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Norepinephrine and Serotonin Alterations Following Chronic Stressor Exposure: Mouse Strain Differences

N. SHANKS,* J. GRIFFITHS† AND H. ANISMAN†[1]

*Douglas Hospital Research Centre, Montreal, Quebec, Canada
†Carleton University, Ottawa, Ontario, Canada

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SHANKS, N., J. GRIFFITHS AND H. ANISMAN. *Norepinephrine and serotonin alterations following chronic stressor exposure: Mouse strain differences.* PHARMACOL BIOCHEM BEHAV **49**(1) 57-65, 1994.—Exposure to acute uncontrollable foot shock influenced the levels and utilization of norepinephrine (NE) and serotonin (5-HT) in several brain regions. These effects varied between the BALB/cByJ and C57BL/6J mouse strains, with the former displaying more pronounced amine variations. Following repeated exposure to foot shock over 15 days, the decline of NE associated with an acute stressor was abrogated. In the hypothalamus, this was accompanied by high MHPG accumulation, suggesting that the increased NE stemmed from a compensatory increase in synthesis. In the locus coeruleus and prefrontal cortex the accumulation of MHPG declined with repeated exposure, possibly suggesting moderation in utilization. In animals exposed to a chronic unpredictable stressor regimen, the NE decline in the hypothalamus was precluded, but pronounced NE reductions were still evident in the locus coeruleus and prefrontal cortex. The data are related to behavioral impairments associated with stressor application, as well as to the particular vulnerability of BALB/cByJ mice to stressor-induced behavioral impairments.

Stress Norepinephrine Serotonin Strains

STRESSORS have reliably been shown to increase the turnover of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) in several brain regions (1,4,18,29). If the stressor is uncontrollable and sufficiently severe, utilization of these amines may exceed synthesis, resulting in a net decline of neurotransmitter levels. It was suggested that the stressor-induced amine reductions diminish the organism's ability to contend with subsequent environmental challenges, culminating in a variety of behavioral disturbances [see (4,30)].

In contrast to the reduced amine concentrations associated with acute stressors, following repeated insults, amine levels may equal or even exceed those of nonstressed animals (2,3, 12,19,29). It seems that repeated stressor application may engender a compensatory increase of NE synthesis, thereby preventing the amine reduction (15,29). The DA reductions ordinarily associated with an acute stressor are likewise absent following chronic stressor exposure (8,19), possibly owing to moderation of the excessive amine utilization ordinarily elicited by the stressor (11). The available data concerning the effects of chronic stressors on 5-HT activity appear to be less clear, although it has been suggested that a compensatory increase in amine synthesis may be provoked with chronic stressor regimens (6,9,14). In addition to alterations of amine synthesis, repeated stressor application may elicit pronounced alterations of NE receptor sensitivity, as well as the β-NE stimulated cAMP response (25,27). Stone (26) reported that chronic stressor exposure provokes the desensitization of cAMP linked NE receptors, including both the β and α_1 postsynaptic receptor subpopulations. Although the functional significance of receptor alterations associated with chronic stressor exposure is not completely understood, it has been suggested that such changes may underlie adaptive processes, particularly since repeated treatments with antidepressant agents (e.g., desmethylimipramine) lead to similar α_1 and β-NE receptor alterations (25,28).

Neurochemical adaptation to repeated stressor exposure depends upon a number of properties of the stressor. For instance, a predictable stressor administered at the same time

[1] Requests for reprints should be addressed to H. Anisman, Carleton University, Life Sciences Research Building, Ottawa, Ontario K1S 5B6, Canada.

of day throughout the regimen readily leads to a neurochemical adaptation (13). In contrast, the adaptation occurs less readily when a more unpredictable stressor regimen is employed (13,17). Furthermore, in contrast to the downregulation of β-NE receptors associated with a chronic predictable stressor, Molina et al. (17) demonstrated that chronic variable stressor application resulted in the upregulation of β-receptors, and this effect could be antagonized by concurrent adminstration of the antidepressant, imipramine. It was, thus, proposed that the absence of receptor desensitization in response to a chronic stressor may represent a failure in adaptive processes necessitating intervention with pharmacological treatments to ameliorate stressor-induced behavioral disturbances (4).

Considerable interindividual variability exists with respect to the behavioral and neurochemical consequences of stressors, likely stemming from factors unrelated to properties of the stressor itself. Indeed, it has been demonstrated that genetic factors contribute to the interindividual variability that exists in the expression of stressor-induced neurochemical and behavioral alterations (7,21,23,24,31,32) and with respect to the effects of antidepressants in antagonizing the behavioral disturbances (22). Given the strain-dependent nature of stressor-provoked behavioral and amine alterations in response to acute stress, it is conceivable that strain differences would also be evident with respect to adaptive processes associated with chronic stressor regimens. Moreover, it is possible that in any given strain the course of the adaptation will be transmitter and brain-region specific. The present investigation was undertaken to assess the alterations of NE and 5-HT, and their respective metabolites, following a chronic stressor regimen in two inbred strains of mice (BALB/cByJ and C57BL/6J), which were previously shown to exhibit differential neurochemical alterations in response to acute stressor exposure.

