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Scopolamine: Effects on Fear or Defense Responses in the Rat

SANDRA MOLLENAUER,[1] ROD PLOTNIK AND PAULA SOUTHWICK

San Diego State University, San Diego, CA 92182

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MOLLENAUER, S., R. PLOTNIK AND P. SOUTHWICK. *Scopolamine: Effects on fear or defense response in the rat.* PHARMAC. BIOCHEM. BEHAV. 5(2) 157–163, 1976. -- In previous research scopolamine reduced fear or defense responses of rats to a cat, and removal of the rats' olfactory bulbs had the same effect. This suggested that scopolamine might have affected defense responses by blocking olfactory perception of the stimulus cat. The present experiments studied this possibility and explored further the effects of scopolamine on defense responses of the hooded rat. In Experiment 1 rats treated with scopolamine were found to be responsive to olfactory cues from a cat. When cat smell, but not a cat, was present in the apparatus, scopolamine-treated rats showed a large and significant suppression of food consumption. In Experiment 2 the effects of scopolamine on defense responses were shown to be generalizable to an inanimate stimulus, mechanical robot. Scopolamine caused significantly less freezing and avoidance and significantly shorter latencies to drink in the presence of the robot. One of the primary findings of the present research is that scopolamine has now been shown to reduce the defensive response of freezing in a variety of stimulus situations. This finding was thought to have important implications for the literature relating anticholinergic drugs and avoidance behavior.

Scopolamine Defense response Fear response Anticholinergic drugs Avoidance behavior Bulbectomy

THE anticholinergic drug, scopolamine, was previously shown to reduce the fear responses of rats to a cat [13]. In the presence of a cat, control rats, treated with saline or methyl scopolamine, showed a marked suppression of feeding behavior and spent a high percentage of the trial time freezing in the perimeter of the apparatus. Rats that had been treated with scopolamine spent significantly less time freezing and significantly more time feeding in the area near the cat. It was hypothesized that cholinergic synapses are somehow involved in the elaboration of fear responses or species-specific defense reactions. As concluded in that report, one possible site of action would be the olfactory system; a central blockade of olfactory perception would account for the reduction of fear or defense responses caused by scopolamine.

In subsequent research it was found that bilateral removal of the olfactory bulbs had essentially the same effect on fear or defense reponses as scopolamine [12]. That is, rats in which the olfactory bulbs had been removed also spent significantly less time freezing and significantly more time feeding in the area near the cat. This suggested that scopolamine might have affected fear or defense responses by acting on the olfactory system to cause a blockade of olfactory cues. It is becoming increasingly evident that olfactory cues play a very significant role in the regulation of emotional behavior in the rat [15].

A number of findings from the literature point to possible actions of scopolamine on the olfactory system. Many of the behavioral effects that are seen following treatment with anticholinergic drugs are also seen following olfactory bulb removal. For example, both anticholinergic drugs and olfactory bulb removal have been shown to cause a failure of habituation [5,20]. Both have been shown to impair passive avoidance [4, 6, 11, 16, 17] and enhance active avoidance [1, 9, 14, 16, 17], and both have been shown to reduce freezing [11, 12, 13, 18]. Other findings point to the possible action of scopolamine on olfactory perception *per se*. In unpublished research with the ether avoidance test for anosmia described by Spector and Hull [19], rats treated with scopolamine consistently failed to make an avoidance response to an ether soaked cotton ball. These various findings implied that one effect of scopolamine might be a blockade of olfactory perception. If that were the case, the drug's effect on fear or defense responses could very well be the indirect consequence of its action on olfactory perception.

Experiment 1 of the present research determined whether scopolamine's effect on fear responses could be attributed to loss of olfactory perception. The same dose of scopolamine that had previously been shown to reduce fear responses to a cat was tested for its effect on fear responses to the stimulus of cat smell. Experiment 2 explored the

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effects of scopolamine using a stimulus that did not involve cat smell, mechanical robot. This experiment determined whether the effects of scopolamine on defense reactions would be generalizable to an inanimate stimulus. The generalizability of the effect of scopolamine on freezing behavior was of particular interest since such an effect would have relevance for the large literature relating anticholinergic drugs and avoidance behavior [1, 2, 4, 6, 8, 9, 10, 14]. Avoidance behaviors have been analyzed by Bolles [3] in terms of species-specific defense responses, such as freezing. However, in the literature on anticholinergic drugs and avoidance behavior, there have been only incidental observations of freezing behavior [1]. The present research includes a systematic examination of the effects of an anticholinergic drug on freezing.

