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Phencyclidine and (+)-MK-801-Induced Circling Preference: Correlation With Monoamine Levels in Striatum of the Rat Brain

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ALI, S. F., G. D. NEWPORT AND H. S. BRACHA. *Phencyclidine and (+)-MK-801-induced circling preference: Correlation with monoamine levels in striatum of the rat brain.* NEUROTOXICOL TERATOL 16(4) 335–342, 1994. – Phencyclidine (PCP; angel dust) is a drug of abuse known to produce a behavioral state in humans resembling schizophrenia/psychosis. PCP is a noncompetitive NMDA receptor antagonist and produces a variety of behaviors in rats including circling. The behavioral effects of other noncompetitive NMDA receptor antagonists such as (+)-MK-801 are still being elucidated. Here, adult female rats were dosed with PCP (10 mg/kg, IP), or (+)-MK-801 (0.1 mg/kg, IP) and circling preference was recorded for 2 h before sacrifice to determine monoamine levels by HPLC/EC. Animals injected with PCP or (+)-MK-801 showed a preference to turn to the left (65% and 72%, respectively). PCP and (+)-MK-801 also produced a significant increase of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in whole striatum on both sides of the brain. Further dissection of the striatum into medioventral and dorsolateral regions revealed that HVA was increased bilaterally except in globus pallidus where we found significant increases in dopamine (DA), DOPAC, and HVA only on the left side after PCP and (+)-MK-801 administration. These data suggest that PCP and (+)-MK-801 produce a greater preference to turn left than right, a finding similar to that found in human psychosis. Furthermore, it is possible that this preference to turn toward the left hemispace is due to an asymmetry in dopamine function found in the globus pallidus after administration of PCP and similar drugs.

Phencyclidine (+)-MK-801 Circling preference Dopamine Striatum Globus pallidus Schizophrenia/psychosis

PHENCYCLIDINE (PCP, angel dust) is one of the most widely used drugs of abuse known to produce psychotic effects in humans (10). PCP also induces several schizophrenia-like symptoms such as hallucination, paranoia, and emotional withdrawal and motor retardation in humans (for review see 20,24). According to Javitt and Zukin (20) the endogenous dysfunction of NMDA-receptor mediated neurotransmission might contribute to the pathogenesis of schizophrenia. One of the most interesting effects of PCP in humans is that PCP-intoxicated patients can not be distinguished from schizophrenic patients on the basis of presenting symptoms alone (9,30,38).

PCP intoxication also causes a variety of behavioral changes in rodents. These behaviors include changes in locomotor activity, stereotypies, ataxia, lateral head weaving, back pedalling, and turning (14,16,21,25,28,31,32,33,37). It

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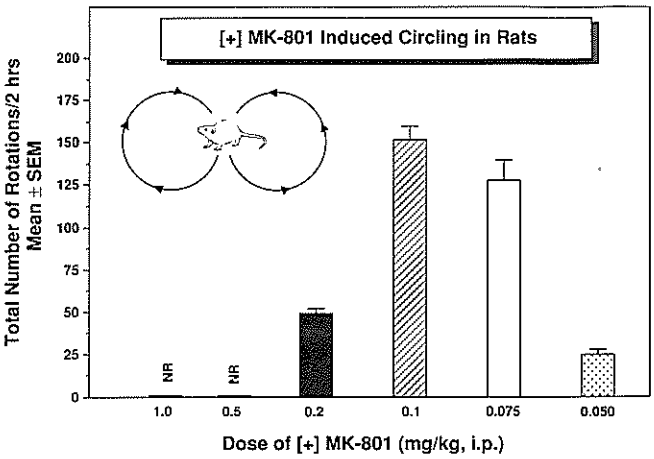

FIG. 1. Effect of a single injection of various doses of (+)-MK-801 on the circling (left and right) in rats. Each value is presented as total rotations per 2 h, Mean ± SEM (n = 4–12).

has been reported that PCP induces ipsilateral rotation in rats after unilateral lesion with 6-hydroxydopamine (11), suggesting that ipsilateral rotation may be mediated via presynaptic effects on dopamine neurons. In addition to PCP, other drugs of abuse such as amphetamine and cocaine also produce circling behavior in rats (4,12,13). Hiramatsu et al. (18) reported comparable behavioral and neurochemical effects of [(+)-5-methyl-10-11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine maleate] (MK-801) and PCP. Like PCP, MK-801, a noncompetitive NMDA-receptor antagonist, also produced several complex behavioral effects in rats, e.g., lateral head weaving, body rolling and falling hyperlocomotion, and ataxia (19,22,23). MK-801 also has a high affinity for the PCP-receptor site in the NMDA channel (29,35,36). Olney et al. (26) reported that acute administration of PCP and related agents like MK-801, teletamin, and ketamine produces acute pathomorphological changes in a specific population of neurons in the rat brain. This neuropathological alteration in posterior cingulate cortex increases in the first 12 h and then gradually diminished over the next 12 h suggesting that it might be involved in the psychotic effects caused by PCP in humans (26).

