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# Influence of Various Acute Stressors on the Activity of Adult Male Rats in a Holeboard and in the Forced Swim Test

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ARMARIO, A., M. GIL, J. MARTI, O. POL AND J. BALASCH. *Influence of various acute stressors on the activity of adult male rats in a holeboard and in the forced swim test.* PHARMACOL BIOCHEM BEHAV **39**(2) 373–377, 1991.—The effects of various acute stressors on the activity of adult male rats in a holeboard and in the forced swim test were studied. When tested immediately or 24 h after 1 h exposure to noise, restraint in tubes or tail shock, no changes in either defecation rate or activity in the holeboard were observed. In contrast, immediately after 1 h immobilization in wood-boards, a reduction of the number of areas crossed and the number of head-dips was found. The inhibitory effect of immobilization on head-dips persisted 24 h later. The behavior of the rats in the forced swim test was classified into three categories: struggling, mild swim and immobility. The changes in behavior were critically dependent on the type of stressor, and more specifically on its intensity, that was evaluated with three different physiological parameters (serum prolactin, corticosterone and glucose levels). Thus, if tested immediately after stress, noise did not alter the response of the rats, restraint in tubes and tail shock-reduced immobility, and the latter stressor increased mild swim. In the second experiment, immobilization in wood-boards reduced struggling. Twenty-four hours after stress, noise, restraint in tubes or tail shock were without effect, but immobilized rats showed increased immobility and reduced mild swim activity. The present data clearly indicate that behavior of rats in a holeboard and in a forced swim situation are not related, and that acute stress could have a differential effect on the various categories of behavior in a forced swim situation.

Acute stress Noise Tail shock Restraint Immobilization Holeboard Forced swim test Prolactin Corticosterone Glucose

ACUTE exposure to stress induces a wide range of changes in behavior, including altered motor and/or exploratory activity (25, 26, 38, 43, 44), analgesia and other sensorial deficits (1, 18, 27), and poor performance in learning-related tasks (2, 32, 40).

Despite some controversies about its theoretical bases (15, 19, 45), the behavior of rodents in forced swim situations has attracted especial attention since Porsolt et al. developed a test for the screening of antidepressants, based on this behavior (34–36). They found that well-established antidepressant treatments resulted in a reduction of the time the rats remained motionless. Further, several authors considered the possibility that experimental manipulations known to induce behavioral depression could increase immobility in forced swim situations. Since stress has been repeatedly related to depression (3, 12, 20, 21, 45), the effect of stress on the behavior of rodents in forced swim situations has been investigated in several laboratories. The results are, however, controversial (16, 17, 31, 33, 37, 44). Although some discrepancies could be due to a differential effect of acute vs. chronic exposure to stress, contradictory results have been reported even with acute stress (31, 33, 37, 44). The present experiment aimed at a more systematic study of the influence of the intensity of the stressor and the time elapsed between stressor exposure and the forced swim test in the rat. In addition, to optimize the information obtained from the test, the behavior of the rats was classified into three categories: struggling, mild swim and immobility. It has been found that the three behaviors do not respond homogeneously to treatments such as severe stress (44) and antidepressant administration (7). In addition, the ambiguity of what is considered immobility is considerably reduced.

Tests of general and exploratory activity have been frequently associated to forced swim tests in order to show whether or not changes in the response to the forced swim tests were related to changes in general activity [e.g., (35)]. Therefore, in the present experiment, the influence of acute stress on general and exploratory activity was also studied.

## METHOD

Adult male Sprague-Dawley rats derived of IFFA-CREDO stocks and reared in the breeding center of our university were used. They were 60 days old (approximately 300 g) upon their arrival at the laboratory, and were housed, two per cage, in controlled conditions (lights on from 0700 to 1900 h, temperature 22°C) for at least ten days before the experiments. Food and water were provided ad lib.

