THE ACTION OF ATROPINE, BENACTYZINE, AND SCOPOLAMINE UPON FIXED-INTERVAL AND FIXED-RATIO BEHAVIOR

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Atropine and scopolamine, perhaps the best known of anticholinergic agents, have been widely studied in a variety of physiological preparations. While the more prominent actions of these drugs are peripheral (such as the mydriatic, the antispasmodic, and the anti-secretory effects), actions attributed to the central nervous system are also known. Changes in EEG waves and antagonism of Parkinsonism tremor have been reported with moderate doses, while higher doses are said to produce assorted effects including excitement, restlessness, delirium, hallucinations, and sedation (Goodman & Gilman, 1955).

In this study, atropine and scopolamine were examined for their effects upon the operant behavior of trained animals. Related work by Dews (1955, 1957) showed that scopolamine decreased the rate at which a pigeon pecked a key on a variable-interval schedule, but did not otherwise interfere with simple or complex visual discriminations or discrimination reversals. In the present experiment, the drugs were studied for their actions upon behavior established by fixed-ratio and fixed-interval behavior. A multiple-schedule technique (Ferster & Skinner, 1957) was used in which the same animal was trained on both schedules with a different stimulus present while each schedule was in force. This technique was selected because it allowed each dose to be studied for its effects upon both schedules in an individual animal during the same session.

Benactyzine was selected for comparison with atropine and scopolamine. Benactyzine has been reported to share certain actions with these drugs, such as mydriasis, antispasmodic action, and slowing of the EEG (Berger, Hendley, & Lynes, 1956). Jacobsen and Sonne (1955) have found that benactyzine increases the frequency of conditioned avoidance responses of rats and reduces the "tenseness" of the animals between trials.

PROCEDURE

The subjects were two male albino rats of the Charles River Sprague-Dawley strain. The animals were approximately 9 months old at the beginning of this experiment. The past history of the animals included the injection of other compounds.

The basic apparatus was an aluminum box (10 × 10.5 × 8 inches) containing a lever which the animal could press. About 20 grams' force on the lever closed a microswitch and permitted automatic recording of the lever-pressing behavior. Stainless steel rods formed the floor of the box. At the narrow end of the box near the lever was a water-reinforcement device, a motor-driven dipper, which delivered about 0.07 milliliter of water. The dipper normally remained in the "up" position; but when a reinforcement was programmed, the dipper was driven down into a water reservoir with a click, then returned to the animal.

Relays, timers, counters, cumulative recorders, and associated equipment were used to record and control automatically the lever-pressing behavior of the subjects. Relay clicks and extraneous noises were kept from affecting the animals by having the controlling equipment in a separate room and by presenting a "white" masking noise in the animal room.

The animals were watered for 2.5 hours after each session and were deprived of water for 43 hours at the beginning of each session. A session lasted for 2.5 hours. The lever-pressing response was originally conditioned by following each lever press with a dipper of

water. After two sessions of continuous reinforcement, the procedure was shifted to a two-component multiple schedule: 1) in the presence of a clicking noise, the reinforcement was delivered after a fixed number of responses (a fixed-ratio or FR schedule); 2) in the presence of a tone, the reinforcement was delivered for the first response after a fixed number of minutes (a fixed-interval or FI schedule). The schedules alternated with each other, with the stimulus change taking place immediately after the reinforcement. At first, the FR schedule required 7 responses, and the FI was set at 1 minute. Then, the values were increased from session to session until the FR was 26 and the FI was 4 minutes. The schedules remained at these values for the remainder of this experiment. Drugs were not administered until the animal's performance had stabilized (i.e., the behavior appropriate to each schedule showed no consistent trends for at least eight sessions).

