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Cholinergic Influences on Escape Deficits Produced by Uncontrollable Stress

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Abstract. A series of experiments assessed the potential role of acetylcholine (ACh) in the escape interference produced by inescapable shock. Treatment with the anticholinesterase, physostigmine, succesfully mimicked the effects of inescapable shock. That is, the drug disrupted performance when escape was prevented for 6 s on any given trial, thereby necessitating sustained active responding. When escape was possible upon shock onset, the drug treatment did not influence performance. The centrally acting anticholinergic scopolamine hydrobromide antagonized the effects of physostigmine, and when administered prior to escape testing antagonized the disruptive effects of previously administered inescapable shock. In contrast, the peripherally acting agent scopolamine methylbromide did not influence the effects of these treatments, suggesting that the effects of physostigmine and inescapable shock involved central ACh changes. Scopolamine hydrobromide administered prior to inescapable shock did not prevent the escape interference from subsequently appearing, but this effect could not be attributed to state dependence. It was argued that the interference of escape following uncontrollable stress was due to non-associative motor deficits. Alterations of the escape deficits by scopolamine were due to elimination of the motor disruption.

Key words: Stress – Acetylcholine – Scopolamine – Physostigmine

Following exposure to uncontrollable shock, rats and mice exhibit marked deficits of avoidance and escape performance (Anisman et al. 1978; Maier and Seligman 1976; Weiss et al. 1976). These deficits are characterized by frequent failures to escape shock, interspersed with successful escape responses. Since the performance deficits do not occur following initial exposure to escapable shock, it has been argued that failure to control the initial stress, rather than the aversive stimulation per se, is the essential feature in determining the behavioral disruption (see reviews in Maier and Seligman 1976; Weiss et al. 1976). While some investigators contend that the interference results from cognitive changes, i.e., learned helplessness (Maier and Seligman 1976), others have argued that the behavioral disruption is due to a variety of neurochemical changes invoked by stress (see Anisman and Sklar 1979; Anisman et al. 1980; Weiss et al. 1975). Consistent with this proposition, it has been shown that exposure to uncontrollable stress produces norepinephrine (NE) depletion, whereas escapable stress either increases NE concentration or has no effect (Anisman et al. 1980; Weiss et al. 1970, 1976). Indeed, the effects of inescapable shock on escape behavior are mimicked by treatments that deplete NE, and the escape deficits can be prevented by pharmacological treatments that increase NE levels (Anisman and Sklar 1979; Anisman et al. 1979, 1980; Glazer et al. 1975).

In addition to NE, there has been some indication that dopamine (DA) depletion and increases of acetylcholine (ACh) are also involved in the behavioral deficits. Uncontrollable stress will result in increased DA turnover in the nucleus accumbens (Thierry et al. 1976) and depletion of DA in the arcuate nucleus of the hypothalamus (Kobayashi et al. 1976). Moreover, drugs that deplete DA or block DA receptors mimic the effects of inescapable shock (Anisman et al. 1979), while administration of DA stimulants effectively prevents or alleviates the behavioral deficits, respectively (Anisman and Sklar 1979; Anisman et al. 1979, 1980). In the case of ACh, stress was shown to increase brain concentrations of this neurotransmitter (Karczmar et al. 1973; Zajaczkowska 1975), and there is some suggestion that stress controllability is a contributing factor in this respect (Karczmar et al. 1973; see review in Anisman 1978). The anticholinergic scopolamine, administered prior to testing, eliminated the escape deficits otherwise observed (Anisman et al. 1979); however, it is not known whether scopolamine administered prior to inescapable shock would prevent later escape deficits. Likewise, it is not clear whether the effects of scopolamine are due to state dependence or to peripheral effects of the drug. The present investigation was undertaken to assess more extensively the effects of cholinergic manipulations on deficits of escape behavior produced by uncontrollable stress.

Experiment 1

Administration of the antimuscarinic (anticholinergic) scopolamine hydrobromide was previously shown to eliminate the disruptive effects of previously applied inescapable shock (Anisman et al. 1979). Experiment 1 repeated this experiment and determined whether scopolamine methylbromide, which lacks the central action of scopolamine hydrobromide, would eliminate the interference effect.

