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Effects of Physostigmine on Novelty-Related Location Preferences

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HUGHES, R. N. *Effects of physostigmine on novelty-related location preferences.* PHARMACOL BIOCHEM BEHAV **43**(1) 125–129, 1992.—Novelty-related location preferences and activity in an exploration box were recorded for male and female Wistar albino rats following intraperitoneal injections of 0.04 or 0.08 mg/kg of either physostigmine or neostigmine. Although rearing was reduced by the highest dose of both drugs and ambulation was reduced by the same dose of neostigmine, neither agent affected the significant preferences for novelty that typified all subjects. In a second experiment designed to assess the effects of 0.08 mg/kg of the two drugs administered during rather than after confinement to the familiar half of the apparatus, neostigmine reduced rearing, walking, and ambulation while increasing defecation, but physostigmine did not affect any response. While some minor motor impairment may have arisen from its peripheral effects, the lack of changes in novelty-related location preferences failed to support facilitation of either novelty avoidance or habituation by physostigmine suggested in previous studies.

Physostigmine Neostigmine Novelty Location preferences Ambulation Walking Rearing Defecation

AS shown in taste aversion studies, rats seem to find the effects of a number of behaviorally active drugs unpleasant (4,32). Since other aversive experiences, such as exposure to electric shock, can lead to novelty avoidance (1,34,39), it has been suggested that decreased choices of novel stimuli following administration of some drugs might arise either from their aversive stimulus properties (17) or from an aversive drug-induced state change (7). This applies particularly to effects of the cholinergic antagonist, scopolamine, on novelty-related location preferences.

Explanations for decreased T-maze spontaneous alternation with the drug have usually involved centrally mediated impairments of habituation to and memory for novelty (6,10,11,37). However, examples of perseveration with atropine and scopolamine (5,12,28) and significant novelty avoidance with both scopolamine (20,21) and the peripherally acting quaternary analog, methylscopolamine (14) are unlikely to have arisen from the drugs' effects on habituation and memory because maximum impairment of these processes must inevitably appear as chance responding rather than a consistent tendency to always choose the least novel option (17). It was therefore proposed that novelty avoidance produced by scopolamine and methylscopolamine (14,20,21) was due to their aversive peripheral properties. This proposition has received support from evidence of conditioned place avoidance induced by both drugs (19,25).

Even though effects of the cholinergic agonist, physostigmine, can be aversive (30,31,36), this drug has been shown to increase spontaneous alternation behavior (12,37), as would be expected if it had facilitated habituation and memory. However, comparable changes do not appear to characterize novelty-related location preferences. In fact, while 0.01–0.08 mg/kg physostigmine failed to have a significant overall effect on choices of the novel side of an exploration box, there was a tentative posthoc suggestion (needing replication) that they might have been reduced by higher doses (22). If this were verified, the outcome would be more in line with the effects of cholinergic antagonists in the same apparatus (14,20,21). The present study was therefore designed to assess whether or not physostigmine was likely to inhibit the novelty-related location preferences that typify nondrugged rats (15).

EXPERIMENT 1

This first experiment examined the effects of physostigmine on novelty-related location preferences. While likely to produce behavioral changes through cholinesterase inhibition (27,40), the doses chosen should have avoided anticholinergic effects through receptor blockade resulting from acetylcholine accumulation (26), namely, 0.1 mg/kg or less (9,33). In addition to physostigmine, the same doses of the related cholinesterase inhibitor, neostigmine, were also administered to assess any importance of peripheral activity in the response. Neostigmine has negligible central effects but similar peripheral properties to physostigmine (8,24).

METHOD

Subjects

Subjects were 30 male and 30 female Wistar albino rats 120–130 days old. They were housed in groups of three or

four same-sexed animals with freely available food and water and maintained on a reversed 12 D : 12 L cycle at a temperature of 21–23°C.

