Pharmacology Biochemistry & Behavior, Vol. 17, pp. 639–643, 1982. Printed in the U.S.A.

Enhanced Neophobia but Normal Plasma Corticosterone Levels in Rats with Dorsal Noradrenergic Bundle Lesions

MATHEW T. MARTIN-IVERSON, MICHELE PISA, ELAINE CHAN AND H. C. FIBIGER

Division of Neurological Sciences, Department of Psychiatry University of British Columbia, Vancouver, B.C. V6T 1W5 Canada

Received 26 February 1982

MARTIN-IVERSON, M. T., M. PISA, E. CHAN AND H. C. FIBIGER. *Enhanced neophobia but normal plasma corticosterone levels in rats with dorsal noradrenergic bundle lesions.* PHARMAC. BIOCHEM. BEHAV. 17(4) 639–643, 1982.—The effects of dorsal noradrenergic bundle (DNB) lesions on plasma corticosterone levels were determined in male albino rats. DNB lesions did not affect baseline plasma corticosterone levels. Furthermore, the increased corticosterone levels produced by various environmental manipulations did not differ between control and DNB lesioned groups. However, the lesioned group did exhibit longer latencies to eat familiar food in novel environments, as well as to eat novel foods in a familiar environment. Latencies to eat novel food in novel environments did not differ between the two groups and this was attributed to a "ceiling" effect. These endocrinological data fail to support the hypothesis that the enhanced "neophobia" observed in DNB lesioned rats is due to an increase in the intensity of the emotional reaction to novel stimuli. The data do not preclude the possibility, however, that the enhanced neophobic reactions reflect impaired habituation to these stimuli.

Neophobia Plasma corticosterone Lesions Dorsal noradrenergic bundle

CONFLICTING reports have appeared concerning the role of the locus coeruleus noradrenaline (NA) system in fear-motivated behavior. Electrolytic lesions in the region of the locus coeruleus (LC) in the stumptail macaque reduces threat-induced behaviors [19], while electrical stimulation of this region produces these behaviors in the absence of external threat [30]. Destruction of the ascending fibers of the locus coeruleus, the dorsal NA bundle (DNB), by the specific neurotoxin 6-hydroxydopamine (6-OHDA), in combination with adrenalectomy can produce deficits in active and passive avoidance learning in the rat [26,31]. Neither of these treatments by themselves impair conditioning. These deficits can be reversed with corticosterone treatment [28], and occur only with fear-motivated behaviors [24]. Furthermore, there is substantial evidence that central NA turnover is increased by the presentation of "stressors" (cf. [2]). Incompatible with some of the above findings are reports that 6-OHDA-induced lesions of the DNB increase apparently fear-related behavioral responses to novel stimuli [5, 21, 23].

A central issue that requires clarification is whether the enhanced reactions to novelty observed after DNB lesions reflect an increase in fear. It is possible that DNB lesions retard habituation processes rather than increase fear. The failure to observe increases in conditioned emotional responses after injection of 6-OHDA into the DNB [22] supports such an interpretation. A recent report has indicated that plasma corticosterone levels exhibit a graded response to novelty [10]. As this may provide a relatively independent assessment of the degree of emotionality experienced by rats with NA depletions, we determined the plasma levels of corticosterone in DNB lesioned rats which had been exposed to a novel parallel arm maze.

A second issue addressed in this report concerns the degree to which different factors contribute to enhanced neophobia after DNB lesions. Mason, Roberts and Fibiger [23] found that DNB rats placed in a novel environment exhibited increases in only some responses thought to be related to the level of emotionality. Therefore, the degree to which both the novelty of environment and food novelty contribute to enhanced neophobia was investigated in a second experiment.

METHOD

Surgical

Male albino rats (Woodlyn Farms, Ontario) weighing 290–310 g at the time of operation were anaesthetized with Nembutal (50 mg/kg, IP) and positioned in a stereotaxic apparatus. Two holes were drilled through the skull to allow a 34 gauge cannula to be lowered bilaterally to the following coordinates: AP −6.0 mm from Bregma, ML ±0.8 mm from the midline suture, and DV −5.0 mm from the dura. Four μg of 6-OHDA HBr (Regis Chemicals, weight expressed as free base) dissolved in 2 μl of 0.9% saline with 0.3 mg/ml ascorbic acid were infused at the rate of 1 μl/min in all rats and the cannula was left in place for a further minute to permit diffusion of the drug. The skin was then sutured. Eleven control rats received similar injections of the vehicle.

