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Interaction of Brain Noradrenaline and the Pituitary-Adrenal Axis in Learning and Extinction

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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(1) 11–16, 1979.—The effect of 6-hydroxydopamine-induced degeneration of the dorsal tegmental noradrenergic (NA) projection alone or in combination with the removal of the adrenal glands was examined on several behavioral tasks. No impairment of acquisition on a continuously reinforced lever pressing response for food reward was seen as a result of the combined treatment. However, resistance to extinction was observed after depletion of forebrain noradrenaline on its own and this effect was prevented by the adrenalectomy. Adrenalectomy on its own failed to affect extinction. Acquisition of a passive avoidance task was slightly impaired after forebrain noradrenaline depletion but only the group with combined noradrenaline loss and adrenalectomy showed a 24 hour retention deficit. No alteration in shock thresholds was found in any group although both adrenalectomized groups consumed less food and were slightly less active in locomotor cages. It is suggested that previous reports of acquisition and retention deficits in avoidance tasks after combined dorsal NA bundle lesions and adrenalectomy are due to alterations in fear motivation rather than to a general learning impairment.

Noradrenaline Locus coeruleus Dorsal bundle Adrenalectomy Learning and memory
Passive avoidance Extinction Corticosterone

CONSIDERABLE investigation has been carried out in the past few years concerning the suggestions made by Kety [10,11] and Crow [3,4] that noradrenaline in the CNS is critically involved in learning and memory. In general, little support for this hypothesis has been found, in that animals depleted of brain noradrenaline (NA) do not show deficits in learning situations [1, 13, 15–19, 24, 28, 30]. However, if depletion of forebrain NA is combined with removal of the adrenal glands a profound learning deficit is found. Thus, Ogren and Fuxe [25] reported that animals receiving both adrenalectomy and depletion of forebrain NA failed to perform a previously learned two-way active avoidance task and also appeared to be unable to relearn this response. Neither adrenalectomy nor NA depletion alone produced this deficit. This has also been extended to one-way active avoidance [24] with similar results. That is, neither surgical procedure on its own produces an effect but the combination of adrenalectomy and depletion of forebrain NA results in an inability to learn the avoidance task. Roberts and Fibiger [27] have also reported that this combined treatment produces a deficit in acquisition learning and 24 hour retention of step-down passive avoidance. To date all the impairments have been observed in fear motivated learning and may reflect a change in fear processes rather than a more general learning deficit. To test the generality of the effect we examined acquisition of a food rewarded lever pressing response. Since forebrain NA loss on its own has been repeatedly found to slow extinction of many forms of learned behaviors [15, 16, 18, 19, 31] we also examined the effect that adrenalectomy would have on this dorsal bundle extinction effect (DBEE).

METHOD

Surgical

Eighteen male albino Wistar rats (Woodlyn Farms, Ontario, weighing 300 g) were anaesthetized with Nembutal (50 mg/kg) positioned in a stereotaxic apparatus (David Kopf Ltd.) and two holes drilled in the skull through which a 34 gauge cannula was lowered to the following coordinates: AP + 2.6 mm from interaural line, ML ± 1.1 mm from midline suture at bregma and DV + 3.7 mm from interaural line. Bilateral infusions of 6-hydroxydopamine (6-OHDA) hydrobromide (4 μg/2 μl expressed as the free base) dissolved in 0.9% saline with 0.2 mg/ml ascorbic acid antioxidant were performed at the rate of 1 μl/min and the cannula left in for an extra minute to permit diffusion of the drug. Twenty control animals received similar infusion of saline-ascorbic vehicle.

One week following the stereotaxic surgery 8 animals from the 6-OHDA group and 10 vehicle injected rats were

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again anaesthetized with Nembutal and subjected to bilateral adrenalectomies, which were achieved via the dorsal approach. The abdominal muscle and fascia were sutured and the skin incision closed with wound clips. The 10 remaining 6-OHDA and 10 vehicle injected rats received an identical operation except that the adrenals were not removed. For two weeks following this surgery all animals were maintained on food and water ad lib, except in the case of the adrenalectomized rats which was given access to 0.9% saline. Each rat was individually housed under a 12 hr light-dark cycle at 20°C.