EXPERIMENT 1

Earlier studies conducted in this laboratory indicated that, in general, BALB/cByJ mice were particularly vulnerable to stressor-induced behavioral, central neurochemical, and plasma corticosterone alterations, although C57BL/6J mice were particularly resilient in these respects (21-24,31). Experiment 1 assessed the effects of acute and repeated uncontrollable foot shock on central NE and 5-HT in the BALB/cByJ and in the C57BL/6J mice.

Method

Subjects. Thirty naive male mice of the BALB/cByJ and of the C57BL/6J strains were obtained from the Jackson Laboratory, Bar Harbor, ME, at 35-40 days of age. Mice were permitted approximately four weeks to acclimatize to the laboratory prior to serving as experimental subjects. During the acclimatization period the animals were housed five per cage, with free access to food and water, and were maintained on a 12L : 12D cycle (lights 0700-1900 h). All experimental manipulations were conducted between 0900-1200 h.

Apparatus and procedure. Inescapable foot shock was administered in six black Plexiglas chambers that measured 30 × 14 × 15 cm. The chamber floors consisted of 0.32 cm stainless steel rods spaced 1.0 cm apart (center to center) and were connected in series by neon bulbs. The end walls of the chambers were lined with stainless steel plates and were connected in series to the grid floor. Shock (300 μA, 60 Hz, AC) was delivered to the floor through a high voltage, high resistance source, thereby assuring relatively constant current. A red Plexiglas roof served to reduce illumination of the chambers. Chambers of the same characteristics and dimensions, but not connected to a power source, were used for pretreatment of the nonshocked groups.

Prior to the experiment, mice were housed individually for a 3-day period. Mice were then assigned to five conditions consisting of no shock treatment, or 1, 5, 10, or 15 shock sessions applied on successive days. The shock treatments consisted of mice being placed individually in the shock chambers and exposed to 360 foot shocks of 2-s duration at 300 microamps (9-s intertrial intervals), while the mice that were not shocked were placed in the shock apparatus for an equivalent period without shock being delivered. Immediately following the final shock treatment, the mice were decapitated and brains sectioned and quickly frozen for subsequent determinations of NE, 5-HT, and their metabolites, MHPG and 5-HIAA, using a slight modification of the HPLC procedure of Seegal, Brosch, and Bush (20), as previously described (24). The protein content of each sample was measured using the method of Lowry et al. (16).

Brain regions were sectioned on a dissecting block fashioned from 0.5 mm thick aluminum templates and separated by brass plates (0.25 mm). The slots created by the brass plates in the block served as guides for single-edged razor blades. The brain sections were teased from the blades onto glass slides and frozen on dry ice. A petri dish filled with powdered dry ice served as a cold stage for sectioning and was situated under a stereomicroscope, which was illuminated by a fiber optic cold light source. Under low magnification, the prefrontal cortex, dorsal hippocampus, and locus coeruleus (LC) were punched with hollow microdissection needles ranging in diameter from 22 to 16 gauge, while the entire hypothalamus was taken prior to microdissection. The punched sections were placed in round-welled titer trays and were frozen at −70°C until assayed.

Results

Analyses of variance were conducted independently for each of the amines and metabolites of each brain region. A number of tissue samples were lost during the course of the experiment and, hence, the degrees of freedom for the analyses varied across brain regions. Because a priori hypotheses had been made concerning neurochemical adaptation in BALB/cByJ and C57BL/6J mice, comparisons of the simple effects comprising the strain × shock treatment interaction were conducted irrespective of the significance of the interaction.

The concentrations of NE and MHPG among BALB/cByJ and C57BL/6J mice as a function of the shock condition are depicted in Fig. 1. Analysis of variance revealed that hypothalamic NE concentrations varied as a function of the strain × shock treatment interaction, $F(4, 50) = 2.65$, $p < 0.05$. Newman-Keuls multiple comparisons ($\alpha = 0.05$) of the simple effects comprising this interaction revealed that hypothalamic NE concentrations of nonstressed BALB/cByJ mice exceeded that of C57BL/6J mice. Concentrations of hypothalamic NE of BALB/cByJ mice were reduced, although not significantly so, after one session of foot shock. Following 5 or 10 sessions of shock, NE levels were significantly reduced relative to nonshocked mice, but after 15 sessions of foot shock the levels of NE increased somewhat, such that they approached control levels. In contrast, one shock treatment produced only a small decline of NE in the hypothalamus of C57BL/6J mice, and after 5, 10, or 15 shock sessions NE