EXPERIMENT 1

Experiment 1 was designed to determine whether scopolamine would block responses to the stimulus of cat smell. Rats were trained to consume a sweet solution near the center of a large arena. They were then injected with physiological saline or the dose of scopolamine previously shown to affect fear responses and were tested with cat smell present in the apparatus.

METHOD

Animals

The animals were 32 male hooded Long Evans rats, weighing 250 350 g at the start of the experiment, purchased from Simonsen Laboratory. One rat was discarded for failure to satisfy training criteria described in the procedure. Beginning one week prior to the start of the experiment rats were housed individually with unlimited access to water and were maintained on a 23 hr food-deprivation schedule. They were fed approximately 20 g at the same time each day, approximately 30 min after the experimental session.

Apparatus

The apparatus, similar to that used in previous research [13], was a circular arena, 110 cm in dia. with 41-cm walls made of 1/8 in Plexiglas, painted black. The apparatus had a wire mesh floor and a hinged lid made of clear Plexiglas.

The rats were clearly visible through the lid, which prevented their jumping out of the apparatus on test trials. In the center of the arena was a wire mesh enclosure, 27.5 cm in dia. and 40 cm high, similar to that used in previous experiments to enclose the stimulus cat. In the present experiment this enclosure contained a pillow covered with a synthetic furry material and measuring 27 x 27 x 14 cm. For the smell test, the pillow was replaced with an identical one having cat odor (see Procedure). Four plastic food cups, 2½ cm in dia., were equally spaced around the enclosure at a distance of 4 cm from the edge of the enclosure. A plywood board, painted black, was placed under the wire mesh floor of the arena. This board was marked off in concentric circles, 11 cm apart, and each circle was divided spoke-fashion to form a total of 48 equal segments.

Above the arena was a large mirror used to observe the rats. The mirror was used for better visibility and for minimal distraction to the animals.

During training and test trials, white noise was used to mask extraneous auditory cues.

Design

Rats were tested under 1 of 2 drug conditions, scopolamine (SCOP) or saline (SAL), and under 1 of 2 apparatus conditions, cat smell present in the apparatus (SMELL) or no cat smell present in the apparatus (CONTROL). Thus, there were 4 independent treatment groups, SCOP-SMELL and SCOP-CONTROL, and SAL-SMELL and SAL-CONTROL. The rats were randomly assigned to these 4 groups with certain restrictions described in the procedure. All behavioral tests were conducted blind.

Procedure

Habituation. Pilot work had shown that habituation and training in a new apparatus were greatly facilitated by the presence of rat odor. Therefore, prior to training, 10 rats (male hooded Long Evans) that had been living together were left in the apparatus overnight with water bottles and large dishes of sucrose (32% solution) available and were removed the following day. Next, the experimental rats were habituated by leaving them in the apparatus overnight in randomly selected groups of 10 or 11, with sucrose and water available. It had previously been established that this procedure did not result in fighting among rats that had been individually housed for only one week.

Training. Training was begun 24 hr after the last overnight habituation session. Each rat was given one 1-min trial per day for 5 days, with sucrose available in each of the 4 food cups. For a given trial the rat was placed about midway between the perimeter and the center of the apparatus, facing the center enclosure; rats were always placed at the same point. From this point a rat had to move forward, toward the center enclosure, in order to reach one of the food cups. Drinking from all 4 cups would necessitate circling the enclosure. During training, some rats drank from only 1 or 2 cups; others drank from all 4. When one min had elapsed the rat was removed from the apparatus and returned to its home cage.

On Day 4 all rats that had not drunk at least 15 sec per trial on 2 consecutive trials were given extra trials until they had met this criterion, or until 6 extra trials had been given. For these extra trials, rats were not removed from the apparatus between trials. On Day 5 one rat failed to satisfy the following training criterion and was discarded; the rat must have drunk 15 sec on that day's trial and have had 3 consecutive trials on which the times were 15 sec or more.

Testing. On Day 6, 30 min before testing, the rats were injected IP with 0.8 mg/kg scopolamine hydrobromide or physiological saline in the same volume, 1 ml/kg. In order to prevent contamination of the CONTROL treatment with cat smell it was necessary to run the CONTROL animals first. The procedure for control trials was exactly the same as in training, except that the pillow in the center enclosure was removed briefly and returned to exactly the same position prior to testing.

