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Effect of Scopolamine on the Reactivity of the Albino Rat to Footshock[1]

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FEIGLEY, D. A., W. BEAKEY AND M. J. SAYNISCH. *The effect of scopolamine on the reactivity of the albino rat to footshock.* PHARMAC. BIOCHEM. BEHAV. 4(3) 255–258, 1976. – To determine if anticholinergic drugs altered reactions to footshock, 9 female albino rats were tested for escape latencies following unsignaled presentations of footshock in a two-chambered shuttlebox. Different intensities of footshock (0, 0.04, 0.07, and 0.10 ma) were varied orthogonally with various doses of intraperitoneally injected scopolamine hydrobromide (0, 1.0, 4.0 and 16.0 mg/kg). Shock trials were randomly alternated with nonshock (pseudoshock) trials to estimate any drug-induced activity increase which might occur independently of any alteration in reactivity to aversive stimulation. Results indicated that scopolamine produced a significant increase in reactivity to footshock (i.e., shorter escape latencies) at near-threshold intensities as well as producing the expected increase in general activity.

Scopolamine Anticholinergic Aversive thresholds Activity

ANTICHOLINERGIC compounds have been consistently found to disrupt passive-avoidance acquisition [10,16] and one-way active avoidance [19]; these drugs also facilitate both two-way active avoidance [1, 2, 13, 19, 22] and barpress avoidance [2,15]. The most commonly accepted explanation of these effects has been that the cholinergic blocking agents interfere with the ability to withhold responses either by increasing the tendency to perseverate or by disrupting inhibitory control mechanisms [1, 2, 6, 7, 19].

However, an alternative hypothesis might also explain some of the effects of cholinergic blocking agents: if the anticholinergics possess analgesic properties of even mild proportions, as has been suggested [14], the effects of anticholinergics such as scopolamine could be predicted without invoking the notion of disruption of inhibition. The concept of decreased sensitivity resulting from scopolamine injections cannot be dismissed lightly since scopolamine can decrease an animal's sensitivity to the discriminative stimulus of a light–dark discrimination [20] or to the less well defined discriminative stimulus of a DRL task [4]. If scopolamine attenuates pain either by acting as a mild anesthetic or by diverting the attention of a subject from the painful stimulus, task performance might be disrupted or facilitated depending upon the nature of the task.

For example, within the commonly used ranges of shock intensities, passive-avoidance performance is a direct function of shock severity [12]. Any factor which attenuates the pain should also disrupt passive avoidance in direct proportion to its effectiveness as either an anesthetic or an attention-diverting device. A similar argument can also be applied to one-way active-avoidance situations in which performance has also been found to be a direct function of shock severity [12,18], at least within the range of shock intensities from mild to moderately severe.

In the case of two-way active avoidance and barpress avoidance, optimal shock intensities are only slightly above aversion thresholds. Performance deteriorates rapidly as shock levels increase beyond that point [8,17]. Moderate intensities of shock which were experienced under the influence of a pain-attenuating drug might well fall functionally within the optimal range of the inverted U-shaped performance curve.

Although an anesthetic or attention-diverting effect is not the most appealing interpretation of anticholinergic action, it cannot be rejected a priori because, if even partially true, it could certainly account for many of the observed behavioral changes which occur following the administration of such compounds. To determine if anticholinergic drugs raise aversion thresholds for electric shock, the present study administered unsignaled electric shock to rats following injections of either saline or scopolamine. If the anticholinergics increased thresholds to shock, the escape latencies of the scopolamine-injected rats should be longer than those of the control rats. However, escape latencies can also be influenced by general activity levels. Scopolamine, the anticholinergic used in the present study, is known to increase activity [5,10]. Thus, trials on which shock was not presented (pseudoshock trials) were randomly interspersed among the actual shock trials in order to evaluate any influence the anticholinergics might have on escape latencies because of a general rise in activity.

Finally, the prediction was made that if scopolamine

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produced mild changes in sensitivity to shock, these changes would be most noticeable at shock intensities which approximated the aversion thresholds of normal animals. At intensities which were decidedly above or below threshold, slight changes in sensitivity might go undetected. Thus, shock intensity was varied orthogonally with various dosages of scopolamine.

METHOD

Animals

The animals were nine female Carworth CFE Sprague-Dawley albino rats aged 100–120 days and weighing 200–250 g at the start of the experiment. The rats were housed individually under conditions of constant illumination and ad lib access to food and water.

