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Effects of Scopolamine and D-Amphetamine on One-way, Shuttle and Inhibitory Avoidance: A Diallel Analysis in Mice

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ANISMAN, H. *Effects of scopolamine and d-amphetamine on one-way, shuttle and inhibitory avoidance: a diallel analysis in mice.* PHARMAC. BIOCHEM. BEHAV. 3(6) 1037–1042, 1975. – The effects of scopolamine (2.0 mg/kg) and d-amphetamine (3.0 mg/kg) on one-way, shuttle and inhibitory avoidance performance were evaluated in 3 strains of mice (A/J, DBA/2J and C57BL/6J) and their 6 reciprocal F_1 hybrids. In the saline condition, intermediate inheritance was observed in the inhibitory task, complete dominance for superior avoidance in the one-way task, and hybrid superiority in the shuttle situation. Administration of d-amphetamine disrupted inhibitory performance in all strains. In the shuttle task no amphetamine effect was observed in C57BL/6J mice, while improvement was seen in A/J and DBA/2J mice, as well as in all the hybrid crosses. No drug effect was seen in the one-way task. As with d-amphetamine, scopolamine disrupted performance in the inhibitory task among the inbreds, but had negligible effects in the hybrids. In the shuttle task, only the A/J mice exhibited improved performance, while a small decline in response rate was seen in one-way avoidance. Results were interpreted in terms of the role of scopolamine and d-amphetamine in modifying non-associative factors involved in avoidance, and the interaction between associative and non-associative factors in modulating avoidance response rate.

Shuttle avoidance One-way avoidance Inhibitory avoidance Scopolamine d-Amphetamine Diallel analysis

ALTHOUGH pharmacological agents such as scopolamine and d-amphetamine have been observed to increase general activity [7, 28, 32] and to augment active avoidance performance [5, 13, 14, 15, 25], the effectiveness of these agents has been found to interact with both strain [1, 2, 3, 9, 12, 27] and task factors [5, 14, 33]. For example, both agents have been found to increase avoidance response rate in a shuttle avoidance task, but have negligible effects, or even disrupt, one-way avoidance performance [5, 33]. Presumably, shuttle performance ordinarily suffers because of strong inhibitory tendencies (i.e., freezing behavior) elicited by shock, which cannot be suppressed readily owing to the conflicting nature of the task [10, 11, 16]. With the reduction of response inhibition following treatment with either scopolamine or amphetamine, avoidance performance is enhanced. In contrast, in the one-way task response inhibitory tendencies elicited by shock can be suppressed readily because the running response is a functionally effective one [10, 11, 16]. Consequently, further disinhibition through pharmacological treatments provides little additional benefit. Parenthetically, if the task is a very difficult one, as in certain go/no-go paradigms, neither drug influences avoidance performance [23]. Apparently, the drugs have little effect on associative processes; thus, when many trials are required for the contingencies of the task to be met, potentially beneficial effects of the drug treatments may be masked.

Recent work [7] has revealed that the effects of both scopolamine and d-amphetamine may also interact with task and strain. Specifically, in three strains of mice (A/J, DBA/2J and C57BL/6J), either drug was observed to eliminate effectively shock-induced response inhibition [12] and to disrupt inhibitory avoidance performance [7]. However, in a shuttle or Y-maze avoidance task the strains are affected differentially by the drug treatments. Whereas, both drugs improve the performance of A/J mice, only amphetamine facilitates performance in DBA/2J mice, and neither drug affects reliably the behavior of C57BL/6J mice [7]. It is not likely that the lack of drug effect on active avoidance in C57BL/6J mice reflects general lack of sensitivity to the d-amphetamine treatment, since substantial changes in behavior are seen in postshock activity and inhibitory avoidance. Rather, it may well be the case that C57BL/6J suffers because of associative deficits in the shuttle task which effectively mask the disinhibitory actions of scopolamine and d-amphetamine. Support for such an assumption is derived from the fact that in an aversively motivated reversal learning task, negligible trans-

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fer of training effects are seen in C57BL/6J mice, whereas predictable transfer effects are seen in both A/J and DBA/2J mice [6]. Moreover, it has been observed that the poor performance of C57BL/6J mice is not restricted to active avoidance performance (see also [24]), but is consistently observed in inhibitory tasks as well [7,18], thus further attesting to the associative difficulties of C57BL/6J mice in avoidance performance.

