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Evidence for a Serotonergic Mechanism of the Learned Helplessness Phenomenon

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BROWN, L., R. A. ROSELLINI, O. B. SAMUELS AND E. P. RILEY. *Evidence for a serotonergic mechanism of the learned helplessness phenomenon.* PHARMAC. BIOCHEM. BEHAV. 17(5) 877–883, 1982.—The present experiments examined the role of the serotonergic system in the learned helplessness phenomenon. In Experiment 1, a 200 mg/kg dose of l-tryptophan injected 30 min prior to testing disrupted acquisition of Fixed Ratio 2 shuttle escape behavior. In Experiment 2, a 100 mg/kg dose of 5-HTP produced interference with the acquisition of the escape response. Furthermore, this interference was prevented by treatment with the serotonergic antagonist methysergide. In Experiment 3, animals were pretreated with a subeffective dose of l-tryptophan in combination with subeffective exposure to inescapable shock. These animals showed a deficit in the acquisition of FR-2 shuttle escape. In Experiment 4, combined exposure to a subeffective dose of 5-HTP and inescapable shock (40 trials) resulted in an acquisition deficit. This deficit was reversed by methysergide. Experiment 5 showed that the detrimental effects of exposure to prolonged (80 trials) of inescapable shock can be prevented by treatment with methysergide. These studies implicate the serotonergic system as a possible mediator of the learned helplessness phenomenon.

Learned helplessness Tryptophan Serotonin Methysergide Inescapable shock Escape

CONTROLLABILITY has been found to be an important determinant of the physiological and behavioral effects of stress [11,23]. Exposure to uncontrollable shock (i.e., inescapable) typically results in proactive interference with the acquisition of escape/avoidance responding, whereas exposure to an equivalent amount of escapable shock does not result in a deficit [11]. This phenomenon has been labeled learned helplessness. In recent years, a great deal of experimental attention has been devoted to investigating the role of catecholamines in the modulation of the behavioral effects of exposure to inescapable shock [3, 24, 25]. α-Methyl-p-tryosine, which decreases catecholaminergic activity, mimics the behavioral effects of inescapable shock, while substances such as L-dopa, which increase catecholaminergic activity, reverse the escape deficits typically observed after exposure to inescapable shock [2].

The evidence implicating catecholamines in the modulation of the behavioral effects of uncontrollable shock does not preclude the possibility that other neurotransmitter systems may also be involved. Stressors, such as immobilization, fighting, or shock, affect serotonin levels and/or turnover [3, 4, 7, 26], suggesting that these systems may also be important in the mediation of the effects of inescapable shock on subsequent behavior. This possibility is further supported by evidence that manipulations which affect levels of serotonin modulate the acquisition and performance of aversively motivated behavior. For example, it has been shown that increasing levels of serotonin by injections of l-tryptophan produced deficits in the performance of a conditioned avoidance [5]. Conversely, reduction of serotonin by para-chlorophenylalanine (PCPA) treatment resulted in improved performance in a shuttle avoidance task [21].

At present, however, little is known concerning the role of the serotonergic systems in the mediation of the learned helplessness phenomenon. The purpose of the present experiment was to determine whether a manipulation known to influence levels of serotonin would mimic the effects of inescapable shock. Thus, in Experiment 1, we treated rats with IP injections of l-tryptophan to increase levels of serotonin. They were then tested for the acquisition of a Fixed Ratio 2 shuttle shock escape task, a test typically employed in learned helplessness experiments with rats [9]. To the extent that serotonin is involved in the mediation of the learned helplessness phenomenon, it would be expected that elevation of serotonin levels would mimic the effects of inescapable shock, thereby interfering with the acquisition of the shuttle escape task.

EXPERIMENT 1

METHOD

Subjects

Subjects were 31 male Holtzman rats approximately 100 days of age. They were maintained on ad lib food and water, and run during the light phase of a 12 hr light/12 hr dark cycle.

