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BRIEF COMMUNICATION

Role of Stimulus Locale on Strain Differences in Active Avoidance After Scopolamine or D-Amphetamine Treatment[1]

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ANISMAN, H. *Role of stimulus locale on strain differences in active avoidance after scopolamine or d-amphetamine treatment.* PHARMAC. BIOCHEM. BEHAV. 4(1) 103–106, 1976. – Three strains of mice were trained in a shuttle avoidance task following treatment with scopolamine (2.0 mg/kg) or d-amphetamine (3.0 mg/kg). When required to run towards light (CS) to avoid shock, A/J mice acquired the response more readily than DBA/2J or C57BL/6J mice. However, when required to run away from the light, the strain differences were eliminated. Under both testing conditions scopolamine and d-amphetamine augmented the performance of A/J mice, but had no effect or even disrupted performance of C57BL/6J. In DBA/2J mice d-amphetamine augmented performance only in the toward condition. Results were interpreted to support the hypothesis that scopolamine and d-amphetamine improve performance by response disinhibition and response excitation, respectively. The presence of associative difficulties limit the effects of these agents.

Avoidance Strain differences Scopolamine d-amphetamine Stimulus factors

NUMEROUS reports have indicated that genetically different strains of mice exhibit varied rates of acquiring aversively motivated responses [2, 13, 14] and also show considerable diversity in the retention of these responses [1, 9, 10]. Performance differences among some strains apparently are a consequence of differential rates of acquiring the response-shock and stimulus-shock contingencies, i.e., associative factors [1, 9, 10]. In contrast, in other strains nonassociative factors, such as unconditioned competing motor responses (shock-induced response suppression) or strain variations in defensive behaviors (e.g., running vs. jumping) contribute to differences in performance [1, 2, 14]. One technique which has been employed to divorce the role of associative from nonassociative factors in avoidance tasks, is that of pharmacologic manipulations which reduce the nonassociative effects of shock, thereby permitting fuller expression of the associative components of the task [2, 5, 6, 7].

One major drawback of the pharmacogenetic or pharmacologic approach, in general, is that the drug treatment may interact with the warning or feedback stimuli in modifying performance. For example, scopolamine, which reduces response inhibition [6] also produces pupillary dilation and may affect avoidance because of a photophobic response when changes in illumination serve as warning or feedback stimuli ([11] see also [6]). Moreover, it is clear that the effectiveness of scopolamine in modifying active or passive avoidance is dependent upon how animals are equipped to use the stimuli in a given situation (i.e., response suppression or activation) in order to meet the response requisites of the task [8,12].

Recent work in this laboratory [2,3] has revealed substantial differences among strains in response to scopolamine and d-amphetamine. Whereas both agents augment active avoidance in A/J mice, only d-amphetamine improves performance in DBA/2J, while neither drug affects the avoidance response rate of C57BL/6J. Although the Strain × Drug interaction may have been due to differences in associative abilities among the strains, thereby differentially minimizing the effectiveness of treatments which reduce response suppression [1,2], the alternative possibility that the drug treatments interacted with stimulus factors cannot be dismissed. This notion is particularly pertinent since the A/J strain is nonpigmented and the C57BL/6J and DBA/2J

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are nonalbino. Specifically, the behavioral effects produced by drug-induced pupillary dilation may be less dramatic in a nonpigmented strain which already is light supersensitive, than in a pigmented strain. Accordingly, in the present investigation an attempt was made to evaluate the role of possible drug induced photophobic responses by requiring mice to run either towards or away from a light CS, and determining whether changes in the effects of the drug treatments would be observed.

METHOD

Animals

A total of 180 mice, composed of equal numbers of males and females of the A/J, DBA/2J and C57BL/6J strains, were procured from the Jackson Laboratory, Bar Harbor, Maine. Mice were housed 5/cage, separated by strain and sex, and were tested between 60–80 days of age. Mice were tested during the light portion of a 12 hr light/dark cycle.

Apparatus

The apparatus was the same as that used in earlier reports [2]. Essentially it consisted of a symmetricial black Plexiglas Y-maze, with one arm of the maze blocked off, thus permitting shuttle avoidance to be carried out. The arms of the maze were 9.0 x 6.0 x 7.0 cm. and were separated by guillotine gates which dropped through the grid floor. Located on the end wall of each compartment was a 6 W lamp covered by an opaque plastic halter. The floor of the apparatus consisted of 0.25 cm stainless steel rods spaced 1.0 cm apart (center to center), and suspended by Plexiglas strips mounted on the outer walls of each arm. Footshock of 300 μA was delivered through the grid floor via a high voltage–high resistance source, providing relatively constant current. The grid floor was wired through a diode bridge connecting every fourth bar, thereby decreasing the probability of the animal finding two bars of the same polarity. The maze was housed in a darkened room and programmed through standard relay switching, timers and circuitry.

