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Forebrain Norepinephrine and Neurobehavioral Plasticity: Neonatal 6-Hydroxydopamine Eliminates Enriched-Impoverished Experience Effects on Maze Performance

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PAPPAS, B. A., M. SAARI, J. SMYTHE, S. MURTHA, K. STANGE AND R. INGS. *Forebrain norepinephrine and neurobehavioral plasticity: Neonatal 6-hydroxydopamine eliminates enriched-impoverished experience effects on maze performance.* PHARMACOL BIOCHEM BEHAV **27**(1) 153–158, 1987.—Newborn male rats were depleted of forebrain norepinephrine (NE) by systemic 6-hydroxydopamine injection and then reared from 25 to 60 days under either isolated or enriched conditions. They were subsequently tested for acquisition of either the Lashley III maze or the Hebb-Williams maze problems. Isolated rearing impaired Lashley maze performance of the controls but not the 6-OHDA injected rats. Similarly, for the Hebb-Williams maze, the isolation-reared controls made more errors than their enriched-reared counterparts while no differences were observed between the isolated and enriched reared, 6-OHDA injected rats. These results are consistent with the hypothesis that forebrain NE is permissive to the deleterious behavioral consequences of restricted experience during maturation.

Norepinephrine 6-Hydroxydopamine Enriched isolation rearing Experience maze learning

THE search for the behavioral significance of forebrain norepinephrine (NE) has raised substantial controversy. Kety [12] was among the first to theorize on this significance when he provocatively modeled a learning mechanism wherein affect-inducing events such as punishment or reward activate the forebrain NE system and this activation facilitates persisting change at other synapses which were also contiguously activated. This model was simple to test since it led to the prediction that learning should be impaired when the forebrain NE system is functionally damaged. Numerous investigations have in fact shown that the loss of forebrain NE either by way of lesion of the locus coeruleus (LC) or the dorsal tegmental NE bundle fails to impair learning or memory in the rat [4, 8, 20, 23].

Recently, Kasamatsu and Pettigrew [10] hypothesized that neurobehavioral plasticity during the brain's critical periods requires the forebrain afferents from the LC. They showed that whereas monocular eye occlusion of the kitten normally causes visual cortex cells to shift from binocular to monocular responsiveness, this effect failed to occur if the cortex was perfused with 6-OHDA. This result suggested that plasticity of the visual cortex required intact cortical NE terminals. This effect of 6-OHDA was counteracted by perfusion of the NE depleted cortex with exogenous NE [11]. Other laboratories have repeated this finding [1,6] and furthermore, it has been shown that NE depletion eliminates the shift in directional sensitivity of visual cortical cells after directional deprivation [6]. It should be noted, however, that at least the monocular deprivation phenomenon may occur only when NE is depleted at the time of the restricted experience but not when NE has been depleted perinatally [2].

These results with the cat suggested to us the possibility that NE may be essential to the shaping of some features of the rat's brain by experience. An earlier experiment from this laboratory [19] showed that neonatal systemic administration of 6-OHDA which permanently lesions NE terminals [9,24] eliminated differences between isolated and enriched reared rats in performance on the Lashley three maze and also differences in regional brain part weight and dopamine levels. The present experiment represents additional inquiry into those phenomena. We replicated (with minor modification) the Lashley maze procedure and also examined for the

generality of the effects of NE lesion by the consequences of differential rearing for problem solving as assessed by the Hebb-Williams maze procedure. The latter was originally standardized as a test of rat intelligence and has been found to be sensitive to differential rearing manipulations [21]. Our results for both mazes indicated that neonatal NE lesion did not impair maze acquisition but rather eliminated differential rearing effects on maze performance. These findings are consistent with a permissive role of forebrain NE in the modification of the brain by experience.

METHOD

Animals

The effects of differential rearing were compared for 100 male Wistar rats that had received either two SC injections of 6-OHDA (50 mg/kg) or vehicle (1.0 mg ascorbic acid/ml normal saline). The rats were offspring of dams received 14 days pregnant from Woodlyn Farms (Guelph). The litters were cross fostered and culled of females to yield 10 males per dam. The first injection was given within 12 hr of birth (at which time the litters were culled); the second 24 hr later. The dams and litters were housed in polypropylene maternity cages (45×23×15 cm) until weaning.