Experiment 1 was designed to study the effects of various stressors presumably differing in their intensity on holeboard and forced swim activities. The rats, 70 days old when tested, were randomly assigned to four conditions: 1) controls (unstressed rats), 2) rats subjected to 1 h of noise provoked by alarm bell (85 dB) in a room separated from the animal house, 3) rats subjected to electric tail shock, and 4) rats subjected to 1 h restraint in tubes (6 cm diameter, 22 cm length) provided with several holes. In the latter case, cork sheets were introduced into the tubes to obtain a relatively high degree of movement restriction and to be sure that all rats were subjected to approximately the same degree of restraint (it is noteworthy to mention here that rats were selected by age rather than by body weight). The shocked rats were restrained in the same tubes as restrained rats (without cork sheets), and their tails taped to avoid body movements and tail retraction. The duration of each shock (0.5 mA) and the intervals between shocks were randomly programmed between 2–5 s and 10–110 s respectively. After being subjected to corresponding stress treatments some rats were immediately killed by decapitation or, alternatively, tested in the holeboard or in the forced swim task. Other rats from the four acute treatments were left undisturbed in the animal house until the next day when they were killed without any additional stress or, alternatively, tested in the holeboard or in the forced swim test. Those animals tested were not killed to avoid the confusion between the influence of previous stress and testing on the physiological variables under investigation. Five to eight rats per group were used. The holeboard apparatus used was similar to that described by File and Wardill (14) except that the floor was divided into 16 areas of approximately the same size. The number of fecal boluses released (defecation), areas crossed, rearing, and head-dips were manually recorded for 4 min. A dip was considered to take place when the head was introduced into the holes at least to the level of the eyes. In the forced swim test the rats were introduced in a transparent cylindrical tank similar to that described by Porsolt et al. (34–36), with water (25°C) up to 15 cm, and their behavior recorded for 5 min with videotapes. Behavior was scored from tape by one experimenter unaware of the treatment of the animals. The time spent making the following behaviors was measured with a stop-watch: (a) struggling, which occurred when the rats were diving, jumping or strongly moving all four limbs, the front limbs breaking around the surface of the water or scratching the walls, b) mild swim, which occurred when the rats swam around the tank while moving all four limbs, c) immobility, which occurred when the rats remained motionless except to maintain the head out of the water. The rats were killed by decapitation in a room adjacent to the animal house and the stress room. The trunk blood was collected and maintained in ice-cold water, and centrifuged at 4°C. The serum was frozen at −20 °C.

The results of Experiment 1 did not show an inhibition of activity in the two behavioral tests. Since such as inhibition has been previously described [e.g., (26,42)], Experiment 2 was designed to study the influence of a well-kown, more severe stressor such as immobilization. This experiment was carried out 6 months later and the rats were 78 days old when tested. They were assigned to control or immobilization groups. The latter rats were subjected to 1 h immobilization in wood-boards as described previously (23). The general procedure, including the killing of some additional animals for physiological measures, was similar to that described for Experiment 1.

Serum prolactin, corticosterone and glucose levels were measured because we have previously demonstrated that they are good indices of the intensity of stress experienced by rats (9,10). Glucose was determined by the glucose-oxidase method using a commercial kit (Boehringer-Mannheim). Prolactin and corticosterone were determined by radioimmunoassay as previously described (4, 5, 9).

The statistical significance of the results was analyzed by parametric test except when the variances were not homogeneous even after log. transformation, in which case nonparametric tests were used. In Experiment 1 serum prolactin, corticosterone and glucose levels and behavior in the forced swim test were analyzed with parametric one-way ANOVA and behavior in the holeboard with the nonparametric Kruskal-Wallis test. Post hoc individual comparison of means was carried out with the Student-Newman-Keuls (SNK) test after parametric ANOVA or the Mann-Whitney U-test after nonparametric ANOVA. In Experiment 2 the Student *t*-test or the Mann-Whitney U-test was used.

TABLE 1

EFFECT OF 1 H OF ACUTE EXPOSURE TO STRESSORS ON THE BEHAVIOR OF RATS IN A FORCED SWIM SITUATION

| Stressor | Defecation (No.) | Struggling (s) | Mild Swim (s) | Immobility (s) |
|---|---|---|---|---|
| | | Immediately After Stress | | |
| Control | 3.2 ± 1.1 | 28.4 ± 6.0 | 79.7 ± 7.2 | 192.0 ± 9.9 |
| Noise | 3.4 ± 0.8 | 49.1 ± 5.1 | 94.3 ± 13.2 | 156.6 ± 13.9 |
| Restraint | 2.7 ± 0.7 | 54.4 ± 12.0 | 120.6 ± 11.5 | 125.1 ± 12.0* |
| Tail shock | 3.6 ± 0.6 | 44.9 ± 15.2 | 135.1 ± 14.3* | 120.1 ± 18.5* |
| | | 24 h After Stress | | |
| Control | 3.1 ± 0.8 | 59.0 ± 15.3 | 73.6 ± 5.0 | 163.7 ± 16.5 |
| Noise | 5.0 ± 0.6 | 47.9 ± 8.9 | 79.1 ± 8.0 | 172.1 ± 5.4 |
| Restraint | 2.5 ± 0.5 | 73.4 ± 9.2 | 77.6 ± 7.6 | 149.1 ± 12.7 |
| Tail shock | 2.8 ± 1.1 | 72.6 ± 10.8 | 86.2 ± 8.4 | 142.4 ± 16.0 |

