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ORIGINAL INVESTIGATION

A comparison of the effects of ketamine and phencyclidine with other antagonists of the NMDA receptor in rodent assays of attention and working memory

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Abstract
Rationale *N*-methyl-D-Aspartate receptor (NMDAR) antagonists such as ketamine induce cognitive symptoms in man similar to those of schizophrenia and therefore might be useful as models of the disease in animals. However, it is unclear which NMDAR antagonist(s) offer the best means to produce cognitive deficits in attention and working memory and to what extent those deficits can be measured selectively in rats.
Objectives The present study systematically compared the effects of eight different NMDAR antagonists—MK-801, phencyclidine, (*S*)-(+)-ketamine, memantine, SDZ-220,581, Ro 25-6981, CP 101-606 and NVP-AAM077—in rats using standard tests of visual attention, the five-choice serial reaction time task (5CSRT), and working memory, the delayed matching to position task (DMTP).
Results Drug-induced responses varied qualitatively and quantitatively in both a compound- and a task-dependent manner. Effects were generally confounded by concomitant motor and motivational disruption, although individual doses of phencyclidine for example appeared to impair selectively cognitive functions. Interestingly, GluN2B selective antagonists were unique in their effects; inducing potential performance benefit in the 5CSRT.
Conclusions Overall, the opportunity to induce a selective cognitive deficit in attention (5CSRT) or working memory (DMTP) in the rat is limited by both the NMDAR antagonist and the dose range used. The importance of a preclinical focus on ketamine, which is used more frequently in clinical settings, is limited by the extent to which cognitive effects can be both detected and quantified using this exposure regimen within these two operant assays.

Keywords NMDA receptor antagonist · GluN2A · GluN2B · Schizophrenia · Psychosis · Working memory · Sustained attention

Abbreviations

NMDAR	*N*-methyl-D-aspartate receptor
DMTP	Delayed matching to position
5CSRT	Five-choice serial reaction time task

Introduction

Schizophrenia is a psychiatric disorder characterised by a diverse set of symptoms encompassing psychotic, affective and cognitive disturbances. Of these, cognitive symptoms are undoubtedly the most enduring feature; thus, understanding the neurobiology of these deficits has become a key research focus in recent years. Initiatives such as MATRICS and CNTRICS have led to greater awareness of the broad and complex nature of cognitive decline observed in schizophrenia, evidently spanning domains of attention, learning, memory and cognitive flexibility (Barch et al. 2009a, b; Carter et al. 2008; Green et al. 2008; Kern et al. 2008; Nuechterlein et al. 2008). Cognitive deficits are not simply epiphenomena; they have been reported to be

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present at first episode and thus likely represent a core trait of the schizophrenic syndrome (Hill et al. 2002, 2004a, b, 2008). Currently available antipsychotic medications do not ameliorate cognitive deficits to any clinically impactful degree (for review, see Miyamoto et al. 2005), and unmet medical need remains substantial. Identification of novel treatments for cognitive symptoms is as critically dependent as ever on the validation of animal models that exhibit equivalent or analogous cognitive deficits to those observed in schizophrenic patients themselves. In this regard, *N*-methyl-D-aspartate (NMDA) receptor antagonist administration has gained acceptance as a potential means to model both aspects of psychosis and cognitive symptoms in animals and humans. For example, NMDA receptor (NMDAR) antagonist-induced behaviours such as hyperlocomotion or disruption of prepulse inhibition of the acoustic startle response can be reversed by currently available antipsychotics, leading to the widespread use of these effects as screening tools in drug discovery efforts. However, a general expectation that such pharmacological deficit models will sustain predictive validity not only for 'classical' antipsychotic efficacy but also for the detection of pro-cognitive agents may be overly simplistic. The NMDA receptor is a complex heterogeneous structure comprising GluN1, GluN2 and GluN3 (NR1, NR2, NR3) subunits, with GluN2 itself being represented by four different genes, GluN2A, GluN2B, GluN2C and GluN2D (Alexander et al. 2008). At present, it is not possible to delineate straightforward relationships between neurotransmission involving NMDA receptor subtypes in specific brain regions with defined behavioural processes, cognitive or otherwise. By extension, a precise description of how systemic administration of a NMDAR antagonist may result in cognitive disturbance is also lacking. To complicate matters further, a range of NMDAR antagonists with varying degrees of subtype selectivity and mechanism of action are available: (1) phencyclidine (PCP), MK-801 and ketamine are prototypical, non-competitive open-channel blockers devoid of subunit selectivity (Lodge and Johnson 1990); (2) memantine acts similarly but with lower affinity (Johnson and Kotermanski 2006), although more recently there has been some suggestion that there is some selectivity for N2C and N2D over N2A/B (Kotermanski and Johnson 2009); (3) the non-competitive antagonists CP 101-606 and Ro 25-6981 have substantial selectivity for GluN2B-containing receptors (Chenard et al. 1995; Menniti et al. 1997; Fischer et al. 1997); and (4) NVP-AAM007 which has some, albeit limited, selectivity for GluN2A-containing receptors (Auberson et al. 2002; Frizelle et al. 2006).

The potential complexity of NMDAR antagonist modelling of schizophrenic symptomatology is readily apparent, yet all too easy to discount. Historically, NMDAR antagonists such as PCP, MK-801 and ketamine have been used interchangeably preclinically on the assumption that they produce essentially analogous effects on a variety of cognitive and non-cognitive behaviours. However, Gilmour et al. (2009) have shown that NMDAR antagonists can have substantially different effects on motor and motivational measures, as indicated by qualitative changes in instrumental responding to variable interval schedules. Furthermore, whilst NMDA receptor-dependent mechanisms are requisite in the acquisition of, for example, a simple conditional discrimination or the consolidation of extinction, their role in working memory and reversal learning tasks appears to be less critical and potentially specific to the paradigm and NMDAR antagonist used (Dix et al. 2010). It is therefore clearly misleading to generalise across NMDAR antagonists with respect to their preclinical cognitive profile.

To this end, the aim of these studies was to extend the systematic profiling of the range of NMDAR antagonists described above into two further tests considered to assay different cognitive domains disturbed in schizophrenics: the five-choice serial reaction time task or 5CSRT (Robbins 2002) and the delayed matching to position task or DMTP (Barch et al. 2009a, b). The 5CSRT is considered to assay the construct of sustained attention in a manner analogous to the human continuous performance task-identical pairs used within MATRICS (Young et al. 2009). DMTP is a test of visuospatial working memory used as part of CNTRICS in humans (Barch et al. 2009a, b), with an effectively equivalent paradigm also available for use in rodents (Dunnett 1985). Both 5CSRT and DMTP represent validated 'workhorse' assays forming a core part of cognitive profiling batteries in many preclinical drug discovery labs. As such, it is imperative for the evolution of translational research in schizophrenia to understand more completely how proposed pharmacological deficit models express in these contexts.

Methods

Subjects

All experiments were conducted in accordance with the regulations laid down in the UK Animals (Scientific Procedures) Act, 1986. Male Lister Hooded rats (DMTP: Harlan, Bicester UK; 5CSRTT: Charles River, Margate, UK) were housed in groups of four in plastic cages containing sawdust bedding and environmental enrichment (Jolly Balls™, Lillico). Rats were maintained on a 0700–1900-hour light/dark cycle under conditions of controlled temperature and humidity. All experiments were conducted in the light phase between 0800 and 1300 hours. Animals were maintained on a food-restricted diet (with ad libitum

water access) which allowed for normal growth; animals weighed 400–500 g at the time of testing.

