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Learning impairments induced by glutamate blockade using dizocilpine (MK-801) in monkeys

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1 This study investigated the effects of dizocilpine (MK-801) on learning ability in a non-human primate. Acquisition and reversal learning of visual discrimination tasks and acquisition of visuo-spatial discrimination tasks were assessed in marmosets using the Wisconsin General Test Apparatus. Dizocilpine impaired acquisition of visuo-spatial (conditional) tasks requiring spatial responses to coloured objects, and perceptually difficult visual discrimination tasks in which stimulus objects are painted black. Dizocilpine did not, however, impair either acquisition or reversal of a simple visual discrimination task using easily discriminated, coloured objects.

2 Motor effects of dizocilpine treatment, which have been seen in other primates, were examined by observation of the marmosets in their home cages, using both an automated locomotor activity monitor and 'blind', subjective counting of the number of abnormal movements in a given time period. Locomotor activity, assessed using the automated monitor, was not significantly affected at any of the doses tested. Incoordination, assessed by human observation of abnormal movements, was significantly increased only at a dose of 30 μg kg^{-1} i.m., which was twice the highest dose used to assess the effects of dizocilpine on cognition.

3 We have, therefore, found an effect of dizocilpine on acquisition and reversal of some types of cognitive task, at a dose which does not cause significant motor effects. This demonstration of a cognitive deficit associated with glutamatergic blockade in a primate may be useful in understanding the contribution of glutamatergic dysfunction to cognitive decline in neurodegenerative disease, especially Alzheimer's disease.

Keywords: Dizocilpine; glutamate; NMDA antagonist; learning; primate; Alzheimer's disease; pyramidal cells; neocortex; hippocampus; cognition

Introduction

Glutamatergic neurones include the pyramidal cells of the cortico-cortical association loops and the cortical-hippocampal-cortical loops (Ottersen, 1991; Van Hoesen, 1982) which are thought to be implicated in cognitive processing (Francis *et al*., 1992). The *N*-methyl-D-aspartate receptor (NMDA receptor) for glutamate is located throughout the central nervous system, and is found at a particularly high density within the hippocampus and in certain forebrain and cortical regions, including the outer layers of the frontal and parietal cortex (Monaghan & Cotman, 1985). Dizocilpine (MK-801) is a highly specific non-competitive NMDA antagonist (Wong *et al*., 1986) which crosses the blood-brain barrier following systemic administration (Iversen & Kemp, 1996). Dizocilpine administration could, therefore, affect cognitive processing by reducing transmission in the pyramidal cell pathways.

Several studies of the behavioural effects of NMDA receptor blockade have been carried out in rodents, with a variety of effects being observed depending on the tasks used. Of particular relevance to the current study is the work by Murray *et al*. (1995; 1997), in which visual, spatial and visuo-spatial discrimination tasks in a rat Y-maze were used. These tasks are two choice discrimination tasks and are, therefore, comparable to tasks performed in the Wisconsin General Test Apparatus (WGTA) with marmosets and other primates. Murray *et al*. (1995) found that dizocilpine impaired both acquisition and reversal of a visual discrimination task, but only impaired the reversal component on a spatial task. Performance of control rats showed that the visual task was more difficult than the spatial task, which was particularly easy. This may explain the lack of effect of dizocilpine on spatial task acquisition in the Y-maze, in contrast to effects which are seen on the type of spatial learning seen in a water or radial maze (e.g. Morris *et al*., 1986; Robinson *et al*., 1989; Shapiro & Caramanos, 1990).

Studies of the effects of glutamatergic blockade in primates have also demonstrated learning impairments, though we are unaware of any previous studies in marmosets. In rhesus monkeys, Buffalo *et al*. (1994) showed effects of $\geqslant$30 μg kg^{-1} i.m. dizocilpine on learning (assessed by an acquisition task in which subjects learnt a series of progressively more complex sequences of lever presses each session) and short term memory (assessed with a delayed matching-to-sample task). Doses $\geqslant$56 μg kg^{-1} i.m. impaired accuracy in performance of previously learnt colour and position discrimination tasks and had a significant effect on motivation, as assessed by a progressive ratio task in which increased number of lever presses were required for each subsequent reinforcement. Boyce *et al*. (1991) found that dizocilpine could induce a deficit in the performance of a spatial delayed response task by well-trained rhesus monkeys; administration of 20 μg kg^{-1} dizocilpine caused a performance decrease which failed to reach significance, while 40 μg kg^{-1} dizocilpine caused a marked disruption in accuracy at long retention intervals. It was noted that two out of nine animals were slightly ataxic and appeared sedated at the higher dose. As well as assessing cognitive tasks in the rhesus monkey, the study also examined

