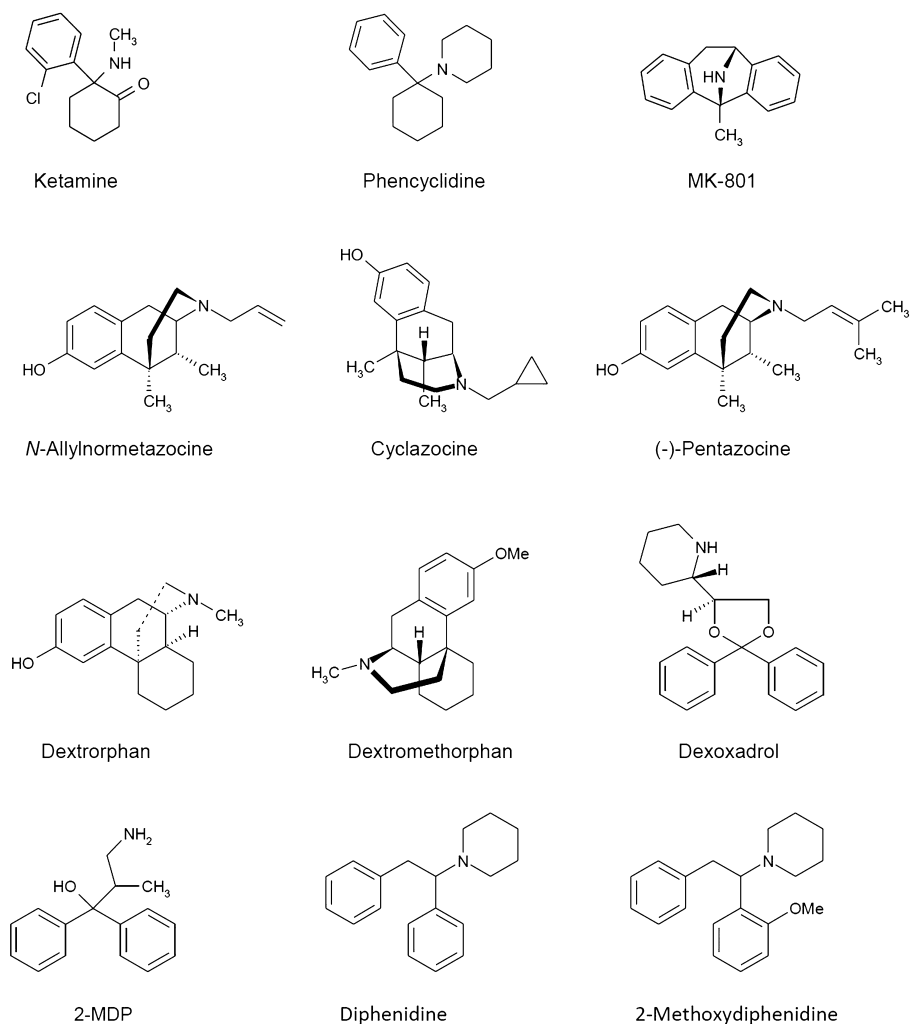
Next, other structurally different psychotomimetics mentioned above (see Figure 2) were examined. The sigma opiates, α -cyclazocine and SKF10 047, proved to be selective antagonists of NMDA, cyclazocine being approximately twice as potent as SKF10 047; the (–) enantiomer of cyclazocine and the (+) enantiomer of SKF10 047 were somewhat more potent than their respective enantiomers (Berry *et al.*, 1984b; Lodge and Anis, 1984; Lodge and Berry, 1984; Lodge *et al.*, 1984). By contrast, two prototypical κ -receptor opiates, ethylketocyclazocine and U50 488H, and the μ -receptor ligands, morphine and naloxone, were without significant or selective effects on responses to NMDA. Furthermore, naloxone did not prevent the effects of cyclazocine or ketamine as NMDA receptor antagonists (Anis *et al.*, 1983; Lodge *et al.*, 1988b). Interestingly at concentrations that reduced responses to NMDA, the (+), but not the (–) enantiomer, of SKF10 047 enhanced responses to acetylcholine on Renshaw cells (Berry *et al.*, 1984a). Etoxadrol and dexoadrol, but not levoadrol, potently blocked responses to NMDA (Berry *et al.*, 1984b) as did dextrorphan and dextromethorphan but not the former's enantiomer, levorphanol (Church *et al.*, 1985).

Three new structurally different classes of phencyclidine-like compounds were published during the course of the above studies. Benz(f)isoquinolines (Mendelsohn *et al.*, 1984), 2-methyl-3,3-diphenyl-3-propanolamine (2-MDP; Tang *et al.*, 1984) and dizocilpine (MK-801) shared binding

and behavioural properties with phencyclidine (Wong *et al.*, 1986; Sircar *et al.*, 1987; Koek *et al.*, 1988). All three showed selective NMDA receptor antagonism: the NMDA receptor antagonist profile within the benz(f)isoquinolines correlated with their phencyclidine-like properties (Berry and Lodge, 1984) as did the threefold greater potency of (–)-, versus (+)-, 2-MDP (Blake *et al.*, 1986). MK-801 was by far the most potent compound as an NMDA receptor antagonist (Davies *et al.*, 1988), as a displacer of phencyclidine binding (Wong *et al.*, 1986) and in phencyclidine discrimination studies (Willets and Balster, 1988). Subsequently, β -cyclazocine was shown to approach MK-801 in potency and stereoselectivity as an NMDA receptor antagonist (Church *et al.*, 1991), but with less selectivity in drug discrimination (Slifer and Balster, 1988) and binding studies (Todd *et al.*, 1990).

Relation to biochemical and behavioural effects of psychotomimetics

The bulk of these early observations was made using the technique of microelectrophoresis to administer both glutamate receptor agonists and potential antagonists into the region of single spinal neurones. This technique, although providing excellent information concerning selectivity between agonists, does not allow accurate assessment of drug concentrations and hence should only be used as a guide to potency. Nevertheless, when comparing activity of compounds with similar physicochemical characteristics and particularly between enantiomers, potency can be reasonably estimated. Figure 3 plots the relative potency of pairs of enantiomers as NMDA receptor antagonists versus their potency in binding assays (Figure 3A) and drug discrimination assays

**Figure 2**

Chemical structure of some channel-blocking NMDA antagonists.

(Figure 3B). It can be seen that there is close agreement between stereoselectivity in these various assays.

