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Neurochemical Lesion of the Nucleus Locus Coeruleus Increases Neophobia in a Specific Exploration Task but Does Not Modify Endocrine Response to Moderate Stress

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VELLEY, L., P. MORMEDE AND E. KEMPF. *Neurochemical lesion of the nucleus locus coeruleus increases neophobia in a specific exploration task but does not modify endocrine response to moderate stress.* PHARMACOL BIOCHEM BEHAV **29**(1) 1–7, 1988.—In order to test more specifically the role of the nucleus locus coeruleus (LC) in reaction to novelty, rats with bilateral 6-hydroxydopamine lesions of this nucleus, vehicle injected rats and non-operated animals were tested in the open-field and in the Hughes apparatus where motor activity is recorded in both a familiar and a non-familiar environment. In the open-field, the LC lesioned animals were significantly less active. A similar decrease of locomotor activity was observed in the Hughes test: the number of passages between the two boxes of the LC lesioned rats was significantly decreased. Likewise when the locomotor activities in the two boxes were pooled, the activity of the rats with lesions was significantly lower than the activity of the control rats, but in this case the locomotor deficit appeared only in the familiar box, the locomotor activity in the novel enclosure being the same in both LC lesioned and control animals. This result suggests that exploratory induced locomotion is not disturbed by the locus coeruleus lesion. The significant locomotor deficit showed by the LC lesioned rats in the familiar box could be due to an increased immobility induced by the stressful situation. Moreover, the deficit observed was the same whether the behavioral test began 4 days or 4 weeks after the lesion. Finally, at the end of the experiment, all rats were submitted to a moderate novel environmental stress and blood samples collected to measure the plasma levels of different stress hormones (ACTH, glucocorticoids, PRL, catecholamines). Hormone levels were the same in the LC lesioned and normal rats in spite of the fact that a significant loss of noradrenaline (53%) was observed in the hypothalamus of the rats with lesions. This result shows that the locus coeruleus is of minor importance in the control of stress induced neuroendocrine responses.

Neurochemical lesions Locus coeruleus Hughes test Open-field Endocrine response Moderate stress Rats

IN two recent studies we tested in the rat, the effect of a bilateral neurochemical lesion of the nucleus locus coeruleus (LC) on the locomotor activity in the open-field [16,17]. It was observed that the locomotor activity of the LC lesioned rats was greatly depressed but returned progressively to normal values with repeated testing. This result was in agreement with some published data showing a decrease in locomotor activity either in the open-field [3,7] or in the holeboard [25] but differed from other results showing that the LC lesion did not change the locomotor activity in these two tests [5,9].

When a locomotor deficit was observed, it was generally interpreted as an increased reactivity to novelty, namely as an increased neophobia. However, this hypothesis rests on the assumption that the locomotor activity of a normal rat represents curiosity induced exploration. Now, one of the main criticisms against the open-field is the fact that this test is a forced exposure task. Therefore, initial activity in the open-field can be motivated either by escape or approach tendencies (discussed in [4,20]). Consequently the locomotor activity decrease after LC lesions can be due either to a decrease of exploration, i.e., increased neophobia, or by a decrease of escape tendency namely decreased reactivity to a stressful event. The increase of neophobic reactions would

confirm the hypothesis after which a major function of the LC is to dampen the organism's response to stressors [1]. On the contrary, if the LC lesion produces a decreased reactivity to stressful events this would mean that in the intact animal the coerulean system increases this reactivity [19].

The main purpose of the present study was to try to overcome the interpretative difficulty summarized above by comparing the effect of the neurochemical LC lesion on the locomotor activity in the open-field and on exploration in a choice-task, the test of Hughes [8]. In this task, since the rat can either enter the novel box or remain in the familiar box, the exploration of the novel box can be more confidently attributed to approach tendency.