The drugs were dissolved in saline and injected intraperitoneally in a volume of approximately 0.75 milliliter. To allow time for absorption, the injections were made 10 minutes prior to an experimental session. Atropine sulfate, benactyzine hydrochloride, and scopolamine hydrobromide were studied in the order named. Each animal received several doses (indicated in Table 1) of each drug in an unsystematic order. At least one control session with no injection was run between each drug session in order that an animal could serve as its own control. Since a control session followed a drug session by at least 4 days, and since drug injections were made no more frequently than once every 6 days, "carry-over" effects from one session to another were never observed.

RESULTS

The results will be presented in two forms. First, graphical cumulative-response records will illustrate changes in the temporal patterning of the lever-pressing response rate. Second, the average rates of responding under each reinforcement schedule will provide quantified information on the rate changes produced by the drug.

At the top of Fig. 1 is shown a cumulative record which illustrates the normal performance obtained from this multiple schedule. At *a* the animal had just received a reinforcement, had gone into the FR schedule, and was exhibiting a brief pause. Then, the animal started responding abruptly at a high rate and continued until the reinforcement (indicated by the cross-mark). The short pause followed by the abrupt acceleration to a high rate was characteristic of this animal's performance on the FR schedule. The lower channel at *b* indicates which schedule is in operation. When the pen is down, the FR schedule is programmed; when the pen is up, the FI schedule is programmed. After a reinforcement on the FR schedule, the schedule changed to FI, and the animal usually paused for a relatively long time, as at *c*. Then, the response rate gradually accelerated to a moderately high terminal rate. The long pause and the gradual acceleration were typical of this animal's behavior on the FI schedule. The reinforcement was delivered at the point indicated by the cross-mark, and the schedule returned to an FR. After every second FI reinforcement, as at *d*, the recording pen reset to the bottom of the page, and another cycle began.

The top record in Fig. 1 was collected during the session prior to the first dose of atropine, while the bottom record was collected during the session prior to the last dose. The records are split into two panels: on the left is shown the first 45 minutes of the 2.5-hour session, and on the right is shown the last 45 minutes. The doses are shown to the left of the appropriate record. (Figures 2, 3, and 4 were constructed in a similar way.) The dose of 1.0 milligram per kilogram produced little observable change in the temporal patterning of the

Figure 1. Cumulative records for Rat A-47 illustrating the effect of atropine upon the multiple-schedule performance.

two schedules. However, the FI components occasionally appeared to contain an increased number of responses (as at *e*).

Additional data on this point appear in Table 1 where the drug/control ratios for each dose are shown. The basic datum in this table is the average rate of responding during each half of the session. Thus, this rate measure does not take into account the temporal pattern produced by each schedule, but merely indicates the total amount of behavior over the total time period. A measure of the normal performances to be expected in the absence of the drug injection was derived by averaging the response rates for six control sessions (two before the first dose, two between the doses, and two after the last dose). These mean rates, in responses per minute, are labeled Control Rates in Table 1. Then, a drug/control ratio was computed by dividing the response rate which was observed during the drug session by the mean rate over six control sessions. Thus, a ratio greater than 1.0 indicates an increased rate, while a ratio less than 1.0 indicates a decreased rate. Rates for the two halves of the session were handled separately to permit some consideration of the time course of the drug. The statistical significance of a rate change was evaluated for each dose by estimating the standard deviation from the range, and by using this estimate in computing the 95% fiducial limits under the assumption of normality. Then, if the drug session rate deviated from the mean control rate so that the fiducial limits were exceeded, significance was

declared at the 5% level. The actual computations require that the rate under drug should differ from the mean control rate by an amount greater than the range of control rates and may be rationalized under several statistical assumptions, although the exact p-value will depend on the particular rationale.

Table 1, in conjunction with Fig. 1, provides a more complete picture of the action of atropine. While the dose of 1.0 milligram per kilogram had relatively little effect upon the temporal patterning of responding, the over-all average response rate for the FI component was slightly increased, especially during the first half of the session. The dose of 2 milligrams per kilogram produced larger changes, although the onset of action was delayed. In Fig. 1 at *f* the post-reinforcement pause on the FI had nearly disappeared along with the smooth acceleration. After *f*, the responding under the FI schedule fluctuated around a moderate rate and showed little or no temporal patterning. The rate, however, was considerably lower than the terminal rate observed during control sessions. Such changes were never observed in over 50 control sessions, and thus can be reasonably attributed to drug action. The performance on the FR schedule was altered but little. The only change seems to be in the variability of the post-reinforcement pause.

