Pharmacology Biochemistry & Behavior, Vol. 3, pp. 809–817.

Differential Effects of Scopolamine and D-Amphetamine on Avoidance: Strain Interactions[1]

HYMIE ANISMAN

University of Waterloo, Waterloo, Ontario, Canada

(Received 19 November 1974)

ANISMAN, H. *Differential effects of scopolamine and d-amphetamine on avoidance: strain interactions.* PHARMAC. BIOCHEM. BEHAV. 3(5) 809–817, 1975. – In a discriminated Y-maze avoidance task it was observed that mice of the A/J strain were superior to mice of the DBA/2J strain, which in turn made more avoidance responses than C57BL/6J mice. Moreover, the A strain was also observed to acquire a discrimination problem more readily than either of the other strains. Administration of scopolamine enhanced active avoidance performance in A, but not DBA/2 or C57BL/6 mice. D-Amphetamine improved performance in both A and DBA/2 mice but had negligible effects on the performance of the C57BL/6 strain. Neither drug affected discrimination performance irrespective of strain. In an inhibitory avoidance task the C57BL/6 strain was found to perform more poorly than the A strain which was inferior to DBA/2 mice. Scopolamine disrupted performance in all three strains, while d-amphetamine was found to disrupt the performance of the A and DBA/2 strains only. The results were interpreted in terms of the role of associative and nonassociative effects of shock in modulating avoidance behavior.

Active avoidance Inhibitory avoidance Strain differences Scopolamine d-Amphetamine

IT is now well documented that in addition to associative factors, the nonassociative effects of shock (i.e. freezing behavior) play a major role in determining the rate at which an avoidance response is acquired [11,17]. In the typical active avoidance situation it is difficult to determine how much of the variance due to a particular treatment is attributable to associative factors, and how much to nonassociative factors, since they are not divorced from each other in most investigations. This factor has proven to be a particularly burdensome one in the investigation of strain differences in avoidance perfromance (e.g., [25, 31, 38, 39, 40]). Strains may differ in the rate at which the response-shock contingencies are learned (i.e., knowing where and when to respond), but in addition, they might also differ in their ability to initiate the response. Thus, even if one particular strain readily learns about those cues signalling safety and those signalling danger, the inability to initiate a locomotor response may effectively limit the rate of acquisition of an avoidance response. Indeed, it has been demonstrated that the rate at which an active avoidance response is acquired is inversely related to the strength of the freezing response produced by shock, and directly related to the rate at which an effective running response can be established [7, 10, 13].

Recently, considerable emphasis has been placed on the role neurochemical changes may play in modifying avoidance behaviors. For example, several experiments have shown that administration of anticholinergic (antimuscarinic) agents such as scopolamine [6, 13, 14, 24, 30], or noradrenergic-dopaminergic stimulants such as amphetamine [9, 13, 14, 18, 28] can modify the acquisition of avoidance responses. Presumably, the facilitative effects are due to nonassociative (response-enhancing or disinhibitory) effects of these agents. It follows that if strain differences in avoidance were primarily a product of response inhibitory factors, then pharmacological manipulations could possibly equate the performance of these strains. The present series of experiments were designed primarily to test such a prediction. In addition to the pharmacological manipulations, the strain and drug treatmenta were systematically examined in different avoidance tasks. The procedure was employed to divorce further the differences in performance attributable to associative factors and those pertaining to the nonassociative effects of shock. More explicitly, mice were tested in either an inhibitory avoidance task or a discriminative Y-maze avoidance task. Thus it could be ascertained whether strain and drug differences were specific to response initiating factors (i.e., enhancing

[1] The research was supported by Grant A9845 from the National Research Council of Canada. The author is indebted to John Pipe and Larry Kokkinidis for faithfully testing animals, and to Doug Wahlsten and Giorgio Bignami for their critical readings of the manuscript. Requests for reprints should be addressed to Hymie Anisman, Department of Psychology, Carleton University, Ottawa, Ontario, Canada, KIS 5B6.

active responding but disrupting inhibitory avoidance), or whether the variables in question dealt with general cognitive processes (i.e., do the treatments enhance performance irrespective of the response requisite).

A second purpose of the present investigation was to examine the similarity of scopolamine and d-amphetamine in terms of the response biases elicited by these agents. Specifically, it has been postulated that since anticholinergic and noradrenergic agents have similar behavior effects and may also act synergistically [19, 20, 27, 35], the adrenergic and cholinergic systems might act in synchrony [21,22]. That is, increasing the action of one system would essentially have behavioral consequences comparable to that of reducing the action in the other system. It follows from such an hypothesis that noradrenergic stimulation via d-amphetamine [26] should affect avoidance behavior, in both active and inhibitory tasks, in a manner comparable to that observed with cholinergic blockade. Differential effects of the drugs among the various strains would suggest that scopolamine and d-amphetamine create basically different response biases.

EXPERIMENTS 1 AND 2

In Experiments 1 and 2 mice of three strains differing in levels of avoidance performance were tested in a discriminated Y-maze avoidance task following injection of scopolamine or d-amphetamine, in order to determine whether cholinergic blockade or increased catecholamine activity would equate the performance in these strains. A Y-maze avoidance task was employed since this technique has been found useful in divorcing associative and nonassociative factors [13]. Specifically, through the use of a Y-maze, a measure cannot only be obtained for avoidance performance (measured by correct avoidance responding), and activity to some extent (as measured by incorrect responding and incomplete responses), but also of discrimination learning ability (i.e., the frequency with which animals initially enter the correct arm of the Y-maze irrespective of whether the response is an avoidance or an escape). In other words, a measure can be obtained not only of whether animals know when to go or are capable of initiating a go response, but whether a particular treatment improves the animals ability to decide where to go. Accordingly, if a particular treatment improves avoidance performance without altering discrimination learning, it is unlikely that the change in avoidance behavior is due to changes in learning ability, but rather the treatment may be acting selectively on response modulating systems. Conversely, if both avoidance learning and discrimination ability are altered, the treatment may, in fact, have altered associative processes (e.g., memory, acquisition processes, attention).