One purpose of the present investigation was to determine whether the Strain × Drug interaction observed previously in a shuttle task would be modified in a one-way avoidance situation. Specifically, it has been observed that these two tasks are a relatively sensitive gauge for determining whether performance differences are due to associative or nonassociative factors. For example, when differences in non-associative factors (e.g., freezing) are responsible for differences in shuttle avoidance, these differences are largely reduced in a one-way task owing to the rapid rate at which freezing can be suppressed [7,10]. However, if differences in shuttle avoidance are due to associative factors, then the performance differences are reflected in the one-way task as well [4]. Thus, if improvements in avoidance are seen in the shuttle task, but not in the one-way task following drug treatments, then the source for the drug-induced improvements in performance would be attributed to reduction in freezing behavior. Similarly, if the strain differences are eliminated in the one-way task, nonassociative factors would be implicated. Conversely, if the strain differences are maintained in both avoidance situations, then the differential performance levels would be attributed to poor associative abilities in avoidance tasks. It is important to note that a non-handling procedure was used in the one-way task and that the apparatus consisted of homogeneous compartment colors which resulted in one-way performance progressing more slowly than it does in the traditionally used one-way tasks. Accordingly, ceiling effects did not limit response rate, and performance was not modified by Drug × Handling interactions [20].

In addition to the one-way and shuttle tasks, an inhibitory avoidance paradigm was employed as well, in an attempt to elucidate further the mechanisms involved in producing the drug facilitation and the strain differences. If a particular treatment improves associative processes, then improvements in performance should be evidenced in both active and inhibitory tasks. However, if the cogent factor in eliciting performance differences involves nonassociative effects such as increased freezing, then inhibitory avoidance should improve and active avoidance should deteriorate. Conversely, if freezing is reduced, inhibitory avoidance should be disrupted and active avoidance response rate augmented.

A second question of interest in the present experiment pertained to the evaluation of the effects of the drugs on the patterns of inheritance observed in the one-way and shuttle tasks in F_1 mice. More explicitly, it was observed previously that F_1 mice of the three strains employed exhibited complete dominance in a one-way avoidance task, and overdominance in the more complex shuttle task. Yet, the levels of activity both before and after shock, as well as performance in an inhibitory avoidance task, were at a level intermediate to the parent strains [8]. Apparently, the observed hybrid vigor was not due to nonassociative factors, but rather to associative factors, such as improved integrative abilities. Accordingly, if treated with scopolamine or d-amphetamine, hybrids with a C57BL/6J parent should exhibit improved performance levels, since the disinhibitory effects of the drugs would not be masked by more potent disruptive associative factors. It could not be argued that the hybrids are more sensitive to drug treatments and thus show facilitation in performance, since C57BL/6J already exhibits responsivity to the drugs in inhibitory paradigms; however, these disinhibitory effects are not manifested in the active avoidance task.

METHOD

Animals

A total of 810 mice from 3 inbred strains (A/J, DBA/2J and C57BL/6J and their reciprocal F_1's were used. All of the mice were bred at the University of Waterloo, from inbred strains procured from the Jackson Laboratory, Bar Harbor, Maine. Females were removed from the breeding cages when visibly pregnant and caged individually. Offspring were weaned subsequently at 21 days of age and housed communally, separated by sex. Animals were tested between 60 and 90 days of age. Throughout the experiment animals were permitted ad lib access to food and water.

