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Neonatal Dopamine Depletions Spare Lateral Hypothalamic Stimulation Reward in Adult Rats

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STELLAR, J. R., M. WARACZYNSKI AND J. P. BRUNO. *Neonatal dopamine depletions spare lateral hypothalamic stimulation reward in adult rats.* PHARMACOL BIOCHEM BEHAV **30**(2) 365–370, 1988.—Previous research has shown that adult rats sustaining near-total depletions of striatal dopamine (DA) as neonates exhibit few of the profound deficits in ingestion and sensory-motor behavior seen in comparably lesioned adults. This study extends these findings to another realm of DA-related behavior, reward function. In a rate-frequency curve-shift measurement paradigm, reward effectiveness of lateral hypothalamic brain stimulation was shown to be normal in adult rats depleted of brain DA as neonates. However, impairments were seen in rapid-initiation operant performance. Neonatally DA-depleted rats were also shown to be subsensitive to the DA receptor antagonist pimozide, suggesting that activity within undamaged DA neurons is not necessary for the elicitation of hypothalamic self-stimulation reward.

Dopamine Neonatal depletions Reward Self-stimulation Reward sparing Plasticity
Lateral hypothalamus Striatum Accumbens Pimozide

BRAIN dopamine (DA) has been shown to play a major role in motor and motivational function in mammals. For example, acute or chronic disruptions of DA transmission in human results in Parkinsonian symptoms characterized by deficits in motor initiation [21], and in reduction of the rewarding impact of such DA-stimulating drugs as cocaine and amphetamine [14]. In rats, near-total depletions of striatal DA produced by the neurotoxin 6-hydroxydopamine (6-HDA), result in akinesia, catalepsy, sensory neglect, and profound ingestive deficits that may last for months [16,32]. Chronic depletions of DA or acute DA receptor blockade reduces or eliminates cocaine and amphetamine self-administration [7,22] and greatly reduces the rewarding impact of lateral hypothalamic brain stimulation [9, 10, 12, 17, 28], for review see: [11, 29, 36].

Given the necessity of DA for the expression of many adult behaviors, it is interesting that near-total depletions of forebrain DA neonatal rats do not result in akinesia and catalepsy or in deficits in ingestive behavior and sensory-motor function even once the animals reach adulthood [3–5]. Our preliminary report [30] and the work of others [33] extend these observations to the realm of affective function by demonstrating a sparing of the reward effect produced by lateral hypothalamic stimulation.

To determine whether the rewarding properties of lateral hypothalamic stimulation have been altered after neonatal DA depletions, it is necessary to use a behavioral measure of self-stimulation where reward effects can be assessed quantitatively and independently of effects on motor/performance capacity. To a first approximation, the rate-frequency (R-F) method [6, 8, 17, 28] satisfies these demands, and was employed in this study. R-F curves are generated by recording self-stimulation response rate at a number of pulse frequencies of square-wave stimulation, and plotting behavioral rate against pulse frequency. Within the resulting sigmoidal R-F curve, the pulse frequency required to sustain half of the maximal rate is calculated by interpolation and is termed the locus of rise (LOR). The LOR has been shown by a number

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of validation experiments to be an index of the stimulation's reward effectiveness [6, 8, 17, 29, 31]. A second statistic from the R-F, the behavioral maximum (MAX), reflects operant performance capacity [6, 17, 29, 31]. The purpose of this study was to compare the LOR and MAX statistics of the R-F in control vs. adults depleted of DA neonates.

METHOD

Subjects and Brain Lesions

Three days after birth, male Sprague-Dawley rats received, under ether anesthesia, lateral ventricular injections of 6-HDA (150 μg, free base weight, in 10 μl) in a vehicle of 0.1% ascorbic acid in 0.9% NaCl, 30 minutes after pretreatment with desmethylimipramine (25 mg/kg SC) to protect norepinephrine-containing terminals [2]. Pups were then returned to the litter and left undisturbed until weaning on Day 27. Further details of injection and rearing procedures are described in previous reports [3,5]. A second group of normally-reared Sprague-Dawley rats served as the control.