Materials and Methods

Subjects. A total of 48 naive Swiss-Webster mice, 65–75 days of age, served as subjects. Mice were obtained from Charles River Breeding

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Laboratories, Boston, Mass., and were acclimatized to the laboratory for at least 7 days prior to being used for experimental purposes. Mice were housed in groups of five and permitted continuous access to food and water.

Apparatus. Escape training was carried out in four identical Plexiglas boxes, the interior dimensions of which were 26.4 cm long, 9.0 cm wide, and 15.5 cm high. The roof of the apparatus, the grid floor and its wiring, and the nature of the shock sources were the same as those of the preshock boxes. Each shuttlebox was divided into two compartments by a stainless-steel wall, partially made up of a solenoid-controlled horizontally movable stainless-steel gate. In the open gate position a stainless-steel hurdle 1.0 cm in height separated the compartments and a 7.0 × 7.7 cm space permitted access to the adjacent compartment. This partition and hurdle, as well as the stainless-steel plates which lined the interior walls of the boxes, were connected in series with the grid floor. Situated 1.5 cm on either side of each hurdle were two infrared photodetector units 1.0 and 4.0 cm above the grid floor. The photodetectors were wired such that if the beams on both sides of the hurdle were crossed simultaneously, as would occur when the mouse was halfway across the hurdle, the cells would not trigger. When the mouse crossed the beam in the shock compartment and broke the beam on the safe side only, the cell was triggered. An additional set of photocells was located 2.5 cm from the end walls, 1.0 cm above the grid floor. Thus, if the mouse jumped over the first set of photodetectors, the latter cells were invariably triggered. The four shuttleboxes were operated by a microcomputer system constructed at Carleton University Science Workshops. Latencies were recorded on each trial independently for each box, and block latencies calculated over five trials. The shuttleboxes were housed in sound-attenuated chambers.

Procedure. Mice were individually placed in the preshock boxes for a 1.1 h period. During this time half the mice received 60 inescapable shocks of 150 μA (60 Hz, AC) of 6 s duration at intervals of 60 s. The remaining mice did not receive any shock. Mice were then housed individually until escape testing, conducted 24 h after termination of the initial stress session. Mice of each shock group were subdivided and 15 min prior to escape testing injected IP with either saline, scopolamine hydrobromide (1.0 mg/kg free base), or scopolamine methylbromide (1.0 mg/kg free base). The drugs were dissolved in distilled water in a concentration of 1 mg/ml.

Escape testing consisted of mice being individually placed in the suttleboxes, 30 s after which training commenced. On each trial a shock was delivered, but the gate separating the compartments remained closed for 6 s thereby preventing escape. The gate was then opened, permitting entry into the adjacent shock-free compartment. Upon crossing a hurdle the gate was closed and the latency recorded. If an escape response was not made within 24 s of gate opening, the trial was terminated. The interval between trials was 30 s. It is noteworthy that the escape delay procedure was employed because deficits of performance are not typically observed when escape is possible immediately upon shock onset. The procedures described here were previously shown to induce escape deficits comparable to those noted in other laboratories (cf. Anisman et al. 1978; Maier and Seligman 1976; Weiss et al. 1976).

Results and Discussion

As previously observed in mice (Anisman et al. 1978, 1979) and rats (Maier and Seligman 1976; Weiss et al. 1976), exposure to inescapable shock subsequently increased the latency to escape from shock [$F(1,42) = 18.12$, $P < 0.001$]. Moreover, performance was also found to be modified by the drug treatment [$F(2,42) = 9.57$, $P < 0.001$]. As seen in Fig. 1, and confirmed by Newman-Keuls multiple comparisons ($\alpha = 0.05$), treatment with scopolamine hydrobromide prior to escape testing produced a marked reduction of escape latencies, whereas the peripherally acting anticholinergic was without effect on performance. Although scopolamine hydrobromide enhanced performance irrespective of the initial stress treatment, Fig. 1 shows the enhancement of performance to be somewhat greater in preshocked mice. The present results thus confirm our previous findings concerning the effects of scopolamine hydrobromide on escape behavior (Anisman et al. 1979), and suggest that the effectiveness of the drug depends on its centrally acting properties.

