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FS Stress Induces Long-Lasting Memory Facilitation: Involvement of Cholinergic Pathways

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JODAR, L., M. TAKAHASHI AND H. KANETO. *FS stress induces long-lasting memory facilitation: Involvement of cholinergic pathways.* PHARMACOL BIOCHEM BEHAV **53**(3) 735–740, 1996.—We tested in vivo the hypothesis that foot-shock (FS) stress-induced prolongation of latencies in the one-trial step-through passive avoidance learning task in mice occurred through a long-term facilitation process. Whereas behavioral responses in control mice lasted for 24 h, decreasing progressively in the subsequent days, FS-stress exposure for 15 min before training (pretraining), immediately after training (posttraining), or 15 min before the test (pretest) resulted in a profound and sustained enhancement of test latencies that lasted for at least 96 h. These facilitating effects disappeared when FS exposure was delivered with a 2- or 3-h difference with respect to the training trial. Scopolamine (Scop) (1 mg/kg, intraperitoneally) 30 min before the training session caused impairment of test latencies in control and pretest stressed animals, but failed to affect both pre- and posttraining FS stress-induced enhancement. Our working hypothesis is that FS stress may increase the levels of acetylcholine in the presynaptic terminal or the firing rate of cholinergic input. Animals pretreated with FS stress daily for 1 or 4 days followed by the acute schedule described above showed no enhancements of test latencies. Pretraining Scop impaired test latencies in pre- and posttraining and pretest stressed animals, suggesting that unpredictability is a critical factor in activating behavioral long-term facilitation.

Foot-shock Stress Learning/memory Passive avoidance Long-term facilitation Scopolamine Cholinergic pathways Mice

ASSOCIATIVE memory retention after classical conditioning in the step-through type passive avoidance task, has been shown to last at least 24 h, which suggests that it is a form of long-term memory. The brain has the capacity to establish different patterns of neural connections in response to the demands of the environment. In this regard, we have shown previously that a few environmental stressors alter learning and memory processes. For instance, whereas forced-swimming stress impairs retention in a passive avoidance paradigm, a single exposure to foot-shock (FS) stress resulted in dramatic increases of test latencies, suggesting a priori that FS exposure facilitates retention (14). However, it remains unclear whether FS stress exclusively produces a transient state of emotional disorder characterized by cognitive disturbances or long-term changes with an altered pattern of synaptic efficacy. We also analyzed whether FS-induced behavioral improvements depend on the time of exposure. Moreover, electric FS has been reported to activate stress circuits involving alterations of neurotransmitter content in presynaptic terminals as well as the active zone of the synapse influencing synaptic efficacy (1,19). In addition, long-term facilitation processes implicate the release of transmitters in both invertebrates and vertebrates (12). Thus, a search for the neurochemical pathways mediating FS stress-induced cognitive modifications was also a preeminent objective.

Repeated exposure to stressors can produce behavioral changes in a variety of learning tasks (9), which have been referred to as part of learned helplessness effects (17). We also considered how repeated FS stress exposure modifies behavioral responses.

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METHOD

Subjects and Experimental Conditions

Male mice of the ddY strain, weighing 18–20 g (Ohtsubo Experimental Animals, Nagasaki, Japan), were housed in 42 × 26 × 15-cm plastic cages with ad lib access to food and water under a natural day–night regime. After they reached 30–32 g of body wt. they were used for the experiments. All experimental procedures were carried out in a quiet, air-controlled laboratory, and animals were equilibrated to these conditions for about 1 h before experimentation. All procedures were carried out between 0900 and 1500 h to minimize diurnal variation in learning responses. Animal handling was gentle so as to reduce handling-induced stress variations in learning behavior as much as possible.

Behavioral Procedure

Step-through, one-trial passive avoidance learning is a particularly fast learning procedure, and thus was selected as the experimental paradigm for these studies.

The apparatus consisted of an illuminated and a dark compartment (each 4 × 13 × 19 cm) adjoining each other through a small gate (3 cm diam.) with a grid floor of 2.5-mm stainless-steel rods set 7 mm apart.

