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Drug-Induced Circling Preference in Rats

Correlation with Monoamine Levels

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Abstract

Drugs of abuse, such as phencyclidine (PCP), methamphetamine (METH), and cocaine (COC) are known to affect several behaviors in rats, such as motor activity, stereotypy, and circling. In this study, we evaluated whether these drugs produce circling preferences in the presence or absence of unilateral 6-hydroxydopamine (6-OHDA)-induced lesions of the caudate nucleus. Adult male CD rats were lesioned with 10 µg 6-OHDA/site. Animals were dosed with PCP (15 mg/kg, ip), its congener, (+) MK-801 (0.15 mg/kg, ip), METH (2 mg/kg, ip), COC (60 mg/kg, ip), or apomorphine (0.2 mg/kg, ip). Circling preference was recorded in control and lesioned rats for 2 h before animals were sacrificed to determine monoamine levels by HPLC/EC. In control animals, administration of these drugs produced 60–70% left circling. In lesioned animals, these drugs produced 78–90% ipsilateral (toward the lesion) circling, except apomorphine, which produced 60–80% contralateral (away from the lesion) circling. Dopamine (DA) and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) concentrations significantly decreased ipsilaterally in lesioned caudate nucleus (CN) and substantia nigra (SN). However, no significant changes were observed in nucleus accumbens (NA) and olfactory tubercles (OT). These data demonstrate that drugs of abuse like PCP, its congener (+) MK-801, METH, and COC produce a greater preference to turn toward the left than the right, a finding similar to that found in human psychosis. Since 6-OHDA lesions enhanced the circling bias and depleted DA and its metabolites DOPAC and HVA, it also suggests that the dopaminergic system may be involved in the circling behavior.

Index Entries: Phencyclidine; MK-801; methamphetamine; cocaine; apomorphine; 6-hydroxydopamine; circling preference; monoamines.

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Introduction

Phencyclidine ("PCP", "angel dust") is a drug of abuse that has central nervous system (CNS)-stimulant, CNS-depressant, hallucinogenic, and analgesic actions, and induces agitation and aggressive behavior in humans (Jaffe, 1990). PCP was introduced as a general anesthetic agent in 1957. However, its clinical use was discontinued owing to postanesthetic hallucinations in patients (Nabeshima et al., 1986). Since then, it has been recognized that PCP's psychotomimetic effects closely resemble schizophrenia.

Circling behavior is one of the best understood behaviors in rodents and is thought to be mediated via the dopaminergic system (Ungerstedt and Arbuthnot, 1970; Christie and Crow, 1971; Glick and Cox, 1978, Glick and Ross, 1981; Bracha, 1987, 1989; Javitt and Zukin, 1991; Ali et al., 1994a). There are reports available in the literature demonstrating that drugs of abuse, like PCP, cocaine (COC), and similar compounds, like MK-801 or amphetamine and apomorphine, induce rotational preference (Christie and Crow, 1971; Jeruss and Glick, 1974; Glick and Cox, 1978; Glick et al., 1980, 1983; Glick and Ross, 1981; Greenberg and Segal, 1985; Ali et al., 1994). However, only a few studies differentiate between left and right circling preference (Glick et al., 1983; Ali et al., 1994a).

Studies with rodents show that PCP produced changes in behaviors, such as motor activity, stereotypic behavior, head weaving, and circling (Nabeshima et al., 1984; Scalzo and Holson, 1992). It has been suggested that phencyclidine's effects on the dopamine system cause this stereotypy (Marwaha, 1982). Other reports, however, suggest that the stereotypy induced by PCP is related to increased serotonergic neuronal activity owing to either the increase in serotonin (5-HT)-releasing action and/or inhibition of 5-HT uptake sites (Nabeshima et al., 1984). In addition to PCP (+) MK-801, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, is used in this experiment because it binds to the same NMDA receptor channel as PCP and produces similar behavioral effects at a lower dose (Ali et al., 1992, 1994a).