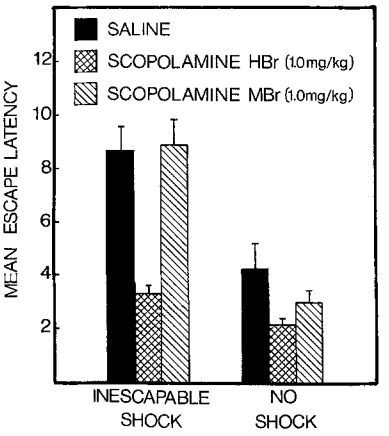

Fig. 1. Mean (± SEM) escape latencies over 25 trials among mice exposed to 60 inescapable shocks or no shock, and tested in the escape task 24 h later. Injection of either scopolamine hydrobromide (*HBr*) scopolamine methylbromide (*MBr*) or saline was administered 0.25 h prior to test (Experiment 1)

Experiment 2

Administration of a centrally acting anticholinergic prior to escape testing effectively antagonized the disruptive influence of prior uncontrollable stress. Experiment 2 was conducted to determine whether scopolamine administered prior to the inescapable shock session would prevent the interference from occurring.

Materials and Methods

Subjects and Apparatus. Forty-eight naive Swiss-Webster mice were used. The subject characteristics and apparatus specifications were the same as those described in Experiment 1.

Procedure. Mice were assigned to one of three conditions and injected IP with either scopolamine hydrobromide (1.0 mg/kg), scopolamine methylbromide (1.0 mg/kg), or saline. Fifteen minutes afterward mice were individually placed in the preshock boxes for a 1.1 h period. Half the mice in each drug condition ($N = 8$/group) received 60 inescapable shocks (150 μA, 6 s duration) at interval of 60 s, whereas the remaining mice were not shocked. Following the initial shock session mice were housed individually until shuttle testing, which was conducted 24 h later. The escape testing procedure was the same as that described in Experiment 1.

Results and Discussion

Exposure to inescapable shock increased the latency to escape from subsequent shock [$F(1,42) = 10.00$, $P < 0.01$] (see Fig. 2). However, neither the drug treatment main effect nor the drug treatment × shock interaction approached statistical significance ($F < 1$). It seems that although scopolamine hydrobromide effectively antagonized the effects of previously administered inescapable shock (Experiment 1), it was ineffective in preventing the adverse consequences of stress when the drug was given prior to the inescapable shock session. This finding stands in marked contrast to our own previous findings concerning the effects of catecholamine

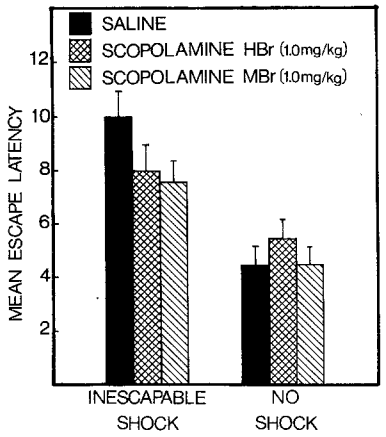

Fig. 2. Mean (± SEM) escape latencies over 25 trials among mice exposed to 60 inescapable shocks or no shock, and tested in the escape task 24 h later. Injection of either scopolamine hydrobromide (*HBr*), scopolamine methylbromide (*MBr*), or saline was administered 0.25 h prior to the inescapable shock session (Experiment 2)

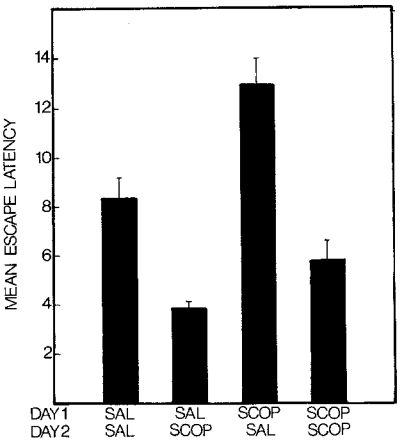

Fig. 3. Mean (± SEM) escape latencies over 25 trials among mice exposed to inescapable shock and tested in the escape task 24 h later. Mice received either scopolamine hydrobromide or saline 0.25 h prior to inescapable shock and 0.25 h prior to test (Experiment 3)

agonists (Anisman and Sklar 1979; Anisman et al. 1979, 1980). In particular, L-dopa, apomorphine, and clonidine were all effective in antagonizing the disruptive effects of previously administered inescapable shock, and in preventing the effects of to-be-administered shock.