An additional purpose of the present experiment was to test the possible role, on the behavioral deficit, of the time interval between the lesion and the exploration tasks, because some data show biochemical compensatory processes after LC lesion [6]. Lastly, evidence from a variety of sources suggests that LC modulates or is modulated by circulating hormones. It has been demonstrated that the LC accumulates radio-labeled corticosterone [11] and that adrenocorticotrophin as well as corticotrophin releasing factor activates LC neurons when applied iontophoretically [18,24]. Moreover, the interruption of the forebrain projections from the LC, namely the dorsal noradrenergic bundle, combined with bilateral adrenalectomy has been reported to cause a severe deficit of exploration [25]. Furthermore, the neurochemical lesion of the dorsal noradrenergic bundle is known to produce a significant loss of noradrenaline in the hypothalamus [2,21]. Taken together, these findings suggest an interactive relation between noradrenaline and pituitary-adrenal hormones, and thus it was possible that the loss of noradrenergic projections in the hypothalamus after LC lesion modify the stress induced activation of the pituitary adrenal axis. Consequently, before the sacrifice of animals, all rats were exposed to a moderate stress and blood samples were collected to measure the plasma levels of adrenocorticotrophin, corticosterone, prolactine, adrenaline and noradrenaline.

METHOD

Animals

Male rats of the Sprague-Dawley strain were individually housed in wire-mesh cages and maintained on a regular 12 hr/12 hr light-dark cycle in a temperature-regulated (21–23°C) animal room. Food and water were provided ad lib. Surgery was performed when the rats were 9 weeks old. Forty seven rats were used. Two main groups were constituted. One group included the rats whose locus coeruleus (LC) was lesioned by a two-stage surgical procedure (see below) and the corresponding vehicle injected and control rats. The second group was constituted with rats whose LC was lesioned by an one-stage procedure, and the corresponding vehicle injected and control rats. For each group, half the rats were successively submitted to the 3 tests (Hughes test, open-field and neuroendocrine response to a moderate stress) while the other half were left undisturbed between the lesion and the neuroendocrine response to the stress.

Surgical Procedures

In order to test the role of the time interval between the lesion and the exploration task, some rats began testing in the Hughes apparatus 4 days after the locus coeruleus (LC) lesion. Consequently, in order to alleviate the effects of the operation a two-stage surgical procedure was used for these rats. In a first stage, two guide-cannulae (i.d.: 240 μm) were chronically implanted above each LC under deep anesthesia (Nembutal 40 mg/kg). The co-ordinates were 1.7 mm posterior to ear bars, $\pm$1.2 mm lateral to the sagittal suture and 4 mm ventral to the top of the skull. The incisor bar was level with the interaural line. Two weeks later, under light anesthesia, each rat was again placed in the stereotaxic apparatus and a cannula (o.d.: 229 μm) was successively inserted in each guide cannula in such a way that the tip of the cannula was positioned 6.5 mm ventral to the top of the skull. The cannula was connected to a micropump which delivered in each LC 4 μg of 6-hydroxydopamine (6-OHDA) expressed as weight of the salt, dissolved in 1 μl of 0.9% saline containing 0.2 mg/ml of ascorbic acid. Each injection was made over 5 min and 8 more min elapsed before the removal of the cannula. Eleven rats were injected with 6-OHDA and 6 other with the vehicle only.

Given that the other rats began to be tested 4 weeks after the lesion, these animals were operated by a one-stage procedure. The drug (n=12) was directly injected with the same dose of 6-OHDA and with the same coordinates as those indicated above. Six other rats were injected with the vehicle only. Finally, 12 non-operated rats were used as controls.

Behavior

Test of Hughes [8]: The apparatus consisted of a plastic box 23 cm high, 60 cm long and 40 cm wide, subdivided in six 20 cm square exploratory units. It could be divided in half by means of 3 temporary partitions. Each half of the box was fitted with a water bottle. The walls and partition faces of one half were gray and those of the other half were beige. The floors of both halves were covered with sawdust. Ten identical boxes were placed in the animal room. The procedure used was as follows: At nine a.m., each rat was placed in one half on one box with the partitions in place. Food and water were provided ad lib. Twenty four hr later, the partitions were removed and the rat was allowed to explore the novel half of the box for 15 min. During this period, the number of passages between the two halves of the apparatus, the activity in each half (number of units crossed) and the total time spent in the novel box (out of 900 sec) were recorded. At the end of the 15 min period, the partitions were again put in place when the rat was in the familiar half of the box. Five consecutive measures, each separated by 24 hr were made. Two experiments were performed. In the first, 6 LC lesioned rats 4 days before, 3 vehicle injected rats and 4 control rats were tested. In the second experiment, 6 rats whose LC was lesioned 4 weeks before, 3 vehicle treated rats and two control rats were tested in the apparatus with the same procedure.

