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BRIEF COMMUNICATION

Effects of Prenatal Diphenhydramine Exposure on Dopaminergic Function in Adult Rats

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CHIAVEGATTO, S. AND M. M. BERNARDI. *Effects of prenatal diphenhydramine exposure on dopaminergic function in adult rats.* PHARMACOL BIOCHEM BEHAV **40**(1) 191–193, 1991.—Female pregnant rats were treated with 20.0 mg/kg diphenhydramine (DPH) or the same volume of saline solution (NaCl 0.9%), SC, daily during pregnancy. As adults, male pups were tested for stereotyped behavior in response to apomorphine (1 mg/kg, SC) administration. No differences between DPH-exposed and control rats were evident. In another group of rats, dopamine (DA) and homovanillic acid (HVA) levels were quantified in striatal samples. DA levels were equivalent, but increased levels of HVA were observed. Based upon these data we suggest that prenatal exposure to DPH, a histamine (H1) receptor antagonist, reduces presynaptic dopaminergic mechanisms without altering postsynaptic dopaminergic function in adulthood.

Histamine Dopamine Diphenhydramine Histamine H1 receptor antagonist Prenatal administration Stereotyped behaviour Homovanillic acid

ACCUMULATING evidence on the distribution, metabolism and action of histamine in brain suggests a possible neurotransmitter, or modulator, function (8, 13, 15). In addition, various findings supporting interactions of histamine with cholinergic, dopaminergic (10,11) and serotonergic (12) neuronal systems have been reported. For example, histamine administration is associated with increased homovanillic acid (HVA), but not dopamine (DA), concentrations in rat striatum. This neurochemical effect is suggested to involve the histamine H1 receptor (9,10).

Recently, we have observed that prenatal exposure to diphenhydramine (DPH), a histamine H1 receptor antagonist, decreased male sexual behaviour of rats in adulthood indicated by an increase in ejaculation latency, in the number of mounts and a decrease in the number of ejaculations up to 30 minutes after the first intromission (2). Some investigators (1, 3–5) have proposed that certain aspects of male sexual behaviour are facilitated by a selective activation of presynaptic dopaminergic autoreceptors. Based on these data, we suggested that alterations in central dopaminergic function induced by prenatal exposure to DPH may underlie the observed alterations in copulatory behavior in adulthood. In the present studies we examine the effects of prenatal DPH on pre- and postsynaptic function in adult male rats.

METHOD

Twenty virgin female rats were mated with previously tested as fertile male rats (2 females to 1 male in each cage). The onset of pregnancy was confirmed by the observation of spermatozoa in vaginal smears (day 0 of pregnancy). These female were individually housed in plastic cages ($32 \times 40 \times 18$ cm) in temperature-controlled ($22 \pm 1°C$) and artificially lighted (12-h light and 12-h dark, lights on at 6:00 a.m.) rooms with free access to food and water. Animals were treated with DPH (20 mg/kg) or the same volume of 0.9% NaCl solution, SC, daily, during the entire pregnancy. Following delivery, eight pups (4 males and 4 females) were left with each dam.

To evaluate postsynaptic dopaminergic function, stereotyped behavioral responses to SC administration of 1 mg/kg apomorphine were evaluated at 100 days of age. Stereotypy was quantified once every 10 minutes for 100 minutes after apomorphine administration. The scoring system has been previously described (14). Briefly, behavioural scores varying from 0 (asleep or stationary) to 6 (continuous licking and gnawing of cage grids) were attributed by two observers who were not aware of the drug treatment. A high degree of inter-observer agreement was evident ($r = .98$). Comparisons between experimental and control scores were done using the Mann-Whitney U-test.

To evaluate possible presynaptic dopaminergic effects of prenatal DPH, other males were decapited at 100 days of age. Brains were rapidly removed, and the striata were dissected out within 3 minutes on dry ice, weighed, immediately homogenized in 0.1 N perchloric acid and centrifuged at $4000 \times g$ for 20 minutes in a refrigerated centrifuge. Following separation/isolation

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TABLE 1

EFFECTS OF PRENATAL DIPHENHYDRAMINE EXPOSURE ON DOPAMINE AND HOMOVANILLIC ACID STRIATAL LEVELS IN MALE ADULT RATS

Groups	n	Striatal Levels (μg/g wet weight; mean ± SEM) Dopamine	Homovanillic Acid
Control	6	8.29 ± 0.79	0.36 ± 0.06
Diphenhydramine	6	7.33 ± 0.28	0.56 ± 0.06*

n = number of animals.
*$p<0.05$ in relation to controls (Student t-test).

on a Sephadex G-10 column (16,17), DA and HVA levels were quantified by a previously described fluorimetric assay (7). Values are expressed as μg/g of tissue. Average weight of striata was 0.077 ± 0.015 g. Comparisons of DA and HVA levels were performed using the Student t-test. In both experiments, the probability of $p<0.05$ was assumed to show significant differences.

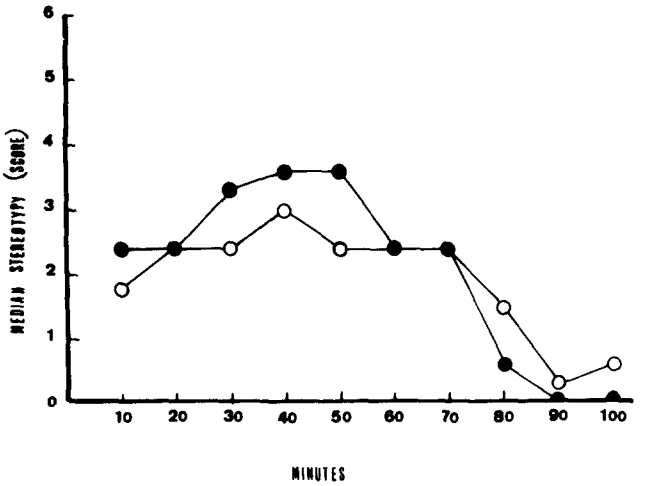

FIG. 1. Effects of prenatal diphenhydramine exposure on stereotyped behaviour induced by 1.0 mg/kg of apomorphine in male adult rats. The white circle denotes the control group (n = 8) and black circle denotes the experimental group (n = 12). No statistical differences were observed.

RESULTS AND DISCUSSION

Prenatal DPH exposure did not alter stereotyped behavior induced by SC administration of 1 mg/kg apomorphine (Fig. 1). Stereotyped behavior induced by apomorphine administration is correlated with the nigrostriatal system, and is thought to be produced by an activation of postsynaptic dopamine receptors (6). Thus these data support the suggestion that prenatal DPH exposure does not modify postsynaptic dopaminergic function in the striata in adulthood. In contrast, we observed increased HVA levels, but not DA levels, in striata of prenatal DPH-exposed rats (Table 1). If we assume that increased HVA is indicative of increased DA utilization, these observations are consistent with increased DA release and metabolism in striata of prenatal DPH exposed rats.

Despite the preliminary nature of these findings, the present results suggest that prenatal DPH exposure modifies dopaminergic function in adulthood, selectively reducing presynaptic mechanisms putatively related to negative feedback inhibition of DA release. This hypothesis is consistent with a prenatal DPH exposure-induced reduction in male sexual behavior previously reported by us (2). In conclusion, since DPH (and other antihistaminic agents) is commonly used in the treatment of allergies, nausea, and vomiting during pregnancy additional studies evaluating the possible long-term consequences of such use in the offspring are indicated.

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