Recognizing the limitations of potency values from the above *in vivo* experiments, *in vitro* studies were used to provide alternative potency values and to study the nature of the interaction between psychotomimetics and the NMDA receptor. Using grease-seal preparations of frog and rat spinal cords and of rat cerebro-cortical slices, many of the above compounds were tested against depolarizations induced by agonists of NMDA, AMPA and kainate receptors. Effects *in vitro* were very comparable with those *in vivo*; ketamine, phencyclidine and other related psychotomimetics selectively antagonized depolarization by NMDA but not by quisqualate/AMPA and kainate (Martin and Lodge, 1985; 1988; Davies *et al.*, 1988; Aram *et al.*, 1989). Because agonist concentration–response curves were not shifted in parallel, potencies were assessed as IC_{50} values versus $40 \mu\text{M}$ NMDA. Such *in vitro* potencies correlated closely with those from phencyclidine binding assays (Figure 4A).

The potencies of compounds following *in vivo* administration can more appropriately be compared with potencies in behavioural assays. Figure 4B shows that there is a good correlation between NMDA receptor antagonism and phencyclidine-like discrimination assays. Such a relationship between compounds of diverse structures speaks to the central role of NMDA receptor antagonism in the common behavioural features of these psychotomimetics.

Correlating potency of compounds as NMDA receptor antagonists with dysphoric and psychotomimetic potency in man is more tenuous. Doses producing such effects, for example, $0.05 \text{ mg}\cdot\text{kg}^{-1}$ MK-801 (Erowid Experience Vaults, 2013), $0.1 \text{ mg}\cdot\text{kg}^{-1}$ phencyclidine (Domino and Luby, 2012) and $2 \text{ mg}\cdot\text{kg}^{-1}$ ketamine (White and Holtzman, 1982; White *et al.*, 1982), overlap with NMDA receptor blocking doses in the rat (Lodge *et al.*, 1988a). Similarly, the doses in man of $0.05 \text{ mg}\cdot\text{kg}^{-1}$ cyclazocine (Martin *et al.*, 1965), $0.3 \text{ mg}\cdot\text{kg}^{-1}$ dexoxadrol (Lasagna and Pearson, 1965), $1 \text{ mg}\cdot\text{kg}^{-1}$ dextrorphan (Isbell and Fraser, 1953) and $2 \text{ mg}\cdot\text{kg}^{-1}$ pentazocine

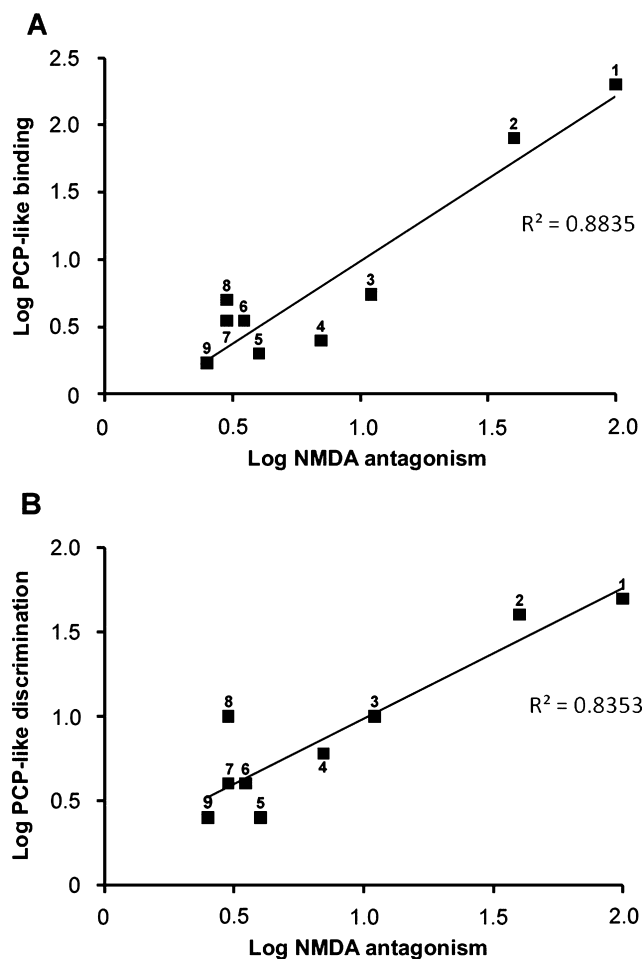


Figure 3

Stereoselective potency between pairs of isomers as NMDA receptor antagonists versus their stereoselectivity in phencyclidine-like binding assays (A) and in drug discrimination assays (B). Data are compiled from references cited in the text, showing potency comparisons between isomers (e.g. Berry *et al.*, 1984a,b; Church *et al.*, 1985; 1991). Each numbered point represents the stereoselectivity of the following pairs of isomers: 1 = (-) versus (+) *s*-cyclazocine: 2 = dexoxadrol versus levoxadrol: 3 = (+) versus (-) 3-methylphencyclidine: 4 = dextrorphan versus levorphanol: 5 = (+) versus (-) SKF10,047: 6 = (-) versus (+) α -cyclazocine: 7 = (+) versus (-) ketamine: 8 = (-) versus (+) 2-MDP: 9 = (-) versus (+) pentazocine β .

(Jasinski *et al.*, 1970) are not dissimilar from those in the rat that antagonize NMDA receptors (Lodge *et al.*, 1988a).

In conclusion, these various potency comparisons strongly suggested that the phencyclidine binding site is linked to the NMDA receptor and that NMDA receptor antagonism underlies the behavioural effects of these structurally diverse compounds in laboratory animals and presumably in man. As the effects in man are reminiscent of schizophrenia (see above), it seemed likely that NMDA receptor dysfunction could be linked to the disease process (Lodge and Berry, 1984).