Although our previous results (Anisman et al. 1979) were suggestive of a DA-ACh balance in mediating the effects of inescapable shock, the role of these two transmitters can be distinguished from one another to some extent. Inasmuch as ACh manipulations do not prevent the development of the interference, the possibility should be considered that ACh changes, although contributing to the interference, are secondary to DA changes that might be produced by shock. Indeed, the increase of ACh does not occur until some time after stress exposure (Saito et al. 1976; Zajaczkowska 1975). In contrast, the stress has effects on NE and DA levels that are detectable upon stress termination, and further, catecholamine stimulants prevent the escape deficits. These facts suggest that DA and NE play a primary role in mediating the interference.

Experiment 3

The antagonism of the escape deficits by scopolamine administered prior to escape testing in Experiment 1 and 2 might have been a consequence of asymmetrical state dependence (see review in Barry 1978). That is, since the drug state at the time of test differed from that prevalent during the inescapable shock session, difficulties in memory retrieval may have been responsible for the elimination of the escape interference. In order to test this possibility, mice received initial training and testing under conditions where the drug states were the same (saline-saline; scopolamine-scopolamine) or different (saline-scopolamine; scopolamine-saline).

Materials and Methods

Subjects and Apparatus. Forty naive male Swiss-Webster mice served as subjects. The subject characteristics and the apparatus specifications were the same as those described in Experiment 1.

Procedure. Mice received IP injections of either scopolamine hydrobromide (1.0 mg/kg) or saline, followed 15 min later by exposure to 60 inescapable shocks (150 μA, 6 s duration) applied at 60 s intervals. Mice were then housed individually until the time of testing, conducted 24 h after the initial stress session. Fifteen minutes prior to testing, half the mice in each drug condition ($N = 10$/group) received IP injections of scopolamine hydrobromide (1.0 mg/kg), whereas the remaining mice received saline. The procedure used in the subsequent escape test was the same as that described in Experiment 1.

Results and Discussion

The mean escape latencies for each group are shown in Fig. 3. Analysis of variance revealed that scopolamine administered prior to testing reduced the latency to escape [$F(1,36 = 18.03$, $P < 0.01$]. In contrast, mice that received scopolamine on Day 1 exhibited longer escape latencies [$F1,36) = 6.86$, $P < 0.05$] than saline treated animals. These results confirm the findings of Experiment 2, in that scopolamine administered prior to inescapable shock did not reduce subsequent latencies to escape relative to nondrugged mice. Moreover, the finding that performance of mice that received scopolamine prior to both inescapable shock and testing exhibited more rapid escape latencies than mice that received saline on both ocassions, suggests that the behavioral effect of the drug was probably not a result of state dependence.

Experiment 4

Although scopolamine effectively eliminated the effects of previously administered inescapable shock, it did not prevent the effects of inescapable shock administered shortly after drug treatment. Experiment 4 determined whether the absence of a carryover effect was unique to the inescapable shock paradigm, or whether the lack of a between days carryover effect would occur even when the paradigm did not involve inescapable shock. In Experiment 4 mice received inescapable shock or no treatment, and were then tested in the escape task on 2 successive days to examine the immediate and carryover effects of scopolamine.

Materials and Methods

Subjects and Apparatus. Eighty naive male Swiss-Webster mice were employed. The subject particulars and the apparatus employed were the same as those of Experiment 1.