Apparatus

The test apparatus consisted of two identical Plexiglas compartments (29.5 x 12.5 x 15.5 cm high) separated by a manually operated guillotine door. The walls of both chambers were black, although the Plexiglas cover of each chamber was clear to allow observation of the animals. The 0.5 cm dia. stainless steel grids of the floor were spaced 2 cm apart from center to center and could be charged with electric shock in such a way that each grid was always live with respect to every other grid within the same compartment. The shock source was composed of a variable transformer which could deliver from 0–5600 V a.c. across 16 neon bulbs connected in series. The grid bars were connected at the junction between the individual bulbs. To estimate the approximate current delivered to the rat at each shock setting, a 25 K resistor was shorted across five grids (and thus was placed in series with the 10 K internal resistor of the shock source). The voltage was determined via an oscilloscope and the current was calculated using Ohm's Law. Because this type of shock source avoids the need for scrambled shock, aversion thresholds are typically found at very low current levels compared to more commonly used constant current shock sources [3].

Design

The basic design was a 4 x 4 factorial in which the same group of nine animals served under every condition. Four shock intensities (0, 0.04, 0.07, and 0.10 ma) were varied orthogonally with four drug dosages (0, 1.0, 4.0, and 16.0 mg/kg) of scopolamine hydrobromide (SCOP-HBr).

Procedure

Each rat was weighed and injected with the appropriate volume and dose approximately 20 min prior to testing. All drug salts had been purchased from Sigma Chemical Co., Saint Louis, Missouri, and were freshly mixed on the day of testing in 0.9% NaCl solution. The injections were IP in a volume of 2 cc/kg for all drug concentrations. Following the injection, the rat was returned to its home cage until testing began. Since each rat served in all conditions, the order in which the conditions were presented was randomly determined. To minimize possible residual effects of the drugs, a minimum of 48 hr separated the individual testing sessions. Each test session consisted of 10 trials; on five of these trials, shock was presented at the intensity appropriate for the given condition, while on the remaining five trials (the pseudoshock trials) no shock was presented. The order of presentation of the shock and pseudoshock trials was randomized within each session throughout the experiment with the restriction that only two trials of the same type (shock or pseudoshock) occurred in succession. At the start of the first trial of a session, the rat was placed in one side of the apparatus facing the closed floor. After 20 sec, the door was raised and the animal was allowed to explore freely for a delay period which varied from trial to trial. Following the variable delay, shock was delivered through the grid floor of that chamber which was occupied by the rat. The variable-delay interval before the onset of the shock or pseudoshock was used to minimize the possibility of the rats learning an avoidance contingency. Five delay intervals were used – 5, 15, 18, 24, or 27 sec delay – and began immediately after the 20 sec intertrial interval. Within a test session, each delay interval was applied to one shock and one pseudoshock trial, with the order of the trials randomly determined within each session. The escape latency was timed manually to the nearest sec from the onset of the shock (or pseudoshock) until the rat had entered the opposite, nonshock chamber with all four feet or until a maximum of 30 sec had elapsed. The door was then lowered and the rat was confined until the 20-sec intertrial interval had elapsed, at which time the procedure was repeated until 10 trials had been administered. The response measures which were recorded were the mean escape latency for the five shock trials and the mean escape latency of the five pseudoshock trials. These means were analyzed using ANOVAs for repeated measures [21]; subsequent individual testing, when justified, was performed with Fisher's Test of the Least Significant Difference [9].

RESULTS AND DISCUSSION

Separate 2 x 4 ANOVAs were carried out at each of the four shock intensities for the variables of Type of Trial (shock vs. pseudoshock) and Drug Dosage respectively. As suspected, SCOP-HBr significantly decreased the escape latencies in the absence of detectable footshock. At both 0 ma (Panel A of Fig. 1) and 0.04 ma (Panel B), there were no significant differences between the shock and pseudoshock trials in the mean escape latencies following any of the injected dosages of SCOP-HBr, including the 0 mg/kg dose (saline). This lack of differences was expected for the 0 ma condition where footshock was never delivered; at 0.04 ma the lack of differences indicated that the voltage was below the threshold of the rats regardless of the dosage injected.

The escape latencies did decrease, however, as the dose of SCOP-HBr was increased. At 0 ma, this reduction in the latencies only approached statistical significance $F(3,24) = 2.56$, $0.10<p<0.05$; but at 0.04 ma the reduction did reach significance $F(3,24) = 3.61$, $p<0.05$. Since the 0.04 ma intensity appeared to be substantially below the aversion threshold as indicated by the lack of differences between the shock and pseudoshock trials and by observations, the faster latencies appear to be the result of increased activity levels. (Preliminary testing had indicated that 0.04 ma was a subthreshold intensity which elicited no overt responses in a jump-flinch test. The 0.10 ma intensity was substantially above threshold, reliably eliciting agitated movements, vocalization, urination, defecation and escape responses.