Procedure

Mice of each strain (n = 10/cell) received intraperitoneal injection of either scopolamine hydrobromide (2 mg/kg), d-amphetamine sulfate (3 mg/kg) or saline (1 ml/kg). Drugs were dissolved in distilled water 0.5 mg/ml. These particular dosages were selected on the basis of earlier work in this laboratory using the same strains of mice and equipment, which indicated that these were the optimal dosages in a shuttle task for the 3 strains [2, 3, 4]. Ten min after injection the mice were placed individually in one compartment of the shuttle box, 30 sec after which avoidance training commenced. Avoidance training consisted of the gates separating the two compartments dropping through the grid floor, and the CS (light) being illuminated simultaneously. For one-half the animals the CS was presented in the safe chamber (i.e., the compartment mice were required to enter into), while for the remaining mice the CS was presented in the danger chamber. If the mouse did not leave the dangerous arm within 10 sec, footshock was delivered until an escape response was made, whereupon the CS was terminated and the gates were raised. If the animal entered the goal compartment within 10 sec, the CS was terminated, the gates were raised, and the shock was withheld. Mice received 60 training trials at 30 sec intervals between trials.

RESULTS AND DISCUSSION

The mean number of avoidance responses for each of the groups is presented in Fig. 1. Analysis of variance of the avoidance scores yielded significant Drug x Strain and Task x Strain interactions, F's(4,162; 2,162) = 5.77, 6.81, p's<0.01. The Drug x Strain x Task interaction approached, but did not reach an acceptable level of significance, $F(4,162) = 2.28$, $p<0.07$. Newman Keuls multiple comparisons were carried out for the higher order interaction because of the a priori predictions made concerning this interaction [15]. Consistent with earlier reports [2], when mice were required to run towards the CS to avoid shock the A/J mice exhibited higher levels of performance than either the DBA/2J or C57BL/6J mice. Moreover, d-amphetamine enhanced performance in the A/J and DBA/2J mice, whereas scopolamine improved performance only in A/J. In fact, the performance of scopolamine treated C57BL/6J mice was significantly poorer than that of the saline control.

When mice were required to run away from the CS, the performance of saline treated DBA/2J and C57BL/6J mice improved somewhat, whereas the performance of the A/J strain did not alter substantially. As a result the strain differences observed in the toward condition were eliminated. The fact that improvement was not observed in A/J mice in the away condition indicates that the light itself did not induce a photophobic response which benefited avoidance in this strain. Since improvement was observed in the nonpigmented strains, which was probably not due to photophobia, it is likely that the cue position affected the discriminative capacities of these strains. Among the light sensitive A/J mice the stimulus was a potent one regardless of the locale of the stimulus. Among the pigmented mice, however, the light at the far end of the compartment (i.e., running towards light) was less effective as a cue or ready signal as compared to when it was above and behind the animal (i.e., running away from light).

As observed in the toward light condition, scopolamine and d-amphetamine both enhanced the performance in the A/J strain when the required response was one of running away from light. This facilitation largely was reduced in the case of scopolamine; however, a partial replication of this study revealed that the scopolamine effect was in fact reliable and significant. Unlike the facilitation observed with d-amphetamine among DBA/2J mice required to run towards the light, no improvement in performance was observed when mice were required to run away from light. Moreover, when required to run away from the light, this strain was disrupted in performance by scopolamine. A subsequent study revealed these results to be reliable, and in addition indicated that when training was distributed over two days, which greatly improves performance in DBA/2J, probably owing to the reduction in freezing behavior (1, 3), d-amphetamine did not improve performance in either the away or toward condition. Apparently, the beneficial effect of d-amphetamine is due to the response excitation elicited by the drug. However, under conditions of relatively high levels of avoidance, d-amphetamine is without effect. The lack of improvement in avoidance following scopolamine treatment in DBA/2J is