Copyright © 1982 ANKHO International Inc.—0091-3057/82/100639-05$03.00/0

TABLE 1
DESIGN OF THE NEOPHOBIA EXPERIMENT

Sequence	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	Ne Nf	Ne Ff	←	Habituation	→	FeNf	FeFf
2	Ne Nf	Ne Ff	←	Habituation	→	Fe Ff	Fe Nf
3	Ne Ff	Ne Nf	←	Habituation	→	Fe Nf	Fe Ff
4	Ne Ff	Ne Nf	←	Habituation	→	Fe Ff	Fe Nf

Each of 11 DNB lesioned rats and 11 control rats were tested under each of the following conditions: (1) novel environment + novel food (Ne Nf), (2) novel environment + familiar food (Ne Ff), (3) familiar environment + novel food (Fe Nf), and (4) familiar environment + familiar food (Fe Ff). Two different boxes (environments) and three different foods were used. Each rat had experience with a particular box-food combination once only. Four different sequences of box-food combinations were followed. Rats were tested for 2 days, habituated to both boxes for 3 days, and tested again for a final 2 days. Boxes and food types were counterbalanced.

Corticosterone

The rats were maintained on an ad lib food and water regimen for 2 weeks, while singly housed in a room with a light period from 08:00 to 20:00. During the second week, the rats received daily handling, involving transport across the colony room, being held and stroked for 3 min and being picked up and put down 10 times. Two weeks after surgery, the rats were taken from their home cages, taken to another part of the colony room, immobilized, and within 3 min of removal from the home cage blood samples of 200 μl were obtained from an incision made in the tail (Treatment 1). All blood samples were collected between 10:30 hr and 14:30 hr. Collection, preparation and fluorometric determination of plasma corticosterone procedures followed those established by Glick, Redlich and Levine [14]. The following week, the animals were deprived of food for 24 hours, then removed from their home cages, and transported to a dimly lit (50 watt red lamp) test room. After 21 min they were returned to the colony room, and another blood sample was obtained (Treatment 2), following the same procedure. The rats were then returned to their home cages, with ad lib access to food.

Seven days after Treatment 1, the animals were again food deprived and 24 hours later they were transported to the dimly lit test room, and placed individually in a parallel arm maze, described previously [21]. Extraneous sounds were masked by low level masking noise. The subjects were left in the maze for 21 minutes after exit from the start box. The maze was wiped thoroughly with a sponge dampened with a weak acetic acid solution before entry by each rat. At the end of the 21 minute period, the rats were removed and transported to the colony room, where the third and final blood sample was obtained (Treatment 3). All three blood samples were taken at the same time of day for each rat.

Behavioral

The rats were given free access to food for a week following removal of the last blood sample. Food was again removed from the home cages, and 22 hours later, the first session of testing for neophobia began. On the first day of testing, animals were placed in one of two novel environments (a narrow wooden box, painted gray, and measuring 9 cm × 26 cm × 24 cm high, or a gray metal box with 3 solid metal sides, a grid floor and 1 wire mesh side, measuring 35 cm × 40 cm × 18 cm high) with either familiar food (Purina Lab Chow, their regular diet) or novel food (either Kellogg's Fruit Loops cereal or Lowry's chocolate-coated peanuts). Latencies to approach food (defined by the rat's nose coming within 2 cm of the food) and to begin eating were recorded. If the rats did not begin to eat the food within 5 min they were removed from the apparatus and given a score of 300 sec. After testing, the rats were given 2 hour access to their regular food in their home cages. On the next day, rats were again tested following this procedure, except that those that were previously placed in novel environments with familiar food, were now placed in a second novel environment with novel food. Rats originally placed in novel environments with novel food were exposed to a second novel environment with familiar food. Environments, food, and the order of presentation were counterbalanced. For the next three days, each rat was placed in each of the two environments for 1 hour. On the fourth day, food was removed from the home cages, and 22 hours later the testing procedure was repeated. Those rats that had previously received Fruit Loops as the novel food now received chocolate-coated peanuts, with the reverse also being true. The environments used on this and the next day were the same as were used on the first two days, except that they were now considered to be familiar on the basis of the 3 1-hour exposures. Rats that received novel food on Day 1 and familiar food on Day 2, now received familiar food on Day 3 and novel food on Day 4, and vice versa. Thus, all factors were counterbalanced except, of course, novelty and familiarity of the environments, which by necessity of the experimental design had to occur in the sequence: novel, novel, familiar, familiar. See Table 1 for a description of the experimental design.