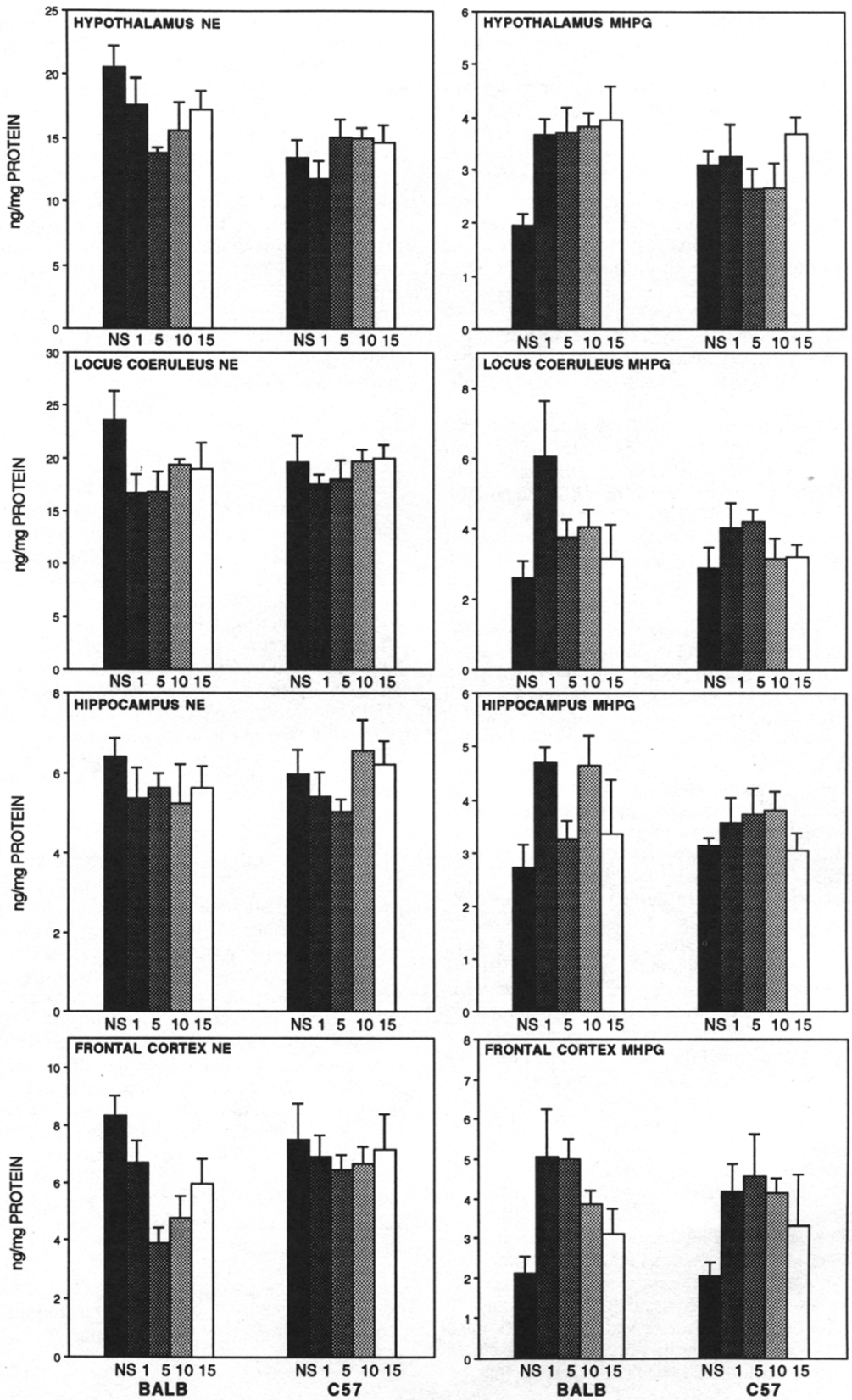

FIG. 1. Mean (±SEM) concentrations of NE and MHPG in several brain regions of BALB/cByJ and C57BL/6J mice following 0 (no shock), 1, 5, 10, or 15 sessions of foot shock.

concentrations were comparable to those of nonstressed mice. The analysis of variance revealed that the shock treatment increased the accumulation of MHPG, $F(4, 50) = 2.52$, $p = 0.05$. Moreover, the strain × shock treatment interaction approached significance, $F(4, 50) = 2.41$, $p = 0.06$. Because a priori predictions had been made concerning this interaction, Newman-Keuls multiple comparisons were conducted to assess the simple effects of this interaction. These comparisons confirmed that in BALB/cByJ mice each of the stressor treatments increased the accumulation of MHPG to a comparable extent relative to nonshocked BALB/cByJ mice. Thus, the differential levels of NE evident with varying number of stressor sessions could not be attributed to differential rates of utilization. In contrast to BALB/cByJ mice, the 1, 5, or 10 stressor sessions did not significantly influence the accumulation of MHPG in C57BL/6J mice, and only a modest, but significant, MHPG increase was evident after 15 shock sessions.