Apparatus

The avoidance apparatus consisted of a black circular Plexiglas runway 11.5 cm wide and 13.1 cm high with an outside circumference of 207.25 cm. The alley was divided equally into 8 compartments by black Plexiglas walls, partially made up of solenoid controlled horizontally moveable gates. In the open gate position, access through a 8.0 × 7.8 cm space was permitted into the adjacent compartment. The floor of the apparatus was made up of 0.25 cm stainless steel rods spaced 1.25 cm apart (center to center) at the exterior wall. The floor was wired through a diode bridge.

Situated at each end of each compartment flush with the end wall and immediately beneath the clear Plexiglas lid of the apparatus was a 6 W lamp encased in a frosted casing which ran the width of the alley. Situated on either side of each gate, 2.5 cm from the floor and 1.1 cm from the gate itself, was an infrared photoelectric relay system wired such that if both beams were broken, as would occur if the mouse was half-way through the gate, the cells would not trigger. If the mouse passed the cell in the start compartment and crossed the second beam, the cell was triggered. In avoidance training the CS (light onset) was accompanied by the simultaneous opening of the gate and by the activation of a sound attenuated Sodeco counter set at 10 counts per sec. Breaking the appropriate photo-electric light beam resulted in CS offset and termination of the Sodeco counter followed by a printout of the latency between CS onset and offset, and closing of the gate. Two modes of operation were employed: (a) the CS, US, photoelectric system and activation of the gate stepped from one compartment to the next in a counter-clockwise manner producing one-way avoidance without handling; (b) only a single gate was raised and the CS, US and photoelectric relay system stepped alternately between two adjacent compartments resulting in a two-way (shuttle) avoidance procedure.

The test chamber for inhibitory avoidance consisted of a 30 × 30 × 30 cm clear Plexiglas chamber with a floor made up of 0.23 cm stainless steel bars spaced 0.83 cm apart. Shock of 300 μA could be delivered via a high voltage-high

resistance source to the grid floor. The grid was wired through a diode bridge connecting every fourth bar making it difficult for mice to find two bars in common. The grid was demarcated into 7.5 x 7.5 cm squares thus making 16 equal sized squares.

Procedure

The shuttle, one-way and inhibitory tasks were carried out as three independent experiments. Animals of each strain were randomly assigned to groups (n = 10/cell) and given intraperitoneal injections of either saline (2 ml/kg), scopolamine hydrobromide (2 mg/kg in a 0.5 mg/ml solution) or d-amphetamine sulfate (3 mg/kg in a 0.5 mg/ml solution). These particular dosages were selected on the basis of earlier experiments [7] which indicated that these were optimal dosages in the inbred strains. Fifteen min after injection animals were placed individually in one compartment of the circular runway, 30 sec after which training commenced. The gate separating the start compartment and the compartment adjacent to it was opened and the CS was presented simultaneously. If the mouse did not cross into the adjacent compartment within 10 sec, shock of 300 μA was delivered until an escape response was made, whereupon the gate was closed and the CS was terminated. If the animal crossed into the adjacent compartment within 10 sec of CS onset, the gate was closed immediately, the CS was terminated and the US was withheld. Animals received 50 trials at 30 sec intervals. For those animals tested in the one-way task, training trials continuously proceeded in a counter-clockwise direction whereas for animals in the shuttle task only a single gate was opened and the response direction alternated from trial to trial.

For inhibitory avoidance training animals were placed in the open field and avoidance training commenced after a 10 sec period. The training consisted of shocking the mouse (300 μA for 2 sec) whenever a crossing of one square was made. Crossings were defined as animals placing all 4 legs in a particular square. Following each shock animals were permitted to locomote for a 10 sec period without being shocked, after which crossings were again punished. This procedure was used because residual running was found to occur often during 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