For the training trial, each animal was placed in the illuminated compartment facing away from the dark one. When the animal entered the dark compartment, an electric shock (ES) of 0.6 mA was delivered through the grid floor until the animal returned to the illuminated compartment. Then, a plastic door closed the adjoining gate between both compartments to avoid reentrance. Ten seconds later, the animal was returned to the home cage. At the test trial, 24 h after the training trial, the animal was placed in the illuminated compartment, and the latency to enter the dark compartment (maximum 600 s) was measured.

Exposure to FS Stress

The apparatus consisted of a chamber (30 × 30 × 30 cm) with a grid floor composed of 1.5-mm stainless-steel rods 7 mm apart from each other and divided into nine compartments (10 × 10 × 30 cm) with transparent plastic walls. Mice were placed individually in each compartment. A scrambled electric shock (2 mA, 1-s duration) was delivered every 5 s for 5 min through the grid floor. To avoid effects on motivation, control animals were placed on the grid floor for 5 min without receiving electric shock. Following stress delivery, mice were returned to their home cages.

The effects of acute FS stress on passive avoidance test latencies were evaluated in three sets of experiments. a) The effects of FS stress at three different stages with respect to the training and test trials: Mice were subjected to FS stress 15 min before training (pretraining), immediately after training (posttraining), and 15 min before testing (pretest). Control groups were placed in the chamber without receiving electric shock. b) Long-lasting effects of FS stress: Pretraining, posttraining, and pretest arrangements were performed as described earlier. The test trial was established for each group at 24, 48, 72, and 96 h after training. c) The effects of FS stress at different times with respect to each arrangement: Different groups were exposed to FS stress 15 min, 30 min, 2 h, or 3 h before training, after training, or before the test trial.

The effects of repeated FS stress on passive avoidance test latencies were measured after daily exposure to 5 min FS stress for either 1 or 4 days consecutively. This was followed by the acute schedule.

Drug Used and Administration Schedule

Scopolamine (Scop)-HCl (Tokyo Kasei, Tokyo, Japan) was administered IP, 30 min before training, in a volume of 0.1 ml/10 g body wt. The dose is expressed as the salt.

Control groups received saline instead of Scop. Timing and dose of Scop were justified based on previous experiences showing its ability to disrupt retention in the test session 24 h later.

Statistical Analyses

Data are expressed as medians and ranges. All data were analyzed using Kruskal–Wallis nonparametric one-way analysis of variance (ANOVA) and subsequently with the two-tailed Mann–Whitney *U*-test for paired comparisons. In all statistical evaluations, we used $p < 0.05$ as the criterion for statistical significance.

RESULTS

FS Stress Exposure Induced the Facilitation of Behavioral Performance in the Passive Avoidance Paradigm

Pretraining, posttraining, and pretest exposure to FS stress resulted in enhanced test trial latencies compared with those elicited by control mice [$\chi^2(3) = 27.12$, $p < 0.01$], showing an incidence of maximum retention latency of 600 s in almost all animals tested, but did not affect avoidance latencies at the training trial (Fig. 1).

Long-Lasting Effects Induced by FS Stress Exposure

Pretraining, posttraining, and pretest FS stress exposure resulted in a profound and sustained increase of test latencies

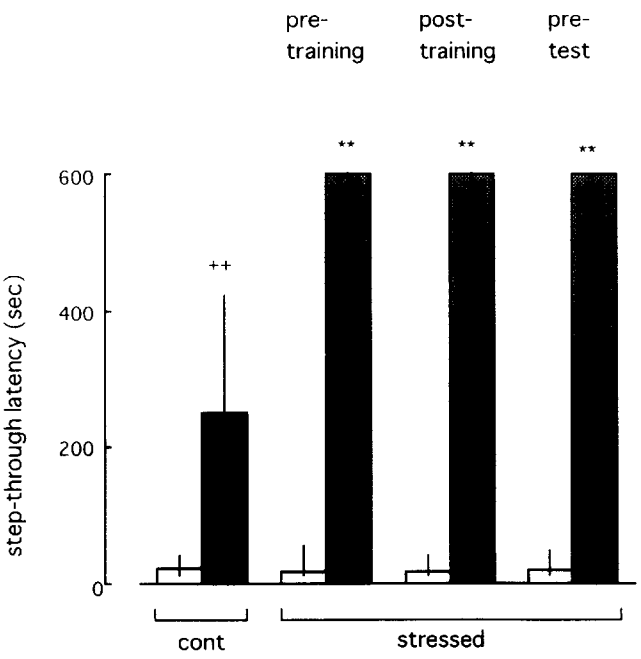

FIG. 1. Effect of FS stress on retention test latencies of the one-trial passive avoidance response in the step-through task. Mice were exposed to FS stress 15 min before or immediately after the training session, or 15 min before test trial. Step-through latencies at the training trial (□) and at the test session (▩). $^{**}p < 0.01$ compared with the test latencies of the control group. $^{++}p < 0.01$ compared with the training latencies of the control animals.

