Pharmacology Biochemistry & Behavior, Vol. 3, pp. 613–618.

Dissociation of Disinhibitory Effects of Scopolamine: Strain and Task Factors

HYMIE ANISMAN[1]

Carleton University, Ottawa, Ontario, K1S 5B6, Canada

(Received 18 October 1974)

ANISMAN, H. *Dissociation of disinhibitory effects of scopolamine: strain and task factors.* PHARMAC. BIOCHEM. BEHAV. 3(4) 613–618, 1975. – In 3 experiments it was observed that 3 strains of mice (A/J, DBA/2J and C57BL/6J) differing in activity exhibited comparable levels of spontaneous alternation, and that scopolamine differentially affected activity in the strains, but uniformly eliminated shock-induced suppression and spontaneous alternation behavior. Data are discussed in terms of the relationship between activity and spontaneous alternation. It was suggested that scopolamine exerts its effects on spontaneous alternation via the effects on acetylcholine activity, independent of any effects on general activity levels.

Scopolamine Strain differences Habituation Spontaneous alternation General activity

SPONTANEOUS alternation and decline in activity over time are two often used indices of habituation [13, 22, 24]. Yet, it is not clear whether these two behaviors are in fact related, or even subserved by common mechanisms. Whereas decline in activity is gauged by baseline activity, thus controlling for individual differences in initial activity levels, this is not the case in the spontaneous alternation task. Specifically, spontaneous alternation may be unduly subject to variation owing to levels of general activity. For example, in an alternation task it is assumed that animals habituate to one arm of a Y or T-maze, and consequently are less apt to reenter this arm [18,24]. In relatively active animals less time may be spent visiting an arm following a particular entry (as may be the case in free running alternation), or the animal may be less attentive to stimuli in that arm, thus resulting in poorer habituation. In a subsequent choice situation the probability of reentering the previously visited arm may be greater than it would be in less active animals. One purpose of the present investigation was to determine whether levels of activity influence spontaneous alternation.

Typically, in manipulating activity levels a treatment variable is imposed on the subject, which in itself may produce confounds. For example, scopolamine is known to effectively decrease acetylcholine (ACh) action [14], increase activity [2, 5, 21] and disrupt alternation behavior [10, 11, 24]. It is not apparent though, whether disruption in alternation is due to alteration in ACh action *per se*, or whether the increase in activity, independent of ACh action, affects spontaneous alternation. Accordingly, in Experiment 1 no such pharmacological manipulation was employed. Rather, 3 strains of mice (A/J, DBA/2J and C57BL/6J) differing in levels of activity [5,20] were examined to see whether in fact alternation behavior would also differ in these 3 strains. Employment of the strain variable allows for both within and between group correlations between activity and alternation. Moreover, a free running alternation task was employed [10,24] allowing for activity and alternation behavior to be monitored simultaneously.

EXPERIMENT 1

METHOD

Animals

A total of 90 mice represented equally from 3 inbred strains (A/J, DBA/2J and C57BL/6J) were used. Mice were bred from stock obtained from the Jackson Laboratory, Bar Harbor, Maine, and were tested between 60–90 days of age. Animals were housed by litter, separated for sex, in standard plastic cages, and were permitted ad lib access to food and water.

Apparatus

The apparatus consisted of a symmetrical black Plexiglas Y-maze with arms 9.0 cm long, 6.0 cm wide and 7.0 cm high, and covered with a clear Plexiglas roof. The floor of the apparatus was made up of 0.25 cm stainless steel rods spaced 1.0 cm apart (center to center). Each arm of the Y-maze could serve as either a start or goal arm.

[1]The research was supported by Grant A9845 from the National Research Council of Canada. Appreciation is extended to Diane Cygan, John Pipe and Larry Kokkinidis for their assistance in the testing of mice. Requests for reprints should be sent to Hymie Anisman, Department of Psychology, Carleton University, Colonel By Drive, Ottawa, Ontario, K1S 5B6, Canada.

