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Scopolamine Induced Changes in Activity and Reactions to Novelty[1,2]

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HUGHES, R. N., N. M. BLAMPIED AND W. J. STEWART. *Scopolamine induced changes in activity and reactions to novelty.* PHARMAC. BIOCHEM. BEHAV. 3(5) 731–734, 1975. – The behavior of hooded rats was observed in an exploration box comprising novel and familiar halves following IP injections of 0.1, 0.25, 0.5, 0.75 or 1.00 mg/kg scopolamine or isotonic saline. Drug administration occurred after, rather than before, exposure to one of the alternative halves. All doses decreased reactions to the previously inaccessible novel half but decreases were greater for the 2 lowest doses. Rearing behavior was also suppressed by each dose whereas the number of apparatus cells entered (locomotion) was decreased by low doses but increased by high. The 3 behavioral measures showed declines in frequency during the course of each experimental session. However, low doses of the drug enhanced and high doses retarded these declines for rearing and cells entered. The study illustrated the difficulty in explaining data by unitary processes (such as attenuated habituation) when several behavioral indices and drug doses are employed within a single investigation.

Scopolamine Novelty Rearing Locomotion Habituation

THE anticholinergic drug, scopolamine, has often been shown to reduce frequencies of spontaneous alternation in Y and T mazes [11, 13, 24, 27, 29]. Since alternation is generally viewed as a tendency to enter the more novel of two maze arms [10], effects of scopolamine are assumed to involve changes in reactivity to novelty. Such changes are often explained as attenuated habituation to the novelty of the arm chosen on Trial 1 [8]. In order to assess the generality of scopolamine's effects on responsiveness to novelty, an experiment was designed in which rats would be administered the drug after exposure to 1 of 2 alternatives rather than before, as is the case with conventional alternation settings. This meant that all animals would have equal opportunities for habituating to the first alternative before introduction of the drug conditions. Thus, habituation of responsiveness to the second alternative could be observed without any possible influence of prior drugged associations with the first [17].

The specific procedure chosen enabled reactions to the more novel of 2 simultaneously presented environments to be recorded at the same time as frequencies of locomotor and rearing activity [16]. Typically, nondrugged rats in this setting show significant tendencies to remain longer in the more novel of the two alternatives [16, 17, 19]. Scopolamine has been reported to enhance locomotion [6, 25, 26, 30] but frequently only one or two relatively high doses have been investigated. It was therefore felt that observations of the effects of a wider dose-range on all 3 responses mentioned would provide additional information about scopolamine's mode of action, as has been the case with other drugs [12, 16, 17, 18, 20].

METHOD

Animals

Forty-eight male hooded rats of a strain developed at the University of Otago, New Zealand, were used. They were housed in group cages of 6 animals each and were approximately 120 days old when tested. All rats received al lib food and water right up until time of testing.

Apparatus

The rats were individually tested in one of several Perspex exploration boxes described previously [19]. Each box consisted of four 20 X 20 X 20 cm cells separated from each other by partial walls containing 7.5 X 20 cm openings. It could be divided into two halves by inserting guillotine slides in the two appropriate 7.5 X 20 cm openings. All outer and cell walls comprised transparent Perspex except the walls and slides which separated the 2 halves – these were made of translucent Perspex. The floor

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of each box consisted of white painted wire mesh and each half was covered by a hinged, transparent Perspex lid. The boxes were kept in 3 glass-fronted enclosures and were illuminated by three 22 W fluorescent lamps. A speaker in each enclosure provided an auditory masking stimulus of about 40 dB. Observations were made by means of closed circuit television, with the TV monitor and observer concealed behind a curtain some distance from the enclosures.

Procedure

The rats were randomly assigned to 1 saline and 5 drug groups of 8 animals each. Each animal was confined for 60 min to one half of an exploration box with the slides separating the two halves in place. It was then removed and injected (1 cc/kg IP) with either isotonic saline or a dose of scopolamine hydrobromide (0.1, 0.25, 0.5, 0.75 or 1.0 mg/kg). Following a 20 min period in a 19 X 19 X 19 cm metal cage, the rat was put back into the same familiar half of the apparatus after the two guillotine slides had been withdrawn. Twenty sec later it was observed for 10 min. During each of 3 successive 200 sec periods the total number of cells entered was counted, and every fifth sec it was noted whether or not the rat was in the previously inaccessible novel half (reactions to novelty) and if it was standing up on its hind legs (rearing). For half of each group the novel side was on the left, and on the right for the other half.

