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Behavioral and Neurochemical Changes in Response to Acute Stressors: Influence of Previous Chronic Exposure to Immobilization

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POL, O., L. CAMPMANY, M. GIL AND A. ARMARIO. *Behavioral and neurochemical changes in response to acute stressors: Influence of previous chronic exposure to immobilization.* PHARMACOL BIOCHEM BEHAV 42(3) 407–412, 1992. – The effect of daily (2 h) exposure to immobilization (IMO) for 15 days on the behavioral and neurochemical responses of adult male rats to acute stress caused by 2-h IMO or 2-h tail-shock was studied. The brain areas studied were frontal cortex, hippocampus, hypothalamus, midbrain, and pons plus medulla. Chronic exposure to IMO did not alter noradrenaline (NA), 3-methoxy,4-hydroxyphenyletileneglycol-SO_4 (MHPG-SO_4), serotonin, or 5-hydroxindoleacetic acid (5-HIAA) concentrations in any brain area as measured approximately 20 h after the last exposure to IMO. Exposure to behavioral tests did not modify neurochemical variables except NA levels in the hypothalamus of nonchronically stressed (control) rats. Both exposure to 2-h IMO or 2-h shock significantly decreased NA levels in hypothalamus and midbrain of nonchronically stressed rats. These decreases in response to the two acute stressors were not observed in chronically stressed rats. However, MHPG-SO_4 levels increased to the same extent in control and chronically stressed rats after exposure to the acute stressors. Likewise, increased 5-HIAA concentrations observed in response to acute stressors were similar in control and chronically stressed rats. The inhibition of activity (areas crossed and rearing) in the holeboard caused by acute IMO was less marked in rats previously exposed to the same stressor than in control rats, but the response to shock was similar. In the forced swim test, acute IMO decreased struggling in control rats but tended to increase it in chronically stressed rats. The response to shock followed the same pattern as that to IMO, although it was slight. These data suggest that: (a) cross-adaptation between stressors might or might not exist, depending upon the behavioral test studied; (b) previous chronic stress did not appear to reduce monoaminergic response to the same or a novel acute stressor as evaluated by the increases in MHPG-SO_4 and 5-HIAA levels; (c) apparently, behavioral adaptation to repeated stress was not related to the changes in noradrenergic or serotonergic activity.

Chronic stress Cross-adaptation Noradrenergic activity Serotonergic activity Holeboard Forced swim

THE influence of previous chronic exposure to stress on animal response to the same or to a novel acute stressor has been extensively investigated with regard to the endocrine system. It is clear that plasma catecholamine and adrenocorticotropin (ACTH) levels are reduced in response to the same acute stressor to which animals were chronically exposed (3,5,8,19). This phenomenon has been termed either adaptation or habituation. Endocrine adaptation to chronic stress appears to be specific for the stressor to which animals were chronically exposed and therefore no cross-adaptation has been demonstrated (3,5,8). Recently, we found evidence that the existence of cross-adaptation to stressors at the physiological level would depend upon the variable studied (5).

The existence of cross-adaptation on behavioral variables has been poorly investigated. Weiss et al. (31) reported that both chronic exposure to uncontrollable shock or cold swim protected against the deficit in the avoidance-escape response of rats caused by either a single shock or cold swim exposure. This suggests the existence of cross-adaptation. In contrast, Rosellini and Seligman (26) observed that previous chronic exposure to inescapable shock did not alter the escape learning deficit caused by acute exposure to the same aversive stimulus. More recently, Prince and Anisman (24) also failed to find in mice a protective effect of previous chronic shock on the acute shock-induced deficit in a forced swim task. Therefore, both the question as to whether or not there is an actual adaptation

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to the negative behavioral effects of acute stress exposure and whether or not this adaptation would be specific for the particular stressor chronically applied remain to be answered.