Procedure

Animals were placed individually in one arm of the Y-maze for a 10 sec period, after which a barrier separating that arm from the rest of the maze was removed and subjects permitted free exploration for a 15 min period. During this time the number of arms entered as well as the sequence of entries were recorded. Entering an arm was defined as all 4 legs crossing over the area dividing an arm from the triangular choice area. Occasionally, mice would enter into the choice area and return to the same compartment they had just previously left. All such responses were included in the analysis of total arm entries, but were not employed in the tabulation of the spontaneous alternation score. A response sequence in which animals entered the arm least recently visited was considered as an alternation (e.g., a sequence of arm entries in this case would be 1, 2, 3 or 1, 3 2). Nonalternation was considered to be the case when animals returned to the compartment they had been in most recently (e.g., 1, 2, 1 or 2, 3, 2). The alternation score was computed by dividing the number of alternations by the sum of alternations plus nonalternations.

RESULTS AND DISCUSSION

The proportion of spontaneous alternations as well as the mean number of arm entries over 3 min periods are shown in Fig. 1. The alternation score is based on the mean individual alternations. The score was found to be comparable regardless of whether it was calculated in terms of proportion for each group or mean individual alternations. Analysis of variance of the number of arm entries yielded a significant Strains X Blocks of Time interaction, $F(8,348) = 3.03$, $p<0.01$. Subsequent Newman Keuls multiple comparisons ($\alpha = 0.05$) of the simple main effects revealed the A strain to be less active than either DBA/2 or C57BL/6 mice. Over the 15 min session a significant decline in activity was evident in each strain. While the absolute decline in activity was greater in the DBA/2 and C57BL/6 mice than in the A mice, this was probably due to a floor effect in the latter strain, since the proportion of decline, calculated from activity levels during the first three minutes, was comparable across strains. It is noteworthy that activity levels do not differ between DBA/2 and C57BL/6 mice, yet when activity is measured in an open field it was consistently observed that C57BL/6 were more active than were DBA/2 mice ([5,20], see also Experiment 2). This suggests that activity levels, and possibly habituation rates, interact with the type of apparatus. Possibly, some test chambers elicit greater fear than others, and such effects are more potent in altering the behavior of DBA/2 mice.

Analysis of the alternation scores revealed that in all three strains the levels of alternation exceeded chance (χ^2's = 10.07, 58.0 and 29.43, $df = 1$, $p<0.01$ for A, DBA/2 and C57BL/6 mice respectively). Similarly, analysis of the number of animals alternating on the second arm entry revealed that regardless of strain, alternation occurred at a greater than chance level (A = 86.6%, DBA/2 = 70.0%, C57BL/6 = 86.6%; χ^2's = 16.12, 4.80 and 16.12, $df = 1$, $p<0.05$). Analysis of variance of the alternation levels revealed that neither the Strains or Strains X Time interaction approached statistical significance. Clearly, the fact that the strains differed in activity did not affect the levels of alternation exhibited. This suggestion was further confirmed by Spearman rho correlations between activity and alternation

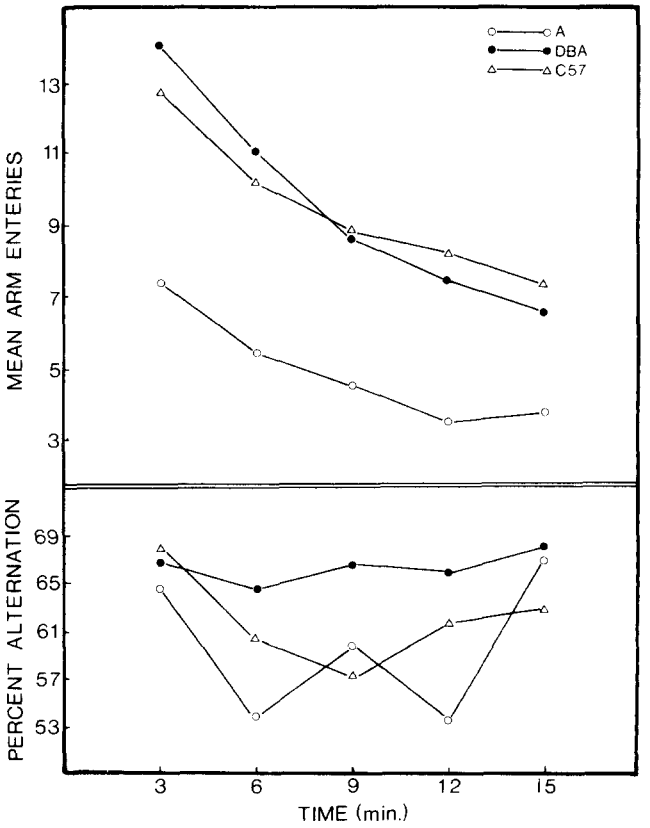

FIG. 1. Mean arm entries and percent spontaneous alternation over five 3 min periods in 3 strains of mice.

behavior within each strain. Specifically, activity was found to be a poor predictor of alternation in that the correlations were low and varied (rho = .08 −0.03 and −0.29 for A, DBA/2 and C57BL/6 mice.