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motor effects in the squirrel monkey, and ataxia, bradykinesia, head-weaving behaviour and a reduction in locomotor activity were seen at a dose of 100 μg kg^{-1}.

Although some of the effects of NMDA blockade may result from non-cognitive effects on performance competence, motor ability or motivation, as shown by the experiments described above, there would appear to be a specific effect of dizocilpine on cognitive processes at doses lower than those which impair these other aspects of performance. Since acquisition of the visual discrimination task and visuo-spatial discrimination task in the WGTA depend on the integrity of the neocortex (Fine *et al*., 1997) and hippocampus (Ridley *et al*., 1988; 1989; 1995) respectively, we decided to examine acquisition of these particular tasks. We also examined the effects of dizocilpine on reversal learning of the visual discrimination tasks. 'Learning curves' for reversal tasks allow demonstration of differences in the effects of drugs on learning and memory processes. Reversal of visuo-spatial tasks was not attempted because the visuo-spatial tasks are difficult for marmosets and reversal of this type of task would have been very demanding, even for saline treated monkeys. In addition to investigation of the cognitive effects of glutamatergic blockade by dizocilpine in the marmoset, the motor effects of dizocilpine were also examined.

Methods

Animals

A total of 14 laboratory bred common marmosets (*Callithrix jacchus jacchus*) were used, but not all marmosets were available for all experiments. All were over 12 months old, i.e. young adults, at the start of the study and weighed 300–350 g. Seven of the monkeys had been well trained in a variety of tasks, since they had previously been part of unoperated control groups in two other studies (Fine *et al*., 1997; Harder *et al*., 1996). Seven experimentally naive marmosets were trained prior to beginning the studies, such that all animals were accustomed to the WGTA, and performed approximately 30 to 40 trials per day. There was no difference in cognitive performance between animals with different training histories. The marmosets were maintained on a diet of bread, eggs, fruit and monkey food pellets (Mazuri), supplemented by vitamin D3, and were fed after testing each day. During performance of tasks in the WGTA, monkeys were rewarded for correct responses with bread bits soaked in syrup and/or pieces of marshmallow.

Drug treatments

Drugs were administered by intramuscular injection 20 min before testing on each day as appropriate. Dizocilpine maleate [(+)-MK-801 hydrogen maleate] (supplied by Sigma-Aldrich Co. Ltd., U.K.) was diluted in 0.85% sterile saline and injected in a volume of approximately 0.1 ml to each marmoset at doses of 6, 15 and 30 μg kg^{-1} i.m. A 0.1 ml injection of saline alone provided a vehicle control treatment.

Cognitive testing and experimental design

Three types of cognitive task were examined. Perceptually simple visual discrimination tasks involved presentation of two easily distinguishable (coloured) junk objects (A and B), one over the left and one over the right hand food wells of the test apparatus. The reward was placed in one of the food wells according to a pseudo-random schedule, and the rewarded (positive) object A, was placed over it, whilst the unrewarded (negative) object B, was placed over the other (empty) food well. When the shutter was raised, the marmoset could reach through the bars of the test cage to move one object and retrieve the reward (if the correct object was chosen). Perceptually complex visual discrimination tasks were identical in form to the perceptually simple tasks, but the objects were spray painted with matt black car paint, thus making discrimination between objects more difficult (i.e. increasing the perceptual processing required). Both of these tasks are 'evaluative', i.e. they involved formation of an association between a particular object and reward (Ridley *et al*., 1991). By contrast, in visuo-spatial discrimination tasks, the objects placed over the right and left hand food wells were identical, either A A or B B. The 'rule' was that when A and A were presented, reward was under the right hand A, whilst when B and B were presented, the reward was under the left hand B. AA trials and BB trials were presented in pseudorandom order. Thus, visuo-spatial discrimination tasks are 'conditional' rather than 'evaluative' (Ridley *et al*., 1991) because AA and BB were equally associated with reward.