On the other hand, behavioral deficits observed after acute exposure to severe stressors have been repeated observed to be associated with norepinephrine (NA) depletion caused by such stressors (1,2,30–32). Since chronic exposure to stressors eliminated the NA depletion caused by a subsequent acute stress (1,31), it has been assumed that disappearance of acute stress-induced behavioral deficits in chronically stressed rats would have been due to the lack of NA depletion during stress.

In the present experiment, we studied the influence of previous chronic exposure to one stressor [immobility (IMO)] on the behavior of rats after acute exposure to the same or to another (shock) stressor. Animals were tested in a holeboard apparatus (12) to measure general/exploratory activity and in a forced swim task as described by Porsolt et al. (23) but without a pretest session in the water. The levels of NA, 4-hydroxyphenyletilenglycol-SO_4 (MHPG-SO_4), serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) in some brain areas were also studied because few studies have tried to relate behavioral and neurochemical variables in chronically stressed rats and both NA and serotonin have been repeatedly implicated in the control of these behaviors.

METHOD

Animals and General Procedure

Male Sprague-Dawley rats 2 months old upon their arrival at the laboratory were used. Rats were left undisturbed for 10 days before starting the experiment and were housed three per cage in a controlled environment (lights on from 0700–1900 h, temperature 22°C). Food and water were provided ad lib. Rats were randomly assigned to two groups: (a) control and (b) IMO, rats that were immobilized in woodboards 2 h daily (at 10:15 a.m.) for 15 days as described previously (20).

On day 16, rats from both groups (n = 6) were killed immediately after being taken from the animal room. Other rats (n = 8 per group) were tested for 4 min in a holeboard and then for 5 min in a water tank. Immediately after testing, animals were killed. The remaining rats were exposed to either IMO (n = 8 per group) or shock (n = 8 per group) for 2 h and then tested in the holeboard and the water tank. After testing, they were killed. The electric shock was applied to the tails of rats while restrained in plastic tubes provides with several holes. The intensity of shocks was 0.5 mA, duration between 2–5 s, and intervals between shock randomly programmed between 10–110 s.

Behavioral Tests

The holeboard consisted of a wooden box with four holes on the bottom (12). Its floor was divided into 16 areas of approximately the same size. The number of boluses produced (defecation), the number of areas crossed, rear episodes, and head-dips were manually recorded. After that, rats were put for 5 min into a plastic cylinder (height = 40 cm, diameter = 20 cm) containing a 15-cm level of water at 25°C. The time spent making the two following behaviors were measured using a stopwatch: (a) struggling, which occurred when rats were diving, jumping, or strongly moving all four limbs, the two front limbs breaking the surface of the water or scratching the walls; (b) immobility, which occurred when animals were making only minor movements to float. The remainder of activity was categorized as mild swim and essentially consisted of swimming around the tank while moving all four limbs.

Neurochemical Analysis

Rats were killed by decapitation. Brains were quickly removed over a cold plate and stored at −80°C. Brains were dissected by the method of Glowinski and Iversen (15) in the following areas: frontal cortex, hippocampus, hypothalamus, midbrain, and pons plus medulla.

These brain regions were homogenized with 10 vol of a medium containing 8% acetonitrile and 92% monosodium phosphate buffer 0.1 M, disodium EDTA 1 mM, and octane sulfonic acid 0.75 mM (pH = 3.2). NA, serotonin, and 5-HIAA were determined by high-performance liquid chromatography (HPLC) using a SP8700 XR pump (Spectra Physics,), a SPH125 automatic injector (Sparck Holland) fitted to a μBondapak C18 column, and an electrochemical detector (Waters 460) with a working electrode potential of 0.7 V. The mobile phase, the same as the homogenization buffer, was fluxed at a rate of 1 ml/min. In the rat, the main metabolite of NA is MHPG-SO_4. To determine total MHPG, a previous hydrolysis with perchloric acid (7) was carried out by adding 50 μl of a solution of perchloric acid to 650 μl of the homogenate to obtain a final 0.1 N concentration of the acid. After 5 min at 100°C, the supernatant was manually injected into the HPLC apparatus. The mobile phase was composed of 3% acetonitrile and 97% monosodium phosphate buffer 0.1 M and 1 mM disodium EDTA (pH = 4.0). The apparatus, column, and conditions were the same as for the other compounds except the voltage was set at 0.75 V. MHPG-SO_4 was determined in the hypothalamus, the region that most consistently responds to stress (14,16,29). In all cases, external standards were used.