Apparatus

The apparatus was one of four Perspex exploration boxes described in detail elsewhere (20). Briefly, each box comprised four 20 × 20 × 20-cm cells and could be divided in half by inserting guillotine slides into two 7.5 × 20-cm gaps in an opaque Perspex wall. All boxes were kept in ventilated, sound-attenuated chambers illuminated by 8-W fluorescent lighting. Observations were enabled by a one-way window in the front of each chamber.

Procedure

In squads of four, equal numbers of male and female rats were individually confined to the left or right half of an exploration box for 60 min. Each rat was then removed from the apparatus and injected (1 ml/kg, IP) with either isotonic saline or one of two doses (0.04, 0.08 mg/kg) of physostigmine salicylate or neostigmine methylsulphate. To avoid the development of any association between the onset of drug action and specific stimulus characteristics of the half to which it had been confined (20), the rat was kept for 30 min in a holding cage. It was subsequently returned to the same side of the same exploration box from which the slides separating the two halves had in the meantime been withdrawn. Twenty seconds later, it was observed for 10 min while, every fifth second, it was noted if the rat was in the previously inaccessible novel half (novelty preference) and if it was rearing up on its hind legs, walking, or grooming itself. The total number of cells entered (ambulation) was also recorded to provide an estimate of the distance traveled in the apparatus.

RESULTS

The data from two males treated with 0.04 mg/kg neostigmine that failed to move from the cell to which they were returned were not included in statistical analyses. For all remaining rats, three (dose) × two (sex) analyses of variance (ANOVAs) followed by Dunnett's *t*-tests were applied to novelty preference and ambulation scores for the two drugs separately. To assess the possibility of walking, rearing, and grooming being affected differently in each side of the apparatus by the drug treatment, frequencies of these activities observed in the novel and familiar halves were subjected to three (dose) × two (sex) × two (half) ANOVAs. Drug effects that were dependent upon the side of the apparatus in which an activity occurred would appear as significant dose × half interactions. The main drug effects for all behavioral measures are outlined in Table 1.

Physostigmine Effects

Although novelty preference was unaffected by physostigmine, significant preferences for occupying the novel rather than familiar half of the apparatus typified the saline, one-sample $t(11) = 2.41$, $p < 0.05$, and both dose groups combined, $t(23) = 2.32$, $p < 0.05$. The only significant dose effect observed was for rearing. This was due to a lower frequency of the response in rats treated with 0.08 mg/kg than in those injected with saline. The difference between saline and 0.04 mg/kg was not significant.

While, not surprisingly (given the longer time spent in it), significantly more rearing and walking occurred in the novel (mean ± SE = 26.42 ± 1.53, 18.81 ± 0.88, respectively) than in the familiar half [rearing = 13.38 ± 0.55), $F(1, 30) = 24.82$, $p < 0.001$, walking = 15.39 ± 1.34, $F(1, 30) = 32.19$, $p < 0.001$], interactions with the drug effect were not significant. Neither the difference in frequencies observed in the two halves nor the dose × half interaction was significant for grooming.

While females groomed less often (4.50 ± 0.64) than males (7.22 ± 0.92), $F(1, 30) = 7.59$, $p < 0.01$, no other sex difference or dose × sex interaction was significant.

Neostigmine Effects

Even though neostigmine did not modify novelty preference, the two drug-treated groups combined showed significant preferences for occupying the novel half, $t(20) = 2.57$, $p < 0.025$. There were significant dose effects for both rearing and ambulation which, as can be seen in Table 1, were due to marked decreases in both responses with 0.08 but not 0.04 mg/kg. A significant dose × sex interaction for walking, $F(2, 28) = 4.03$, $p < 0.05$, followed by one-way ANOVAs revealed that this measure was affected by neostigmine for males (saline = 29.83 ± 1.90, 0.04 mg/kg = 28.50 ± 4.35, 0.08 mg/kg = 17.83 ± 2.54), $F(2, 13) = 6.11$, $p < 0.025$, but not for females (saline = 30.50 ± 1.98, 0.04 mg/kg = 30.00 ± 3.73, 0.08 mg/kg = 34.67 ± 4.20). This effect for males was obviously due to less walking with the higher dose of neostigmine only. Grooming was not affected by the drug.