Open-Field

All rats used in the apparatus of Hughes were also tested in the open-field. This testing began one day after the end of the measures in the test of Hughes. The locomotor activity was tested in a square wooden open-field that measured 100×100×50 cm [16]. The floor was white and divided into 25 squares of equal size. The open-field was evenly lit by overhead lighting (1100 lux at the floor). The activity of each rat was recorded by means of a closed-circuit television coupled to a video recorder. Each day and during 5 consecutive days, the rat was placed in the center of the open-field

and the number of squares crossed was recorded for a 5 min period.

Neuroendocrine Measures

For the rats implanted with the guide-cannulae, this last experiment took place 15 days after the lesion while for the rats lesioned in one-stage operation, this last experiment was performed 49 days after the lesion.

In order to test the activity of the neuroendocrine systems toward stress, the experimental animals were submitted to a mild psychological stress of novel environment exposure before sacrifice. Since endocrine reactivity may be reduced by multiple manipulations of the animals related to behavioral testing, the second groups of rats operated at the same time as the first groups and the corresponding vehicle and non-operated rats (L=11, V=6, C=6) were included in this experiment. Rats were placed individually in buckets with sawdust litter, in a room with a background masking noise and sacrificed 30 minutes later by decapitation [14]. Trunk blood was collected in chilled tubes using EDTA as an anticoagulant. After centrifugation, plasma aliquots were frozen until analysis. Animals were sacrificed between 9:00 and 12:00 a.m. to avoid nycthemeral variations of plasma hormone levels. Plasma corticosterone was measured by radiocompetitive binding assay after methylene chloride extraction, using pregnant human serum as the source of transcortin, tritiated corticosterone as the tracer and dextran-coated charcoal as the absorbent of free radioactivity. Plasma ACTH was measured by direct radioimmunoassay (kit ACTHK, C.E.A., Gif-sur-Yvette, France) [14]. Plasma PRL was determined with a double antibody RIA using materials and procedures supplied by the National Hormone and Pituitary Program of the NIADDK. Results are expressed in terms of rat PRL RP-3 [15]. Plasma catecholamines were measured by high performance liquid chromatography and electrochemical detection after aluminium hydroxide extraction.

Biochemical Assays

The brains were quickly removed. Hippocampus and hypothalamus were dissected on ice and immediately frozen in liquid nitrogen until use. For the hypothalamus samples noradrenaline (NA), dopamine (DA), 3-4-dihydroxyphenylacetic acid (DOPAC), serotonin (5HT) and 5-hydroxyindolacetic acid (5-HIAA) were determined simultaneously using reverse phase chromatography coupled with electrochemical detection. The same procedure was used for the hippocampus samples but NA, 5HT and 5-HIAA only were determined.

On the day of analysis frozen samples of hypothalamus and hippocampus were weighed and homogenized in HC104 0.1 N containing Na-metabisulfite 6 mM and EDTA 1 mM. The homogenates were centrifuged at 10,000×g for 20 min at 4°C. Aliquots of the supernatant were transferred into the LCEC system with a Wisp automatic injector (Waters). The LCEC system consisted of a Bioanalytical systems LC4 amperometric detector with a glassy carbon working electrode and a pump (Waters).