Inspection of Fig. 1 clearly illustrates that in addition to a lack of correlation, activity varies over time in a manner different from that of spontaneous alternation. Whereas activity is a monotonic declining function, alternation fluctuates in an unpredictable manner. Additional analysis performed on a trial by trial basis revealed that although the level of alternation declines slightly over time, probably owing to habituation to all arms, there is no systematic pattern to the alternation scores. Fluctuations occurred throughout the testing period regardless of the time spent in a particular arm. Moreover, this analysis revealed no systematic pattern in terms of the probability of an alternation occurring given that the previous trial had been either an alternation or nonalternation.

EXPERIMENT 2

It is clear that spontaneous alternation is independent of baseline activity levels. Moreover, over time alternation does not vary in a predictable manner as does general activity. It is quite possible that separate mechanisms are involved in these habituation processes. For example, it has been demonstrated that antimuscarinics effectively disrupt habituation in an exploratory situation [2] and water approach task (cf. [8]), serotonergic mechanisms alter habitu-

ation to a startle stimulus [9], and serotonergic agents act synergistically with adrenergic mechanisms in modifying spontaneous alternation [24]. In Experiment 2, an attempt was made to determine whether anticholinergics alter habituation in an exploratory task. Typically, habituation has been examined some time after a drug treatment since the drug itself may have motorigenic effects [8]. Thus, in Experiment 2 the motorigenic effects of scopolamine were divorced from its effects on habituation. In Experiment 3 a similar attempt was made in order to evaluate the effects of scopolamine on spontaneous alternation such that the dishabituative effects were not confounded with its possible motorigenic effects.

Although the disinhibitory properties of scopolamine have been demonstrated repeatedly [7,8], it has been observed that such effects are strain dependent [1, 2, 5, 21]. Whereas increased levels of activity are seen in A, DBA/2 and Balb/c mice, either no effect or decreased activity levels are seen among C57BL/6 following scopolamine treatment. Accordingly, in Experiment 2, A, DBA/2 and C57BL/6 mice received treatment with scopolamine to determine whether cholinergic blockade would differentially affect activity and habituation. If scopolamine reduced activity in C57BL/6 mice but retarded the normal decline in activity over time, it would suggest that the motorigenic effects of scopolamine are independent of its dishabituating properties. The dosages selected were based on previous work in this laboratory (1 and 10 mg/kg) which indicated that 1 mg/kg had minimal effects on activity in C57BL/6 but increased activity in A and DBA/2 mice, whereas the 10 mg/kg dosage slightly increased activity in A mice but retarded activity in the C57BL/6 strain. Thus, the effects of the drug on activity could be varied both between and within strains.

A second question dealt with in Experiment 2 concerned the disinhibitory nature of scopolamine. Specificially, it is well known that shock induces response inhibition and that scopolamine deters these inhibitory tendencies [3, 4, 6, 7]. It was previously observed that although scopolamine does not increase general activity in C57BL/6 mice, it does reduce response inhibition elicited by shock in this strain [5]. Thus in Experiment 2 mice received shock after habituation in order to replicate the previously observed data. If scopolamine deters shock-induced suppression as well as habituation, it might suggest that both these inhibitory tendencies are subserved by a common mechanism.

METHOD

Animals

A total of 90 mice from each of 3 strains (A/J, DBA/2J and C57BL/6J) were used. Mice were bred from stock obtained from the Jackson Laboratory, and were tested between 60 and 90 days of age.

Apparatus

The apparatus consisted of a clear Plexiglas open field measuring 30 X 30 X 30 cm, with a grid floor made up of 0.23 cm stainless steel rods spaced 0.83 cm apart. Footshock of 300 mA could be delivered through the grid floor from a high voltage – high resistance source. The grid floor was wired through a diode bridge connecting every fourth bar in an effort to reduce the probability of a mouse finding 2 bars of the same polarity. The floor beneath the grid was divided into 7.5 X 7.5 cm squares, thus demarcating the open field into 16 equal sized squares.