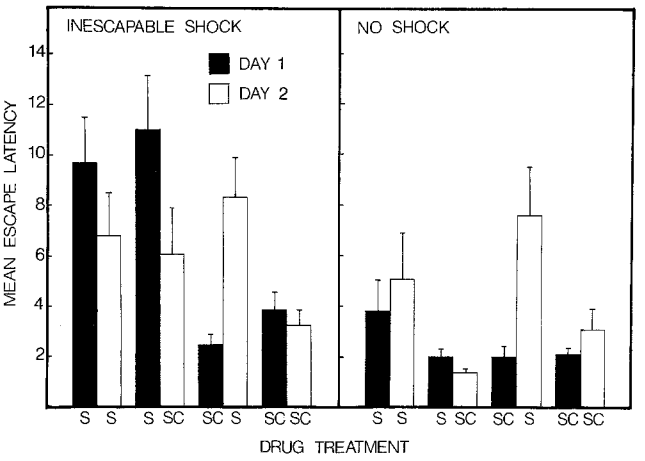

Fig. 4. Mean (± SEM) escape latencies over 25 trials on 2 successive days among mice exposed to inescapable shock or no shock 24 h prior to the first test session. On each of the 2 test days mice received an injection of either scopolamine hydrobromide (*SC*) or saline (*S*) 0.25 h prior to test (Experiment 4)

Procedure. Half the mice were exposed to 60 inescapable shocks (150 μA, 6 s duration) at 60 s intervals, while the remaining mice spent an equivalent uneventful period in the preshock boxes. Mice were tested in the shuttle task as described in Experiment 1, 24 h after the initial stress session. Fifteen minutes prior to testing, half the mice received an IP injection of scopolamine hydrobromide (1.0 mg/kg) while the remaining mice received saline. Mice were retested in the shuttle test 24 h after the first shuttle test. Half the mice in the original scopolamine group received a second injection of scopolamine hydrobromide (1.0 mg/kg) 15 min prior to testing while the remaining mice received saline. Likewise, half the mice that received saline prior to the first test session received saline again, while the remaining mice received scopolamine hydrobromide (1.0 mg/kg).

Results and Discussion

The mean escape latency on each day as a function of the drug treatment is shown in Fig. 4. Analysis of variance yielded a Drug treatment on Day 1 × Drug treatment on Day 2 × Days interaction [$F(1,72) = 5.73$, $P < 0.05$]. Newman-Keuls multiple comparisons ($\alpha = 0.05$) revealed that relative to saline treated mice, enhanced performance was seen among animals that received scopolamine on Day 2. If the drug was administered on Day 1, enhanced performance was seen on that day. Upon testing following saline injection on Day 2, however, the response enhancement on Day 1 was entirely absent. Indeed, mice that received scopolamine on Day 1 followed by saline on Day 2 exhibited latencies on the latter day that were significantly slower than those of mice that received saline throughout.

It appears that the beneficial effects of scopolamine on escape behavior will be evident only so long as animals are tested in the drug state. If mice are retested in the nondrug condition, response enhancements that had previously been observed are no longer evident. In the inescapable shock condition, mice that received scopolamine on both test days exhibited performance superior to that of mice that received scopolamine only on the second test day, but this effect was not significant. Moreover, a similar effect was not witnessed in Experiment 3 (see Fig. 3). Taken together, it appears that the effects of scopolamine on escape behavior were probably not due to state dependent effects. It might be argued that scopolamine administered on Day 1 disrupted learning or memory, thereby increasing the response latencies on Day 2 among mice tested with saline. However, in both Experiments 3 and 4 the latencies of mice in this group actually exceeded those seen on Day 1 in saline treated mice (see performance of no shock animals in Fig. 4), making such a possibility very unlikely. The source for the Day 2 performance disruption induced by scopolamine administered on Day 1 cannot be deduced from the available data.

As observed in Experiments 1 and 2, inescapable shock disrupted subsequent performance [$F(1,72) = 12.99$, $P < 0.001$]. In addition, analysis of variance indicated that the effectiveness of inescapable shock in disrupting performance varied with the Day of Testing and Drug administered on Day 1 [$F(1,72) = 4.92$, $P < 0.05$], as well as Day of Testing, Drug administered on Day 2 and Blocks of Trials [$F(4,288) = 3.38$, $P < 0.01$]. Newman-Keuls multiple comparisons ($\alpha = 0.05$) were conducted between the means of the simple effects comprising these interactions. These comparisons revealed that the effectiveness of the inescapable shock in disrupting performance was greater on Day 1 than on Day 2. Scopolamine administered on Day 1 enhanced performance on that day, such that performance of preshocked mice that received the drug exhibited response latencies comparable to nonshocked mice. Upon testing on Day 2 the effects of the previously administered drug were absent. When scopolamine was administered on Day 2 performance was enhanced among mice that had previously received inescapable shock.

