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Scopolamine and Amphetamine Effects on Discrimination: Interaction with Stimulus Control*

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Abstract. A parametric examination of the interaction between drug-induced behavioral changes and the degree of predrug stimulus control was conducted with rats. A discrete-trial simultaneous discrimination was used, with the controlling stimuli varied over 6 values of distinctiveness. The effects of graded doses of scopolamine, *d*-amphetamine, and methylscopolamine on these performances were studied, with both scopolamine and *d*-amphetamine showing no increase in error rate under strong stimulus control, and dose-related increases in error rate under weak stimulus control. The similar interaction between drug effect and stimulus control for scopolamine and *d*-amphetamine indicates that the interaction reflects the degree of susceptibility of the behaviors to drug action, rather than two specific drug-behavior interactions.

Methylscopolamine produced a slight effect on error rate and no significant interaction with stimulus control. A decrease in the number of trials responded to was found with both scopolamine and methylscopolamine, but not with *d*-amphetamine.

Key words: Scopolamine – Amphetamine – Stimulus Control – Discrimination – Rats.

Several recent studies have shown that behavior which is strongly controlled by discriminative stimuli is less susceptible to drug influences than behavior which is less strongly controlled by the stimulus situations. This differential effect has been demonstrated with *d*-amphetamine and scopolamine in pigeons (Laties, 1972; Laties and Weiss, 1966), amobarbital in pigeons (McKearney, 1970), chlorpromazine in pigeons (Terrace, 1963), and scopolamine and amphetamine in rats (Heise and Lilie, 1970; Rosic and Bignami, 1970; Ksir, 1974).

In each study cited two different levels of control were obtained by either presenting different sets of discriminative stimuli to different groups of subjects (Rosic and Bignami, 1970; Ksir, 1974), by providing different training histories (Terrace, 1963), by intensifying a controlling stimulus (McKearney, 1970), or by adding additional discriminative stimuli to one condition (Laties and Weiss, 1966; Heise and Lilie, 1970; Laties, 1972). In each of these studies, the more strongly-controlled behavior was the less influenced by a given dose of some drug.

Since only two levels of stimulus control were examined in each of these studies, the function relating stimulus control to drug effect is not fully known. If a subject is responding under strong stimulus control such that a given drug has little effect on the behavior, what will happen if the stimulus control is gradually decreased? It is possible that at some level a critical point of stimulus control will be reached and a "full blown" drug effect will emerge, or it is possible that the drug effect will gradually increase over a wide range of stimulus control. Dews (1971) has reviewed the relationship between discrimination and stimulus control and pointed out the lack of data on such a function.

The current study began with a two-key simultaneous brightness discrimination. On each trial one of the response keys was illuminated and the other was not. The voltage applied to the originally unlit lamp was gradually increased during the study, thereby decreasing the physical difference between the

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two stimuli and decreasing the degree to which the stimuli controlled differential responding. Drug injections were given after each baseline level of stimulus control was reached.

Heise and Lilie (1970) found that both scopolamine and amphetamine had large effects under their weak stimulus control condition, but only scopolamine had an effect on behavior under stronger stimulus control. While the present hypothesis is that behavior under strong stimulus control should be less sensitive to all drugs than behavior under weak stimulus control, it is possible that different drugs show different types of interaction with stimulus control. For this reason, scopolamine and amphetamine were each injected, in varying doses, at different levels of stimulus control. Methylscopolamine, a more ionizable compound which does not readily enter the brain, was administered to measure the influence of peripheral cholinolytic effects (mydriasis, decreased salivation etc.) on these behaviors.

Method

Subjects

The eight male albino rats were each maintained at approximately 75% of their free-feeding weight by supplemental feedings after each experimental session. Water was available in the home cages and in the experimental chamber.

Apparatus and Procedure

General. All sessions were carried out in a single Plexiglas operant conditioning chamber. The chamber contained two Gerbrands model B response keys mounted approximately 3 cm above the grid floor. A $7^1/_2$-w (at 115 v) white lamp was mounted in an aluminum box behind each key. A 2 cm hole in each box allowed transillumination of the key by the lamp. Resistances placed in series with the lamps were used to provide the following intensities: at 90 v, 4100 mW/m^2; at 70 v, 2100 mW/m^2; at 60 v, 1500 mW/m^2; at 50 v, 880 mW/m^2; at 40 v, 450 mW/m^2; and at 30 v, 190 mW/m^2 (measured with a calibrated photometer with approximately equal sensitivity to all wavelengths from 450–950 nm). Food pellets (0.25 g, SK & F formula) could be presented via a delivery tray mounted between the two keys. A water tube was mounted at the opposite end of the chamber from the food tray and keys. A $7^1/_2$ w white houselight was mounted behind the water tube, outside the chamber.