METHOD

Animals

Experiments 1 and 2 each employed 20 female and 20 male mice of each of three inbred strains (A/J, DBA/2J and C57BL/6J). Mice were derived from brother X sister matings in our laboratories from stock originally procured from the Jackson Laboratory, Bar Harbor, Maine. Animals were separated by sex and strain and housed 3 to 5 per cage. Mice were permitted ad lib access to food and water for the duration of the experiment. Animals were tested when they were 70–90 days of age, and weighed between 19–26 g. All testing was carried out during the light portion of a 12 hr on – 12 hr off light cycle.

Apparatus

The apparatus consisted of a symmetrical black Plexiglas Y-maze with three arms 9.0 X 6.0 X 7.0 cm. Each arm was separated by a guillotine-like gate which dropped through the grid floor, thus permitting access to that arm. Each compartment could serve as a goal or as a start area. 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 side 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

Two independent experiments were carried out, each consisting of a 3 (Strains) X 4 (Drug Treatments) factorial design. Mice of each strain (N = 5 male and 5 female/cell) received intraperitoneal (IP) injection of either scopolamine hydrobromide (Experiment 1), d-amphetamine sulfate (Experiment 2), or saline. Drugs were administered in dosages of 1, 2 or 3 mg/kg in a 0.5 mg/ml solution of bacteriostatic water. Physiological saline was administered in a volume of 1 ml/kg. Ten minutes after injection the mice were placed individually in one start section of the Y-maze. Thirty seconds after placement in the Y-maze, the gate in each arm was dropped through the grid floor, and one compartment of the maze was illuminated. If the mouse did not leave the start chamber and enter the illuminated compartment within 10 sec, foot-shock was delivered until an escape response was made, whereupon the CS was terminated and the gates were raised. If the animal entered the illuminated goal compartment within 10 sec, the CS was terminated, the gates were raised and the shock was withheld. Entry into the non-illuminated arm at any time was punished by electric shock; the mouse was permitted to escape the compartment. Safe and dangerous compartments were randomly alternated on a predetermined quasi-random schedule. Animals received 60 training trials at 30 sec intervals between trials. Responding was categorized as (a) avoidances – entering the illuminated compartment within 10 sec of CS onset, (b) correct discriminations – where the initial response, whether avoidance or escape, was to enter the illuminated arm, (c) incorrect avoidances – entering the non-illuminated arm within 10 sec of CS onset, and (d) incomplete response – stepping into the triangular choice area without entering either choice arm of the Y-maze prior to shock onset.

RESULTS AND DISCUSSION

Scopolamine

The mean correct avoidance responses as a function of Strain and Scopolamine Treatment are depicited in Fig. 1. An analysis of variance of the avoidance scores yeilded

significant main effects for Strains, $F(2,108) = 31.22$, $p<0.01$, and Drug Treatment, $F(3,108) = 3.59$, $p < 0.01$. Newman-Keuls multiple comparisons between the means involved in these main effects revealed that (a) mice of the A strain performed better than DBA/2 mice, which in turn demonstrated avoidance performance superior to that of C57BL/6 mice, and (b) relative to the saline treatment, administration of scopolamine enhanced avoidance performance. Although the Strain x Drug Treatment interaction did not approach statistical significance, $F(6,108) = 1.71$, $p>0.05$, Newman-Keuls multiple comparisons ($\alpha = 0.05$) were carried out since an *a priori* prediction had been made concerning this interaction [41]. These comparisons revealed (see Fig. 1) that scopolamine at each of the dosages used enhanced performance in the A strain but had negligible effects among both DBA/2 and C57BL/6 mice.

The data for incorrect avoidance responses were very similar to those of correct avoidance responses. The analysis of variance yielded a significant Strain x Drug Treatment interaction, $F(6,108 = 2.19$, $p < 0.05$, which was due to scopolamine increasing the frequency of incorrect avoidance responses in the A strain without substantially altering the performance of DBA/2 and C57BL/6 mice (see Table 1). In the saline condition both A and DBA/2 mice made more incorrect responses than did C57BL/6 mice, while the difference between the former strains was not statistically significant. It would appear that the higher rate of correct avoidance responses among A mice given scopolamine might be due to the greater probability of these animals initiating a running response. That is, following administration of scopolamine animals of the A strain are more likely to initiate a running response, and simply by chance demonstrate a greater frequency of incorrect avoidance responses. The supposition regarding the relationship between correct and incorrect avoidances is also supported by the finding that in 9 of 12 instances the Pearson product correlations between these two variables were statistically significant (correlations ranged from .21 to .95; $\bar{X}$ correlation = .67).

The data for correct discriminations do not support a memory or cognitive position with respect to the effects of scopolamine. Neither the main effect for Drug or the Drug x Strain interaction approached statistical significance ($F< 1$), suggesting that scopolamine improved avoidance performance by acting exclusively on response modulating

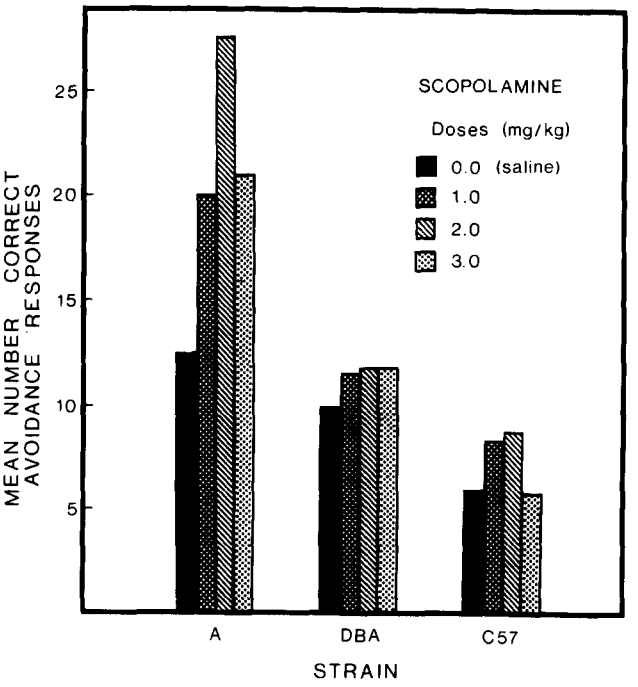

FIG. 1. Mean number of correct avoidance responses/60 trials as a function of Strain and dosage of scopolamine.