The potential was set at 800 mV (vs. Ag-AgCl reference electrode). The column, a Bondapak phenyl column (10 μm particle size, 300×3.1 mm i.d.) was purchased from Waters Assoc. The flow rate was 1.4 ml/min, and the sensitivity was set at 5 nA/V (1 volt full scale). The mobile phase consisted of 3% methanol in 0.1 M Na-phosphate buffer pH 2.5, Na2 EDTA 0.1 mM, and 1-octane sulfonic acid Na salt (BDH) 2 mM. 3,4-dihydroxyhydrocinnamic acid (Adlrich) was used as internal standard.

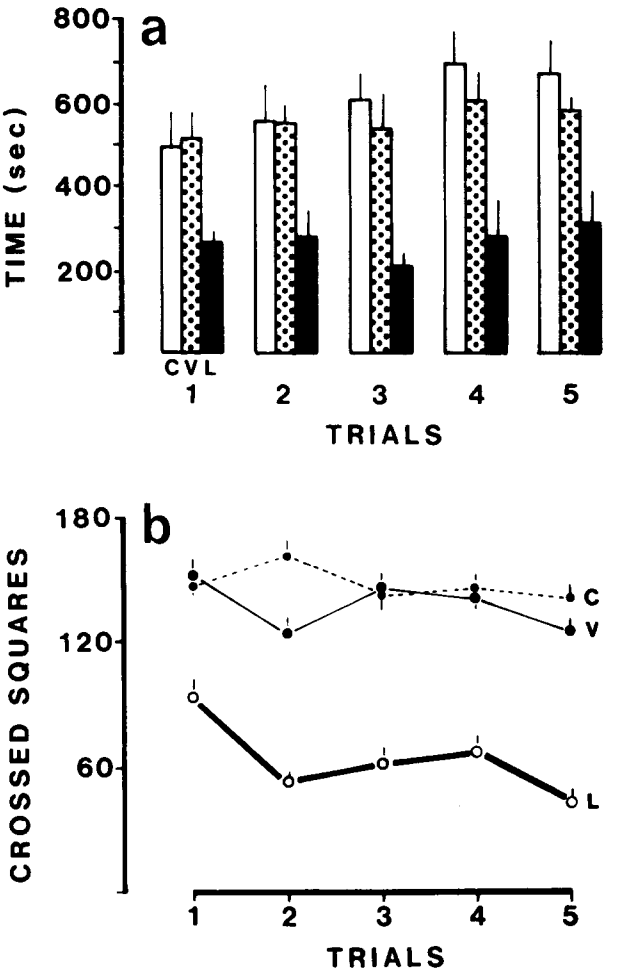

FIG. 1. First experiment: (a) mean time (±SEM) spent in the novel box of the Hughes apparatus by the rats lesioned (L) 4 days before the first trial, by vehicle injected (V) and by non-operated rats (C). Abscissa: the five trials; ordinate: time in sec out of 900 sec. (b) mean number (±SEM) of squares crossed during 5 min (ordinate) in the open-field. Same groups of rats as in a. Abscissa: the 5 trials.

RESULTS

Behavior

In the test of Hughes the LC lesioned rats showed a different pattern of responses compared to the intact animals. As soon as the partitions were removed the control and the vehicle treated rats entered the novel enclosure and explored it. In contrast, the rats with lesions did not enter the box and remained immobile in front of one of the open doors. Eventually, after a variable delay each LC lesioned rat cautiously entered the novel box and began to explore it. Moreover, when the intact rats returned to the familiar box, they exhibited high locomotor activity in this box whereas the LC lesioned rats remained motionless soon after returning to this box.

Figure 1 summarizes the results in the Hughes test of the rats lesioned 4 days before the beginning of the behavioral tests and the corresponding results of the two unlesioned groups of rats. Figure 1a shows the mean total time spent in