Apparatus

Five-choice serial reaction time task

Standard five-choice chambers housed in sound- and light-attenuating chambers were used (Med-associates, Vermont, CT, USA). Each chamber contained a house light and a recessed magazine where food pellets (Noyes, 45 mg, Formula P) were delivered from an automatic pellet dispenser. There were five recessed apertures (each 2.5×2.5×2.5 cm in size at a height of 2.5 cm from the grid floor) on a curved panel on the wall facing the food magazine. Stimulus lights were found in each aperture. Entrances to all apertures, including the magazine, were monitored with the use of photocells placed across each entrance. Experimental sessions were controlled and data were recorded using in-house programmes written with MedPC-IV software (Med-Associates) and prepared for analysis using two excel macros designed for the experiment.

Delayed matching to position task

Standard operant chambers housed in sound- and light-attenuating chambers were used (Med-associates). Each chamber contained a house light and two retractable levers, each of which had a stimulus light positioned above it. The levers were located either side of a recessed magazine where food pellets (Noyes, 45 mg, Formula P) were delivered from an automatic pellet dispenser. Control of experimental sessions, data collection and preparation were as for the 5CSRTT studies.

Experimental design

Five-choice serial reaction time task

Rats (n=48) were trained to respond for food reward by making a head entry to a visual stimulus presented in one of five spatial locations. House light onset signalled the start of a session. The first trial of a session began with presentation of a visual stimulus in one of the five apertures. Response to this cue, or response during the period following cue offset (the limited hold period), led to the delivery of a food pellet reward and was recorded as a correct response. Additional responses in the correct location had no behavioural consequence, but were recorded as perseverative responses. A response in another location during the cue presentation or the limited hold period was recorded as an incorrect response. Failure to respond in any location before the end of the limited hold period was recorded as an omission. Both incorrect responses and omissions were punished with a 5-s timeout period. A response to collect the food pellet reward in the case of a correct response, or end of a timeout in the case of an incorrect response or omission, initiated the next trial. Each trial began with a 5-s intertrial interval (ITI) before another visual cue was presented. Responses in any location during this ITI were recorded as premature responses. Premature responses were punished with a 5-s timeout and resetting of the ITI. Test sessions terminated after either presentation of 100 cues or 30 min had elapsed. During a session, a balanced number of cues appeared randomly in each location.

For the first training session, the visual stimulus duration and the limited hold period were both set at 1 min. These variables were altered on subsequent sessions according to individual animal performance until each rat was responding at a criterion level of >80% accuracy and <20% omissions with a stimulus duration of 0.5 s and a limited hold period of 5 s. Approximately 50 sessions were required for animals to attain this criterion. Once stable responding had been achieved, animals were tested weekly (i.e. no more than once per week) using a stimulus duration of 0.25 s. The stimulus duration was shortened on test day so that animals would display a lower baseline accuracy (i.e. 70–80%), which also allowed for potential increases in accuracy to be measurable (Day et al. 2007). Each test was preceded by three daily training sessions; only animals that met baseline criteria for inclusion (>80% accuracy, <20% omissions on training stimuli) were tested.

Delayed matching to position task

Following acquisition of basic lever press response behaviour, animals (n=64) underwent DMTP training. House light onset signalled the start of a session. Each trial began with a sample phase where extension of one lever into the chamber was signalled by the stimulus light located above it. Sample lever extension occurred on a pseudo-random basis. There was no time limit on sample phase response. Pressing the sample lever resulted in retraction of the lever, switching off the stimulus light and initiating a delay period (pseudo-randomly chosen from periods of 1, 2, 4, 8 or 16 s during training or 1, 4, 12, 24 or 32 s during test). Following conclusion of the delay, animals were given 10 s to make a head entry to begin the choice phase. In practice, this resulted in animals making consecutive head entries until the end of the delay period and was included to reduce (but likely not eliminate) mediating strategies that have been reported with this assay (Chudasama and Muir 1997). Failure to make a head entry at this point was punished with a 5-s timeout period. The choice phase was a 10-s-long period where both levers were extended into the

chamber with both stimulus lights illuminated above them. A correct response consisted of an animal pressing the same lever presented during the sample phase. Correct responding led to the retraction of both levers and the delivery of a single food pellet reward. An incorrect response (i.e. pressing the opposite lever to that presented during the sample phase) retracted both levers and resulted in a 5-s timeout period. If the animal failed to respond within the choice phase, an omission was recorded, both levers retracted and a timeout period administered. All choice phase response options were followed by a 5-s ITI, after which the next trial began. Test sessions terminated after either 75 trials (15 presentations each of delay set) were completed or 45 min had elapsed.

During initial DMTP training, no delay period was used in the protocol and animals were reinforced with food pellet rewards following completion of both sample and choice components. When performance on this task variant was stable, food reward was subsequently restricted only to correct choices. Finally, delay periods were gradually introduced until animals were performing at criterion (>70% accuracy and <10% omissions). Approximately 40 sessions were required for animals to attain this criterion. Once stable responding had been achieved, animals were tested weekly (i.e. no more than once per week). Each test was preceded by three daily training sessions.

Measures

Five-choice serial reaction time task

Accuracy of performance was measured as the number of correct responses divided by the sum of correct and incorrect responses [(number of correct responses/total number of correct + incorrect responses) × 100]. The percentage of omissions was also calculated [(number of omissions/total number of trials presented) × 100)]. Two measures of inhibitory control were also recorded. Premature responses were defined as the number of responses made in any aperture during the ITI. Perseverative responses were defined as repeated responses in the same aperture following a correct response. Response speed was assessed by measuring two different latencies. The first was the latency to respond correctly, defined as the time between the onset of the visual stimulus and nose poke of the correct aperture. The second measure was magazine latency, defined as the time between nose poke of the correct aperture and nose poke of the food magazine.

Five-choice serial reaction time task

Accuracy of performance was measured as the number of correct responses divided by the sum of correct and incorrect responses [(number of correct responses/total number of correct + incorrect responses) × 100]. The percentage of omissions was also calculated [(number of omissions/total number of trials presented) × 100]. Each of these parameters was calculated per session and per delay. Head entries were also recorded to potentially provide another measure of motor/motivational capacity. Response speed was assessed by measuring two different latencies: the latency to respond during the sample phase and the latency to respond on either correct or incorrect lever during the choice phase.

Statistical analysis

All statistics were calculated using Statistica v. 7 (Statsoft, UK). A general linear model, a priori approach was used for all analyses of variance (ANOVAs) conducted for the measured parameters. Statistical significance was set at $p<0.05$, although there were some instances where planned comparisons have been conducted following trend-level main and interaction effects ($0.05<p<0.1$). Pretest and test day datasets were analysed in a similar manner for both assays.

Five-choice serial reaction time task

Datasets were subject to between-subjects ANOVA with the factor of (assigned) treatment. The dependent variables analysed were accuracy, per cent omissions, head entries, premature responses, perseverative responses, correct response latencies and magazine latencies. For inclusion in the statistical analyses of accuracy and latency variables, animals were required to complete a minimum of ten trials on test day and for there to be at least an $n=5$ sample size per treatment group. Significant main effects or trend-level effects of treatment for each variable were further investigated with planned comparisons against the vehicle treatment group.