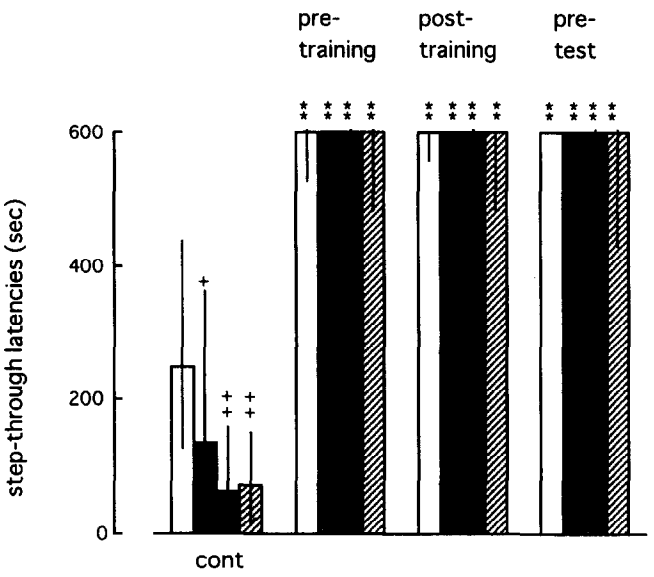

FIG. 2. FS stress-induced behavioral long-term facilitation measured at different intervals of time. Mice were exposed to FS stress 15 min before or immediately after training, or 15 min prior to test session, and retention latencies were measured at 24 (□), 48 (▨), 72 (■), and 96 (▨) h after the training session. $^{**}p < 0.01$ compared with the control group at the corresponding time. $^{+}p < 0.05$ and $^{++}p < 0.01$ compared with the control group tested 24 h posttraining.

that reached a maximum of 600 s at least for 4 days in most of the animals tested. Kruskal-Wallis ANOVA of test latencies at 24, 48, 72, and 96 h revealed a significant effect of time [$\chi^2(3) = 27.12$, $p < 0.01$; $\chi^2(3) = 29.15$, $p < 0.01$; $\chi^2(3) = 18.00$, $p < 0.05$; and $\chi^2(3) = 18.04$, $p < 0.05$, respectively] (Fig. 2).

In contrast, nonstressed animals subjected to one trial in the passive avoidance learning paradigm showed a weaker behavioral response compared with stressed groups when tested 24 h after training, which decreased time-dependently over the following days. Animals tested at 72 or 96 h posttraining showed poor behavioral responses compared with those tested 24 h posttraining [$\chi^2(3) = 16.55$, $p < 0.01$] (Fig. 2).

FS Stress-Induced Facilitation of Retention Latencies is Time Dependent

FS stress exposure 15 or 30 min pretraining, posttraining, or pretest provoked a marked increase of retention latencies during the test session, which disappeared when the interval between FS stress exposure and any of these arrangements was 2 or 3 h [$\chi^2(12) = 66.33$, $p < 0.01$] (Fig. 3).

Effect of Scop on FS Stress-Enhanced Latencies

Pretraining Scop in nonstressed animals resulted in a profound decrease of test trial latencies. However, test latencies from animals subjected to pre- and posttraining FS stress were not affected by pretraining Scop. In other words, the Scop-induced amnesic effect was blocked by stress exposure. In contrast, pretest stressed mice failed to antagonize the impairing effects of Scop, exhibiting a marked loss of behavioral performance [$\chi^2(7) = 58.34$, $p < 0.01$] (Fig. 4).

In addition, the administration of Scop elicited amnesic effects in mice exposed to FS stress 2 or 3 h pretraining, which was blocked when animals were subjected to FS stress 15 or 30 min before the training trial [$\chi^2(9) = 63.84$, $p < 0.01$] (Fig. 5).