A single stressor session provoked a 28% reduction of NE within the locus coeruleus of BALB/cByJ mice, whereas in C57BL/6J the reduction was only 10%. The decline of NE following repeated stressor exposure was only 18% in BALB/cByJ and entirely absent in C57BL/6J. The analysis of variance, however, revealed that these differences were not statistically significant ($p = 0.11$). The accumulation of MHPG within this region, however, was found to vary with stressor exposure, $F(4, 49) = 2.69$, $p < 0.05$. Multiple comparisons confirmed that a single session of stressor application resulted in a significant increase of MHPG in both strains. However, the increase did not reach significance following 5, 10, or 15 sessions of stressor exposure ($p < 0.10$ following 5 and 10 sessions, and NS following 15 sessions).

As noted previously, stressor exposure did not influence hippocampal NE as readily as in hypothalamus. Although there was a hint of a reduction of NE in the hippocampus of stressed animals, this effect did not approach significance. The accumulation of MHPG, however, was influenced by the stressor treatment, $F(4, 49) = 2.61$, $p < 0.05$. The multiple comparisons revealed that following 1 or 10 sessions of foot shock MHPG was increased, but this effect was not evident at the other intervals.

The variations of NE within the prefrontal cortex were similar to those seen in hypothalamus. Among C57BL/6J mice NE levels were not affected by stressor exposure, whereas in BALB/cByJ mice NE levels varied with different number of stressor sessions, $F(4, 24) = 3.11$, $p < 0.01$. Newman-Keuls multiple comparisons confirmed that in BALB/cByJ mice the NE reductions became more pronounced with increasing stressor exposure, such that 5 and 10 sessions of foot shock provoked a significant decline of the amine levels. With 15 stressor sessions the decline was less marked and NE levels did not differ significantly from nonstressed mice. In addition to the NE alterations, the stressor treatment was found to influence MHPG accumulation, $F(4, 44) = 4.95$, $p < 0.01$. Multiple comparisons indicated that the increase of MHPG associated with a small number of stressor sessions tended to decline with repeated stressor exposure. Indeed, relative to nonshocked animals, metabolite levels were increased in the 1, 5, and 10 session groups, but not in mice that received 15 shock sessions. Moreover, MHPG accumulation in mice that received 15 shock sessions were significantly lower than in mice that received 5 shock sessions.

The alterations of 5-HT and 5-HIAA associated with stressor exposure (see Fig. 2) were considerably less marked than those of NE. Stressor exposure did not influence 5-HT or its metabolite in either the hypothalamus or the hippocampus. In contrast, 5-HT in the prefrontal cortex was found to vary significantly as a function of the shock treatment × strain interaction, $F(4, 45) = 2.74$, $p < 0.05$. Multiple comparisons of the simple effects revealed that in BALB/cByJ mice 1 or 15 stressor sessions increased 5-HT concentrations significantly, although the 5 and 10 session treatments produced moderate increases of this amine ($0.05 > p < 0.10$). In C57BL/6J mice, five sessions of foot shock increased 5-HT concentrations, but none of the other stressor treatments influenced the levels of this amine. Analysis of the 5-HIAA concentrations revealed that the stressor treatment × strain interaction approached significance, $F(4, 44) = 2.34$, $p = 0.069$. In BALB/cByJ, each of the stressor treatments provoked a modest increase of the metabolite, which did not reach statistical significance ($p < 0.10$), although in C57BL/6J there was no indication of such a rise.

EXPERIMENT 2A AND 2B

The results of Experiment 1 suggest that the utilization of NE is more readily induced by stressors in BALB/cByJ than in C57BL/6J mice. Moreover, it seems that reductions of NE are more readily attained in the former strain. With repeated stressor application the NE alterations associated with one to five shock sessions in BALB/cByJ mice were minimal or were entirely absent. Among C57BL/6J mice the modest NE alterations associated with an acute stressor were likewise absent after repeated shock and, in fact, were absent after as few as 10 shock sessions. Experiment 2A and 2B were conducted to assess the effects of repeated stressor application on NE and MHPG concentrations. However, given that the course of the adaptation may occur more readily using a predictable than an unpredictable stressor regimen, both such routines were assessed in Experiment 2A and 2B, respectively.

Method

Experiment 2A and 2B involved 24 and 16 mice of the BALB/cByJ and C57BL/6J strains, respectively. The subjects' characteristics and housing conditions were the same as those of Experiment 1. In Experiment 2A, mice received either no shock or 15 sessions of shock using the procedures described in Experiment 1. In Experiment 2B, half the mice of each strain were not stressed and remained in their home cages, while the remaining mice received 15 stressor sessions over successive days (one stressor session per day). The stressor sessions consisted of one of the following: foot shock (FS: 360 shocks, 2 s duration, 150 μA over a 1.1-h period), tail-shock (TS: 6 shocks, 0.5 s duration, 150 μA over a 9-min period), restraint (R: 30 min in a semicircular Plexiglas tube with the mouse's tail taped outside the tube to prevent the mouse from moving), light presentations (L: illumination of a dim light for 5 s at 30 s intervals, over a 1.1-h period, while animals were in chambers similar to those in which foot shock had been delivered). The sequence of stressors applied over successive days was FS, TS, R, L, TS, R, FS, L, R, TS, FS, R, L, TS, FS. Immediately following the last stressor session mice were decapitated, brains removed and sectioned, and stored at -70°C for subsequent determinations of NE, MHPG, 5-HT, and 5-HIAA.