Experiments 5a—5c

It has been argued that if stress-induced changes of a particular neurotransmitter are causally related to the escape interference, then it should not only be possible to eliminate the interference by pharmacological manipulations, but it should also be possible to mimic the shock-induced interference by pharmacological means. Indeed, in the case of catecholamine manipulations, increasing DA or NE levels antagonized the interference, whereas drug-induced depletions mimicked the effects of inescapable shock (Anisman et al. 1979). Experiment 5a was conducted in order to determine whether increasing ACh levels by physostigmine would induce an escape interference like that engendered by inescapable shock. Previous experiments showed that neither inescapable shock nor drug treatments that depleted catecholamines disrupted escape behavior when escape was possible upon shock onset, but were quite pronounced when escape was not possible immediately upon shock onset (Anisman et al. 1979). Accordingly, in Experiment 5a mice were tested using a 6 s escape delay procedure (see Experiments 1–4). In Experiment 5b, escape was possible upon shock onset. Experiment 5c assessed the effects of scopolamine hydrobromide and scopolamine methylbromide on the interference of escape behavior elicited by physostigmine.

Materials and Methods

Subjects and Apparatus. Experiments 5a–c involved 40, 20, and 40 naive male Swiss-Webster mice, respectively. The subject characteristics and the apparatus details were the same as those described in Experiment 1.

Procedure. Mice of Experiment 5a were assigned to four treatment groups and injected IP with either physostigmine salicylate (0.05, 0.10 or

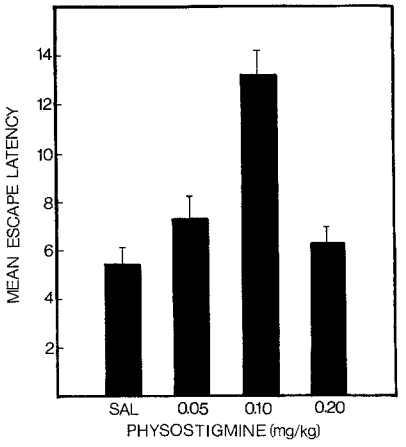

Fig. 5. Mean (± SEM) escape latencies over 25 trials among mice treated with various doses of physostigmine salicylate 10 min earlier (Experiment 5a)

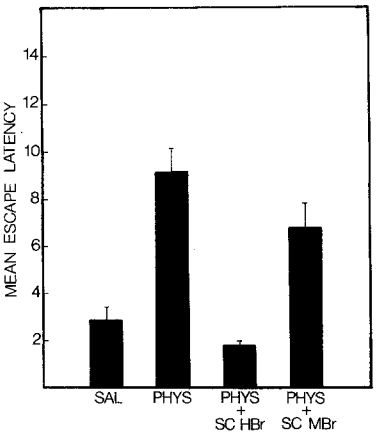

Fig. 6. Mean (± SEM) escape latencies over 25 trials among mice treated with saline, physostigmine (0.1 mg/kg), a combination of physostigmine (0.10 mg/kg) plus scopolamine hydrobromide (1.0 mg/kg) or plus scopolamine methylbromide (1.0 mg/kg) (Experiment 5c)

0.20 mg/kg) or saline. Drugs were administered in a volume of 10 ml/kg. Ten minutes after injection mice were tested in the escape task using a 6 s escape delay procedure as described in Experiment 1. In Experiment 5b, mice ($N = 10$/group) received injection of either physostigmine salicylate 0.10 mg/kg (dosage determined from Experiment 5a) or saline. Ten minutes later, mice received 25 shuttle escape trials where escape was possible immediately upon shock onset. Otherwise the procedure was identical to that of Experiment 5a.