Electrode Implantation

Approximately 4–5 months later, rats were anesthetized with Nembutal (55 mg/kg, IP) and implanted with monopolar electrodes constructed of stainless steel insect pins (size 00) insulated to within 0.5 mm of the tip with Formvar enamel. Electrodes were positioned in the lateral hypothalamus using the level-skull coordinates of Ap −3.0 (from bregma), ML ±1.7 (from midsagittal sinus), DV −7.5 (from cortex). A ground wire was attached to the skull screws which also anchored the electrode. Electrode and ground were accessible through a two-channel Plastic Products connector mounted on the skull with dental acrylic. Further details of surgical procedures are described in previous reports [26].

Reward Summation Function Procedure

One week after surgery, all rats were trained to lever-press in a standard operant chamber for a 1.0 second burst of 0.1 millisecond, square-wave, monophasic, constant-current pulses of brain stimulation delivered at a frequency of 63 Hz. Rats were first trained on a continuous reinforcement schedule and then switched to a VI 3 second schedule for all further testing. An important feature of the VI schedule was that during each stimulation burst, responses were not collected and the VI schedule was stopped to prevent stimulation-elicited motor effects (e.g., rearing, lever-biting) from distorting the measure of operant responding. A reinforcement light next to the response level signaled each delivery of brain stimulation and a house light was illuminated when the lever was active. During training, the optimal current was determined yielding the highest rate of responding with minimal signs of either forced movements (e.g., rearing) or aversiveness (e.g., retreat from lever, defacation, vocalization). Control of operant chamber lights, delivery of stimulation, and monitoring of lever pressing was conducted by a microcomputer system.

The R-F was generated by varying the pulse frequency at which the stimulation was delivered. Stimulation pulses frequency was changed every 3 minutes with a 30 second rest period (house light black-out) between the different frequencies during which lever pressing did not deliver stimulation. Data from the first minute of responding were discarded to allow the rat to adjust its response rate to the new frequency condition, and data from the last two mintutes were averaged to arrive at the response rate for that frequency. One R-F was collected each day in a single session. Each session began with a warm-up consisting of a high frequency (e.g., 63 Hz) condition and an extinction condition (1 Hz). Then, for successive conditions, the pulse frequency was increased in 0.2 log unit steps in the range of 1.4–2.4 log Hz (25–251 Hz). Sessions were run until stability was reached in both the LOR and MAX rats measures of the R-F. Stability was judged to occur when the LOR and MAX data showed no increasing or decreasing trend and when the LOR score for each day was within 0.1 log units of the previous test day.

Experiments

In the first experiment, lateral hypothalamic stimulation reward was measured on the R-F for 7 adult rats lesioned as neonates (Day 3) and 7 adult normal control rats, matched for stimulating current. For each rat, between 6 and 10 stable R-F's were collected and the LOR and MAX scores averaged. The individual average scores were then averaged within a group.

In the second experiment, sensitivity to the DA receptor antagonist, pimozide, was tested. Five neonatal DA-depleted rats from the first experiment and 6 normal controls (2 from the first experiment) were tested on the R-F paradigm as described above. Five days of stable baseline were taken before drug administration. Pimozide (Janssen Pharmaceutical Co.) was dissolved in tarturic acid (9 parts tarturic:1 part pimozide) and administered (IP) 4 hours before self-stimulation testing. Pimozide doses ranged from 0.125 to 1.0 mg/kg and were given in random order. Between each drug day were no-drug test days. If the rat's LOR or MAX did not return to within 10% of baseline following a drug day, additional no-drug test days were run. All behavioral testing was concluded within 2 months.

For both the DA-depleted and normal groups, data were analyzed by constructing pimozide dose-response curves showing the difference from baseline performance on LOR and MAX statistics, the difference was found between the average baseline conditions (n=5) and an individual R-F test under a particular dose of pimozide. Then, these difference scores were averaged across the rats in a group but within a particular pimozide dose and a type of R-F statistic. For the MAX statistic, differences were expressed as percent of baseline.