systems. In contrast to the lack of drug main effect, the analysis of variance did reveal a significant main effect for Strain, $F(2,108) = 5.71$, $p<0.01$. Subsequent multiple comparisons revealed that the A strain made significantly more correct discriminations ($\bar{X}$ correct discriminations ± SEM = 38.3 ± 1.27) than either the DBA/2 or C57BL/6 strains ($\bar{X}$ correct discriminations = 35.1 ± 0.90 and 36.3 ± 1.07, respectively). These differences appeared late in training as animals exhibited an initial aversion towards the illuminated compartment early in training. The fact that the A strain demonstrated both superior avoidance performance and discrimination learning might suggest that the strain differences observed were due to cognitive factors. This of course does not preclude the possibility that the A strain was also more capable of initiating the running

TABLE 1

MEAN NUMBER ± S.E.M. OF INCORRECT AVOIDANCE RESPONSES AS A FUNCTION OF STRAIN AND DRUG TREATMENT

		Scopolamine (mg/kg)		
Strain	Saline	1	2	3
A	5.50 ± 1.22	7.30 ± 1.50	10.00 ± 1.51	7.70 ± 1.45
DBA/2	4.70 ± 1.00	4.30 ± 0.89	2.60 ± 0.92	4.20 ± 0.96
C57BL/6	1.20 ± 0.44	2.40 ± 0.86	1.50 ± 0.94	1.00 ± 0.42

response necessary for successful avoidance. In any event, together with previous reports indicating that relative to A and DBA/2 mice the C57BL/6 strain is slow in acquiring an operant bar pressing discrimination task for positive reinforcement [33] and a spatial discrimination reversal [4] this finding suggests that the poor performance of C57BL/6 mice is due to associative factors.

Finally, the analysis of variance of incomplete responses yielded only a significant Drug effect, $F(3,108) = 7.15$, $p<0.01$. The source of the variation was found to be due to the fact that scopolamine increased incomplete responses regardless of strain ($\bar{X}$ incomplete responses = 2.6, 5.5, 5.8 and 5.9 for the saline and 1, 2, and 3 mg/kg groups, respectively). It is interesting that although scopolamine did not affect active avoidance responding in the DBA/2 and C57BL/6 strains, imcomplete responding was increased, and inhibitory avoidance behavior was disrupted (see Experiment 3). This finding supports the hypothesis that scopolamine has disinhibitory properties in each strain, but these effects are not in evidence in the relatively insensitive Y-maze task.

d-Amphetamine

Analysis of variance of the avoidance scores yielded main effects for Strains, $F(2,108) = 12.21$, $p<0.01$, and Drug Treatment, $F(3,108) = 5.82$, $p<0.01$. Consistent with Experiment 1 (see Fig. 2), subsequent multiple comparisons revealed that the A strain made more avoidance responses than either of the other two strains, and d-amphetamine was generally found to enhance avoidance performance. Closer examination of the data revealed that the effectiveness of d-amphetamine in altering performance was in fact strain specific. That is, 1 and 3 mg/kg of d-amphetamine significantly improved performance in the DBA/2 strain, whereas the 1 and 2 mg/kg doses improved performance among A mice. The 3 mg/kg dosage did not lead to a statistically reliable increase in the performance of A mice. A subsequent partial replication of these data revealed that 3 mg/kg of d-amphetamine was very effective in improving performance in the A mice. In contrast to the effects observed in the A and DBA/2 strains, none of the dosages employed yielded a significant improvement in performance among C57BL/6 mice. It is of interest to note that the results of Experiments 1 and 2 are not restricted to the Y-maze avoidance task, in that the same Drug × Strains interaction have been observed in this laboratory when a shuttle task was employed.

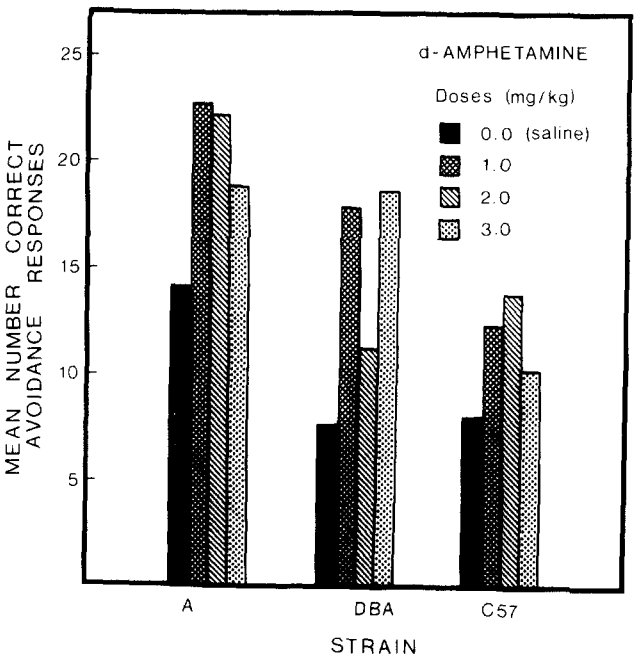

FIG. 2. Mean number of correct avoidance responses/60 trials as a function of Strain and dosage of d-amphetamine.