After weaning at 25 days, the rats were randomly assigned to either the environmental enrichment condition (E) or the normal, isolation condition (I). E consisted of 35 days of communal living (5 rats per 48×38×20 cm polypropylene cage) in housing containing a variety of objects such as tunnels, platforms and balls (all of which were regularly rotated), as well as a daily session of 30 min duration in an open field. I consisted of 35 days of relative isolation (excepting routine watering, feeding and cleaning of cages); the rats housed singly in stainless steel, wire-mesh, hanging cages (20×24×18 cm).

Lashley III Maze Training

The Lashley maze consisted of 8 cul-de-sacs requiring alternate left and right turns and was similar to that described by Lashley [13]. Training began the day following the 35 days of differential rearing. Ten rats from each of the four groups received three trials per test day at approximate 1 hr intervals and were run for ten test days with a one day interval between each test day. The rats were 24 hr water deprived prior to each test session. Water, available through a bottle spout, served as the reward in the goal box. On all trials on the first test day and on the first trial on subsequent days the rats were primed by placement in the goal box until either they initiated drinking or 5 min elapsed. Subsequently, the rats were placed in the start box and the time required to reach the goal box and initiate drinking was recorded. If 5 min elapsed without drinking the trial was terminated. Four identical mazes were used, with the order of the rats counterbalanced across mazes and time according to the treatment group affiliations. The experimenter was blind to the identity of the rats.

Hebb-Williams Maze Test

Fifteen additional rats from each of the four groups (with the exception of the 6-OHDA group from which one rat developed a tumor and was sacrificed), were submitted to training in the Hebb-Williams maze. For the duration of the adaptation to the maze, the rats were maintained on ad lib water while food rations were restricted to an average of 20–25 g per rat per day. Once adapted, the rats were individually housed in single cages. Food intake was restricted to 10–20 g per day with small daily adjustments to motivate better maze performance. Once the rats performance stabilized and they approached training criterion, their daily ration was fixed.

The closed-field, problem solving maze was as described by Rabinovitch and Rosvold [21] except that the walls and barriers were 1.12 cm higher. The 6 practice and 12 test problems were also as described.

The initial week of adaptation consisted of daily 0.5 hr sessions during which the 5 occupants of one colony cage were allowed to explore the maze and eat the chow available in the goal box. A different practice problem was placed on

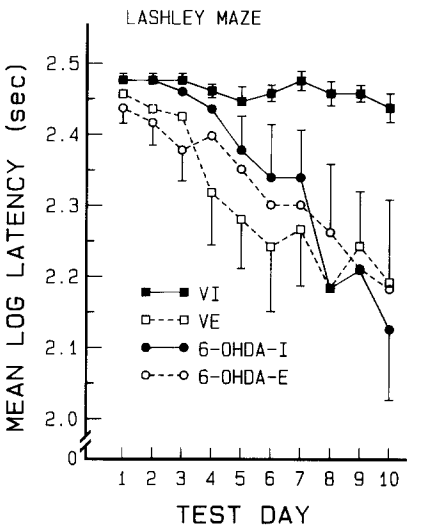

FIG. 1. Mean (±s.e.) log latencies to traverse the Lashley III maze are plotted across the ten test days for 6-OHDA or vehicle (V) injected rats raised under either enriched (E) or impoverished (I) conditions.

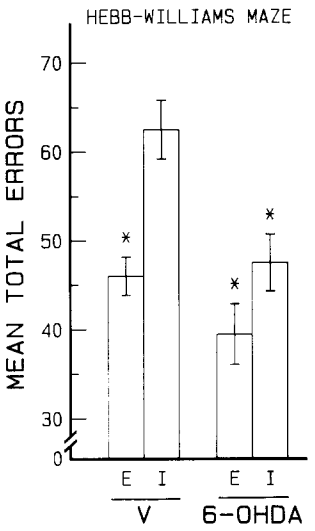

FIG. 2. Mean (and s.e.) total errors for the 12 problems of the Hebb-Williams maze. The data are for vehicle or 6-OHDA injected rats reared under either enriched or impoverished conditions.

the maze each day. Following this group adaptation, individual rats were allowed to traverse from start to goal box where they were allowed to consume chow for 20–30 sec. The 6 practice problems were the same as during group adaptation and were sequenced such that no problem appeared two days in a row. Because of their lengthy problem solving times early in training, the rats were run on alternate days. As their times shortened, they were run on consecutive days. Criterion performance was the completion of the 9 trials for a problem within 60 sec on 2 consecutive days (with 2 different problems). Subsequent to attaining criterion and until all the other rats reach criterion, the rat was given only 5 trials per day to maintain their familiarity with the maze. This procedure repeated that of Rabinovitch and Rosvold [21].