Neurochemistry and Histology

Our pilot work indicated that it was extremely difficult to conduct neurochemical and histological analyses on the same brain. As a result, animals from each group were randomly selected for each type of analysis. This decision was supported by two methodological observations in our laboratories: The extent and pattern of DA depletions in neonatal rats are extremely reproducible (cf. [3–5]), and the established relationship between lateral hypothalamic electrode placement and steady high-rate self-stimulation behavior [20,26] makes responding a direct indicator of electrode tip location in the hypothalamic region.

For neurochemical analysis, rats were sacrificed by decapitation, the brains were rapidly removed, and frozen on a freezing microtome. Tissue punches (approximately 1 mm^3) were taken from the medial striatum and nucleus accum-

TABLE 1

MEAN (S.E.M.) LEVELS OF DA AND DOPAC (pmoles/mg Pr.) IN CONTROL AND LESIONED RATS

Group	Striatum		N. Accumbenns	
	Dopamine	DOPAC	Dopamine	DOPAC
Controls (n=5)	355 ± 20	33 ± 9	86 ± 25	29 ± 7
Neonatal 6HDA (n=5)	40 ± 13	15 ± 11	16 ± 2	4 ± 1

bens. Levels of DA and its princple metabolite, dihydroxyphenylacetic acid (DOPAC) were determined using high performance liquid chromotography with electrochemical detection (HPLC-ED) according to methods previously described [4].

For histological analysis, rats were anesthetized with Nembutal (60 mg/kg) and perfused with saline (0.9%) and formalin (10%) made from the saline. Brain sections were cut at 40 microns, stained with cresyl violet, and electrode tips were localized as reported previously [28].

RESULTS

Electrode localization histology revealed that electrode tips were located within the lateral hypothalamus. HPLC-ED analysis revealed that treatment with 6-HDA on Day 3 resulted in near total depletion of DA in striatum (89%) and nucleus accumbens (81%, Table 1). The specificity of the DA depletion was shown by the fact that septal norepinephrine was altered by less than 18% (1.08±0.12 μg/g control, 0.89±0.10 μg/g 6-HDA lesion). The permanence, extensiveness, and specificity of these DA depletions are consistent with our previous findings [3–5].

The results of the first behavioral experiment are shown in Table 2 and for three representative subjects in Fig. 1. Neonatal DA-depleted rats tested as adults showed vigorous self-stimulation behavior as evidenced by the ability to collect the R-F data. Figure 1 illustrates that the neonatally DA-depleted rats had a lower maximum response asymptote at high frequencies, but that the rising portion of the R-F occurred in approximately the same frequency region for both depleted and normal subjects. These observations are presented for the entire group in Table 2, where the LOR is shown not to differ between the control (1.78±0.09 log Hz) and depleted (1.78±0.10 log Hz) groups in a two-tailed t-test ($df=12$, $p<0.894$), indicating no impairment in the efficiency of the lateral hypothalamic stimulation pulses in generating the self-stimulation reward effect in the depleted group. However, using the same statistical test, the MAX score of the DA-depleted group (38.1±24.1 resp./min) was significantly depressed compared to normals (65.4±16.9 resp./min), indicating impaired capacity for high-rate operant responding following the depletions ($df=12$, $p<0.029$, Table 2).

In the second experiment, the pimozide dose-response curves (Fig. 2) of the R-F were shifted toward higher doses for the neonatal DA-depleted rats as compared to controls, indicating a subsensitivity to pimozide in the DA-depleted group on both the LOR and MAX statistics of the R-F. Figure 2 (upper portion) shows that the control rats were unaffected by 0.125 mg/kg of pimozide and began to show reward impairments (LOR increases) at 0.25 mg/kg. At the dose of 0.5 mg/kg, 3 of 6 rats from this control group extinguished responding in the high frequency warm-up phase of the RF test and generated fewer than 5 responses per minute in all subsequent stimulation frequencies tested. This prevented the calculation of a meaningful LOR for these subjects and for the control group at this point on the dose-response curve. However, taking the extinction behavior to indicate no or low reward, LOR can be projected to be at least as high as the next highest frequency step. This would then yield a group average LOR for 0.5 mg/kg of at least +0.26 log units. By comparison, the DA-depleted group required 0.5 mg/kg to show the first increase in LOR, and were still able to generate the full R-F at 1.0 mg/kg.