Repeated FS Stress Exposure Neither Elicits Long-Term Facilitation nor Affects Scop-Induced Impaired Effects on Memory

Daily exposure to FS stress for 1 or 4 consecutive days followed by the acute schedule failed to enhance test latencies compared with those of the control group in the three arrangements tested.

Pretraining Scop administration elicited impaired test latencies in all stressed groups. Nevertheless, whereas pretreatment with FS exposure only once in posttraining stressed animals blocked partially the Scop impairing effect, 4 days of FS pretreatment failed to affect Scop-induced impairment of behavioral responses [$\chi^2(7) = 36.57$, $p < 0.01$, after 2 days of FS stress exposure and $\chi^2(7) = 36.01$, $p < 0.01$, after 5 days of FS stress exposure] (Fig. 6).

DISCUSSION

The present data confirmed our previous experiment in which test trial latencies were significantly prolonged in animals exposed to pre- or posttraining or pretest FS stress, indicating that memory retention might be facilitated by FS stress exposure (14).

The one-trial, step-through passive avoidance learning task is useful to investigate neurochemical mechanisms of long-term memory storage. Avoidance by mice entering the dark room when a 20-V FS was applied in the training trial lasted 24 h, decreasing progressively in the following days. Then, 72 or 96 h following training, mice had a severe loss of behavioral memory, indicating the progressive loss of activity of the molecular cascades that give rise to long-term memory. Animals exposed to pre- or posttraining or pretest FS stress reached

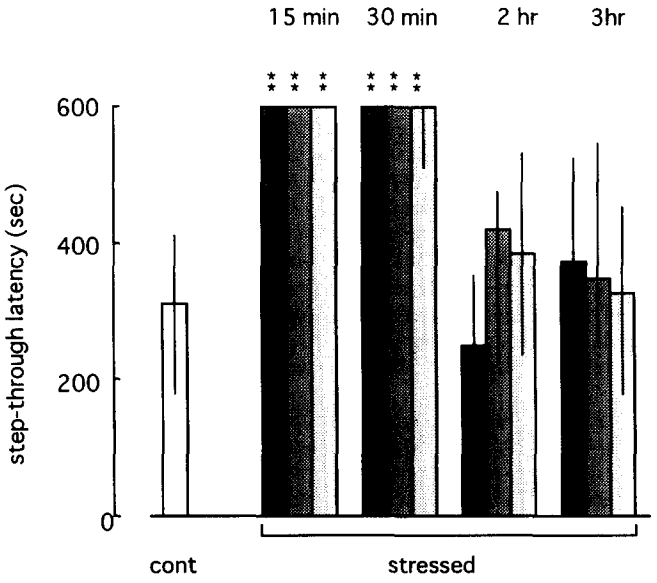

FIG. 3. Effect of FS stress exposure on test latencies measured at different intervals of time. Animals were subjected to FS stress 15 min, 30 min, 2 h, or 3 h pretraining (■), posttraining (▨), and pretest (□). Step-through latencies at the test session were assessed 24 h after training. $^{**}p < 0.01$ compared with the control group.