Statistical Analysis

The statistical significance of the behavioral data was evaluated by two-way analysis of variance (ANOVA) with acute stress (no stress, stress) and chronic stress (control, chronic IMO rats) as the main factors. When the interaction between the two main factors was significant, appropriate comparisons between individual means were done with Student's t-test or the Mann–Whitney U-test (if the variances were not homogeneous). Since in the neurochemical data an additional group (no stress test) was introduced, we considered it more appropriate to compare the neurochemical response to the different situations with separate one-way ANOVAs for the stress-naive and chronically stressed rats. To find the acute treatments responsible for the significance in the ANOVA, posthoc individual comparisons of means were done with the Student–Newman–Keuls test (α = 0.05) after the parametric ANOVA or the Mann–Whitney U-test after the nonparametric ANOVA (which was used when the variances were not homogeneous). Where appropriate, comparisons between control and chronic IMO rats under the same acute treatment with the Student's t-test were done.

RESULTS

Behavioral Data

With regard to the response of animals to the holeboard (Fig. 1), two-way ANOVA revealed that acute IMO reduced the number of areas ($p < 0.001$), rearings ($p < 0.001$), and head-dips ($p < 0.001$). The overall effect of chronic IMO was significant regarding the number of areas ($p < 0.02$) and rearings ($p < 0.04$). The interaction acute × chronic IMO was highly significant for the number of areas ($p < 0.002$) and