Behavioral

CRF acquisition and extinction. Animals were placed on a two hr per day food access schedule and reduced to 90% of their free-feeding weight. They were subsequently fed 15 g of laboratory chow at the end of the daily testing session. Animals were lever shaped as described elsewhere [15,18] and placed on a continuously reinforced schedule for 15 min each day in standard operant test chambers (BRS/LVE) for the next ten days. At the end of this acquisition period, extinction testing commenced. During extinction no food or click of the automatic feeder was presented and the animal remained in the test chamber until the extinction criterion of no lever press for two consecutive minutes had been reached. The time to achieve this criterion and the number of lever presses emitted during this period were recorded. Four days of extinction testing were given.

Locomotor activity. Animals were placed in photocell activity cages (BRS/LVE) for two hours. The number of photocell beam interruptions were accumulated over ten minute segments and automatically printed out by a printout counter (BRS/LVE).

Passive avoidance. The animals were next tested on the acquisition and 24 hour retention of passive avoidance. Animals were placed on a shelf measuring 7.5 cm by 26.7 cm and being 9.4 cm above a wire grid floor of a Plexiglas cubicle measuring 30 cm by 25 cm by 43 cm in height. Upon stepping down from the shelf onto the floor the animal received 3 mA of electric footshock from a Lafayette constant current AC shock generator and scrambler. This footshock continued until the animal stepped back up onto the shelf. Additional stepdowns also resulted in footshock and the animal was removed when it had met the acquisition criterion of having remained on the shelf for three consecutive minutes. Measures taken during this acquisition phase included latency to initial stepdown, number of stepdowns and total time in apparatus prior to reaching the acquisition criterion. Twenty-four hours later the animals were again placed in the apparatus and the retention measure of time to stepdown was taken. Animals not stepping down within 3 minutes were given a value of 180 seconds.

Shock thresholds. Following passive avoidance testing all animals were tested in a different apparatus to determine their sensitivity to electric footshock. This procedure was modified from Evans [7] and comprised administration of a series of ascending intensities of inescapable electric footshock. The reaction of the animal was categorized as flinch (any bodily movement), forepaw jump (one or both forepaws leave the grid), hindpaw jump (one or both of the hindpaws leave the grid) or vocalization. The intensity of shock at which a given reaction, or a more intense one, occurred on three or more of five presentations of that intensity was taken as the threshold for that response.

Food intake. Food intake was measured over a 2 hr period by the weight difference of Purina Rat Chow pellets before and after the feeding session. This was performed on two successive days in the home cage when the animals were deprived of food for 22 hours. Large food pellets which fell through the bottom of the cages were collected, but otherwise the measure was uncorrected for spillage.

Biochemical

Following completion of behavioral testing all animals were sacrificed by decapitation, trunk blood collected for corticosterone determinations [6] and the brain rapidly removed and dissected into regions as described elsewhere [15,16]. The hippocampus-cortex, hypothalamus and striatum were assayed for endogenous catecholamines by the method of McGeer and McGeer [23].

RESULTS

Biochemical

The results of the brain amine assays are shown in Table 1 and serve to confirm that severe and permanent loss of forebrain noradrenaline was produced as a result of the intracerebral 6-OHDA injection. Hippocampus-cortex values were reduced to less than 5% of controls and hypothalamus NA was reduced to some 30–40% of normal. Almost complete sparing of striatal dopamine was seen.

The results of the corticosterone assays confirmed that the adrenalectomy had reduced the circulating levels of corticosterone, the vehicle adrenalectomized group had a value of 52.6 ± 4.2 ng/ml (27% of control), the 6-OHDA adrenalectomized group 42.8 ± 6.7 ng/ml (23%) and the combined control value was 188 ± 4.0 ng/ml.