Catecholamines

One month after behavioral testing, the rats were killed by cervical dislocation, and their brains removed and dissected on ice. The brains of 5 control and 5 experimental rats were dissected into cortex-hippocampus, hypothalamus and striatum as previously described [34], and the remaining

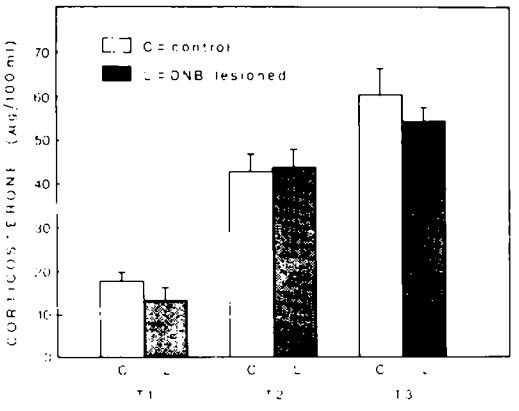

FIG. 1. Plasma corticosterone levels (μg/100 ml ± SEM) in rats with 6-OHDA (DNB lesioned) or vehicle injections (control) into the dorsal noradrenergic bundle after removal from home cage (T1), after food deprivation and transport to test area (T2), and after food deprivation and exposure to a novel maze (T3). See text for details.

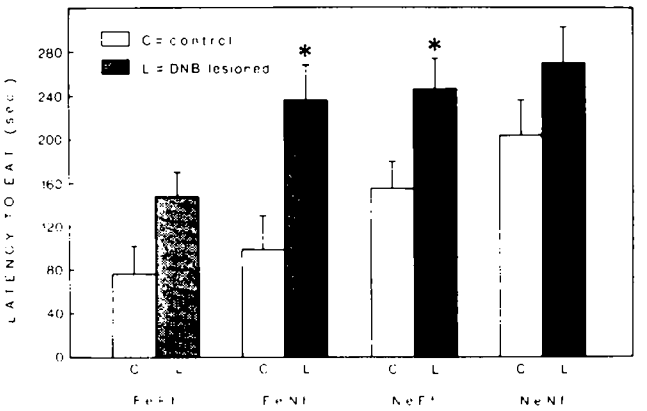

FIG. 2. Latency in seconds (±SEM) of 6-OHDA DNB lesioned and control rats to eat either familiar food (Ff) or novel food (Nf) in familiar (Fe) or novel (Ne) environments. *Significantly different from controls in the same condition ($p<0.05$).

brains were dissected into cortex-hippocampus only. Catecholamines were assayed by the method of McGeer and McGeer [25].

RESULTS

Corticosterone

The results of the corticosterone assay are presented in Fig. 1. Results were analyzed by analysis of variance with repeated measures on the treatment factor (i.e., removal from home (T1), food deprivation and transport to test area (T2), and food deprivation, transport to test area and exposure to a novel maze (T3)) and Scheffe's test. No significant differences in the plasma corticosterone levels were found between DNB 6-OHDA rats and vehicle injected controls under any of the experimental conditions, $F(1,20)=1.57$, $p>0.05$. The treatment effect was significant, $F(2,40)=66.07$, $p<0.001$. Analysis with Scheffe test ($p<0.005$) indicated that both the increase in plasma corticosterone levels from T1 to T2 and from T2 to T3 were significant. The interaction between groups and treatment was not significant, $F(2,40)=0.065$, $p>0.1$. Thus, both 6-OHDA (n=11) and control (n=11) rats showed increases in plasma corticosterone levels when food deprived and transported, and further increases when food deprived, transported and exposed to a novel maze.