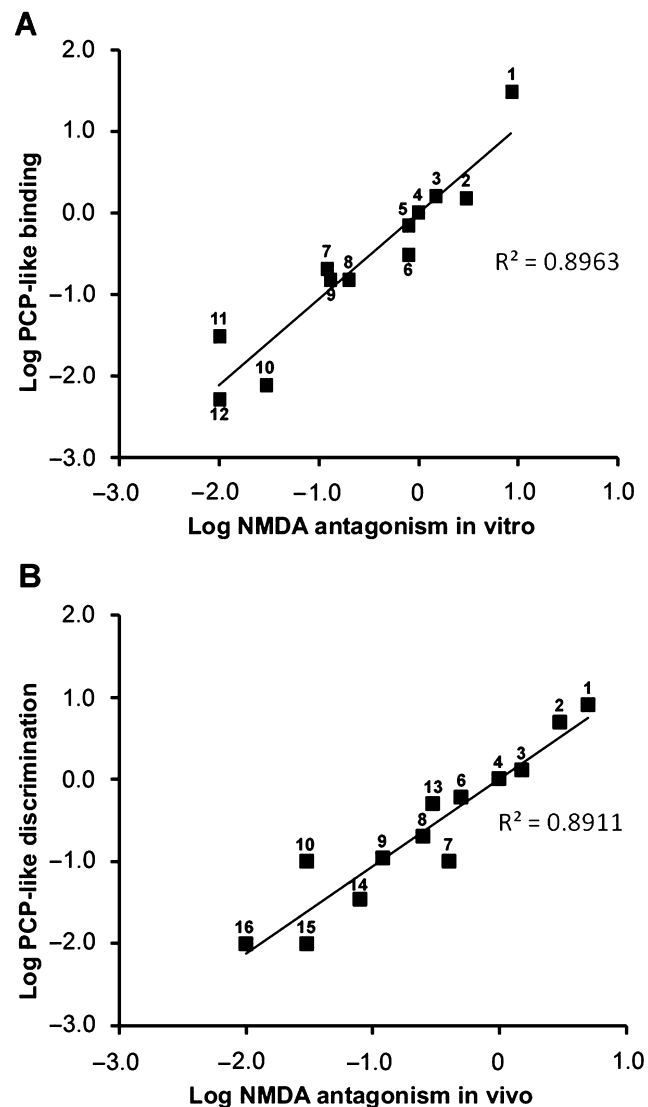


Figure 4

Comparison of potency of structurally diverse compounds, expressed relative to phencyclidine, as NMDA receptor antagonists *in vitro* versus relative potency in binding assays (A) and as NMDA receptor antagonists *in vivo* versus relative potency in drug discrimination assays (B). Data are compiled from references cited in the text; potencies were compared in the same animals and often on the same neurones (e.g. Berry *et al.*, 1984b; Church and Lodge, 1990). Each numbered point represents a single compound: 1 = MK-801: 2 = (-)- β -cyclazocine: 3 = thienylcyclohexylpiperidine: 4 = phencyclidine: 5 = LY154045: 6 = α -cyclazocine: 7 = dextrorphan: 8 = SKF10,047: 9 = ketamine: 10 = (+)-*s*-cyclazocine: 11 = pentazocine: 12 = LY154005: 13 = dexoxadrol: 14 = dextromethorphan: 15 = levorphanol: 16 = levoxadrol: Note that the compounds plotted in (A) are not identical to those in (B).

Mechanism of action

Ion channels coupled to NMDA receptors (Figure 5) are activated by synaptically released L-glutamate, are permeable to calcium (Ascher and Nowak, 1986; MacDermott *et al.*, 1986),

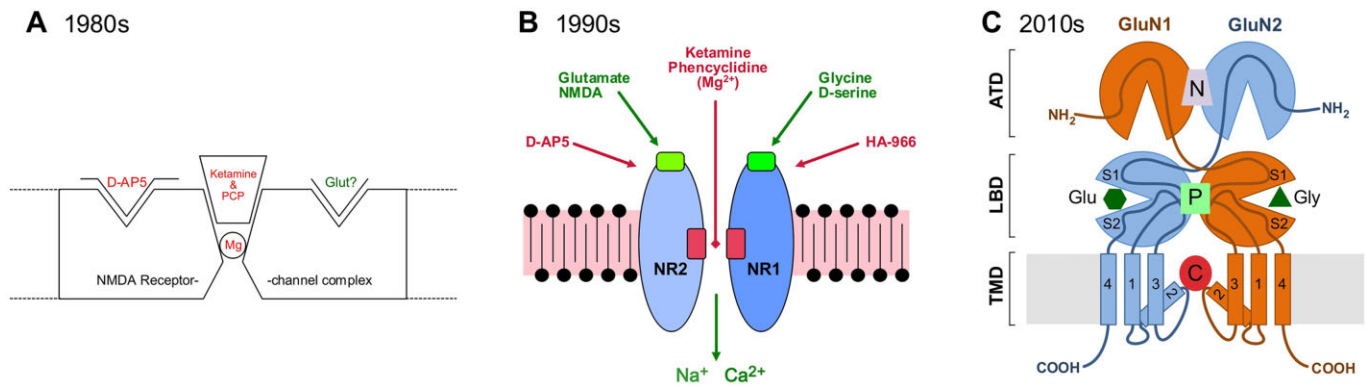


Figure 5

Historical development of crude models of NMDA receptor-channel complexes with putative sites of action of key compounds. (A) and (B) were used by Lodge at conferences during the 1980s and 1990s, respectively, reflecting his knowledge of structure function early in each decade. (C) reflects current ideas showing the relationship of the amino terminal (ATD), ligand binding (LBD) and transmembrane (TMD) domains with putative binding sites for negative allosteric (N; e.g. ifenprodil), positive allosteric (P; e.g. pregnenolone) and channel-blocking (C; e.g. ketamine) compounds, kindly provided by David Jane and www.hellobio.com.

require co-activation with glycine or D-serine (Johnson and Ascher, 1987) and are inhibited by magnesium ions (Evans *et al.*, 1977) in a voltage-dependent manner (Mayer *et al.*, 1984; Nowak *et al.*, 1984). Competitive interaction at the glutamate recognition site of the NMDA receptor depends on the amino and two carboxylic moieties of glutamate (Curtis and Watkins, 1960). No such charge distribution can be assigned to the above psychotomimetic structures (Figure 2). The non-parallel shift in agonist concentration–response curves by higher concentrations of these NMDA receptor antagonists (Lodge and Johnston, 1985; Snell and Johnson, 1985) and the non-additive effects of combinations of these drugs with competitive antagonists (Harrison and Simmonds, 1985; Lodge and Johnston, 1985; Martin and Lodge, 1985) confirmed that these compounds act at a site distinct from the agonist recognition site (Figure 5A). This was quickly followed by electrophysiological demonstrations that the action of ketamine was use- and voltage-dependent (MacDonald *et al.*, 1987) and further confirmed with other compounds (Wong *et al.*, 1986; Davies *et al.*, 1988; Huettner and Bean, 1988). Similarly, binding to the phencyclidine site was shown to be agonist dependent (Fagg, 1987; Foster and Wong, 1987; Loo *et al.*, 1987; Kloog *et al.*, 1988). The above findings are all consistent with open channel block of the NMDA receptor by the arylcyclohexylamines and related compounds (Figure 5B).