Although more rearing and walking understandably occurred in the novel (rearing = 21.50 ± 1.98, walking = 16.21 ± 1.06) than in the familiar half of the apparatus [rearing = 15.74 ± 1.82, $F(1, 28) = 8.66$, $p < 0.01$, walking = 12.35 ± 0.97, $F(1, 28) = 7.69$, $p < 0.01$], interactions with the drug effect were not significant. Neither differences in the amount observed in each half of the apparatus nor the dose × half interaction were significant for grooming.

Levels of rearing, walking, and ambulation, respectively, were significantly higher for females (44.44 ± 4.23; 31.72 ± 1.93; 41.27 ± 2.82) than for males [29.13 ± 4.30, $F(1, 28) = 13.19$, $p < 0.001$, 25.00 ± 2.07, $F(1, 28) = 5.86$, $p < 0.025$, 24.69 ± 3.57, $F(1, 28) = 18.83$, $p < 0.001$]. However, females groomed less often (6.5 ± 0.58) than males (11.56 ± 2.26), $F(1, 28) = 7.59$, $p < 0.01$. The sex difference for novelty preference was not significant (males = 72.88 ± 7.89, females = 68.72 ± 3.74) nor was the dose × sex interaction for any measure except walking (described above).

DISCUSSION

There was no indication that aversions to the central or peripheral properties of physostigmine determined novelty preferences in the manner described for scopolamine (14, 20,21) because this response was not decreased by either drug. Like saline-treated subjects, all drugged rats showed significant preferences for remaining in the novel rather familiar half of the apparatus. An earlier suggestion that higher doses might lower novelty preferences was not verified (22). While it is possible that physostigmine's failure to depress novelty choices may have been due to it being less aversive than scopolamine (31), its lack of effects on this response also suggests that habituation and memory had not been affected by central cholinergic stimulation.

In view of its depression of rearing, the highest dose of physostigmine was clearly sufficient to elicit some behavioral changes. Similar effects of the drug on rearing and ambula-

TABLE 1

MEAN (± SEM) 5-s OBSERVATIONS AND CELLS ENTERED (AMBULATION) IN RATS TREATED WITH PHYSOSTIGMINE OR NEOSTIGMINE AND RESULTS OF F AND t-TESTS

		Physostigmine (mg/kg)			Neostigmine (mg/kg)		
Measure	Saline	0.04	0.08	$F(2, 30)$	0.04	0.08	$F(2, 28)$
Novelty preference	71.58 (4.80)	68.75 (5.38)	69.75 (6.11)	<1	62.40 (5.70)	76.67 (9.64)	<1
Rearing	48.83 (3.53)	40.50 (3.51)	36.25* (3.88)	3.32†	46.90 (3.98)	17.56* (3.54)	30.42‡
Walking	30.17 (1.31)	33.25 (2.33)	34.50 (1.76)	1.35	29.40 (2.69)	26.25 (3.45)	<1
Grooming	6.00 (0.58)	4.33 (0.75)	7.25 (1.46)	2.47	10.60 (3.11)	10.33 (1.90)	2.11
Ambulation	40.75 (4.31)	43.17 (3.41)	38.58 (3.50)	<1	38.00 (3.52)	23.08* (4.13)	8.58§

*Significantly different from saline group, $p < 0.05$, Dunnett's test.
†$p < 0.05$.
‡$p < 0.001$.
§$p < 0.01$.

tion, as well as on nonspecific general activity, have been reported previously (22,29,38). However, because in the present experiment neostigmine also decreased ambulation (distance traveled), rearing, and (for males only) walking and because these effects on the latter two responses were not dependent upon whether the novel or familiar half of the apparatus was occupied it is likely that the changes with both agents arose from their peripheral action on motor capacities rather than from modified responsiveness to environmental stimuli. Such changes may originate in enhanced muscle weakness as can occur in humans treated with cholinergic agonists (8).

Sex differences in the activity measures were in line with those reported earlier (15,16) but, as occurred previously (22), appeared to be attenuated by physostigmine.