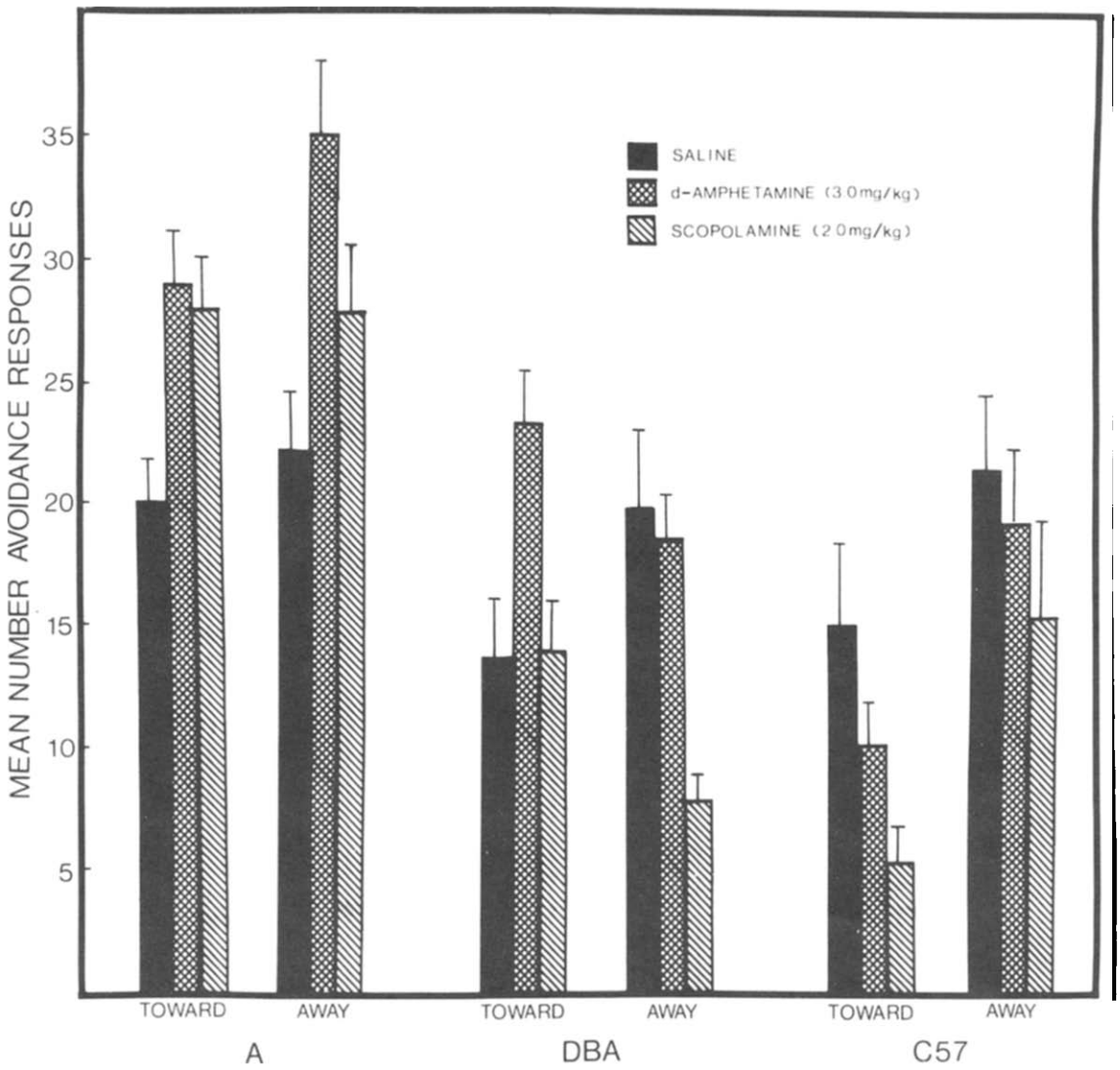

FIG. 1. Mean number avoidance responses over 50 trials as a function of drug treatment in three strains of mice required to run either towards or away from a light CS.

probably a result of the weak effects of this agent following shock in this strain [4]. Finally, among C57BL/6J mice neither scopolamine nor d-amphetamine improved performance. The lack of drug effect in C57BL/6J is apparently not a consequence of a deficiency in the disinhibitory effects of the drugs in this strain, since shock-induced response suppression is reduced in C57BL/6J following treatment with either drug [4]. Rather, it is likely that owing to the poor associative capacities and concomitant difficulties in the acquisition of the signal-shock and response-shock contingencies in this strain [1], the response disinhibition elicited by these drugs are not manifested in the avoidance task.

Taken together, it appears that although the effects of scopolamine and d-amphetamine may be modified by stimulus factors, the strain differences in performance following drug treatments are not a result of such an interaction. A more parsimonious explanation is that the drugs improve performance by reducing inhibitory tendencies. When response inhibition is not intense, following distributed practice or in the away condition in DBA/2J, as well as in a one-way task [3], the disinhibitory effects of the drugs are not apparent. Furthermore, when performance is hampered because of associative difficulties, then the reduction in nonassociative factors by pharmacologic means will not enhance performance.

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