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BRIEF COMMUNICATION

Disruptive Effects of Epinephrine on Active Avoidance Behavior: Alteration by Scopolamine and d-Amphetamine

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REMINGTON, G. AND H. ANISMAN. *Disruptive effects of epinephrine on avoidance behavior: alteration by scopolamine and d-amphetamine.* PHARMAC. BIOCHEM. BEHAV. 2(3) 427–430, 1974. – Following intraperitoneal (ip) injection of either epinephrine (0.25 mg/kg) or saline, rats received treatment with either scopolamine (0.5 mg/kg), d-amphetamine (0.5 mg/kg) or saline, and they were subsequently tested in an open field activity task as well as in a shock motivated situation. Epinephrine effectively decreased both activity levels and avoidance behavior. Treatment with either scopolamine or d-amphetamine eliminated the disruptive effects of epinephrine in the avoidance task, but had negligible effects upon general activity in the absence of the drug treatment. Results were interpreted in terms of inhibitory properties of epinephrine and response disinhibitory effects of scopolamine and d-amphetamine.

Epinephrine Scopolamine d-Amphetamine Avoidance learning

ALTHOUGH several reports have indicated that exogenous administration of epinephrine may depress both active avoidance behavior [12,13] and general activity [14], the physiological source for this disruption is not clear. It has been suggested that epinephrine may trigger a central cholinergic rebound which results in response inhibition [14] and consequently limits active responding [1,3]. Indeed, within an exploratory situation it has been demonstrated that administration of scopolamine, but not methylscopolamine, tends to eliminate the epinephrine induced decrement in performance, thus implicating the involvement of central cholinergic mechanisms [14].

One purpose of the present investigation was to determine whether scopolamine could deter the disruption in avoidance behavior produced by epinephrine treatment, as it does in the open field exploratory situation in the absence of shock treatment. Moreover, since cholinergic mechanisms may be involved in both avoidance learning and in general activity, it might be expected that scopolamine would have comparable effects on both behaviors. A second purpose of the experiment was to determine whether d-amphetamine could also reverse successfully the inhibitory effects of epinephrine. Specifically, several investigators [1, 2, 10, 11] have suggested that adrenergic and cholinergic systems act in a balanced manner thereby modulating levels of response inhibition. Essentially, decreasing the action of the inhibitory cholinergic system should affect behavior in a manner comparable to that produced by increasing the activity of the excitatory adrenergic system. Accordingly, it would be predicted that scopolamine and d-amphetamine would both be effective in mitigating the inhibitory effects produced by epinephrine.

METHOD

Animals

Sixty experimentally naive male Holtzman rats, 90 days of age, and weighing approximately 250 g upon arrival, were procured from the Holtzman Company, Madison, Wisconsin. Animals were individually housed in standard wire cages for at least 3 days prior to testing, and they had been maintained in the laboratory with ad lib food and water for at least 10 days following arrival.

Apparatus

Activity was recorded in a 90 x 30 x 20.5 cm black compartment whose floor was made up of 0.25 cm stainless steel rods spaced 1.0 cm apart (center to center). Spaced at intervals of 15.0 cm on each wall, 5.0 cm above the grid floor, were photoelectric light beams. Crossing a beam resulted in a single count. In order to avoid activity counts

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due to head bobbing or slight body movements, the photoelectric unit was connected such that a single photocell could not be energized more than once without a second cell being triggered.

Avoidance training was carried out in a shuttle box previously described [3]. Briefly, it consisted of a circular Plexiglas runway 12.0 cm wide and 20.5 cm high with an outside circumference of 204.1 cm. The alley was divided into 4 compartments by stainless steel gates which rested 1.27 cm above a 5.0 cm hurdle. The floor of the runway consisted of 0.25 cm stainless steel rods spaced 1.25 cm apart at the exterior wall, through which shock of 0.5 mA (constant current, 60 cycle, a.c.) could be delivered. Situated on either side of each gate was a lamp 2.5 cm beneath the Plexiglas roof, and a photoelectric relay system 4.5 cm above the floor and 7.0 cm from the gate at the exterior wall. In the present experiment, only the shuttle mode of operation involving two of the compartments, was employed. Latency of responding was recorded by a Sodeco counter activated concurrently with CS (light) onset and terminated by the rat breaking the photoelectric light beam in the adjacent compartment.

