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BRIEF COMMUNICATION

# Neonatal-6-Hydroxydopamine Treatment: Model of Susceptibility for Self-Mutilation in the Lesch-Nyhan Syndrome

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BREESE, G. R., A. A. BAUMEISTER, T. J. McCOWN, S. G. EMERICK, G. R. FRYE AND R. A. MUELLER. *Neonatal-6-hydroxydopamine treatment: Model of susceptibility for self-mutilation in the Lesch-Nyhan syndrome.* PHARMACOL BIOCHEM BEHAV 21(3) 459–461, 1984.—Neonatal-6-OHDA treated rats given L-DOPA after a decarboxylase inhibitor showed a high incidence of self-mutilation behavior (SMB) and self-biting. These behaviors were not observed in adult-6-OHDA-treated rats or in controls. Since inhibition of dopamine-β-hydroxylase did not prevent or inhibit the SMB exhibited in neonatal-6-OHDA-treated rats after L-DOPA, norepinephrine is not likely to be contributing to this response. The age dependent effects observed are consistent with the hypothesis that neonatal reduction of dopamine-containing fibers is responsible for the SMB susceptibility observed in Lesch-Nyhan disease, making the neonatal-6-OHDA-treated rat a model of this neurological syndrome.

6-Hydroxydopamine Neonatal treatment L-DOPA Apomorphine Receptors Supersensitivity Neuroleptics Model: Lesch-Nyhan Syndrome Adaptation Parkinson's disease

LESCH and Nyhan [8] described a syndrome of self-mutilation, mental retardation and choreoathetoid movements associated with hyperuricemia [7]. While deficiency in the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) [11] has provided a molecular basis for the purine metabolism dysfunction [7], the role of the HGPRT deficiency in the neurological symptoms of patients with Lesch-Nyhan disease remains unclear. Recently, Lloyd *et al.* [9] reported that biochemical measures of dopaminergic function were reduced in basal ganglia of Lesch-Nyhan patients and suggested that this alteration may account for some of the symptoms. However, adults with Parkinson's syndrome do not display self-mutilation or the same type motor dysfunction as Lesch-Nyhan patients, even though they also have diminished central dopaminergic function [6]. One obvious difference in the pathogenesis of these syndromes is the age at which they occur. Since the disruption of dopaminergic neurons observed in both clinical syndromes can be produced in animals by central administration of 6-hydroxydopamine (6-OHDA) [1,2], the present investigation sought to explore whether the age at which dopaminergic neurons are destroyed may explain the different neurological profiles in patients with Parkinson's and Lesch-Nyhan syndromes.

## METHOD

In order to disrupt catecholamine-containing fibers, neonatal rats, five days of age, were given 100 μg of 6-OHDA intracisternally to reduce brain catecholamines [2,12] and adult male rats (225 g) were treated with 200 μg 6-OHDA after 50 mg/kg pargyline on one occasion, with an additional 200 μg 6-OHDA administered one week later [1]. Controls received appropriate vehicle and drug pretreatment. Adult-treated rats showing any aphagia or adipsia were given a liquid diet by intubation until these symptoms abated [4].

Experiments were initiated when adult animals had recovered (approximately 60–70 days of age) and when neonatal male rats were approximately 70 days of age. The incidence of self-biting and self-mutilation behavior (SMB) to 100 mg/kg L-dihydroxyphenylalanine (L-DOPA) administered IP 60 min after 50 mg/kg of RO-4-4602, (a peripheral

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TABLE 1

INCIDENCE OF SMB TO L-DOPA ADMINISTRATION IN CONTROL, NEONATAL- AND ADULT-6-OHDA-TREATED RATS

| Treatment‡ | Incidence of SMB to L-DOPA Treatment (Number/Total) | Striatal Dopamine (ng/mg Protein) |
|---|---|---|
| Control | 0/10 | 95.8 ± 2.8 |
| 6-OHDA (Adult-Treated) | 0/10 | 2.9 ± 0.5** |
| 6-OHDA (Neonatal-Treated) | 8/11*† | 3.6 ± 0.9** |

‡Male rats from the various groups received RO-4-4602 (50 mg/kg) 60 min before 100 mg/kg of L-DOPA and were observed every ten minutes for up to two and one-half hours after L-DOPA. If the skin was broken by self-biting during this period, the rat was considered positive for SMB and was immediately anesthetized with pentobarbital sodium (40 mg/kg). Control rats are half saline-treated neonates and half-adult rats that received saline. Striatal dopamine was determined in at least six rats fitting into the treatment categories, but are not the same rats given L-DOPA.