Behavioral

Figure 2 displays the results of the behavioral test of neophobia. Analysis of variance with 1 between factor (lesion) and 2 repeated factors (environment and food) failed to indicate a significant difference between groups in the latency to approach food (data not shown). However, 6-OHDA treated rats (n=11) differed significantly from controls (n=11) in their latency to eat, $F(1,20)=10.75$, $p<0.005$. The Scheffe test for multiple comparisons indicated that group differences occurred when either food or environment were novel but not when both were novel, or when both were familiar. Thus, novelty of environment had a significant effect, $F(1,20)=25.23$, $p<0.001$, on latency to eat food, as did novelty of food, $F(1,20)=7.31$, $p<0.025$.

TABLE 2

REGIONAL NORADRENALINE (NA) AND DOPAMINE (DA) CONCENTRATIONS IN CONTROL AND 6-OHDA DNB LESIONED RATS

	Control	DNB Lesion	Lesion % of Control
NA			
Hippocampus/cerebral Cortex (N=11)	0.330 ± 0.05	0.020 ± 0.02	6.1
Hypothalamus (N=5)	1.770 ± 0.16	1.000 ± 0.43	56.5
DA			
Striatum (N=5)	9.32 ± 1.53	9.39 ± 0.59	100.8

Values are means (±SEM) in μg/g wet weight of tissue.

Catecholamines

Table 2 displays the results of the assay for catecholamines and indicates a 93% depletion of NA in the cortex-hippocampus tissue, a 43.5% reduction in hypothalamic NA and no effect on striatal dopamine.

DISCUSSION

Evidence concerning the role of central NA in the regulation of the hypothalamic-hypophyseal-adrenal axis is presently unclear. *In vitro* studies suggest that there may be an α_1-adrenergic mechanism that ultimately results in corticosterone secretion through a direct release of adrenocorticotropin hormone (ACTH) or through ACTH secretion mediated by NA-induced release of corticotropin releasing factors (CRF) [4, 13, 39]. Data collected from both *in vitro* and *in vivo* experiments indicate that activation of α_2-adrenergic receptors inhibits stress or acetylcholine-induced ACTH release [8, 11, 12, 17, 31, 35]. Also, α-methyl-para-tyrosine induced increases in plasma corticosterone levels are reduced by α_2 agonists [36]. There is also evidence that the spontaneous release of ACTH from the pars intermedia of the pituitary may be mediated by α_1-adrenergic receptors [37]. However, intraventricular injections of 6-OHDA in neonatal [20] or mature [18] rats, or bilateral electrolytic lesions of the mouse LC [15], fail to significantly alter basal corticosterone levels after a recovery period following surgery, and in animals maintained on a 12 hr light-dark cycle. The experiment reported here is consistent with the latter results in that DNB lesions do not affect baseline corticosterone levels. Nor was the increase in plasma corticosterone induced by environmental manipulations such as food deprivation, transport and exposure to a novel maze different between lesioned and control rats. Although it is possible that compensatory changes occur in response to the loss of 50% of hypothalamic NA, the present results suggest that the DNB does not participate in the regulation of ACTH secretion. This raises the possibility that it is the ventral NA bundle [38] that regulates ACTH secretion.

Plasma corticosterone levels are an insensitive index of stress when rats are subjected to "major stressors" [26], probably because a relatively mild stress produces maximum corticosterone secretion. However, plasma corticosterone levels do exhibit a monotonic relationship to various degrees of environmental change [16] or novelty [10]. The present data provide further evidence in support of this relationship in that we observed higher plasma corticosterone after exposure to a novel maze than after transport to the testing area alone (Fig. 1).