Delayed matching to position task

The dependent variables analysed were: trials completed, accuracy and per cent omissions per session, accuracy per delay, head entries, sample and choice latencies. For inclusion in the analyses of accuracy and choice latencies, animals needed to complete at least 30 trials (minimum of six trials of each delay type) and for there to be at least an $n=5$ sample size per treatment group. As the trials completed variable was not normally distributed, it was subjected to Kruskal–Wallis one-way analysis of ranks followed by pairwise multiple comparisons. The accuracies per delay variable was subjected to a two-way mixed repeated measures ANOVA with a within-subjects factor of delay and a between-subjects factor of (assigned) treatment. Analyses of simple effects (the effect of treatment at each level of delay) and planned comparisons of each drug treatment group versus the vehicle

group were also conducted. All other variables were analysed using a one-way ANOVA with a between-subjects factor of treatment and planned comparisons of each drug treatment group versus the vehicle group.

Drugs

The following drugs were used in this study: phencyclidine hydrochloride (Sigma-Aldrich, UK); (*S*)-(+)-ketamine hydrochloride (Sigma-Aldrich); memantine hydrochloride (Tocris, UK); MK-801 hydrogen maleate (dizocilpine, Sigma-Aldrich); SDZ 220,581 ((*S*)-1-amino-2′-chloro-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic acid), Tocris); Ro 25–6981 ([(*R*:(+), *S*:(−))-1-(4-hydroxyphenyl)-1-methyl-4-(phenylmethyl)-1-piperidinepropanol, Lilly Research Labs); CP 101-606 ((1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol, Lilly Research Labs); and NVP-AAM077 ([(*R*)-[(*S*)-1-(4-bromo-phenyl)-ethylamino]-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)-methyl]-phosphonic acid, Lilly Research Labs). The vehicle for all drugs was 5% (*w*/*v*) glucose solution, and pH was adjusted when necessary. All drugs were formulated at a volume of 1 ml/kg and administered via the subcutaneous route, except NVP-AAM077 which was administered via the intraperitoneal route. Compounds were typically administered 30 min before the start of the test session. Exceptions were CP 101-606 which was administered 60 min before test and *S*-(+)-ketamine which was administered 5 min before test. All doses refer to the base weights of compounds. Doses and routes of administration were chosen on the basis of previously conducted studies (Gilmour et al. 2009; Dix et al. 2010) and a general assessment of existing published literature in this field.

Group assignment and dosing

For both 5CSRT and DMTP studies, a different NMDAR antagonist was pseudo-randomly chosen for testing each week. A between-subjects design was used such that each rat received no more than one dose of each antagonist (or vehicle), but that each rat could receive more than one antagonist across weeks. Data from the last training day were used to rank animals on the basis of session performance. Animals were pseudo-randomly assigned to drug treatments with respect to those ranks. These data were analysed to ensure that treatment groups did not differ significantly prior to drug administration. Finally, as a precautionary measure, test day data were also subjected to an analysis of variance where the treatment effects of the previous week were included as a covariate to determine that no significant carryover effects could have influenced the contemporary study (results not presented).

Results

Full details of all statistical results calculated for both 5CSRT and DMTP assays can be found as Electronic supplementary material (ESM). To facilitate comparison between compounds tested and to aid comprehension of the multivariate nature of the dataset, results are presented for each compound in a consistent manner.

Five-choice serial reaction time task

For 5CSRT, parameters potentially more reflective of attentional processes (namely accuracy, correct response latency and per cent omissions) are discussed first, followed by the more ‘motor/motivational’ parameters (number of included subjects, head entries and magazine latency). Finally, potential measures of impulsivity (premature responses) and compulsivity (perseverative responses) are described. Figure 1 illustrates the effects of each compound on accuracy and per cent omissions. Table 1 provides details of all other parameters measured during testing. Table 2 provides an overall summary of the direction of statistically significant effects found for each compound.

PCP (1–3 mg/kg) PCP dose-dependently decreased accuracy across the dose range tested in the absence of a significant change in correct response latency. A concomitant dose-dependent increase in omissions was observed. PCP decreased the number of subjects eligible for analysis such that accuracy and latency parameters could not be reliably determined for the 3-mg/kg dose group. Interestingly, the number of head entries made significantly increased at 1 mg/kg PCP, but decreased at 3 mg/kg. Magazine latencies for animals that completed at least ten trials did not significantly change across treatment groups. Premature and perseverative responses were not significantly altered by PCP treatment.

MK-801 (0.025–0.1 mg/kg) MK-801 at a dose of 0.1 mg/kg significantly decreased accuracy and increased per cent omissions. Correct response latencies significantly increased at 0.05 mg/kg. At a dose of 0.1 mg/kg MK-801, the number of animals that could be included in the analysis dropped from 12 to 5. Significant increases in magazine latencies, head entries and premature responses were found for the 0.05-mg/kg group, whereas increase in perseverative responding did not achieve statistical significance at this dose.

S-(+)-ketamine (2.5–10 mg/kg) Ketamine dose-dependently decreased accuracy across the range tested without changing correct response latency. A concomitant dose-dependent increase in omissions was also observed. Following

