

Research report

Memory-dependent novelty-related location preferences: Sex-related attenuation of forgetting by D-glucose and tacrine

Robert N. Hughes*

Department of Psychology, University of Canterbury, Private Bag 4800, Christchurch, New Zealand

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Abstract

Following confinement to one chamber of a two-chamber exploration box (acquisition trial), male and female rats were intraperitoneally injected with saline, glucose (50, 100 mg/kg) or tacrine (1, 3 mg/kg). Twenty-four hours later they were given free access to this chamber and an identical novel one (retention trial). Tendencies to occupy the novel chamber (novelty-related location preferences) were increased by both doses of glucose for females and by the higher dose for males. While neither dose of tacrine affected this response for females, increased preferences occurred for males following the higher dose. However, when the higher doses of both agents were administered 2 h after acquisition, there were no significant effects for either sex. In view of the rats' lack of significant preferences for the novel chamber when treated with saline both immediately and 2 h after acquisition, the results were interpreted as sex-dependent attenuation of forgetting by post-acquisition treatment with both agents.

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1. Introduction

Rats and mice have been frequently shown to have preferences for the more novel of two mirror-image halves of an exploration box when allowed to choose freely between them ([8,9,13,30]; for a review see [14]). As memory is likely to be involved in the animals' ability to distinguish between the more and the less novel alternatives, novelty-related location preferences may provide a useful way of measuring drug-modified memory that does not depend on learning and conventional reinforcement. However, if distinctions between drug effects on attentional/encoding processes and consolidation (or storage) are required, then it is necessary to adopt the equivalent of post-acquisition treatment in studies of memory based on learning [4,32]. Within a novelty preference paradigm, this equivalent would comprise drug treatment after exposure to the alternative that will comprise the less novel during testing. To ensure that subsequent

behavior is determined by effects on memory, rather than on performance or some motivational state such as fear, testing should also be carried out after sufficient time has elapsed for acute effects of the drug to have worn off [19].

Glucose has been shown to improve memory in a variety of experimental situations possibly through facilitated synthesis of the "memory transmitter" acetylcholine (ACh), although alternative mechanisms have been proposed, such as improved glucose uptake in brain areas where extracellular glucose is low [29]. Likewise, there is abundant evidence that increased brain ACh levels following treatment with the acetylcholinesterase inhibitor, tetrahydroaminoacridine (tacrine), are associated with memory improvements [6]. The present study aimed to investigate the potential of novelty-related location preferences as a quick, valid test of memory by assessing the effects of glucose and tacrine on rats' ability to distinguish between the novel and less novel ("familiar") halves of an exploration box. Since both compounds enhance memory, their effects on novelty-related location preferences could enable an assessment of the extent to which such preferences reflect the operation of memory processes.

* Tel.: +64 3 364 2879; fax: +64 3 364 2181.

E-mail address: rob.hughes@canterbury.ac.nz.

The apparatus and procedure adopted were modified versions of those used by the present author and co-workers for determining acute effects of a range of behaviorally active drugs on preferences for novelty and activity [8,10,13,20,21,25].

Sex differences in effects of behaviourally active drugs and other influences have been a frequent outcome in studies of both novelty-related location preferences [8,11,22,26] and related recognition of novel stimulus changes in a Y maze [16,18,23]. Therefore, the possibility of similar outcomes was taken account of in the present study by examining the effects of the drug treatments in male and female rats separately.

2. Experiment 1: treatment with glucose and tacrine immediately following acquisition

In earlier work (referred to above), novelty-related location preferences have usually been determined by confining rats to one half of a square four-chamber exploration box for 2 h followed by drug administration and then, 20 min later, allowing them to freely venture into the novel mirror-image half from the two previously experienced familiar chambers. For 10 min, the time spent in the novel versus familiar half, and ambulation within and between each were typically recorded. While this would enable drugs to act on consolidation of information acquired during confinement, acute pharmacological effects on other processes could not be ruled out because the subjects were tested while still under the drugs' influence. Therefore, the procedure adopted in the present experiment was essentially the same as earlier except that a two (rather than four)-chamber box was used and, 24 h later, the rats were tested for 5 (rather than 10) min after the agents' acute effects had worn off. The shorter time of testing reflected the smaller size of the apparatus and the goal of achieving a quick but valid test of memory that does not depend on learning. Previous unpublished observations had supported a memory basis for this task by establishing significant preferences (but without a sex difference) for the more novel chamber when eight male and eight female rats were confined to one chamber, injected with isotonic saline and tested 20 min later (mean (\pm S.E.M.) preference = 55.26 (\pm 2.42)%, one-sample $t(15) = 2.17$, $P < 0.05$).

