EFFECTS OF SCOPOLAMINE ON A MULTIPLE SCHEDULE^{1,2}

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Therapeutic doses of scopolamine are often associated with marked behavioral effects (Goodman & Gilman, 1955). Patients receiving this drug are likely to become "euphoric," or "amnesic," and certain clinical applications use its "sedative" action. In addition, descriptions of stramonium poisoning (probably involving a number of the belladonna alkaloids) have contained references to a kind of drunkenness.

Although these clinical observations suggest strongly that scopolamine acts upon the learned behavior of individuals, little is provided for a detailed understanding of what particular aspect of behavior is affected and in what way. Dews (1955, 1957), using trained pigeons as experimental subjects, studied the effects of this drug in a situation in which the subject's behavior was carefully controlled. He was able to show only the sedative or depressant action, without obtaining any indication of the amnesic or euphoric effects. The present experiment is another attempt to study quantitatively the behavioral effects of scopolamine.

METHOD

Subjects

The subjects were three male albino rats, which were approximately 550 days old at the start of this experiment. They were maintained at 60 per cent of their 200-day weights and had been at this level of food deprivation for about a year. During the preceding year, two of the Ss (A-20 and A-40) had been used to investigate the properties of the particular behavioral situation which, in the present experiment, is used as a base line for the effects of scopolamine (Herrnstein & Brady, 1958).

Apparatus

The experimental chamber has been described previously (Herrnstein & Brady, 1958). It is a light-insulated box containing a response lever, a liquid-reinforcement mechanism, and the means for presenting electric shocks and a variety of visual and auditory stimuli. The food reinforcer is 0.3 cubic centimeter of sweetened condensed milk. The electric shock has an intensity of 2 milliamperes and a duration of 0.4 second, and is presented, via a "grid scrambler," to the floor, walls, and lever.

Procedure

Rats A-20 and A-40 were used daily for experimental sessions lasting not more than 5 hours. A session was composed of repeating cycles of a 4-ply multiple schedule. The components of the schedule were as follows: a 5-minute fixed interval

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for food reinforcement:³ a 5-minute period during which responses had no explicitly programmed consequence (S_1^A); 5 minutes of shock avoidance; and a second 5-minute S^A period (S_2^A). These components always followed each other in the order just mentioned. Each component was associated with a particular stimulus condition, as follows: the fixed-interval, illumination of two small (about 2 watts each) lamps; S_1^A , none; avoidance, a continuous tone; and S_2^A , a clicking noise. In addition, two 7-watt lamps were continuously illuminated throughout the experimental session.

The avoidance procedure is the one developed by Sidman (1953). During the avoidance component, each lever response postpones the brief electric shock for 20 seconds. In the absence of lever responses, the shock is presented every 20 seconds. The duration of all shocks is 0.4 second; there is no shock-escape contingency.

Experimental sessions for Rat A-4 were of not more than 2 hours' duration. The procedure was a 2-ply multiple schedule consisting of two of the components of the schedule described above. The 5-minute, fixed-interval component alternated with the S_1^A component. The same stimuli were used.

Scopolamine hydrobromide, dissolved in isotonic saline, was occasionally injected intraperitoneally during an experimental session. The volume of solution injected was never greater than 1.0 cubic centimeter and was usually less than 0.5 cubic centimeter. All Ss were thoroughly habituated to the routine of being removed from the experimental chamber, injected, and returned. The administration of scopolamine during a session divides that session into a control and an experimental portion. For A-20 and A-40, the experimental portion was always 2 hours; for A-4, it was always 1 hour. The control, or pre-injection, portion varied between 2 and 3 hours for A-20 and A-40, and between 40 minutes and 1 hour for A-4. Scopolamine was never given during two consecutive experimental sessions. On those days when the drug was omitted, the animals were given complete sessions on the base-line schedules. These days showed that the behavior during the earlier and later portions of a day's run did not differ in any systematic way in the absence of the drug.

For A-20, the doses, per kilogram of body weight, were 0.05, 0.1, 0.2, 0.4, and 0.8 milligram of scopolamine. For A-40, 1.6 milligrams was used in addition. Each dose was administered three times in an irregular order. Rat A-4 was given 0.1 milligram per kilogram on nine occasions.

RESULTS

Figure 1 presents six aspects of the effects of scopolamine on the 4-ply multiple schedule for A-20 and A-40.

The abscissas give the dose in milligrams per kilogram of scopolamine on a logarithmic scale. The values plotted at a dose of zero are averages of all the pre-injection data, which were obtained from the earlier portions of sessions involving the drug. It was felt that these averages were the best available measures of the non-drugged performance on the multiple schedule. The values at the different doses are

³Actually a fixed interval with a "limited hold" of 2 minutes. The reinforcement is available for 2 minutes following the end of the 5-minute interval. If no response occurs during this 2-minute period, the schedule automatically advances to the next component and the reinforcement is lost.