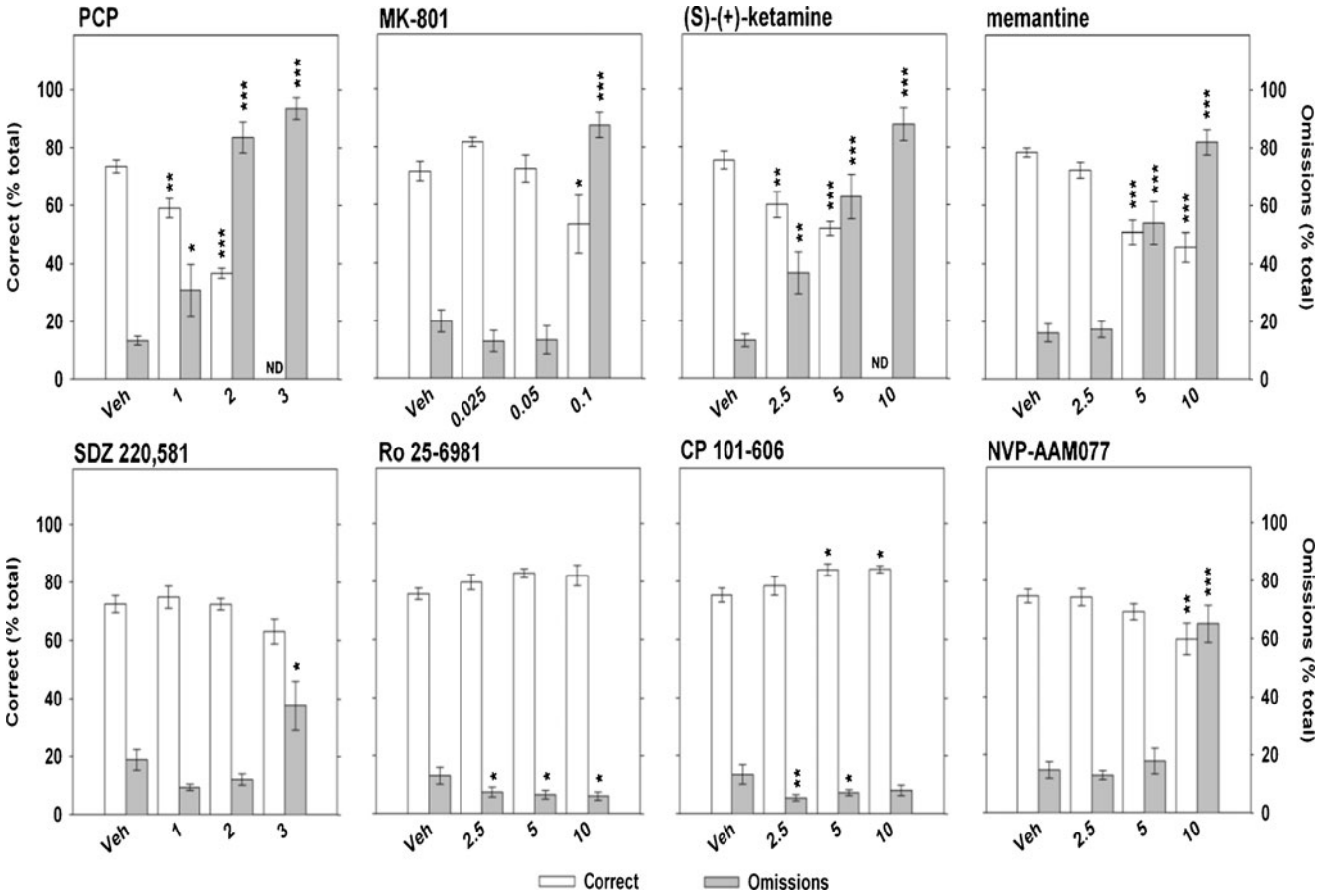

Fig. 1 Effects of NMDAR antagonists on accuracy and omissions in the five-choice serial reaction time task of sustained attention in male Lister hooded rats. All results are presented as mean ± SEM, where the *white bar* depicts accuracy and the *grey bar* depicts omission levels. Statistical significance refers to planned comparisons of each treatment group with the vehicle group following main effect of treatment in an ANOVA: *$p<0.05$; **$p<0.01$; ***$p<0.001$. *ND* not determined due to insufficient sample size for statistical analysis

treatment with 10 mg/kg *S*-(+)-ketamine, accuracy and latency parameters could not be reliably measured because too few animals completed the minimum of ten trials. The number of head entries and premature and perseverative responses made also decreased at 10 mg/kg, but only head entries achieved statistical significance.

Memantine (2.5–10 mg/kg) Memantine dose-dependently decreased accuracy and correct response latencies whilst also increasing omissions. The number of subjects completing the minimum of ten trials dropped from 12 to 8 at the 10-mg/kg dose, and magazine latencies significantly decreased at this dose as well. Head entries and premature and perseverative responses were not significantly altered at any dose tested.

SDZ 220,581 (1–3 mg/kg) Only one significant effect was found following treatment with SDZ 220,581: an increase in omissions at 3 mg/kg.

Ro 25-6981 (2.5–10 mg/kg) Across all doses tested, Ro 25-6981 significantly decreased the number of omissions compared to vehicle-treated rats. No other significant effects of the drug were found.

CP 101-606 (2.5–10 mg/kg) Like the other GluN2B selective antagonist, CP 101-606 treatment decreased the number of omissions at both 2.5 and 5 mg/kg, but also significantly increased accuracy at both 5 and 10 mg/kg, No other effects of the drug were statistically significant.

NVP-AAM077 (2.5–10 mg/kg) All significant effects were found following the 10-mg/kg dose of NVP-AAM077 which significantly decreased accuracy, both correct response and magazine latencies, whilst increasing omissions.

Delayed matching to position task

Parameters that more likely reflect cognitive processes (accuracy per session and per delay, correct response

Table 1 Effects of NMDAR antagonists on additional measures in the five-choice serial reaction time task

Drug	Dose (mg/kg)	Sample size (*n*)	Head entries (*n*)	Premature resp. (*n*)	Perseverative resp. (*n*)	Correct latency (ms)	Magazine latency (ms)
PCP	Veh	12/12	161±33	13±3	4±1	1,070±20	1,450±60
	1	9/10	275±36 *	24±8	6±2	1,110±80	1,730±130
	2	5/12	163±29	12±5	3±2	1,220±230	1,780±270
	3	1/12	65±21 *	3±1	02±0.2	ND	ND
MK-801	Veh	11/11	134±15	10±2	4±1	1,010±20	1,380±70
	0.025	12/12	179±16	18±7	3±1	1,110±60	1,380±80
	0.05	12/12	279±39 **	32±11 *	7±3	1,200±80*	1,680±200*
	0.1	5/12	195±31	9±5	2±2	840±140	1,360±460
(*S*)-(+)-ketamine	Veh	12/12	150±12	13±2	3±1	1,070±20	1,420±70
	2.5	12/12	157±15	17±3	8±2 *	1,040±40	1,500±100
	5	11/12	153±18	17±4	3±1	1,010±60	1,520±140
	10	3/11	73±25 **	7±4	1±1	ND	ND
Memantine	Veh	11/11	158±14	14±3	4±1	1,070±20	1,370±40
	2.5	12/12	178±12	14±2	3±1	1,070±30	1,460±80
	5	11/12	152±15	19±4	4±2	940±60*	1,370±130
	10	8/12	127±17	6±1	1±1	740±40***	1,060±80*
SDZ 220,581	Veh	12/12	169±34	13±2	4±1	1,030±30	1,440±90
	1	11/11	176±19	14±3	5±2	1,090±30	1,480±90
	2	11/11	228±17	13±3	5±2	1,060±20	1,430±60
	3	11/12	219±29	15±2	2±1	1,020±20	1,350±70
Ro 25-6981	Veh	11/11	182±28	11±2	3±1	1,040±20	1,350±50
	2.5	12/12	156±10	10±2	3±1	1,060±20	1,370±60
	5	12/12	166±10	8±1	3±1	1,050±10	1,290±30
	10	12/12	195±16	15±4	2±1	1,120±40	1,410±80
CP 101-606	Veh	11/11	199 ± 15	14 ± 3	4 ± 2	1050 ± 20	1370 ± 50
	2.5	12/12	201 ± 25	17 ± 4	5 ± 1	1130 ± 30	1480 ± 80
	5	12/12	187 ± 19	8 ± 1	1 ± 0.4	950 ± 90	1280 ± 40
	10	11/11	188 ± 7	14 ± 4	3 ± 1	1070 ± 30	1300 ± 40
NVP-AAMO77	Veh	11/11	173±23	11±2	2±0.4	1,030±10	1,350±50
	2.5	12/12	199±27	15±2	3±1	1,090±20	1,450±70
	5	12/12	201±24	16±2	5±2	1,060±30	1,520±70
	10	11/12	141±24	11±2	2±1	840±50***	1,080±60**

Sample size refers to the number of animals eligible for inclusion in all statistical analyses relative to the original number of animals in each treatment group, e.g. 5/12 means that 5 out of 12 animals were fully included subjects. For the other results in the table, these have been presented as the mean ± SEM. Statistical significance refers to planned comparisons of each treatment group with the vehicle group following main effect of treatment in an ANOVA

ND not determined due to insufficient sample size for statistical analysis

*$p<0.05$; **$p<0.01$; ***$p<0.001$

latency and per cent omissions) are presented first for each compound, followed by the more motor/motivational parameters (number of included subjects, number of trials completed, head entries and sample latency). Figure 2 illustrates the effects of each compound on accuracy and per cent omissions across the DMTP session as a whole. Figure 3 illustrates accuracy per delay for doses of compounds where statistical analysis warranted consideration of the dose dependency of the effects under question. Table 3 provides details of all other parameters measured during testing. Finally, Table 4 provides an overall summary of the direction of statistically significant effects found for each compound.