Apparatus

Four shuttle boxes were used for the shock escape test. Each shuttle box was 45.7 cm long, 24.5 cm high, and 21.6 cm wide. The side walls and door were constructed of aluminum and the ceiling of clear Plexiglas. The floor was con-

structed of stainless steel rods 6.3 cm in diameter and spaced 1.90 cm apart. The chamber was divided in half by an aluminum wall which had a 10.8 cm high by 6.35 cm wide opening in the center at floor level. A cue light was centered 20.3 cm above the grid floor on each end wall. Photocells were located 4.5 cm above the grid floor and 8 cm from the end walls. Shock could be delivered to each chamber by a Coulbourn solid state shock source (Model #13–16). Control of experimental events and recording of data were accomplished by use of a TRS-80 microcomputer.

Procedure

On the first day of the experiment, the animals were randomly assigned to one of three drug conditions—200 mg/kg (N=8), 100 mg/kg (N=12), or 0 mg/kg (N=11) of l-tryptophan in a saline vehicle. In the present and all following experiments, injection volumes for serotonin precursors (tryptophan and 5-HTP) were held constant at 1.5 ml/kg. Animals were transported to the experimental room and given an IP injection of the appropriate dose. Thirty minutes later, they were placed in the shuttle boxes and the escape test was conducted.

The escape test consisted of 45 trials presented on a Variable Time 60-sec schedule. Maximum trial duration was 30-sec and shock intensity was 0.60 mA. During the first five trials, shock could be terminated by the animal crossing from one side of the shuttle box to the other (FR-1). On the remaining 40 trials, an FR-2 schedule was in effect where the animal had to cross from one side to the other and then back to terminate shock.

RESULTS

l-Tryptophan had no effect on the first five FR-1 trials of the test. All animals rapidly escaped shock during these trials, with no differences observed between groups ($F<1$).

More importantly, at the highest dose employed, l-tryptophan disrupted the acquisition of the FR-2 shuttle escape task. As can be seen in Fig. 1, the 200 mg/kg group showed escape latencies equivalent to the 100 mg/kg and the saline control groups during the first two blocks of five trials. Thereafter, however, they showed increasing response latencies while the saline and 100 mg/kg group showed decreasing latencies throughout the test. A Group (3) × Blocks of trials (8) analysis of variance showed a significant effect of Group, $F(2,28)=4.33$, $p<0.05$, and a Group × Blocks interaction, $F(7,14)=2.01$, $p<0.025$. Orthogonal decomposition of the trend components showed the quadratic component of the Group × Blocks interaction to be significant, $F(2,28)=7.58$, $p<0.025$. Further, Newman-Keuls post-hoc analysis showed that the saline and the 100 mg/kg group did not differ from each other ($p>0.10$), but both showed shorter escape latencies than the 200 mg/kg group (p's<0.05).

DISCUSSION

These results demonstrate that the 200 mg/kg injection of l-tryptophan produced a deficit in the acquisition of FR-2 shuttle escape behavior. Thus, they implicate the serotonergic systems in the modulation of the acquisition of shock escape. This is consistent with work demonstrating an involvement of the serotonergic systems in other aversively motivated behaviors such as conditioned avoidance [5,7].

The effect of l-tryptophan on the acquisition of shuttle escape behavior appears very similar to that typically observed in the rat following exposure to inescapable shock [9, 18,19]. In both cases, we observe an organism who is capable of crossing from one side of a shuttle box to the other to escape shock, as evidenced by the performance on the FR-1 trials. These animals are also capable of emitting two crossings to escape shock during the early portions of the FR-2 test. However, continued trials do not result in a decrease of the response latency, indicative of the acquisition of the escape response. Indeed, additional trials show these animals' performance to deteriorate. It must be noted that our l-tryptophan manipulation does not rule out the possibilities that the l-typtophan affected the acquisition of the shuttle escape behavior by a peripheral mechanism or by indirectly affecting other neurotransmitter systems such as the catecholamines [3].

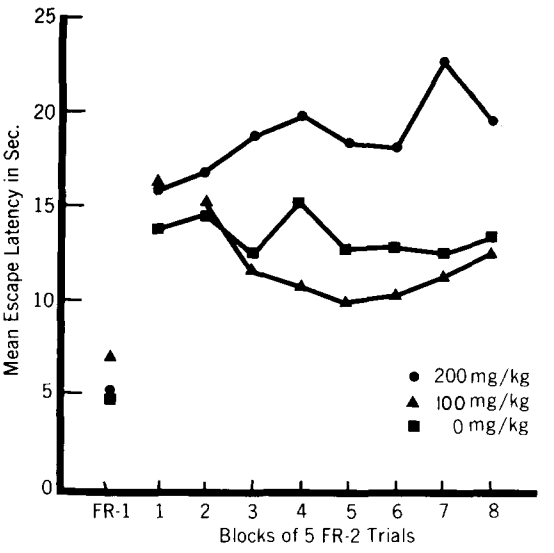

FIG. 1. Mean escape latency in sec on the first five Fixed Ratio 1 and 40 Fixed Ratio 2 trials in blocks of five trials for the three l-tryptophan dose groups.