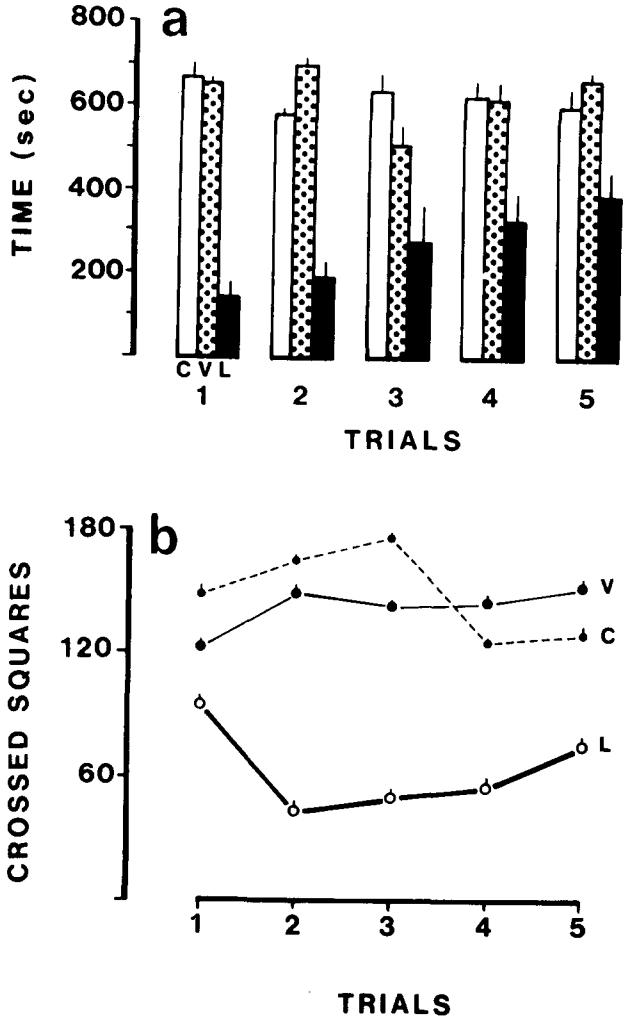

FIG. 2. Second experiment: Effect of the locus coeruleus lesion performed 4 weeks before, on exploration in the Hughes apparatus (a) and on locomotor activity in the open-field (b). See Fig. 1 legend for details.

the novel half of the apparatus. A (3×5) ANOVA showed that the time of the vehicle injected rats was not different from the time of the control rats, $F(1,5)=0.66$, n.s., while the time of the LC lesioned rats was significantly shorter than the time of the two other groups, $F(1,11)=22.9$, $p<0.001$. Moreover, the daily repetition of the test did not modify the response of each group. Figure 1b shows that in the open-field also the locomotor activity of the LC lesioned rats is significantly inferior to the activity of the two other groups, $F(1,11)=29.3$, $p<0.001$.

Figure 2 summarizes the results of the rats lesioned 4 weeks before and the results of the corresponding vehicle injected and control rats, in the test of Hughes (Fig. 2a) and in the open-field Fig. 2b). By comparing the data of the Figs. 1 and 2 it can be observed that the behavioral deficit was about the same whether the LC was lesioned 4 days or 28 days before the behavioral tests. In fact the differences for each parameter were not significant either between the 2 LC lesioned groups or between the two unlesioned groups.

Consequently the data of the two experiments were pooled for further analysis.