2.1. Materials and methods

2.1.1. Animals

The subjects were 24 male and 24 female Long-Evans hooded rats, approximately 5 months old. They were housed in cages of 3 or 4 same-sexed animals and kept in 12-h light:12-h dark conditions with an ambient temperature of 20 ± 1 °C, and with ad libitum food and water. They were tested during the dark phase of their light/dark cycle. All rats were maintained and tested in accordance with requirements of Parts 5 (Codes of Welfare) and 6 (Use of Animals in Research, Testing, and Teaching) of the New Zealand

Animal Welfare Act, 1999. All drug treatment and testing procedures were approved by the University of Canterbury's Animal Ethics Committee.

2.1.2. Apparatus

The rats were tested in one of four exploration boxes that were positioned beside each other (55 cm apart) on a table in the center of a room illuminated by overhead fluorescent lighting. Each box comprised two 20 cm \times 20 cm \times 20 cm chambers (internal dimensions) connected by an 8 cm \times 20 cm-high doorway in the wall between them. During acquisition trials, this doorway was closed by means of a retractable guillotine slide. The back and side walls of each chamber and the guillotine slide were constructed from wood and were painted black, and the roof and front wall comprised clear Perspex. The light levels on the floor of the four boxes ranged from 42 to 45 lx. A computer and keyboard sat on another table facing the clear front walls of the boxes from where a seated observer recorded the animals' behavior. No rat was able to see the occupants of the other three boxes.

2.1.3. Memory-enhancing agents

Rats were intraperitoneally injected with either isotonic saline (0 mg/kg), 50 or 100 mg/kg D-glucose, or 1 or 3 mg/kg tacrine (1,2,3,4-tetrahydro-9-amino-acridine hydrochloride, Sigma–Aldrich, Australia) in volumes of 1 ml/kg. Both compounds were dissolved in fresh saline. The doses chosen were within the ranges of those shown to improve rats' memory in other experimental situations [24,33].

2.1.4. Procedure

Half the rats were assigned to a group that would be administered saline or glucose, and the other half was assigned to a group to receive saline or tacrine. In squads of four, each rat was confined for 2 h to one chamber of an exploration box with the slide separating the two chambers in place i.e., an acquisition trial. It was then removed and administered either saline, or a dose of the compound appropriate to the group it had been assigned to. Twenty-four hours later, it was returned to the same chamber of the same box from which the slide separating the two chambers had been removed. For exactly 5 min, the total time the rat spent in each chamber and, as an estimate of locomotor activity, the number of transitions it made between the two were recorded i.e., a retention trial. Every 2 or 3 days later, the whole procedure was repeated until the rat had experienced two acquisition trials (being confined to the left chamber for one, and to the right for the other) followed by two retention trials with saline and each dose of the compound appropriate to its group.

The order of administration of the three doses was randomised for each rat. As novelty-related location preferences are partially dependant on the presence of self-generated odor cues [12,15], the box was not cleaned between acquisition and retention trials, but, between different rats, it was thoroughly washed with a 4% solution of Powerquat Blue (150 g/l alkylbenzyltrimethylammonium chloride).

2.2. Results

For each rat in each memory-enhancing agent group, the percent time/day that the novel chamber was occupied (novelty-related location preference) and the transitions/day between the two chambers was calculated. The effects of