Consistent with the correct avoidance data, the analysis of variance of the incorrect avoidance responses yielded a significant Drug × Strains interaction, $F(6,108) = 2.28$, $p<0.05$. Multiple comparisons for the simple main effects involved in this interaction, shown in Table 2, revealed that among A mice 1 mg/kg of d-amphetamine increased the occurrences of incorrect avoidance responses. Similarly, incorrect avoidances were found to increase among DBA/2 mice following injection of 3 mg/kg of d-amphetamine but did not affect the performance of C57BL/6 mice. It would thus appear that the increased probability of avoidance responding among A and DBA/2 mice treated with d-amphetamine was due to the motorigenic effects of the drug. This interpretation is supported by the fact that the

TABLE 2

MEAN NUMBER ± S.E.M. OF INCORRECT AVOIDANCES AS A FUNCTION OF STRAIN AND DRUG TREATMENT

	d-Amphetamine (mg/kg)			
Strain	Saline	1	2	3
A	2.5 ± 0.57	7.0 ± 1.35	5.4 ± 0.72	5.0 ± 0.79
DBA/2	3.2 ± 0.55	3.7 ± 0.71	3.2 ± 0.58	6.6 ± 1.55
C57BL/6	2.4 ± 0.59	2.5 ± 0.29	3.2 ± 0.55	3.5 ± 0.79

correlations between incorrect and correct avoidances were significant in 10 of 12 instances (correlations ranged from .31 to .91; $\bar{X}$ correlations = .71). Moreover, the ratio of correct to total avoidance responses revealed that the d-amphetamine treatment did not increase the overall proportion of correct avoidance responses in either the A or DBA/2 mice.

Analysis of variance of the correct discrimination scores did not yield any significant differences. ($\bar{X}$ correct discriminations = 37.7, ± 1.31, 35.9 ± 1.00 and 36.6 ± 1.40 for the A, DBA/2 and C57BL/6 strains respectively). This finding was contrary to the results of Experiment 1 where the A strain was found to show a greater number of correct responses than the other two strains. A subsequent partial replication (N = 5/cell) without any drug treatments was thus carried out. Consistent with Experiment 1, the A strain was found to make more correct discriminations than either the DBA/2 or C57BL/6 strains ($\bar{X}$ correct discriminations = 43.0 ± 1.01, 36.8 ± 0.97 and 36.2 ± 0.99, respectively). It is apparent that the A strain is in fact superior to the other strains in acquiring the discrimination problem. As with scopolamine, within each strain d-amphetamine did not improve the frequency of correct discrimination responding. Apparently the improvement of avoidance responding was not due to a general improvement in learning ability, but rather involved response disinhibition produced by d-amphetamine.

Finally, unlike the effects observed with scopolamine, administration of d-amphetamine did not increase the frequency of incomplete responses in any of the strains. In fact, the occurrences of incomplete responses decreased among A and DBA/2 mice, although this effect was significant only in the A strain ($p < 0.05$ for all three doses). It is likely that motorigenic effects were increased by the drug, since both correct and incorrect avoidance responses were increased. Similarly, if the drug treatment had not produced response bias, then incomplete responding should have occurred equally frequently in drugged and saline animals. It seems that d-amphetamine tends to elicit response initiation, and that once animals initiate the running response and enter the choice area, more often than not animals continue locomoting and enter one of the choice arms. In the scopolamine condition, initiation of the locomotor response by no means insures that the response will be culminated by a choice. This would suggest that a qualitative difference might exist in the nature of the response biases exerted by the two drugs.

EXPERIMENT 3

One possible source for the differential effects of the drugs on avoidance behavior in the three strains may involve interaction between the disinhibitory effects of the drugs and particular task variables. That is, in some strains the constraints imposed by the difficult Y-maze task may limit the disinhibitory action of the drugs, and as a result no facilitation in avoidance is observed. What is thus necessary is to demonstrate that in a simpler, or more sensitive task, the drug treatments will become more evident in each of the strains.

One technique which has proven particularly useful in detecting disinhibitory properties of pharmacological agents as well as determining whether strain differences are due to different levels of response inhibition is the use of both an active and inhibitory task [9,25] or a GO/NO-GO avoidance paradigm [14, 16, 36]. More explicitly, if a specific agent improves performance in an active avoidance task but disrupts performance in an inhibitory avoidance situation, it cannot be argued that the agent in question is primarily affecting cognitive processes and thereby altering behavior. On the contrary, such a finding would imply that disinhibitory factors are responsible for the observed drug effects. In the case of strain differences, a similar prediction can be made. If the strain differences are due to cognitive factors, then those strains performing most poorly on the active avoidance task should likewise demonstrate the poorest performance in the inhibitory avoidance situation. In contrast, if the strain differences were due to inhibitory factors, strains showing the poorest performance in one task should demonstrate the most superior performance in the other task [25].

The use of an inhibitory avoidance task, in conjunction with an active avoidance task, has another advantage in that the inhibitory task may be more sensitive to drug effects, and as a result, the disinhibitory action of drugs which are not apparent in an active avoidance situation might be more detectable in the inhibitory situation. Specifically, in the active avoidance situation animals must learn to run in a certain direction at a certain point in time, thus making the task a fairly difficult one. In the inhibitory avoidance situation the animal must simply learn not to make a locomotor response at any time. Thus the latter task may be more sensitive to response disinhibition than is the former task. The present study employed a continuous inhibitory avoidance situation where mice received shock for making a locomotor response of some given distance. In order to avoid shock, animals must inhibit active responding without having to differentiate cues signalling danger and safety. Over a given session, animals generally receive several shocks before responding is entirely suppressed. Thus a latency measure can be obtained as in the one-trial inhibitory task (i.e., latency to the second shock), but in addition the number of shocks animals receive can be measured over some period of time without the necessity for handling the animal. Since this task neither depends on specific apparatus cues as danger signals nor involves responses which are directed towards certain locales, the disinhibitory properties of a pharmacological treatment may be more observable. Moreover, since this task is not acquired after a single trial, ceiling effects are not a limiting factor in detecting response inhibition.

METHOD

Animals

Fifteen male and 15 female mice of the A/J, DBA/2J and C57BL/6J strains were procured from the Jackson Laboratory. Animals were maintained as in Experiment 1 and tested between 70–90 days of age.