Figure 3 shows for the 12 rats with lesions, for the 6

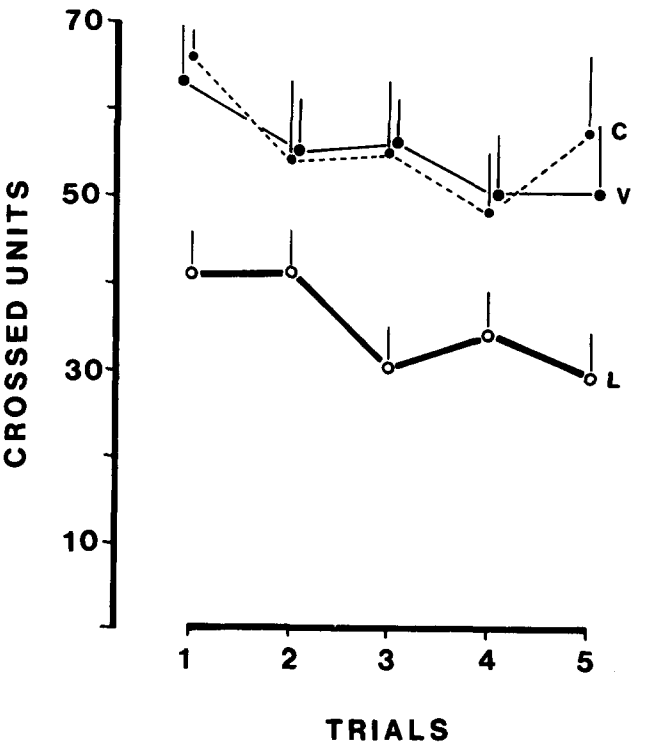

FIG. 3. Total number of units crossed (±SEM) in the two boxes of the Hughes apparatus. The values of the two groups of rats were pooled. (L=12, V=6, C=6). Ordinate: number of units crossed during 900 sec.

vehicle injected animals and for the 6 control rats, the mean number of units crossed in the two boxes of the Hughes apparatus. This result confirms that, in the test of Hughes, like in the open-field, the mean locomotor activity of the LC lesioned rats was significantly lower than the activity of the 2 other groups, $F(1,22)=11.7$, $p<0.01$. Likewise, while the number of passages of the vehicle and of the non-operated rats did not differ, $F(1,10)=0.05$, n.s., the number of passages of LC lesioned rats was significantly inferior to the number of the two other groups pooled, $F(1,22)=16$, $p<0.001$. Moreover, to estimate the influence of the lesion on locomotor activity in each half of the Hughes apparatus, we calculated for each rat the mean number of units crossed during 100 sec in the familiar box and in the novel box.

Figure 4 shows that during each daily trial the unlesioned rats were very active in the novel box as well as in the familiar enclosure. In this last case the locomotor activity did not change throughout the experiment. The locomotor activity of the rats with lesions in the familiar box was greatly depressed, $F(1,22)=20.5$, $p<0.001$, whereas their activity in the novel box was similar to that of the unlesioned animals, $F(2,24)=0.17$, n.s.

Neuroendocrine Measures

Results were analyzed by two-way analysis of variance. F-values, means and standard deviation are given in the table. Neither the main factors of lesion, previous manipulation, nor their interaction were significant for any parameter.

Biochemical Data

As showed in Table 2, the differences between the

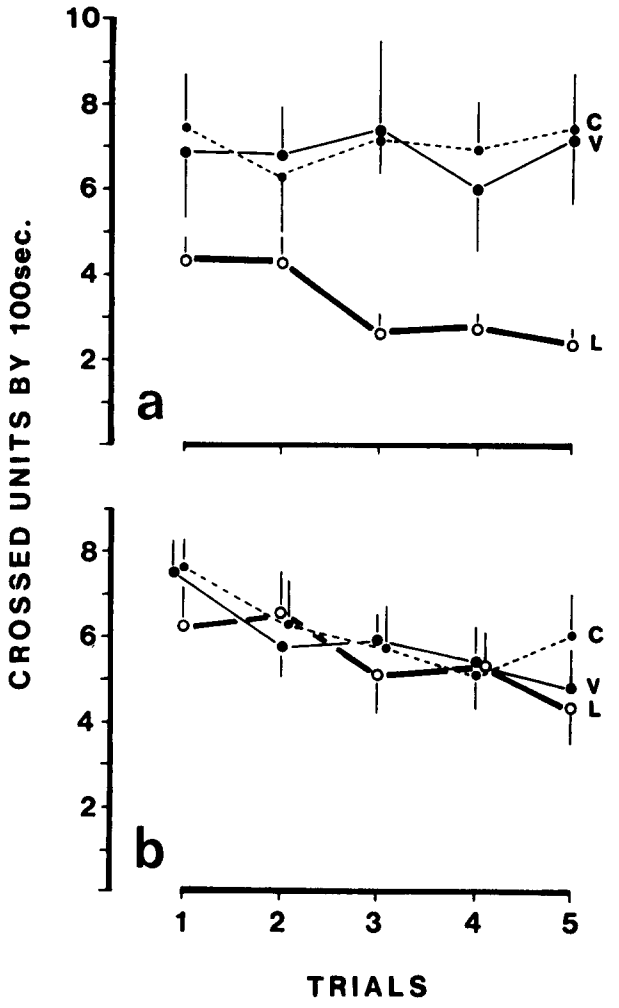

FIG. 4. Number of units crossed in the familiar box (a) and in the novel box (b) of the Hughes apparatus. The activity is expressed as the number of units crossed in each box per 100 sec spent in that particular box.