When all the rats in a replicate reached criterion (there were no group differences in days to criterion), they were then tested over 3 days on the 12 test problems as described by Rabinovitch and Rosvold [21]. This procedure yielded an error score for each problem. An error occurred when the rat entered established error zones (see Rabinovitch and Rosvold for these zones) while attempting to reach the goal box.

Hebb-Williams maze training began when the rats were 70 days of age and required 3 replications of 20, 20 and 19 rats respectively. Approximately 90 days elapsed between the replications and each replication contained a random sample of rats from each of the four groups. The experimenter who carried out the maze testing was blind as to the group identities of the rats.

Monoamine Assay

Within 2–3 weeks after completion of the Hebb-Williams test, these rats were decapitated and their brains dissected over a saline rinsed, ice cold plate. The brains were blunt dissected into cerebellum, medulla, pons, midbrain, hypothalamus, caudate, hippocampus, and cortex. The whole cortex was then laid flat, ventral surface down, on an etched template and divided into frontal, middle and posterior sections. The frontal cortex was severed by a coronal cut at about the level of the genu of the corpus callosum. The mid cortex was defined by a cut to remove the striate and entorhinal cortex (which comprised the posterior cortex) and contained the amygdala. The tissues were blotted dry, weighed and then placed in liquid nitrogen subsequent to which they were transferred to a −70°C freezer. About 30 days later the tissues were assayed for norepinephrine and dopamine by high performance liquid chromatography with electrochemical detection using the method described by Mefford [15]. The chromatography system consisted of an Altex 110A pump, an Altex ultrasphere ODS 5 μ column and a Bioanalytical LC-5A glassy carbon electrode and LC-4A amperometric detector. Analysis of the chromatograms was carried out by a Hewlett Packard 3390A integrator, programmed to compute areas under individual peaks.

RESULTS

Lashley Maze

The latencies from start box placement to the initiation of drinking in the goal box (range 6–300 sec) were converted to logarithms (see Fig. 1) and then submitted to analysis of variance (ANOVA) with neonatal treatment and rearing condition as between subject variables and test day as a repeated measures variable. Besides the general shortening of solution times over test days, the only other statistically significant effect was the neonatal treatment by rearing condition by test day interaction, $F(9,324)=2.14$, $p<0.027$. Inspection of Fig. 1 shows that this interaction reflects that the enriched-reared control rats and both the enriched- and impoverished-reared 6-OHDA rats showed a progressive shortening of maze solution times over test days. As the figure shows, the rate of this shortening was equivalent for these three groups. Conversely, the impoverished-reared control rats failed to show a reduction of maze solution times over the 10 test days. Analyses of the data for individual days with Tukey's test showed significant effects only on day 10. On that day, log latencies did not differ between the two 6-OHDA groups nor did these differ from the enriched-reared control group. The mean day 10 log latency for the impoverished-reared, 6-OHDA group was significantly less than that of the impoverished control group ($p<0.05$). Mean latencies for the enriched control and 6-OHDA groups fell slightly short of significant differences from the impoverished control group ($0.10<p$'s>0.05). Thus these results suggest that enriched rearing facilitated Lashley performance in otherwise normal rats or conversely, that isolated rearing retarded such performance in these rats. Significantly, isolated rearing did not retard the maze performance of the 6-OHDA injected rats.

Hebb-Williams Maze

The rats' solution of the maze was assessed by ANOVA with neonatal treatment and rearing condition as orthogonal factors, of the total errors committed during solution of the 12 test problems. The means for the four groups are shown in Fig. 2. The ANOVA showed significant main effects due to neonatal treatment, $F(1,49)=11.33$, $p<0.002$, and to rearing environment, $F(1,49)=13.90$, $p<0.001$. Inspection of Fig. 1 shows that overall, the 6-OHDA rats made fewer errors than did their vehicle controls and that the enriched reared rats made fewer errors than the impoverished reared rats. Individual comparisons of the four groups with the Neuman-Keuls test showed that the impoverished control group made more errors than the three other groups and that the latter did not differ among one another (p's<0.05). Thus, impoverished rearing of control rats elevated their maze error scores in comparison to their enriched counterparts. Impoverished rearing of the 6-OHDA rats did not significantly elevate their error scores in comparison to their enriched reared counterparts.