PCP (0.5–2.5 mg/kg) PCP dose-dependently decreased accuracy across the session as a whole. Analysis of the delay-dependent nature of these effects showed that 2 mg/kg PCP significantly decreased accuracy only at

Table 2 Summary of NMDAR antagonist effects in the five-choice serial reaction time task

Drug	Attention			Motor/motivation			Impulsivity	Flexibility
	% Correct	% Omissions	Correct latency	Included subjects	Head entries	Magazine latency	Premature responses	Perseverative responses
PCP	↓1, 2, 3 ND	↑1, 2, 3	3 ND	↓2, 3	↑1, ↓3	3ND		
MK-801	↓0.1	↑0.1	↑0.05	↓0.1	↑0.05	↑0.05	↑0.05	
(*S*)-(+)-ketamine	↓2.5, 5, 10 ND	↑ 5, 10	10 ND	↓10	↓10	10 ND		↑2.5
memantine	↓5, 10	↑5, 10	↓5, 10	↓10	↓10			
SDZ 220,581		↑3						
Ro 25-6981		↓2.5, 5, 10						
CP 101-606	↑5, 10	↓2.5, 5						
NVP-AAM077	↓10	↑10	↓10			↓10		

This table summarises the direction of all statistically significant effects found and the doses at which they occurred. An up arrow indicates an increase in the parameter at the dose(s) indicated, relative to the vehicle group. A down arrow indicates a decrease in the parameter at the dose(s) indicated, relative to the vehicle group. Doses at which statistical analyses could not be conducted due to insufficient sample size have also been presented and have been suffixed with the term

ND not determined

the 4-s delay, whilst the 2.5-mg/kg dose decreased accuracy at both 1- and 4-s delays. Interestingly, correct response latencies significantly decreased across the 0.5- to 2-mg/kg range, whilst omissions increased at the 2.5-mg/kg dose. The number of subjects completing at least 30 trials dropped from ten to six at 2.5 mg/kg, a dose which also significantly decreased head entries and increased sample latencies.

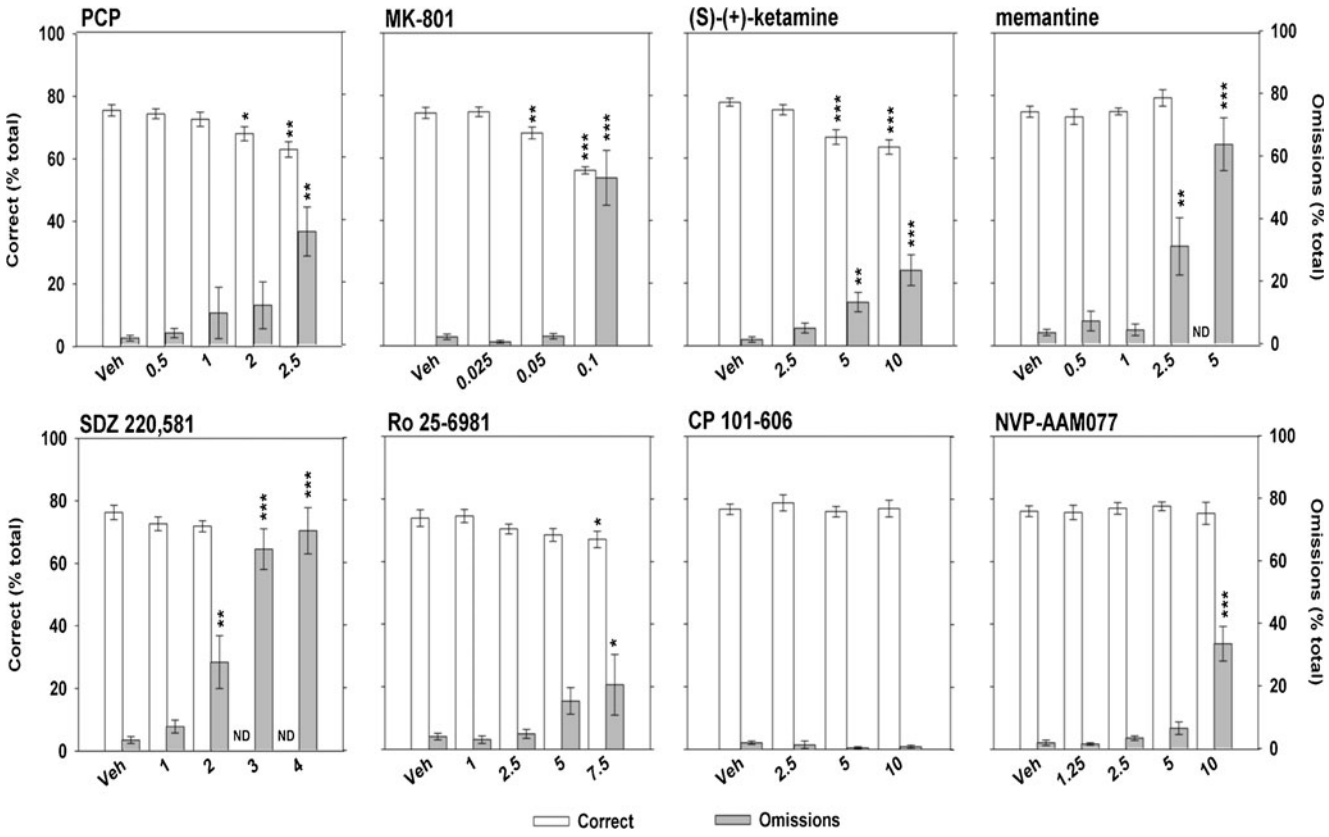

Fig. 2 Effects of NMDAR antagonists on accuracy and omissions in the delayed matching to position task of working memory in male Lister hooded rats. All results are presented as mean ± SEM, where the *white bar* depicts accuracy and the *grey bar* depicts omission levels. Statistical significance refers to planned comparisons of each treatment group with the vehicle group following main effect of treatment in an ANOVA: *$p<0.05$; **$p<0.01$; ***$p<0.001$. *ND* not determined due to insufficient sample size for statistical analysis