Results

The mean concentrations of NE for each of the brain regions of Experiment 2A is shown in Fig. 3 as a function

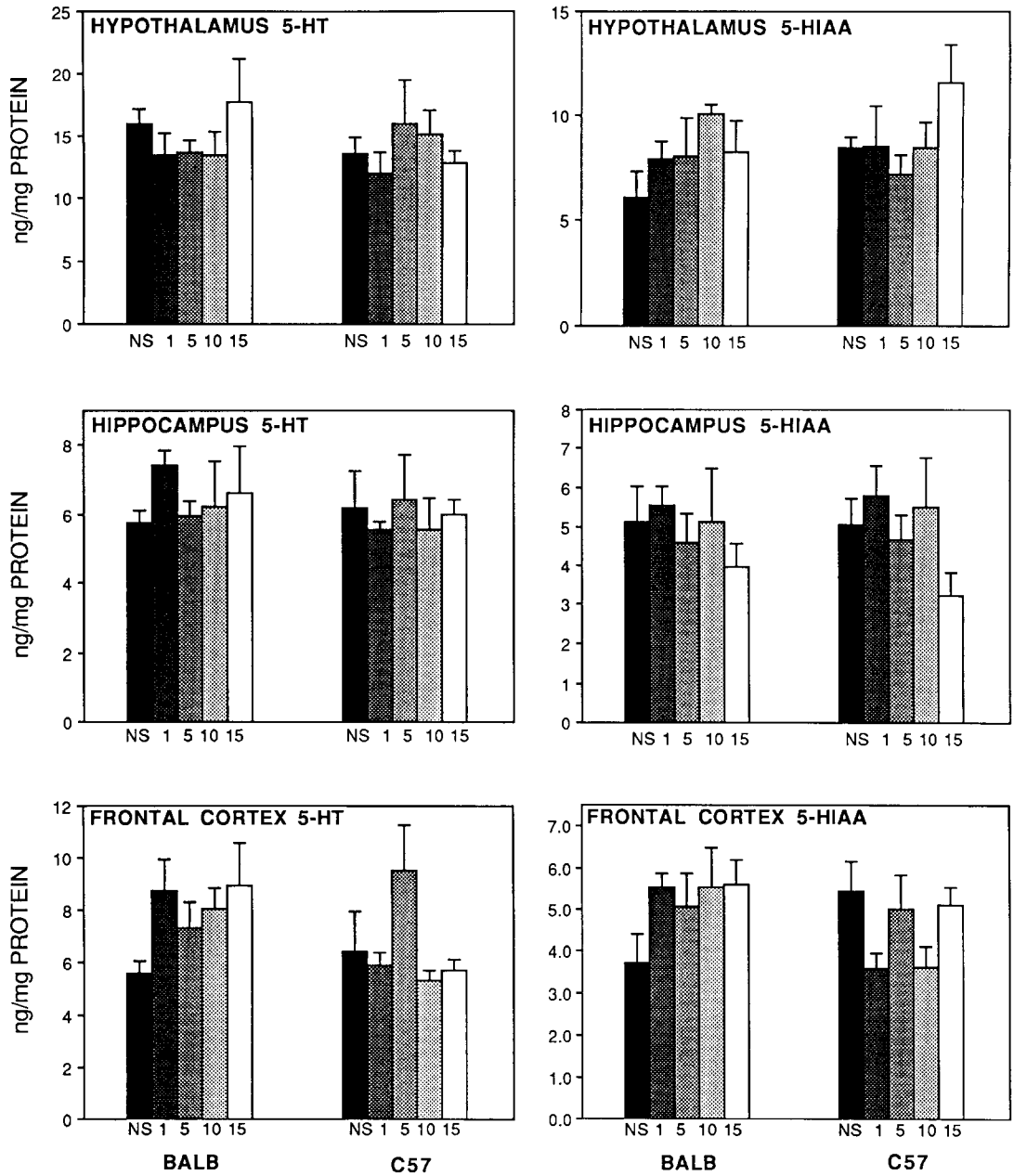

FIG. 2. Mean (±SEM) concentrations of 5-HT and 5-HIAA in several brain regions of BALB/cByJ and C57BL/6J mice following 0 (no shock), 1, 5, 10, or 15 sessions of foot shock.

of the strain and shock treatment. Analysis of variance confirmed that after 15 shock sessions hypothalamic NE levels were not different from control values in either of the strains, although MHPG accumulation was increased by the stressor, $F(1, 42) = 20.25$, $p < 0.01$. The NE concentrations within the locus coeruleus, in contrast, were reduced in the stressed mice of both strains, $F(1, 42) = 3.94$, $p < 0.05$, whereas a modest, nonsignificant increase of MHPG was apparent ($0.05 > p < 0.10$). Neither NE nor MHPG in the hippocampus and frontal cortex was affected by 15 stressors sessions in either of the strains. Levels of NE within the hippocampus were found to be higher among nonstressed C57BL/6J than BALB/cByJ mice. However, inasmuch as such an effect was not observed in either Experiment 1 or 2B, this finding was likely a spurious one.