Apparatus

The inhibitory chamber was a 30 × 30 × 30 cm clear Plexiglas open field with a grid floor consisting of 0.23 cm stainless steel rods spaced 0.83 cm apart. The floor beneath the grid was divided into 7.5 × 7.5 cm squares, thus demarcating the open field into 16 areas of equal size. The shock source was the same as in Experiment 1.

Procedure

Experiment 3 involved a 3 × 3 factorial design consisting of three strains and three drug treatments (scopolamine hydrobromide, 2 mg/kg, d-amphetamine sulfate, 3 mg/kg and saline, 1 ml/kg). Ten minutes after injection animals were placed into the open field, 10 sec after which avoidance training commenced. The training consisted of shocking the animal (300 μA for 2 sec) whenever a crossing of one square was made (defined as all four legs being placed into one of the adjacent squares). Following each shock animals were permitted to locomote for a 10 sec period without shocked, after which crossings were again punished. This procedure was employed because of the transient excitation produced by shock [12,34] and because residual running is often found to occur in the first few seconds following shock offset. Animals were tested for a 15 min period during which time the number of shocks received and the time between shocks were recorded.

RESULTS AND DISCUSSION

The latency between the first and second shock and the number of shocks received as a function of the Strain and Drug Treatment are shown in Fig. 3. An analysis of variance of the latency scores revealed a significant Strain × Drug Treatment interaction, $F(4,81) = 2.52$, $p<0.05$. Newman-Keuls multiple comparisons on the simple main effects involved in this interaction revealed that the C57BL/6 mice made the second crossing significantly sooner than either the DBA/2 or A strains. The difference between the latter two strains did not reach an acceptable level of significance ($0.10<p>0.05$). In terms of the Drug Treatments, both d-amphetamine and scopolamine decreased the latency to the second shock in the DBA/2 and A mice but did not substantially affect the performance of C57BL/6 mice.

Analysis of variance of the number of shocks received revealed a Strain × Drug Treatment interaction, $F(4,81) = 2.61$, $p<0.05$. Subsequent multiple comparisons revealed that the A strain made more crossings than did DBA/2 mice. The differences between A and C57BL/6, and C57BL/6 and DBA/2 mice did not approach statistical significance. It seems that although the C57BL/6 strain made the second crossing sooner than the A mice, the number of shocks required to suppress active responding did not differ between the two strains. Turning to the drug effects, d-amphetamine was found to disrupt performance in the A and DBA/2 mice, but it did not affect the performance of C57BL/6 mice. Scopolamine on the other hand, disrupted the performance of all three strains, with only minor effects occurring in the A strain. It appears that in the A strain scopolamine increased the frequency with which active responses occurred early in training but did not substantially affect the number of shocks required to suppress locomotor responding. Among C57BL/6 mice scopolamine increased the number of shocks received but did not decrease the latency to the second shock. Inspection of Fig. 3 clearly reveals that this was a result of the relatively short latency to the second shock demonstrated by saline animals. Thus the possibility of shorter latencies, given the relatively large variance occurring in inhibitory avoidance situations, was precluded. Nevertheless, the drug effect among C57BL/6 was in the direction of a disruption of performance.

The effects of d-amphetamine in Experiment 3 are quite

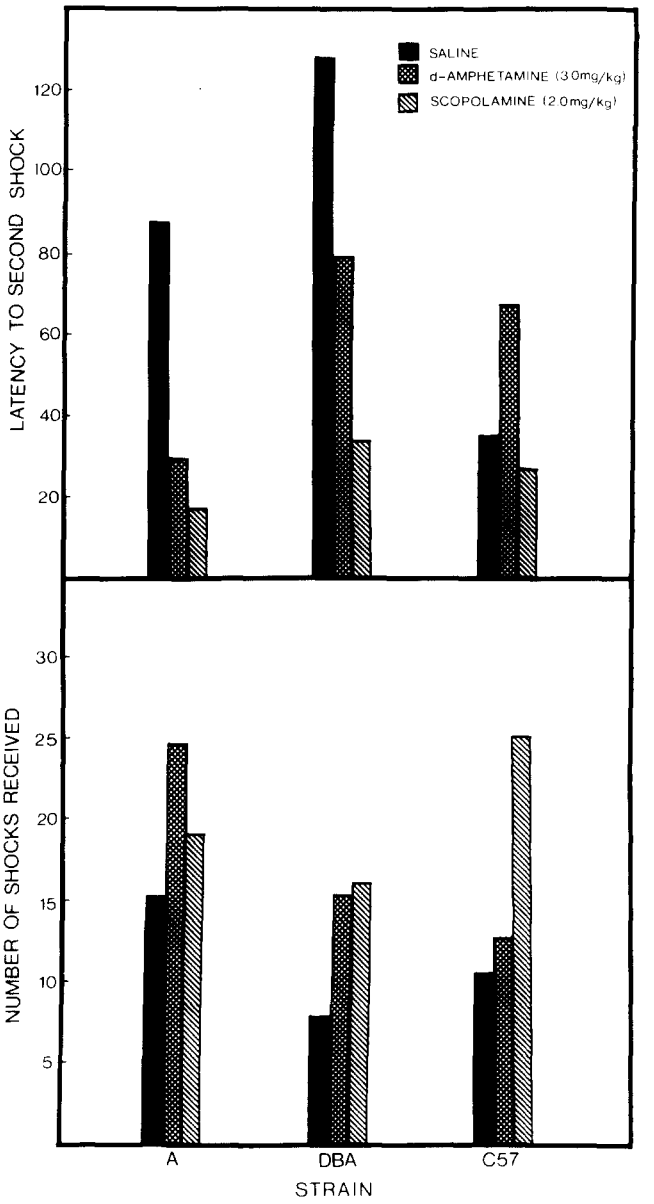

FIG. 3. Response latency to the second shock (upper panel), and number of shocks received (lower panel) as a function of Strain and Drug Treatment.

predictable from a disinhibitory notion. Where the drug improved performance in the active avoidance situation (i.e., among A and DBA/2 mice), a significant retardation of avoidance behavior was noted in the inhibitory paradigm. Where the drug had no effect in the active avoidance situation, as in C57BL/6 mice, no effect was similarly observed in the inhibitory avoidance task. With respect to scopolamine the data also seem to support a disinhibition notion, in that performance was disrupted among A mice, whereas the same drug treatment improved performance in the active avoidance task. However, where scopolamine had no effect in the active avoidance situation (as in DBA/2 and C57BL/6 mice), a significant reduction in performance was observed in the inhibitory avoidance situation. It seems that

the effects of scopolamine were not sufficiently potent to affect the behavior of the C57BL/6 and DBA/2 mice in the active avoidance situation, but in the more sensitive inhibitory situation the drug effects were more detectable.