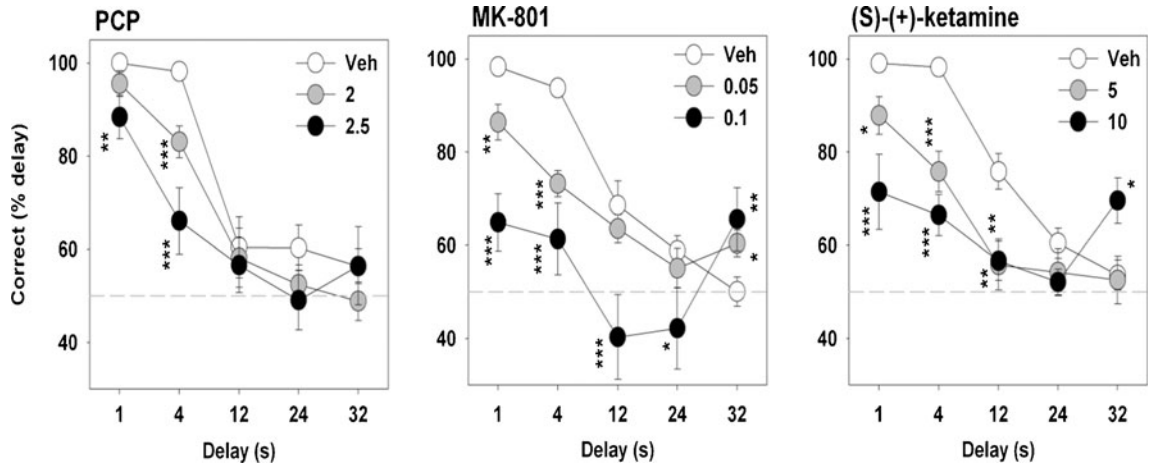

Fig. 3 Effects of NMDAR antagonists on accuracy per delay in the delayed matching to position task of working memory in male Lister Hooded rats. All results are presented as mean ± SEM. Statistical significance refers to planned comparisons of each treatment group with the vehicle group at each level of delay (following treatment × delay interaction in an ANOVA). For ease of visual inspection, only dose groups that warranted further statistical investigation have been presented in each graph. The *grey dashed line* depicts 50% accuracy, or chance performance levels: *$p<0.05$; **$p<0.01$; ***$p<0.001$

MK-801 (0.025–0.1 mg/kg) MK-801 dose-dependently decreased overall session accuracy: The 0.05-mg.kg dose significantly decreased accuracy at 1- and 4-s delays, whilst the 0.1-mg/kg dose decreased it at nearly all delays. Surprisingly, both of these doses significantly increased accuracy compared to vehicle-treated controls at the 32-s delay, but this probably reflects the loss of completed trials that can be included in the analysis. Correct response latencies and omissions significantly increased at 0.1 mg/kg when the number of rats that completed at least 30 trials dropped from 16 to 9. As for PCP, head entries decreased and sample latencies increased significantly at the highest dose of MK-801 tested.

S-(+)-ketamine (2.5–10 mg/kg) Ketamine also dose-dependently decreased session accuracy: the 5- and 10-mg/kg doses significantly decreased accuracy at 1-, 4- and 12-s delays. As with MK-801, *S*-(+)-ketamine (10 mg/kg) increased accuracy at the 32-s delay, again probably because the total number of trials available for analysis was markedly reduced. Correct response latencies and omissions were both dose-dependently increased at 5 and 10 mg/kg. The number of trials completed and the number of animals completing at least 30 trials significantly decreased at 10 mg/kg. Head entries decreased whereas sample latencies increased dose-dependently with *S*-(+)-ketamine.

Memantine (0.5–5 mg/kg) Memantine did not significantly affect accuracy or correct response latencies across the dose range for which this parameter could be measured. Omissions dose-dependently increased in the 2.5- and 5-mg/kg treatment groups. The number of subjects completing at least 30 trials decreased across these two doses to the point where only 2 out of 12 animals were eligible for analysis in the 5-mg/kg dose group. Trials completed decreased and sample latencies significantly increased at 5 mg/kg, whilst head entries decreased at both the 2.5- and 5-mg/kg doses.

SDZ 220,581 (1–4 mg/kg) Accuracy was not significantly affected by SDZ 220,581 at any dose at which it could be measured. A significant increase in correct latency was observed at 2 mg/kg, and a pronounced dose-dependent increase in omissions was observed across the whole dose range tested. The number of subjects completing at least 30 trials dropped at 2 mg/kg (8 out of 12 animals), 3 mg/kg (1 out of 12) and 4 mg/kg (2 out of 12). At doses of 3 and 4 mg/kg, a marked decrease in trials completed and increase in sample latencies were also seen, concomitant with a dose-dependent decrease in the number of head entries across the whole dose range tested.

Ro 25-6981 (1–7.5 mg/kg) A significant decrease in accuracy and increase in omissions was observed for the 7.5-mg/kg dose of Ro 25-6981, whilst correct response latencies were actually significantly decreased at all doses tested. Only one animal failed to complete 30 trials at a dose (7.5 mg/kg) that also increased sample latencies.

CP 101-606 (2.5–10 mg/kg) CP 101-606 had significant effects on only two parameters: As with Ro 25-6981, correct response latencies were significantly decreased, whilst head entries were also significantly increased at all doses tested.

Table 3 Effects of NMDAR antagonists on additional measures in the delayed matching to position task

Drug	Dose (mg/kg)	Sample size (*n*)	Trials (*n*)				Head entries (*n*)	Sample latency (s)	Correct latency (ms)
PCP	Veh	11/11	75	IQR	75	75	1,518±63	4±0.7	1,150±50
	0.5	12/12	75	IQR	75	75	1,764±121	5±1.6	970±30**
	1	11/12	75	IQR	75	75	1,714±172	4±0.7	950±30**
	2	12/13	75	IQR	75	75	1,516±171	7±2	1,010±50*
	2.5	6/10	50	IQR	19	75	760±169**	146±8*	1,100±50
MK-801	Veh	16/16	75	IQR	75	75	1,769±103	3±0.4	1,060±40
	0.025	16/16	75	IQR	75	75	2,037±95	3±0.4	800±30
	0.05	15/15	75	IQR	75	75	2,066±174	4±0.9	1,050±60
	0.1	9/16	36	IQR	24	57***	597±123***	50±8***	3,450±490***
(*S*)-(+)-ketamine	Veh	15/15	75	IQR	75	75	1,733±71	2±0.3	990±40
	2.5	15/15	75	IQR	75	75	1,697±109	8±2	1,120±30
	5	14/15	75	IQR	61	75	1,255±147 **	14±3	1,350±70 **
	10	9/15	48	IQR	13	66***	804±133***	62±22***	1,590±170***
Memantine	Veh	12/12	75	IQR	75	75	1,664±122	4±0.6	1,200±40
	0.5	12/12	75	IQR	75	75	1,575±130	5±2	1,220±70
	1	12/12	75	IQR	75	75	1,625±98	6±2	1,150±60
	2.5	9/12	53	IQR	39	75	964±198***	66±32	1,310±80
	5	2/12	10	IQR	5	24***	198±59***	470±182***	ND
SDZ 220,581	Veh	11/11	75	IQR	75	75	1,597±114	3±0.3	1,130±40
	1	12/12	70	IQR	67	75	1,503±98	12±2	1,150±50
	2	8/12	47	IQR	26	68	832±150***	75±29	1,450±100**
	3	1/12	9	IQR	4	16***	265±68***	282±90**	ND
	4	2/11	10	IQR	5	17***	313±69***	259±84**	ND
Ro 25-6,981	Veh	11/11	75	IQR	75	75	1,559±125	3±0.2	1,240±40
	1	12/12	75	IQR	75	75	1,606±143	3±0.5	1,100±50*
	2.5	12/12	75	IQR	75	75	1,747±199	3±0.4	1,090±50*
	5	12/12	75	IQR	75	75	1,383±197	9±3	990±40**
	7.5	9/10	75	IQR	69	75	1,409±213	9±5*	1,000±60**
CP 101-606	Veh	14/14	75	IQR	75	75	1,726±74	2±0.2	1,020±40
	2.5	15/15	75	IQR	75	75	2,501±196**	2±0.4	890±30*
	5	15/15	75	IQR	75	75	2,518±154**	2±0.2	870±30**
	10	15/15	75	IQR	75	75	2,408±157**	3±0.9	890±30*
NVP-AAM077	Veh	11/12	75	IQR	75	75	1,696±125	3±0.5	1,050±40
	1.25	12/12	75	IQR	75	75	1,670±108	2±0.2	960±50
	2.5	12/12	75	IQR	75	75	1,671±123	3±0.6	1,000±30
	5	12/12	75	IQR	75	75	1,409±101	7±2	1,170±60
	10	8/12	39	IQR	24	56**	529±118***	27±6.1**	1,670±110***