Demonstration of its channel-blocking site curtailed search for displacers of phencyclidine binding as antipsychotics but brought the NMDA receptor to the forefront of schizophrenia research. Inasmuch as phencyclidine and ketamine model the disease symptoms, NMDA receptor dysfunction is the cornerstone of the glutamate hypothesis of schizophrenia.

This use and voltage dependency of the open channel block, defined by on and off kinetics, varies considerably between individual compounds within the various compound classes. For example, ketamine and memantine are less use and more voltage dependent than MK-801, with phencyclidine and dextrophan being intermediate (Davies

et al., 1988; MacDonald *et al.*, 1991; Parsons *et al.*, 1993; 1995; Gilling *et al.*, 2009). It should be noted that most pharmacodynamic measures are conducted *in vitro* at temperatures below the normal physiological ranges, and therefore likely to slow the on and off kinetics and hence exaggerate apparent use dependency (Davies *et al.*, 1988).

These pharmacodynamic properties all contribute towards the different profiles of these uncompetitive NMDA receptor antagonists. They do not, however, appear to explain why ketamine is a dissociative anaesthetic and analgesic whereas memantine has found a niche for the neurodegeneration of Alzheimer's disease, as both compounds have similar potencies and pharmacodynamics (Gilling *et al.*, 2009; Emnett *et al.*, 2013). Interestingly, the pharmacokinetics of memantine are closer to those of MK-801 than of ketamine, and it seems likely that this property, along with the diversity of their effects on other voltage- and receptor-coupled channels rather than their pharmacodynamics *per se*, determines their different therapeutic profiles (Gilling *et al.*, 2009).

Subunit selectivity

Further likely influences on the different behavioural profiles of non-competitive NMDA receptor antagonists are potency differences between subtypes of NMDA receptors; excitatory NMDA receptors are tetrameric combinations usually comprising of two GluN1 and two GluN2 subunits, with four possible genes (A–D) coding for the latter (Monaghan *et al.*, 2012). The binding site for uncompetitive NMDA receptor antagonists, and for magnesium, is deep within the channel near the asparagine residues (the N-site) of the pore-lining M2 loops of the GluN1 and GluN2 subunits (Burnashev *et al.*, 1992; Kashiwagi *et al.*, 2002; Kotermanski and Johnson, 2009; see Figure 5C). In earlier studies, MK-801 was suggested to be more potent on NMDA receptors containing the GluN2A and GluN2B subunits (Yamakura *et al.*, 1993; Bresink *et al.*, 1996). More recently, potencies of phencyclidine-like compounds

were shown to vary between the four GluN2 subunits. For example, (+)-ketamine, memantine and phencyclidine were respectively about nine, five and four times less potent on GluN1/GluN2A than on GluN1/GluN2B-D, whereas dextrorphan showed a small preference for GluN2C subunits and (+)-MK-801 was almost equipotent across all four subtypes (Dravid *et al.*, 2007). Interestingly (+)-ketamine was less potent than the racemate on GluN1/GluN2A and GluN1/GluN2B receptors, but about 1.5 times more potent on GluN1/GluN2C and GluN1/GluN2D heteromers. If these data on receptors expressed in oocytes reflect the *in vivo* situation, they suggest the possibility that the behavioural effects of ketamine are more likely to be mediated by GluN2C- or GluN2D-containing receptors rather than GluN2A or GluN2B subunits. In agreement with this is the observation that phencyclidine-induced locomotor activity is significantly less in GluN2D knockout mice than in wild-type mice (Hagino *et al.*, 2010; Yamamoto *et al.*, 2013). Against this are the important roles for GluN2A and GluN2B subunits in synaptic activity in higher centres (Bartlett *et al.*, 2007; Anastasio *et al.*, 2009; McNally *et al.*, 2011; Kocsis, 2012; Hanson *et al.*, 2013). Furthermore, GluN2B antagonists have psychotomimetic properties in man (Preskorn *et al.*, 2008) and generalize to the phencyclidine cue in rats and monkeys (Chaperon *et al.*, 2003; De Vry and Jentsch, 2003; Nicholson *et al.*, 2007).

The early therapeutic promise

Developed as an anaesthetic, it was the analgesic property of ketamine that attracted most early clinical interest. Although its use is limited by emergent psychotomimetic episodes, ketamine is still widely used in acute, neuropathic and palliative care cases (Chizh, 2007; Teasell *et al.*, 2010; Niesters *et al.*, 2013; Persson, 2013). Because it blocks the NMDA receptor-mediated plasticity that results in 'wind-up' of spinal neurones in response to repetitive nociceptive stimuli (Davies and Lodge, 1987), ketamine is useful in reducing the allodynia and hyperalgesia of neuropathic pain.

Coincident with the discovery of ketamine as an NMDA receptor antagonist, the anticonvulsant and neuroprotective properties of competitive NMDA receptor antagonists (Croucher *et al.*, 1982; Simon *et al.*, 1984) indicated other potential therapeutic considerations for non-competitive NMDA receptor antagonists. Indeed, the rank order of potency as neuroprotectants *in vitro*, MK-801 > phencyclidine > ketamine > (±)SKF10 047 = cyclazocine > pentazocine (Olney *et al.*, 1986), closely parallels their potency as NMDA receptor antagonists. Evidence for such a correlation was supported by the *in vivo* demonstration of the effectiveness of ketamine and MK-801 in global ischaemia in both gerbils, rats and cats (Church *et al.*, 1988; Gill *et al.*, 1988; Marcoux *et al.*, 1988; Park *et al.*, 1988a,b). Such neuroprotective potential was however confounded by other data from Olney's group, which showed that, when administered alone at doses somewhat above those required for neuroprotection, MK-801, phencyclidine and ketamine induced neuronal vacuoles and cell death in the rat cerebral cortex (Olney *et al.*, 1989). The extension of such neurotoxic effects of dissociative anaesthetics to large increases in apoptosis in fetal and

neonatal rat brains following repeated dosing (Ikonomidou *et al.*, 1999; Wang *et al.*, 2001) has further questioned the use of ketamine as an analgesic/anaesthetic agent, particularly in paediatric practice (Rappaport *et al.*, 2015).