Prior to testing the rats in the SMELL condition the pillow in the center enclosure was removed and replaced with an identical pillow that had been left overnight in the home cage of an adult male Siamese house cat. In addition, the cat was placed in the arena and walked around it for a period of 5 min at the beginning of the session. The order of testing for SCOP and SAL rats was randomized.

Assignment to Treatments

Each rat's drinking times over the first 4 trials were summed, and the rats were ranked from highest to lowest in drinking times. The rats were then assigned to treatments as follows. The 4 rats having the highest drinking times were randomly assigned, 1 to each of the 4 groups; the 4 rats having the next highest drinking times were randomly assigned one to each group, and so on. This procedure was followed because previous research had shown that scopolamine had different effects depending upon emotionality, as measured by consummatory behavior in a novel environment [11].

Measures

On all training days and the test day itself, 4 measures were recorded for each animal.

Drinking was the cumulative time during a 1-min trial that the animal spent drinking from any or all of the 4 food cups near the pillow enclosure.

Latency to drink was the time elapsed from placement of the rat in the apparatus to its initiation of consummatory behavior. Latency was scored as 60 sec for rats that failed to drink.

Center time was the cumulative time the rat spent with its two front feet within the concentric circle nearest the enclosure, 30 cm from the edge of the enclosure.

Freezing was the cumulative time the animal spent rigidly immobile. The experimenter was trained to record freezing using video tapes; it was previously reported that the interobserver reliability coefficient for freezing for two independent observers was $r = .96$ [13].

The above measures were not independent. Rather they represented a constellation of responses that, together, serve to define fear operationally. Thus, fear would be indicated by freezing, suppression of center time, suppression of drinking time, and, if drinking did occur, longer latencies to drink.

RESULTS

The data were evaluated using unweighted means ANOVA. Analyses paralleling those on the test data were performed on the data from the last day of training. There were no significant differences among groups on any measures in the baseline data.

As shown Fig. 1, the cat smell stimulus was an effective unconditioned fear stimulus for the hooded rat. In the SMELL condition rats showed the constellation of behaviors that have been used to define fear: Compared to the CONTROL condition, there was a significant suppression of center time, i.e., time near the odor-impregnated pillow ($F(1,27) = 11.1$, $p<0.01$); significantly longer latencies to drink ($F(1,27) = 10.1$, $p<0.01$); a significant suppression of drinking time ($F(1,27) = 26.7$, $p<0.001$); and significantly more freezing ($F(1,27) = 4.31$, $p<0.05$). The analyses based on SAL rats alone served to evaluate the effectiveness of the stimulus of smell, independently of drug effects. For SAL rats the SMELL condition, as compared to CONTROL, caused a significant suppression of center time ($F(1,13) = 11.6$, $p<0.01$); significantly longer latencies to drink ($F(1,13) = 15.0$, $p<0.01$); a significant suppression of drinking time ($F(1,13) = 16.2$, $p<0.01$); and increased freezing that was not significant ($F(1,13) = 4.1$, $p<0.06$).

In the SMELL condition, scopolamine caused some attenuation of fear responses particularly in freezing and latency to drink. Compared to SAL, SCOP rats showed less freezing in the SMELL condition ($F(1,14) = 4.8$, $p<0.05$); since SCOP had no effect in the CONTROL condition, this resulted in a significant interaction between drug and stimulus conditions ($F(1,27) = 4.5$, $p<0.05$). The SCOP rats also showed showed higher center time than SAL rats in the SMELL condition, but this difference was not significant ($F(1,14) = 3.7$, $p = 0.08$); again, SCOP had no effect in the CONTROL condition, and the interaction was not signifi-