Trials of all three types of task were presented according to a pseudo-random schedule of left or right reward placements, until marmosets achieved a 90% correct criterion, i.e. the marmoset made 27 correct responses out of 30 consecutive trials, in order for the task to be considered 'learnt'. The number of trials undertaken by the marmoset before the 30 criterion trials was the 'learning score' (LS). The higher the LS, the more trials were needed to learn the task, and thus the more difficult the animal had found it to learn the task.

In each acquisition experiment, the marmosets learnt four consecutive tasks, using new objects for each task. All tasks were presented in the same order, such that interference between stimuli was kept equivalent between monkeys. Treatments were given daily for the duration of learning each task, in the order saline, dizocilpine, dizocilpine, saline (SDDS) for half of the marmosets tested, and in the order dizocilpine, saline, saline dizocilpine (DSSD) for the other half, thus balancing treatments across tasks. This design was used for perceptually simple visual discrimination acquisition, perceptually complex visual discrimination acquisition and visuo-spatial discrimination acquisition. The acquisition experiments were repeated, using new objects each time, for each dose of dizocilpine tested (6 and 15 μg kg^{-1}).

Reversal learning experiments used only the 15 μg kg^{-1} dose of dizocilpine. Again, four consecutive tasks were used for perceptually simple visual and perceptually complex visual discrimination experiments. Again, the SDDS or DSSD regimens were used, but in this case all acquisition took place without treatment and it was only during the reversal training that drug/saline treatment occurred. Thus, initial drug free learning of each task to a 27/30 criterion was followed, after a minimum of 24 h, by dosing with either drug or saline, and then reversal of the reward contingency, again to a criterion of 27/30.

The learning scores were averaged for the tasks learnt under saline and the tasks learnt under dizocilpine treatment, thereby balancing for practice effects.

Assessment of motor effects of dizocilpine

Four marmosets were observed in their home cage by an experimenter who was blind to the dose of dizocilpine received by the monkey for a period of 110 min following injection. Each marmoset received each dose of dizocilpine (or saline)

once only on separate days. Scores were taken for a 5 min period out of each 15 min following injection for each monkey. Behaviours such as missing a footing, staggering, or poor landings on jumps were counted to make up the 'incoordination count'. Any abnormal lack of co-ordination was easily seen in these marmosets because they are extremely sure-footed in their home cage under normal circumstances, and are very active. A very low subjective criterion was used for incoordination scoring such that any behaviour that could possibly have been evidence of motor dysfunction was scored; normal behaviour under saline treatment had a low, positive incoordination count and a small, raised incoordination count did not indicate that the animal had any difficult achieving the objectives of the movement. The mean incoordination count for each dose of dizocilpine was calculated over time.

During this period, the animals were also monitored by a motion detector mounted on the home cage. The detectors were connected to a BBC microcomputer running a program designed to measure locomotor activity in time bins, and activity was taken for each 15 min period during the first 105 min following drug treatment. The total activity for each marmoset at each dose of dizocilpine and saline was recorded, and the means of these activity scores were calculated.

Two independent assessments of motor effects were used because it was expected that any gross changes in motor behaviour would be picked up by automated scoring, while more subtle changes would be more easily detected by human observation.

Statistical analysis

Data were analysed using the Statview II software package on an Apple Macintosh computer. The mean learning scores for saline and drug treated tasks for each marmoset were compared using a matched pairs two-tailed *t*-test. Motor data were analysed using repeated measures ANOVA followed by *post hoc* Scheffé *f*-test, for both automated locomotor activity scores and incoordination counts, to compare the different doses with one another. In all cases, $P<0.05$ was considered to show a significant difference.

Results

Acquisition of perceptually simple visual discrimination tasks (coloured objects)

Neither dose of dizocilpine (6 or 15 μg kg^{-1}) affected learning of simple discriminations (two tailed matched pairs *t*-test for each dose compared to relevant saline control, $P>0.05$). See Table 1.