All rats were first trained to depress the keys by a food pellet delivered after each response. They were then trained on a simultaneous intensity discrimination procedure. During the 10 sec (maximum duration) trial period, one of the keys was illuminated (90 v) and the other was not illuminated. The illuminated key was always correct for four of the rats (Lt+), and the dark key was always correct for four of the rats (D+). A single response on the correct key during the trial produced a food pellet and terminated the trial. A single response on the incorrect key during the trial terminated the trial without producing a food pellet. The location of the correct response was varied equally between the two keys in a randomized sequence which repeated every 20 trials. During the intertrial interval (ITI, 40 sec minimum duration) the houselight was on and both keys were either illuminated (for the D+ rats) or dark (for the Lt+ rats). Responses during the ITI delayed the onset of the next trial until 40 sec after the last response. Each session consisted of 40 trials. Performances were considered sufficiently stable after 35 training sessions, during which occasional test injections of atropine, scopolamine, or *d*-amphetamine were given.

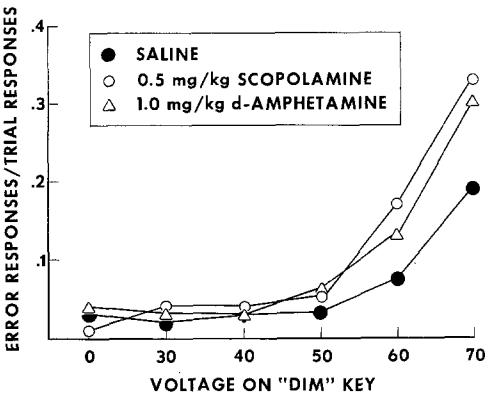

Fig. 1. Mean error probability for saline, 0.5 mg/kg scopolamine, and 1.0 mg/kg *d*-amphetamine. Level of stimulus control is indicated by the voltage applied to the dim lamp (brighter lamp was at 90 v)

Since there were no significant differences between the D+ and Lt+ groups in acquisition, predrug stimulus control, or on the preliminary test injections, this variable was ignored in subsequent analyses, and the pooled means were used for all the figures. One D+ rat died before experimental injections were begun; the data given are for the remaining 7 rats.

All drugs were dissolved in 0.9% NaCl solution (saline) and were administered intraperitoneally in a volume of 1 ml/kg approximately 30 min before a session. Drugs were given on Tuesdays and Fridays, with Thursday sessions (saline vehicle injections) used as control periods. Sessions were not normally conducted on Saturday or Sunday.

Dose-Effect Determinations under Strong Stimulus Control (0 v vs. 90 v). Each rat received one injection of each of the following doses: scopolamine hydrobromide, 0.25, 0.50, and 1.0 mg/kg; methylscopolamine bromide, 0.25, 0.50, and 1.0 mg/kg; and *d*-amphetamine sulfate, 0.50, 1.0, and 2.0 mg/kg (salt weights). All scopolamine injections were given before all amphetamine injections, and methylscopolamine injections were given last. The various doses of a given drug were administered in counterbalanced orders.

Manipulation of Stimulus Control. After drug tests were completed on the simple discrimination, the voltage supplied to the originally unlit lamp was increased from 0 v to 30, 40, 50, 60, and 70 v. At each level of stimulus control a few sessions were allowed for the performances to restabilize before drug injections were begun. Each rat received two injections of 0.50 mg/kg scopolamine hydrobromide and two injections of 1.0 mg/kg *d*-amphetamine sulfate at each level of stimulus control. The order of injection was always: scopolamine, amphetamine, amphetamine, scopolamine.

Dose-Effect Determinations under Weak Stimulus Control (60 and 70 v vs. 90 v). Since the 60 v *vs.* 90 v discrimination provided clear drug effects at the doses employed, additional injections were given to provide dose-effect data. The ad-