EXPERIMENT 2

Unlike most studies of the effects of cholinergic agonists and antagonists on spontaneous alternation, the procedure adopted in Experiment 1 involved drug treatment after rather than before exposure to what subsequently became the familiar or less novel alternative. While this should not be important for drug aversion-induced novelty avoidance, it might modify a habituation-based result even though drug effects on consolidation of the process should ensure similar outcomes to treatment before experience with either choice alternative (6). Therefore, a study was made of the effects of physostigmine and neostigmine when administered during rather than after confinement to one half of an exploration box.

METHOD

A further 18 male and 18 female Wistar albino rats served as subjects. The apparatus and procedure were the same as for Experiment 1 except 30 min after being confined to one half of a box each rat was removed and injected (IP) with either saline or the dose of physostigmine salicylate or neostigmine methylsulphate shown to affect motor activity in Experiment 1, namely, 0.08 mg/kg. Following this, it was immediately put back in the apparatus and, a further 30 min later, briefly removed again while the slides separating the two halves were withdrawn. The rat was finally returned to the original half for the commencement of observation when the same responses were recorded as earlier, with the addition of numbers of fecal boli dropped. Because, unlike the present experiment, immediate reactions to the drug effect occurred while out of the apparatus, this index of emotionality (2) was not appropriate for rats tested in Experiment 1.

RESULTS AND DISCUSSION

Due to their failure to emerge from the cell to which they were returned, data from one male and one female treated

TABLE 2

MEAN (± SEM) 5-s OBSERVATIONS, CELLS ENTERED (AMBULATION), AND FECAL BOLI COUNTS IN RATS TREATED WITH PHYSOSTIGMINE (0.08 mg/kg) AND NEOSTIGMINE (0.08 mg/kg), AND RESULTS OF F AND t-TESTS

Measure	Saline	Physostigmine	Neostigmine	$F(2, 28)$
Novelty preference	78.00 (3.29)	68.33 (3.88)	68.40 (5.27)	<1
Rearing	31.50 (2.71)	35.42 (3.10)	10.10* (3.67)	19.00†
Walking	32.92 (3.42)	25.42 (1.22)	17.00* (2.25)	8.60‡
Grooming	10.92 (2.12)	16.83 (3.10)	7.50 (3.75)	<1
Ambulation	33.92 (4.11)	32.33 (3.79)	15.80* (3.90)	5.67‡
Fecal boli	4.58 (0.83)	6.00 (1.40)	8.30* (0.87)	3.35§

*Significantly different from saline group, $p < 0.05$, Dunnett's test.
†$p < 0.001$.
‡$p < 0.01$.
§$p < 0.05$.

with neostigmine were not included in statistical analyses. For the remaining subjects, statistical treatment of scores on the various measures was the same as for Experiment 1. Main effects of the drug treatment can be seen in Table 2.

While the drug effect was not significant for novelty preference and grooming, all subjects combined preferred to occupy the novel more often than the familiar half of the apparatus, one-sample $t(33) = 2.49$, $p < 0.025$. All other measures were significantly affected by the drug treatment. While for each the difference between the saline and physostigmine groups was not significant, neostigmine-treated rats reared and walked less often, traveled shorter distances, and dropped more fecal boli than control animals.

Again, significantly more rearing and walking occurred in the novel (17.12 ± 1.67, 15.62 ± 1.28, respectively) than in the familiar half of the apparatus [rearing = 9.47 ± 1.07, $F(1, 28) = 44.56$, $p < 0.001$, walking = 9.88 ± 0.76, $F(1, 28) = 26.54$, $p < 0.001$]. However, this difference was not significant for grooming and the drug × half interaction was not significant for any measure.

No sex difference or interaction involving sex was significant for any measure except the number of fecal boli dropped, $F(1, 28) = 4.94$, $p < 0.05$. As often observed (3), males dropped more boli (7.53 ± 0.99) than females (4.82 ± 0.78).