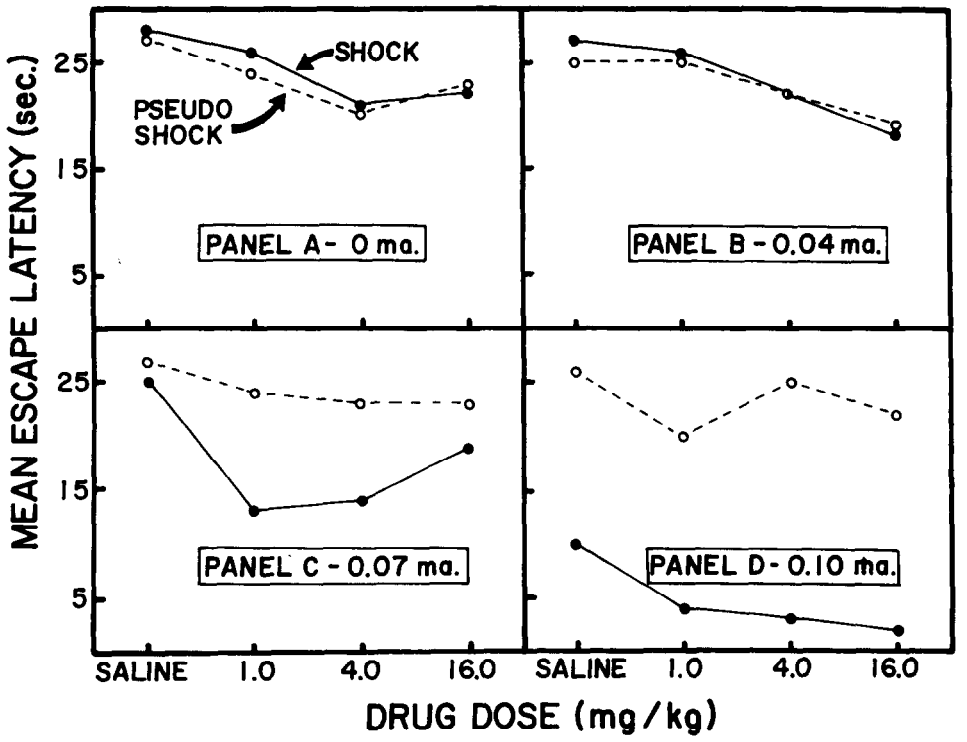

FIG. 1. Mean escape latencies for rats following unsignaled presentations of different intensities of electric shock randomly alternated with presentations of no shock (pseudoshock) after injections of various doses of scopolamine hydrobromide.

The 0.7 ma intensity was near threshold, eliciting mild jump-flinch reactions in about half of the animals tested.)

At 0.07 ma, the SCOP-HBr clearly did not reduce the rats' reactivity to the footshock; in fact, it actually produced faster escape latencies. Although the decrease in the latencies on the pseudoshock trials at 0.07 ma following the SCOP-HBr injections indicated a general increase in activity, the drug-induced activity increase was not of sufficient magnitude to account for the even greater decrease in the escape latencies observed on the shock trials. The SCOP-HBr produced significantly faster escapes on the shock trials than on the pseudoshock trials despite the fact that on the pseudoshock trials the latencies of the SCOP-HBr-injected rats were significantly shorter than those of the saline-injected rats. This situation was reflected statistically by a significant interaction between Type of Trial and Drug Dosage $F(3,24) = 6.18$, $p<0.005$, Least Significant Difference = 4.0 sec. Panel C of Fig. 1 illustrates the separation of the general activity effects from the effects of the drug on reactivity to footshock. Just why the effect of SCOP-HBr was minimal at the highest dosage (16.0 mg/kg) is not clear.

At 0.10 ma (Panel D), the situation remains somewhat ambiguous. The footshock was definitely aversive to the rats; their escape latencies on the shock trials were significantly faster than on the pseudoshock trials at all dosages tested, $F(1,8) = 317.11$, $p<0.001$. However, as the dose level was increased, the reduction in the escape latencies was approximately the same magnitude for both shock and pseudoshock trials, $F(3,24) = 4.40$, $p<0.025$. The failure to observe larger latency reductions on the 0.10 ma shock trials relative to the pseudoshock trials following the SCOP-HBr injections might be the result of a measurement problem. On the shock trials, the saline-injected rats were already escaping very quickly; perhaps significantly greater latency reductions in this situation were not possible.