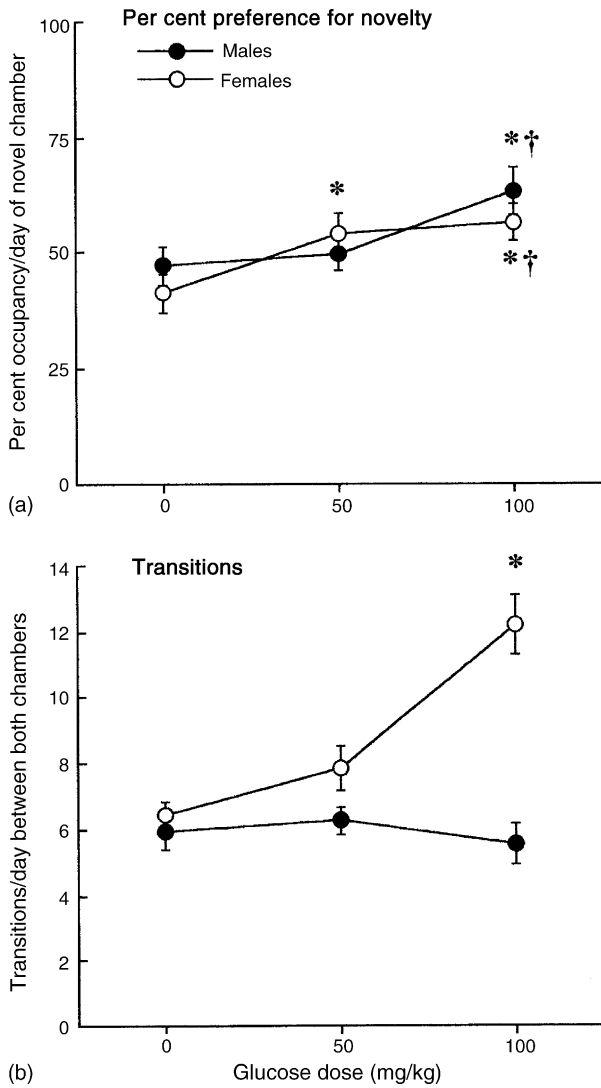


Fig. 1. Mean (\pm S.E.M.): (a) percent time/day spent in the novel chamber (preference for novelty) and (b) transitions between the two chambers following post-acquisition treatment with glucose for males ($n = 11$) and females ($n = 12$). *Significantly different from saline (0 mg/kg) treatment condition. †Significantly greater than a chance expectancy of 50%.

the two agents on the two responses were assessed by independent two-way repeated measures ANOVAs for each sex separately.

2.2.1. Effects of glucose

The data from one male rat was excluded from analyses because of a failure to move from the familiar chamber on most occasions. Results of the post-acquisition glucose treatment for all other rats are outlined in Fig. 1.

The glucose effect on later occupancy of the novel chamber was significant for both males ($F(2,20) = 4.11$, $P < 0.035$) and females ($F(2,22) = 6.95$, $P < 0.005$). As shown by Scheffé tests, this was due to significantly higher occupancy following 100 mg/kg for males, and following both doses for females. As shown by one-sample t -tests, preference for occupying the novel chamber was significantly greater than chance after

treatment with the higher dose for both males ($t(10) = 2.51$, $P < 0.035$) and females ($t(11) = 2.32$, $P < 0.05$). According to a between-groups t -test, the overall difference between the two sexes was not significant ($t(21) = 0.88$, NS).

While the dose effect on transitions was highly significant for females ($F(2,22) = 24.54$, $P < 0.0001$) because of increases following 100 mg/kg alone, there was no significant glucose effect on this response for males ($F(2,20) = 0.37$, NS). However, females made significantly more transitions than males ($t(21) = 2.93$, $P < 0.008$).

2.2.2. Effects of tacrine

Later effects of post-acquisition THA are shown in Fig. 2.

The drug effect on occupancy of the novel chamber was significant for males ($F(2,22) = 3.81$, $P < 0.04$) due to an