EXPERIMENT 2

In the following experiment, in order to further test the role of serotonin in the acquisition of this behavior, we attempted to elevate levels of serotonin by injections of 5-HTP. Furthermore, in order to determine if these effects might be peripherally mediated, 5-HTP injections were preceded by RO-4-4602, a decarboxylase inhibitor. In addition, if the deficit observed in the above experiment indeed resulted from alterations in the serotonergic systems, we would expect that the deficit would then be blocked by a serotonergic antagonist. Thus, in the present experiment, a group of animals treated with 5-HTP was also treated with methysergide, a serotonin antagonist, in an attempt to block the deficit in the acquisition of shuttle escape presumably resulting from elevation of serotonin.

METHOD

Subjects

The subjects were 34 male Holtzman rats approximately

100 days of age. All housing conditions and apparatus were identical to those described in Experiment 1.

Procedure

On the first day of the experiment, the animals were assigned to one of four conditions. The first group (N=8) received 100 mg/kg of 5-HTP, the second (N=11) received 50 mg/kg of 5-HTP, the third (N=7) received 0 mg/kg of 5-HTP, and the fourth received the 100 mg/kg of 5-HTP in combination with a 5 mg/kg dose of methysergide. The methysergide was injected one-half hour prior to the 5-HTP. All animals were pretreated with a 50 mg/kg injection of RO-4-4602 one hour prior to the 5-HTP treatment. In the present and all subsequent experiments, injection volumes of RO-4-4602 and methysergide were held constant at 1 ml/kg. Thirty min following the 5-HTP treatment, all animals were placed in the shuttle boxes and the escape test was conducted.

RESULTS

The 5-HTP treatment had no effect on the first five trials of the test. When shock could be terminated by a single crossing, all animals escaped rapidly and no differences between groups were observed ($F<1.0$).

The drug manipulation, however, affected the acquisition of the shuttle response when the FR-2 contingency was operative. Figure 2 shows that the animals receiving the 100 mg/kg dose of 5-HTP had longer escape latencies than the control animals which received the 0 mg/kg dose. The 50 mg/kg did not appear to have interfered with the acquisition of the FR-2 shuttle response as indicated by escape latencies similar to the 0 mg/kg control. The methysergide treatment appeared to have prevented the detrimental effects of the 100 mg/kg dose of 5-HTP. These animals showed escape latencies which were approximately equivalent although somewhat faster than the controls. A Group (4) × Blocks of trials (8) analysis of variance of these escape latencies showed a significant effect of Group, $F(3,30)=4.53$, $p<0.01$. Newman-Keuls post-hoc comparisons showed the 100 mg/kg group to have longer escape latencies than all other groups (p's<0.01), while the remaining groups did not differ from each other (p's>0.10).

These data demonstrate that pretreatment with 5-HTP, like l-tryptophan in the preceding experiment, results in a deficit in the acquisition of an FR-2 shuttle escape response. In addition, a serotonergic antagonist, methysergide, was capable of preventing this deficit. It should be noted that these effects were most probably centrally mediated, since the pretreatment with RO-4-4602 should reduce the peripheral conversion of 5-HTP to serotonin.

The behavioral similarities of the effects of l-tryptophan and inescapable shock suggest that the neurochemical systems modulated by l-tryptophan may also be involved in the mediation of the effects of inescapable shock. This suggestion must be entertained with caution since the existence of a behavioral similarity does not dictate the existence of a common underlying mechanism.