Procedure

Mice of each strain (n = 10) received intraperitoneal injection of either scopolamine hydrobromide 1.0 mg/kg or 10.0 mg/kg in a 0.5 mg/ml solution, or physiological saline 2 ml/kg. Ten minutes following injection mice were individually placed in the test chamber and activity (defined in terms of square crossings in which a crossing consisted of the mouse placing all four legs in a particular square) was recorded. Following the 10 min. period a single 2 sec shock (300 mA) was delivered. Following shock, activity was again recorded for a 10 min period exclusive of the 10 sec period immediately following shock. The square crossing procedure had previously been found to produce better than 98 percent agreement between raters.

RESULTS AND DISCUSSION

The mean number of square crossings over 10 two min periods as a function of Strain and Drug Treatment are shown in Fig. 2. Analysis of variance of the number of squares crossed revealed a significant Strains X Drug X Time interaction, $F(36,729) = 5.11$, $p<0.01$. Newman Keuls multiple comparisons ($\alpha = 0.05$) showed that in the saline condition C57BL/6 mice were more active than DBA/2 mice, which in turn were more active than mice of the A strain. Each strain exhibited a monotonic decline in activity during the preshock period. In absolute terms the decline was greater in C57BL/6 than in A or DBA/2 mice. However, proportional to the level of activity during the first 2 min period, the decline in activity is greater in A and DBA/2 mice than in C57BL/6. The introduction of shock resulted in response inhibition in each strain with C57BL/6 maintaining higher levels of activity than either of the other strains. The shock induced decline in activity is not statistically apparent in A mice owing to floor effects in the level of preshock activity.

Turning to the effects of scopolamine, consistent with other reports [1, 2, 5, 21] at the 1 mg/kg dosage general activity was increased in both A and DBA/2 mice, but had relatively small effects on mice of the C57BL/6 strain. When the data are examined over time it is evident that in DBA mice the typical decline in activity was abated with the scopolamine treatment. In A and C57BL/6 mice absolute levels of activity were found to decline equally in saline and scopolamine treated animals. With the 10 mg/kg dosage activity was increased in A mice; however, less so than with 1 mg/kg of scopolamine. In DBA/2 mice 10 mg/kg had no effect on activity levels, and in the C57BL/6 strain this dosage significantly retarded activity relative to saline treated animals. Interestingly though, the drug treatment effectively diminished the rate of decline of activity in C57BL/6 mice. This was clearly not due to a floor effect, as these animals still exhibit a relatively high level of activity. This particular finding suggests that the effects of scopolamine on activity levels are independent of the effects on habituation rate.

Following shock, the scopolamine treatment abated the inhibition which is typically seen in saline animals. Of prime importance here is the fact that this was the case in C57BL/6 mice at both dosages. Clearly, the drug can have

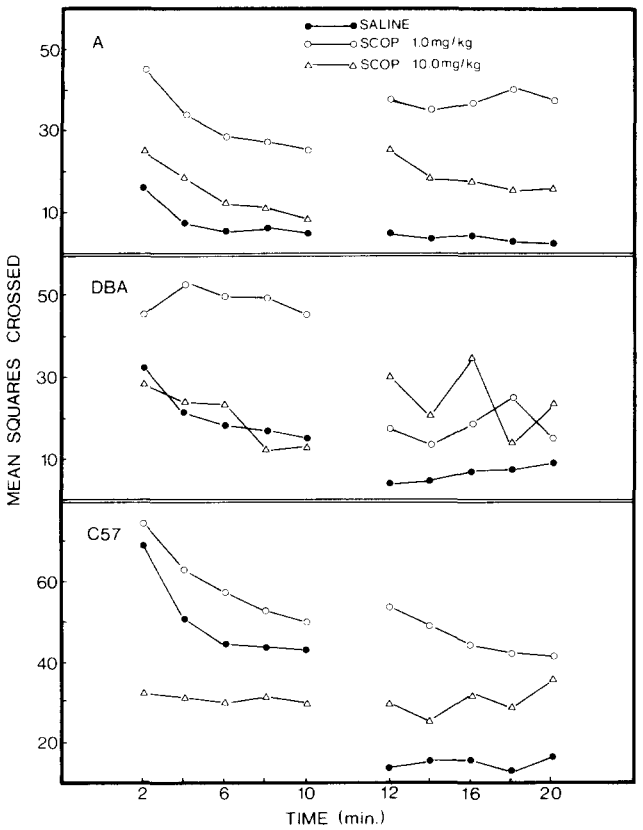

FIG. 2. Mean square crossings in 3 strains of mice as a function of drug treatments. Note: Preshock activity is seen during the first 10 min and post shock activity during the latter 10 min.