These considerations, together with sympathomimetic and emergent psychotomimetic effects, have largely prevented these drugs from becoming established as neuroprotective agents (reviewed by Hudetz and Pagel, 2010), although there is still some enthusiasm for their candidature (e.g. Gakuba *et al.*, 2011). Interestingly, the reduced pH of ischaemic and hypoxic tissues would enhance the potency of these channel blockers (Dravid *et al.*, 2007).

Similarly, despite early enthusiasm for uncompetitive NMDA receptor antagonists as potential anticonvulsants (Aram *et al.*, 1989; Chapman and Meldrum, 1989; Tricklebank *et al.*, 1989), their use in epilepsy is largely limited to refractory status epilepticus where ketamine is relatively effective and safe (Gaspard *et al.*, 2013; Zeiler *et al.*, 2014).

Ketamine, phencyclidine, schizophrenia and NMDA receptor antagonism

As stated above, behavioural effects of phencyclidine and ketamine in man replicate to a large degree the positive, negative and cognitive symptoms of schizophrenia and exacerbate symptoms in schizophrenic patients (Javitt and Zukin, 1991; Krystal *et al.*, 1994; Malhotra *et al.*, 1996; 1997; Lahti *et al.*, 2001). So, at face value, the actions of ketamine and phencyclidine could provide insights into the aetiology and treatment of schizophrenia. Indeed, arguments have been made that these drugs can be used to provide animal models of certain aspects of the disease (e.g. Jentsch and Roth, 1999; Cunningham *et al.*, 2006; Buccafusco and Terry, 2009). To think, however, that a single drug can recreate in animals a disease with such complex aetiologies as that of human schizophrenia is clearly naive, but as a way of testing potential therapies against some of the symptoms of schizophrenia, the concept is more plausible (but see Gilmour *et al.*, 2012). Nevertheless, the possibility of modelling particular symptom domains is likely to be a more feasible goal using genetic and environmental perturbations concerned with the aetiology of schizophrenia (Pratt *et al.*, 2012; Lustig *et al.*, 2013; Foussias *et al.*, 2015; Young and Geyer, 2015).

One oft stated concern in relation to implying a purely glutamatergic hypothesis is that many of the above non-competitive NMDA receptor antagonists act on molecular substrates other than NMDA receptors (see above) and that these make important contributions to their schizophrenia-like symptoms (Lodge and Johnson, 1990). However, in addition to the work cited above, many other studies have tried and failed to correlate activity on non-NMDA receptor substrates with behavioural effects. Some useful comparisons follow: Lacey and Henderson in 1986 showed that phencyclidine was 10 times more potent as an NMDA receptor antagonist (IC₅₀ 0.4 µM) compared with effects on noradrenaline, enkephalin and action potentials and had no effect on membrane currents at up to 100 µM; furthermore, only

NMDA receptor antagonism showed stereoselectivity with methyl-phencyclidine (Lacey and Henderson, 1986). In a recent review, the potency of ketamine at sigma, κ , muscarinic, cannabinoid and GABA receptors was shown to be two orders of magnitude less than at NMDA receptors; only as a stimulant of D₂ dopamine receptors was submicromolar equipotency reported (Frohlich and Van Horn, 2014). Tellingly, in contrast to their psychotomimetic effects, ketamine had similar and phencyclidine greater potency relative to MK-801 as activators of D₂ receptors (Seeman *et al.*, 2009)! Potassium channels and monoaminergic systems are a target for phencyclidine and ketamine but require dissociative concentrations in the tens of micromolar (and see Fletcher *et al.*, 1989), except for HCN1 channels (Chen *et al.*, 2009), but the latter appear not to be sensitive to 80 μ M MK-801 (Tokay *et al.*, 2009). Ketamine blocks ganglionic, α 3 β 4 and α 7 nicotinic receptors with an IC₅₀ of about 1.4, 3.1 and 20 μ M respectively (Friederich *et al.*, 2000; Yamakura *et al.*, 2000; Moaddel *et al.*, 2013). Memantine and MK-801 were somewhat less potent as α 3 β 4 channel blockers (Buisson and Bertrand, 1998); rank orders that do not correlate with the above behavioural effects. It is however important to note that nicotine and/or nicotinic agonists may nevertheless help in the treatment of schizophrenia (e.g. Buccafusco and Terry, 2009).

Although it is undoubtedly true that some of the non-NMDA receptor actions contribute to the behavioural profile of each dissociative compound, there are compelling arguments supporting NMDA receptor antagonism as the likely major contributor to the psychotomimesis:

- (1) There is a good correlation between potency of drugs, including between enantiomers, as NMDA receptor antagonists and their psychotomimetic effects in laboratory animals and to a limited extent in man (see above and Figures 3 and 4).
- (2) Competitive NMDA receptor antagonists share some behavioural effects with phencyclidine-like compounds, including drug discrimination cues (Koek *et al.*, 1987; see Willetts *et al.*, 1990 for critical review), but more importantly have psychotomimetic effects in man (Grotta *et al.*, 1995; Herrling, 1997; Davis *et al.*, 2000; Muir, 2006).
- (3) NMDA receptor antibodies have been implicated in the aetiology of some schizophrenias, although causality is unproven (Deakin *et al.*, 2014; Kayser and Dalmau, 2014; for reviews see Coutinho *et al.*, 2014; Pearlman and Najjar, 2014).
- (4) Genetic risk factors for schizophrenia include several genes that impinge directly or indirectly on NMDA receptor function (Harrison and Weinberger, 2005; Gilmour *et al.*, 2012; Labrie *et al.*, 2012a; Weickert *et al.*, 2013; Harrison, 2015).
- (5) Genetic manipulations in mice affecting NMDA receptor activity induce (Belforte *et al.*, 2010; Labrie *et al.*, 2012b; Wei *et al.*, 2014; Born *et al.*, 2015; Takagi *et al.*, 2015) or reduce (Hagino *et al.*, 2010; Yamamoto *et al.*, 2013) aspects of a schizophrenia-like phenotype.
- (6) Some clinical trials with drugs designed to up-regulate NMDA receptor function have had positive outcomes (reviewed in Coyle, 2012). Other manipulations of glutamatergic transmission show promise in animal models and are being assessed therapeutically (reviewed in Javitt, 2012 and Dunlop and Brandon, 2015).
- (7) Agonists of group II metabotropic glutamate receptors reduce hyperlocomotion induced by NMDA receptor antagonists in rats (Moghaddam and Adams, 1998; Cartmell *et al.*, 1999), ketamine-induced cognitive deficits in man (Krystal *et al.*, 2005), and positive and negative symptoms of schizophrenia in man (Patil *et al.*, 2007). Subsequent trials have however failed to confirm efficacy in schizophrenics; explanations of this discrepancy will be of value for future therapies.