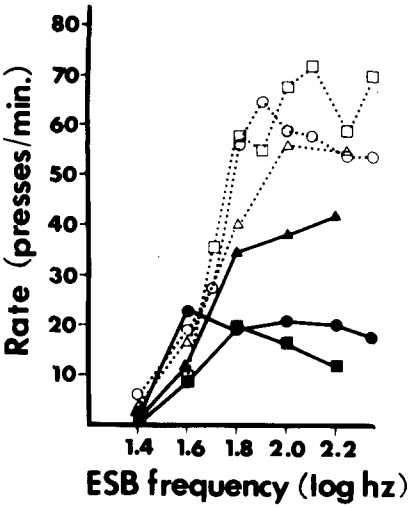

FIG. 1. A rate-frequency function (R-F) for three representative rats from the DA-depleted group (filled symbols, solid lines) and from the normal control group (open symbols, dotted lines).

The results from the MAX statistic are shown in the lower portion of Fig. 2 where a steady decline in percent of MAX is shown in normal rats given increasing doses of pimozide. MAX was cut by 50% at 0.25 mg/kg and below 25% of baseline at 0.5 mg/kg. In contrast, the MAX score for the DA-depleted rats remained at baseline at 0.5 mg/kg and showed the first depression at 1.0 mg/kg.

DISCUSSION

These experiments demonstrate that adult rats sustaining near-total depletion of forebrain DA as neonates will display vigorous self-stimulation of the lateral hypothalamus. This strongly contrasts with the severe deficits seen when such depletions are made in adults or when intact adults are treated with high doses of DA-receptor blockers such as pimozide [6, 10, 11, 27–29, 36]. Furthermore, psychophysical reward measurement with the R-F technique reveals that the efficiency of lateral hypothalamic stimulation in generating the self-stimulation reward effect is equal to that of normally reared subjects. In general, this sparing of limbic function is reminiscent of earlier reports on the sparing of ingestive behaviors and basic sensory-motor functioning in rats depleted of brain DA as neonates [3–5], and agrees with other published work on self-stimulation behavior using sine-wave current-threshold procedures [33].

TABLE 2

LATERAL HYPOTHALAMIC STIMULATION REWARD AND MOTOR FUNCTION IN NEONATALLY DA-DEPLETED AND CONTROL RATS TESTED AS ADULTS

Neonatal DA-Depleted	LOR	MAX	Current	Normal Control	LOR	MAX	Current
JS108	1.67	25.4	300	MW4	1.75	63.9	300
JS109	1.65	41.3	200	MW6	1.95	45.8	250
JS110	1.92	37.1	200	MW7	1.83	44.1	300
JS114	1.80	21.2	300	MW9	1.67	93.0	300
JS117	1.75	16.4	300	MW11	1.80	68.5	250
MW16	1.84	36.4	250	MW12	1.72	67.0	200
MW19	1.84	88.6	350	MW13	1.72	75.6	300
Mean	1.78	38.1	271		1.78	65.4	271
Standard Deviation	±0.10	±24.1	±57		±0.09	±16.9	±39