The experiments reported here may help to resolve some of the controversy surrounding the putative role of the locus coeruleus and central NA in fear-motivated behaviors. According to one hypothesis, destruction of the LC reduces fear and anxiety [19]. If the ascending fibers of the LC mediate this effect, then DNB lesions might have been expected to reduce corticosterone secretion in response to novel stimuli. On the other hand, if the enhanced behavioral reactions to novel stimuli observed in DNB lesioned rats reflect increases in fear of novelty, then higher plasma corticosterone levels in the DNB lesioned group after exposure to a novel maze might have been predicted. To the extent that circulating corticosterone levels reflect emotionality, the present results provide no evidence that DNB lesioned rats are either more or less fearful or reactive to the stress of novelty than are control animals. Therefore, neither of the above hypotheses was supported. In this regard, it is important to note a major limitation of the data upon which the LC "fear" hypothesis is founded. Specifically, it has yet to be demonstrated that behavioral effects of either electrical stimulation or electrolytic lesions in the region of the LC are mediated by noradrenergic neurons [6, 19, 30, 33].

An alternate hypothesis concerning the effect of destruction of the DNB on reactions to novelty is that under some circumstances such lesions can produce deficits in habituation. This interpretation is consistent with: (1) our finding of similar increases in plasma corticosterone levels in DNB lesioned and control rats, (2) Mason and Fibiger's [22] failure to observe increases in the conditioned emotional response of DNB lesioned rats, and (3) the lack of difference between rats with DNB lesions and controls in a test of "anxiety" [9]. Crow and colleagues [7] found that rats with 6-OHDA-induced lesions of the ascending and cerebellar NA fibres exhibited normal motor activity and exploration, and normal habituation of these behaviors. We have also observed that exploration appears normal in DNB lesioned rats [29], and DNB rats in the present experiment did not differ from controls in their approaches to food when either food and environment, or both, were novel. Therefore, it appears that DNB lesions may produce deficits in habituation in some, but not all, behavioral reactions to novelty.

The behavioral experiment reported here established that novelty of either environment or food can produce increased reactions to novel stimuli in DNB lesioned rats. That lesioned rats did not differ significantly from controls when both food and environment were novel can be attributed to a "ceiling" effect because the latencies for both control and DNB lesioned groups in the novel food and novel environment condition were close to the maximum possible value (Fig. 2). A report by Archer, Ogren and Ross [3] has indicated that NA depletion induced with the neurotoxin, DSP-4, does not produce increases in taste neophobia, and, in fact, reduces neophobic reactions when a novel taste is paired with a novel exteroceptive cue. Treatment with DSP-4 results in a pattern of NA depletion that includes all of the projections of the LC, similar to the depletion pattern observed after LC lesions. DNB lesions do not deplete NA in the spinal cord or cerebellum; in fact, NA levels in these areas are increased by these lesions. This may be a critical difference in terms of the habituation hypothesis of DNB lesion-induced increase in "neophobia," for 6-OHDA lesions of the LC reduce both the time required for response habituation to sensory stimulation and the magnitude of the startle reflex, whereas DNB lesions do not [1].

ACKNOWLEDGEMENTS

Supported by the Medical Research Council. M.T.M.-I. was supported by an NSERC postgraduate Fellowship and M.P. was supported by an MRC Centennial Fellowship.

REFERENCES

1. Adams, L. M. and M. A. Geyer. Effects of 6-hydroxydopamine lesions of locus coeruleus on startle in rats. *Psychopharmacology* 73: 394–398, 1981.

2. Anisman, H. Neurochemical changes elicited by stress: Behavioral correlates. In: *Psychopharmacology of Aversively Motivated Behavior*, edited by H. Anisman and G. Binami. New York: Plenum, 1978, pp. 119–172.