Methamphetamine (METH) is a drug of abuse that has been suggested to be a neurotoxicant because it reduces dopamine (DA) and 5-HT levels, and inhibits the activity of tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis (Seiden, 1975; Kogan et al., 1976; Ellison et al., 1978; Ali et al., 1994b). This stimulant produces varied behavioral effects, including paranoid delusions, aggression, hyperactivity, and agitation. Recently, we have reported that METH produced dose- and time-dependent depletion of DA in mouse striatum, which can be blocked by a change in environmental temperature or by pretreatment with drugs known to cause decreased body temperature (Ali et al., 1994b). Most studies report that amphetamine produces rotation in naive rats. However, to our knowledge there is no report available that describes the effect of METH on left and right circling preference.

COC is one of the most widely used drugs of abuse. It is also used as a local anesthetic, and has been shown to increase heart rate and blood pressure since it causes vasoconstriction (Thadani and Whitsett, 1991). It has been proposed that serotonergic and dopaminergic neurons have binding sites for COC, and thereby prevent reuptake of DA and 5-HT. The locomotor stimulant effects of COC are thought to be mediated by inhibition of DA uptake, which results in an increase of dopaminergic transmission (Reith et al., 1982; George and Ritz, 1990). COC has been shown to produce circling behavior (Glick et al., 1983). However, no one has reported the effects of COC on left or right circling preference.

The majority of cell bodies that synthesize DA are located in the substantia nigra (SN). It has been observed that in rats lesioned with 6-OHDA unilaterally in the SN, PCP induced ipsilateral rotation, whereas DA receptor agonists and antagonists induced contralateral rotation (Ungerstedt and Arbuthnot, 1970; Kanner et al., 1975; Fessler et al., 1979; Arnt and Hyttel, 1985; Herrera-Marschwit and Unger-

stedt, 1985; Karlsson et al., 1988). The objective of the present study was threefold: first, to evaluate the effects of acute injection of PCP, MK-801, METH, COC, and apomorphine on circling behavior in rats, second, to evaluate the acute effects of these drugs on circling preference after caudate nucleus (CN) lesion on each side of the brain, and third, to evaluate whether the observed circling preferences correlate with the levels of catecholamines in selected DA-rich areas (CN, nucleus accumbens [NA], olfactory tubercles [OT], and SN) on both sides of the brain after a unilateral lesion with 6-OHDA.

Materials and Methods

Subjects

The subjects were adult male Sprague- Dawley rats, approx 10–12 wk old, weighing 300 ± 10 g. The rats were housed individually with wood chip bedding and maintained on a 12-h light–dark cycle (light, 7:00 AM; dark, 7:00 PM) in a temperature-controlled (25 ± 1°C) room. Standard rat food and tap water were available ad libitum. The rats were randomly assigned to groups for different experiments.

Apparatus and Procedure

Testing was conducted in a cylindrical glass enclosure with a 40-cm diameter and a 28-cm height. Rats were allowed 30 min to become adjusted to the cage before injections. Animals were divided into five groups and dosed with PCP (15 mg/kg, ip), (+) MK-801 (0.15 mg/kg, ip), METH (2.0 mg/kg, ip), COC (60 mg/kg, ip), or apomorphine (0.2 mg/kg, ip). Following injection, each rat was monitored for up to 2 h, and complete left or right rotations were counted as described by Ali et al. (1994a).

Lesion Studies

Animals to be lesioned were anesthetized with sodium pentobarbital (50 mg/kg, ip) and placed into a stereotaxic instrument (Kopf, Tujunga, CA). Unilateral intracaudate injections of 6-OHDA were made via a CMA/10 microdialysis probe (0.5-mm diameter at tip) (Bioanalytical Systems, West Lafayette, IN) attached to a CMA-100 microinjection pump (Carnegie Medicine, Stockholm, Sweden). The 6-OHDA was dissolved in sterile saline solution and injected at a rate of 1 μg/μL for all rats. Coordinates were AP 0.2 mm; Lat 3 mm; and DV 6.5 mm relative to the bregma (Paxinos and Watson, 1986). Each lesioned rat was allowed at least 7 d following surgery to recover before testing began.

Neurochemical Studies

Following completion of the dosage schedule and behavioral testing, the rats were sacrificed by decapitation. The CN, OT, NA, and SN were dissected from left and right sides of the brain separately from each rat, placed on dry ice, and stored at –70°C for determination of monoamine levels.