Procedure

Animals were randomly subdivided such that one-half received intraperitoneal injection of epinephrine hydrochloride (0.25 mg/kg in a 0.5 mg/ml solution), while the remaining animals received injection of saline (1.0 ml/kg). Forty-five min after the initial injection animals in each group were further subdivided (n = 10/cell) such that animals in each group received intraperitoneal injection of either scopolamine hydrobromide (0.5 mg/kg in a 0.5 mg/ml solution), d-amphetamine sulfate (0.5 mg/kg in a 0.5 mg/ml solution) or saline (1.0 ml/kg). Fifteen min after the second injection animals were placed in the activity chamber for a single 5 min period during which activity was recorded.

Upon termination of the activity measure animals were immediately placed in the avoidance apparatus, 30 sec after which avoidance training commenced. The avoidance procedure consisted of the CS being presented and the gate between the two compartments being raised. If the rat crossed into the adjacent compartment within 7 sec the gate was immediately lowered, the CS was terminated, and the US was withheld. If the response was not made within 7 sec, a 0.5 mA shock was presented until an escape response was made, after which the CS and US were terminated, and the gate was lowered. Throughout, the intertrial interval was 30 sec in duration. Animals were tested for a total of 50 trials.

RESULTS

The number of avoidance responses and the level of activity for each individual animal are shown in Fig. 1. An analysis of variance of the activity scores yielded a significant main effect for the Initial Drug Treatment, $F(1,54) = 37.64, p<0.01$. Subsequent Newman Keuls multiple comparisons [16] revealed that epinephrine resulted in a significant lowering of the activity level ($p<0.05$). Neither scopolamine nor d-amphetamine successfully altered the response inhibition produced by the epinephrine treatment. With respect to the avoidance scores, an analysis of variance revealed significant Initial Drug Treatment as well as Subsequent Drug Treatment main effects, F's = 11.54 and 3.26, *df*'s = 1/54 and 2/54, $p<0.05$. Multiple comparisons on the simple main effects revealed that epinephrine effectively decreased the avoidance response rate relative to saline treated animals ($p<0.01$), while both scopolamine and d-amphetamine resulted in substantial improvement in avoidance performance as compared to animals which received saline treatment immediately prior to training ($p<0.05$). Moreover, among animals which received epinephrine injection, both scopolamine and d-amphetamine successfully eliminated the avoidance decrement ($p<0.05$).

DISCUSSION

Consistent with earlier reports, epinephrine significantly reduced avoidance performance [12,13] as well as general activity [14]. As previously noted, scopolamine [1, 4, 7, 8] and d-amphetamine [2, 4, 6, 9] improved avoidance performance. Moreover, both of these agents effectively eliminated the avoidance decrement induced by epinephrine. In contrast to earlier reports [14], neither scopolamine nor amphetamine treatment eliminated the decline in activity precipitated by the epinephrine treatment. The source for these different results is unclear; however, differences in procedure might well be responsible for these findings. In any event, it seems clear that epinephrine promotes response inhibition, whereas scopolamine and d-amphetamine produce response disinhibition. Antagonistic drug effects were apparent, however, only in the avoidance task. This could of course be due to differential levels of drug dosages necessary in altering the two behaviors, or due to a drug × shock treatment interaction. For example, it is possible that (a) shock results in the excitation of a third system, possibly a serotonergic one, which amplifies the effects of amphetamine and scopolamine [15], or (b) shock elicits increased levels of norepinephrine [2] which interact with the drug treatments. It should be noted that recent work in our laboratories [2] has in fact revealed that shock exacerbates the excitatory effects of d-amphetamine, and that these effects are strain specific.

Although the action of scopolamine and d-amphetamine on the epinephrine induced behavior may represent no more than an additive, rather than interactive, effect of the drug treatments, the improvement in avoidance behavior typically observed with scopolamine and d-amphetamine is possible even when general activity is artificially depressed. The fact that the epinephrine induced decrement in activity was not reversed by either scopolamine or d-amphetamine further suggests that the simple reduction of activity by epinephrine was not responsible for any avoidance decrement observed. This hypothesis is further supported by the finding that correlations between avoidance behavior and general activity measured in the activity cage were low and nonsignificant. In any event, it is not unlikely that the inhibition produced by the epinephrine treatment results from a cholinergic rebound. Accordingly, scopolamine is effective in eliminating the response inhibitory tendencies thereby augmenting avoidance behavior. If interaction between these drugs is assumed, the fact that d-amphetamine affected avoidance behavior in a manner comparable to that of scopolamine, may imply an interaction between the adrenergic and cholinergic systems as has previously been suggested [1, 10, 11].