In Experiment 5c mice received two IP injections at 5 min intervals. Mice of one group received two injections of saline, (10 ml/kg), the second group received saline followed by physostigmine salicylate (0.10 mg/kg), the third received scopolamine hydrobromide (1.0 mg/kg) and physostigmine (0.10 mg/kg), and the fourth group received scopolamine methylbromide (1.0 mg/kg) and physostigmine (0.10 mg). Escape testing was conducted 10 min after the second injection, using the procedure of Experiment 1.

Results and Discussion

The mean escape latencies for each group of Experiment 5a are shown in Fig. 5. Analysis of variance revealed that the drug treatment influenced response latencies [$F(3, 36) = 5.81$, $P < 0.01$]. Newman-Keuls multiple comparisons ($\alpha = 0.05$) indicated that performance varied in a nonmonotonic fashion as a function of the dosage of physostigmine. Whereas the 0.05 mg/kg dosage had a small nonsignificant effect on performance, the 0.10 mg/kg dosage severely retarded performance. With the highest dosage (0.20 mg/kg) the disruptive influence induced by physostigmine was absent. Such dose dependent effects of physostigmine are not unique, and it is possible that the response enhancements after high doses stem from a functional receptor blockade owing to excessive levels of ACh (see discussions in Bignami and Michalek 1978; Carlton 1969).

In contrast to the effects of physostigmine on escape performance when a 6 s escape delay procedure was used, the results of Experiment 5b indicated that mice in the physostigmine (mean ± SEM = 4.66 ± 0.51) and saline (mean ± SEM = 4.35 ± 0.35) groups displayed comparable response latencies when escape was possible upon shock onset. It seems that the disruptive effects of physostigmine, like those of inescapable shock and catecholamine depleting agents, are apparent only when an escape delay procedure is employed. This finding is consistent with the contention that the escape deficits reflect a difficulty in maintaining sustained active responding to strong stimulation. When an escape response can be accomplished readily (i.e., where sustained response maintenance is not required), then behavioral deficits are not expected (see Anisman et al. 1978, 1979).

Analysis of the response latencies of Experiment 5c indicated that escape performance was influenced by the drug treatment [$F(3, 36) = 5.80$, $P < 0.01$]. Newman-Keuls multiple comparisons ($\alpha = 0.05$) indicated that physostigmine treated mice exhibited longer escape latencies than saline treated animals (see Fig. 6). The disruptive effect of physostigmine was eliminated by treatment with scopolamine hydrobromide, such that mice in this group exhibited response latencies equal to that of saline treated mice and faster than that of mice that received physostigmine alone. In contrast, pretreatment with scopolamine methylbromide did not reduce the escape deficits provoked by physostigmine.

General Discussion

The finding that stress may increase levels of brain ACh (Zajaczkowska 1975), and that failure by the organism to control stress was an important feature in determining such an effect (Karczmar et al. 1973), led to the suggestion that cholinergic mechanisms might be involved in the interference with escape behavior induced by uncontrollable stress (see Anisman 1975). Although the neurochemical data alone provide only correlational evidence for such a supposition, somewhat greater support for a causal relationship between ACh activity and the escape deficits is derived from the pharmacological studies of the present investigation (see also Anisman et al. 1979).

It was argued previously that if the escape interference produced by inescapable shock is due to particular neurochemical changes, then it should be possible to (a) mimic the neurochemical changes induced by shock through pharmacological means, thereby provoking an escape interference, and (b) antagonize the neurochemical effects of shock by drug treatments, resulting in the amelioration of the behavioral deficits that would otherwise be evident. In accordance with such predictions, treatment with the anticholinesterase physostigmine, which is known to increase levels of brain ACh, will induce behavioral deficits reminiscent of those induced by uncontrollable shock. To be

more explicit, we previously observed that over the course of a long duration shock, levels of shock-elicited activity would decline rapidly. Both physostigmine and inescapable shock further magnified the rate of decline of shock-elicited activity, although the levels observed within 1–2 s of shock onset were relatively high (Anisman et al. 1979). The present report shows that physostigmine, like inescapable shock, will disrupt escape performance provided that the task necessitates sustained active responding. That is to say, if escape can be accomplished soon after shock onset (i.e., using a 0 s escape delay procedure), physostigmine will not appreciably influence escape performance. However, a pronounced escape deficit is evident when a 6 s escape delay procedure is used in the escape task. It seems that upon shock onset the high levels of shock elicited activity favor rapid escape latencies, thereby masking potential effects of the previous shock or drug treatments when escape is immediately possible. After several seconds of shock (i.e., when a brief delay is employed) the low levels of shock-elicited activity, particularly in mice that received inescapable shock or pretreatment with physostigmine, favor poor escape behavior and consequently the effects of these treatments are evident.