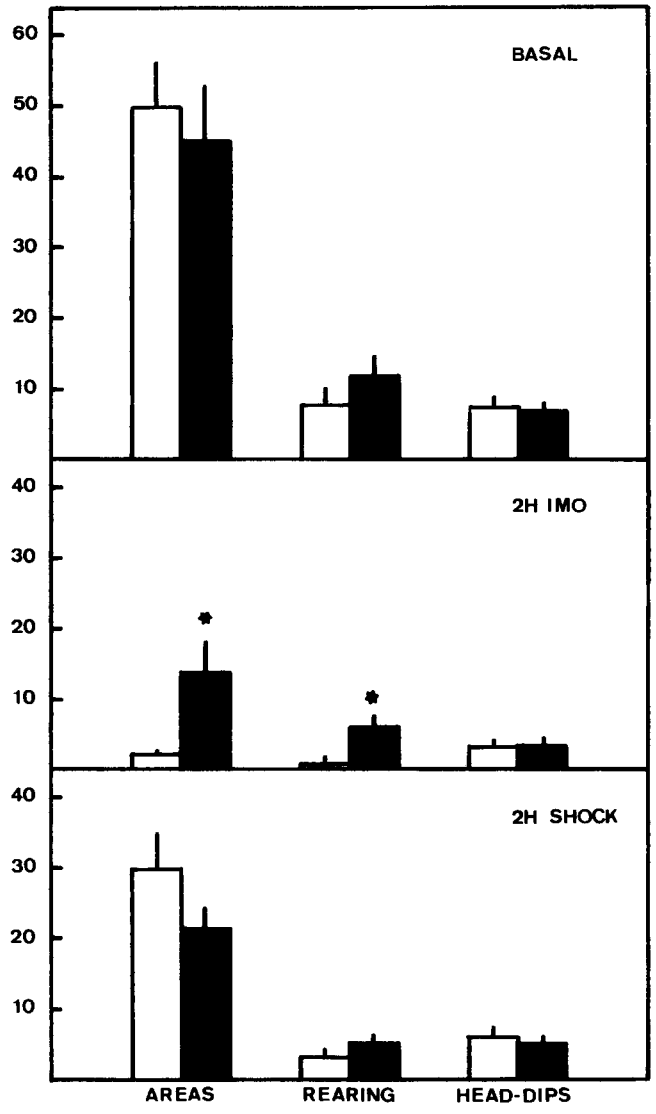

FIG. 1. Effects of chronic IMO on behavior of rats in the holeboard in unstressed (basal) and in stressed (IMO or shock) conditions. Means and SEM (n = 6–8 per group) of how many times animals exhibited each behavior are represented. Open bars indicate controls and closed bars chronic IMO rats. *At least $p < 0.05$ vs. corresponding control group under the same acute treatment. For other statistical results, see text.

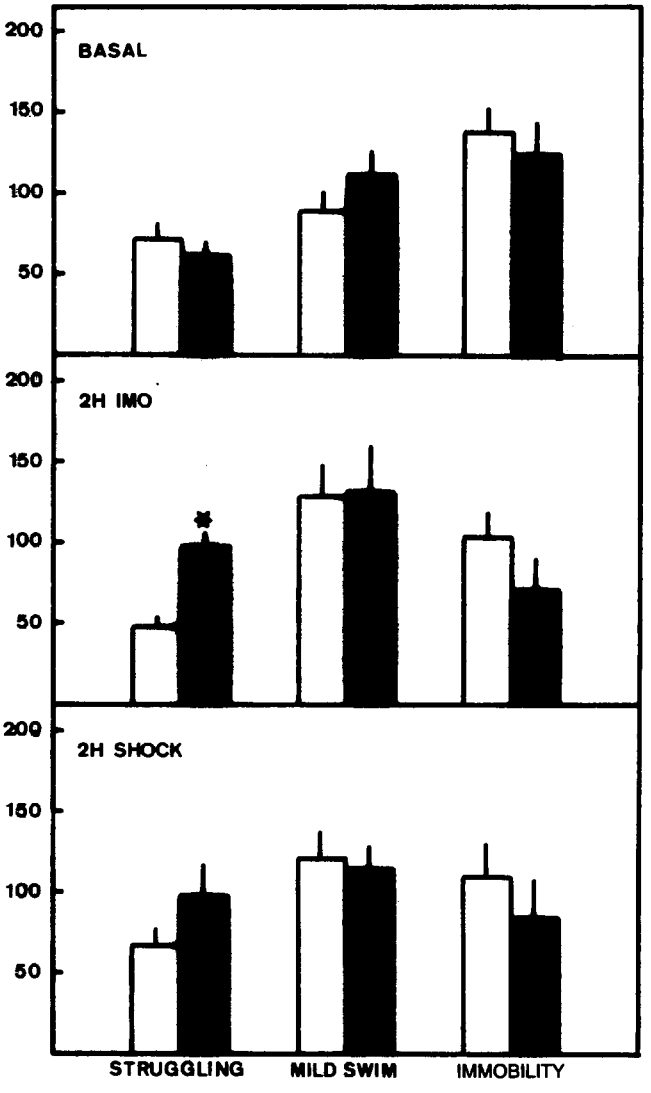

FIG. 2. Effects of chronic IMO on behavior of rats in the forced swim test in unstressed (basal) and stressed (IMO or shock) conditions. Means and SEM (n = 6–8 per group) of time (in seconds) spent making each type of behavior are represented. Open bars indicate controls and closed bars chronic IMO rats. *$p < 0.001$ vs. corresponding control group under the same acute treatment. For other statistical results, see text.

marginally significant for the number of rearings ($p = 0.084$). The reason for these interactions was that inhibition of activity caused by acute IMO was more marked in control than in chronically stressed rats ($p < 0.05$ for the number of areas, $p < 0.005$ for the number of rearings). In response to acute shock, two-way ANOVA revealed an inhibitory effect of shock on the number of areas ($p < 0.001$), rearings ($p < 0.02$), and head-dips ($p < 0.05$). Neither the effect of previous chronic IMO nor the interaction acute shock × chronic stress were significant in any case.