Acquisition of perceptually complex visual discrimination tasks (black painted objects)

There was no significant effect of dizocilpine at a dose of 6 μg kg^{-1} on the acquisition of visual discrimination tasks using black objects. At the higher dose of dizocilpine (15 μg kg^{-1}), there was a significant increase in the number of trials taken to reach criterion ($P<0.005$, two tailed matched pairs *t*-test). (Table 1).

Acquisition of visuo-spatial discrimination tasks

6 μg kg^{-1} dizocilpine produced a non-significant increase in learning score, whilst the 15 μg kg^{-1} dose produced a significant increase in the number of trials required to achieve criterion ($P<0.05$, two-tailed matched pairs *t*-test). (Table 1).

Reversal of simple visual discrimination tasks (coloured objects)

15 μg kg^{-1} dizocilpine had no effect on learning scores (Table 2). Learning curves for this experiment (Figure 1) show that under saline marmosets very rapidly abandoned the association between stimulus and reward. Under dizocilpine, marmosets were significantly above chance only for the first ten trials. Thereafter, they learnt the reversal at almost the same rate as under saline.

Reversal of perceptually complex visual discrimination tasks (black painted objects)

15 μg kg^{-1} dizocilpine increased the learning score for reversal learning, i.e. marmosets were impaired at learning the new

Table 2 The effect of 15 μg kg^{-1} dizocilpine on reversal learning of cognitive tasks in the marmoset

Task	*Saline*	*15 μg kg^{-1} dizocilpine*	P
Simple visual discrimination (coloured objects)	51.3±17.4	106.5±31.3	NS
Perceptual visual discrimination (black objects)	82.6±8.6	158.8±19.2	<0.05

Significant differences from saline control determined by matched pairs *t*-test, $n=5-6$.

Table 1 The effect of dizocilpine on acquisition of cognitive tasks in the marmoset

A: 6 μg kg^{-1} dizocilpine *Task*	*Saline*	*6 μg kg^{-1} dizocilpine*	P
Simple visual discrimination (coloured objects)	29.6±12.9	17.3±4.4	NS
Perceptual visual discrimination (black objects)	15.1±8.6	25.3±8.2	NS
Visuo-spatial discrimination	51.3±15.8	101.4±32.3	NS
B: 15 μg kg^{-1} dizocilpine *Task*	*Saline*	*15 μg kg^{-1} dizocilpine*	P
Simple visual discrimination (coloured objects)	11±1.5	15.3±2.9	NS
Perceptual visual discrimination (black objects)	24.4±7.8	78.5±12.3	<0.005
Visuo-spatial discrimination	32.8±9.5	90.9±5.0	<0.02

Significant differences from saline determined by matched pairs *t*-test, $n=4-6$.

reward contingency (in which the previously rewarded object was now unrewarded, and the previously incorrect object now indicated reward) (Table 2). Learning curves for this experiment (Figure 2) show that marmosets began reversal learning with worse than chance performance under either saline or dizocilpine, suggesting that dizocilpine does not impair memory of the previously acquired reward contingency. However, the subsequent improvement to criterion (<10% errors), i.e. the learning of the new reward contingency, occurs more slowly under dizocilpine than under saline.

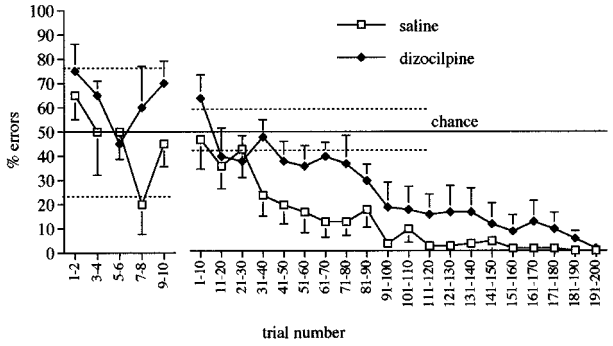

Figure 1 Learning curves for the reversal of perceptually simple (coloured object) visual discrimination tasks. The number of errors in blocks of trials from both tasks learnt under saline and both tasks learnt under dizocilpine (15 μg kg^{-1}) were averaged for each marmoset, and expressed as a percentage of trials performed. The left hand side of the graph shows the first ten trials in blocks of two trials, whilst the right hand panel shows all trials (including the first ten) in blocks of ten trials. Maximum number of trials is 200, as animals who had not successfully achieved a criterion of 27 correct responses out of 30 consecutive trials after 200 trials were given a learning score of 200 and went onto the next task. $n=5$.