The FI rate shown in Table 1 was not significantly changed in the last half of the session, in spite of marked changes in temporal patterning of the FI responding. This dose of atropine caused the animal to respond after the reinforcement, when it normally paused, and to respond slowly toward the end of the FI, when it normally responded rapidly. The combination of these two drug-induced changes resulted in an over-all average rate which approximated the control values. In this case, as in those to be discussed below, the average rates in Table 1 are quite difficult to interpret except in conjunction with the cumulative records.

With the dose of 4 milligrams per kilogram the atropine effects were seen early in the first half of the session. At point *g* in Fig. 1 the post-reinforcement pause was missing; at *h* a ratio-like run occurred during the FI schedule; and at *i* the typical ratio run did not occur. During the last part of the session the response rate was quite low and displayed no temporal patterning normally associated with reinforcement schedules.

The results for the second animal (Rat A-43) at a dose of 2 milligrams per kilogram corroborated the effects described above, but at lower doses the animal did not show the increase in rate.

The effects of benactyzine upon the performance of Rat A-47 may be assessed from Table 1 and Fig. 2. Doses of 0.1 and 0.5 milligram per kilogram increased the average response rates and thus produced what might be described as a "stimulating action." These doses did not noticeably change the temporal patterning (only the dose of 0.5 milligram per kilogram is shown in Fig. 2). With 4 milligrams per kilogram, however, the post-reinforcement pause typical of the FI schedule decreased sharply, as at *a*; the more or less steady rate of responding was usually less than the normal terminal rate. Thus, the increased average rate shown in Table 1 for 4 milligrams per kilogram is related to the alteration of the temporal pattern. The fixed-ratio record usually maintained its typical shape, although the post-reinforcement pause was somewhat shorter than usual; the shortened pause probably accounts for most of the increased average rate of FR responding shown in Table 1 rather than an increase in the running rate. The duration of action of benactyzine was relatively brief, and the fixed-interval performance recovered its normal scalloped shape before the end of the session.

In addition to the FI effects described above for 4 milligrams per kilogram, the dose of 8 milligrams per kilogram disrupted the ratio performance, as at *b*; the normal temporal

TABLE 1
The Effects of Atropine, Benactyzine, and Scopolamine Upon the Average Rate
of Responding During the FR and FI Components of the Multiple
Schedule in Terms of a Drug/Control Ratio