Brain Monoamines

Table 1 presents the results of the assays. ANOVAs with neonatal treatment and rearing condition as orthogonal factors were calculated separately for NE and DA for each tissue. As expected, neonatal 6-OHDA drastically reduced NE levels in the hippocampus and the 3 cortical tissue samples. The greatest NE depletions were in the hippocampus and posterior cortex where the levels were reduced to less than 5% of control values. Isolation rearing was not found to affect the extent of the 6-OHDA induced depletions of any of these 4 tissues.

As has typically been found, neonatal 6-OHDA significantly elevated NE levels in the cerebellum, medulla, pons and midbrain. Furthermore in the medulla, there was a significant interaction between neonatal treatment and rearing environment, $F(1,48)=10.05$, $p<0.003$. As Table 1 indicates, this reflected that neonatal 6-OHDA induced a lesser (29%) increase of medullary NE in the enriched as compared to the

TABLE 1

REGIONAL BRAIN WEIGHTS (wt.), MEAN ± s.e. mg, AND NE AND DA CONCENTRATIONS (MEAN ± s.e. ng/g TISSUE) FOR NEONATAL SYSTEMIC VEHICLE (V) OR 6-OHDA INJECTED RATS THAT WERE RAISED UNDER EITHER ENRICHED (E) OR IMPOVERISHED (I) CONDITIONS

Tissue		VE	VI	6-OHDA-E	6-OHDA-I
Cereb.	wt.	278 ± 9	292 ± 5	277 ± 9	265 ± 6
	NE	293 ± 28	277 ± 17	509 ± 24	439 ± 20
Med.	wt.	101 ± 5	105 ± 6	79 ± 6	92 ± 4
	NE	1281 ± 36	1170 ± 36	1653 ± 55	1915 ± 90
Pons	wt.	112 ± 3	115 ± 4	119 ± 8	115 ± 4
	NE	628 ± 22	583 ± 29	1156 ± 133	1354 ± 85
M. Br.	wt.	103 ± 7	97 ± 4	96 ± 5	96 ± 4
	NE	715 ± 23	724 ± 23	1186 ± 53	1207 ± 66
Hypoth.	wt.	85 ± 3	80 ± 3	81 ± 2	82 ± 2
	NE	1429 ± 50	1375 ± 48	1315 ± 50	1291 ± 106
	DA	203 ± 11	189 ± 13	207 ± 13	172 ± 14
Caud.	wt.	102 ± 6	128 ± 4	124 ± 5	116 ± 4
	NE	153 ± 10	169 ± 17	166 ± 37	130 ± 20
	DA	3449 ± 173	3339 ± 129	3562 ± 134	3575 ± 164
Hippo.	wt.	162 ± 3	162 ± 5	154 ± 6	152 ± 4
	NE	534 ± 28	732 ± 107	29 ± 4	26 ± 5
A. Ctx.	wt.	207 ± 10	197 ± 8	200 ± 8	203 ± 6
	NE	602 ± 27	576 ± 31	192 ± 36	171 ± 25
	DA	1288 ± 63	1391 ± 83	1313 ± 63	1344 ± 52
M. Ctx.	wt.	509 ± 12	509 ± 9	488 ± 12	491 ± 9
	NE	529 ± 28	405 ± 42	92 ± 24	124 ± 10
	DA	640 ± 83	755 ± 74	521 ± 55	546 ± 50
P. Ctx.	wt.	166 ± 10	171 ± 11	175 ± 11	151 ± 10
	NE	295 ± 20	312 ± 14	14 ± 3	15 ± 3
	DA	28 ± 3	37 ± 2	29 ± 3	32 ± 1

N's=13 per group.

Tissue abbreviations represent cerebellum (Cereb.), medulla (Med.), midbrain (M. Br.), hypothalamus (Hypoth.), caudate (Caud.), hippocampus (Hippo.), anterior (A.), mid (M.), and posterior (P.) cortex (Ctx.).

isolated (63%) rats. There was a similar but non-significant ($F(1,43)=2.05$) tendency for this effect in the pons. Here the 6-OHDA induced increase was 84% in the enriched reared as opposed to 132% in the isolation reared.

In a previous study [19], we had reported that isolation rearing decreased hypothalamic DA in control but not neonatal 6-OHDA treated rats. In the present experiment, the main effect of rearing in the ANOVA for hypothalamic DA fell just short of significance, $F(1,48)=3.56$, $p<0.07$. As Table 1 shows, there was a tendency for isolation rearing to decrease DA in both the control and the NE depleted rats.