Behavioral

CRF acquisition and extinction. The acquisition of the continuously reinforced lever pressing response is shown in Fig. 1 and it can be seen that the adrenalectomy resulted in considerably lower terminal response rates. Both groups of adrenalectomized rats pressed at less than half the rate of sham-adrenalectomized groups. The depletion of forebrain NA had no additional effect, either in adrenalectomized or sham-adrenalectomized groups. This effect was confirmed by analysis of variance in which a three factor design with repeated measures on one factor (days) was used [34]. The effect of adrenalectomy was highly significant, $F(1,34)=152.5$, $p<0.001$, but neither the effect of dorsal bundle injection of 6-OHDA nor its interaction with adrenalectomy was significant. The time course over days was highly significant, indicating that learning had occurred, $F(9,306)=69.9$, $p<0.001$, and this interacted significantly with adrenalectomy, $F(9,306)=18.5$, $p<0.001$. However, neither the dorsal bundle term nor the three way interaction achieved significance.

Extinction is shown in Fig. 2. On the left is the response rate measure and on the right the time to criterion measure. Dorsal bundle injection of 6-OHDA produced a significant resistance to extinction in sham-adrenalectomized rats but this was prevented in rats without the adrenal glands. Adrenalectomy on its own failed to alter the response rates in extinction. Given the alteration in terminal CRF response rates caused by adrenalectomy it is virtually impossible to conclude what effect adrenalectomy had on extinction per se. These effects were confirmed statistically by analysis of

TABLE 1

POST-MORTEM AMINE ASSAYS

	Sham Vehicle (n=10)	Sham 6-OHDA (n=10)		Adrex Vehicle (n=10)	Adrex 6-OHDA (n=8)	
Noradrenaline						
Hippocampus-cortex	0.355 ± 0.032	0.016 ± 0.002	(5%)	305 ± 12	0.015 ± 0.003	(5%)
Hypothalamus	2.470 ± 0.108	1.000 ± 0.594	(40%)	2790 ± 170	0.914 ± 0.133	(32%)
Dopamine						
Striatum	12.100 ± 0.20	11.600 ± 0.357	(95%)	11.800 ± 0.297	10.900 ± 0.557	(92%)

Post-mortem amine assays on adrenalectomised (adrex) and 6-OHDA injected rats. Values are means (± SEM) in micrograms of amine per gram of wet weight of tissue. Numbers in parentheses are the percentage of respective control values remaining in 6-OHDA lesioned tissues.

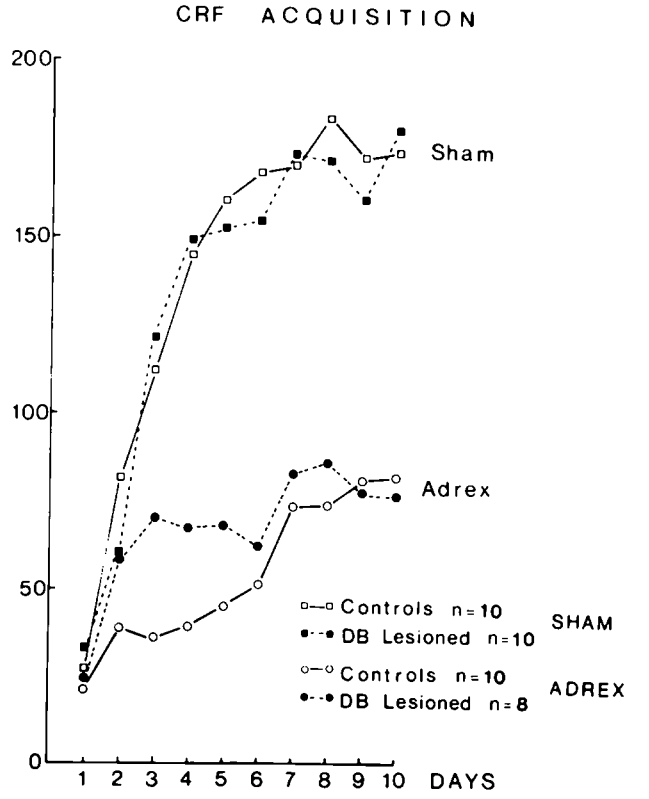

FIG. 1. Acquisition of CRF for food reward in intact (sham) and adrenalectomized (adrex) animals. Animals also received injection of 6-hydroxydopamine into the dorsal bundle to deplete forebrain noradrenaline (DB lesioned) or injection of saline-ascorbic vehicle (controls). Values are mean number of lever presses emitted in a fifteen minute daily session.

