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Short communication

Effects of the competitive NMDA receptor antagonist CGP 37849 on performance of reference and working memory tasks by rats

Robert M.J. Deacon *, J. Nicholas P. Rawlins

Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD, UK

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Abstract

The effects of the competitive NMDA receptor antagonist CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid) were tested in rats performing (1) a nonspatial working memory task, and (2) a reference memory task that was either partly or fully learnt. CGP 37849 attenuated accuracy in all three tests, suggesting that sensorimotor effects may obscure any drug effects on memory itself.

Keywords: CGP 37849; Working memory; Reference memory; NMDA receptor

1. Introduction

NMDA receptors are involved in the development of long-term potentiation, the facilitated synaptic functioning which may underly certain types of memory (Bliss and Collingridge, 1993). CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid) is a compound which potently and competitively blocks these receptors, and so is a potential tool in the investigation of the cellular basis of learning and memory (Fagg et al., 1990).

NMDA receptor antagonists can attenuate learning and memory, particularly in spatial tasks. Impairments do not, however, always occur, and when they do may be related to task requirements, particularly the construction of new spatial representations (Shapiro and Caramanos, 1990). Paradoxically, facilitation of learning has sometimes been seen with CGP 37849, depending on task and dose variables (Lederer et al., 1993; Mondadori and Weiskrantz, 1993). Careful work is necessary to distinguish effects of NMDA receptor antagonists on learning from nonspecific sensorimotor deficits (Morris, 1990; Mondadori and Weiskrantz, 1993). One such approach is to vary the requirement for the formation of new memories. We assessed the performance of the same rats in a working memory recognition task in which multiple stimuli were presented, whose significance changed from one test session to the next, and in a reference memory task, in which only two stimuli of unchanging significance were used. This latter task, whose performance presumably made far less demand on the acquisition of new memories, was tested when partly learnt and later after a period of overtraining, further differentiating the memory component from task performance itself.

2. Materials and methods

2.1. Subjects

The subjects were 12 male rats of the Dark Agouti strain (Bantin and Kingman, Hull, UK), housed in pairs in a room lit on a 12:12 h light-dark cycle (lights on at 07.00 h). They were maintained on water ad libitum and restricted to 15–25 g laboratory chow per pair (motivation and food wastage was variable), fed after testing each day. Rats were approximately 18 months old when the present studies took place, and had been extensively trained on working memory tasks for lists of stimuli (Deacon and Rawlins, 1995).

* Corresponding author. Tel. 01865 271428, fax 01865 310447.

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2.2. Apparatus

A Y-shaped enclosed maze was made of sheet alloy with walls 20 cm high and a clear Perspex lid. Each arm was 27 cm long and 12.5 cm wide. Distinctive goal boxes, each containing different objects, could be inserted into the ends of the maze arms (Aggleton, 1985). Guillotine doors separated the maze arms from these goal areas, and there was a central trefoil door at the junction of the three arms. Twenty different goal boxes were used for the working memory task and only two for the reference memory task.

2.3. Working memory task

The rats were initially trained on a nonmatching-to-sample paradigm in which they were rewarded with two food pellets (Noyes, 45 mg) when they avoided a recently seen goalbox and chose one that they had not seen before on that day (Aggleton, 1985). This task was then modified so that memory for lists of stimuli could be studied. Each day rats were rewarded for running to each of a set ('list') of ten boxes (list acquisition phase). They were then run to a 'blank' box (containing no objects), signalling the start of the test phase, and were subsequently given a series of ten choices between boxes seen during acquisition and boxes not seen before on that day; only choices of the latter were rewarded. Once the rats had made a choice they were detained in the goal box for 15 s and rewarded if correct. The list was tested backwards, so the last box of the acquisition phase was the first to be tested. The left-right position of all boxes during the forced acquisition run and of the correct box at test was predetermined according to a balanced schedule. The sequence of 20 boxes was individually randomised for each rat each day.

Approximately 30 min before the start of list acquisition each rat was given an i.p. injection of 3 or 6 mg/kg of CGP 37849 or the vehicle, saline, 1 ml/kg. The two doses were tested in separate consecutive experiments, the lower dose first. Each rat served as its own control, and received drug or saline on alternate days. On some control days a rat did not complete a run, so it was tested with a different box series the next day. This appeared to be a consequence of affective reactions to the injection procedure and did not occur in CGP 37849-treated animals, apparently due to sedative/anxiolytic actions of the drug. There were three saline and three drug days at each dose.

2.4. Reference memory task

Following the working memory task, rats were taught to discriminate between two entirely novel different goal boxes. One box was always rewarded, the other never. Box allocation was counterbalanced between subjects. Each rat ran 20 trials (in one block) a day. The first ('partly learnt') test day was the one following the first day an individual rat scored 80%. Rats were consecutively allocated to saline or CGP 37849 (6 mg/kg i.p.), given 30 min before testing. Rats served as their own controls, and received the complementary dose the next day.

After all rats had completed the two 'partly learnt' test days, five further training days were given. Following this overtraining period, the drug testing procedure was repeated for two 'fully learnt' test days.