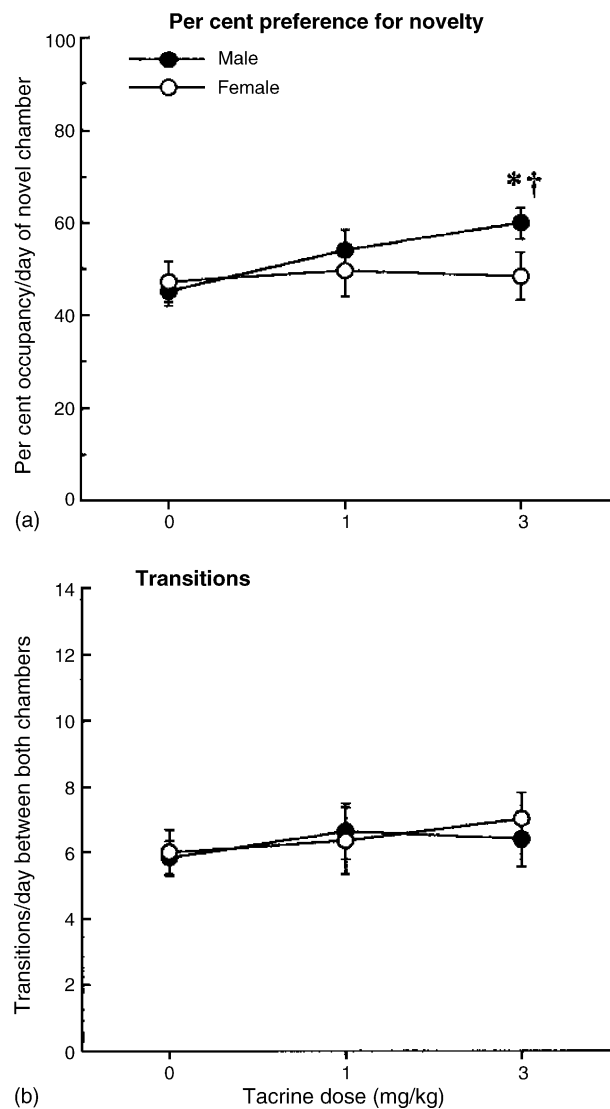


Fig. 2. Mean (\pm S.E.M.): (a) percent time/day spent in the novel chamber (preference for novelty) and (b) transitions between the two chambers following post-acquisition treatment with tacrine for males ($n = 12$) and females ($n = 12$). *Significantly different from saline (0 mg/kg) treatment condition. †Significantly greater than a chance expectancy of 50%.

increase with 3 mg/kg to the extent that it was significantly preferred to the familiar alternative ($t(11) = 3.04$, $P < 0.015$). However, the drug effect was not significant for females ($F(2,22) = 0.06$, NS). The overall sex difference was also not significant ($t(22) = 1.35$, NS).

The tacrine effect on transitions was significant for neither males ($F(2,22) = 0.07$, NS) nor females ($F(2,22) = 1.03$, NS), and the overall sex difference was not significant ($t(22) = 0.19$, NS).

2.3. Discussion

The effects of both compounds on occupancy of the novel chamber suggested sex-related improvements of memory through better recall of the chamber to which the affected animals had been previously confined, and thus greater preferences for the more novel alternative. However, as there were no obvious preferences for occupying the novel chamber following treatment with saline for both sexes, 50 mg/kg glucose and 1 mg/kg tacrine for males, and both doses of tacrine for females, it seems likely that, under these conditions, the rats may have forgotten which chamber they had been confined to 24 h beforehand. So, any increases in occupancy of the novel chamber (to the point where this chamber was preferred to the more familiar alternative) were probably due to attenuated forgetting. Because treatment with glucose and tacrine occurred after acquisition and was followed by testing in the apparent absence of their acute effects, it is reasonable to suggest that both compounds had acted on central memory processes.

The only effect of post-acquisition treatment on transitions was a subsequent increase following 100 mg/kg glucose for females only. Since this response is more likely to indicate heightened general activity rather than attenuated forgetting, it is difficult to account for the result. One possibility is glucose-induced establishment of an association with reduced fear of the apparatus and thus a greater tendency to shuttle between the two chambers. Although there is some limited evidence of anxiolytic or “calming” effects of glucose [3], this would not explain why generally less emotionally reactive female rats [2] would be more affected than males. Alternatively, it is possible that, even after 24 h, females were still experiencing a type of acute energising effect of the compound, which to some extent could have also determined their novelty-related location preferences. It was therefore deemed advisable to investigate the effects of post-acquisition glucose and tacrine administered to both sexes outside of a reasonable time-frame for any influence on the consolidation of acquired information to occur.

The greater number of transitions made by females in the glucose- (but not tacrine-) treated group reflected their higher level of locomotor activity compared with males. This type of sex difference in rats has been consistently reported for many years [2].