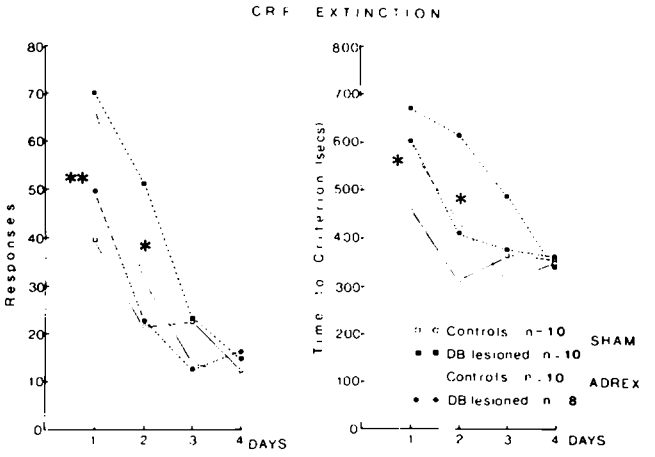

FIG. 2. Extinction of CRF for the same animals as in Fig. 1. The graph on the left shows the response measure and that on the right the time to criterion measure (see text). Stars indicate that the sham DB lesioned group differs from the sham vehicle group at the following significance level; **1%; *5%. The adrex DB lesioned group failed to differ from the adrex vehicle control group on any day.

variance. For the rate measure in extinction the days term was highly significant, $F(3,1029)=47.9$, $p<0.001$, indicating that progressive extinction occurred over days. Neither the adrenalectomy nor the 6-OHDA term were individually significant but the interaction was, $F(1,34)=9.0$, $p<0.005$, indicating that the 6-OHDA injection altered extinction behavior in sham-adrenalectomized rats but was without effect in the group without adrenal glands. This interaction of 6-OHDA injection with adrenalectomy was further illustrated in the time course over days where neither the 6-OHDA by days nor the adrenalectomy by days interaction was significant but the three-way interaction was significant, indicating that the effect of the 6-OHDA injection on the time course of extinction was modified by prior adrenalectomy, $F(3,102)=5.15$, $p<0.002$. A similar pattern was seen with the time to criterion measure (Fig. 2 right) in which adrenalectomy prevented the development of the usual resistance to extinction in 6-OHDA lesioned rats (DBEE).

Locomotor activity. The locomotor activity over two hours in photocell activity cages is shown in Fig. 3 and is generally very similar for all groups. Repeated measures analysis of variance revealed, however, as well as the expected time course effect, $F(11,374)=61.7$, $p<0.001$, a significant time course by adrenalectomy interaction, $F(11,374)=3.11$, $p<0.001$. Inspection of Fig. 3 reveals that this is due to both adrenalectomized groups being slightly less active in the first ten minutes in the apparatus and more noticeably, in habituating to a lower level of activity during the last thirty minutes in the apparatus. No additional effect

TABLE 2
PASSIVE AVOIDANCE LEARNING AND RETENTION

	Sham Vehicle (n=10)	Sham 6-OHDA (n=10)	Adrex Vehicle (n=10)	Adrex 6-OHDA (n=8)
Initial stepdown latency (secs)	3.3 ± 0.6	2.5 ± 0.5	5.3 ± 2.1	7.9 ± 2.8
No. of stepdowns to acquisition criterion	3.9 ± 0.6	5.1 ± 0.9*	2.3 ± 0.4	5.6 ± 0.7*
Time in apparatus to acquisition criterion (secs)	239 ± 11	288 ± 39*	232 ± 11	304 ± 22*
24 hr retention stepdown time (secs)	88 ± 24	100 ± 27	135 ± 20	53 ± 32*

Acquisition and 24 hr retention of passive avoidance for adrenalectomised (adrex) and noradrenaline depleted rats. Values are means with standard error of the mean. The Sham groups were tested on a different day from the Adrex groups and therefore individual comparisons are limited to groups tested on the same day. (*Students t, $p<0.05$).