Sample size refers to the number of animals eligible for inclusion in all statistical analyses relative to the original number of animals in each treatment group, e.g. 5/12 means that 5 out of 12 animals were fully included subjects. The number of trials completed has been presented as the median and interquartile range. For the other results in the table, these have been presented as the mean ± SEM. Statistical significance refers to planned comparisons of each treatment group with the vehicle group following main effect of treatment in an ANOVA (or the non-parametric equivalent for the trials completed measure)

ND not determined due to insufficient sample size for statistical analysis

*$p<0.05$; **$p<0.01$; ***$p<0.001$

NVP-AAM077 (1.25–10 mg/kg) This compound only had effects at the highest dose tested, namely 10 mg/kg. At this dose, correct response latencies and omissions were significantly increased, but accuracy was not altered. The number of subjects completing at least 30 trials dropped from 12 to 8 animals, and the number of completed trials

Table 4 Summary of NMDAR antagonist effects in the delayed matching to position task

Drug	Cognitive				Motor/Motivational			
	% Correct	Delay dependency	% Omissions	Correct latency	Included subjects	Trials complete	Head entries	Sample latency
PCP	↓2, 2.5	Yes at 2, No at 2.5	↑2.5	↓0.05, 1, 2	↓2.5		↓2.5	↑2.5
MK-801	↓0.05, 0.1	No	↑0.1	↑0.1	↓0.1	↓0.1	↓0.1	↑0.1
(*S*)-(+)-ketamine	↓5, 10	No	↑5, 10	↑5, 10	↓10	↓10	↓5, 10	↑5, 10
memantine	5 ND		↑2.5, 5	5 ND	↓2.5, 5	↓5	↓2.5, 5	↑5
SDZ 220,581	↓2, 3 ND, 4 ND		↑2, 3, 4	↑2, 3 ND, 4 ND	↓2, 3, 4	↓3, 4	↓2, 3, 4	↑2, 3 ND, 4 ND
Ro 25-6981	↓7.5		↑7.5	↓1, 2.5, 5, 7.5				↑7.5
CP 101-606				↓2.5, 5, 10			↑2.5, 5, 10	
NVP-AAM077			↑10	↑10	↓10	↓10	↓10	↑10

This table summarises the direction of all statistically significant effects found and the doses at which they occurred. An up arrow indicates an increase in the parameter at the dose(s) indicated, relative to the vehicle group. A down arrow indicates a decrease in the parameter at the dose(s) indicated, relative to the vehicle group. Delay dependency of effects on accuracy have also been summarised; "YES" refers to the fact that accuracy was intact at the shortest delay tested but decreased at a later delay, "NO" refers to the fact that accuracy was impaired even at the shortest delay tested. Doses at which statistical analyses could not be conducted due to insufficient sample size have also been presented and have been suffixed with the term ND, not determined.

also significantly decreased. Finally, the 10-mg/kg dose also resulted in a significant decrease in head entries and increase in sample latencies.

Discussion

The overall aim of this work was to extend the profiling of a range of NMDAR antagonists into two further tests assessing cognitive domains disturbed in schizophrenia and thereby to validate the use of acute NMDAR antagonism in rats as models of (a) the cognitive impairment induced by ketamine in healthy volunteers and (b) the cognitive impairment seen in schizophrenic patients. As a whole, two points are readily apparent from the present work: firstly, the limited extent to which different NMDAR antagonists are functionally equivalent in producing effects and, secondly, the limited extent to which the cognitive effects of ketamine in healthy volunteers are reflected in and can be both detected and quantified using these two operant assays.

Effects of *S*-(+)-ketamine and PCP

Ketamine and PCP had essentially similar effects on 5CSRT performance. Robust decreases in accuracy and increases in omissions could be seen with each drug, potentially suggesting marked effects on attentional performance (Robbins 2002; Amitai and Markou 2010). There were doses of ketamine (2.5 mg/kg) and PCP (1 mg/kg) where attentional impairment seemed to be relatively selective, with little or no negative change in other parameters. However, as the dose increased, a background of concomitant and marked motor/motivational disturbances manifested, making it more difficult to reach any strong conclusion about the cognitive nature of the deficit now present. In DMTP, both ketamine and PCP dose-dependently reduced choice accuracy. However, these effects were not delay-dependent, and significant effects on accuracy could be seen at the shortest delays tested. As such, this does not represent convincing evidence that the drugs are directly affecting working memory processes. Indeed, increased errors induced by PCP were associated with decreased correct response latencies, perhaps suggesting that choices were being made incorrectly because of increased impulsivity. Correct response latencies and omissions increased with the administration of the highest dose of ketamine tested, consistent with a contribution to impairment from motor function. In summary, both PCP and ketamine impair the performance of the 5CSRT and DMTP tasks, but the dose–response relationship is such that the possibility of identifying a dose that produces selective impairment in the absence of non-cognitive confounds is limited, problematic and could hinder the search for pharmacological mechanisms capable of pro-cognitive actions. There seems little doubt that ketamine can impair working memory in man, though this seems to be more to do with the manipulation rather than maintenance of information (Morgan and Curran 2006), an aspect of working memory not tested in the DMTP task. Although not extensively tested in man, ketamine is reported not to influence the performance of sustained-attention tasks at exposures that seem to influence working memory (Malhotra et al. 1997; Newcomer et al. 1999). Clearly, there is a need

for more detailed parallel human and animal studies of the effects of ketamine on attentional processes before definitive conclusions can be reached here.

MK-801

After ketamine and PCP, MK-801 is perhaps the most popular non-competitive NMDA receptor antagonist used as a preclinical pharmacological model of schizophrenia and/or cognitive impairment because of its higher affinity and greater selectivity for NMDA receptors (Wong et al. 1986). At relatively low doses, MK-801 is unusual in that it has a stimulatory effect on instrumental responding (Gilmour et al. 2009) and also increases head entries and premature responding in 5CSRT. At higher doses, all of these effects diminish or become significantly inhibitory, but effects on accuracy are relatively slight in terms of effect size. In DMTP, as with ketamine and PCP, there is one dose of MK-801, 0.05 mg/kg (the same dose that is stimulatory in instrumental responding and 5CSRT), where accuracy is diminished in the absence of increased omissions or changes in response latency. However, the impairment shows little dependency on delay and so cannot be unequivocally attributed as a selective impairment of working memory per se. Interestingly, the same dose of MK-801 has no effect on accuracy in 5CSRT. Overall, the use of MK-801 in these tasks would seem to offer little advantage over ketamine as a model of impairment of attention or working memory.

