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BRIEF COMMUNICATION

Methylscopolamine and Conditioned Location Avoidance

R. N. HUGHES, N. M. BLAMPIED, G. J. ANDERSON AND G. J. WOOLLETT

Department of Psychology, University of Canterbury, Christchurch 1, New Zealand

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HUGHES, R. N., N. M. BLAMPIED, G. J. ANDERSON AND G. J. WOOLLETT. *Methylscopolamine and conditioned location avoidance*. PHARMACOL BIOCHEM BEHAV **33**(4) 913–914, 1989.—On alternate days, rats were confined to one side of a shuttlebox following IP administration of saline and to the other following the peripherally-acting muscarinic antagonist, methylscopolamine (1.2 mg/kg). They later avoided the side associated with the drug effect. By duplicating an earlier finding with centrally- and peripherally-acting scopolamine, this result identified aversive peripheral actions of the two drugs as mainly responsible for the effects observed.

Methylscopolamine Drug state aversion Conditioned location avoidance Rats

IT has been proposed that some of the effects of muscarinic antagonists on exploratory behavior in rats are due to the drugs' aversive stimulus properties rather than to modifications of central cholinergic processes underlying habituation to novelty (6). Peripherally-acting quaternary as well as centrally- and peripherally-acting tertiary forms of these drugs appear aversive since they are both capable of producing conditioned taste aversions (2, 3, 8, 9, 12). Both forms disrupt preferences for novelty (5,7) in a similar manner to aversive experiences such as electric shock (1,4). Since the peripherally-acting quaternary antimuscarinic, methylscopolamine, was at least as effective in this respect as centrally- and peripherally-acting scopolamine, it seems likely that aversive peripheral properties of both drugs were primarily responsible for the effects observed (5).

Evidence more directly supporting the determination of an environmental preference by scopolamine's aversive action was provided by MacMahon, Blampied and Hughes (11) who observed rats later avoid a location associated with the drug's effects. If scopolamine's peripheral properties had been mainly responsible, then a similar outcome should follow treatment with a peripherally-acting muscarinic. The present investigation therefore assessed the effects of methylscopolamine on location avoidance. While having negligible central effects, this compound is superior to scopolamine in peripheral potency (10).

METHOD

Subjects

The subjects were 8 male and 8 female New Zealand random-bred hooded rats approximately 140 days old. They were housed in same-sexed groups of 4 with ad lib food and water and kept in reversed 12-hr light-dark conditions at an ambient temperature of 24 ± 1°C.

Apparatus

All conditioning and testing was carried out in a 61 × 25 × 28 cm (L × W × H) Lafayette shuttlebox (model A550) described in detail elsewhere (11). Briefly, the box was divided in half by a partition containing a 9 × 12 cm (W × H) guillotine door. Superimposed on one end wall were 3-cm black and white vertical stripes while on the other end wall were 3-cm black and white horizontal stripes.

Procedure

Each subject experienced one 10-min session per day for 22 consecutive days.

Adaptation. On days 1–4 the rats were individually confined to one side of the apparatus. On alternate days they were confined to either the side with vertical stripes (VS) on the end wall or to the side with horizontal stripes (HS).

Baseline location preference test. During days 5 and 6 individual subjects were allowed free access to both sides and the total time spent in each was manually recorded with an electric timer. On day 5 half of each sex were introduced into the apparatus on the VS side and half on the HS side. This was reversed on day 6.

Conditioning. On days 7–18 each subject was again confined to one side, but this time immediately following an intraperitoneal injection of either isotonic saline or 1.2 mg/kg methylscopolamine bromide (2 ml/kg). The drug and saline conditions were experienced on alternate days with half of each sex being confined to the

VS side following methylscopolamine administration and the other half being confined to the HS side. Order of injection over days was counterbalanced for these groups.

