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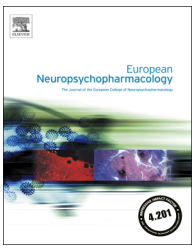

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Temporally distinct cognitive effects following acute administration of ketamine and phencyclidine in the rat

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Abstract
Non-competitive *N*-methyl-D-aspartate receptor (NMDAR) antagonists such as phencyclidine (PCP) and ketamine are commonly and interchangeably used to model aspects of schizophrenia in animals. We compared here the effects of acute administration of these compounds over a range of pre-treatment times in tests of instrumental responding (VI 30 s response schedule), simple reaction time (SRT) and cognitive flexibility (reversal learning and attentional set shifting digging task) in rats. At standard pre-treatment times (15–30 min), both ketamine and PCP produced overall response suppression in VI 30 and increased reaction times in SRT suggesting that any concomitant cognitive performance deficits are likely to be confounded by motor and/or motivational changes. However, the use of extended pre-treatment times produced deficits in cognitive flexibility measured up to 4 h after drug administration in the absence of motor/motivational impairment. Generally, PCP increased impulsive responding in the SRT indicating a possible loss of inhibitory response control that may have contributed to deficits observed in reversal learning and attentional set-shifting. In contrast to PCP, ketamine did not have the same effect on impulsive responding, and possibly as a consequence produced more subtle cognitive deficits in attentional set-shifting. In summary, acute treatment with NMDAR antagonists can produce cognitive deficits in rodents that are relevant to schizophrenia, provided that motor and/or motivational effects are allowed to dissipate. The use of longer

Abbreviations: NMDAR, non-competitive *N*-methyl-D-aspartate receptor; PCP, phencyclidine; VI, variable interval; SRT, simple reaction time

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pre-treatment times than commonly employed might be advantageous. Also, ketamine, which is more frequently used in clinical settings, did not produce as extensive cognitive deficits as PCP.

1. Introduction

In the search for putative treatments of schizophrenia, *N*-methyl-D-aspartate receptor (NMDAR) antagonists have played a prominent role as a pharmacological model of various aspects of the disorder. Compounds such as phencyclidine (PCP) and ketamine are claimed to induce a spectrum of symptoms in rodents, primates and humans that bear similarity to aspects of the disorder itself (Krystal et al., 1994; Jentsch and Roth, 1999). Such potential for cross-species translational research is critical given that non-human homologues of schizophrenia are unknown at present. However, a review of the literature on the ability of NMDAR antagonists to model any specific *cognitive* aspect of schizophrenia suggests somewhat limited or unrealized potential (Gilmour et al., 2012). Nevertheless, the importance of NMDAR hypofunction to schizophrenia is not to be dismissed easily given evidence that human autoimmunity to NMDA receptors induces psychotic states indistinguishable from schizophrenia (Irani et al., 2010; Dalmau et al., 2011; Zandi et al., 2011).

One major problem regarding use of acute doses of NMDAR antagonists in assays of cognition in rodents has been their motor and motivational effects (Gilmour et al., 2009; Dix et al., 2010; Smith et al., 2011). The contrast to human studies here is marked, as volunteers and patients are impaired in several cognitive domains following administration of ketamine (Krystal et al., 1994, 2005; Malhotra et al., 1996, 1997; Adler et al., 1999; Rowland et al., 2005; Fletcher and Honey, 2006; Pomarol-Clotet et al., 2006), without disruption of motor or motivational function being reported as a concern in these studies. This might be due to fundamental differences between rodents and humans in the level of motor capacity or effort needed for solution of the cognitive tasks administered. However, another difference between rodent and human studies lies in the dosing regimens used. Typically, in human studies intravenous infusion of ketamine provides a steady state plasma exposure level during testing (Absalom et al., 2007), whereas rodent studies use parenteral bolus doses of NMDAR antagonists that deliver a qualitatively different pharmacokinetic profile. Apparent differences in the magnitude of motor confound between species could therefore be the result of pharmacokinetic properties of the models employed.

Accordingly, the aim of this study was to identify whether longer pre-treatment times allow the possibility of observing cognitive disruption in the absence of confounding motor/motivational effects. The behavioural effects of two non-competitive NMDAR antagonists – PCP and (S)-(+)-ketamine – were compared over a range of pre-treatment times, from 15 to 120 min, and in a variety of tests of motor and cognitive function. Instrumental responding was assessed in animals performing under a variable interval 30 s (VI 30) schedule, whilst effects on vigilant attention were assessed in animals performing a simple reaction time (SRT) task. Aspects of cognitive flexibility were assessed using the intra-dimensional/extra-dimensional (IDED) set shifting digging task. For operational reasons, different strains of rats were used in each behavioural paradigm. As a consequence, pharmacokinetic "bridging" studies were conducted in which plasma and brain drug exposure profiles over time were also measured for each compound in each strain of rat tested.

2. Experimental procedures

2.1. Animals

Adult Lister-Hooded (VI 30 study, $n=64$), Wistar (SRT study, $n=68$), and Sprague-Dawley (IDED study, $n=35$) male rats (Charles River, UK) were used. They were housed in standard housing conditions (two to four per cage, 07:00–19:00 h light phase, controlled temperature and humidity, *ad libitum* water) and kept for a minimum of 7 days before any behavioural training commenced. During this time, rats were acclimated to food restriction regimens (*i.e.*, maintained at no less than 85% of their free-feeding weight) and were handled during weighing and general husbandry procedures. All experiments were conducted in accordance with the regulations laid down in the United Kingdom Animals (Scientific Procedures) Act 1986.

2.2. VI 30 schedule

VI 30 testing was conducted in Lister Hooded rats using standard operant chambers housed in sound and light attenuation chambers (Med Associates, USA), according to the protocol described by Gilmour et al. (2009). Animals were pseudorandomly assigned to treatment groups based on task performance on the day prior to drug testing. For both pre-test and test sessions, the number of lever presses and head entries were recorded for each treatment group and subjected to ANOVA and planned comparisons as appropriate. In all cases, $p<0.05$ indicated a significant difference.

2.3. Simple reaction time task

SRT testing was conducted in Wistar rats using standard operant chambers. Animals were progressively trained during daily 30 min sessions to respond for food reward by making a head entry following presentation of a visual stimulus in the food magazine. During the first stage of training, the magazine light (imperative cue) remained illuminated for 10 s periods during which a nose poke response earned a food pellet reward. Food reward was delivered upon termination of the imperative cue even if no nose poke was made. The house light (preparatory cue) remained illuminated throughout the session except for a 5 s timeout period that occurred while the animal collected food reward, and also during the inter-trial intervals. Imperative cues were subsequently presented at a fixed inter-trial interval of 30 s. Animals were required to make at least 10 nose pokes under this contingency before starting the second stage of training, where all rewards had to be