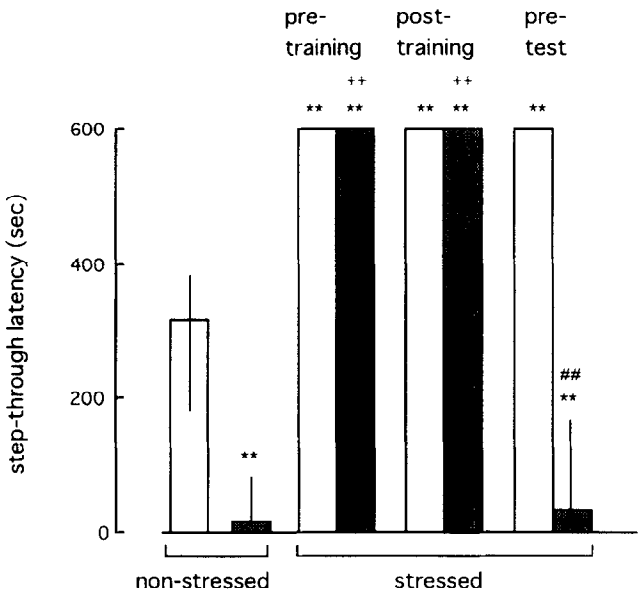

FIG. 4. Effect of FS stress on Scop-induced amnesic effects. Scop, 1 mg/kg, was administered 30 min before training. FS stress was delivered 15 min before or immediately after training, or 15 min before testing. Step-through latencies at the test session, control groups (given saline, ☐); Scop groups (▩). $^{**}p < 0.01$ compared with the nonstressed control group; $^{++}p < 0.01$ compared with the nonstressed Scop group; $^{\#\#}p < 0.01$ compared with the correspondent stressed group given saline.

latencies up to 600 s even 96 h after training, which appears to represent a more stable phase of long-term memory storage.

Sensitization is a form of nonassociative learning in which the response to a test stimulus is enhanced as a consequence of delivering a strong, usually noxious stimulus to an animal. It has been studied widely in the gill- and siphon-withdrawal reflex in *Aplysia californica*, which involves changes in synaptic effectiveness produced by the modulation of transmitter release at a common locus (7,8). In vertebrates, LTP is the most common experimental model to describe how newly acquired information can be converted into a more long-lasting form of memory (5). Our results support the idea that animals exposed to environmental stress exhibit increased passive behavioral responses when subsequently confronted with a novel stressful situation (16,21), and suggest the development of a long-term facilitation process (sensitization) as an explanation of the molecular changes that might be involved in the transition to forms of memories of longer duration, dependent not only on the intensity of the stimuli (14) but also on the time of application.

It can be argued, however, that longer latencies in the test trial may not necessarily be due to memory reinforcements but to deficits in locomotor activity or emotional alterations caused by an aversive stimulus such as FS. Neither emotionality nor motor activity are likely to be the main explanations for FS-induced increases of test latencies, for several reasons. First, abnormal behavior such as freezing was not observed in the training or test trials of both stressed and nonstressed animals. Second, in each arrangement, several circumstances eliminate emotional and locomotor disturbances as being the main causes of behavioral facilitation: a) In the pretraining arrangement, exposure to FS stress both 15 and 30 min prior to the training trial elicited a significant enhancement of test latencies, indicating that either memory or emotional/motor activity factors were altered. First, training latencies of nonstressed and stressed groups did not differ from each other, ruling out an emotional or motor component at least on the training trial. Second, the possibility that FS stress could produce a long-term effect on motility or emotion was tested by exposure to FS stress 2 or 3 h before training. If either motor or emotional factors were involved in FS-induced test latency enhancements, one would expect those latencies to be increased in the test trial 24 h later. On the contrary, latencies were not different from those of control animals. In addition, it is doubtful that emotional factors remained persistent 72 or 96 h after the training trial. Third, because an essential role of central cholinergic systems is well recognized, FS stress effects on Scop-treated animals support the idea that FS acts as a sensitizing stimulus on passive avoidance learning. Scop, a muscarinic receptor antagonist, is capable of impairing test latencies when administered before training. As shown in Fig. 5, Scop-induced impairing effects were blocked when animals were exposed to FS stress 15 or 30 min pretraining, but not 2 or 3 h before. b) In the posttraining arrangement, the same line of reasoning can be followed to explain FS stress-induced enhancements of test latencies. Here, nevertheless, training latencies measured before exposure to stress cannot exclude emotionality or motor disturbances. c) In the pretest arrangement, the fact that 72 or 96 h after training, mice exposed to FS stress 15 min before the test were able to remember the task that control mice have almost completely forgotten made emotionality an important factor. Although 2 or 3 h pretest exposure to FS stress did not increase latencies significantly,