In the forced swim test (Fig. 2) after acute IMO two-way ANOVA revealed a significant effect of acute IMO on immobility ($p < 0.05$), a marginally significant effect of acute IMO on struggling ($p = 0.062$), and a highly significant interaction of acute IMO × chronic stress with regard to struggling ($p < 0.001$). Thus interaction was due to the fact that, in response to acute IMO, stress-naive rats tended to decrease struggling whereas chronically stressed rats tended to increase it, resulting in a significant difference between control and chronically stressed rats ($p < 0.001$). In response to shock, no overall significant effects of either acute or chronic treatments were found, but the interaction acute shock × chronic stress approached significance ($p = 0.079$) for the same reason as in response to acute IMO.

Neurochemical Data

Table 1 depicts NA levels. In stress-naive rats, ANOVA revealed significant effects of the acute treatments on NA

TABLE 1

EFFECT OF CHRONIC AND ACUTE STRESS ON NA (ng/g) CONTENT IN FRONTAL CORTEX (FC), HIPPOCAMPUS (HP), HYPOTHALAMUS (HT), MIDBRAIN (MB), AND PONS PLUS MEDULLA (PM)

Stressors						
Chronic	Acute	FC	HP	HT	MB	PM
None	None	338 ± 14	367 ± 34	1943 ± 63	529 ± 32	603 ± 24
	Tests	333 ± 19	344 ± 32	1650 ± 73*	493 ± 20	522 ± 27
	IMO	314 ± 20	312 ± 30	1439 ± 54*	419 ± 21*	480 ± 26
	Shock	341 ± 41	303 ± 34	1460 ± 161*	441 ± 21*	543 ± 48
IMO	None	339 ± 20	357 ± 45	2109 ± 109	550 ± 36	627 ± 38
	Tests	364 ± 21	383 ± 20	2036 ± 129	500 ± 22	684 ± 33
	IMO	366 ± 20	332 ± 28	1833 ± 166	532 ± 20	540 ± 42
	Shock	378 ± 23	398 ± 30	2002 ± 145	560 ± 23	643 ± 29

Means ± SEM (n = 5-6 in nonacutely stressed animals, n = 7-8 in other groups) are represented.
*$p < 0.05$ vs. corresponding nonacutely stressed rats (Student-Neuman-Keuls test).

levels in the midbrain ($p < 0.01$) and hypothalamus ($p < 0.007$). In the latter region (Fig. 3), a significant effect on MHPG-SO_4 levels was also observed ($p < 0.001$). NA levels in the midbrain were not altered by exposure to the tests, but were decreased by IMO and shock. In the hypothalamus, the three stressful situations reduced NA levels to the same extent. MHPG-SO_4 levels were significantly increased by exposure to the test, but the increase was greater after IMO and after shock. In chronic IMO rats, NA levels were not altered by the various acute treatments in any of the regions studied. However, MHPG-SO_4 levels were modified by the treatments ($p < 0.001$), resulting in significant increases after both acute IMO and acute shock. No differences were observed between control and chronic IMO rats under the same acute treatment.

Serotonin levels were not altered by the acute treatments either in control or in chronic IMO rats (data not shown). In contrast, the acute treatments resulted in changes in 5-HIAA levels in pons-medulla ($p < 0.004$), midbrain ($p < 0.001$), hypothalamus ($p < 0.03$), and frontal cortex ($p < 0.001$) of control rats. In chronic IMO rats, all regions showed significant changes: pons-medulla ($p < 0.004$), midbrain ($p < 0.03$), hypothalamus ($p < 0.001$), hippocampus ($p < 0.03$), and frontal cortex ($p < 0.002$). In no case were differences observed between control and chronic IMO rats under the same acute treatment (Table 2).