Means ± SEM (n = 7–8) are represented. *$p<0.05$ vs. control group (SNK test).

RESULTS

*Experiment 1*

The effect of the stressors on the response to the forced swim test is depicted in Table 1. The one-way ANOVA revealed a significant effect of the treatments on mild swim activity

TABLE 2

EFFECT OF 1 H EXPOSURE TO STRESSORS ON BEHAVIOR OF RATS IN A HOLEBOARD

| Stressor | Defecation (No.) | Areas Crossed (No.) | Rearing (No.) | Head-Dips (No.) |
|---|---|---|---|---|
| | | Immediately After Stress | | |
| None | 1.7 ± 1.0 | 31.0 ± 7.8 | 7.8 ± 2.3 | 13.7 ± 2.7 |
| Noise | 1.4 ± 0.8 | 40.4 ± 8.1 | 9.6 ± 1.9 | 14.6 ± 2.2 |
| Restraint | 0.2 ± 0.2 | 38.5 ± 7.3 | 6.8 ± 1.6 | 14.3 ± 4.8 |
| Tail shock | 0.6 ± 0.4 | 35.8 ± 10.0 | 7.4 ± 0.9 | 18.2 ± 3.0 |
| | | 24 h After Stress | | |
| None | 1.0 ± 0.5 | 48.3 ± 8.6 | 12.0 ± 4.7 | 11.2 ± 1.6 |
| Noise | 2.2 ± 0.7 | 32.7 ± 9.2 | 7.0 ± 2.4 | 10.0 ± 2.0 |
| Restraint | 2.8 ± 0.8 | 36.5 ± 6.7 | 6.2 ± 2.4 | 8.8 ± 1.8 |
| Tail shock | 2.2 ± 0.2 | 47.5 ± 10.5 | 6.5 ± 1.6 | 9.8 ± 1.1 |

Means ± SEM (n = 5–7) are represented.

TABLE 3

EFFECT OF 1 H EXPOSURE TO VARIOUS STRESSORS ON SOME PHYSIOLOGICAL VARIABLES

| Group | Prolactin (ng/ml) | Corticosterone (μg/dl) | Glucose (mg/dl) |
|---|---|---|---|
| Control | 3.7 ± 0.6 | 4.0 ± 0.4 | 139.3 ± 2.0 |
| Noise | 8.1 ± 2.0 | 14.0 ± 3.3† | 143.0 ± 4.3 |
| Restraint | 15.0 ± 4.0* | 47.7 ± 3.4* | 184.7 ± 11.3* |
| Tail shock | 14.3 ± 2.9* | 53.1 ± 3.3* | 162.3 ± 3.8* |

Means ± SEM (n = 6) are represented. Means having different superscripts differ statistically (SNK test).

($p<0.02$) and immobility ($p<0.005$), but not on struggling, as measured immediately after stress. Individual comparisons indicated that noise had no effect on behavior, shock significantly increased mild swim activity, and both restraint and shock significantly decreased immobility. Twenty-four hours after stress no significant effect of the treatments was found.

Neither immediately after stress nor 24 h later, acute exposure to the various stressful stimuli altered defecation rate or the variables related to activity/exploration (Table 2).

As Table 3 shows, serum prolactin, corticosterone and glucose levels were significantly increased by stress as revealed by ANOVA ($p<0.007$ for prolactin, $p<0.001$ for corticosterone and glucose). Individual comparisons of means revealed that serum prolactin levels were significantly increased in restrained and shocked rats, but not in noise-stressed rats, that showed intermediate levels between control and restrained (or shocked) rats. Corticosterone levels were increased by the three stressors, the effect being milder after noise than after restraint or tail shock. Glucose was not modified by noise but did by restraint and tail shock.