The above experiment suggests that the deficit observed in the acquisition of FR-2 shuttle escape following exposure to inescapable shock may in part be mediated by its effects on the serotonergic systems. This view is consistent with the demonstration that exposure to uncontrollable stress results in elevation of serotonin levels [7]. To the extent that this is correct, it may be possible to demonstrate an additive effect of inescapable shock with pharmacological manipulations of

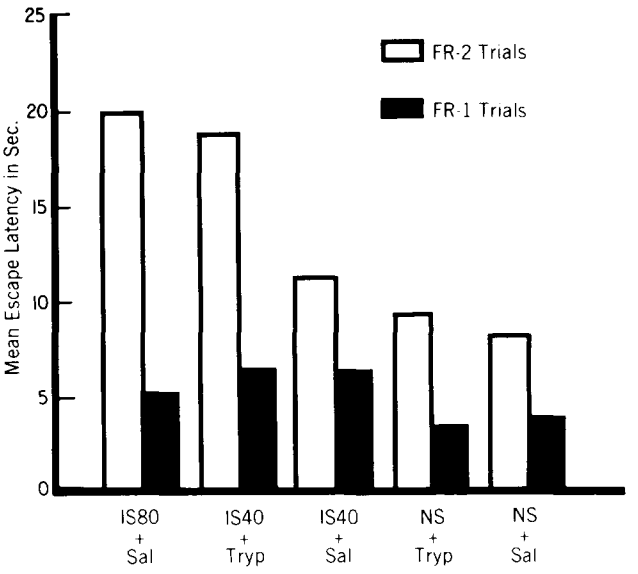

FIG. 2. Mean escape latencies in sec on the first five FR-1 and 40 FR-2 trials as a function of drug treatment (METH=methysergide).

the serotonergic systems. In the following two experiments, we tested this possibility by first injecting animals with a dose of a serotonin precursor, either l-tryptophan or 5-HTP, which in Experiment 1 or 2 was found not to produce a deficit in escape behavior. We then exposed these animals to a series of inescapable shocks which by themselves will not produce a behavioral deficit. Finally, the animals were tested on the acquisition of the FR-2 escape response. To the extent that elevated levels of serotonin mediate the deficit observed following exposure to inescapable shock, it was expected that combined exposure to both inescapable shock and the serotonin precursor would interfere with the acquisition of shuttle escape behavior. Furthermore, in order to make the test paradigm more comparable to that employed in investigations of the effects of inescapable shock [11], the shuttle escape acquisition test was conducted 24 hours following the inescapable shock and drug treatment.

EXPERIMENT 3

METHOD

Subjects

The subjects were 41 male Holtzman rats approximately 140 days of age at the start of the experiment. Housing conditions were identical to those of Experiment 1.

Apparatus

Four chambers were used to administer inescapable shock. These measured 30 cm long, 27.5 cm high, and 30 cm wide. The front and back walls were constructed of aluminum and the side walls and ceilings of Plexiglas. The floors were made of 0.3 cm diameter stainless steel rods spaced 1.25 cm apart. All chambers were housed in sound and light attenuating boxes which were equipped with a house light, a speaker for delivery of white noise, and a ventilating fan.

The shuttle boxes and the inescapable shock chambers were housed in separate experimental rooms. The shuttle boxes described above were used for the escape test.

Procedure

On Day 1 of the experiment, the animals were randomly assigned to one of five treatment groups. The pretreatment consisted of either 40 trials of inescapable shock (IS40) of 5 sec duration and 0.90 mA intensity and/or a 100 mg/kg injection of l-tryptophan (TRYP). Inescapable shock trials were presented on a Variable Time schedule of 60 sec. Group IS40+TRYP (N=9) was given a 100 mg/kg injection of l-tryptophan 30 min prior to receiving 40 inescapable shocks. Three groups, which served as controls, were given only one of these pretreatments. Group IS40+SAL (N=9) was given an injection of saline (SAL) and 30 min later 40 trials of inescapable shock. Group NS+TRYP (N=8) was injected with 100 mg/kg of l-tryptophan and 30 min later was placed in the shock chambers but not exposed to shock (NS). Group NS+SAL (N=7) was injected with saline and 30 min later was placed in the shock chambers but not shocked. The last group (IS80+SAL) was injected with saline and 30 min later exposed to 80 trials of inescapable shock (IS80). This group (N=8) was employed as a shock control to assess the disruptive effects of prolonged exposure to inescapable shock known to produce a deficit on the FR-2 shuttle test. Twenty-four hours following these treatments, all animals were tested for the acquisition of the FR-2 shuttle escape response. This test procedure was identical to that employed in Experiment 1.