3. Experiment 2: treatment with glucose and tacrine 2 h after acquisition

In view of the effect of 100 mg/kg post-acquisition glucose on transitions in females, a second experiment was designed to assess the possibility that both glucose and tacrine were still exerting some acute action during retention trials. It was therefore decided to essentially repeat Experiment 1 but to administer the higher dose of each compound 2 h following (rather than immediately after) acquisition trials, by which time most consolidation in this type of task could reasonably be expected to have occurred. Thus, if the enhancement of novelty-related location preferences observed in Experiment 1 had been due to attenuated forgetting, the treatment might be expected to have no effect on this response. However, if persisting acute effects of the compounds had been responsible for the results, then there should be a similar outcome.

3.1. Materials and methods

The subjects were a further 20 male and 20 female hooded rats (approximately 4.5 months old) kept in the same conditions as for Experiment 1, and given acquisition and retention trials in the same exploration boxes. Post-acquisition intraperitoneal injections of either saline, 100 mg/kg glucose (for half the rats) or 3 mg/kg tacrine (for the other half) were given 2 h after each 2-h acquisition trial, when individual rats were confined to one chamber in a box. The rest of the procedure was identical to that adopted in Experiment 1. Each rat experienced two acquisition and two retention trials with either saline or, depending on its group, glucose and tacrine.

3.2. Results

Tables 1 and 2 outlined the effects of treatment with both compounds (for each sex separately) and the results of t -tests performed on novelty-related location preferences and transitions.

Neither compound had a significant effect on novelty-related location preferences for either sex. As shown by one-sample t -tests, there were no significant preferences for either chamber shown by males or females in any treatment condition. Nor was the overall sex difference significant

Table 1

Mean (\pm S.E.M.) per day of percent time spent occupying the novel chamber and total transitions between both chambers following treatment with glucose 2 h after acquisition, and results of repeated measures t -tests

	Saline	100 mg/kg	t (9)
Males			
Percent/day occupancy of the novel chamber	45.94 (± 6.09)	47.43 (± 6.22)	0.33
Transitions/day	6.00 (± 0.76)	4.80 (± 0.57)	2.48**
Females			
Percent/day occupancy of the novel chamber	47.69 (± 4.59)	50.03 (± 2.26)	0.50
Transitions/day	7.60 (± 0.71)	8.00 (± 0.60)	0.62

** $P < 0.04$.

Table 2
Mean (\pm S.E.M.) per day of percent time spent occupying the novel chamber and total transitions between both chambers following treatment with tacrine 2 h after acquisition, and results of repeated measures *t*-tests

	Saline	3 mg/kg	<i>t</i> (9)
Males			
Percent/day occupancy of the novel chamber	47.97 (\pm 2.67)	45.92 (\pm 3.47)	0.52
Transitions/day	9.65 (\pm 1.10)	6.95 (\pm 0.99)	2.20*
Females			
Percent/day occupancy of the novel chamber	52.92 (\pm 3.85)	56.38 (\pm 4.21)	1.13
Transitions/day	10.15 (\pm 0.95)	11.30 (\pm 0.82)	1.32

* $P > 0.05 < 0.10$.

in either treatment group (glucose—males = 46.68 (\pm 5.72), females = 48.86 (\pm 2.77), $t(18) = 0.34$, NS; tacrine—males = 46.95 (\pm 2.39), females = 54.65 (\pm 3.73), $t(18) = 1.74$, NS).

For males only, transitions were significantly reduced by glucose, and a similar reduction with tacrine approached significance. The overall sex difference (favoring females) in this response was significant in both treatment groups (glucose—males = 5.40 (\pm 0.63), females = 7.80 (\pm 0.57), $t(18) = 2.84$, $P < 0.015$; tacrine—males = 8.30 (\pm 0.84), females = 10.73 (\pm 0.78), $t(18) = 2.12$, $P < 0.05$).

3.3. Discussion

Because of the lack of effects on novelty-related location preferences of treatment with either glucose or tacrine 2 h after acquisition, the results of this experiment support the likelihood that, increases in this response with both compounds observed in Experiment 1, were due to attenuated forgetting, rather than to any persisting acute effects. However, the decrease in transitions for male (but not female) rats following treatment with both compounds suggests a currently inexplicable additional sex-dependent effect that is probably unrelated to modified memory processes. Although it is remotely possible that there may have been some acute effects still operating for males only, this seems unlikely because, while such effects were consistent with what can accompany activity changes with acute tacrine [31], they were contrary to what characterizes glucose [16].