DISCUSSION

In stress-naive rats, acute exposure to IMO for 2 h drastically decreased measures of activity in the holeboard such as

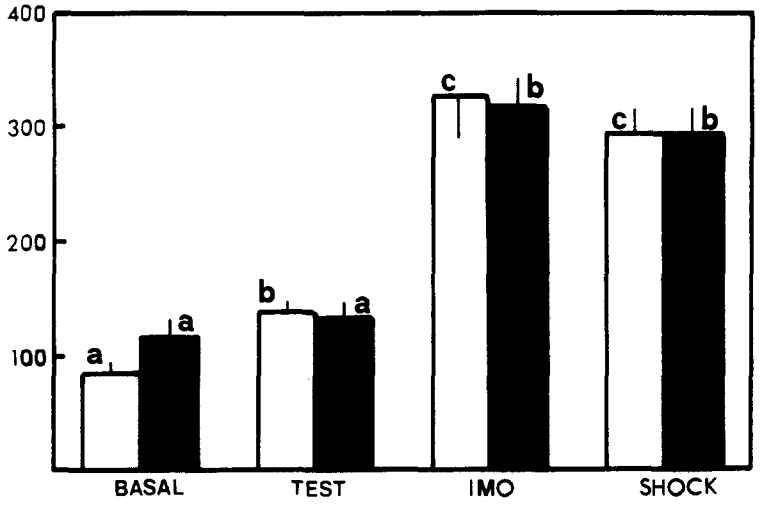

FIG. 3. Hypothalamic MHPG-SO_4 (ng/g) response to acute stressors in control and chronic IMO rats. Means and SEM (n = 5-8 per group) are represented. Open bars indicate controls and closed bars chronic IMO rats. Within the same chronic treatment, bars labeled with different letters differ statistically (Student-Neuman-Keuls test). Significant differences between control and chronic IMO rats under the same acute treatment were found.

TABLE 2

EFFECT OF CHRONIC AND ACUTE STRESS ON 5-HIAA CONTENT (ng/g) OF FRONTAL CORTEX (FC), HIPPOCAMPUS (HP), HYPOTHALAMUS (HT), MIDBRAIN (MB), AND PONS PLUS MEDULLA (PM)

Treatments						
Chronic	Acute	FC	HP	HT	MB	PM
None	None	462 ± 11	526 ± 27	779 ± 31	864 ± 23	650 ± 47
	Tests	500 ± 22	602 ± 42	890 ± 90	995 ± 40	643 ± 42
	IMO	772 ± 43*	684 ± 42	1017 ± 66*	1139 ± 53*	859 ± 47*
	Shock	691 ± 29*	649 ± 51	1033 ± 94*	1129 ± 56*	830 ± 60*
IMO	None	541 ± 62	548 ± 35	833 ± 57	918 ± 65	592 ± 30
	Tests	485 ± 28	545 ± 26	819 ± 31	966 ± 51	649 ± 33
	IMO	693 ± 31*	662 ± 46*	1009 ± 40*	1083 ± 42	813 ± 58*
	Shock	657 ± 20*	638 ± 27	1026 ± 36*	1130 ± 45*	814 ± 24*

Means ± SEM (n = 5–6 in nonacutely stressed animals, n = 6–8 in other groups) are represented.
*$p < 0.05$ vs. corresponding nonacutely stressed group (Student–Neuman–Keuls test).