Consistent with a neurochemical hypothesis, treatment with scopolamine hydrobromide prior to escape training eliminated the disruptive effects of previously administered inescapable shock. This effect seemed to be due to the centrally acting properties of the drug, since the peripherally acting agent, scopolamine methylbromide, did not influence the effects of previously administered inescapable shock. Predictably, the latter agent did not influence the effects of physostigmine, whereas the former agent antagonized the interference produced by the anticholinesterase.

Although scopolamine eliminated the disruptive effects of previously administered inescapable shock, it was ineffective in preventing the escape interference when injected prior to inescapable shock. Indeed, scopolamine administered prior to inescapable shock or prior to escape training on the first of two escape sessions actually disrupted performance of mice when subsequently tested in the nondrug state.

An overview of the literature suggests that the effects of scopolamine on performance in aversive tasks are due to nonassociative changes (Bignami 1976; Bignami and Michalek 1978). However, it has been proposed that behavioral decrements that occur upon drug withdrawal may be due to stimulus change (Barrett et al. 1972). An explanation based exclusively on stimulus change does not adequately account for the results of the present investigation, since scopolamine administered prior to testing eliminated the interference, regardless of the animal's prior drug history. The most parsimonious explanation for the present results is that the interference with escape induced by inescapable shock is due to nonassociative response tendencies (e.g., deficits of response maintenance) and scopolamine eliminated these effects, thereby antagonizing the interference. It is not clear, however, why an anticholinergic is without carryover effects to the nondrug state, as occurs in the case of catecholamine stimulants (Anisman et al. 1979, 1980).

The differential effects of scopolamine and catecholamine stimulants (L-Dopa, apomorphine, clonidine) provide information concerning the mechanisms by which agents such as L-dopa prevent inescapable shock from disrupting performance. Glazer and Weiss (1976a, b) have suggested that depending on the shock parameters, inescapable stress may result in neurochemical change and/or the establishment of learned motor responses that are incompatible with later escape behavior, thus resulting in the behavioral deficit. A further possible argument is that the increase in shock-elicited activity by catecholamine stimulants might prevent the establishment of learned competing motor responses, hence eliminating the escape interference. Inasmuch as scopolamine enhances shock-elicited activity just as L-dopa does (Anisman et al. 1979), such an explanation would also predict that scopolamine would prevent the escape interference. The fact that scopolamine and L-dopa administered prior to inescapable shock differentially influence performance indicates that effects on learned competing motor tendencies are probably not responsible for the effects of L-dopa on escape behavior.

It was previously argued that the long term effects of inescapable shock (i.e., 24 h and beyond) were due to sensitization or conditioning of NE activity (Anisman and Sklar 1979). That is, although the NE depletion induced by shock was relatively transient, re-exposing mice to even a few shocks would restore the amine depletion, and thus would result in deficits of performance even over long intervals between inescapable shock and test. One important condition for the interference to occur is that the initial stress result in NE depletion. Preventing the NE depletion or maintaining high levels of catecholamine receptor activity would prevent the interference from occurring. In light of the fact that the ACh changes induced by stress are not evident until some time after stress termination, e.g., 40–240 min (Saito et al. 1976; Zajaczowska 1975) it is possible that this transmitter is less essential in the induction of the interference. However, modification of ACh activity will influence the behavioral manifestations of previously administered shock. Moreover, it seems that although ACh-DA balances influence escape behavior (Anisman et al. 1979), ACh blockers and catecholamine stimulants cannot be used interchangeably in altering stress provoked behavioral pathology.

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