RESULTS

No difference between the groups was observed on the first five FR-1 trials ($F<1$). More importantly, differential escape behavior was observed during the FR-2 component of the test as a function of Group, $F(4,36)=4.85$, $p<0.025$. Figure 3 shows the mean escape latencies for the five treatment groups. As can be seen in Fig. 3, 40 trials of inescapable shock or the 100 mg/kg injection of l-tryptophan when experienced in isolation was not sufficient to produce a deficit in the acquisition of the FR-2 escape response. That is, Groups I40+SAL and NS+TRYP did not differ from Group NS+SAL which was exposed to neither shock nor l-tryptophan (p's>0.10). However, exposure to the combination of 40 trials of shock and l-tryptophan did produce a deficit in the acquisition of the escape response. Group I40+TRYP showed escape latencies which were significantly longer than the above three control groups (p's<0.05). In addition, this group did not differ from Group I80+SAL which was exposed to 80 trials of inescapable shock and saline ($p>0.10$).

In agreement with the learned helplessness literature [9, 11, 18], exposure to 80 trials of inescapable shock produced a deficit in the acquisition of the FR-2 shuttle escape response as evidenced by the longer latencies to escape in Group IS80+SAL compared to those of Group NS+SAL. Exposure to either 40 trials of inescapable shock or a 100 mg/kg injection of l-tryptophan was not sufficient to interfere with the acquisition of FR-2 shuttle escape responding as evidenced by the lack of difference in escape behavior in Groups IS40+SAL, NS+TRYP, and NS+SAL. More importantly, combined exposure to both 100 mg/kg of l-tryptophan and 40 trials of inescapable shock did produce a severe deficit in the acquisition of FR-2 shuttle escape. Thus, the effects of inescapable shock do combine with the effects of l-tryptophan to control the acquisition of shuttle escape behavior.

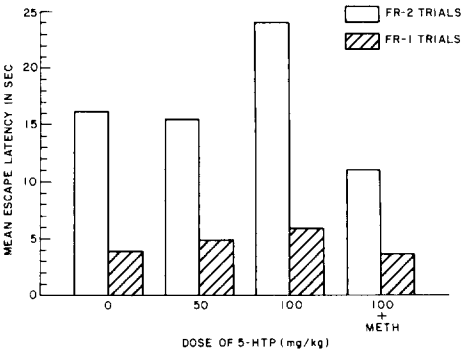

FIG. 3. Mean escape latency in sec for the five Fixed Ratio 1 and 40 Fixed Ratio 2 trials as a function of inescapable shock and drug treatment (IS=inescapable shock—40 trials, NS=no shock, SAL=saline, and TRYP=l-tryptophan).

EXPERIMENT 4

This experiment was identical to the previous one with the exception that levels of serotonin were elevated by means of treatment with 5-HTP. In addition, since in Experiment 2 we found the deficit produced by 5-HTP to be blocked by methysergide, in this study we sought to determine whether the deficit obtained as a result of the subeffective dose of 5-HTP and subeffective exposure to inescapable shock could also be blocked by treatment with methysergide. Thus, the present experiment was a replication of Experiment 3, using the 50 mg/kg dose of 5-HTP found not to result in a learning deficit in Experiment 2. In addition, a group of animals treated with 5-HTP and inescapable shock was also treated with methysergide.

METHOD

Subjects

The subjects were 48 male Holtzman rats approximately 100 days of age at the start of the experiment.

All housing conditions and apparatus were identical to those described for Experiment 3.

Procedure

The procedure was similar to that of the previous study. All animals were injected with a 50 mg/kg dose of RO-4-4602. Sixty minutes following this, two groups were injected with a 50 mg/kg dose of 5-HTP and two with an equivalent volume of isotonic saline (SAL). Thirty minutes later, one group from each of these two treatments was exposed to 40 trials of inescapable shock as described above while the other two groups were not shocked. Thus, Group IS+5-HTP (N=13) received the 5-HTP and the inescapable shock, Group NS+5-HTP (N=8) received the 5-HTP and no shock, Group IS+SAL (N=8) received saline and inescapable shock, and Group NS+SAL (N=8) received saline and no shock. In addition, a fifth group (N=11) was employed which was identical to Group IS+5-HTP with the exception that it re-