Rat No.	Atropine										Benactyzine										Scopolamine									
	Drug/Control Ratio										Drug/Control Ratio										Drug/Control Ratio									
	FR					FI					FR					FI					FR					FI				
	I.P. Dose mg./kg.	1st Half	2nd Half	1st Half	2nd Half	I.P. Dose mg./kg.	1st Half	2nd Half	1st Half	2nd Half	I.P. Dose mg./kg.	1st Half	2nd Half	1st Half	2nd Half	I.P. Dose mg./kg.	1st Half	2nd Half	1st Half	2nd Half	I.P. Dose mg./kg.	1st Half	2nd Half	1st Half	2nd Half	I.P. Dose mg./kg.	1st Half	2nd Half	1st Half	2nd Half
A-47	1.0	1.01	1.16	1.53*	1.23	0.1	1.21*	0.93	1.14	0.89	0.1	1.21*	0.93	1.14	0.89	0.1	1.20	1.44*	1.15	0.52	0.1	1.20	1.44*	1.15	0.52	0.1	1.20	1.44*	1.15	0.52
	2.0	1.09	1.03	1.31	1.07	0.5	1.53*	0.85	1.79*	1.02	0.4	0.49*	0.36*	1.04	0.98	0.4	0.49*	0.36*	1.04	0.98	0.4	0.49*	0.36*	1.04	0.98	0.4	0.49*	0.36*	1.04	0.98
	4.0	0.31*	0.20*	1.10	0.22*	4.0	1.53*	1.23*	2.60*	1.56*	0.8	0.56*	0.50*	1.15	1.29	0.8	0.56*	0.50*	1.15	1.29	0.8	0.56*	0.50*	1.15	1.29	0.8	0.56*	0.50*	1.15	1.29
						8.0	0.78*	0.88	2.34*	2.21*	1.6	0.42*	0.29*	1.30	1.00	3.2	0.67	0.67	1.58*	1.84*	3.2	0.67	0.67	1.58*	1.84*	3.2	0.67	0.67	1.58*	1.84*
Control Rates		25.7	26.5	16.5	18.0		24.0	30.6	13.5	14.8		22.2	26.8	11.5	12.1		22.2	26.8	11.5	12.1		22.2	26.8	11.5	12.1		22.2	26.8	11.5	12.1
A-43	0.1	1.00	1.11	1.00	1.13	0.1	1.13	1.48*	1.61*	1.59*	0.1	1.11	1.23	1.38*	1.44*	0.1	1.11	1.23	1.38*	1.44*	0.1	1.11	1.23	1.38*	1.44*	0.1	1.11	1.23	1.38*	1.44*
	1.0	0.98	1.00	0.84	0.83	0.5	1.22*	1.11	0.87	0.98	0.2	0.22*	0.35*	0.68*	0.76	0.2	0.22*	0.35*	0.68*	0.76	0.2	0.22*	0.35*	0.68*	0.76	0.2	0.22*	0.35*	0.68*	0.76
	2.0	0.82	0.20*	0.87	0.75	2.0	0.36*	0.31*	0.52	0.83	0.8	0.18*	0.22*	0.65*	0.34*	0.8	0.18*	0.22*	0.65*	0.34*	0.8	0.18*	0.22*	0.65*	0.34*	0.8	0.18*	0.22*	0.65*	0.34*
						4.0	0.89	1.43*	1.27	1.23	1.6	0.22*	0.25*	0.76	0.43*	3.2	0.21*	0.28*	0.78	0.55*	3.2	0.21*	0.28*	0.78	0.55*	3.2	0.21*	0.28*	0.78	0.55*
Control Rates		45.9	47.5	15.5	13.1		49.1	36.6	16.3	14.1		47.1	35.1	17.7	16.1		47.1	35.1	17.7	16.1		47.1	35.1	17.7	16.1		47.1	35.1	17.7	16.1

*Significant at the 0.05 level.

Figure 2. Cumulative records for Rat A-47 illustrating the effect of benactyzine upon the multiple-schedule performance.

patterning was replaced by a rough-grained, fluctuating rate. In Table 1 this effect shows up as a lowered average rate. In the second half of the session, however, the ratio performance recovered, and shortly thereafter the interval performance also recovered.

The benactyzine results for the second animal (A-43) were in general accord with those described above, in that 1) the temporal patterning on both the FI and the FR was modified; 2) rate increases due to briefer post-reinforcement pauses were seen on both the FI and the FR; and 3) the terminal rates were lowered on both schedules by the higher doses.

The effects of scopolamine upon the temporal patterning of the behavior is illustrated in Fig. 3 by Rat A-43's cumulative records. At point *a* in the upper control record an important aspect of the multiple-schedule baseline behavior was demonstrated. At this point, instead of the usual FI FR alternation, two consecutive FI's were programmed. The animal, however, responded with a ratio run before lapsing back into the more appropriate interval scallop. This "test probe" (along with a number of others not shown) suggests that the animal was probably alternating between the two schedule patterns rather than discriminating the clicker and the tone stimuli. Other evidence for this interpretation was provided, first, by a later experiment in which the animals continued to alternate ratio and interval behavior even though the order had been changed to three FR's followed by one FI, and, second, by an experiment by Ferster and Skinner (1957), in which rats trained on a similar FR FI multiple schedule continued with an alternating "multiple-type" perform-

ance after the stimuli had been removed. Thus, the control of the multiple-schedule performance should be ascribed, at least in part, to a *sequence* discrimination (rather than solely to a stimulus discrimination). This point is mentioned because a multiple schedule based upon a sequence discrimination might respond to drugs differently from a multiple schedule based upon an external stimulus discrimination.