3. Archer, T., S. Ogren and S. B. Ross. N-2-chloroethyl-N-ethyl-2-bromobenzylamine hydrochloride (DSP4), a new selective noradrenaline neurotoxin, and taste neophobia in the rat. *Physiol. Psychol.* **9:** 197–202, 1981.
4. Beny, J.-L. and A. J. Baertschi. Corticotropin-releasing factors (CRF) secreted by the rat median eminence in vitro in the presence or absence of ascorbate acid: quantitative role of vasopressin and catecholamines. *Endocrinology* **109:** 813–817, 1981.
5. Britton, D. R., C. Ksir and G. Koob. Effects of dorsal noradrenergic bundle lesions on measures of conflict, learning and locomotion. Presented at Society for Neuroscience 11th Annual Meeting, Los Angeles, CA, 1981.
6. Crawley, J. N., J. W. Maas and R. H. Roth. Evidence against specificity of electrical stimulation of the nucleus locus coeruleus in activating the sympathetic nervous system in the rat. *Brain Res.* **183:** 301–311, 1980.
7. Crow, T. J., J. F. W. Deakin, S. E. File, A. Longden and S. Wendlandt. The locus coeruleus noradrenergic system—evidence against a role in attention, habituation, anxiety and motor activity. *Brain Res.* **155:** 249–261, 1978.
8. Eisenberg, R. M. Further evidence of central alpha-adrenergic inhibitory influence on the hypothalamo-pituitary-adrenal axis in the rat. *Neuroendocrinology* **17:** 154–166, 1975.
9. File, S. E., J. F. W. Deakin, A. Longden and T. J. Crow. An investigation of the role of the locus coeruleus in anxiety and agonistic behavior. *Brain Res.* **169:** 411–420, 1979.
10. File, S. E. and L. A. Peet. The sensitivity of the rat corticosterone response to environmental manipulations and to chronic chlordiazepoxide treatment. *Physiol. Behav.* **25:** 753–758, 1980.
11. Ganong, W. F. Participation of brain monoamines in the regulation of neuroendocrine activity under stress. In: *Catecholamines and Stress: Recent Advances*, edited by E. Usdin, R. Kvetnansky and I. J. Kopin. New York: Elsevier/North Holland, 1980, pp. 115–124.
12. Ganong, W. F., N. Kramer, J. Salmon, I. A. Reid, R. Lovinger, U. Scapagnini, A. T. Boryczka and R. Shackelford. Pharmacological evidence for inhibition of ACTH secretion by a central adrenergic system in the dog. *Neuroscience* **1:** 167–174, 1976.
13. Giguere, V., J. Cote and F. Labrie. Characteristics of the α-adrenergic stimulation of adrenocorticotropin secretion in rat anterior pituitary cell. *Endocrinology* **109:** 757–762, 1981.
14. Glick, D., D. Von Redlich and S. Levine. Fluorometric determination of corticosterone and cortisol in 0.02–0.05 milliliters of plasma or submilligram samples of adrenal tissue. *Endocrinology* **74:** 653–655, 1964.
15. Gray, H. E., S. E. Wenzel, W. G. Luttge and S. F. Zornetzer. Effect of lesions of the locus coeruleus complex on the circadian rhythm of plasma corticosterone in the mouse. *Experientia* **35:** 1126–1127, 1979.
16. Hennessey, M. B. and S. Levine. Sensitive pituitary-adrenal responsiveness to varying degrees of psychological stimulation. *Physiol. Behav.* **21:** 295–297, 1978.
17. Hillhouse, E. W., J. Burden and M. T. Jones. The effect of various putative neurotransmitters on the release of corticotrophin releasing hormone from the hypothalamus of the rat in vitro. I. The effect of acetylcholine and noradrenaline. *Neuroendocrinology* **17:** 1–11, 1975.
18. Honma, K.-I. and T. Hiroshige. Participation of brain catecholaminergic neurons in a self-sustained circadian oscillation of plasma corticosterone in the rat. *Brain Res.* **169:** 519–529, 1979.
19. Huang, Y. H., D. E. Redmond, D. R. Snyder and J. W. Maas. In vivo location and destruction of the locus coeruleus in the stumptail macaque (Macaca arctoides). *Brain Res.* **100:** 91–97, 1975.