The most dramatic effect of the SCOP-HBr was to increase the rats' responsiveness to the near-threshold shock intensity – an intensity which went undetected following injections of saline. This increased reactivity has been observed in other, nonavoidance situations such as responding to novel, photic stimuli [11]. Although the argument could be made that scopolamine might decrease sensitivity slightly while simultaneously increasing reactivity even more and, thus, account for the present results, the fact that the increased responsiveness was most obvious at near-threshold shock intensities argues against such an interpretation. A decrease in sensitivity near threshold would eliminate the stimulus to which the animal could respond. Thus, despite the animal's tendency to overreact, there would be no detectable stimulus to elicit a reaction.

The activity-increasing effects of scopolamine have been well documented [5,10], but the effects of the drug on reactivity to shock involve more than a mere increase in activity. The present results suggest that perhaps the increased sensitivity–reactivity to the shock stimulus following scopolamine injections has led to an underestimation of the drug's ability to produce disinhibition in avoidance situations.

REFERENCES

1. Bignami, G., L. Amorico, M. Frontall and N. Rosic. Central cholinergic blockade and two-way avoidance acquisition: The role of response disinhibition. *Physiol. Behav.* 7: 461–470, 1971.
2. Bignami, G. and N. Rosic. Acquisition and performance effects of scopolamine and of treatment withdrawal in avoidance situations. *Physiol. Behav.* 8: 1127–1134, 1972.
3. Brown, C. C., J. F. Reus and G. A. Webb. A new constant current stimulation circuit. *Proceedings of the International Conference of Medical Electronics.* 1961, p. 200.
4. Brown, K. and D. M. Warburton. Attenuation of stimulus sensitivity by scopolamine. *Psychonom. Sci.* 22: 297–298, 1971.
5. Calhoun, W. H., A. A. Smith and R. M. Adams. Passive avoidance learning: The relation of activity and retest latency. Paper presented at the meeting of the Psychonomic Society, Chicago, October, 1967.
6. Carlton, P. L. Cholinergic mechanisms in the control of behavior by the brain. *Psychol. Rev.* 70: 19–39, 1963.
7. Carlton, P. L. Brain acetylcholine and inhibition. In: *Reinforcement: Current Research and Theories,* edited by J. Tapp. New York: Academic Press, 1969, pp. 286–327.
8. D'Amato, M. R., J. Fazzaro and M. Etkin. Discriminated barpress avoidance maintenance and extinction in rats as a function of shock intensity. *J. comp. physiol. Psychol.* 63: 351–354, 1967.
9. Federer, W. T. *Experimental Design.* New York: Macmillan, 1955.
10. Feigley, D. A. Effects of scopolamine on activity and passive-avoidance learning in rats of different ages. *J. comp. physiol. Psychol.* 87: 26–36, 1974.
11. Feigley, D. A. and L. W. Hamilton. Response to novel environment following septal lesions or cholinergic blockade in rats. *J. comp. physiol. Psychol.* 76: 496–504, 1971.
12. Feigley, D. A. and N. E. Spear. Effect of age and punishment condition on long-term retention by the rat of active- and passive-avoidance learning. *J. comp. physiol. Psychol.* 73: 515–526, 1970.
13. Hamilton, L. W. and S. P. Grossman. Behavioral changes following disruption of central cholinergic pathways. *J. comp. physiol. Psychol.* 69: 76–82, 1969.
14. Innes, I. R. and M. Nickerson. Drugs inhibiting the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves (antimuscarinic or atropinic drugs). In: *The Pharmacological Basis of Therapeutics* (3rd Ed.), edited by L. S. Goodman and A. Gilman. New York: Macmillan, 1965, pp. 521–545.
15. Leaf, R. C. and S. A. Muller. Effects of scopolamine on operant avoidance acquisition and retention. *Psychopharmacologia* 9: 101–109, 1966.
16. Meyers, B. Some effects of scopolamine on a passive avoidance response in rats. *Psychopharmacologia* 8: 111–119, 1965.
17. Moyer, K. E. and J. H. Korn. Effect of UCS intensity on the acquisition and extinction of an avoidance response. *J. exp. Psychol.* 67: 352–359, 1964.
18. Moyer, K. E. and J. H. Korn. Effect of UCS intensity of the acquisition and extinction of a one-way avoidance response. *Psychonom. Sci.* 4: 121–122, 1966.
19. Suits, E. and R. L. Isaacson. The effects of scopolamine hydrobromide on one-way and two-way avoidance learning in rats. *Int. J. Neuropharm.* 7: 441–446, 1968.
20. Warburton, D. M. and K. Brown. Attenuation of stimulus sensitivity induced by scopolamine. *Nature* 230: 126–127, 1971.
21. Winer, B. J. *Statistical Principles in Experimental Design,* New York: McGraw-Hill, 1962.
22. Worsham, E. and L. W. Hamilton. Acquisition and retention of avoidance behaviors following septal lesions or scopolamine injections in rats. *Physiol. Psychol.* 1: 219–226, 1973.