3. Results

The compound produced overt behavioural effects. At the lower dose rats were slightly tranquillised, with muscle tone lower than normal. At 6 mg/kg these effects intensified and slight to moderate sedation and ataxia occurred. Perhaps due to the apparent anxiolytic effects, rats often ran better after administration of CGP 37849.

3.1. Working memory

There was a dose-related impairment of accuracy by CGP 37849 (see Fig. 1). Statistical analysis by Student's t-test (paired) showed both dose effects were significant. For 3 mg/kg: $t = 2.40$, $df = 11$, $P = 0.035$; for 6 mg/kg: $t = 2.97$, $df = 11$, $P = 0.013$.

3.2. Reference memory

The rats partly learnt the task in a mean of 3.5 days (includes the 80% criterion day). CGP 37849 reduced

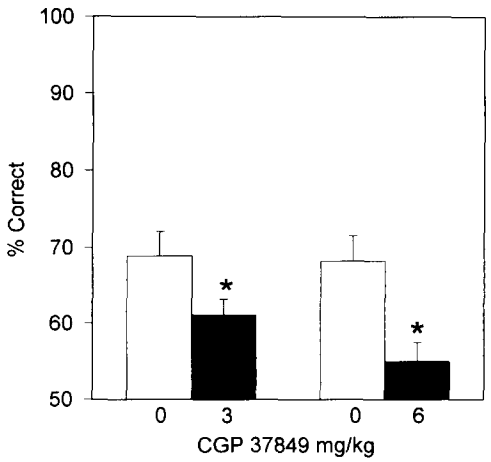

Fig. 1. Percentage correct scores (mean and S.E.M.) in the working memory task for rats given 3 or 6 mg/kg i.p. of CGP 37849, 30 min pre-test. Asterisks denote $P < 0.05$, Student's t-test.

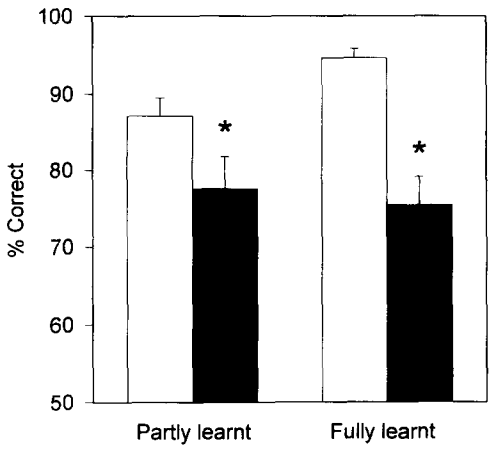

Fig. 2. Percentage correct scores (mean and S.E.M.) in the reference memory task for rats given 6 mg/kg i.p. of CGP 37849, 30 min pre-test when the task was partly or fully learnt. Asterisks denote $P < 0.05$, Student's t-test.

accuracy to a similar level irrespective of whether the task was partly or fully learnt (see Fig. 2). For the partly learnt task: $t = 2.82$, $df = 11$, $P = 0.017$: for the fully learnt, $t = 5.06$, $df = 11$, $P = 0.0004$.

4. Discussion

CGP 37849 not only impaired performance on a working memory task requiring recognition memory of ten different stimuli a day, but also performance on a reference memory task using only two unchanging stimuli. Moreover, in the reference memory task, the accuracy impairment was not alleviated by overtraining in the 'fully learnt' condition. Assuming that the three paradigms place very different demands on acquisition of new memories, but similar demands on purely performance-related factors such as attention, perception and motor function, drug effects on performance would seem to predominate. Detailed studies might possibly show working memory tasks to be slightly more susceptible to CGP 37849 within a very narrow dose range. However, although a dose of 6 mg/kg was necessary to notably impair a working memory task which placed high demands on acquisition of new memories (the effect of 3 mg/kg being only just statistically significant) this dose had major effects on a reference memory task that required no new memory acquisition at all. For all practical purposes, therefore, the non-specific effects of CGP 37849 on task performance mask any putative specific effects on new memory acquisition.

An alternative interpretation is that the compound affects retrieval of memory to a similar extent regardless of the strength or age of the memory. However, NMDA receptor antagonists impair acquisition but not retention in other paradigms (Heale and Harley, 1990; Miserendino et al., 1990).

NMDA receptor antagonists are known to produce alterations in muscle tone and motor activity; CGP 37849 (4 mg/kg i.p.) approximately halved locomotor activity in rats in an open field (Kretschmer et al., 1992). The noncompetitive NMDA receptor antagonist MK-801 decreases responses to environmental stimuli (Dai and Carey, 1994), and produces hyperactivity, hyper-reactivity and sensorimotor deficits (Hargreaves and Cain, 1992).

Caramanos and Shapiro (1994) and Shapiro and Caramanos (1990), using the competitive NMDA receptor antagonist APV (aminophosphonovaleric acid) and the noncompetitive antagonist MK-801 in spatial tasks, also concluded that these drugs were not selectively affecting working rather than reference memory. In contrast, the competitive antagonists 3-[(±)-2-carboxypiperazin-4-yl]propyl-1-phosphonic acid (CPP) and *cis*-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755) have been reported to impair working but not reference memory in a three-panel runway task (Ohno et al., 1992). Differences in drugs, procedure and mnemonic requirements between studies may underly these discrepancies.

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