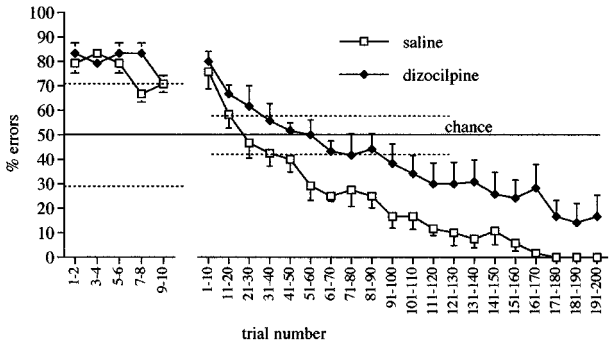

Figure 2 Learning curves for the reversal of perceptually complex (black painted object) visual discrimination tasks. The number of errors in blocks of trials from both tasks learnt under saline and both tasks learnt under dizocilpine (15 μg kg^{-1}) were averaged for each marmoset, and expressed as a percentage of trials performed. The left hand side of the graph shows the first ten trials in blocks of two trials, whilst the right hand panel shows all trials (including the first ten) in blocks of ten trials. Maximum number of trials is 200, as animals who had not successfully achieved a criterion of 27 correct responses out of 30 consecutive trials after 200 trials were given a learning score of 200 and went onto the next task. $n=6$.

Motor effects

There was no significant effect of dizocilpine on mean locomotor activity as measured using the automated equipment at the doses tested (6–30 μg kg^{-1}).

The highest dose (30 μg kg^{-1}) of dizocilpine had a significant effect on the number of uncoordinated movements, assessed by human observation ($P<0.05$, ANOVA followed by Scheffé *f*-test). Neither 6 nor 15 μg kg^{-1} dizocilpine had a significant effect on uncoordinated movement counts ($P>0.05$, ANOVA followed by Scheffé *f*-test) suggesting that the doses used in the cognitive studies did not have substantial motor side effects. (Table 3).

Discussion

Dissociation of cognitive and motor effects of dizocilpine

Marmosets treated with dizocilpine display deficits in the acquisition and reversal of perceptually complex visual discrimination tasks and the acquisition of visuo-spatial discrimination tasks. No deficits are seen in acquisition or reversal of perceptually simple visual discrimination tasks. The selective nature of this impairment, with deficits on some tasks but not on others, suggests that the impairments are not caused by non-specific changes in motivation or motor ability, since the motor skills required to select objects and retrieve rewards are identical in all tasks. Furthermore, marmosets treated with dizocilpine showed worse than chance performance comparable to that shown by saline treated marmosets at the beginning of reversal of the perceptually difficult discrimination. In order to perform at 'worse than chance' the marmosets must have been capable of all the cognitive skills required to make a non-random choice and to show good memory of previously acquired information. Nonetheless, they were impaired at learning the reversal. Finally, the motor impairments seen in our motor assessment were limited to a mild loss of coordination, with no change in locomotor activity. These data are qualitatively similar to those reported by Boyce *et al*. (1991), who observed incoordination in the squirrel monkey at a dose of 100 μg kg^{-1} dizocilpine, but did not report any change in locomotor activity. The highest dose used in our study (30 μg kg^{-1}) induced mild loss of coordination over a period lasting approximately 1 h following injection. The lack of any significant effect in either locomotor activity or coordination at 15 μg kg^{-1} dizocilpine suggests that impairments seen in the WGTA were not caused by motor side effects. During cognitive testing with this dose the animals were behaving normally, i.e. marmosets were reaching accurately through the bars of the test cage to touch small objects and were able to retrieve small rewards with precision.