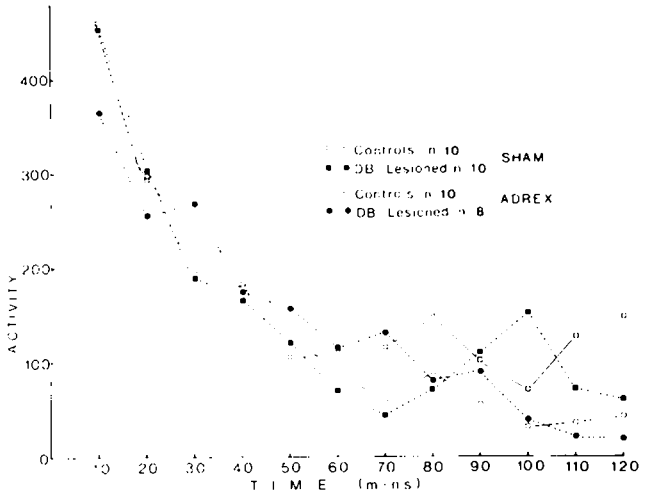

FIG. 3. Locomotor activity for the same animals as in Fig. 1. Values are cumulative photocell beam interruptions over ten minute periods from introduction of the animals into the apparatus for a two-hour session.

of 6-OHDA injection was seen either in the sham-adrenalectomized rats or in the group without adrenal glands, and the three way interaction with time was not significant.

Passive avoidance. Acquisition and 24 hour retention of stepdown passive avoidance is shown in Table 2. The initial stepdown latency showed a tendency to be higher for both adrenalectomized groups than for shams but this failed to reach significance, $F(1,34)=2.95$, $p<0.095$. No other term approached significance for the initial stepdown latency. The acquisition of the passive avoidance task was significantly retarded by the 6-OHDA injection on both the measure of number of stepdowns and that of time in apparatus prior to achieving criterion, $F(1,34)=10.25$, $p<0.003$ for number of stepdowns and $F(1,34)=6.43$, $p<0.016$ for time in apparatus. However, the adrenalectomy was without additional effect since neither the adrenalectomy term nor the interaction achieved significance. On the other hand, the 24 hour retention data revealed that neither the 6-OHDA injection nor the adrenalectomy per se had any significant effect but the combined insult impaired retention (interaction $F(1,34)=3.5$, $p<0.05$, one-tailed).

Shock thresholds. Sensitivity to electric footshock is shown in Table 3 and no alteration was seen as a result of either adrenalectomy or 6-OHDA induced depletion of forebrain NA.

Food intake. The average 2 hr food intake on two consecutive days for each group of animals is presented in Table 4. A significant reduction in intake is seen in the adrenalectomized animals, $F(1,34)=55.5$, $p<0.01$, but neither the 6-OHDA treatment nor the interaction term achieved significance.

DISCUSSION

Previous authors have reported that neither depletion of forebrain NA by intracerebral 6-OHDA nor adrenalectomy on their own affect learning, but that the combined insult results in severe learning and retention deficits [24, 25, 27]. All the previous work made use of fear motivated tasks and it is apparent from the failure to find such a deficit with positively reinforced lever pressing in the present experiment that the effect of the combined insult may be on fear processes rather than a general learning deficit. Thus, on acquisition of CRF, the adrenalectomy per se resulted in significantly lower response rates. This effect would not appear to be due to a motor deficit since locomotor activity was not greatly altered by adrenalectomy. However, a more likely cause may be a reduction in appetite as shown by the reduced food intake of both adrenalectomized groups consequent to hormonal imbalance rather than a learning impairment. Of greater importance to the current investigation is the fact that addition of a 6-OHDA injection did not further impair performance after adrenalectomy. It did not slow or prevent acquisition or alter the terminal response rates when compared with adrenalectomized rats with intact forebrain

TABLE 3

SHOCK THRESHOLDS IN μAMPS

	Flinch	Forepaw Jump	Hindpaw Jump	Vocalise
Sham-adrenalectomy vehicle injection	312 ± 30	408 ± 42	745 ± 66	660 ± 75
Sham-adrenalectomy 6-OHDA injection	258 ± 42	420 ± 48	642 ± 54	642 ± 54
Adrenalectomy vehicle injection	243 ± 30	432 ± 51	801 ± 57	717 ± 66
Adrenalectomy 6-OHDA injection	246 ± 42	408 ± 63	708 ± 96	696 ± 111

Flinch-jump thresholds for adrenalectomised and noradrenaline depleted rats.