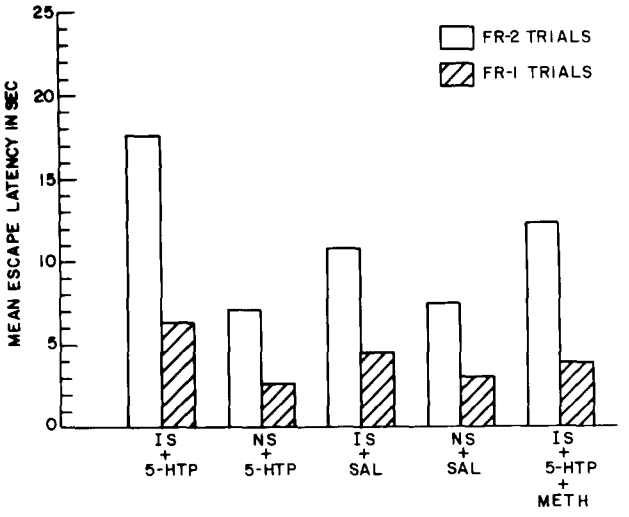

FIG. 4. Mean escape latencies in sec for the five FR-1 and 40 FR-2 trials as a function of shock and drug treatment (IS=inescapable shock—40 trials, NS=no shock, 5-HTP=5 hydroxy-tryptophan, SAL=saline, and METH=methysergide).

ceived a 5 mg/kg injection of methysergide thirty minutes prior to the 5-HTP treatment.

RESULTS

No significant differences between the groups were observed on the five FR-1 trials, $F(4,43)=1.22$, $p>0.10$. However, as can be seen in Fig. 4, the group which received both the 5-HTP and the inescapable shock (IS+5-HTP) showed longer escape latencies on the FR-2 trials than the groups exposed to 5-HTP (NS+5-HTP) or to inescapable shock (IS+SAL) in isolation, or to neither (NS+SAL). In addition, the group which received the methysergide in addition to the inescapable shock and 5-HTP showed escape latencies approximately equivalent to those of the above three control groups. Analysis of variance of the mean escape latencies on the FR-2 trials as a function of Group (5) and Blocks of trials (8) showed a significant effect of Group, $F(4,43)=3.01$, $p<0.05$. Subsequent Newman-Keuls post-hoc tests showed Group IS+5-HTP to have significantly longer escape latencies than any of the other groups (p's<0.05, while these latter groups did not differ from each other (p's>0.10).

DISCUSSION

These results demonstrate that combined exposure to inescapable shock and elevated levels of serotonin via 5-HTP produces a deficit in the acquisition of the FR-2 shuttle escape response, whereas isolated exposure to the shock or the 5-HTP is not sufficient to produce such a deficit. In addition, the deficit produced by this combined exposure can be prevented by treatment with the serotonergic antagonist methysergide.

The above studies demonstrate that elevation of serotonin produces deficits in the acquisition of shuttle escape behavior which appear similar to those produced by prolonged exposure to inescapable shock alone. Furthermore, the effect is a central serotonergic one, since animals were pretreated with RO-4-4602 at a dose that reduces the peripheral conversion of 5-HTP to serotonin. In addition, the effects of elevation of serotonin and inescapable shock at levels which by themselves are below threshold appear to combine to produce a deficit. This deficit can also be reversed by methysergide, again suggesting an involvement of the serotonergic systems.

On the basis of the above experiments it is tempting to speculate that the effects of prolonged exposure to inescapable shock on the subsequent acquisition of FR-2 shuttle escape responding are at least partially mediated by the effects of inescapable shock on the serotonergic systems. However, it should be noted that while the above findings demonstrate the involvement of this neurotransmitter in the acquisition of this behavior, it cannot be concluded that the behavioral deficit observed following exposure to inescapable shock results from the same mechanism as that observed following treatment with serotonin precursors alone. The possibility that two independent or interacting pathways are responsible for the behavioral deficit is left open. However, if it can be demonstrated that a serotonergic antagonist can at least partially reverse the detrimental effects of exposure to a prolonged series of inescapable shocks, then this would provide more direct evidence of the mediation of the effects of inescapable shock by the serotonergic systems. In order to test this possibility, a group of animals was exposed to the typical series of 80 trials of inescapable shock following treatment with the serotonergic antagonist methysergide, and then tested for the acquisition of the FR-2 shuttle escape response 24 hours later.