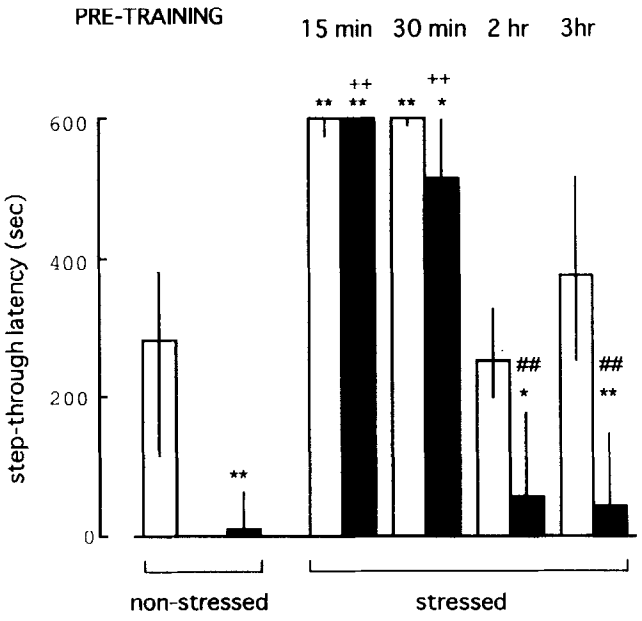

FIG. 5. Effect of pretraining FS stress on Scop-induced amnesic effects measured at different intervals of time. Animals were exposed to FS stress 15 min, 30 min, 2 h, and 3 h before training. Scop. 1 mg/kg, was administered 30 min before training. Step-through latencies at the test session, control groups (given saline, ☐); Scop groups (▩). $^{**}p < 0.01$, $^{*}p < 0.05$ compared with the nonstressed control group; $^{++}p < 0.01$ compared with the nonstressed Scop group; $^{\#\#}p < 0.01$ compared with the correspondent stressed group given saline.

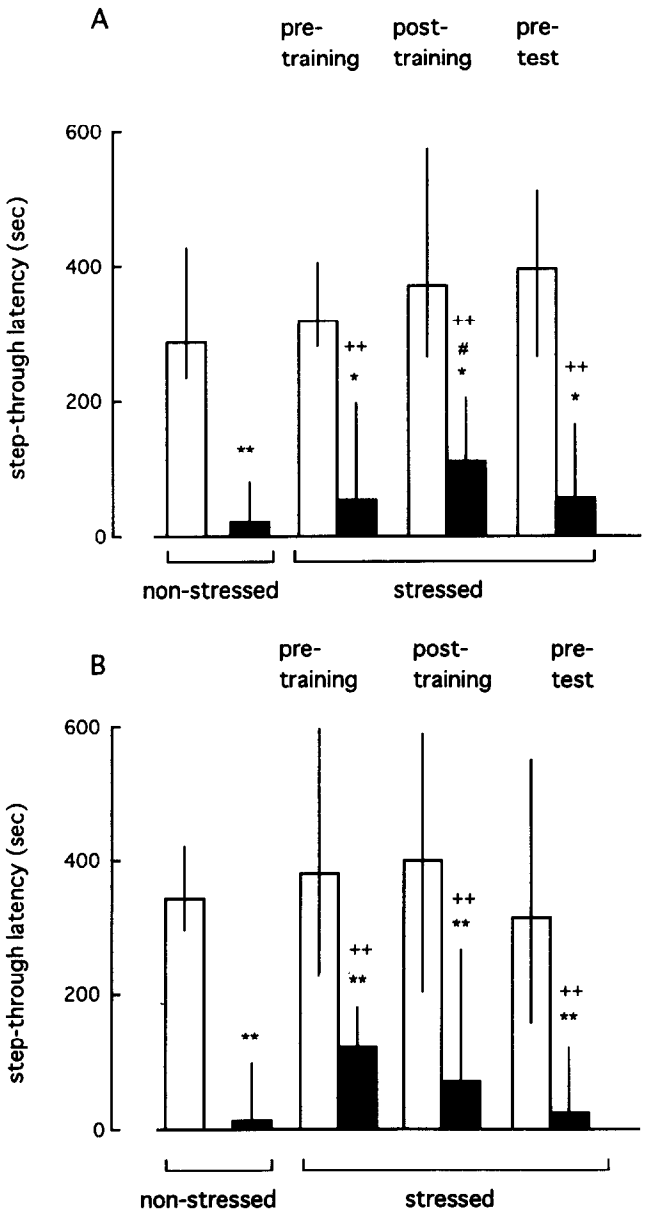

FIG. 6. Effects of repeated FS stress exposures and Scop on acute FS stress-induced facilitation of retention latencies. (A) Mice were exposed to FS stress on the 1st day. On the 2nd day, the same schedule used for the acute exposure was followed. (B) Mice were exposed daily to FS stress for 4 consecutive days. On the 5th day, the same schedule used for the acute exposure was followed. Scop, 1 mg/kg, was always injected 30 min before training. Step-through latencies at the test session, control (given saline, □); Scop (▩). $^{*}p < 0.05$, $^{**}p < 0.01$ compared with the respective control; $^{++}p < 0.01$ compared with the correspondent control of the stressed groups; $^{\#}p < 0.05$ compared with the correspondent stressed group given saline.

