Scopolamine, methylscopolamine, and response conditioned inhibition in rats

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To test Carlton's hypothesis that behavioral inhibition is mediated by central cholinergic systems, rats were trained to a 50% response to reinforcement criterion on drl and were injected IP with a .5 mg/kg of saline, methylscopolamine, or the centrally active anticholinergic scopolamine. Scopolamine significantly reduced the ratio of reinforcements to responses and significantly increased the variability of emitted responses. Whereas the methylscopolamine reduced the number of responses, the ratio of reinforcements to responses was not significantly different from the saline control. The results give support to Carlton's hypothesis.

Carlton (1963, 1969) has hypothesized that behavioral inhibition is mediated by central cholinergic systems. He has presented data, from his own work and that of others, showing that centrally acting anticholinergic agents such as atropine and scopolamine interfere with the inhibitory process in a variety of situations. On the other hand, methylatropine and methylscopolamine, which do not readily cross the blood-brain barrier but have similar peripheral effects of the nonmethylated compounds, do not produce disinhibitory effects centrally (Goodman & Gilman, 1965; Manto, 1967).

From Carlton's hypothesis, it is necessary to assume that the inhibitory processes can be conditioned. It is suggested that an anticholinergic agent such as scopolamine would disrupt response inhibition as measured in terms of differential reinforcement of low-rate (drl) performance. The drl schedule should be particularly sensitive to deterioration of response inhibition in that with the drl a pause of some specified time interval or longer must occur after the last response before the next response will result in reinforcement. On the other hand, methylscopolamine should not disrupt drl performance.

METHOD

Subjects

Ten naive male 90-day-old Sprague-Dawley rats were obtained from Holtzman (Madison, Wisconsin). The rats weighed approximately 290 g and were maintained on a 23.5-h food deprivation schedule with ad lib water.

Apparatus

The apparatus consisted of three standard single-level

Gerbrands operant boxes placed in a sound-deadened chamber equipped with a circulating fan and masking white noise. All reinforcement contingencies were programmed by standard relay equipment. The reinforcers were 45-mg Noyes pellets and were given under the reinforcement contingency schedule of drl 15 sec. The responses and reinforcements were recorded on counters.

Procedure

All animals were shaped to barpress during a single 1-h session and on the following day each subject was on a continuous reinforcement schedule for 1 h. On each successive day the animals were trained under the drl 15-sec schedule until each rat reached the criterion performance of three successive daily sessions, during which time the animal received reinforcements on at least 50% of the responses. Upon reaching the criterion performance, each animal, on alternate days and in a counterbalanced order, was injected intraperitoneally (IP) with .5 mg/kg of scopolamine hydrobromide (molecular weight 438), methylscopolamine (molecular strength 398 for scopolamine methylbromide), or an equal volume of saline (Manto, 1967). The injection volume was .1 cc/100 g of body weight of all drugs and saline. The animals were tested for 12 consecutive days, with a day without injection following each drug treatment day. All injections were given 10 min prior to testing. The data were the number of responses per session and the number of obtained reinforcers.

RESULTS

The mean percentage of reinforcements to responses and the mean number of responses for the criterion period and for each drug treatment condition are presented in Figure 1. Analysis of variance (matched groups design, Meyer, 1975) of these data revealed a significant difference among conditions for both percentage of reinforcements/responses ($F = 11.32$, $df = 3/27$, $p < .05$) and in response ($F = 9.55$, $df = 3/27$, $p < .05$).

In the subsequent analyses (Newman-Keuls multiple comparisons) of the percentage of reinforcements to responses, the scopolamine treatment significantly

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Figure 1. Percentage of reinforcements to responses, standard deviations (SD), and the mean number of responses for criterion (C), scopolamine (S), methylscopolamine (M), and saline control (SC) conditions.

decreased the percentage of reinforcements/responses ($p < .05$) in comparison with all other conditions. While the percentage of reinforcements/responses for the methylscopolamine condition was significantly greater than the scopolamine treatment, the methylscopolamine condition was significantly lower than the criterion ($p < .05$); it did not differ statistically ($p > .05$) from the saline control. All other comparisons were not significant. For the response data, the subsequent analyses showed that the methylscopolamine condition resulted in significantly fewer responses from all other conditions ($p < .05$) and that all other statistical comparisons were not significant ($p > .05$).

Figure 1 also shows the variability expressed in standard deviations. For the percentage of reinforcements/responses data, the variance for the treatment conditions of injections (scopolamine, methylscopolamine, and saline control) were statistically equal and homogeneous ($p > .05$). However, all treatment conditions were significantly greater in variability from the criterion ($F_{\max}$ test = 8.92, $df = 9$, $p < .05$). From the analyses of the number of responses, the scopolamine condition resulted in significantly greater variability ($p > .05$) in comparison with all other conditions which were homogeneous.

DISCUSSION

In general, the data support the hypothesis that

scopolamine interferes with the conditioned inhibitory processes and further support Carlton's generalization that anticholinergics are disruptive of the inhibitory processes. The disinhibition effect of scopolamine was shown by the significant lower ratio of reinforcements/responses which was a function of the increase in the number of nonreinforced responses. While the mean number of responses under the scopolamine condition did not increase significantly between the criterion level or the saline control, there was a marked and significant increase in the variability of the behavior with scopolamine as compared among the other treatment conditions. It is suggested that the normal activity of brain acetylcholine which is required for retention of conditioned inhibition was attenuated by the central effect of scopolamine and that responses normally inhibited were emitted.

The effects of approximately 10% stronger molar solution of methylscopolamine, on the other hand, did not disrupt appreciably the conditioned inhibition when compared with the saline controls. However, the drug effects are clearly shown by the significant decrease in the mean number of emitted responses. This decrease in responses supports the assumptions underlying the drug's peripheral effects (Goodman & Gilman, 1965; Manto, 1967), as two animals failed to consume the food pellets given as reinforcers even though they continued to respond to the schedule.

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