Shuttle Avoidance

The mean number of avoidance responses in the shuttle task for each of the inbred and hybrid strains as a function of the drug treatment are shown in Fig. 1. Analysis of variance of the number of avoidance responses yielded significant main effects for Strains, $F(8,243) = 7.74$, $p<0.01$, and Drug Treatment, $F(2,243) = 5.62$, $p<0.01$. Subsequent orthogonal comparisons ($\alpha = 0.05$) were carried out both between and within each Drug Condition. In the saline condition, A/J mice exhibited performance superior to that of either DBA/2J or C57BL/6J mice. Differences between the latter two strains did not approach statistical significance. In each of the hybrid strains, performance exceeded the average of the two parent strains; and in all but the C57BL/6J x DBA/2J cross, the performance level exceeded that of the extreme parent score. Over-dominance

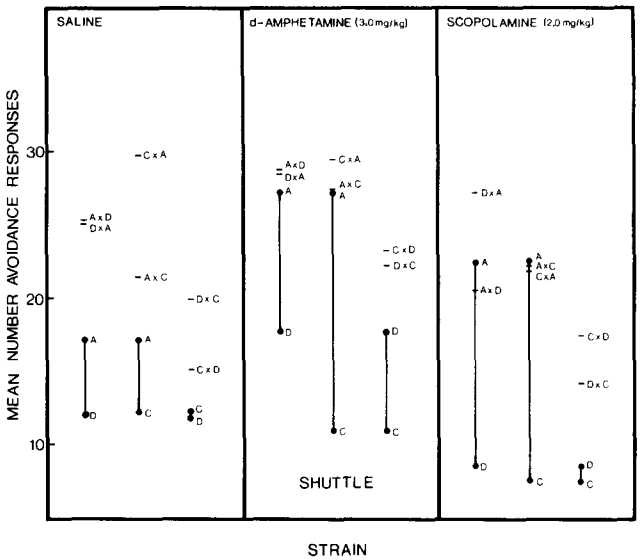

FIG. 1. Mean number of shuttle avoidance responses in inbred strains and their reciprocal F_1 crosses as a function of d-amphetamine and scopolamine treatment.

was the apparent mode of inheritance in the shuttle task, regardless of the strains involved.

Consistent with earlier reports [7], d-amphetamine improved performance in both A/J ($p<0.05$) and DBA/2J mice ($p<0.10$), but had no effect on the performance of C57BL/6J mice. Comparing the F_1 d-amphetamine animals to the saline treated hybrids revealed that d-amphetamine produced somewhat of an increase in performance ($p<0.06$). As in the saline condition, the hybrid scores exceeded that of the mid-parent scores. However, only in the crosses between C57BL/6J and DBA/2J did the hybrid score exceed that of the extreme parent score.

In contrast to the effects of d-amphetamine, scopolamine improved performance in A/J mice, but produced a small non-significant decline in the performance of both DBA/2J and C57BL/6J mice. Similarly, the avoidance response rate of the F_1's did not exceed that seen in saline treated animals.

One-way Avoidance

The mean number of one-way avoidance responses as a function of Strain and Drug Treatment are shown in Fig. 2. Analysis of variance of the avoidance scores revealed significant main effects for Strain, $F(8,243) = 11.46$, $p<0.01$, and Drug Treatment, $F(2,243) = 5.76$, $p<0.01$. Orthogonal comparisons indicated that in the saline condition the performance of A/J mice exceeded that of either DBA/2J or C57BL/6J mice, which did not differ from one another. In all the F_1 crosses except C57BL/6J x DBA/2J, performance exceeded the mid-parent value, but not the extreme parent score. In the C57BL/6J x DBA/2J cross, performance was, in fact, superior to that of either of the parental strains. Thus, the primary mode of inheritance was one of complete dominance rather than overdominance which was observed in the shuttle task.