EXPERIMENT 5

METHOD

Subjects

The subjects were 48 male Holtzman rats approximately 100 days of age at the start of the experiment. All housing conditions and apparatus were identical to those described above.

Procedure

On day one of the study, animals were randomly assigned to one of four groups. One group (IS+METH) was injected with a 5 mg/kg dose of methysergide sixty minutes prior to exposure to 80 trials of inescapable shock as described in Experiment 2. A second group (IS+SAL) was injected with the same volume of saline and then exposed to the inescapable shock. A third group (NS+METH) was injected with methysergide and placed in the inescapable shock apparatus for the same amount of time as the above groups but did not receive shock. The last group (NS+SAL) was injected with saline but not exposed to shock. Twenty-four hours later, all animals were tested on the FR-2 shuttle escape task as described above.

RESULTS

Figure 5 shows the mean escape latencies for the groups on the first five FR-1 trials and the 40 FR-2 trials. The groups showed equivalent escape latencies on the five FR-1 trials as indicated by an analysis of variance, $F(3,27)=2.35$, $p>0.05$. Differential escape latencies were observed on the 40 FR-2 trials. As can be seen in Fig. 5, Group IS+SAL showed longer escape latencies as compared to any of the other groups. This again demonstrated the interference of prior

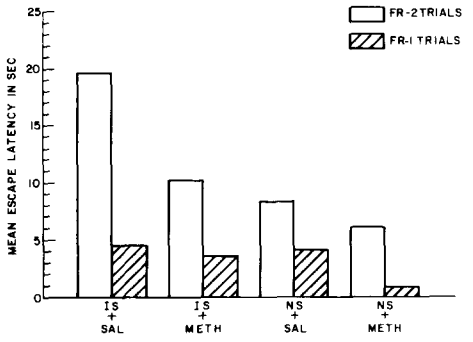

FIG. 5. Mean escape latency in sec for the five FR-1 and 40 FR-2 trials as a function of shock and drug treatment (IS=inescapable shock—80 trials, NS=no shock, SAL=saline, and METH=methysergide).

exposure to inescapable shock with the acquisition of the shuttle escape response. More importantly, the Group IS+METH which had also received 80 trials of inescapable shock but had been pretreated with the methysergide, did not show a deficit in the acquisition of the FR-2 shuttle escape response. The escape latencies of this group were equivalent to those exhibited by the two non-shocked control groups (NS+SAL or NS+METH). Analysis of variance of these data showed a significant effect of Group, $F(3,27)=8.68$, $p<0.01$. Subsequent post-hoc comparisons showed the IS+SAL group to have longer escape latencies than the other three groups (p's<0.05), which did not differ from each other (p's>0.10).

GENERAL DISCUSSION

The present study demonstrates that treatments with the serotonin precursors, l-tryptophan and 5-HTP, produce a deficit in the acquisition of shuttle escape behavior which can be prevented by treatment with the serotonergic antagonist methysergide. This is in agreement with the work of others [5,21] demonstrating the involvement of serotonin in the acquisition of aversively motivated behavior. The deficit appears similar to that produced by prolonged exposure to inescapable shock in that both manipulations, while not affecting escape behavior when a single response is required to escape shock, result in a deficit in the acquisition of the response when the FR-2 contingency is in effect. In addition, the effects of inescapable shock and injections of the serotonergic precursors combined to interfere with the acquisition of the escape response, while each treatment in isolation was not sufficient to produce the deficit. This combined effect was reversed by the serotonin antagonist methysergide, further suggesting the involvement of the serotonergic systems in the effects of inescapable shock. Furthermore, methysergide was capable of preventing the deficit typically produced by prolonged exposure to inescapable shock. This last finding provides strong evidence for at least a partial mediation of the effects of inescapable shock by the serotonergic systems.