The strain differences in avoidance performance do not appear to be due solely to differential levels of inhibition. Were this the case, the poorest active avoidance strain should have shown the most superior inhibitory avoidance behavior, and vice versa. The fact, however, is that the C57BL/6 strain, which consistently demonstrated the poorest active avoidance behavior, also demonstrated the poorest inhibitory avoidance performance. Evidently response inhibition does not entirely account for the strain differences in avoidance behavior. Yet, when only the A and DBA/2 strains are considered an inverse relationship is observed between the active and inhibitory tasks. That is, the high active avoidance A strain does poorly in the inhibitory task, whereas the low active avoidance DBA/2 mice perform well on the inhibitory task. Perhaps response inhibition accounts for some degree of the variability between the A and DBA/2 strains while this factor is less pertinent as concerns the behavior of C57BL/6 mice.

GENERAL DISCUSSION

Because of the differential effects of scopolamine and d-amphetamine on the behavior of the three strains of mice, and since these effects also interact with task, a resume of the studies is indicated. (a) The A strain is superior to both the DBA/2 and C57BL/6 mice in both active avoidance and discrimination performance. The DBA/2 strain appears to make somewhat more avoidance responses than the C57BL/6 mice; (b) scopolamine improved active avoidance behavior in the A strain but not in the DBA/2 or C57BL/6 strains. The drug was ineffective in altering the rate of correct discriminations; (c) d-amphetamine improved the avoidance performance of A and DBA/2 mice, but did not alter the avoidance rate among C57BL/6 mice; as with scopolamine, administration of d-amphetamine did not alter the frequency of correct discrimination responses; (d) when tested in the more sensitive inhibitory avoidance task, saline animals of the C57BL/6 strain performed more poorly than did either of the other two strains. Unlike the results observed in the active avoidance situation, scopolamine disrupted the performance of all three strains, whereas d-amphetamine disrupted the inhibitory avoidance performance of the A and DBA/2 strains.

Clearly, associative and nonassociative factors contribute to the rate at which an avoidance response is acquired. However, a factor which accounts for a major portion of the variance between any two strains may account for considerably less variance when two other strains are considered. For example, the fact that the DBA/2 and C57BL/6 strains were inferior to the A strain in acquiring the discrimination and the avoidance response would suggest that associative factors are responsible for the superior avoidance performance of the A strain. However, the difference in discrimination performance is small and only marginally significant in two of three experiments, whereas the avoidance difference is large and clearly a robust effect. Indeed, in one of the studies where the difference in discrimination ability did not reach statistical significance, the avoidance performance of the A mice was far superior to that of either of the other two strains. Taken together, these results suggest that differences in response modulation (response activation and/or response inhibition) are pertinent factors in accounting for at least a substantial part of the strain differences.

When the inhibitory and active avoidance data are considered together it is clear that nonassociative response inhibitory tendencies are not responsible for the poor performance of C57BL/6 mice. If response inhibition were a cogent factor in determing performance, then the strain exhibiting the poorest active avoidance behavior should demonstrate the best inhibitory avoidance performance. The behavior of the C57BL/6 strain is not congruent with such a model. This strain shows the poorest active avoidance performance, but also performs poorly on the inhibitory task. Again these data support the notion that the poor performance of the C57BL/6 mice is not due to response inhibition, but possibly to factors which are exclusive to the ambiguous nature of the Y-maze task. Indeed, in tasks where inhibitory tendencies play somewhat of a role, but associative competing response tendencies are not present (e.g., one-way or jump out avoidance), the performance of C57BL/6 mice is at a reasonably high level [37, 38, 39, 43]. Thus it seems quite probable that the low level of inhibition of C57BL/6 mice following shock [8] is responsible for the high level of performance in simple active avoidance tasks and the poor performance in an inhibitory avoidance situation, but in the shuttle task cognitive factors effectively limit the level of performance. In support of such an interpretation, it has been observed recently [5] that in an aversively motivated reversal learning task A and DBA/2 mice exhibit negative transfer effects when required to run towards cues previously associated with shock, whereas positive transfer is observed when mice are required to run away from cues associated with shock. In contrast, among C57BL/6 mice negligible transfer of training effects are observed. It seems that associative difficulties may exist which limit the performance of C57BL/6. Earlier reports (e.g., [42]) have also suggested that performance differences between C57BL/6 and DBA/2 may deal with associative processes.

In considering the poor performance of the DBA/2 strain, an entirely different picture from that of the C57BL/6 becomes apparent. First, when the A and DBA/2 performances are examined independently, it is apparent that an inverse relationship exists with respect to the performance of these strains in the active and inhibitory tasks. While the DBA/2 strain is inferior to the A strain in the active tasks, the opposite is true in the inhibitory task. As indicated previously, such a finding would implicate the involvement of response inhibitory factors (see [25]).