Unlike the drug effects seen in the shuttle task, d-amphetamine did not enhance performance in either the inbred or hybrid mice. For scopolamine, the overall analysis

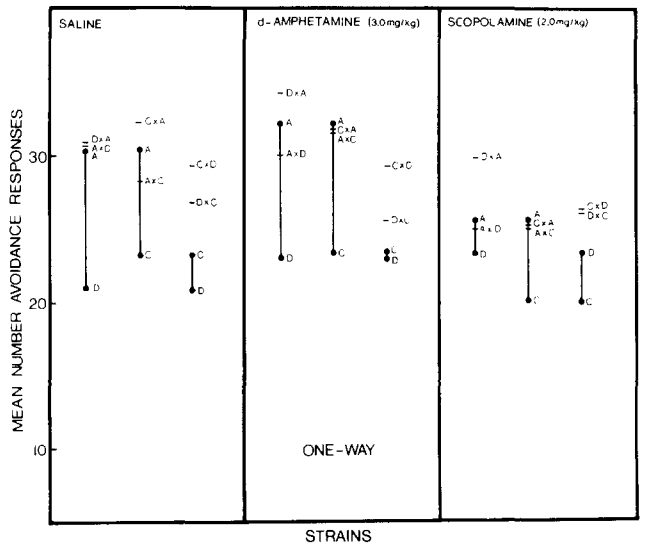

FIG. 2. Mean number of one-way avoidance responses in three inbred strains and their reciprocal F_1 crosses as a function of d-amphetamine and scopolamine treatment.

indicated that the drug treatment produced a small but significant retardation of the avoidance response rate.

Inhibitory Avoidance

Separate analyses were performed for the number of shocks received and for latency between the first and second crossings. The mean scores for each of these measures as a function of Strain and Drug Treatment are shown in Fig. 3. Analysis of variance of the number of shocks received revealed a significant Strains × Drugs interaction, $F(16,243) = 5.74$, $p<0.01$. Orthogonal comparisons on the simple main effects revealed that in the Saline condition A/J and C57BL/6J mice received more shocks than did DBA/2J mice. Differences between the former two strains did not approach statistical significance. Among the hybrids treated with saline, performance did not differ from the mid-parent value except in the A/J × DBA/2J cross where performance resembled that of the A/J parent. Clearly, the simple response-shock contingency resulted in intermediate inheritance, while increased task complexity resulted in heterosis and overdominance.

With the administration of d-amphetamine, the number of shocks received increased in all strains relative to saline treated animals. Comparisons among the inbred mice revealed that C57BL/6J mice received more shocks than A/J mice, while animals of the DBA/2J strain were intermediate between A/J and C57BL/6J mice. However, relative to saline animals, the increase in shocks received was greatest in DBA/2J. In all the F_1's except the DBA/2J × C57BL/6J cross, the number of shocks received exceeded that of the respective mid-parent value.

Scopolamine was found to increase the number of shocks received among inbred mice. However, no such change in performance was observed among the hybrids. In fact, in most of the crosses the number of shocks received was less than that of the mid-parent values, and often were also lower than that of the dominant parent (see Fig. 3).

Analysis of variance of the latency between the first and second crossings revealed a significant Strains × Drug