Determination of Monoamine Concentration

Concentrations of DA and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were quantified by modified high-performance liquid chromatography (HPLC) combined with electrochemical detection as described by Ali et al. (1993a). Briefly, each region of the brain was weighed and diluted with a measured volume (20% w/v) of 0.2*N* perchloric acid containing 100 ng/mL of the internal standard 3,4-dihydroxybenzylamine (DHBA). Brain tissue was then disrupted by ultrasonication, centrifuged (15,000*g*: 7 min), and 150 μL of the supernatant were removed and filtered through a 0.2-μ*M* Nylon-66 microfilter (MF-1 microcentrifuge filter, Bioanalytic System [BAS], W. Lafayette, IN). Aliquots of 25 μL representing 2.5 mg of brain tissue were injected directly onto the HPLC/EC system for separation of the neurotransmitter DA and its metabolites DOPAC and HVA.

The analytical system included a Waters Associates 510A pump (Milford, MA), a Rheo-

dyne 7125 injector (Rheodyne, Inc., Cotati, CA), a Sipelco Supelcosil LC-18, 3 μm (7.5 cm × 4.6 mm) analytical column, an LC-4B amperometric detector, and LC-17 oxidative flow cell (BAS) consisting of a glassy carbon electrode (TL-5) vs Ag-AgCl reference electrode maintained at a potential of 0.75 V. The mobile phase consisted of 0.07*M* potassium phosphate, pH 3.0, 8% methanol, and an ion pairing reagent of 1.02 m*M* 1-heptane sulfonic acid. Chromatograms were recorded and integrated on a Perkin-Elmer LCI-100 integrator (Perkin-Elmer Corp., Norwalk, CT). The concentration of DA and its metabolites (DOPAC and HVA) were calculated using a standard curve. The standard curves were generated by determining, in triplicate, the ratio between three different concentrations of DA or its metabolites (DOPAC and HVA) and a constant amount of internal standard.

Statistical Analysis

Data were analyzed by analysis of variance, followed where appropriate by Duncan's multiple range test (Duncan, 1955). A value of $p < 0.05$ was taken as significant.

Results

A single injection of PCP, (+) MK-801, METH, C0C, and apomorphine in rats produced a significant left circling preference (78–90%), a finding similar to that found in human psychosis (Fig. 1). A single injection of these drugs in unilateral CN-lesioned by 6-OHDA in rats produced ipsilateral circling preference (78–90%) except for apomorphine-treated rats in which (60–80%) contralateral circling was produced (Figs. 2 and 3).

In 6-OHDA-lesioned rats, the concentration of DA decreased significantly in CN and SN only on the lesioned side. There were no significant changes in DA concentration on either side of OT or NA (Fig. 4). The concentrations of DOPAC and HVA showed the same significant trend of depletion in CN and SN. However, in OT and NA, this trend was not significant (Figs. 5 and 6).

Discussion

The present study has demonstrated that PCP, its congener (+) MK-801, METH, COC, and apomorphine produced a left-circling preference in naive rats. Furthermore, a single injection of these drugs produced ipsilateral circling preference after unilateral lesion in CN by 6-OHDA, whereas apomorphine produced contralateral circling. 6-OHDA lesion also produced significant depletion of DA and its metabolites DOPAC and HVA in CN and SN, but not in NA and OT. Recently, we reported that PCP, TCP, and a noncompetitive NMDA receptor antagonist (+) MK-801 produced left circling turning preference in rats, a finding similar to that found in human psychosis (Ali et al., 1993a, 1994b). Neurochemical data from these studies demonstrated a significant increase in DA and its metabolites DOPAC and HVA in the left globus pallidus. It has been reported by others that PCP induces rotation in the rat (Glick and Cox, 1978; Glick et al., 1980; Iversan et al., 1988; Hiramatsu et al., 1989; Scalzo and Holson, 1992) and psychotic behavior in humans (Luby et al., 1962; Domino and Luby, 1981; Javitt and Zukin, 1991). Similar effects have been reported with others drugs, like COC and METH (Christie and Crow, 1971; Glick and Cox, 1978; Glick et al., 1980, 1983). In most of these studies, however, the authors also reported several other behaviors, such as locomotor activity, stereotypic behavior, wall climbing, ambulation, and rearing along with the rotations. Futhermore, they did not describe the preference bias after these drugs. In the present study, our objective was to evaluate only circling behavior, and to differentiate between left and right circling preferences.