potent effects on performance, but this is dependent upon the specific experimental conditions. Where response inhibition is present, either through habituation or following shock treatment, cholinergic blockade effectively eliminates inhibition. It might be the case that because C57BL/6 has relatively low levels of choline acetyltransferase and acetylcholinesterase [12,19] and thus probably low levels of ACh as well, scopolamine is relatively ineffective in increasing activity in most situations. If ACh levels are increased as has been observed with shock treatment [16] and possibly even habituation, the disinhibitory effects of scopolamine emerge. Given the consonant effects of scopolamine on habituation and shock-induced suppression, it may be the case that both these behaviors are subserved by some common mechanisms.

EXPERIMENT 3

The results of Experiment 2 suggest that habituation of locomotor activity involves cholinergic action, and that the dishabituation effects of scopolamine are not due to the possible motorigenic effects of the drug. In Experiment 3 an attempt was made to determine whether spontaneous alternation would likewise be modified by scopolamine, and that these effects are not dependent on activity changes induced by scopolamine. Specifically, it has been demonstrated repeatedly that scopolamine disrupts spontaneous alternation. Yet, the possibility exists that this disruption is due to changes in the levels of general activity produced by scopolamine. Experiment 1 demonstrated that general activity does not affect spontaneous alternation, but it might be the case that this is true only in the absence of drug treatments. When activity is modified by drug treatments, then spontaneous alternation might be altered. Thus in Experiment 3, scopolamine effects were examined in the three strains employing a 10 mg/kg dosage, such that general activity would be increased in A mice, remain unaltered in DBA/2 and decreased in C57BL/6 mice. The data of Experiment 2 suggest that although scopolamine may not affect general activity, habituation rate may well be decreased. Thus, it was expected that scopolamine would disrupt spontaneous alternation regardless of the effects on activity level.

METHOD

Animals and Apparatus

A total of 60 mice, represented equally from 3 strains (A/J, DBA/2J and C57BL/6J) were tested at 60–90 days of age. The apparatus was the same as that used in Experiment 1.

Procedure

Mice received intraperitoneal injections of either scopolamine hydrobromide (10 mg/kg in a 0.5 mg/ml solution) or physiological saline (2 mg/kg). Ten min after injection mice were tested in the spontaneous alternation. The procedure was the same as that described in Experiment 1.

RESULTS AND DISCUSSION

The percent spontaneous alternation score and the number of animals alternating on the second arm entry as a function of the Drug Treatment and strain are shown in Fig. 3. Analysis of the number of alternations over the 15 min test period revealed that in the saline condition the frequency of alternation exceeded chance levels ($\chi^2 = 8.39$, 17.93 and 13.47, $df = 1$, $p<0.05$ for A, DBA/2 and C57BL/6 mice); whereas in the scopolamine condition, alternation frequency did not exceed chance. Analysis of variance of the percent alternation yielded only a significant Drug effect, $F(1,54) = 13.47$, $p<0.01$. Neither the strain or Strain X Drug interaction approached significance ($F<1$). Inspection of Fig. 3 also shows comparable results for the number of subjects alternating on the second trial. Clearly, scopolamine effectively reduced the frequency of alternation. The fact that the drug differentially affects activity in the three strains rules out the possibility that scopolamine-induced reduction in alternation is due to changes in levels of general activity. It seems that spontaneous alternation was modified by changes in ACh activity per se.