Again the overall sex differences in transitions reflected the higher locomotor activity of female rats observed in a variety of other experimental settings [2].

4. Conclusions

The results of both experiments support dependence of novelty-related location preferences in an exploration box on rats' memory for the chamber to which they had been previously confined during acquisition trials. The sex-related increases in this response with both glucose and tacrine suggest enhanced memory in the form of attenuated forgetting. A related paradigm, spontaneous alternation behavior,

involves choosing the more novel of two T-maze arms based on memory for the more familiar alternative [19]. Spontaneous alternation is disrupted by hippocampal lesions and also by anticholinergic drugs injected either systemically or directly into the hippocampus [5]. Decreased exploration of a novel environment with repeated exposure (habituation learning or familiarization) is accompanied by increased activity of hippocampal acetylcholine [34]. Therefore, it is not unreasonable to propose that modified cholinergically based memory processes involving the hippocampus were mainly responsible for the effects of glucose and tacrine on responsiveness to novelty in the present study. Consequently, the procedure adopted in the two experiments would seem to have some potential as a quick and simple test of forgetting that does not rely on learning or conventional reinforcement.

The sex-related effects suggest sex differences in sensitivity to each of the compounds, namely, greater sensitivity to glucose by females, but greater sensitivity to tacrine by males. While in the related response-to-change paradigm pre-acquisition administration of glucose improved female (but not male) rats' ability to recognise an inter-trial change in Y-maze-arm brightness [16], this sex difference did not occur following post-acquisition treatment [17,24]. It is therefore possible that any sex difference (favoring females) in sensitivity to glucose could depend on the particular experimental setting in which the rats are tested. Nevertheless it is still possible that, in both the earlier study [16] and Experiment 1 of the present investigation, apparently greater sensitivity of females to glucose may have been due to sex differences in glucose utilization. Therefore, four male and four female rats of the same strain and age that were housed in the same conditions as those tested in Experiments 1 and 2 were intraperitoneally injected with 100 mg/kg glucose. Twenty minutes later, the saphenous vein in a hind leg of each rat was punctured with a hypodermic needle, and a sample of blood pipetted in accord with a procedure developed for small laboratory animals [7]. The glucose content of the samples was then determined by means of an Arkrey Super Glucocard II glucose meter. The mean (\pm S.E.M.) levels for males and females were 4.70 (\pm 0.11) and 4.16 (\pm 0.26) mmol/l, respectively. The difference between the groups was not significant ($t(9) = 1.50$, NS) thereby suggesting that there was probably no sex difference in glucose utilization at least 20 min after administration (when pre-acquisition glucose treatment has been shown to affect females' behavior more than males' [16]).

Although tacrine did not appear to affect novelty-related location preferences in female rats, it is possible that this outcome was merely due to a shifted dose-response curve. A dose higher than 3 mg/kg might produce an effect similar to that observed for males following this dose in the present study. If so, this would suggest that the males were more sensitive to the memory-enhancing effects of the drug. While a possible sex difference in rats' sensitivity to tacrine does not appear to have been reported previously, there is some evidence that men afflicted with Alzheimer's disease may

derive more short-term cognitive benefits from tacrine therapy than women [28]. Male rats also required lower doses of the NMDA agonist, D-cycloserine, than females to restore their memory-related recognition of a brightness change [18]. This outcome probably involved facilitation of glutamate activity through partial agonism of the NMDA receptor and consequential interactions with ACh in its actions on memory-associated septo-hippocampal mechanisms [1,27]. It therefore seems possible that these sex differences in effects of both tacrine and D-cycloserine may reflect greater responsiveness of males to increased ACh levels. Alternatively, lower responsiveness to both drugs by females may have been at least partially due to some interference with their action arising from estrus cyclic influences on behavior. Even so, the greater effectiveness of glucose for females suggests that any attenuation of their forgetting may have arisen not from increased synthesis of ACh, but from some other central action of the compound, such as increased glucose uptake by the brain [29].

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