PCP is known to produce psychotic behavior in animals and could be used to develop an animal model for studying the underlying mechanisms of psychosis. PCP-induced psy-

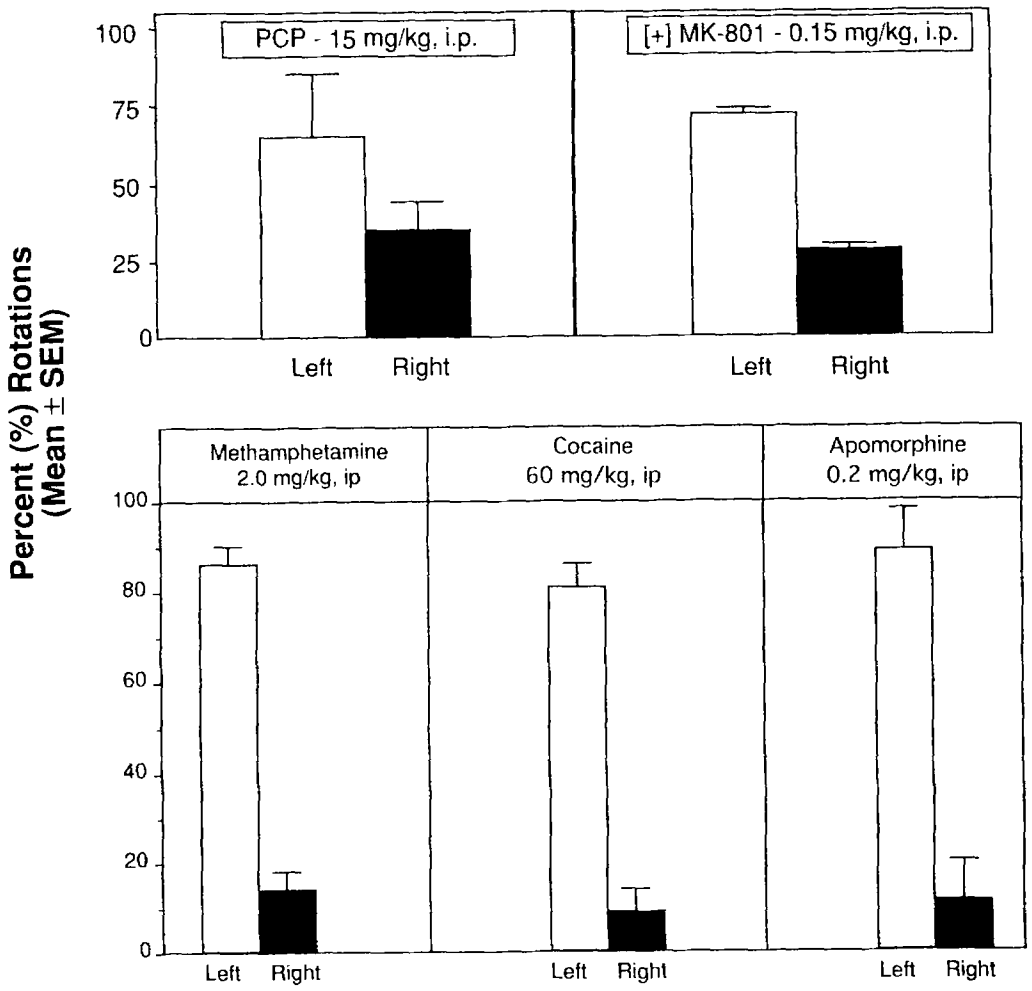

Fig. 1. Effects of a single injection of PCP (15 mg/kg, ip), (+) MK-801 (0.15 mg/kg, ip), METH (2 mg/kg, ip), cocaine (60 mg/kg, ip), or apomorphine (0.2 mg/kg, ip) on the circling preference presented as percent rotations in rats (N = 12–18).

chosis in animals and humans has been summarized recently by Javitt and Zukin (1991). The proportion of nonschizophrenic subjects who develop a psychotic state after acute administration of PCP is at least 25%, which is more than the rate of psychosis after acute exposure to amphetamine or methylphenidate (Javitt and Zukin, 1991). They also describe the difference between PCP vs amphetamine psychosis. PCP-induced psychosis incorporates both positive (e.g., hallucinations, paranoia) and negative (e.g., emotional withdrawal, flat effect) schizophrenic systems. PCP-induced psychosis also uniquely incorporates the formal thought disorder and neuropsychological deficit associated with schizophrenia (Javitt and Zukin, 1991). Furthermore, Bracha et al. (1993) have recently demonstrated a good correlation between the severity of the unmedicated schizophrenic patient's delusions and the severity of his or her left turning behavior bias. The authors describe "spontaneous, subtle preference for turning toward the left hemispace while moving around" (which they monitored with a device worn by the patient during walking hours for several days) to "inat-