Brain Part Weight

The brain part weights are also shown in Table 1. ANOVAs were carried out separately for each brain part and only for the hippocampus was there a significant effect. This ANOVA showed a significant effect for neonatal treatment, $F(1,48)=4.22$, $p<0.05$. As Table 1 shows, this is accounted for by the lighter hippocampi of the 6-OHDA treated rat. In addition, ANOVAs were performed on total brain weights, total cortical weight and the ratios of total cortex to total brain weights. While isolation rearing decreased total cortical weight by 0.6% and 2.2% and the ratios of cortex to rest of brain by 1.6% and 1.2% in the control and 6-OHDA rats respectively, there were no statistically significant effects.

DISCUSSION

The results of the Lashley and the Hebb-Williams maze tests were consistent. Isolation rearing had a deleterious effect on performance of the control rats. On neither test, however, did such rearing affect the performance of the 6-OHDA injected rats. Indeed, both the isolation- and the enriched-reared 6-OHDA injected rats performed comparably to the enriched-reared control rats. Hence the effect of the 6-OHDA injections was to eliminate the negative influence of isolation rearing on maze performance. Considered from this perspective, these results are in agreement with those from experiments where cats were raised under conditions of monocular deprivation or of binocular deprivation of movement [6,10]. However, this effect with cats appears to occur only when the 6-OHDA depletion of cortical NE occurs concurrent with the deprivation and not when the cats are depleted of NE perinatally [1,2]. This could reflect differing neural consequences of isolated rearing and visual deprivation and thus differing sensitivities to antecedent depletion of NE. It should be noted that in

agreement with our results, Mirmiran and colleagues have reported that both neonatal 6-OHDA administration [18] and preweaning administration of clonidine (which suppresses activity of the locus coeruleus [17]) eliminated the effects of subsequent enriched/impoverished rearing on cortical weight in the rat.

It should also be noted that the Lashley maze results from this experiment differ from those of an earlier report from this laboratory [19]. In that experiment, both enriched- and isolation-reared NE depleted rats performed at the level of the isolation-reared control rats. All three of these groups were inferior to the enriched reared controls. Hence, in that experiment neonatal systemic 6-OHDA administration appeared to eliminate the enhancing effect of enriched rearing on Lashley maze performance whereas the present experiment suggests that it eliminates the deleterious effect of isolated rearing. It is conceivable but seems unlikely that the minor procedural differences between the two experiments (i.e., three vs. five trials per day, ten vs. five test days) could account for their different results. Additional research is needed to explain this difference.

The present results may help to explain discrepant findings concerning the effects of neonatal systemic 6-OHDA on behavior. If for example the effects of such a lesion is assessed in rats raised only under isolated conditions which may be the routine housing procedure in many laboratories, then as the present results indicate, the 6-OHDA treated rats would show superior performance in complex mazes. Conversely, if only rats raised under relatively enriched conditions (which could be an inadvertent feature due say to multiple behavioral testing during development) were compared, then there would be no apparent difference between the control and the lesioned rats. It is important to note that after neither type of rearing would the result be consistent with either a learning or an attentional deficit [15] in the rat which sustains neonatal lesion of NE terminals.

We have previously reported that isolation rearing following the procedures used here, decreased forebrain and increased hypothalamic weight and also decreased the DA levels of the hypothalamus and posterior cortex (including the amygdala) [19]. Since none of these effects appeared in the neonatal 6-OHDA injected rats, we concluded that intact forebrain NE terminals were requisite to these effects. This conclusion is supported by results from two other laboratories that have reported that either perinatal clonidine [17] or the DSP-4 derivative xylamine [3], which respectively suppress NE release or damage NE terminals, can eliminate the effect of isolated rearing on regional brain weight. In the present experiment however, no effects of isolation rearing on brain part weight and catecholamine levels were observed in the vehicle control rats and hence, there was no possibility of observing an absence of such an effect in the 6-OHDA treated rats. Substantial procedural difference between the two experiments may account for their different results. Prior to sacrifice and assay, the rats of this experiment underwent a very lengthy training procedure in the Hebb-Williams maze. The enrichment provided by this training for those rats that had been raised in isolation, probably affected their brain morphology and chemistry and so may have eliminated any effects of the rearing variable. That enrichment affects brain morphology in the adult rat [7] supports this possibility. In fact, training on the Hebb-Williams maze is reportedly sufficient to cause an enrichment effect on brain part weight even in the aged rat [5].

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