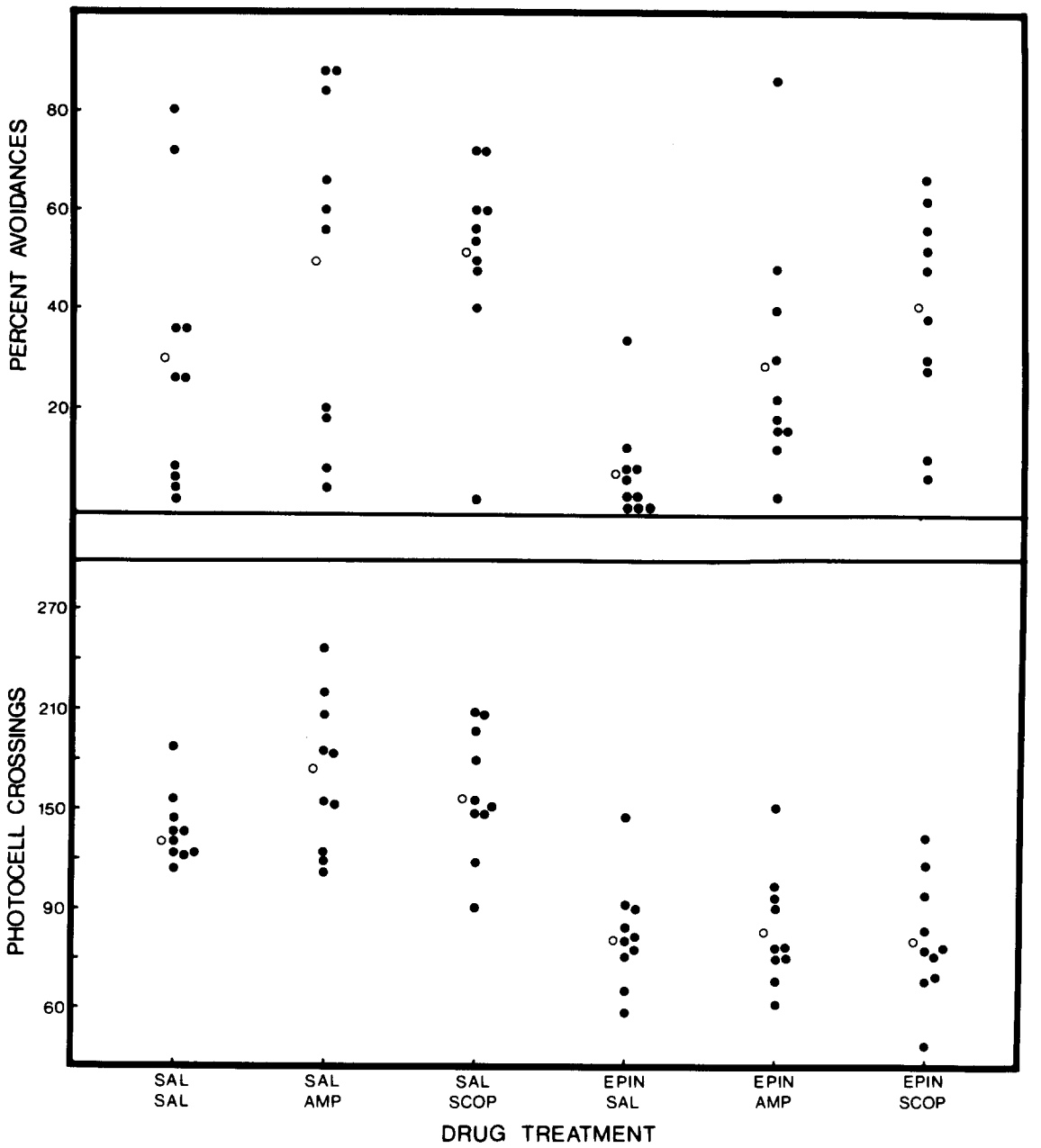

FIG. 1. Mean (open circles) and individual avoidance and activity scores (closed circles) as a function of drug treatments.

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