Memantine and NVP-AAM077

In 5CSRT, both compounds are similar to PCP and ketamine in that they both reduce accuracy and increase omissions, but differ because the effective doses concomitantly reduced both response and magazine latencies. The pattern is indicative of a generally disruptive effect on motor responding. Such an interpretation would be more consistent with the markedly inhibitory profile of these compounds on instrumental responding (Gilmour et al. 2009) and increases in response latencies and omissions in the absence of any negative impact on accuracy in the DMTP task. However, previous work has shown that NVP-AAM077 is relatively ineffective at blocking both acquisition and extinction of a visuo-auditory discrimination, whilst memantine clearly blocks both of these effects in this task (Dix et al. 2010) at doses that decrease response latencies in the present 5CSRT, consistent with findings of mnemonic deficits in otherwise normal animals by others (Creeley et al. 2006). Also consistent with this are reports of deficits in recognition memory in normal humans given memantine (Rammsayer 2001). Another study demonstrated that memantine in volunteers produced no effects on mood, attention, verbal or visuospatial memory, but did impair the acquisition of classical eyeblink conditioning, a non-declarative memory task (Schugens et al. 1997). As NVP-AAM077 has some degree of selectivity for GluN2A- over GluN2B-containing receptors, it is tempting to suggest from the evidence cited above that blockade of GluN2A is more 'cognitively benign' than blocking GluN2B. However, the preferential activity of memantine for selective NMDA receptor subtypes is somewhat unclear (Johnson and Kotermanski 2006; Kotermanski and Johnson 2009), and compounds with a much greater selectivity for GluN2A than that displayed by NVP-AAM077 need to be identified and tested (also ideally in humans) before any weight can be given to this hypothesis.

Whilst memantine may show signs of inducing cognitive disruption in normal animals and humans, a number of papers have reported positive effects in preclinical models of cognitive impairment, e.g. transgenic mice engineered to overexpress amyloid proteins and lesioned rats (Creeley et al. 2006; Minkeviciene et al. 2004, 2008; More et al. 2008; Yuede et al. 2007). Also, memantine appears to provide some clinical benefit to Alzheimer's patients (Witt et al. 2004). This apparent discrepancy between positive effects on cognition in deficit models and negative effects in normal animals may potentially be a consequence of differences in glutamatergic state or tone between animals (Parsons et al. 2007), highlighting the potential importance of evaluating putative pro-cognitive agents in conjunction with manipulations that impair cognition.

Ro 25-6981 and CP 101-606

These two GluN2B-preferring NMDA receptor antagonists were unique in their effects among the set of compounds tested: decreasing correct response latencies in DMTP, decreasing omissions and increasing accuracy in 5CSRT (significantly so for CP 101-606). Interestingly, CP 101-606 also significantly enhanced accuracy in the delayed discrimination phase of the four-stage cognitive battery devised by Dix et al. (2010). Whilst this effect was neither delay- nor dose-dependent, it corroborates, in combination with the present findings, a previous report in which CP 101-606 improved accuracy in DMTP (Higgins et al. 2005). Altogether, these data might suggest that clinical (and potentially cognitive) benefit might be achieved by selective blockade of GluN2B-containing receptors. This has certainly been a hope of those wishing to exploit the neuroprotective effects of GluN2B-containing NMDAR antagonists (Leaver et al. 2008; Tzschentke 2002; Williams et al. 2002), but the neuropsychopharmacological profile of CP 101-606 for example has not been extensively tested in man. Interestingly, the interoceptive stimulus properties of GluN2B-preferring antagonists in rats are indistinguishable

from those of PCP (Chaperon et al. 2003; Gilmour et al., unpublished observations), and on this basis, it seems likely that the compound would induce similar subjective effects to PCP in man.

SDZ 220,581

This was the only competitive NMDA receptor antagonist examined. Amongst its pharmacological class, it is unusual in that it shares gross motor stimulatory and interoceptive stimulus effects to those of PCP and ketamine (Bakshi et al. 1999; Chaperon et al. 2003), probably because of its greater ability to penetrate the CNS (Bakshi et al. 1999). As a pharmacological model of glutamatergic hypofunction, it should theoretically be more sensitive than non-competitive NMDAR antagonists to putative anti-schizophrenic agents that act by augmenting glutamate availability. Like most of the compounds studied here, SDZ 220,581 suppressed instrumental responding (Gilmour et al. 2009). In both 5CSRT and DMTP, no dose tested was capable of selectively influencing task accuracy in the absence of a marked response inhibition, i.e. decreases in the number of trials completed, increased omissions or increased response latencies.

Finally, perhaps surprising is the ability of the two tests to illustrate seemingly opposite effects of some compounds. For example, the 10-mg/kg dose of NVP-AAM077 increases sample and correct latencies in DMTP, but decreases magazine and correct latencies in 5CSRT. Ro 25-6981 decreases omissions at all doses tested in 5CSRT, but increases them at 7.5 mg/kg in DMTP. Of course, the two tasks differ in their motor and attentional demands. The behavioural outcome is therefore probably a function of the motor/cognitive load × drug dose interaction, the dose–motor response relationship for NMDAR antagonist often following an inverted U-shaped function (Gilmour et al. 2009).

Conclusions

A group of mechanistically diverse NMDAR antagonists have now been examined in a wide range of operant behavioural tasks in the rat, and it is very clear that the drug-induced responses are qualitatively and quantitatively different, in both a compound- and task-dependent manner. In the variable interval responding experiments of Gilmour et al. (2009) and the four-stage cognitive battery of Dix et al. (2010), the profile of PCP appeared to be most similar to that of MK-801 and somewhat different from ketamine. In the present work, PCP and ketamine were broadly similar and somewhat different from MK-801. The most consistent and the least ambiguous effect in terms of motor or motivational confounds has been the blockade of task acquisition and consolidation of extinction (Dix et al. 2010). Unambiguous effects on the cognitive processes underlying DMTP and 5CSRT performance might well be detectable, but achieving such effects at a given dose in every experiment, as would be necessary in a drug discovery programme where quantitative efficacy discriminations between compounds need to be made, has not proved easy (unpublished data). The initial aim in exploring different NMDAR antagonists was motivated to a certain degree by the possibility that one or other of the less well-studied compounds might prove superior in its ability to disrupt cognition without engaging behavioural confounds. That has not been the case and only reinforces the conclusions of Dix et al. (2010) that as ketamine is most frequently used drug in human neuropsychological and biomarker studies, it would make sense to focus on ketamine as the predominant preclinical tool. However, as shown in these studies, there are important limitations of the translational value of an acute exposure regimen of ketamine for evaluating schizophrenia-related cognitive deficits in these operant tests. Others have hypothesized that the motor and/or motivational confounds of NMDAR antagonists seen in preclinical studies may be overcome by repeated administration of the NMDAR antagonist, e.g. PCP (Amitai et al. 2007; Amitai and Markou 2009a, b). This is also in accordance with Dix et al. (2010) who found a progressive decrease in the omission rate with dosing across days of acquisition of a simple conditional discrimination. This repeated exposure regimen might therefore allow the development of a degree of tolerance to motor and motivational confounds, thus permitting investigation of schizophrenia-like cognitive deficits induced by ‘acute’ re-exposure to NMDAR antagonists. However, such an approach minimizes the real translational value of studying the acute effects of ketamine in both preclinical and clinical settings. Even though chronic abusers of ketamine can be found, it is not possible to control their exposure in any systematic way without raising ethical concern. Finally, it is hoped that this present series of studies will encourage yet more detailed study of the neuropsychological effects of NMDAR antagonists in man, not only with ketamine but also, where possible, with PCP and CP 101-606 and, most importantly, in comparison to the deficits in these same measures found in schizophrenics.

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