Consider next the drug effects observed in the various strains. Had response inhibition per se been the prepotent factor in accounting for the strain difference, then the drugs should have equated the performance of the strains. This prediction was clearly not verified. Neither C57BL/6 nor DBA/2 mice demonstrated any improvement in the active avoidance situation following administration of scopolamine. Yet, in the inhibitory avoidance situation scopolamine dramatically altered the performance of all three strains. Clearly, response inhibition is involved in the inhibitory task, and scopolamine is effective in eliminating these response tendencies. The question which arises, then, is whether the inhibitory factor which is involved in shock motivated situations is a prepotent factor in the active avoidance task. It is quite likely that inhibition is a cogent factor, but is masked by more potent effects, possibly the

associative aspects of returning to a compartment in which mice had previously been shocked. Specifically, it may well be the case that the lack of drug effect in C57BL/6 tested in the active avoidance task is due to the difficult nature of the task. That is, if the contingencies of the avoidance situation cannot be established readily, then potentially beneficial effects of response disinhibition will not become apparent. Alternatively, the factor responsible for response inhibition in C57BL/6 may be a transmitter other than ACh (e.g., serotonin), thus accounting for the lack of effect of an antimuscarinic.

Inasmuch as A mice have good associative abilities but suffer, at least to some degree, from the nonassociative effects of shock, it is not surprising that disinhibition exerted by scopolamine and d-amphetamine enhance performance. Similarly, because of associative limitations, the disinhibitory effects of the drugs have little effect on the active avoidance performance of C57BL/6. The drug effects in DBA/2, however, appear to be an enigma. The improvement in performance following d-amphetamine can be attributed to improved response initiating abilities. The question then essentially becomes one of determining why scopolamine, which presumably also has disinhibitory properties, did not enhance the performance of DBA/2 mice in the active avoidance task, but altered the behavior pattern in the inhibitory task. In doing this it must be considered that, although scopolamine did not increase the frequency of avoidances, the frequency of incomplete responses was increased. Moreover, scopolamine altered inhibitory avoidance performance in a manner predictable from a disinhibitory position. Evidently scopolamine affects response inhibition but is not sufficiently potent to alter the behavior of DBA/2 mice in the active avoidance task. However, the consistent finding that d-amphetamine enhances active avoidance performance in DBA/2 mice suggests that the difficulty of the task in itself is probably not responsible for the lack of a scopolamine effect in the DBA/2 mice. Rather, it appears that the actions of scopolamine and d-amphetamine differ in terms of the response biases exerted by the drugs. Quite possibly, cholinergic action involves response inhibition, and antimuscarinic agents eliminate inhibition. In contrast, catecholaminergic action involves excitation of behavior beyond a given baseline. It seems that, although scopolamine-induced response disinhibition may enhance active avoidance performance, much more potent effects on avoidance behavior may be exerted when the drug action also involves excitation of behavior. Consistent with earlier reports [13], neither drug appears to affect performance via associative processes, in that although active avoidance performance was enhanced, discrimination performance was unaffected. Moreover, the fact that the drugs augmented active but disrupted inhibitory avoidance suggests that response bias is modulated by the drug treatments [see also 6, 8, 14, 16, 24].

Summarizing, the basic tenet of the present paper is that the differential performance levels of the three strains appear to be due to both associative factors, nonassociative effects of shock, and task specific inhibition of responding. The avoidance acquisition process can effectively be limited by any one of these factors. If the limiting factor is one dealing with nonassociative processes, then agents which have disinhibitory properties will effectively enhance performance. On the other hand, if the avoidance response rate suffers because of associative deficits, or both associative deficits and response inhibitory tendencies, then reduction of the nonassociative effects of shock will have negligible effects on performance. In order to adequately evaluate the effects of pharmacological treatments it is necessary to determine whether the base levels of performance are limited by associative or nonassociative factors. This objective can be achieved through the use of a variety of tasks such as inhibitory and active avoidance, as well as discriminative performance tasks.

REFERENCES

1. Abeelen, J. H. F. V., L. Gilissen, T. Hanssen and A. Lenders. Effects of intrahippocampal injections with methylscopolamine and neostigmine upon exploratory behaviour in two inbred mouse strains. *Psychopharmacologia* **24**: 470–475, 1971.
2. Abeelen, J. H. F. V., A. J. M. Smits and W. G. M. Raaijmakers. Central location of a genotype-dependent cholinergic mechanism controlling exploratory behaviour in mice. *Psychopharmacologia* **19**: 324–328, 1970.
3. Abeelen, J. H. F. V. and H. Strijbosch. Genotype-dependent effects of scopolamine and eserine on exploratory behaviour in mice. *Psychopharmacologia* **16**: 81–88, 1969.
4. Alpern, H. and J. G. Marriott. An analysis of short term memory and conceptual behaviour in three inbred strains of mice. *Behav. Biol.* **7**: 543–551, 1972.
5. Anisman, H. Acquisition and reversal learning of an active avoidance response in three strains of mice. *Behav. Biol.* **14**: 51–58, 1975.
6. Anisman, H. Cholinergic mechanisms and alterations in behavioural suppression as factors producing time dependent changes in avoidance performance. *J. comp. physiol. Psychol.* **83**: 465–477, 1973.
7. Anisman, H. and D. Wahlsten. Response initiation and directionality as factors influencing avoidance performance. *J. comp. physiol. Psychol.* **87**: 1119–1128, 1974.
8. Anisman, H., D. Wahlsten and L. Kokkinidis. Effects of d-amphetamine and scopolamine on activity before and after shock in three mice strains. *Pharmac. Biochem. Behav.* **3**: 819–824, 1975.
9. Anisman, H. and T. G. Waller. Effects of methamphetamine and shock duration during inescapable shock exposure on subsequent active and passive avoidance. *J. comp. physiol. Psychol.* **77**: 143–151, 1971.
10. Anisman, H. and T. G. Waller. Facilitative and disruptive effects of prior exposure to shock on subsequent avoidance performance. *J. comp. physiol. Psychol.* **78**: 113–122, 1972.
11. Anisman, H. and T. G. Waller. Effects of inescapable shock on subsequent avoidance performance: Role of response repertoire changes. *Behav. Biol.* **9**: 331–355, 1973.
12. Anisman, H. and T. G. Waller. Foot-shock produced excitation and inhibition of activity in rats. *Anim. Learn. Behav.* **1**: 93–95, 1973.
13. Barrett, R. J., N. J. Leith and O. S. Ray. A behavioural and pharmacological analysis of variables mediating active-avoidance behaviour in rats. *J. comp. physiol. Psychol.* **82**: 489–500, 1973.
14. Bignami, G., L. Amorico, M. Frontali and N. Rosic. Central cholinergic blockade and two-way avoidance acquisition: The role of response disinhibition. *Physiol. Behav.* **7**: 461–470, 1971.