†With the first challenge of L-DOPA, 10/11 of the rats displayed self-biting. When challenged a second time with L-DOPA (100 mg/kg with RO-4-4602), 10/11 neonatal-treated rats showed a positive SMB response; control and adult-treated rats showed no SMB to this additional challenge.

*$p<0.001$ when compared to control or adult-6-OHDA-treated groups.

**$p<0.001$ when compared to striatal dopamine content in controls.

decarboxylase inhibitor) was determined in rats placed in a transparent plastic box (23×44 cm) containing wood chips. Rats were observed for self-biting and SMB every 10 min for a period of 2.5 hr. The occurrence of SMB was defined as self-biting sufficient to break the skin. If SMB was noted, the rat was immediately anesthetized with pentobarbital sodium (40 mg/kg).

## RESULTS

As shown in Table 1, administration of 100 mg/kg L-DOPA induced no self-biting or SMB in controls or rats treated with 6-OHDA as adults. In contrast, all but one of the rats given 6-OHDA neonatally demonstrated self-biting when given this L-DOPA challenge and 8/11 of the rats elicited SMB. When challenged with a second dose of L-DOPA, all but one (10/11) of the neonatally-treated rats showed a positive SMB response (Table 1, legend). Dopamine content in the striatum of adult- and neonatal-6-OHDA-treated rats was not significantly different (Table 1), suggesting that degree of dopamine depletion produced by 6-OHDA is not a contributing factor in the different behavioral responses observed in these groups. Thus, these observations provide striking evidence that the age at which catecholamine-containing neurons are destroyed can produce markedly different behavioral effects after L-DOPA.

It has also been determined that the incidence of SMB elicited by L-DOPA in the neonatal-6-OHDA-treated rats (N=6) was not reduced by pretreatment (60 min) with 50 mg/kg U-14,624 (a dopamine-$\beta$-hydroxylase inhibitor). This latter observation suggests that norepinephrine formed endogenously from L-DOPA does not contribute to the SMB (see [3]).

## DISCUSSION

The incidence of SMB following L-DOPA in adult- and neonatal-6-OHDA-treated rats provides the first evidence that the age at which catecholamine-containing fibers are destroyed can produce remarkably different behavioral results. In preliminary studies, rats with dopamine preferentially reduced during development [12] have also been found to be susceptible to SMB when challenged with L-DOPA (unpublished data). These data suggest that destruction of dopamine-containing fibers are responsible for the increased SMB susceptibility observed in rats treated with 6-OHDA neonatally. However, the potential importance of dopamine receptors in the induction of SMB by L-DOPA has been confused by our recent finding that a high dose of haloperidol (1 mg/kg) would not antagonize the L-DOPA-induced SMB once initiated and only partially reduced the incidence of SMB when administered prior to the L-DOPA challenge (unpublished data). Such findings suggest either that mechanisms other than dopaminergic ones are contributing to the SMB response or that receptors not associated with the action of haloperidol but essential for the action of L-DOPA are involved. However, resistance to the action of haloperidol against the actions of dopamine agonists has also been observed in rats treated with 6-OHDA as adults [5,10]. Additional work will be necessary to define whether age at which dopaminergic fibers are destroyed affect the action of neuroleptics.

The age-dependent difference to elicit SMB in neonatal- and adult-6-OHDA-treated rats appears to have particular relevance to the symptomatic differences between Parkinson's disease and the Lesch-Nyhan syndrome. Since Lesch-Nyhan patients and neonatal-6-OHDA-treated rats have a common neurochemical deficit during development and a parallel increase in susceptibility for SMB, we suggest that neonatal treatment with 6-OHDA can serve as a model of the neurological deficits observed in the Lesch-Nyhan syndrome. Such a neurochemical model should be useful for screening new therapeutic approaches to treat SMB in

Lesch-Nyhan patients. In this regard, the resistance neonatal-6-OHDA-treated rats show to haloperidol antagonism of SMB parallels the lack of therapeutic efficacy of neuroleptic drugs in the treatment of this syndrome [7,13]. Future experiments will focus on potential adaptive neural mechanisms associated with neonatal destruction of dopamine-containing fibers, in order to define the neurobiological basis for their increased susceptibility for SMB.

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