vehicle treated rats and the control animals are small and did not reach significance.

Likewise no significant difference appeared between the rats sacrificed 15 days after the lesion and the animals sacrificed 49 days after the lesion. The only significant modifications observed between the LC lesioned rats and the vehicle injected rats is a loss of noradrenaline in the hippocampus (residual content: 29 and 22%) and in the hypothalamus (residual content: 47%).

DISCUSSION

The main purpose of the present study was to evaluate whether the neurochemical lesion of the LC increases neophobia in the rat. To test appropriately this possibility we combined the use of the open-field test with a choice task, the Hughes test.

The first observation concerns the role of the time interval between the lesion and the behavioral tests. In our experimental conditions, the deficit observed in the Hughes test and in the open-field was the same whether the LC was destroyed 4 days or 4 weeks before. This suggests that the behavioral effect of the LC lesion was not reversible and that no compensatory processes took place in the interval of 4 weeks. Moreover, our biochemical data do not show significant differences between the two groups of rats in spite of the fact that the animals of one group were sacrificed 15 days after the lesion while the rats of the second group were killed 49 days after the lesion (Table 2). This results is in agreement with neurochemical data showing that the main presynaptic markers of the coerulean system were not significantly modified after a neurochemical lesion of the LC whether the biochemical assays were performed 2 or 8 weeks after the lesion [6,10]. However, in one of these studies [6] a significant increase of dopaminergic activity was observed in the cerebral cortex deprived of its noradrenergic innervation by unilateral lesion of the LC and it was suggested that such enhanced dopaminergic input may play a role in mediating compensatory processes. In the present experiment dopamine was not assayed in the cortex. Thus, an increase of dopaminergic activity in this region can not be excluded. However, our behavioral data show that whatever the biochemical compensations induced by the lesion, these modifications did not attenuate the deficit observed.

The second main observation concerns the behavioral deficits observed in the open-field and in the Hughes apparatus. The results obtained in the open-field confirm our previous data [16,17] as well as other published observations [3,7], namely that the LC lesion produced as significant decrease of locomotor activity. Moreover, the total time spent by the rats with lesions in the novel box of the Hughes apparatus was significantly shorter than the time spent by the unlesioned rats. This result strongly suggests that the lesion produced increased avoidance behavior to novelty, namely enhanced neophobia. These data are in agreement with the hypothesis of Amaral and Sinnamon [1] but do not confirm the results of Redmond *et al.* [19] (see Introduction). Furthermore, in agreement with the open-field data, the locomotor activity of the LC lesioned rats was significantly lower than the activity of the unlesioned animals when the locomotor activities in the two boxes of the Hughes apparatus were pooled (Fig. 3). Nevertheless, the mean locomotor activity by 100 sec of the unlesioned rats was similar in each box (Fig. 4). The locomotion in the novel enclosure was probably due to exploratory behavior, but because the rats lived during 5 consecutive days in the familiar box, it is unlikely that locomotion recorded in this box was exploratory activity. Thus, it is possible that this locomotor activity was a response to the stressful situation induced by the exploration of the novel enclosure. Another possibility would be that locomotion in the familiar as well as in the novel boxes was not associated to exploratory behavior proper, but resulted from some unspecific factor as for example stimulus-elicited random activity. This last hypothesis is, however, not confirmed by the present data since the LC lesion decreased the locomotion in the familiar but not in the novel box, suggesting that locomotor activities recorded in each box of the Hughes apparatus are not induced by the same mechanisms and that the exploration induced locomotion is not disturbed by the LC lesion. The significant locomotor activity decrease of the LC lesioned rats in the familiar box could be due to an enhanced immobility reaction when these animals were confronted to the new enclosure. This hypothesis, after which the locomotion of the normal rat in a new enclosure is made up of two different components suggests, in agreement with the previous criticisms (see Introduction), that the usual open-field test is not a reliable measure of exploration in-