15. Bignami, G., F. Robstelli, I. Janku and D. Bovet. Action de l'amphetamine et de quelques agents psychotropes sue l'acquisition d'un conditionnement de fuite at d'evitement chez des rats selectionnes en fonction du niveau particulierement bas de leurs performance. *C. r. hebd. Seanc. Acad. Sci., Paris.* **260:** 4273–4278, 1965.
16. Bignami, G. and N. Rosic. The nature of disinhibitory phenomena caused by central cholinergic (Muscarinic) blockade. In: *Advances in Neuropharmacology,* edited by O. Vinar, Z. Votava and P. B. Bradley. Amsterdam: North Holland Publishing Co., 1971.
17. Bolles, R. C. Species-specific defense reactions and avoidance learning. *Psychol Rev.* 77: 32–48, 1970.
18. Cardo, B. Action of dextrorotatory amphetamine and of eserine on conditioned flight and on phenomena of discrimination. *J. Physiol., Paris* **51:** 845–860, 1959.
19. Carlton, P. L. Augmentation of the behavioural effects of amphetamine by scopolamine. *Psychopharmacologia* **2:** 377–380, 1961.
20. Carlton, P. L. Some effects of scopolamine, atropine and amphetamine in three behavioral situations. *Pharmacologist* **3:** 60, 1961.
21. Carlton, P. L. Cholinergic mechansims in the control of behaviour by the brain. *Psychol. Rev.* **70:** 19–39, 1963.
22. Carlton, P. L. Brain-Acetylcholine and inhibition. In: *Reinforcement and Behaviour,* edited by J. T. Tapp. New York: Academic Press, 1969.
23. Carlton, P. L. and P. Didamo. Augmentation of the behavioural effects of amphetamine by atropine. *J. Pharmac. exp. Ther.* **134:** 91–96, 1961.
24. Carlton, P. L. and B. Markiewicz. Behavioural effects of atropine and scopolamine. In: *Pharmacology Biophysical Agents and Behaviour,* edited by E. Furchtgott. New York: Academic Press, 1971.
25. Fuller, J. L. Strain differences in effects of chlorpromazine and chlordiazepoxide upon active and passive avoidance in mice. *Psychopharmacologia* **16:** 261–271, 1970.
26. Glowinski, J. Effects of amphetamine on various aspects of catecholamine metabolism in the central nervous system of the rat. In: *Amphetamines and Related Compounds,* edited by E. Costa and S. Garattini. New York: Raven Press, 1970.
27. Goldberg, M. E. and V. B. Ciofalo. Alteration of the behavioural effects of amphetamine by agents which modify cholinergic action. *Psychopharmacologia* **14:** 142–149, 1969.
28. Krieckhaus, E. E. Reduction of freezing behaviour and improvement of shock avoidance by d-amphetamine. *J. comp. physiol. Psychol.* **60:** 36–40, 1965.
29. Krieckhaus, E. E., N. E. Miller and P. Zimmerman. Decrements in avoidance behaviour following mamillothalamic tractotomy in rats and subsequent recovery with d-amphetamine. *J. comp. physiol. Psychol.* **60:** 31–35, 1965.
30. Longo, V. G. Behavioural and electroencephalographic effects of atropine and related compounds. *Pharmac. Rev.* **18:** 965–996, 1966.
31. Oliverio, A., C. Castellano and P. Messeri. Genotype dependent effects of septal lesions on different types of learning in the mouse. *J. comp. physiol. Psychol.* **82:** 240–246, 1973.
32. Oliverio, A., B. E. Eleftheriou and D. W. Bailey. Exploratory activity: Genetic analysis of its modification by scopolamine and amphetaminee. *Physiol. Behav.* **10:** 893–899, 1973.
33. Padeh, B., D. Wahlsten and J. C. DeFries. Operant discrimination learning and operant bar-pressing rates in inbred and heterogeneous laboratory mice. *Behav. Genet.* **4:** 383–394, 1974.
34. Pinel, J. P. J., M. E. Corcoran and C. W. Malsbury. The incubation effect in rats: a decline of foot-shock produced activation. *J. comp. physiol. Psychol.* 77: 271–276, 1971.
35. Rech, R. H. Effects of cholinergic drugs on poor performance of rats in shuttle-box. *Psychopharmacologia* **12:** 371–382, 1968.
36. Rosic, N. and G. Bignami. Scopolamine effects on go/no-go avoidance discriminations: Influence of stimulus factors and primacy training. *Psychopharmacologia* **17:** 203–215, 1970.
37. Schlesinger, K. and R. Wimer. Genotype and conditioned avoidance learning in the mouse. *J. comp. physiol. Psychol.* **63:** 139–141, 1967.
38. Wahlsten, D. Phenotypic and genetic relations between initial response to electric shock and rate of avoidance learning in mice. *Behav. Genet.* **2:** 211–240, 1972.
39. Wahlsten, D. Contributions of the genes albinism (c) and retinal degeneration (rd) to a strain-by-training procedures interaction in avoidance learning. *Behav. Genet.* **3:** 303–316, 1973.
40. Wilcock, J. and D. W. Fulker. Avoidance learning in rats: Genetic evidence for two distinct behavioural processes in the shuttle box. *J. comp. physiol. Psychol.* **82:** 247–253, 1973.
41. Winer, B. J. *Statistical Principles of Experimental Design.* New York: McGraw-Hill, 1961.
42. Winer, R. E., L. Symington, H. Farmer and P. Schwartzkroin. Differences in memory processes between inbred mouse strains C57BL/6J and DBA/2J. *J. comp. physiol. Psychol.* **65:** 126–131, 1968.
43. Zerbolio, D. J. Difference between three inbred mouse strains on a wheel-turn avoidance task. *Psychon. Sci.* 7: 201–202, 1967.