*Experiment 2*

Immediately after stress, immobilization significantly reduced struggling ($p<0.01$) without altering mild swim activity or immobility (Table 4). Twenty-four hours later, immobilized rats showed reduced mild swim activity ($p<0.01$) and increased immobility ($p<0.05$).

Behavior in the holeboard is depicted in Table 5. Immediately after 1 h immobilization, stressed rats showed reduced number of areas crossed ($p<0.01$) and head-dips ($p<0.01$). Twenty-four h later the effect persisted with regard to head-dips only ($p<0.05$).

TABLE 4

EFFECT OF 1 H IMMOBILIZATION (IMO) ON BEHAVIOR OF RATS IN A FORCED SWIM SITUATION

| Stressor | Defecation (No.) | Struggling (s) | Mild Swim (s) | Immobility (s) |
|---|---|---|---|---|
| | Immediately After Stress | | | |
| Control | 5.1 ± 0.7 | 59.5 ± 8.9 | 125.6 ± 12.7 | 114.9 ± 17.9 |
| | † | † | | |
| IMO | 1.0 ± 0.4 | 16.1 ± 1.3 | 150.9 ± 16.8 | 133.0 ± 17.5 |
| | 24 h After Stress | | | |
| Control | 4.7 ± 0.6 | 60.2 ± 7.4 | 138.2 ± 8.2 | 101.6 ± 10.5 |
| | | | † | * |
| IMO | 2.2 ± 0.9 | 77.3 ± 9.3 | 91.4 ± 31.8 | 131.3 ± 25.5 |

Means ± SEM (n = 7–8) are represented. *$p<0.05$, †$p<0.01$.

TABLE 5

EFFECT OF 1 H IMMOBILIZATION (IMO) ON BEHAVIOR OF RATS IN A HOLEBOARD

| Stressor | Defecation | Areas Crossed | Rearing | Head-Dips |
|---|---|---|---|---|
| | | Immediately After Stress | | |
| Control | 1.3 ± 0.8 | 24.8 ± 8.5 | 5.7 ± 2.7 | 8.5 ± 1.3 |
| | | † | | † |
| IMO | 0.1 ± 0.1 | 5.6 ± 0.9 | 3.1 ± 1.6 | 4.1 ± 0.7 |
| | | 24 h After Stress | | |
| Control | 1.6 ± 0.8 | 22.2 ± 6.9 | 5.5 ± 1.9 | 9.0 ± 1.7 |
| | | | | * |
| IMO | 1.7 ± 0.5 | 9.8 ± 1.7 | 5.1 ± 1.6 | 3.0 ± 0.4 |

Means ± SEM (n = 6–8) are represented. *$p<0.05$, †$p<0.01$

The prolactin, corticosterone and glucose levels from the second experiment are shown in Table 6. IMO caused a strong increase in the three variables ($p<0.001$ vs. unstressed group in the three cases).

## DISCUSSION

The present data demonstrate that the effect of acute stress on rat behavior in a forced swim situation is critically dependent on the type of stressor and the time elapsed between stress and testing. In the present experiment we tried to relate the changes in behavior to the intensity of the stressor. This was evaluated in the present experiment by three independent physiological variables, prolactin, corticosterone and glucose levels in serum, all of which have been repeatedly considered as good markers of stress intensity (9,10). Although the results obtained with the three measures were not strictly similar, taken together it appears clear that noise stress was less severe than restraint or tail shock. The latter stressors which presumably differ in various characteristics show a similar elevation of prolactin, corticosterone and glucose levels, and also a very similar effect on the test. Therefore, it might be tentatively assumed that stressor intensity could exert a major effect of the behavior of rats in the forced swim test.