Figure 1. Effects of various doses of scopolamine on six aspects of a 4-ply multiple schedule, for two rats. See text for explanation.

averages of three administrations. Four of the graphs present the average rate of responding (in responses per minute) during the four components of the multiple schedule. S_1^A , it should be recalled, follows the fixed-interval component and precedes the avoidance component; S_2^A follows avoidance and precedes the fixed inter-

val. The effects of scopolamine on rate of responding are different for each component of the schedule. For any given component the two rats show similar effects.

Scopolamine decreases the rate of responding during the fixed-interval component. This effect is found with doses of 0.1 milligram per kilogram and greater, and both *Ss* show a slight reversal at 0.8 milligram per kilogram. The changes in rate of responding during the two S^A periods show a considerably different pattern from that during the fixed-interval component. The level of responding during S^A is low in the absence of the drug. With small and medium doses, the level is increased substantially, but more for A-20 than for A-40. At the higher dose levels, the two S^A 's seem to have slightly different characteristics. The rate of responding during S_1^A drops with the high doses; for A-40, at 1.6 milligrams per kilogram, the rate has returned to the control level. During S_2^A , the drop in rate with higher doses seems to be less pronounced or, at least, somewhat retarded. It might be pointed out that this difference between the two S^A 's and the reversal mentioned above in connection with the fixed-interval component fall into the category of minor, or even questionable, effects of the drug. They do, however, deserve attention in view of their presence for both *Ss*.

To some extent, the changes in the rate of avoidance responding resemble those for S^A responding in that the former also contains an increase at the lower doses and a decrease at the higher ones. The important difference is that the decrease in the case of avoidance responding ultimately brings the rate well below that obtained without the drug. As the rate of avoidance responding decreases, the frequency of electric shocks delivered to the animal would be expected to increase. The graph for shock frequency shows this to be the case. This graph shows, however, that the small doses, which were associated with an increased rate of avoidance responding, were also increasing the shock frequency.

The quarterlife, which is shown in the upper left-hand graph, is a measure of the temporal patterning of responses within the fixed-interval component (Herrnstein & Morse, 1957). The quarterlife of an interval is the time taken for the emission of the first quarter of the total number of responses emitted in that interval. Thus, if responses tend to occur mainly toward the end of an interval, the quarterlife will be large. This is the tendency that is typically present when reinforcement is delivered on a fixed-interval schedule. If responses are uniformly distributed throughout the interval, the quarterlife will be equal to one-quarter of the size of the interval. The quarterlife can therefore be considered a measure of the extent to which responding within the interval is correlated with the passage of time. Without the drug, both *Ss* have quarterlives of about 2.9 minutes. If responding were uniformly distributed within the interval, the value would be 1.25 minutes (i.e., one-quarter of 5 minutes). The effect of scopolamine is to reduce the quarterlife to around 1.25 minutes. There is a relatively small reversal of this effect with doses of 0.4 and 0.8 milligram per kilogram.

In Fig. 2, the effects of scopolamine are shown relative to the non-drugged performance. All of the measures plotted in Fig. 1 are divided by the corresponding pre-injection value to give the points plotted in Fig. 2. The value of this ratio is, therefore, 1.0 for both *Ss* at a dose of 0 milligram per kilogram for all six measures, and is also 1.0 wherever the drug failed to have any effect. One reason for replotting

Figure 2. The data from Fig. 1 replotted relative to the non-drugged performances. The Xs show the effects of one dose of scopolamine on a 2-ply multiple schedule studied with a third rat.

the data this way is that a more direct comparison between the two *S*s is possible when the differences between them in the control performances are thus canceled out. Another reason is that it permits comparison, among the six measures, of the relative magnitudes of the drug effects. In general, with relative values the two *S*s are brought closer together throughout the dose range. This is particularly evident for the rates of responding during the fixed-interval and the *S*₂^A components and for the frequency of shock. It is also clear from this figure that in terms of relative magnitude, scopolamine has its greatest effects on the frequency of shock and on the rate of *S*^A responding.

The relative values for A-4 are shown by the X s in Fig. 2. This rat, it will be recalled, was run on a 2-ply multiple schedule, consisting of the fixed-interval and the S_1^Δ components. Since a dose of 0.1 milligram per kilogram was the only one studied for this S , only one point is shown on each of the three relevant graphs (i.e., quarterlife, FI rate, and S_1^Δ rate). The relative magnitudes of the effects of scopolamine on the quarterlife and the S_1^Δ rate are similar for the three S s. The rate of responding during the fixed-interval component is, however, substantially more reduced by 0.1 milligram per kilogram when this component is part of the 2-ply multiple schedule than when it is part of the 4-ply multiple schedule.