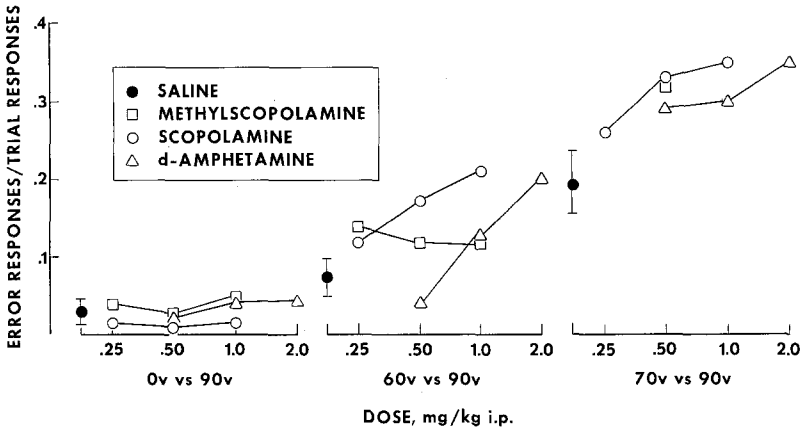

Fig. 2. Dose-effect curve of error probability for scopolamine, amphetamine, and methylscopolamine. Three levels of stimulus control are represented: 0 v *vs.* 90 v; 60 v *vs.* 90 v; 70 v *vs.* 90 v. Brackets on saline points indicate ± standard error of the mean

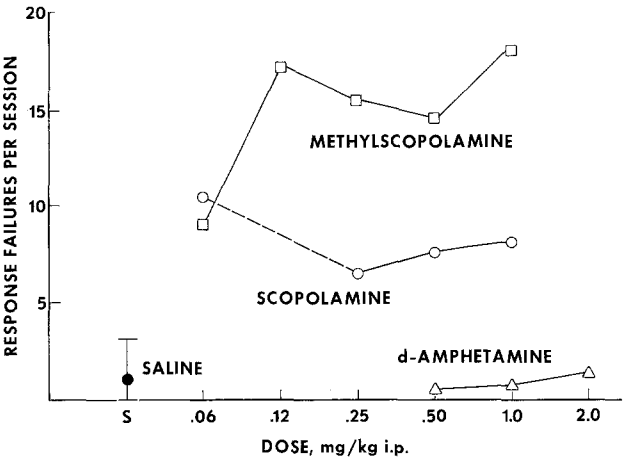

Fig. 3. Combined dose-effect curve of response failures per session for scopolamine, amphetamine, and methylscopolamine. Saline point also shows ± standard error of the mean

ditional doses were: 0.06, 0.12, 0.25, 0.50, and 1.0 mg/kg methylscopolamine, 0.06, 0.25, and 1.0 mg/kg scopolamine, and 0.50 and 2.0 mg/kg *d*-amphetamine.

Additional doses were also given on the 70 v *vs.* 90 v discrimination, so that dose-effect curves could be compared at 2 levels of stimulus control. These additional doses were: 0.25 and 1.0 mg/kg scopolamine, 0.50 mg/kg methylscopolamine, and 0.50 and 2.0 mg/kg *d*-amphetamine.

The index of discrimination performance was incorrect responses/trial responses. Failure to press either key during a trial was not called an error, but these occurrences were tabulated separately as "response failures". Responses on either key during the ITI were also tabulated.

Results

Fig. 1 presents group mean error proportions for the saline, 0.5 mg/kg scopolamine, and 1.0 mg/kg *d*-amphetamine sessions at the various levels of stimulus control. It is apparent that stimulus control did influence the effects of amphetamine and scopolamine on this measure, since the drug and control curves are very close at 0 v, 30 v, and 40 v, grow slightly apart at 50 v, and farther apart at 60 v and 70 v. This interaction is demonstrated more vividly in Fig. 2, which presents dose-effect data for all the drugs on the 0 v, 60 v, and 70 v discriminations. An analysis of variance compared error proportions at these three levels of stimulus control for saline, 0.25, 0.50, and 1.0 mg/kg scopolamine. The effect of discrimination difficulty on error rate was significant ($F = 26.3$, $df = 2,12$, $P < 0.001$), the dosage effect was significant ($F = 4.9$, $df = 3,18$, $P < 0.025$), and the interaction between dosage and difficulty was significant ($F = 3.9$, $df = 6,36$, $P < 0.005$). A similar analysis for 0.5, 1.0, and 2.0 mg/kg *d*-amphetamine found a significant effect of difficulty ($F = 38.3$, $df = 2,12$, $P < 0.001$), a significant dosage effect ($F = 9.2$, $df = 3,18$, $P < 0.001$), and a significant interaction ($F = 2.6$, $df = 6,36$, $P < 0.05$). The effects of 0.5 mg/kg methylscopolamine were compared with control at the 0 v, 60 v, and 70 v discriminations. The effect of difficulty was again significant ($F = 15.6$, $df = 2,10$, $P < 0.001$). Whereas the drug effect was slightly significant ($F = 7.7$, $df = 1,5$, $P < 0.05$), there was no significant interaction between difficulty and drug effect ($F = 1.6$, $df = 2,10$). Although Fig. 2 shows a large increase in error rate with 0.5 mg/kg methylscopolamine at 0 v *vs.* 70 v, those data were quite variable, preventing both a more significant drug effect and a significant drug × difficulty interaction effect. Data for one rat for methylscopolamine were incomplete, and were eliminated from the analysis.