Thus, immediately after stress, a mild stressor such as noise was without effect and two middle intensity stressors such as shock and restraint in tubes decreased immobility, this decrease being not at expense of an increase in struggling (a more escape-oriented response) but in mild swim activity. When a more

TABLE 6

PHYSIOLOGICAL RESPONSE TO 1 H IMMOBILIZATION (IMO)

| Group | Prolactin (ng/ml) | Corticosterone (μg/dl) | Glucose (mg/dl) |
|---|---|---|---|
| Control | 1.7 ± 0.6 | 1.2 ± 0.1 | 144.5 ± 2.1 |
| | * | * | * |
| IMO | 45.9 ± 4.7 | 55.4 ± 4.1 | 315.9 ± 23.8 |

Means ± SEM (n = 6–8) are represented. *$p<0.001$.

severe stressor such as immobilization was used (Experiment 2), it specifically inhibited struggling behavior. Although unstressed animals showed somewhat different values for the behavioral variables analyzed, it should be taken into consideration that the first experiment was carried out 6 months before the second and such as differences are not unexpected in behavioral studies. In addition, the effect of acute immobilization on the forced swim test has been repeatedly observed in our laboratory (unpublished results).

Only the most severe stressor (immobilization) modified behavior in the test carried out 24 h after stress, the immobilized rats showing normal struggling behavior, decreased mild swim activity and increased immobility.

The finding that the three components of behavior in the forced swim test are not homogeneously influenced by stress, supports the validity of separating them. Although the theoretical interpretation of the changes observed could be at present speculative, mild swim might be the reflection of arousing properties of middle intensity stressors, while struggling behavior could be a more escape-oriented response only reduced by extremely severe and debilitating situations [see (44)].

Other studies have focussed on the effect of stress on behavior in forced swim situations. Comparison with the present work reveals important methodological differences. Thus two laboratories have used mice as subjects. Whereas Nomura et al. (27) observed that acute exposure to tail shock increased immobility when the mice were tested between 30 min and 7 days after the stress session, Prince and Anisman (37) reported that shocked mice showed reduced immobility when tested just after stress and increased immobility when tested 24 h later. In rats, Weiss et al. (44) exposed rats to 2 h of severe electric shock and 90 min later they tested the rats in a water tank for 15 min. They found that inescapable, but not escapable, shock decreased struggling in the first 5 min of exposure to the tank. It appears likely in view of our present results that contradictory results could be partially explained assuming that nonsevere stressors cause invigoration, whereas severe stressors cause debilitating effects. Even with a severe stressor such as immobilization, the duration of exposure to it might be important since we have found no effect of 15 min immobilization on the response to the same forced swim test carried out 24 h after stress (unpublished data). In sum, in addition to the influence of the intensity of the stressor, the effect of the species as well as the time elapsed between stressor exposure and testing appear to influence the results.

It was found that 1 h exposure to a mild (noise) or middle intensity (restraint in tubes) stressors did not alter holeboard activity in adult male rats. It is, therefore, unlikely that the enhancement of mild swim activity observed in restrained rats would have been due to an unspecific increase in activity in all novel situations. With a severe stressor such as immobilization in wood-boards a profound inhibition of some components of activity/exploration such as the number of areas crossed and the number of head-dips was observed. This inhibition of activity in the holeboard was accompanied by an inhibition of struggling, a behavior which presumably requires higher motor effort than mild swim. It is, therefore, tempting to assume that immobilization caused a debilitating action on several motor activities. The inhibitory effect of immobilization on these variables related to activity/exploration is consistent with previous reports using various stressors (11, 24, 26, 29, 38, 42, 43). The persistency of some of the effects 24 h later is also consistent with a previous report (22).

Other authors have reported that acute stress increases activity in the open-field, especially by increasing the exploration of inner areas, in rats and mice (26,40). The reasons for the discrepancies are unclear. Changes in the characteristics of the apparatus used in the test, the intensity of the stressors and the duration of the test should be taken into account. In addition, the procedures used in manipulating the animals during the days of acclimation to the laboratory might also contribute. Thus various laboratories have found that previous exposure to chronic unpredictable stress reduced the behavioral activation caused by acute exposure to a novel stressor (16, 21, 41). It might be hypothesized that chronic exposure to stressors unspecifically desensitizes the animals in response to an unknown stressor. In this case the process of desensitization might be restricted to behavioral activation because pituitary-adrenal response to a novel stressor is not reduced by previous chronic exposure to stress (6,8). Failure to find behavioral activation after various nonsevere stressors in the present experiment would be the consequence of the ordinary entry into the animal room and handling of the rats.

From the present results it could be concluded that: 1) no simple relationship exists between stress and forced swim behavior, the effect being critically dependent of the intensity of the stressor; and 2) classification of behavior into various categories might contribute to a better understanding of the effects of experimental manipulations such as stress exposure [(44), present data] and antidepressant administration (7).

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