RESULTS

Main Drug Effects

Separate 6 X 3 analyses of variance were performed on the 3 measures to determine drug effects and within-session changes (successive 200 sec periods). All 3 were significantly affected by scopolamine (reactions to novelty, $F = 4.11$; rearing, $F = 30.92$; cells entered, $F = 10.92$; $df = 5/42$, $p<0.01$ in all cases; see Fig. 1). Individual t tests showed that for all drug doses, both reactions to novelty and rearing were significantly lower than saline levels ($p<0.05$). Whereas the number of cells entered was lower following administration of 0.1 ($p<0.01$) and 0.25 mg/kg scopolamine ($p<0.05$) than it was following saline, higher scores characterised the other 3 doses ($p<0.05$, 0.01,· 0.01 respectively).

Separate one-sample t tests performed on reactions to novelty scores showed that, whereas saline controls were seen significantly more often in the novel side of the apparatus than in the familiar, the reverse relationship typified all drug groups ($p<0.05$).

Within-session Changes

Reactions to novelty significantly decreased in frequency during the course of the 10 min sessions (200 sec period 1 = 18.1, period 2 = 15.1, period 3 = 14.1, $df = 2/84$, $p<0.01$). Similar decreases occurred for the other 2 measures but interactions with drug effects were also significant (rearing, $F = 2.81$; cells entered, $F = 3.67$; $df = 10/84$, $p<0.01$ in both cases). These interactions reflected differences between drug groups in changes in frequency of the 2 measures during successive 200 sec periods. The differences are illustrated in Table 1, which shows (for rearing and cells entered only) relative declines from the first to the third period as well as individual cell means.

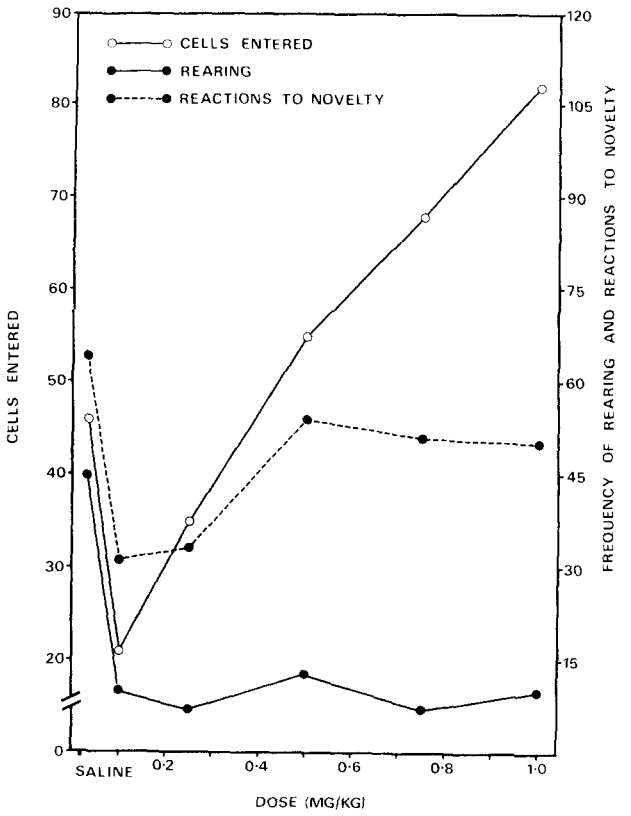

FIG. 1. Mean frequencies of the 3 behavioral measures following administration of saline or 5 doses of scopolamine.