Other studies have demonstrated similar parallels between the effects of inescapable shock and those observed following manipulations of serotonin. The incidence of shock induced aggression decreases when animals are given doses of l-tryptophan or 5-HTP equivalent to those employed in the present studies [17]. Similarly, inescapable shock of the intensity and duration approximating the prolonged exposure employed in the present studies is also known to decrease shock induced aggression [10,27]. Furthermore, elevation of serotonin results in depression of appetitively motivated behavior [6, 12, 13], which complements the finding that inescapable shock interferes with the subsequent acquisition of appetitively motivated behaviors [15,16]. The similarities of the above studies, when taken in conjunction with the results of the present studies, strongly suggest that the serotonergic systems may partially mediate the effects of inescapable shock.

It should be noted that while the present results implicate the serotonergic systems in the modulation of the acquisition of aversively motivated behavior in general and in the effects of inescapable shock in particular, they do not preclude the possible involvement of other neurotransmitter systems in these behaviors. Indeed, there is ample evidence that inescapable shock can modify catecholamine activity [2, 24, 25]. It is possible that while the acute effect of inescapable shock is increased release of all brain amines [14], continued exposure to inescapable shock may result in both depletion of the catecholamines [3, 24, 25] and in elevation [7] or increased utilization of serotonin [22]. Hence, the effects of inescapable shock on subsequent learning may be mediated by the balance or interaction of the catecholamines and indoleamines, or by their independent contributions. Indeed, Palkovits, Mezey, and Feminger [14] suggest that CNS reactions be considered as coordinated activity across a complex network of aminergic cells, and that no one neurotransmitter be attributed selective responsibility for a given stress reaction. This view is amenable to the reversal of these detrimental effects by pharmacological manipulations which return either of the systems to relative normality, such as treatment with catecholaminergic agonists or serotonergic antagonists. Additional pharmacological and biochemical research, however, must be conducted to determine the validity of this speculation.

Learned helplessness has been proposed as an animal model of human depression. To the extent that this model is valid, the present results suggest that the serotonergic systems may be important modulators of certain human depressions. However, this suggestion would appear to be at odds with biochemical theories of depression based on serotonergic deficiency [8]. In support of the serotonin deficiency explanation of depression, Sherman and Petty [19] report reversal of the behavioral effects of inescapable shock with the administration of serotonin into the frontal neocortex and septum. It should be noted, however, that the experimental parameters employed in their research differ greatly from the procedures traditionally used in learned helplessness research. Sherman *et al.*'s test [19] of the effects of inescapable shock involved an FR-1 barpress to escape shock, while in past research demonstration of the learned helplessness effect has necessitated an FR-2 contingency on shuttle escape tasks [9] or an FR-3 contingency on the barpress escape task [18]. In addition, tests for learned helplessness are usually performed 24 hours after the inescapable shock treatment, whereas Sherman *et al.* [19] tested animals two hours after induction procedures. It is quite possible that the procedural and temporal differences influence the results attained. For instance, Sherman *et al.* [19] observed no reversal of the effects of inescapable shock with the administration of norepinephrine to various brain areas, while Anisman, Remington and Sklar [2] find reversal of

learned helplessness with the systemic administration of norepinephrine precursors when using a more traditional learned helplessness paradigm. Furthermore, the regional administration of serotonin to specific brain substrates might selectively activate very different mechanisms than those activated by the systemic administration of serotonin precursors employed in the present studies. In short, the generalizability of Sherman *et al.*'s work [19] to the traditional learned helplessness research remains unclear.

An animal model of human depression more concordant with the present studies has been developed by Nagayama and his coworkers [12,13]. They have amassed a considerable amount of evidence that certain types of depression may result from a post-synaptic serotonergic hypersensitivity. Their animal model of human depression is based on the premise that the outcome of experimentally elevated levels of serotonin is an analog of the post-synaptic hypersensitivity to stress-induced fluctuations of serotonin levels. This conceptualization is supported by their finding that a behavioral deficit produced by elevation of serotonin by 5-HTP can be prevented by a post-synaptic serotonergic antagonist such as methysergide. In addition, when serotonin levels are reduced over a seven day period by injections of PCPA, behavioral depression follows the administration of a dose of 5-HTP which is ineffective in disrupting behavior in animals not given PCPA [6]. The results of the present experiments are in agreement with these findings. Thus, the present results attest to the utility of the learned helplessness paradigm in the examination of the psychophysiological bases of human depression, and invites further research to clarify the roles and possible interactions of the various neurotransmitter systems.

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