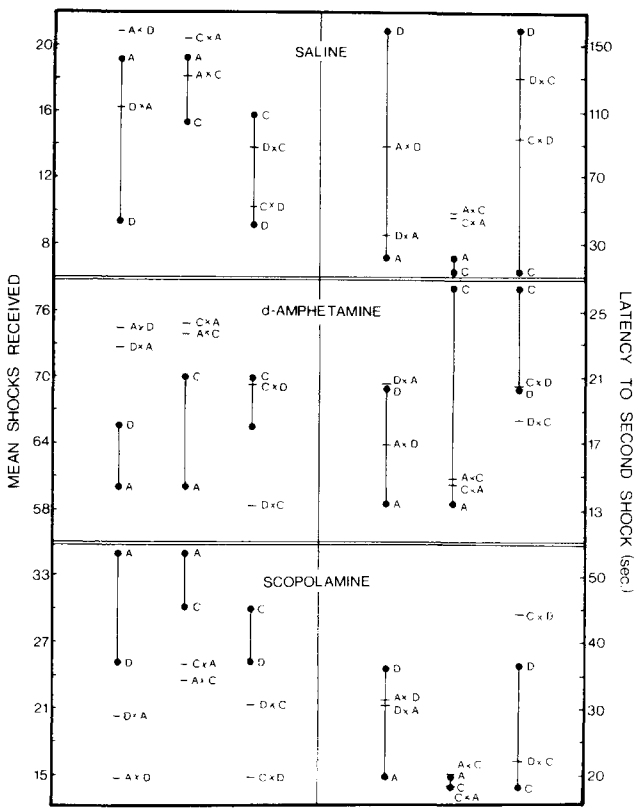

FIG. 3. Mean number of shocks received (left-hand panels) and mean crossing latency following the first shock trial (right-hand panel) in the three inbred strains and their reciprocal F_1 crosses as a function of drug treatment.

Treatment interaction, $F(16,243) = 2.01$, $p<0.05$. Orthogonal comparisons revealed that A/J and C57BL/6J mice made the second crossing earlier than DBA/2J mice. Among the hybrids intermediate inheritance was observed in the A/J × DBA/2J and C57BL/6J × DBA/2J crosses. However, in the reciprocal crosses performance resembled the A/J and DBA/2J parents respectively. The presence of these maternal effects makes it difficult to ascertain the true patterns of inheritance. However, together with the data for number of shocks received it is probable that the mode of inheritance is of an intermediate nature.

Because of the rapidity with which most of the F_1 mice made the second crossing the effects of scopolamine and d-amphetamine were largely obscured. Nevertheless, it is apparent that as a whole both drugs tended to decrease response latency, with d-amphetaine being more potent than scopolamine in this respect. Owing to the narrow band within which scores occurred, inheritance patterns could not be evaluated. Parenthetically, the existence of floor effects attests to the importance of employing a dual measure task in an inhibitory paradigm.

DISCUSSION

Consistent with earlier reports [6,7] the A/J strain exhibited active avoidance performance superior to that of the DBA/2J and C57BL/6J mice. The fact that this difference was also maintained in the one-way task, and

that A/J and C57BL/6J mice did not differ in inhibitory avoidance, suggested that the performance difference between these two strains probably involves associative factors. Had non-associative effects been responsible for the strain differences, then the rapid rate at which freezing behavior could be suppressed in the one-way task should have resulted in performance differences between these strains being reduced. Moreover, under these circumstances C57BL/6J should have exhibited inhibitory performance superior to A/J mice. In contrast, the finding that the A/J strain exhibits active avoidance superior to that of DBA/2J mice, but inhibitory avoidance inferior to that of DBA/2J would implicate the involvement of nonassociative factors as being involved in the performance differences between these two strains. This particular conclusion is supported to some extend by the earlier finding that C57BL/6J exhibits negligible transfer of training effects in an aversively motivated reversal learning task, whereas both A/J and DBA/2J mice exhibit appropriate transfer effects [6].

With respect to the behavior of the hybrid mice, the primary mode of inheritance was of an intermediate nature in the inhibitory task, complete dominance for high performance levels in the one-way task, and hybrid superiority in the shuttle situation. Given that intermediate inheritance is also observed in general activity and activity following shock [8], suggests that the hybrid supremacy does not reflect changes in non-associative factors. Rather, consistent with previous suggestions [22,34], these data imply that the poor performance seen in inbred mice is due to a loss in biochemical versatility, which is regained in the hybrids. In effect, the implication here is that the improved performance of hybrids is due to greater associative or integrative abilities than those seen in inbreds, and that these differences in associative abilities become accentuated as task complexity is increased.