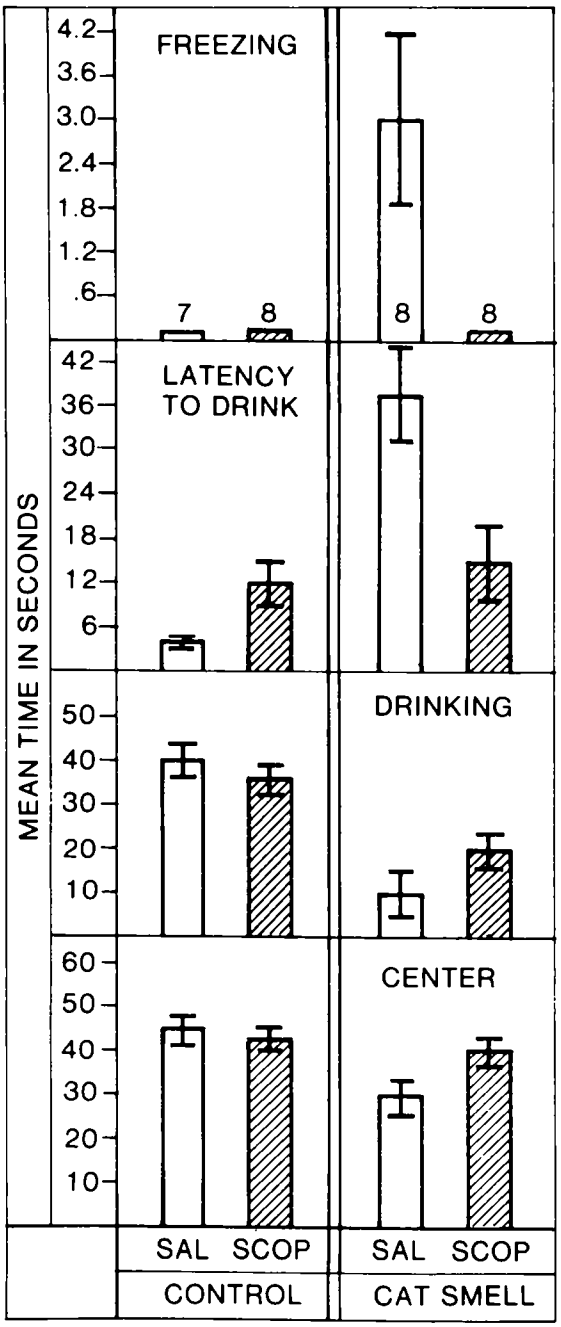

FIG. 1. Mean time in seconds (± SEM) for fear measures in CAT SMELL and CONTROL conditions. The numbers on the graph refer to groups n's.

cant ($F(1,27) = 3.6$, $p = 0.07$). The latencies to drink in the SMELL condition were significantly shorter for SCOP rats than for SAL ($F(1,14) = 4.8$, $p<0.05$), and there was a singificant interaction between drug and stimulus conditions ($F(1,27) = 8.0$, $p<0.01$). As Fig. 1 shows, the significant interaction on latency to drink also reflects the fact that the SCOP rats had significantly longer latencies to drink than SAL rats in the CONTROL condition ($F(1,13) = 5.6$, $p<0.05$).

There was a different pattern of results for drinking time in that SCOP failed to attenuate the effect of the SMELL stimulus this behavior. Although SCOP rats showed slightly higher drinking times than SAL rats in the SMELL condition, the effect was not significant. Nor was the interaction between the drug and stimulus conditions significant. On the contrary, the SCOP rats, like the SAL rats, showed a significant suppression of drinking time in the presence of cat smell. The drinking times of the SCOP rats in the SMELL condition were significantly lower than those of SCOP rats in the CONTROL condition ($F(1,4) = 9.99$, $p<0.01$).

DISCUSSION

The results of Experiment 1 show that the stimulus of cat smell elicits the pattern of behaviors used previously to define fear [13]. As compared to the CONTROL condition, rats in the SMELL condition showed significantly more freezing, a significant suppression of center time, significantly longer latencies to drink, and a significant suppression of drinking time. These results are consistent with early findings, which suggested that the odor of a cat played an important part in its capacity to elicit defense reactions [7].

The primary question considered in Experiment 1 was whether scopolamine had affected fear resonses to the cat by blocking perception of cat smell. The results indicated that rats treated with SCOP showed a substantial suppression of drinking time in the cat smell condition; that is, SCOP rats tested in the cat smell condition spent significantly less time drinking than SCOP rats tested in the control condition. Since the rats treated with scopolamine did show a significant suppression of drinking time in the presence of cat smell, it seems clear that the animals were responding to the smell cue. However, the possibility cannot be ruled out that scopolamine had produced some subtle olfactory impairment not evident in testing with cat odor. There were no significant differences on the other measures between SCOP rats in the smell condition and SCOP rats in the control condition. On the measures of freezing and latency to drink scopolamine significantly attenuated fear responses to the smell stimulus. This result was consistent with its effect on fear or defense responses to the cat stimulus [11,13].