DISCUSSION

Clearly, the drug had quite different effects on the 3 behavioral measures all of which have been used as indices of exploratory behavior [3, 9, 14, 16, 19]. In addition, all 3 responses showed a decline in frequency from the first to the third 200 sec period but the rate of this decline was dependent upon dose strength for rearing and cells entered. Examination of Table 1 shows that maximum declines occurred with the two lowest doses for both activities. The order of decreasing magnitude was then saline, 0.5, 0.75 and 1.0 mg/kg, a relationship indicative of retarded decrements in responding with increasing dosage. Grant [14] has recently demonstrated inhibited within-session activity declines in mice (measured by photocells) following 1.0 mg/kg of scopolamine. This is consistent with the present findings but does not necessarily confirm an attenuated habituation explanation (as he maintains) because of the difficulties in equating locomotor or general activity with exploration of novelty [9, 16, 22]. Without taking into account relationships between behavior and collative properties of environmental stimulation, it is almost impossible to determine to what extent such responses validly reflect reactivity to novel or complex stimuli [16]. Therefore, declines in such activities may not necessarily be synonymous with habituation to novelty. In the present study, all that can really be concluded is that in addition to the overall drug effects on the 3 measures, low doses may enhance, and high doses retard decrements in ambulatory

TABLE 1

MEAN REARING AND CELLS ENTERED SCORES FOR EACH GROUP DURING THREE SUCCESSIVE 200 SEC PERIODS AND DECLINES FROM FIRST TO THIRD PERIODS EXPRESSED AS PERCENTAGES OF THE FIRST

Measure and Group	Successive 200 Sec Periods 1	2	3	Percent Decline
Rearing				
Saline	17.5	16.4	11.5	34.3
0.1 mg/kg	6.9	2.1	1.1	83.6
0.25 mg/kg	5.1	1.9	1.3	75.6
0.5 mg/kg	4.8	4.6	3.5	26.3
0.75 mg/kg	3.1	2.1	2.4	24.0
1.0 mg/kg	3.8	2.5	3.4	10.0
Cells Entered				
Saline	24.8	12.0	9.1	63.1
0.1 mg/kg	15.3	3.6	2.5	83.6
0.25 mg/kg	19.9	8.4	6.6	66.7
0.5 mg/kg	22.9	19.4	13.1	42.6
0.75 mg/kg	26.4	24.4	17.5	33.7
1.0 mg/kg	30.3	30.9	20.6	32.2

and rearing activities which are presumably controlled by both environmental and organismic influences to varying degrees. The findings also support earlier observations [5,31] that behavioral changes will result from much lower doses of scopolamine than those commonly administered to rats. The total results are obviously difficult to interpret by a single process explanation of scopolamine's behavioral effects such as that proposed by Carlton [7,8].

It has been shown that stressful environmental and chemical stimulation can decrease preferences in rats for the more novel of two alternatives even to the point where the less novel is preferred [1, 3, 15, 23, 28]. As the peripheral action of scopolamine appears to be aversive [2], some degree of stress may accompany its administration thereby enhancing novelty avoidance. In other words, through either peripheral or central aversive effects, the drug may have merely induced the rats to avoid the more novel half of the apparatus thereby spending significantly more time in the less novel. A stress explanation might also account for the quantal type suppression of rearing behavior but it would not explain why the greatest tendencies for novelty-avoidance occurred with the lowest doses, nor would it easily explain the U-shaped dose-response relationship with cells entered. It does however provide an additional confounding issue for single process explanations of scopolamine effects.

The effects of scopolamine on ambulation (cells entered in Fig. 1) are consistent with accounts of its effects on human activity. Low doses typically exert depressant influences, whereas high doses act more in a stimulant capacity [21]. Only stimulant effects are usually reported in studies of rat locomotion [6, 25, 26, 30]. Differences between the dose-response curves for rearing and cells entered argue against both measures independently reflecting the same levels of nonspecific general activity, as is sometimes suggested [17]. At higher doses, these differences appear consistent with studies showing facilitation of active avoidance in tasks requiring horizontal locomotion, and interference in tasks involving vertical movements such as pole-climbing [4].

In view of the complicated relationship between dose-strength, within-session response decrements and the three separate measures recorded, the present study illustrates the difficulty in accounting for the behavioral effects of scopolamine in terms of unitary central processes. Similar complexities of cholinergic activity have been suggested by Bignami and Rosic [4] when describing interactions between experimental variables which can determine scopolamine effects on avoidance learning. Recent work on relationships between scopolamine and the ontogeny of spontaneous alternation, strongly supports central cholinergic involvement in novelty oriented behavior [13]. But the precise way in which such involvement operates to influence activity and responses to novelty in experimental settings other than conventional alternation needs to be further clarified.

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