TABLE 4

2 HOUR FOOD INTAKE

Sham Vehicle	Sham 6-OHDA	Adrex Vehicle	Adrex 6-OHDA
16.6 ± 2.8	14.7 ± 2.7	10.5 ± 2.2	8.6 ± 1.9

Values represent mean (± SEM) intake of Purina Rat Chow food pellets in grams averaged over two consecutive daily 2 hr feeding sessions. The animals were 22 hr food deprived at the beginning of the test periods.

NA. Neither did depletion of forebrain NA in sham-adrenalectomized rats alter CRF acquisition. Thus, depletion of forebrain NA did not impair acquisition learning of this positively reinforced task, either on its own or in combination with adrenalectomy. This argues that the previously reported learning impairments seen after the combined insult are due to the nature of the tasks used, and reflect a possible change in fear motivation rather than a general learning impairment.

In extinction of the CRF response, on the other hand, the double insult did produce an effect different from those seen after each individual manipulation. Given the difference in terminal response rates on the CRF schedule as a result of adrenalectomy it is not possible to conclude what effect adrenalectomy per se had on extinction. Depletion of forebrain NA by 6-OHDA injection resulted in resistance to extinction as has been reported previously [15, 16, 18, 19]. Prior adrenalectomy had the effect of preventing the occurrence of the DBEE. Thus, animals without both forebrain NA and adrenal glands failed to show the resistance to extinction seen in animals lacking only forebrain NA. This suggests that the effect of forebrain NA loss in causing resistance to extinction is in some way dependent on an intact adrenal-pituitary axis. At this time it cannot be further specified but various possibilities can be suggested. Thus, it may be that the chronically high levels of ACTH that occur following adrenalectomy are incompatible with the mechanism of the DBEE. In this regard it is of interest to note that ACTH levels are affected by NA manipulations (lesion to the ventral bundle) [26] although these do not appear to be the same as those required to cause resistance to extinction (lesion to the dorsal bundle) [31]. Another possibility may be that the low levels of corticosterone produced by the adrenalectomy in some way alter the usual mechanism of the DBEE. Thus, corticosterone is found to bind heavily to the hippocampus [22], a brain area rich in NA [32] and known from ablation studies to be involved in extinction [5,12]. A parallel between fear and frustration has been suggested by some authors [2, 8, 9, 14, 33] and may explain why the double insult affects avoidance tasks (fear) and extinction (frustration) but not positively reinforced acquisition learning. Considerable additional work will be required to elucidate this noradrenaline adrenal-pituitary interaction in extinction.

Passive avoidance learning was affected in the present study by depletion of forebrain NA. A similar effect has been noted elsewhere in the absence of any interaction with the adrenal glands [20,21] and has been shown to be dependent on the intensity of electric footshock used and the exact nature of stepdown paradigm. The impairment appears from these other data to represent reduced freezing response to electric footshock and as such makes the 6-OHDA lesioned rats more active after shock and hence more likely to step off the shelf. That it is not a global learning deficit is shown by the fact that lower levels of shock (such as those used in our previous study on noradrenaline-adrenal interactions) [27] do not elicit differential freezing and hence acquisition is not impaired at these intensities. Nor is acquisition affected in passive avoidance paradigms which do not allow the freezing response to occur during acquisition [20,21]. More interesting from the point of view of the current study are the 24 hour retention data. Even after training all groups to the same acquisition criterion, 24 hour retention was markedly impaired in the group with the combined insult. Adrenalectomy or 6-OHDA injection per se did not affect 24 hour retention whereas the combination impaired retention, as has been seen before in this laboratory [27]. These effects on fear motivated passive avoidance learning and retention are not due to changed sensitivity to footshock as is shown by the flinch-jump thresholds. In conclusion, the retention impairment caused by the combined lesion in passive avoidance serves to highlight the fear related nature of the task rather than a general learning deficit.

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