EXPERIMENT 2

From the results of Experiment 1 it seemed clear that scopolamine had not reduced reactions to the cat by making the rats insensitive to smell cues. However, partial impairment could not be ruled out. Experiment 2 was designed to determine whether scopolamine would reduce defensive reactions to a stimulus in which cat smell played no part and, thereby, demonstrate the generalizability of the phenomenon.

METHOD

Animals

The animals, purchased from Simonsen Laboratory, were 30 male hooded Long Evans rats, weighing 250- 350 g at the start of the experiment. Three rats were discarded for failure to satisfy training criteria described in the procedure. The housing and maintenance conditions were the same as for Experiment 1.

Apparatus

The apparatus used in the present experiment was an arena of identical design and dimensions as that used in Experiment 1. Prior to the start of the experiment the apparatus was steam cleaned and repainted with black high-gloss enamel, in order to remove any possible cat odors from previous experiments. The apparatus was placed in an experimental room, not previously used in cat-rat research.

On training trials, the robot stand (described below) was present in the center of the arena surrounded by a wire mesh enclosure, similar to that used in Experiment 1. As in the previous experiment, 4 small food cups were spaced equally around the enclosure. The wire mesh enclosure was used during training trials in order to prevent the rats from developing the habit of crossing the center area to reach food cups. Had this happened, the presence of the robot in the center on test days would have forced the rats to alter their normal route; thus, differences in drinking time and latency to drink could have been attributed to changes in route rather than avoidance of the robot. With the enclosure present, the rats learned to approach the various food cups without crossing the center area. On the test day, the wire mesh enclosure was removed and the robot was placed on the stand in the center of the arena.

Stimulus Robot

The stimulus robot was a commercially-made, battery-operated mechanical robot, 32 cm by 17 cm by 13 cm, from which the head and arms sections were removed. All external parts were constructed of hard plastic. The robot was suspended from a stand in the center of the apparatus so that its base was 3 cm above the wire mesh floor. The stand consisted of 2 vertical bars, 40 cm high, connected at the top by a 25 cm cross-bar, and affixed at the base to the wood floor beneath the wire mesh floor of the arena.

The robot was activated continuously throughout the trial. When the robot was activated it made a loud grinding noise (72 db), and its legs moved back and forth continuously (1.6 times per sec) in a walking motion, each leg moving a distance of approximately 2.8 cm. Every 6 sec the entire lower half of the robot rotated 180°; the rotation lasted for approximately 2 sec, during which time the noise rose to approximately 79 db. The robot was always operated so that a rotation was just beginning at the start of a trial.

Design

All the rats were randomly assigned to the saline (SAL), or scopolamine (SCOP) condition and tested with the stimulus robot (ROBOT). Each rat served as its own control for the non-robot condition. That is, responses on the test day were compared with responses on the preceding baseline day (CONTROL) during which the robot had not been present. All behavioral tests were conducted blind.

Procedure

Training. Habituation procedures were the same as used in Experiment 1, including the use of other rats to place rat odor in the apparatus. Also the training procedures were the same as for Experiment 1. Each rat was given one 1-min trail per day for 5 days, with extra trials administered on Day 4, following the criteria used in Experiment 1. Three of the rats in this experiment had extremely low cumulative drinking times; these rats were discarded since previous work had shown that such animals had aberrant drug responses [11].

Assignment to treatments. Rats were randomly assigned to the 2 drug treatments, 18 to SCOP and 9 to SAL, following the same restrictions as in Experiment 1.

Testing. On Day 6, 30 min before testing, rats were injected IP with .8 mg/kg scopolamine hydrobromide or physiological saline, in a volume of 1 ml/kg. The procedure on the test trial was exactly the same as on training except that the robot had been substituted for the wire mesh enclosure and was activated at the beginning of the trial. The placement of the rat in the apparatus, near the center and facing the robot, was such that it would have to make an active retreat in order to reach the perimeter of the apparatus; rats did frequently make active retreats and were never observed to freeze in this center area. Also, the placement of the rat was such that it would have to make an active approach toward the robot in order to reach the 4 food cups. The cups were positioned so that the rat could drink from them without being struck by the revolving robot, provided they remained out of the center area. No rat was ever observed to come in physical contact with the robot.