Levels of 5-HT and 5-HIAA in hypothalamus did not differ as a function of the stressor treatment. In the hippocampus, 5-HT levels of C57BL/6J mice exceeded those seen in BALB/cByJ, $F(1, 42) = 9.39$, $p < 0.05$, although 5-HIAA levels varied as a function of the strain × shock treatment interaction, $F(1, 43) = 3.68$, $p < 0.05$. Multiple comparisons indicated that nonshocked BALB/cByJ mice exhibited higher metabolite levels than the remaining groups. Again, however, the high levels of hippocampal 5-HIAA in BALB/cByJ mice

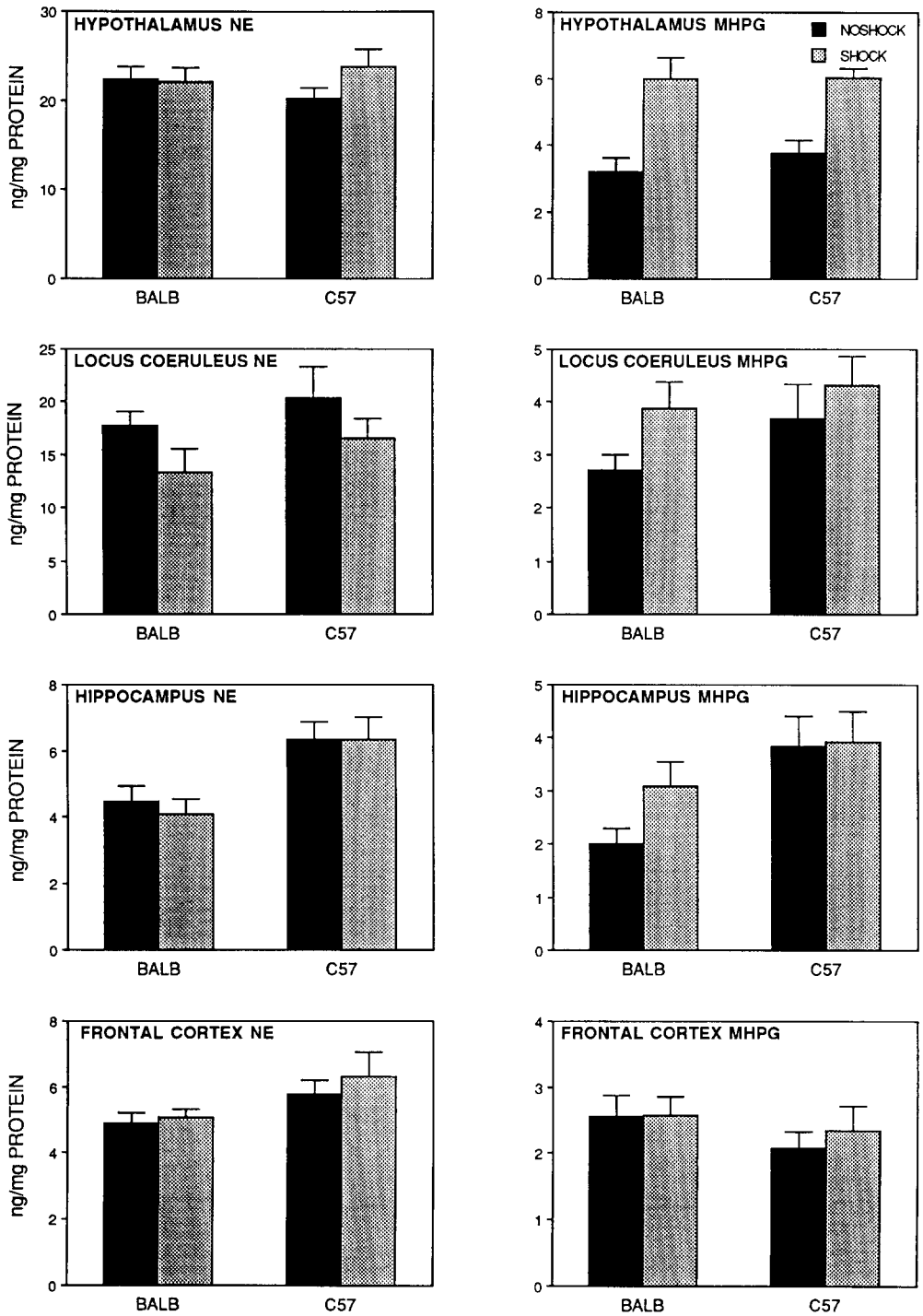

FIG. 3. Mean (±SEM) concentrations of NE and MHPG in several brain regions of BALB/cByJ and C57BL/6J mice following 0 (no shock) or 15 sessions of foot shock (predictable stressor).

were not reliable as they were unique to this experiment. Finally, in the prefrontal cortex the stressor treatment did not affect 5-HT concentrations or accumulation of 5-HIAA.