Figure 3. Cumulative records for Rat A-43 illustrating the effect of scopolamine upon the multiple-schedule performance. In the third, fifth, and sixth records, the pen reset to the baseline after the fourth FI rather than the second.

The scopolamine effects were similar in most respects to those described above for atropine and benactyzine and need not be described in detail. The dose of 0.2 milligram per kilogram, for example, eliminated A-43's characteristic temporal pattern of both ratio and interval responding. Higher doses did much the same thing. Table 1 shows that these higher doses markedly decreased the average rates of responding; the lowest scopolamine dose studied (0.1 milligram per kilogram), however, increased A-43's FI rate. The results for Rat A-47, shown in Fig. 4 and Table 1, were similar to those for A-43 except that the depressant effect of the higher doses upon the FI rate was not observed. (Indeed, 3.2 milligrams per kilogram increased the FI response rate.) This difference between the animals may be related to the fact that A-47 normally exhibited a longer pause after the reinforce-

ment than A-43; and since scopolamine caused the post-reinforcement period to be filled with responding (even though the *terminal* rate under the drug was clearly reduced), the *over-all* average rate could not be decreased as much for A-47 as for A-43. This argument holds also for the other two drugs and may explain, at least in part, why both atropine and benactyzine caused more prominent or more frequent rate increases in A-47 than in A-43.

Figure 4. Cumulative records for Rat A-47 showing the action of scopolamine upon the multiple-schedule behavior. In the second, fifth, and sixth records, the pen reset to the baseline after the fourth FI rather than the second.

DISCUSSION

While the three compounds differed in certain respects, they also shared a number of effects in common. 1) At appropriately high doses, the temporal patterning of both the FR and the FI components of the multiple schedule was disrupted and changed to more or less steady responding. The average FR rate decreased at these doses, but the average FI rate did not necessarily do so even though the terminal rate was decreased. The cases where the average FI rate did not decrease were related to the fact that the normal post-reinforcement pause was replaced by responding. 2) At certain medium doses or at selected times after in-

jection, the FI was changed in temporal pattern but the FR was not. Thus, the two schedules were differentially sensitive to the drugs. 3) At low doses which did not alter the temporal patterning, there was some evidence of "stimulation" in that the average FI and/or FR rates were increased.

Since anticholinergic compounds, including the three studied here, are known to reduce salivary secretion and since water reinforcement was used, a "dry mouth" might be a mechanism through which the compounds exerted their effects. Data relating response rate and dryness of mouth are not available; but if it is assumed that the effects of a dryer mouth would be simulated by increased deprivation, then it might be argued that the rate increases produced by low doses were caused by a dry mouth. On the other hand, inconsistent data were provided in a study by Schmidt, Moak, and Van Meter (1958) where it was shown that atropine, even in doses of less than 1 milligram per kilogram, decreased the water intake of rats. Furthermore, the "dry mouth" mechanism would not account for the rate decreases at the higher doses or for the large changes in temporal patterning.

Without information that more anticholinergic compounds have the particular behavioral effects described above and that other classes of compounds do not, any broad generalization about anticholinergic compounds would be unwarranted. However, it is interesting to note that three compounds possessing anticholinergic properties in common also produce some behavioral effects in common.

SUMMARY

Atropine, benactyzine, and scopolamine were studied for their effects upon fixed-interval and fixed-ratio behavior in a multiple schedule. At high doses the compounds eliminated the characteristic temporal patterns of both the FR and the FI. Low doses increased the response rates slightly.

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