The findings for A-4 are not presented in Fig. 1, largely because its performance differed markedly from that of the other two rats in terms of absolute measures. Its rate of responding during the fixed-interval component was reduced from 63.1 responses per minute in the absence of the drug to 13.1 responses per minute with 0.1 milligram per kilogram. The rate of S_1^Δ responding was increased from 0.26 to 1.64 responses per minute. The value of the quarterlife was reduced from 3.26 to 1.53 minutes.

DISCUSSION

The depressant effects of scopolamine on learned behavior that were reported by Dews (1955, 1957) are supported by the findings of the present experiment. The rates of both positively and negatively reinforced responding are decreased by doses greater than 0.4 milligram per kilogram. Unlike the earlier studies, the present work contains, in addition, evidence that may account for the so-called amnesic effects of scopolamine. The increase in responding during S^Δ periods, that is caused by scopolamine, indicates that the behavior becomes less precisely controlled by environmental stimuli. The S^Δ 's are strictly comparable to the negative stimulus of studies of discrimination. Thus, scopolamine is shown to disrupt discriminations among a number of stimuli. The reduction in the quarterlife may also be viewed as a loss of discrimination, although it is difficult to state just what stimuli are involved. Finally, the increase in the frequency of shock is only partly due to the depression of the rate of avoidance responding. At the lower doses, shock frequency increases about sixfold, even though avoidance responding is occurring at a rate that is higher than the control level. This conjunction of effects shows that the drug has interfered with the effective temporal spacing of avoidance responses. A shock is delivered, during the avoidance component, every time 20 seconds elapses without a response. The average rate of avoidance responding and the frequency of shocks can both increase if the drug reduces the degree of control exerted by the 20-second avoidance interval.

These disruptive effects of scopolamine on the various kinds of discriminations may not appear to be a satisfactory counterpart to the clinical observations of amnesia. In the present experiment, scopolamine has interfered with a number of well-learned patterns of responding, whereas the clinical descriptions deal with an inability of a subject to recount what went on while he was drugged. It is true that a subject seems confused or disoriented while in the drugged state, but he would then be expected to report that he was confused and perhaps even the nature of his confusion. But such recall may, in fact, be impossible for any drug that is suf-

ficiently disruptive in its effects. The primary effect may be the disruption of stimulus control, which is in itself a kind of amnesia, and the inability to recall may be a secondary effect that results from the relation between stimulus control and memory.

It is interesting that similar effects on discrimination did not occur in Dews' studies. The widespread effects obtained in the present work make it seem unlikely that the particular discrimination situation he used happens to be especially resistant to the action of this drug. His situation is, in fact, not resistant to the action of pentobarbital and methamphetamine (Dews, 1955). Nor is it likely that the discrepancy is the result of the dose ranges investigated, since Dews used a range that went from no effect to almost complete depression of responding. The most reasonable conclusion seems to be that the discrepancy is due to the species of animal used. Dews' experimental subjects were pigeons; in the present study, rats were used.

The decrease in the level of S^A responding with the large doses is not to be considered a diminution of the disruptive effects of the drug. Rather, this tendency for responding to be closer to normal with large doses probably represents the superimposition of the depressant effects of scopolamine upon its disruptive effects. The discrimination is not restored, but the behavior is sufficiently depressed that the loss of this form of stimulus control becomes less apparent.

Table 1

Development of Tolerance to Scopolamine

Measure	Control	.1 mg/K Scopolamine	Drug/Control
FI Rate (responses/minute)			
Injections 1-5	60.8	6.5	.11
Injections 6-9	66.0	21.4	.32
S^A_1 Rate (responses/minute)			
Injections 1-5	.20	1.86	9.3
Injections 6-9	.32	1.37	4.3
1/4 Life (minutes)			
Injections 1-5	3.33	1.44	.43
Injections 6-9	3.18	1.63	.51

Human subjects are known to develop a degree of tolerance to scopolamine as a result of continued exposure to the drug (Goodman & Gilman, 1955). The repeated administrations of 0.1 milligram per kilogram to A-4 showed progressively smaller effects. This finding is summarized in Table 1. The results of the first five and the last four injections are averaged separately for the three relevant measures. In addition, the pre-injection values are similarly separated. The last column of the table shows that in every case the relative magnitude of the drug effect is diminished in the last four injections. Unfortunately, the irregular sequence of doses used for the other two Ss does not permit a satisfactory analysis of the development of tolerance to the drug.

SUMMARY

Two rats were trained on a 4-ply multiple schedule, consisting of a food-reinforcement component, an avoidance component, and 2 S^Δ's. The effects of a range of doses of scopolamine were studied. The two major effects of the drug were a depressant action and the disruption of the various discriminations that result from the procedure. A third rat was trained on a 2-ply multiple schedule that omitted the avoidance component and one of the S^Δ's. Effects of scopolamine on the two remaining components were similar for all three rats.

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