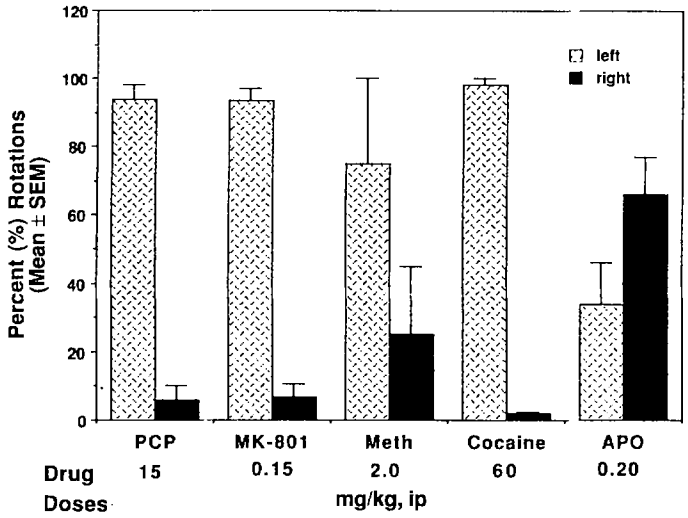

Fig. 2. Effects of a single injection of different drugs on the circling preference presented as percent rotations in rats after lesioning with 10 μg 6-hydroxydopamine (6-OHDA) in left caudate nucleus. Dose of drugs were the same as in Fig. 1 ($N = 6$).

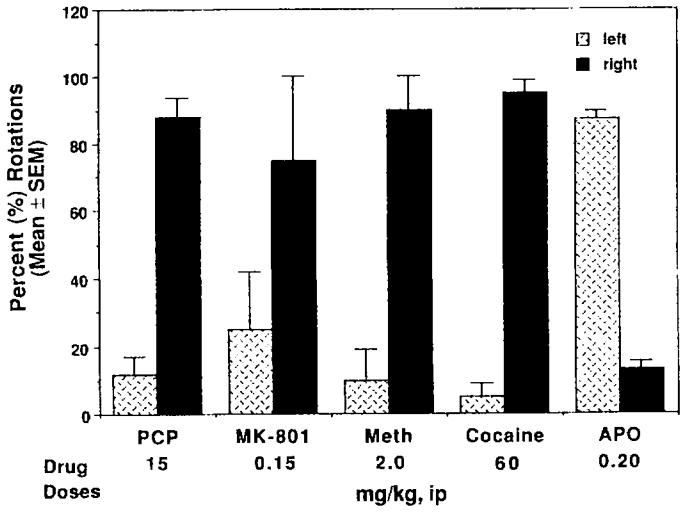

Fig. 3. Effects of a single injection of different drugs on the circling preference presented as percent rotations in rats after lesioning with 10 μg 6-hydroxydopamine in right CN. Dose of drugs were the same as in Fig. 1 ($N = 6$).

tention to the right hemispace" (Bracha et al., 1993). The present study clearly demonstrates that drugs of abuse, such as PCP, COC, and METH, can produce a similar left turning preference, and therefore, these behaviors in rats may be used to develop an animal model to understand the etiology of schizophrenia in humans further.

One of the most interesting findings of this study is that the naive rat shows a left turning preference after drug administration. Lesioned animals show ipsilateral circling, except for apomorphine, which produced contralateral circling. In a previous study, we found an increase in DA and its metabolites in the globus pallidus after PCP and (+) MK-801 injection. Contrary to this, the present study showed a depletion of DA and its metabolites in CN, which was caused by the 6-OHDA lesion, and the animals showed a turning preference toward the lesion. There are several studies suggesting left hemispheric dysfunction in patients with schizophrenia. These studies used several conventional neuropsychological measures, such as evoked potential, auditory threshold, electroencephalograph, performance on psychometric test, and more sophisticated tests, such as hemispheric blood flow and signals from computerized positron emission tomography (PETSCAN) (Gur et al., 1985; Early et al., 1987, 1989). Early et al. (1987) used PETSCAN to identify abnormalities in regional cerebral blood flow in newly diagnosed, never-medicated patients with schizophrenia. These authors found no other abnormalities, except high blood flow in the left globus pallidus. This study correlated with our previous and the present neurochemical findings, where earlier we found an increase of DA and its metabolites on the left side of the globus pallidus, and in the present study, we found that the animals circle toward the lesioned side. Further studies are under way to determine if these drugs also produce similar effects after chronic administration of low doses.

