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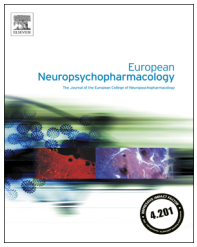

The effects of acute and repeated administration of ketamine on attentional performance in the five-choice serial reaction time task in rats

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Abstract
Ketamine, the non-competitive antagonist of the N-methyl-D-aspartate receptors, is used in clinical and preclinical studies to produce schizophrenia-like cognitive impairments. However, the impact of ketamine on attentional functions remains poorly characterised. In the present study, we further examine the effects of ketamine on attentional processes assessed in the five-choice serial reaction time task (5-CSRTT) in rats. The applied schedules of ketamine administration have been previously demonstrated to evoke frontal-dependent set-shifting impairments. Rats were trained to reach a stable baseline performance. Afterwards, animals received a single injection of ketamine (0, 3 and 10 mg/kg, IP) 45 min before the 5-CSRTT session (experiment 1). In experiment 2, ketamine (0 and 30 mg/kg, IP) was administered after the daily test session for 10 consecutive days. The rats' performance was assessed at 22 h following ketamine administration and for 4 days after the last dose. Acute and repeated administration of ketamine disrupted rats' performance on the 5-CSRTT. Reduced speed of responding and an increased number of omissions were noted in the absence of reduced food motivation. The within-session pattern of responding differed between rats treated acutely and repeatedly with ketamine. Specifically, repeated drug administration evoked an increase in omissions toward the end of the session, and this effect was not secondary to the reduced motivation. Ketamine affected performance during the withdrawal period only when testing with variable inter-trial intervals. The repeated administration of ketamine can impair rats' ability to sustain attention over the course of session, suggesting some utility for modelling attentional disturbances.

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1. Introduction

It is widely accepted that cognitive deficits are a core feature of schizophrenia (Elvevag and Goldberg, 2000). Attention has been identified as one of seven cognitive domains that encompass the primary deficiencies of schizophrenia (Nuechterlein et al., 2004). Schizophrenia patients perform worse than normal control participants in the Continuous Performance Test (CPT) (Cornblatt and Malhotra, 2001), a task that is used to quantify attention in humans. To assess sustained attention in rodents, the five-choice serial reaction time task (5-CSRTT) and its modified version, the five-choice continuous performance test (5C-CPT), have been used. These tests are analogous to the CPT and has been characterised to have high face and predictive validities (Bari et al., 2008; Lustig et al., 2013; Young et al., 2009). In this task, rats are required to detect and respond to brief light stimuli that are presented randomly in one of the five holes. The animal indicates detection of the stimulus by nose-poking the illuminated hole. Correct responses are rewarded with a food pellet, whereas incorrect responses result in a brief timeout period. The task allows for the simultaneous examination of multiple aspects of performance (Bari et al., 2008). Crucially, the ratio of correct responses to total responses (i.e., correct+incorrect) offers a measure of the accuracy of attentional processes. Additionally, motor impulsivity is measured by premature responses (nose pokes made before the stimulus is presented) and perseverative responses (i.e., continued nose pokes after a correct response) may reflect compulsivity. The latency to correct response reflects the speed of processing. The 5C-CPT version of the paradigm also includes non-target trials in which the subject must inhibit responding, thereby more closely mimicking human CPT paradigms (Young et al., 2009).

One of the most widely applied pharmacological models of schizophrenia is based on the blockade of the N-methyl-D-aspartate receptors (NMDARs) (Neill et al., 2010). Non-competitive antagonists of NMDARs, such as phencyclidine (PCP), ketamine and MK-801 (dizocilpine), produce a broad range of schizophrenia-like symptoms, including cognitive deficits. Importantly, ketamine is commonly used in clinical settings to model transient neurocognitive impairments in healthy volunteers (Krystal et al., 1994). Therefore, ketamine-induced cognitive impairments as having reference to clinical data may represent a valuable tool in preclinical research. Available animal studies indicated that ketamine administration produced deficits across several cognitive domains (Enomoto and Floresco, 2009; Floresco et al., 2009; Nikiforuk and Popik, 2012; Rushforth et al., 2011). Our previous studies investigating the attentional-set shifting task (ASST) in rats indicate that ketamine impairs executive functions that are dependent on the frontal cortex. Accordingly, acute administration of ketamine evoked a selective impairment of performance during the extra-dimensional set-shifting stage of the ASST that is regarded as an index of cognitive flexibility (Nikiforuk et al., 2010). Moreover, our subsequent study showed that repeated (10-day) administration of ketamine produced persistent (at least up to 2 weeks following ketamine exposure) cognitive inflexibility (Nikiforuk and Popik, 2012).

Nevertheless, the impact of ketamine on attentional functions remains equivocal. According to the limited available data, acute administration of ketamine tends to produce unspecific impairments of 5-CSRTT performance (Nemeth et al., 2010; Oliver et al., 2009; Smith et al., 2011), whereas the repeated drug regimen has not been evaluated in that task (see Section 4). The effects or acute or repeated administration of other NMDAR antagonists, i.e. PCP or MK-801, in the 5-CSRTT were evaluated in several studies (Amitai et al., 2007; Auclair et al., 2009; Grottick and Higgins, 2000; Paine and Carlezon, 2009; Smith et al., 2011; Thomson et al., 2011). Moreover, Barnes et al. (2012) used the 5C-CPT in rats to assess the PCP-induced deficits.

Therefore, the present study sought to further examine the impact of ketamine on processes that are assessed in the 5-CSRTT in rats. To this aim, the schedules of drug administration that had been previously effective in evoking cognitive deficits on the ASST were used. In experiment 1, we assessed the effects of acute administration of relatively low ketamine doses (i.e., 3 and 10 mg/kg). A repeated schedule of ketamine (30 mg/kg) injections was applied in experiment 2, in which rats were tested the next day following ketamine administration. As this regimen of drug administration was able to produce long-lasting deficits of ASST performance (Nikiforuk and Popik, 2012), the rats performance on the 5-CSRTT was also assessed for several days after the last ketamine injection.

2. Experimental procedures

2.1. Animals

Male Sprague-Dawley rats (Charles River, Germany) weighing 350-370 g on arrival were used in this study. They were group-housed (4 rats/cage) in a temperature – (21±1 °C) and humidity – (40-50%) controlled colony room under a 12/12-h light/dark cycle (lights on at 06:00 h). Rats were allowed to acclimatise for at least 7 days before the start of the experimental procedure. For one week prior to testing, rats were food-deprived (17 g of food pellets per day) with ad libitum access to water. Behavioural testing was performed during the light phase of the light/dark cycle. The experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee for Animal Experiments, Institute of Pharmacology.

2.2. Five-choice serial reaction time task (5-CSRTT)

2.2.1. Apparatus

Eight five-choice operant chambers (Med Associates, USA), measuring $56 \times 56 \times 40.5\ cm^3$, were housed in sound-attenuated and ventilated cubicles. In each chamber, an array of five square nose-poke holes ($2.5 \times 2.5 \times 2.5\ cm^3$) was arranged on a curved panel and raised 2.5 cm from the grid floor. Each hole was equipped with an infrared detector and a yellow stimulus light at its rear. The food magazine, equipped with photocell beams and light, was located on the opposite wall. Food pellets (45 mg, Bioserves, USA) were delivered via a dispenser connected to the food magazine. A house light was located 17 cm above the top edge of the food magazine. Online control of the apparatus and data collection was performed using MED-PC (Med Associates, USA).

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