Implications for schizophrenia

So what can studies with NMDA receptor antagonism by ketamine and phencyclidine teach us about schizophrenia and potential therapeutic strategies? Other than the overt behavioural effects, are there other features of the disease spectrum that are replicated by the non-competitive NMDA receptor antagonists mentioned above? Two such features to be considered are changes in dopaminergic transmission and the neuropathology of schizophrenia.

Thus, one key question is the compatibility of the glutamate and dopamine hypotheses. The main tenets of the dopamine hypothesis of schizophrenia are that dopamine, particularly D₂, receptor antagonists are antipsychotic and that amphetamine by increasing dopamine release can mimic aspects of the disease. Disruptions in dopaminergic activity especially in prefrontal cortical and striatal areas are a hallmark of schizophrenia and aspects of these complex changes are replicated by acute and chronic ketamine or phencyclidine dosing (Javitt and Zukin, 1991; Jentsch and Roth, 1999; Javitt, 2007; Coyle, 2012; Moghaddam and Krystal, 2012). In particular, systemic phencyclidine and SKF10 047 indirectly excite midbrain dopaminergic neurones (Freeman and Bunney, 1984), acute ketamine treatment increases dopamine release in prefrontal cortex rather than striatum (Verma and Moghaddam, 1996) whereas chronic treatment with phencyclidine increases striatal and reduces prefrontal dopamine (Jentsch *et al.*, 1997; 1998), more consistent with the hypofrontality of schizophrenia. The complex neurotransmitter feedback loops between prefrontal cortex, hippocampus, ventral tegmentum and striatum suggest that, for example, reduced glutamatergic activity in the hippocampus can result in the above dopaminergic pattern of schizophrenia (Goto and Grace, 2007; Howes *et al.*, 2015) and the reduced glutamate activity in the frontal areas of this disease (Marsman *et al.*, 2013).

The second key question, the ability of dissociative anaesthetics to mimic aspects of the disease pathology, is covered in the next section.

Neuropathology underlying cognitive dysfunction

The potential of NMDA receptor antagonists to disrupt normal synaptic development of neuronal circuitry follows from the seminal observation by Collingridge *et al.* (1983).

Using the newly discovered competitive NMDA receptor antagonist, D-2-amino-5-phosphonovalerate (D-APV; D-AP5; Davies *et al.*, 1981), the requirement for NMDA receptor activation in plasticity was established in 1983 with the classical demonstration of its role in long-term potentiation (LTP; Collingridge *et al.*, 1983). Coincidentally in the same year, without knowledge of their NMDA receptor antagonist properties, phencyclidine and ketamine were shown to reduce LTP (Stringer and Guyenet, 1983). NMDA receptors not only mediate LTP but also long-term depression (reviewed in Collingridge *et al.*, 2013). Early observations, that local NMDA receptor antagonism disrupted the normal pattern of synaptic connections in the visual cortex *in vivo* (Cline *et al.*, 1987; Kleinschmidt *et al.*, 1987), indicated the importance of these receptors in neurodevelopment. This trophic role of NMDA receptors, likely mediated by the entry of calcium through the NMDA receptor channel (Collingridge and Singer, 1990; Cline and Tsien, 1991) during development, is potentially a key aetiological factor predisposing to schizophrenia. For example, during critical phases of development, exposure to ketamine, phencyclidine or other disruptors of NMDA receptor function is likely to result in dysregulation of synapse formation and brain circuitry (see below), characteristics of schizophrenic brain (Harrison, 1999; Snyder and Gao, 2013).

In contrast to established neuroprotective properties of NMDA receptor antagonists (see above), severe acute neuropathology occurs with high doses of dissociative anaesthetics. Thus, Olney and colleagues showed that acute high doses of ketamine, phencyclidine and MK-801 led to neuronal cytotoxicity including that of cortical pyramidal cells and inhibitory interneurons in adult rats, drawing parallels at that time with the neuropathology of schizophrenia (Olney *et al.*, 1989; Olney and Farber, 1995). Similar lesions were also reported following prolonged administration of competitive NMDA receptor antagonists (Ellison, 1994; 1995).

Chronic administration of lower doses during the perinatal period and into adulthood results in more subtle effects on neurogenesis, cell survival, migration, proliferation and synaptogenesis (Ikonomidou *et al.*, 1999; Wang *et al.*, 2001; Keilhoff *et al.*, 2004; Maeda *et al.*, 2007; Namba *et al.*, 2011; Toriumi *et al.*, 2012; Sabbagh *et al.*, 2013; Musaelyan *et al.*, 2014; Uchida *et al.*, 2014). Such changes are more representative of schizophrenic brains, which have reduced cortical neuropil, disturbed neuronal migration and circuitry but lack severe degenerative pathology (Bogerts, 1997; Jones, 1997; Weinberger, 1997; Harrison, 1999; Catts *et al.*, 2013). Such chronic exposure to dissociative anaesthetics also leads to behavioural correlates of the disease (Jentsch and Roth, 1999; Wang *et al.*, 2001; Egerton *et al.*, 2008; Rodefer *et al.*, 2008; Goetghebuer and Dias, 2009; Amitai and Markou, 2010; Neill *et al.*, 2010).

Importantly, in addition to these similarities to schizophrenia, chronic administration of ketamine and phencyclidine also disrupted metabolic connectivities (Cochran *et al.*, 2003; Dawson *et al.*, 2013) and desynchronized electrical activity between prefrontal cortex and thalamic (Troiano-Rodriguez *et al.*, 2014) and hippocampal (Moran *et al.*, 2015) regions.