TABLE 1

F-VALUES OF THE TWO-WAY ANALYSIS OF VARIANCE PERFORMED ON PLASMA HORMONE LEVELS ACCORDING TO THE EXPERIMENTAL CONDITION (LESION, VEHICLE INJECTION, CONTROL) AND THE PREVIOUS BEHAVIORAL TESTING (MANIPULATION OR NOT)

Source	Lesion	Manipulation	Interaction		
df	2,41	1,41	2,41	Mean	S.D.
Corticosterone	0.68	2.31	0.23	229 ng/ml	109
ACTH	0.40	1.37	0.19	156 pg/ml	101
PRL	0.02	0.48	2.21	66 ng/ml	63
Adrenaline	0.00	0.41	0.10	8.1 ng/ml	2.4
Noradrenaline	0.35	0.00	0.26	3.3 ng/ml	1.6

df: degrees of freedom. No value reached statistical significance. The grand means and their standard deviation (S.D.) are given in the last columns (N=47).

TABLE 2

EFFECT OF THE LOCUS COERULEUS LESION IN THE CONTENT OF DIFFERENT MONOAMINES AND THEIR METABOLITES IN HYPOTHALAMUS AND THE HIPPOCAMPUS

	Hypothalamus					Hippocampus		
	NE	5HT	5-HIAA	DA	DOPAC	NE	5HT	5-HIAA
Controls (12)	1807 ±84	1055 ±70	405 ±12	428 ±41	71 ±5	361 ±31	499 ±16	325 ±18
Vehicles (12)	1706 ±93	963 ±74	382 ±19	355 ±31	66 ±3	349 ±18	524 ±21	285 ±28
Rats lesioned 15 days before death	808* ±147	994 ±72	356 ±14	357 ±20	56 ±3	100* ±24	530 ±15	277 ±20
%	47	103	93	100	85	29	101	97
Rats lesioned 46 days before death	795* ±151	995 ±86	382 ±11	339 ±30	53 ±3	78* ±21	575 ±30	286 ±13
%	47	103	100	95	80	22	110	100

Values in ng/g ± SEM. Statistical significance: *t*-test was used to compare each mean value of each lesioned group with the corresponding mean value of the vehicle injected rats.

*$p<0.001$. %: residual content expressed as percentage of the corresponding values of the vehicle group.

duced locomotion because in this task, the two components of locomotor activity are confounded.

Lastly, our results show that the LC lesion did not modify the neuroendocrine response to a moderate stress and that this response was the same whether the rats were first used in two behavioral experiments or were left undisturbed between the lesion and the exposure to a moderate stress. Although unstressed rats were not used as controls in the experiment, the stress levels of plasma hormones are in agreement with other published data [14, 15, 26]. Given the significant loss of the noradrenaline level in the hypothalamus (53%), this result was unexpected. However, it is well known that the hypothalamic noradrenergic innervation from the LC is limited and that the major source of this innervation is the lower brainstem cell groups of the lateral tegmentum [12,13]. Of particular relevance is the fact that about 90% of NA supply of the paraventricular nucleus is provided by the A1 and A2 neuronal complexes, whereas the LC participation is estimated to be about 8% [22]. In agreement with these data it was recently demonstrated that the neurochemical lesion of the ventral noradrenergic bundle inhibits the ACTH stress-response [23]. Taken together, these data show that it is possible to suppress about half of the hypothalamic noradrenergic innervation without modifying the neuroendocrine response to a psychological stress. This suggests that most fibers of the A1 and A2 neuronal complexes supplying the paraventricular nucleus, located ventrally in the brainstem, are spared by the lesion.

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