20. Krieger, D. T. Effect of intraventricular neonatal 6-OH dopamine or 5,6-dihydroxytryptamine administration on the circadian periodicity of plasma corticosteroid levels in the rat. *Neuroendocrinology* **17:** 62–74, 1975.
21. Mason, S. T. and H. C. Fibiger. Altered exploratory behavior after 6-OHDA lesion to the dorsal noradrenergic bundle. *Nature* **269:** 704–705, 1977.
22. Mason, S. T. and H. C. Fibiger. Noradrenaline, fear and extinction. *Brain Res.* **165:** 47–56, 1979.
23. Mason, S. T., D. C. S. Roberts and H. C. Fibiger. Noradrenaline and neophobia. *Physiol. Behav.* **21:** 353–361, 1978.
24. Mason, S. T., D. C. S. Roberts and H. C. Fibiger. Interaction of brain noradrenaline and the pituitary-adrenal axis in learning and extinction. *Pharmac. Biochem. Behav.* **10:** 11–16, 1979.
25. McGeer, E. G. and P. L. McGeer. Catecholamine content of the spinal cord. *Can. J. Biochem.* **40:** 1141–1151, 1962.
26. Natelson, B. H., W. N. Tapp, J. E. Adamus, J. C. Mitller and B. E. Levine. Humoral indices of stress in rats. *Physiol. Behav.* **26:** 1049–1054, 1981.
27. Ogren, S.-O. and K. Fuxe. Learning, brain noradrenaline and the pituitary-adrenal axis. *Med. Biol.* **52:** 399–405, 1974.
28. Ogren, S.-O. and K. Fuxe. On the role of brain noradrenaline and the pituitary adrenal axis in avoidance learning. I. Studies with corticosterone. *Neurosci. Lett.* **5:** 291–296, 1977.
29. Pisa, M., M. T. Martin-Iverson and H. C. Fibiger. Noradrenaline, extinction and spatial learning. Presented at Society for Neuroscience 11th Annual Meeting, Los Angeles, CA, 1981.
30. Redmond, D. E., Y. H. Huang, D. R. Snyder and J. W. Maas. Behavioral effects of stimulation of the nucleus locus coeruleus in the stump-tailed monkey (Macaca arctoides). *Brain Res.* **116:** 502–520, 1976.
31. Renzo, G. D., G. Schettini, A. Quattrone, M. Holmes, U. Scapagnini and M. Jones. Monoaminergic control of hypothalamic-hypophyseal-adrenal axis activity. In: *Catecholamines and Stress: Recent Advances*, edited by E. Usdin, R. Kvetnansky and I. J. Kopin. New York: Elsevier/North Holland, 1980, pp. 189–193.
32. Roberts, D. C. S. and H. C. Fibiger. Evidence for interactions between central noradrenergic neurons and adrenal hormones in learning and memory. *Pharmac. Biochem. Behav.* **7:** 191–194, 1977.
33. Roberts, D. C. S., M. T. C. Price and H. C. Fibiger. The dorsal tegmental noradrenergic projection: analysis of its role in maze learning. *J. comp. physiol. Psychol.* **90:** 363–372, 1976.
34. Roberts, D. C. S., A. P. Zis and H. C. Fibiger. Ascending catecholamine pathways and amphetamine induced locomotor activity: Importance of dopamine and apparent non-involvement of norepinephrine. *Brain Res.* **93:** 441–454, 1975.
35. Scapagnini, U., L. Annunziato, G. Lombardi, Ch. Oliver and P. Preziosi. Time-course of the effect of α-methyl-p-tyrosine on ACTH secretion. *Neuroendocrinology* **18:** 272–276, 1975.
36. Steiner, J. A. and D. G. Grahame-Smith. Central pharmacological control of corticosterone secretion in the intact rat. Demonstration of cholinergic and serotonergic facilitatory and α-adrenergic inhibitory mechanisms. *Psychopharmacology* **71:** 213–217, 1980.
37. Tilders, F. J. H., M. Post, S. Jackson, P. J. Lowry and P. G. Smelik. Beta-adrenergic stimulation of the release of ACTH-and LPH-related peptides from the pars intermedia of the rat pituitary gland. *Acta endocr.* **97:** 343–351, 1981.
38. Ungerstedt, U. Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta physiol. scand.* Suppl. **367:** 1–49, 1971.
39. Vale, W., C. Rivier, L. Yang, S. Minick and R. Guillemin. Effect of purified hypothalamic corticotropin releasing factor and other substances on the secretion of adrenocorticotropin and β-endorphin like immunoreactivities in vitro. *Endocrinology* **103:** 1910, 1978.