Because neither drug had any effect on novelty preference, procedural differences between Experiment 1 and earlier studies were unlikely to account for their failure to modify novelty choices in the exploration box. But, the stage at which injections are experienced might affect some activity measures because the decrease in rearing observed in Experiment 1 did not occur in the present experiment. A comparison of Tables 1 and 2 suggests that this influence might have been due to a depression of rearing by the procedural change for saline- but not physostigmine-treated rats. The difference between the two experiments was significant for the former, $t(22) = 3.90$, $p < 0.001$, but not the latter animals. It is possible that the extra handling experienced in Experiment 2 was somehow responsible for this effect. However, none of the between-experiment differences were significant for those measures that were affected by neostigmine in one or both experiments.

As well as again decreasing rearing and ambulation, neostigmine also led to less walking than saline controls. In view of increased defecation with this drug, it is possible that these effects may have been due to enhanced emotionality arising from the aversive nature of its action (30,31,36) rather than to direct effects on peripheral motor mechanisms. However, if so, depression of novelty preferences would also have been expected (7). Besides, from casual observation of neostigmine-treated subjects it was obvious that they had difficulty in moving both horizontally and vertically. It is therefore likely that rats' increased defecation was entirely unrelated to their emotional state and may have merely reflected neostigmine-induced stimulation of the alimentary tract in conjunction with relaxation of the anal sphincter (8). The failure for physostigmine to affect those responses modified by neostigmine was no doubt due to the latter drug's greater peripheral effectiveness (24) arising from the fact that it was administered at a molar dose approximately 24% higher than for the same mg/kg dose of physostigmine.

GENERAL DISCUSSION

The main results of this study demonstrated that, irrespective of whether they were administered before or after confinement to one half of an exploration box, neither depression nor enhancement of novelty-related location preferences accompanied the action of either physostigmine or neostigmine. While the procedures adopted might appear to have favored the development of either a delayed (Experiment 1) or concurrent (Experiment 2) conditioned place preference (or aversion) in the manner shown for a number of other compounds such as nicotine (13) and morphine (35), the drugs' lack of effects on the novelty measure clearly ruled out this possibility. The results accordingly failed to confirm an earlier posthoc suggestion that, through its aversive action, physostigmine may lead to novelty avoidance and instead upheld the results of an overall analysis that indicated the drug had no significant effect on preferences for novelty (22).

The results were also at variance with reports of physostigmine-induced increases in spontaneous alternation frequencies (12,37). It is possible that the failure to replicate effects of the drug on such novelty approaches may have been due to dose differences between the studies. Whereas the doses used in the present investigation were chosen to avoid anticholinergic-type effects in rats arising from receptor blockade by accumulated acetylcholine (26), the dose found to augment spontaneous alternation (12,37) was approximately four times higher than the recommended maximum of 0.1 mg/kg (9,33). However, pilot work in this laboratory has shown that physostigmine doses of such a magnitude produce degrees of motor impairment that render inoperable any behavioral test dependent upon even a moderate level of locomotor activity for more than just a few minutes.

Alternatively, because recognition of novelty in an exploration box depends upon the availability of odor cues (18) and physostigmine's effects on spontaneous alternation (37) seem to involve mainly enhanced memory of movements in space it is possible that, because experimental sessions involved limitless opportunities for rats to freely shuttle between them, the two halves of the apparatus may have become insufficiently spatially distinguishable for the appropriate memorial process to be affected by the drug. In this respect, it should be noted that there have been other instances of the drug's lack of effect on responsiveness to novelty in situations where novel stimuli are less spatially distinguishable from each other than is the case in most spontaneous alternation settings. For example, Leaton (23) observed no effects of the drug on the reinforcing value of novelty experienced while investigating objects, and Stewart and Stewart (38) found that it did not modify habituation of exploratory responses. Whatever the case, it is clear that, even though rearing activity was reduced, physostigmine in doses that inhibit cholinesterase activity (27,40) without markedly incapacitating rats is not sufficiently aversive to lead to novelty avoidance in the manner shown for cholinergic antagonists (14,20,21).

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