Individual comparisons between specific doses and control data for error rate were made by *t*-tests. The doses of scopolamine given at 30 v, 40 v, and 50 v did not significantly influence error rate. The small

doses of scopolamine (0.06 mg/kg) and methylscopolamine (0.06, 0.12, and 0.25 mg/kg) given at 60 v which were not included in the analysis of variance produced one marginally significant t (2.55, $df = 6$, $P < 0.05$), for 0.25 mg/kg methylscopolamine. A significant t was not found for 1.0 mg/kg methylscopolamine at 60 v.

Analyses of variance were performed on the response failure data for the 0 v, 60 v, and 70 v discriminations for the same doses of scopolamine, amphetamine, and methylscopolamine as were used in the error rate analyses. For the *d*-amphetamine data, discrimination difficulty did not influence response failures, amphetamine did not significantly influence response failures, and there was no difficulty × drug interaction. For the scopolamine data, difficulty was not an influence, the effect of scopolamine was significant ($F = 15.4$, $df = 3,18$, $P < 0.001$), and there was no significant interaction. For the methylscopolamine data, difficulty was not an influence, methylscopolamine had a significant effect ($F = 15.7$, $df = 1,5$, $P < 0.025$), and there was not a significant interaction. Since difficulty of the discrimination had no influence on response failures or on drug effects on response failures, the dose-effect data for 0 v, 60 v, and 70 v for each drug were pooled and are presented in Fig. 3. It is apparent from Fig. 3 that both scopolamine and methylscopolamine increased response failures, while *d*-amphetamine had a (nonsignificant) tendency to decrease response failures.

Individual t-tests showed significant increases in response failures even at the low doses of scopolamine and methylscopolamine given at 60 v *vs.* 90 v (for 0.06 scopolamine, $t = 2.95$, $P < 0.05$; for 0.12 methylscopolamine, $t = 7.01$, $P < 0.001$).

The number of ITI responses per session showed considerable variability. Analyses of variance for scopolamine, *d*-amphetamine, and methylscopolamine at the 0 v, 60 v, and 70 v discriminations showed no significant drug effects, difficulty effects, or interaction effects. Methylscopolamine tended to decrease ITI responding, whereas scopolamine and *d*-amphetamine tended to increase ITI responding.

Since control sessions occurred on Thursdays, frequently only 2 days after a drug injection, comparisons were made between control days which happended to be preceded by more than 2 drug-free days and control days which followed by only 2 days doses of 0.5 or 1.0 mg/kg scopolamine or 1.0 or 2.0 mg/kg *d*-amphetamine. Sufficient data were available at the 60 v *vs.* 90 v discrimination so that each rat could be represented at each of these points. Neither error rate nor response failure rate showed dose-related trends or significant differences on these comparisons.

Discussion

Clear interactions between stimulus control and drug effects on error rate were found for both scopolamine and *d*-amphetamine. Since Fig. 1 shows a slight, but nonsignificant, effect of both drugs on error rate at 50 v, a greater effect at 60 v, and apparently an even greater effect at 70 v, and since Fig. 2 shows a greater effectiveness of lower doses of *d*-amphetamine at 70 v than at 60 v, it appears that the interaction between stimulus control and drug effects on error rate can be characterized as graded rather than discontinuous. Future studies of this interaction should probably focus intensely on the behavior of individual animals, which was unfortunately not possible in the current study due to the small number of trials per session.

Since scopolamine and *d*-amphetamine both began to increase error rates at the same level of stimulus control, and showed very similar patterns of interaction with stimulus control, it is likely that the interaction has more to do with the susceptibility of the behavior to drug action in general than to two specific drug-behavior interactions.

As for the drugs themselves, it is interesting that scopolamine had effects similar to those of *d*-amphetamine on error rate but not on response failures. Methylscopolamine, which only slightly increased error rates and showed little interaction with stimulus control, was even more effective than scopolamine in increasing response failures. Scopolamine clearly has multiple effects on this behavioral schedule, with the response-failure effect appearing at lower doses than the error-increasing effect, and with only the error-increasing effect showing an interaction with stimulus control. Methylscopolamine, which primarily influences the peripheral nervous system, mimics the response-failure effect to a greater extent than it does the error-increasing effect.

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