The NE changes induced by the multiple stressor treatment (Experiment 2B) in the hypothalamus, locus coeruleus, and hippocampus were essentially similar to those seen following the predictable (foot shock) treatment (see Fig. 4). Only in the prefrontal cortex were the two stressor regimens found to differentially influence NE. Hypothalamic NE levels were unaffected by the multiple stressor, whereas MHPG concentrations were increased, $F(1, 27) = 21.33$, $p < 0.01$. In the locus coeruleus, the stressor treatment reduced NE levels, $F(1,$

24) = 6.78, $p < 0.05$, while increasing MHPG accumulation, $F(1, 22) = 6.94$, $p < 0.05$. The stressor treatment did not influence hippocampal NE or MHPG accumulation. In the prefrontal cortex the multiple stressor treatment yielded lower NE levels relative to those seen in nonstressed mice, $F(1, 27) = 10.54$, $p < 0.01$, although MHPG accumulation was marginally increased, $F(1, 28) = 3.80$, $p = 0.06$. The latter effect was largely attributable to a rise of MHPG in C57BL/6J mice, and was essentially absent in the BALB/cByJ strain. The stressor treatment did not influence the 5-HT or 5-HIAA levels in any of the brain regions. It will be recalled that the reduced NE concentrations associated with a small number of predict-

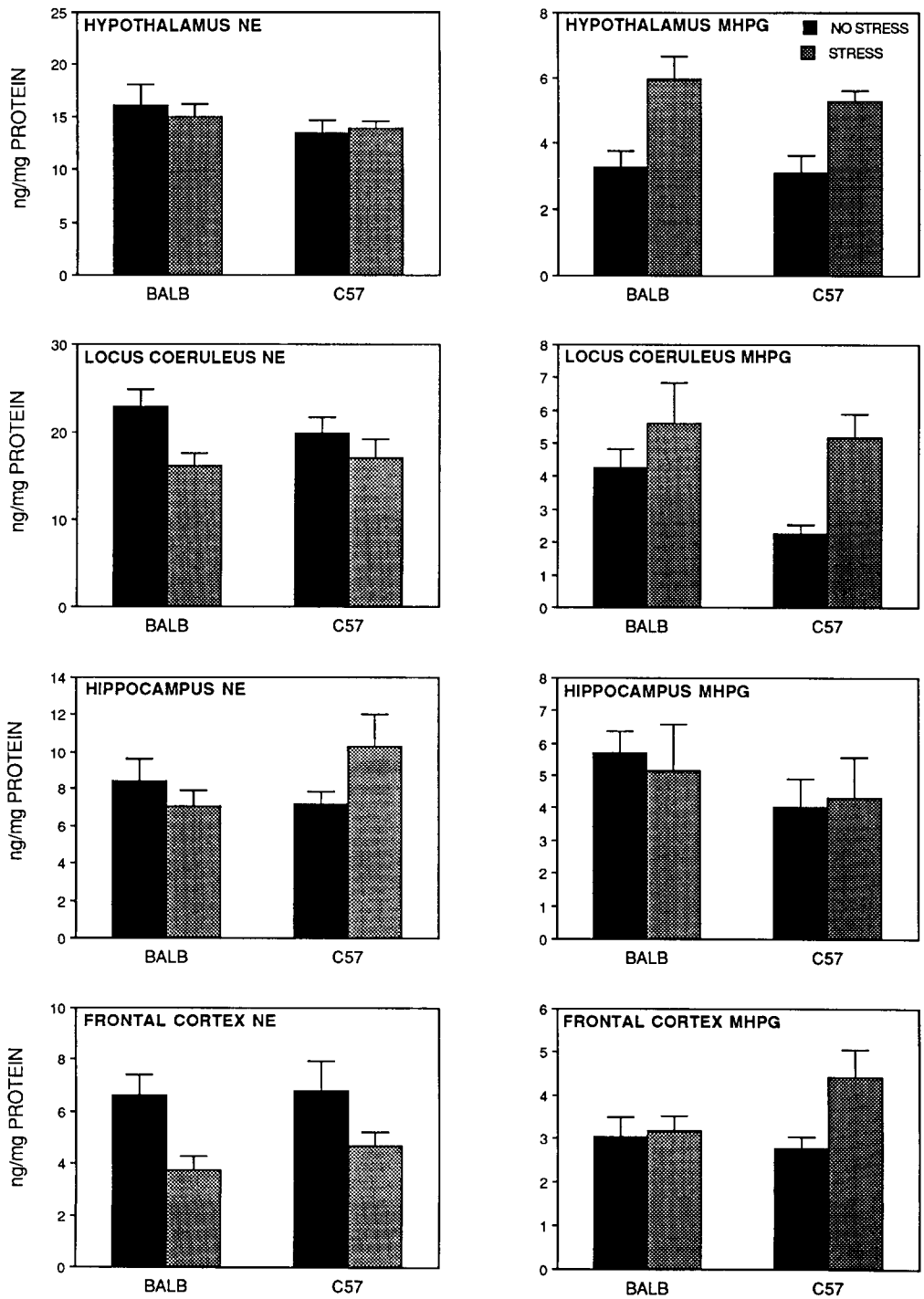

FIG. 4. Mean (±SEM) concentrations of NE and MHPG in several brain regions of BALB/cByJ and C57BL/6J mice following 0 (no shock) or 15 unpredictable stressor sessions.