this may not imply time-dependent sensitization but the partial loss of the emotional component added by FS. Experiments using Scop gave some support to the hypothesis that considers FS stress to be a sensitizing stimulus. In this regard, if FS stress acted as an anxiogenic, one would expect that Scop-induced impairing effects would be blocked as they were in the pre- and posttraining arrangements. Surprisingly, Scop-treated animals showed an acute impairment when exposed to FS-stress 15 min pretest. Moreover, repeated daily exposure to FS stress for just 2 days was able to return test latencies to control levels. Thus, the primary exposure to FS stress, as an unpredictable event, seems critical for the activation of behavioral long-term facilitation. In any case, further experiments are required to find definite answers to these questions.

The existence of a consolidation period implies that synaptic modification, and thus the formation of long-term memory, can be disrupted by external events interfering with the cellular and biochemical consolidation cascade. In addition, it has been established that the increase in synaptic effectiveness mediating long-term synaptic facilitation results from an enhancement of transmitter release (5,7,8). In this regard, it is generally believed that cortical cholinergic inputs, as well as organized cholinergic projections in the striatum and basal nuclear complex, are involved in cognition—that is, attention and learning and memory processes (11).

This study showed that FS stress-induced increases on test latencies lasted at least 96 h, which is consistent with other reports indicating that ACh-induced excitability changes can be long-lasting and thus represent a mechanism of neural plasticity (3,10,15,20). Our working hypothesis is that FS stress may increase the firing rate of ACh in the brain. Higher levels of ACh would increase synaptic effectiveness of the neural circuit controlling passive avoidance response. This possibility is empirically supported by systemic administration of a single dose (1 mg/kg) of Scop causing a profound amnesic effect that completely disappeared by exposing the mice to 15 min of pretraining FS, or by immediate posttraining FS. This suggests that increased levels of endogenous ACh induced by FS exposure would compete with exogenously administered Scop for muscarinic binding, and shows selective blocking of the Scop-induced amnesic effect and a sustained enlargement of behavioral responses. On the contrary, exposure to FS stress 15 min before the test failed to enhance test latencies in animals given pretraining Scop, indicating that Scop antagonism of muscarinic receptors before training would block the triggering signal responsible for the induction of the consolidation process in the passive avoidance behavioral task. Further, exposure to FS stress 2 or 3 h before training failed to block Scop-induced impairing effects, presumably because of the progressive decrease of ACh levels, thereby being unable to antagonize Scop actions.

Application of repeated FS stress did not significantly enhance test trial latencies compared with those elicited by the nonstressed group. In animal models of chronic stress, the acute response to a stressor often habituates when the stressor is presented repeatedly (4,18). The data revealed in our experiment indicate that daily pretreatment to FS stress for 1 or 4 consecutive days followed by the acute schedule was enough to return test latencies to control levels. Unpredictability of the stressor seems to be a critical factor when considering habituation (16). Furthermore, previous experiments in our laboratory showed that FS stress-induced analgesia was reduced to 50% by a single repetition of FS stress (13). On the other hand, repeated FS stress-induced behavioral disturbances in several learning tasks have been frequently associated with learned helplessness effects (2). However, because animals repeatedly stressed rendered latencies similar to those of the control groups, it seems that the passive avoidance response is not affected in itself, and only the behavioral facilitation induced by acute FS disappears.

It is possible that repeated stress exposure provoked weaker cholinergic input stimulation, and thus a lower release of ACh

failing to activate the long-term consolidation process. Supporting this assertion, administration of Scop in a dose that elicited no effects when followed by a single exposure to FS stress provoked a loss of behavioral responses in both pretraining and posttraining stressed animals when subjected to daily pretreatment for 1 or 4 days to FS stress.

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