Measures. The same measures were recorded as in Experiment 1.

RESULTS

The data were analyzed using mixed design ANOVA. Figure 2 presents the data from the robot test (ROBOT) as compared to baseline (CONTROL) performance. In the CONTROL condition the groups are labeled (SCOP) and (SAL), according to the treatment they received on the test day. Analyses of the data from the CONTROL days showed that there was no significant pretest difference between the SCOP and SAL groups on any measure.

As Fig. 2 shows, the ROBOT was clearly an effective fear stimulus. Compared to the CONTROL condition there was a significant suppression of center time ($F(1,25) = 158.1$, $p<0.001$); significantly longer latencies to drink ($F(1,25) = 92.2$, $p<0.001$); a significant suppression of drinking time ($F(1,25) = 536.0$, $p<0.001$) and significantly more freezing ($F(1,25) = 4.08$, $p<0.001$). Comparisons between the CONTROL and ROBOT conditions based on the SAL animals only, yielded the same pattern of results: A significant suppression of center time ($F(1,25) = 77.4$, $p<0.001$); significantly longer latencies to drink ($F(1,25) = 97.9$, $p<0.001$); a significant suppression of drinking time ($F(1,25) = 195.0$, $p<0.001$) and significantly more freezing ($F(1,25) = 67.1$, $p<0.001$).

Figure 2 also shows that scopolamine caused an attenuation of fear or defense responses. Compared to SAL, SCOP rats showed significantly less freezing ($F(1,25) = 30.4$, $p<0.001$), spent significantly more time in the center area ($F(1,25) = 6.1$, $p<0.05$), showed significantly shorter latencies to drink ($F(1,25) = 28.1$, $p<0.001$) and more, though not significantly more, time drinking ($F(1,25) = 3.06$).

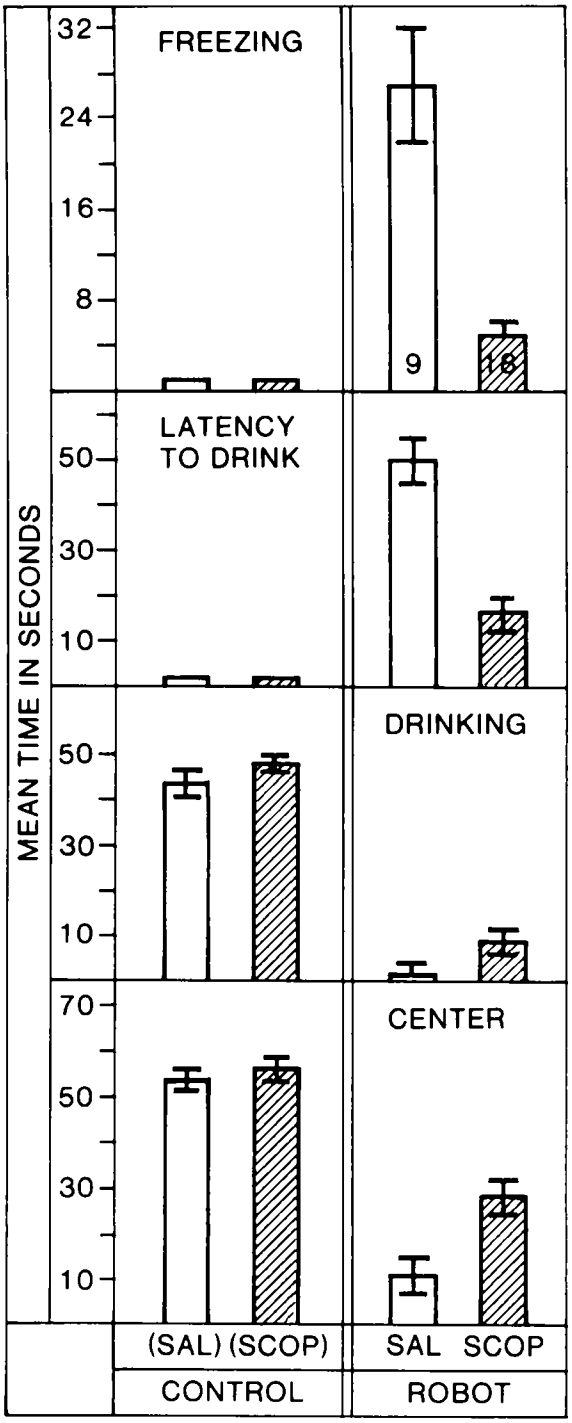

FIG. 2. Mean time in seconds (+ SEM) for fear measures in ROBOT and CONTROL conditions. Rats were not injected for the CONTROL conditions; labels (SAL) and (SCOP) indicate group assignment for ROBOT test. The numbers on the graph refer to groups n's.