able stressor sessions is absent following five such sessions (Experiment 1 and 2A). Thus, it seems that when a chronic multiple stressor session is employed this adaptation is less likely to develop within the prefrontal cortex.

GENERAL DISCUSSION

As previously observed (9,12,29), following limited stressor exposure the utilization of NE and 5-HT increased, and levels of NE declined. However, as observed in earlier investigations (2,13,19), with repeated exposure to a predictable stressor the reduction of hypothalamic NE was absent. The development of this adaptation appeared to be brain-region specific and dependent on the stressor schedule employed. For instance, the hypothalamic NE reductions associated with a modest number of stressor sessions were absent in mice that were exposed to the stressor on 15 occasions. This was the case irrespective of whether the chronic stressor regimen was predictable (foot shock) or unpredictable (involving a series of different stressors). In the locus coeruleus, however, where a chronic predictable stressor produced only a modest, nonsignificant decline of NE, the chronic unpredictable stressor resulted in a significant NE reduction. Likewise, it appeared that in the prefrontal cortex the NE alterations were maximal after five foot shock sessions, but was less marked or entirely absent with further stressor exposure. In contrast, the NE reduction observed after a chronic unpredictable stressor was marked in both strains of mice. It has been reported that a chronic predictable stressor regimen also leads to a downregulation of β-NE receptor sensitivity (25,26), whereas an unpredictable stressor regimen does not (17). It remains to be determined whether the occurrence of such effects are likewise brain-region or strain dependent.

The enhanced hypothalamic NE levels associated with a chronic stressor have been reported to be accompanied by increased accumulation of MHPG (12,13). Accordingly, it was suggested that the increased NE was due to a compensatory increase of NE synthesis. Indeed, in the present report the MHPG concentrations within the hypothalamus were as great following a chronic stressor as they were after an acute stressor. However, in the locus coeruleus and frontal cortex, the elevated MHPG accumulation evident after a single shock session was attenuated following repeated stressor application. It seems that the adaptation in different brain regions may involve different mechanisms. In some regions the increased levels may represent a compensatory increase of synthesis, whereas in other regions the altered NE levels may involve moderation of excessive utilization otherwise observed following acute stressors. Alternatively, it is possible that these variations of MHPG may reflect region-specific differences in tissue uptake of the metabolite, or different rates at which MHPG is degraded.

Commensurate with earlier findings from this laboratory (5), the BALB/cByJ mice exhibited more pronounced NE and 5-HT alterations than did the C57BL/6J mice. The strain differences, however, were dependent on the brain region examined. For instance, in both the hypothalamus and prefrontal cortex the foot shock treatment provoked greater NE reductions in BALB/cByJ than in C57BL/6J. In the prefrontal cortex the accumulation of MHPG in the two strains was comparable, whereas in hypothalamus the increased MHPG characteristic of BALB/cByJ mice was not apparent in the C57BL/6J strain. Moreover, even when NE levels were altered in C57BL/6J mice, the adaptation occurred more readily than in the BALB/cByJ strain. In both strains, however, the adaptation was less likely to occur following an unpredictable stressor regimen, at least in prefrontal cortex and locus coeruleus.

It has been demonstrated that the behavioral disturbances (e.g., voluntary consumption of a highly palatable diet, responding for rewarding stimulation from some brain regions, shuttle escape performance, Morris water-maze performance) engendered by stressors are more pronounced in BALB/cByJ than in several other strains, including C57BL/6J (21,24,31). Thus, it is tempting to speculate that these behavioral differences might be related to the vulnerability of BALB/cByJ to stressor-provoked amine or endocrine alterations. Indeed, it seems that the particular vulnerability of BALB/cByJ mice to stressor effects are apparent with respect to central NE and DA, as well as plasma corticosterone concentrations (23). Hence, it is premature at this juncture to ascribe the behavioral disturbances to any particular stressor-provoked neurochemical or endocrine change. Nevertheless, it has been our contention that owing to the marked neurochemical and behavioral alterations induced by acute stressors in BALB/cByJ mice, this strain may be ideally suited for the analysis of stressor-related pathologies (5). The present results suggest that the BALB/cByJ strain is not only more reactive to acute stressors, but also that the neurochemical adaptation ordinarily associated with repeated stressor exposure is somewhat slower to occur than in the relatively hardy C57BL/6J strain.

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