There is however compelling evidence in schizophrenia for specific disruption of GABAergic function, which led to

the modern GABAergic hypothesis of schizophrenia; down-regulation of fast-spiking parvalbumin (PV)-containing and GAD67-positive GABAergic neuronal networks is proposed as a major contributor to schizophrenia, potentially explaining aspects of glutamatergic and dopaminergic dysregulation (Olney and Farber, 1997; Lewis and Gonzalez-Burgos, 2006; Nakazawa *et al.*, 2012; Lewis, 2014). Synaptic excitation of PV-containing GABAergic interneurons, chandelier and basket cells, depends largely on NMDA receptor activation (Jones and Bühl, 1993; Grunze *et al.*, 1996; Goldberg *et al.*, 2003). This may underlie the intriguing parallels between schizophrenia and dissociative anaesthetics (see Table 1).

The similarities in Table 1 suggest that exposure to dissociative anaesthetics during early development and adolescence could contribute to the PV cell damage and lead to schizophrenic symptoms later in life. This, however, is likely to explain a very small minority of cases. Rather than dissociative anaesthetics, other influences, such as oxidative stress, viral infections along with genetic predisposition, are likely causes of GABAergic dysfunction in the majority of schizophrenics (reviewed in Harrison *et al.*, 2012; Nakazawa *et al.*, 2012; Powell *et al.*, 2012; Lewis, 2014).

Thus, to conclude this section, ketamine and phencyclidine offer two ways of mimicking aspects of schizophrenia pathology. Firstly, chronic doses during development and in adulthood result in dysregulation of the synaptic connectivity that mirrors schizophrenic pathology and behaviour. Secondly, in more mature brains, acute and sub-acute doses of ketamine or phencyclidine, by blocking the excitatory drive of PV-GABAergic interneurons and thus disinhibiting hippocampal and cortical networks, results in psychotomimetic activity. Such behaviours will be more marked if development of GABAergic pathways has been compromised during development.

Modern-day recreational use of ketamine and related drugs

Because of its lower potency and shorter duration of action, 'Special K' has less severe psychiatric issues than 'Angel Dust', but can lead to death in combination with other illicit drugs and/or alcohol and fatal accidents due to disturbed perceptions. The difference between the two drugs has long been recognized by UK and US drug authorities, which classified phencyclidine and ketamine as Class A/Schedule II and Class C/Schedule III drugs respectively. The use of ketamine in the UK alone is likely to be in excess of 100 000 each year (Morgan and Curran, 2012). Ketamine is in the top 6 drugs of abuse for causing social and physical harm (Nutt *et al.*, 2007), being implicated in tens of deaths each year; the major risk of physical harm is a result of ketamine's dissociative and analgesic properties (see Morgan and Curran, 2012; Office of National Statistics, 2013). In 2014, ketamine was upgraded to Class B in the UK. In addition to psychiatric effects, continued abuse of ketamine can lead to systemic toxicities, including chronic and painful urinary cystitis (Shahani *et al.*, 2007; Chu *et al.*, 2008; Morgan and Curran, 2012). In attempts to avoid such pathology and also legislative strictures, numerous analogues of ketamine and phencyclidine have been

made available on the street (Roth *et al.*, 2013; Morris and Wallach, 2014). One of the latest is diphenidine, a diarylethylamine, an old compound (Christiaen, 1924) that disappeared from the scientific literature until patented for neurotoxic shock (Gray and Cheng, 1989). It subsequently reappeared, along with some of its derivatives, as a recreational drug in 2013, coincident with the rescheduling of ketamine! The non-medical uses of this and other NMDA receptor antagonists have been thoroughly reviewed recently (Morris and Wallach, 2014). As with ketamine, diphenidine and its 2-methoxy derivative inhibit NMDA receptor-mediated synaptic events in the CNS (Figure 6). The slow onset of diphenidine (Figure 6) approaches the kinetics of MK-801 in slice preparations (Wong *et al.*, 1986; Davies *et al.*, 1988) and may reflect a greater use dependency or possibly trapping of the antagonist in the NMDA receptor channel compared with ketamine.

It appears that clandestine synthetic medicinal chemists will always be able to outwit legislation based on known structures because the possibilities of finding novel compounds to modulate NMDA receptor activity are near to infinite! But the consequences of their subsequent misuse can be fatal (Elliott *et al.*, 2015).

Future therapeutic potential of ketamine and related drugs

In addition to the previously considered therapeutic uses of non-competitive NMDA receptor antagonists, the recent exciting discovery of antidepressant-like effects of ketamine in man (Berman *et al.*, 2000; Zarate *et al.*, 2006) has re-awakened interest in these drugs. The background to this discovery is worthy of consideration.

Largely, because depression is treated by drugs that enhance monoaminergic neurotransmission albeit with delayed onset, depression is considered mainly a monoaminergic disorder (Schildkraut and Kety, 1967; Millan, 2004). However, there is a long history suggesting a potential glutamatergic role in the aetiology and treatment of depression (see Alt *et al.*, 2006), including the observation that some antidepressants are NMDA receptor antagonists (Evans and Watkins, 1981; Reynolds and Miller, 1988; Sernagor *et al.*, 1989; Sills and Loo, 1989; Watanabe *et al.*, 1993). Two major observations from Skolnick's laboratory, however, clearly demonstrated the link between antidepressant activity and glutamate. Firstly, 25 years ago, they made the crucial observation that competitive channel-blocking and glycine-site NMDA receptor antagonists were all effective in animal models of depression (Trullas and Skolnick, 1990). Secondly, positive allosteric potentiators of AMPA receptors were similarly effective in such animal models (Li *et al.*, 2001; 2003). A third later observation that antagonists of glutamatergic autoreceptors have antidepressant potential (Chaki *et al.*, 2004; Yoshimizu *et al.*, 2006) confirmed the importance of glutamatergic systems to mood disturbances.