GENERAL DISCUSSION

Taken together, the results of the present investigation revealed that (1) Differences in general activity are not related to performance in a free running spontaneous alternation task. This conclusion is derived from three sources. Namely, strains which differ in levels of activity all showed comparable levels of alternation; whereas activity levels show a monotonic decline over a 15 min period, alternation levels are variable and do not follow the course for habitua-

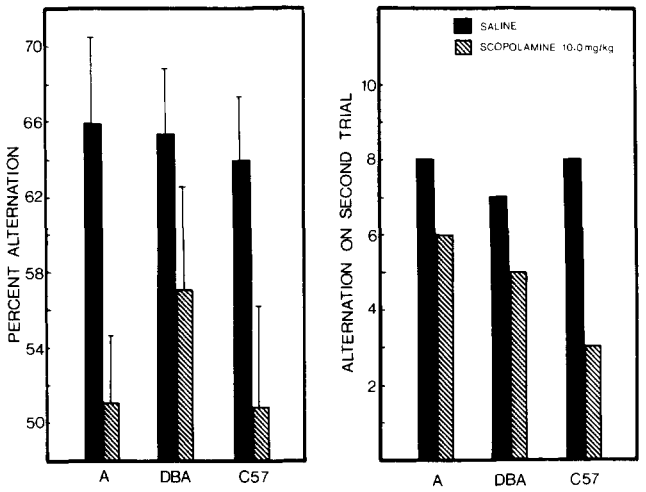

FIG. 3. Percent alternation (plus standard error) over 15 min, and number of animals alternating on the second trial as a function of Strain and Drug Treatment.

tion of general activity; within each strain correlations between activity and alternation are low and vary for the three strains employed. (2) Scopolamine differentially affects activity in the three strains of mice. Low dosages (1 mg/kg) increase activity in A and DBA/2 mice, but have only a small effect in C57/6. High dosages (10 mg/kg) produced a small but significant increase in activity among A mice, had negligible effects in DBA/2, and retarded general activity in C57/6. Nevertheless, scopolamine eliminated the normal decline in activity over time in C57/6 mice. It seems that scopolamine effects on activity levels may be independent of changes in habituation. (3) Finally, scopolamine induced changes in activity levels are not responsible for the drug's effects on spontaneous alternation. Specifically, although scopolamine had differential effects on activity in the 3 strains of mice, spontaneous alternation was equally eliminated in each strain.

It seems that as previously observed, blockade of ACh action effectively eliminates alternation behavior [10, 11, 18, 24] presumably by disruption of habituation. It is interesting that in most pharmacological studies of habituation, animals are placed into a particular situation following drug or saline treatment and tested sometime later in the absence of the drug treatment [8]. This particular procedure is employed because of the potential confound introduced by the motorigenic effects of the drug. The present investigation demonstrates that spontaneous alternation is not subject to such confounds since the behavior in question is independent of the actual level of activity of the animal. This is true regardless of whether analysis is performed on alternation of individual subjects or on the percent of total alternations (cf. [24]). Moreover, the present investigation also presents a potentially useful tool, namely that of strain comparisons, in examining the independence or dependence of specific behaviors in psychopharmacological studies.

It is interesting that although scopolamine differentially affects general activity in the three strains of mice, the drug treatment uniformly reverses shock induced response inhibition as well as behaviors thought to be dependent on habituation. It may well be the case that these behaviors are subserved by some common mechanisms. This is not to say, of course, that these are the only mechanisms involved. After all, it is clear that other neurotransmitters, e.g., serotonin, are involved in spontaneous alternation [24], while transmitters such as dopamine and norepinephrine are involved in stress situations [15, 17, 25]. Indeed, the very fact that the three strains differ in levels of cholinesterase and choline acetyltransferase [12, 19, 23], yet show comparable levels of habituation and differential levels of shock-induced immobility, implies the involvement of other transmitters in modulating these behaviors. In any event, it is clear from the present data that the responses biases elicited by scopolamine are not only strain specific [21], but also interact with stimulus factors.