In summary, the data from the present study demonstrate that drugs of abuse, like PCP, METH, and COC, and similar chemicals, like (+) MK-801 and apomorphine, produce a greater preference to turn left than right, a finding similar to that found in human psychosis. Taken together with our previous reports, the

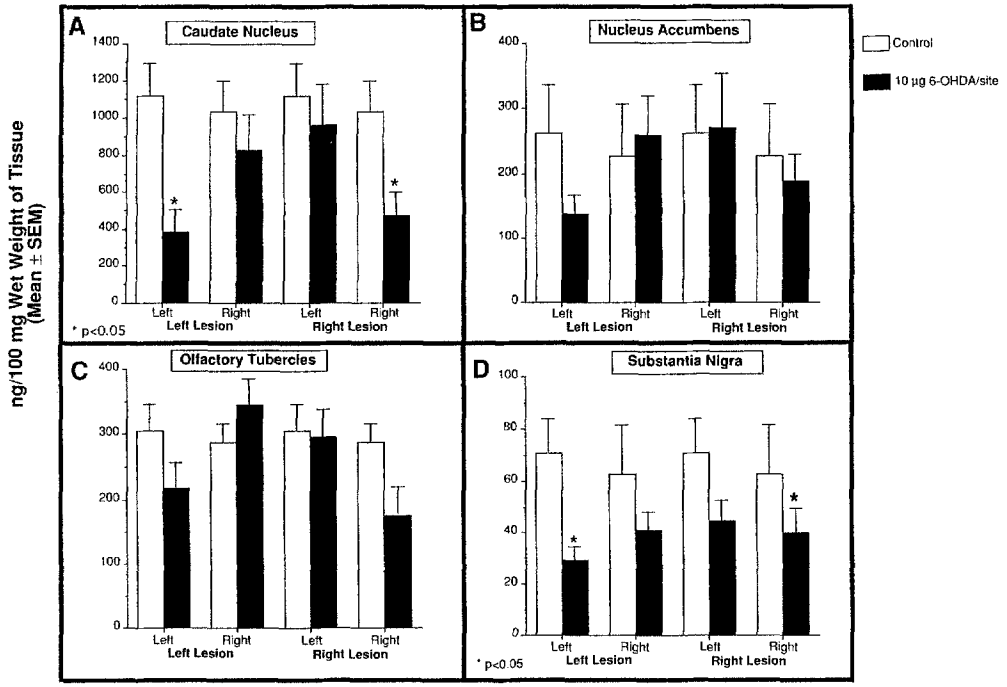

Fig. 4. Concentrations of dopamine in left and right sides of CN, NA, OT, and SN of rats after lesioning with 10 µg 6-hydroxydopamine. Each value is represented as ng/100 mg wet wt of tissue, mean SEM ± (N = 6).