Conditioned effects posttest. On days 19–22 the baseline test was repeated without any prior injections. The side of entry to the apparatus was not alternated. Instead, one male and one female from each subgroup was placed into the VS side on each posttest day while another male and female was always placed in the HS side.

RESULTS

Preference for being in the side of the apparatus eventually and currently associated with saline was estimated for each subject by applying the following formula:

$$\text{saline preference proportion} = \frac{T_{SAL}}{T_{SAL} + T_{METH}}$$

where, T_{SAL} = time spent in the side associated with saline; T_{METH} = time spent in the side associated with methylscopolamine. With this procedure a score of 0.50 would represent no preference for either side.

Proportions for each sex are outlined in Fig. 1. A two-way ANOVA (pre-post conditioning × sex) performed on averaged proportions for days 5 and 6 (baseline), 19 and 20, and 20 and 21 revealed a significant conditioning effect, $F(2,28) = 9.59$, $p<0.001$, but no sex, $F(1,14)<1$, n.s., or sex × conditioning interaction effects, $F(2,28) = 2.87$, n.s.

According to one-sample *t*-tests, there were no preferences for either side of the apparatus on both baseline test days, $t(15)$ day $5 = 0.13$, n.s., $t(15)$ day $6 = 0.09$, n.s. However, after conditioning, there was a significant preference for the saline side on day 19, $t(15) = 3.41$, $p<0.01$, which was still evident on the last posttest day, $t(15) = 3.79$, $p<0.01$.

DISCUSSION

The results clearly demonstrate that, like scopolamine (11), methylscopolamine led to a preference for being in the side of the apparatus associated with saline injections. This suggests that the rats found the effects of methylscopolamine aversive and accordingly avoided the location associated with them. The conclusion that the effects of methylscopolamine were aversive requires an assumption that the rats were avoiding the drug-associated side rather than approaching the saline side. Given the preconditioning demonstration of equal preference (indifference) any methylscopolamine-induced impairment of the conditioning process or the development of drug tolerance should have attenuated the preference for the saline side and produced continuing indifference.

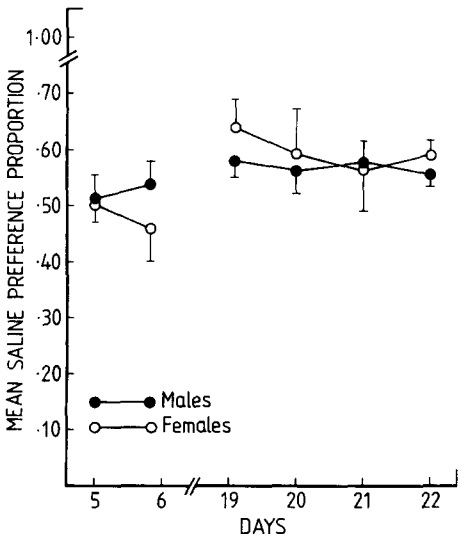

FIG. 1. Mean (± SEM) proportion of time spent on the side associated with saline before and after conditioning trials.

The observation that, contrary to earlier results with scopolamine (11), conditioned avoidance did not extinguish over the four posttest days is most simply explained by the shorter sessions used in the present experiment. Since total nonreinforced exposure to the aversive side of the apparatus was only half that experienced in the previous study [i.e., 10 vs. 20 min sessions (11)] less extinction would be expected. As both drugs produced location avoidance which failed to extinguish with more peripherally potent methylscopolamine (10), it seems likely that peripheral actions were mainly responsible for their conditioned aversive effects.The results are consistent with observations of unconditioned suppression of novelty preferences by both compounds (5) thereby supporting the proposal that location preferences arising from peripheral aversive properties of antimuscarinics at times determine what might appear as centrally-mediated habituation deficits (6). However, this does not entirely preclude the possibility of central as well as peripheral effects of scopolamine being aversive. Further research with systemically-administered scopolamine in combination with peripherally- and centrally-acting muscarinic agonists or, alternatively, centrally-administered antimuscarinics would help clarify this issue.

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