Turning to the effects of scopolamine and d-amphetamine on avoidance, as previously observed [7], in a shuttle task both drugs improved performance among A/J mice, d-amphetamine but not scopolamine augmented performance in DBA/2J, while neither drug affected the behavior of the C57BL/6J mice. In the one-way task neither drug improved performance regardless of strain. In fact, scopolamine produced a small, but significant, retardation in the avoidance response rate. The source for this disruption is difficult to specify, but it is clear that it is not due to associative deficits produced by the drug, since in the shuttle task scopolamine repeatedly improved the performance of A/J mice, and has also been reported to improve shuttle avoidance employing other strains of mice and rats [5, 13, 14, 15]. A more likely possibility is that the disinhibitory effects of scopolamine result in increased exploration, which disrupts the acquisition of simple responses [5,33] and well established shuttle responses [26]. Thus, in simple tasks, the exploratory response induced by scopolamine competes with the running response necessary for successful avoidance (see also [16]). In contrast, in the more complex shuttle task, the increased exploratory behavior may have a beneficial effect by competing with the disruptive freezing response, which ordinarily cannot be suppressed readily. In any event, the finding that both drugs may improve shuttle avoidance, but uniformly disrupt inhibitory avoidance suggests that both these drugs affect performance by reducing shock-induced response inhibition, and do not alter associative abilities. Moreover, the very fact that C57BL/6J exhibits a response to both drugs in the inhibitory task clearly indicates that the drugs alter levels of inhibition in this strain; however, these effects are masked in the shuttle task. It is likely that because C57BL/6J suffers from an associative deficit, any potentially beneficial effects of the drug induced disinhibition do not emerge, just as is the case in very difficult tasks [23]. Parenthetically, it was previously reported [27] that the lack of effect of scopolamine in C57BL/6J may be due to the effects of a single major gene. The finding that the drug modifies inhibitory avoidance in C57BL/6J, and also modifies shock induced response suppression [12] as well as habituation [12] indicates that the influence of the gene is situation specific.

Among the hybrid mice, d-amphetamine was found to improve shuttle avoidance performance. It is important to note that this was also true of crosses involving the C57BL/6J strain. This is not altogether surprising if it is assumed that the hybrid mice in fact have superior associative abilities [5]. Specifically, with adequate associative abilities, performance improves relative to inbred mice; however, non-associative factors still limit performance to some degree. Thus with the reduction of these inhibitory tendencies, avoidance performance is further augmented. In the one-way task, negligible drug effects are observed, probably owing to the relatively efficient suppression of inhibitory tendencies even in the absence of the drug treatments.

The response to scopolamine in the F_1's was very different from that seen with d-amphetamine. That is, no improvement was evident even in the shuttle task. The very fact that the two drugs differentially affected the performance of the F_1 mice suggests that the drugs have qualitatively different effects. For example, while scopolamine has disinhibitory effects, amphetamine appears to have an excitatory action beyond that of simple disinhibition (see also [29,30]). Thus, in F_1 mice, where performance is at a relatively high level, the disinhibitory effects of scopolamine may not be sufficient to improve performance. However, excitation of behavior beyond disinhibition may result in beneficial effects on avoidance. Data recently collected in our laboratories [12] has revealed that the response to shock is very different in d-amphetamine and scopolamine treated animals. Typically, shock decreases the level of general activity, and scopolamine reduces these inhibitory tendencies. Administration of shock to d-amphetamine treated animals, on the other hand, results in excitation of behavior beyond that produced by d-amphetamine alone. It is quite likely that the effects of d-amphetamine in increasing synthesis and release of catecholamines [19, 21, 31] act synergistically or additively with increases in norepinephrine activity induced by stress [9,35].

Summarizing briefly, it appears that the facilitative effects of scopolamine and d-amphetamine on shuttle avoidance behavior are due to the disinhibitory or excitatory effects of these drugs. However, these drugs facilitate performance only when inhibitory factors limit response rate. If the inhibitory response normally can be suppressed quickly, then the potentially beneficial effects of these drugs are not apparent. In fact, they may disrupt performance by invoking a competing exploratory response. If the limiting factor in an avoidance situation involves associative factors, such as in very difficult tasks [23], or among strains suffering from poor associative abilities in an avoidance task, then the beneficial effects of response

disinhibition will not be manifested. In hybrid mice, associative abilities are superior to those witnessed in inbred mice. Accordingly, d-amphetamine may result in improved performance even though the excitatory effect of the drug may not be any greater than that seen in the inbred parent strains.

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