the number of areas crossed and the number of rearings. More specific measures of exploration such as head-dips (12) were less affected. In our conditions, shock appears to be less stressful than IMO as suggested by the weak inhibition of activity and also by the less degree of hyperglycemia it causes (4). The inhibitory action of stress on measures of activity-exploration is in accordance with previous results (4,17,21, 25,30). The behavioral deficit caused by acute IMO in the holeboard was less marked in chronic IMO rats, which suggests that rats became partially adapted to the situation as a consequence of the daily repetition of exposure to the stressor. Adaptation of other physiological variables such as ACTH and glucose has been observed in other experiments with similar experimental designs (5,6). However, in response to shock a similar inhibition of rearing and number of areas crossed was observed in control and chronic IMO rats. These data clearly indicate that adaptation was specific for the stressor to which rats were chronically exposed. This is in good agreement with the conclusions reached using endocrine variables (3,5,8). In contrast, Weiss et al. (31) reported that cross-adaptation to stressors took place in rats when the avoidance-escape response of the rats in a shuttlebox was evaluated. It appears that the existence of cross-adaptation might depend upon the variable under investigation. Thus, in the forced swim test the influence of acute IMO was strongly dependent upon the previous exposure to chronic IMO: In stress-naive rats it tended to reduce struggling, in accordance with a previous report (4), whereas in chronic IMO rats the opposite was found. After shock, a similar but less weak pattern was found so in this case some sign of cross-adaptation was found.

Changes in NA, serotonin, and 5-HIAA are consistent with most results from other laboratories. Acute stress did not alter serotonin content but increased its metabolite 5-HIAA in almost all brain regions studied, in good agreement with previous reports (10,11,22). Also in accordance with results using IMO as chronic stressor, this treatment did not modify either resting levels of serotonin and 5-HIAA (9,13,15) or 5-HIAA response to acute stress (submitted). Our data argue against a major role of the serotonergic system in the behavioral changes observed after chronic IMO. In fact, we have evidence that inhibition of serotonin synthesis with parachlorophenylalanine (PCPA) did not alter the behavior of rats in the two tests (unpublished results), corroborating the more indirect results presented here. In stress-naive rats, both acute IMO and acute shock significantly decreased NA content in the hypothalamus and midbrain. In the hypothalamus, even exposure to the test significantly decreased NA content. This finding corroborates that the hypothalamus is one of the areas more sensitive to stressors. In contrast, in chronic IMO rats no change in NA content was observed after acute exposure to IMO or shock. It appears that chronic IMO protects the rats from NA depletion caused not only by IMO but by a novel stressor (shock), suggesting that a nonspecific neurochemical adaptation was present in chronic IMO rats. This was most likely the result of increased NA synthesis in chronically stressed rats (13,27,28,33) rather than decreased utilization because after both acute IMO or acute shock MHPG-SO_4 levels in the hypothalamus were similar in control and chronic IMO rats.

Behavioral deficit after exposure to severe stressors has been attributed to NA depletion (1,2,30–32). However, the actual meaning of this depletion in terms of brain noradrenergic activity is unclear. Thus, in the present work NA depletion was observed in stress-naive rats but not in chronically stressed rats and the NA release, as judged by MHPG-SO_4 concentration, was similar in both groups. If NA depletion could lastly provoke noradrenergic hypoactivity, this should be reflected in MHPG-SO_4 levels.

Even if we assume that NA depletion might affect, through unknown mechanisms, behavior in the holeboard, our results indicate that this behavior was, at least partially, independent on NA levels. First, in chronic IMO rats behavioral deficit in the holeboard was reduced in response to IMO but not to shock, in spite of a similar behavior of NA in the two situations. Second, a partial behavioral deficit was observed in chronically stressed rats after acute IMO without change in NA. Most likely, other neurotransmitters are also involved in stress-induced changes in the holeboard. With regard to struggling behavior in the forced swim test, our data fit well with a possible positive role of NA because chronic IMO prevented both NA depletion and behavioral inhibition in response to acute IMO and acute shock.

In sum, the present data indicate that chronic exposure to

IMO protected animals against the negative effect of acute exposure to the same stressor on two behavioral tests. This adaptation was specific for the chronically applied stressor in one test (holeboard) but not in the other (forced swim). Neither noradrenergic nor serotonergic activities were modified by chronic IMO and therefore a major contribution of the activity of both monoamines to the stress-induced behavioral changes are unlikely. Nevertheless, the possible role of stress-induced NA depletion in behavioral changes would require further studies.

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