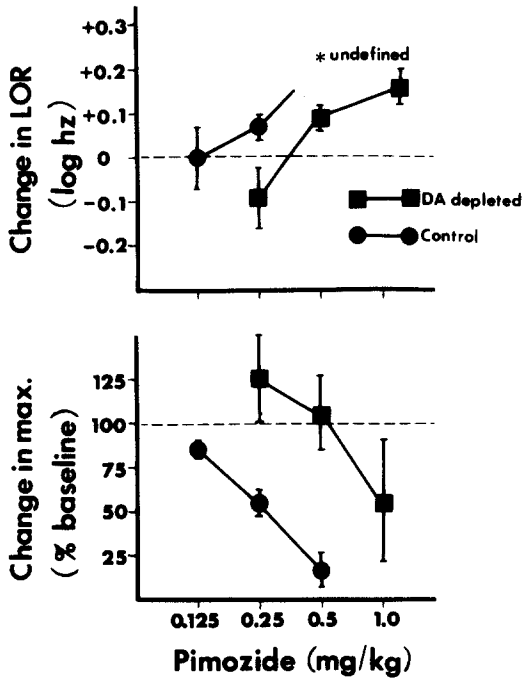

FIG. 2. Changes in locus of rise (LOR) and percent maximum (MAX) of the R-F under pimozide treatment for the normal control group and the neonatal DA-depleted group. Note: a rising LOR in the upper graph indicates a growing reward degradation with increasing pimozide dose, and error bars equal 1 standard deviation. The point labeled "undefined" indicates a dose where LOR could not be determined because 3 of the 6 control rats extinguished in the warm-up condition.

Using the R-F method, a number of laboratories have demonstrated that pimozide treatment in adults leads to a loss of stimulation efficiency in generating lateral hypothalamic reward [6, 10, 17, 28]. The finding in our report that neonatal DA-depleted animals are subsensitive to pimozide suggests that enhanced transmission within residual DA neurons does not underlie the sparing of lateral hypothalamic reward. If DA receptor proliferation and/or enhanced release from surviving neurons were the mechanisms of sparing, one would expect enhanced sensitivity to a DA receptor antagonist like pimozide.

Our second major observation is that neonatal DA-depleted rats exhibit about half the maximum high-rate operant response capacity of normal controls. Similar but smaller deficits have been reported [33] for neonatal DA-depleted rats self-stimulating in the VTA on a different but related paradigm as mentioned above. This operant capacity deficit, locomotor hyperactivity [23,24], failure to respond to acute homeostatic imbalances [5], self-mutilation behaviors in response to DA agonists [1], and limb/tongue-use as well as other deficiencies [35] make it clear that neonatal DA-depleted rats do exhibit behavioral abnormalities. Thus, the "sparing phenomenon" is not a complete one. Our use of this term here is to stress the fact that in many cases the breadth and severity of the impairments are far less extensive than those seen in comparably lesioned adults.

We recognize the fact that the striatal and accumbens DA lesions of 89% and 81%, respectively, do not necessarily preclude a dopaminergic mediation of the observed self-stimulation reward effect. The ability of small amounts of residual DA within the striatum to underlie sensory-motor behavior in rats lesioned as adults is well-documented [32]. However, we discount this possibility here, due to the marked subsensitivity to pimozide—a situation that is not predicted by reliance on a heightened residual DA transmission. If it is accepted that residual DA does not mediate the self-stimulation reward effect in our study, then one must turn elsewhere for neural mechanisms underlying the sparing phenomenon. While this mechanism is by no means clear, one possible candidate is forebrain serotonin (5-HT).

The 5-HT sparing hypothesis is supported by two observations. First, 5-HT levels increase in both the striatum and nucleus accumbens after depletions of DA in neonates but not after comparable depletions in adults [1,25]. The accumbens has been shown with the R-F and neuroleptic brain injection method to be involved with lateral hypothalamic self-stimulation reward [26], and the accumbens has been implicated in a variety of motivational behaviors [15, 18, 19], as has the striatum [32]. Second, there is evidence indicating, at least within striatum, that DA- and 5-HT-containing neurons exhibit similar postsynaptic actions, such as inhibit-

ing acetylcholine release [13,34]. However, it should be noted that there is no reason to suspect that these elevations in 5-HT content underlie the apparently intact ingestive and sensory-motor functions observed in adult rats lesioned as neonates (J. P. Bruno, unpublished observations).

In addition to testing the 5-HT hypothesis discussed above, DA depletions in specific regions (i.e., accumbens vs. caudate) during development, and studies of the age dependency of the sparing effect should also reveal important aspects of the mechanisms underlying the sparing of lateral hypothalamic reward function in neonatal lesioned animals. Such studies would be interesting not only from the perspective of neuroplasticity, but may also serve as a comparative window on the neural basis of reward in normal animals.

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