Although scopolamine produced a reduction of fear responses, it is clear from Fig. 2, that the SCOP rats were

responsive to the stimulus. Compared to their own CONTROL performance, the SCOP rats showed more, though not significantly more freezing ($F(1,25) = 4.13$); a significant suppression of center time ($F(1,25) = 84.25$, $p<0.001$); significantly longer latencies to drink ($F(1,25) = 22.7$, $p<0.001$); and significantly shorter drinking time ($F(1,25) = 431.5$, $p<0.001$).

DISCUSSION

The results of Experiment 2 show that the mechanical robot was an effective fear stimulus, and the magnitude of the differences suggest that it was a potent one. The SAL rats spent approximately 50% of the trial time freezing, and drinking time was suppressed about 90% from control levels. On all measures performance in the robot condition differed significantly from performance in the control condition.

The effect of scopolamine on responses to the robot paralleled its effect on responses to the cat [11,13]. Scopolamine attenuated but did not block defense reactions. Compared to SAL the SCOP rats spent less time freezing, spent more time in the center area, showed shorter latencies to drink, and spent more time drinking. All of these differences were significant, except for drinking time. These results show that the effect of scopolamine was not unique to the cat stimulus. Thus, they give generalizability to the finding that scopolamine affects defense reactions of the hooded rat.

GENERAL DISCUSSION

Previous research had suggested the possibility that scopolamine reduced fear responses to the cat stimulus by producing a state of anosmia. Although the results of Experiment 1 cannot rule out some subtle impairment of olfactory perception, they would seem to rule out the possibility that scopolamine had reduced fear responses by blocking the response to cat smell. Experiment 1 showed that scopolamine-treated rats were responsive to cat odor in particular. SCOP rats showed a large and significant suppression of drinking time in response to cat smell, showing that the animals were, in fact, registering this stimulus. Thus, it is clear that the drug did not affect fear or defense responses indirectly through actions on olfactory perception. At the same time, these results would not rule out the possibility that the drug had other actions on the olfactory bulbs and related brain structures. It has been observed that the olfactory bulbs are involved in a variety of limbic system functions and are probably doing more than processing olfactory stimuli [20].

Experiment 2 of the present research showed that the robot was an extremely potent fear stimulus. It not only caused a substantial suppresssion of feeding behavior and avoidance of the center area; it also caused a considerable amount of freezing, nearly 50% of the trial time. With the stimulus robot, scopolamine caused the same pattern of reduction in fear responses that it had caused with the stimulus cat. Rats treated with scopolamine showed significantly less freezing, spent significantly more time in the center area near the robot, had significantly shorter latencies to drink. Thus, scopolamine affected fear responses to a stimulus that did not involve cat smell. These results show that the effect of the drug is not specific to the cat stimulus. Rather, they attest to the generalizability of the finding that scopolamine reduced fear responses or defense reactions to an unconditioned stimulus.

The above findings could be interpreted in terms of Bolles' [3] species-specific defense reactions and would be relevant to the literature on anticholinergic drugs and avoidance behavior. In an analysis of avoidance literature, Bolles has shown how the same species-specific defense reaction, such as freezing, would be expected to enhance performance in one avoidance paradigm and impair it in another. In light of this analysis, the finding that scopolamine has now been shown to reduce freezing in a variety of stimulus conditions ([11,13], Experiments 1 and 2 of the present research) is very important. A reduction in the species-specific defense reaction of freezing would account for the finding that anticholinergic drugs impair passive avoidance [4, 6, 8, 10] in which freezing is assumed helpful for successful performance. Also, a reduction in freezing would explain the fact that anticholinergic drugs enhance two-way active avoidance [1, 9, 14] in which freezing is presumably detrimental to performance. Thus, the finding that scopolamine reliably reduced freezing would help to explain much of the literature on anticholinergic drugs and avoidance behavior.

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