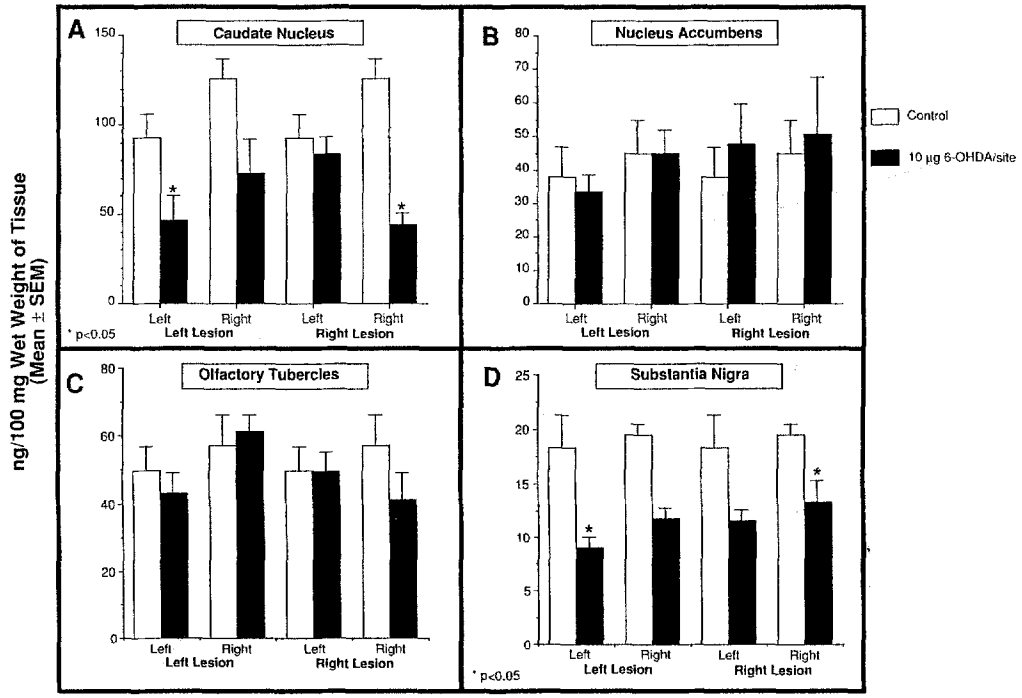

Fig. 5. Concentrations of 3,4-dihydroxyphenylacetic acid (DOPAC) in left and right sides of CN, NA, OT, and SN of rats after lesioning with 10 µg 6-hydroxydopamine. Each value is represented as ng/100 mg wet wt of tissue, mean ± SEM (N = 6).

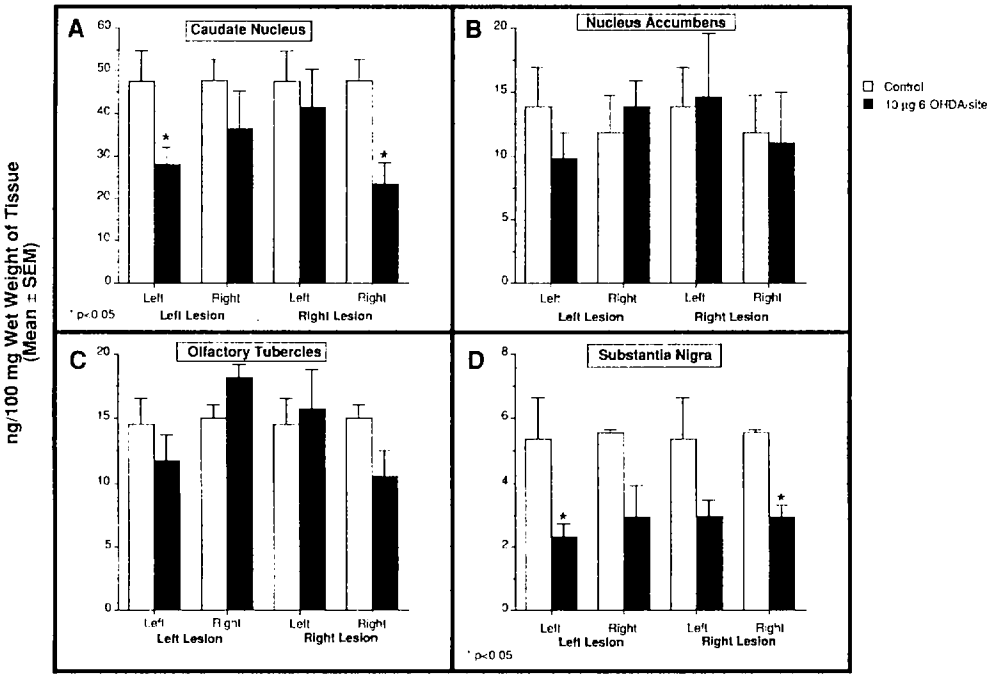

Fig. 6. Concentrations of HVA in CN, NA, OT, and SN of rats after lesioning with 10 µg 6-hydroxydopamine. Each value represents ng/100 mg wet wt of tissue, mean ± SEM ($N = 6$).

data suggest that the DA system is involved in these circling preferences, as demonstrated by lesion in CN with 6-OHDA.

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