Table 3 Effect of dizocilpine on motor behaviour in the marmoset

	Vehicle (saline)	*6 μg kg^{-1} dizocilpine*	*15 μg kg^{-1} dizocilpine*	*30 μg kg^{-1} dizocilpine*
Counts by automatic activity monitor (counts/15 min)	1980±462	2028±210	2122±513	3271±1525
'Wobble' score of atypical movements (occurrences/5 min)	0.75±0.48	0.25±0.25	6.75±1.93	20.5±7.44*

*Significant difference from saline determined by repeated measures ANOVA followed by *post hoc* Scheffé *f*-test ($P<0.05$) ($n=4$).

Neural substrates of the cognitive effects of dizocilpine

Pyramidal neurones form both corticocortical association pathways and connections from the rhinal cortex to the hippocampus and back (Ottersen, 1991; Van Hoesen, 1982). Glutamatergic pyramidal cells are, therefore, likely to be involved in cognitive processing, although the information which they handle is likely to depend on the area of cortex or hippocampus involved. Glutamatergic pyramidal cells in both the cortex and hippocampus are modulated by cholinergic and serotonergic afferents (Francis *et al*., 1992; 1994). Since acetylcholine increases glutamate release, providing positive modulation to the pyramidal pathways, one would predict that cholinergic and glutamatergic blockade would have similar cognitive effects. The effects of scopolamine on acquisition of simple visual discriminations, perceptually complex visual discriminations and visuo-spatial discriminations are comparable to the effects of dizocilpine seen in this study; the acquisition of visuo-spatial tasks is most severely affected, acquisition of perceptually complex visual discriminations is significantly affected, whilst acquisition of simple visual discriminations is least affected by glutamatergic or cholinergic blockade (Harder *et al*., 1998).

Visual discrimination tasks using coloured objects and black objects both require an association to be made between the objects and the reward which is used to motivate responding. These tasks differ in that the black object discrimination requires an analysis of the visually integrated shape of the objects, whereas the coloured object discrimination can be solved by identifying distinctive coloured components of the objects (e.g. a red top or a green base). Specific destruction of the cholinergic projections to the neocortex (particularly the temporal association cortex) results in a greater impairment on black object than on coloured object discriminations (Fine *et al*., 1997). This impairment may be equivalent to the visual agnosias seen after temporal association lesions in humans. The effect of dizocilpine on black object discrimination may be located within the temporal association cortex which contains glutamatergic corticocortical projections.

Analysis of reversal learning curves indicates that for coloured object discriminations, dizocilpine does not disrupt the ability to abandon one reward association rapidly when reward is not forthcoming, and then learn the opposite reward association. The reversal curve for the black object tasks indicates that dizocilpine does not affect memory for reward association, and reversal learning is retarded throughout acquisition of the reversed reward contingency. This is consistent with impaired perceptual analysis of the black object stimuli.

Lesions of the fornix (Harder *et al*., 1996) or hippocampus (Ridley *et al*., 1995) produce a specific and severe impairment on visuo-spatial tasks. From this it may be supposed that it is the effect of dizocilpine on glutamatergic cortico-hippocampal projections which is responsible for the visuo-spatial impairment.

Neuropathological studies have shown that the glutamatergic corticocortical and hippocampal pyramidal cell pathways degenerate early in Alzheimer's disease (Braak & Braak, 1991) and several studies have indicated that the loss of corticocortical pyramidal neurones correlates with the severity of dementia (DeKosky & Scheff, 1990; Terry *et al*., 1991). Pharmacological compensation for the loss of glutamatergic function may provide the basis for a treatment for the cognitive symptoms in Alzheimer's disease (Francis *et al*., 1992; 1994; Bowen *et al*., 1992; 1994). Such treatment could employ partial glutamate agonists, 5-HT_{1A} antagonists or muscarinic agonists (Francis *et al*., 1994; Bowen *et al*., 1992), or a combination of these treatments. The demonstration of cognitive deficits following glutamatergic blockade provides an experimental situation in which the therapeutic effects of drugs which act directly or indirectly on glutamate transmission can be assessed.

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