REFERENCES

1. Abeelen, J. H. F. V., L. Gilissen, T. Hanssen and A. Lenders. Effects of intrahippocampal injections with methylscopolamine and neostigmine upon exploratory behavior 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 behavior in mice. *Psychopharmacologia* **19**: 324–328, 1970.
3. Anisman, H. Differential effects of scopolamine and d-amphetamine on avoidance: strain interactions. *Pharmac. Biochem. Behav.* **3**: 1975, in press.
4. Anisman, H. Cholinergic mechanisms and alternations in behavioral suppression as factors producing time dependent changes in avoidance performance. *J. comp. physiol. Psychol.* **83**: 465–477, 1973.
5. Anisman, H., D. Wahlsten and L. Kokkinidis. Effects of scopolamine and d-amphetamine on activity before and after shock in three strains of mice. *Pharmac. Biochem. Behav.* 1975'
6. 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.
7. Bignami, G. and N. Rosic. The nature of disinhibitory phenomena caused by central cholinergic (Muscarinic) blockade. In: *Advances in Neuropharmacology*, edited O. Vinar, Z. Votava and P. B. Bradley. Amsterdam: North-Holland Publishing Co., 1971.
8. Carlton, P. L. Brain-acetylcholine and inhibition. In: *Reinforcement and Behavior*, edited by J. T. Tapp. New York: Academic Press, 1969, pp. 286–327.
9. Carlton, P. L. and C. Advokat. Attenuated habituation due to parachlorophenylalanine. *Pharmac. Biochem. Behav.* **1**: 657–663, 1973.
10. Drew, W. G., L. L. Miller and E. L. Baugh. Effects of Δ^9-THC, LSD-25 and scopolamine on continuous spontaneous alternation in the Y-maze. *Psychopharmacologia* **32**: 171–182, 1973.
11. Douglas, R. J. and R. L. Isaacson. Homogeneity of single trial response tendencies and spontaneous alternation in the T-maze. *Psychol. Rep.* **16**: 87–92, 1965.
12. Ebel, A., J. C. Hermetet and P. Mandel. Comparative study of acetylcholinesterase and choline acetytransferase enzyme activity in brain of DBA and C57 mice. *Nature* **242**: 56–57, 1973.

13. Egger, G. J., P. J. Livesey and R. G. Dawson. Ontogenetic aspects of central cholinergic involvement in spontaneous alternation behavior. *Devl Psychobiol.* **6:** 289–299, 1973.
14. Innes, I. R. and M. Nickerson. Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them (Sympathomimetic drugs). In: *The Pharmacological Basis of Therapeutics.* (3rd ed.) edited by L. S. Goodman and A. Gilman. New York: Macmillan, 1965, pp. 477–520.
15. Javoy, F., A. M. Thierry, S. S. Kety and J. Glowinski. The effect of amphetamine on the turnover of brain norepinephrine in normal and stressed rats. *Communs Behav. Biol.* **1A:** 43–48, 1968.
16. Karczmar, A. G., C. L. Scudder and D. L. Richardson. Interdisciplinary approach to the study of behavior in related mice types. In: *Chemical Approaches to Brain Function,* edited by S. Ehrenpreis and I. J. Kopin. New York: Academic Press, 1973.
17. Korf, J., G. K. Aghajanian and R. H. Roth. Increased turnover of norepinephrine in the rat cerebral cortex during stress: Role of the locus coeruleus. *Neuropharmacology* **12:** 933–938, 1973.
18. Leaton, R. N. and M. J. Utell. Effects of scopolamine on spontaneous alternation following free and forced trials. *Physiol. Behav.* **5:** 331–334, 1970.
19. Mandel, P. and A. Ebel. Correlations between alternation in cholinergic system and behavior. In: *Neurochemistry of Cholinergic Receptors,* edited by E. de Robertis and J. Schadts. New York: Raven Press, 1974.
20. Messeri, P., A. Oliverio and D. Bovet. Relations between avoidance and activity. *Behav. Biol.* **7:** 733–742, 1972.
21. Oliverio, A., B. E. Eleftheriou and D. W. Bailey. Exploratory activity: Genetic analysis of its modification by scopolamine and amphetamine. *Physiol. Behav.* **10:** 893–899, 1973.
22. Payne, R. and D. C. Anderson. Scopolamine-produced changes in activity and in the startle response: Implications for behavioral activation. *Psychopharmacologia* **12:** 83–90, 1967.
23. Pryor, G. T., K. Schlesinger and W. H. Calhoun. Differences in brain enzymes among five inbred strains of mice. *Life Sci.* **5:** 2105–2111, 1966.
24. Swonger, A. K. and R. H. Rech. Serotonergic and cholinergic involvement in habituation of activity and spontaneous alternation of rats in a Y maze. *J. comp. physiol. Psychol.* **81:** 509–522, 1972.
25. Welch, B. L. and A. S. Welch. Control of brain catecholamines and serotonin during acute stress and after d-amphetamine by natural inhibition of monoamine oxidose: An hypothesis. In: *Amphetamines and Related Compounds,* edited by E. Costa and S. Garattini. New York: Raven Press, 1970.