The innovative translation to man using ketamine (Berman *et al.*, 2000) and the subsequent double-blind confirmation in treatment-resistant patients (Zarate *et al.*, 2006) gave a massive impetus to the search for glutamatergic, rather

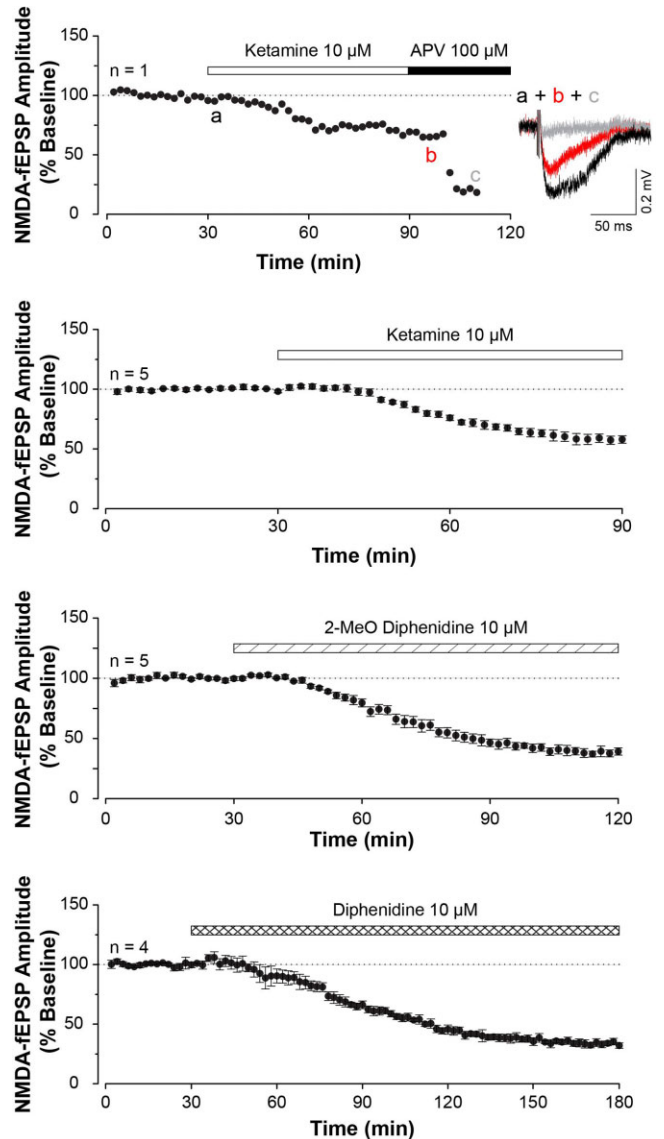


Figure 6

Newer diarylethylamine street drugs, like ketamine, reduce NMDA receptor-mediated synaptic excitation. The graphs plot the amplitude of field EPSPs in the CA1 region of a hippocampal slice following stimulation of the Schaffer collateral input. Slices had been treated with AMPA and GABA receptor antagonists to isolate the NMDA receptor component of the synaptic event. The top graph is a single experiment showing the effect of ketamine 10 µM and D-AP5 100 µM, demonstrating that these were NMDA receptor-mediated responses. The inset shows the raw traces. The subsequent three graphs show pooled data from four or five experiments illustrating NMDA receptor antagonism by ketamine, 2-methoxy-diphenidine and diphenidine. Note the slower time course to reach near plateau reduction of the EPSP. These data suggest that diphenidine is somewhat more potent than 2-methoxydiphenidine, which in turn is more potent than ketamine.

than monoaminergic, antidepressants. An interesting feature of these new antidepressant therapies is the rapid onset of the change in mood both in animal models and in man. This feature is particularly valuable for suicidal patients. Unlike

the weeks of therapy required for 5-HT (serotonin) and noradrenaline uptake inhibitors, mood is elevated rapidly after single injections of ketamine which provide relief for days and even weeks (see Aan Het Rot *et al.*, 2012; Caddy *et al.*, 2014; Duman, 2014). Although the antidepressant activity of ketamine is not doubted, mild psychotomimetic effects may alert the patients to the administration of drug rather than placebo. The low doses, typically 0.5 mg·kg⁻¹, providing plasma levels of approximately 0.5 μM and presumably similar brain levels, are likely to show preference for GluN2B-, C- and D-, rather than GluN2A- containing NMDA receptors, but with only partial antagonism (Dravid *et al.*, 2007). In addition to NMDA receptor-channel blockers including magnesium (see Serefko *et al.*, 2013; Zarate *et al.*, 2013), glycine-site (Danysz and Parsons, 1998), GluN2B allosteric and gaseous (Preskorn *et al.*, 2008; Lima-Ojeda *et al.*, 2013; Miller *et al.*, 2014; Nagele *et al.*, 2014) NMDA receptor antagonists have shown rapid antidepressant potential in man and/or animal models. Similarly AMPA receptor potentiators (Alt *et al.*, 2006) and group II metabotropic glutamate receptor antagonists (Chaki *et al.*, 2004; Dwyer *et al.*, 2012) have rapid antidepressant effects.

Although these diverse drugs have different modes of action, a functional increase in glutamatergic neurotransmission is hypothesized as the linker. In the case of ketamine and other NMDA receptor antagonists, this is most likely via inhibition of GABAergic pathways (see above). The resulting surge in excitatory transmission is presumably the trigger for changes to long-term plasticity that underlies the depressed mood. Antagonism of AMPA receptors prevents the rapid antidepressant action of ketamine (see Koike and Chaki, 2014). Brief periods of increased excitatory transmission are known to de-potentiate and/or de-depress established plasticity (Collingridge *et al.*, 2010). Brain-derived neurotrophic factor (BDNF), tropomyosin-related kinase B, mammalian target of rapamycin (mTOR), PKB, glycogen synthase kinase-3 (GSK-3) and synapse remodelling are well documented mediators of such processes (Duman *et al.*, 2012; Duman, 2014) and provide further therapeutic targets. However, the ubiquitous nature of these latter targets raises concerns of deleterious on-target secondary actions, including non-neuronal tissues.

Whether ketamine itself, with its potential psychotomimetic and other unwanted side effects, could become an accepted therapy is still under discussion. It is interesting to speculate why other similarly acting NMDA receptor antagonists such as memantine, phencyclidine and MK-801 do not show such robust antidepressant effects. Presumably some combination of NMDA subunit selectivity, pharmacodynamics and pharmacokinetics gives ketamine its advantage. The challenge is now to find and replicate that advantageous combination and to avoid ketamine's unwanted side effects.

Conclusion

The history of ketamine and phencyclidine as therapeutics has been a roller coaster of optimism and pessimism. Ketamine's accepted positions as an adjunct in anaesthesia and in pain management and as a dangerous street drug illustrate this dichotomy. The value of ketamine in providing insights

into the role of NMDA receptors in brain function, into the understanding of schizophrenia and potentially into new antidepressant drugs has led to the present swell of interest in this enigmatic molecule. Like the past, the future will no doubt contain surprises.

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Author contributions

D. L. and M. S. M. wrote the first draft and collated the bibliography. D. L. and M. S. M. revised the manuscript. M. S. M. contributed the data in Figure 4.

Conflict of interest

D. L. and M. S. M. have no conflicts of interest to disclose.

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