Circling behavior has recently been described in patients with severe psychotic symptoms (2,3). Circling behavior is one of the best understood behaviors in rodents and is thought to be mediated via dopaminergic pathways (2,4,12,15,20,34). To our knowledge, there are a only few reports in the literature demonstrating PCP-induced circling in rats, and none reporting circling after (+)-MK-801. In the present study, we evaluated the effect of acute injections of PCP or (+)-MK-801 on circling preference in rats and on lateralization of activity in the dopamine system of the forebrain.

METHOD

Subjects

The subjects were adult naive Sprague–Dawley female rats, approximately 10- to 12 weeks old, weighing 300 ± 10 g. The rats were housed 2–3 per cage with wood-chip bedding and maintained on a 12L : 12D cycle (light, 0700 h; dark 1900 h) in a temperature-controlled (25 ± 1°C) room. Food (Purina Laboratory Chow, St. Louis, MO) and tap water were available ad lib. The rats were randomly divided into groups for different experiments.

Apparatus and Procedure

Testing was conducted in a cylindrical glass enclosure with a 16" diameter and a 10" height. Each animal was placed in this cylinder and circling behavior was recorded by an observer who was unaware of the experimental conditions. Complete (360°) left or right rotations were counted. Before injections, rats were allowed 30 min, and number of rotations was recorded. For the dose-finding studies, animals (n = 4–6) were injected with different doses of PCP (NIDA, Rockville, MD) (5, 7.5, 10, 15, or 20 mg/kg, IP), or (+)-MK-801 (RBI, Natick, MA) (0.05, 0.1, 0.2, 0.5, or 1.0 mg/kg, IP) and rotations were recorded at 5-min intervals for 2 h. In our preliminary experiments, we tested whether sites of injection would change the circling behavior. We found that different injection sites of either PCP or (+)-MK-801 did not make any difference in the circling behavior. PCP at the dose of 10 mg/

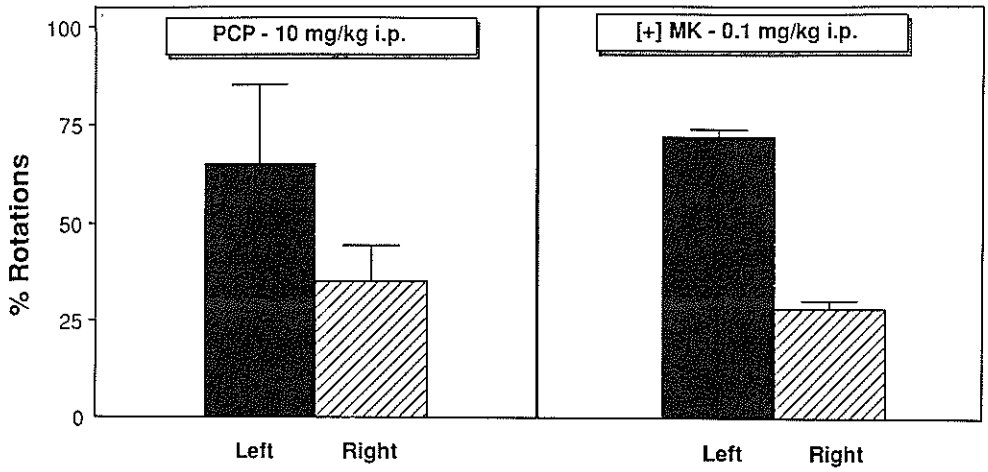

FIG. 2. Effect of a single injection of PCP or (+)-MK-801 on the circling preference presented as percent rotation in rats. Mean ± SEM (n = 12 for PCP group and n = 13 for (+)-MK-801 group).

kg, IP, and (+)-MK-801 at a dose of 0.1 mg/kg, IP induced the most rotation with the least anesthetic effect. Therefore, these doses were used for subsequent experiments.

Animals were divided into two groups. One group of animals was dosed with PCP (10 mg/kg, IP) and complete rotations were recorded for 2 h. A second group of animals was dosed with 0.1 mg/kg (+)-MK-801 and complete rotations were recorded for 2 h. Two to 3 weeks later, the animals were injected again with the same dose of PCP or (+)-MK-801, placed in the circling apparatus to observe the circling, and sacrificed by decapitation 1 h after administration. Brains were rapidly removed and each side of the striatum were dissected separately. In a follow-up experiment, two groups of animals were dosed with PCP (10 mg/kg, IP) or (+)-MK-801 and sacrificed 1 h after the dose administration. Brains were quickly removed and each striatum was further dissected into medioventral, dorsolateral, and globus pallidus, placed on dry ice and stored at -70°C for monoamine assays. Each side of the dissected regions was analyzed separately.

Determination of Monoamine Concentrations

Concentrations of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were quantified by a modified method of high performance liquid chromatography combined with electrochemical detection (HPLC/EC) as described by Ali et al. (1). Briefly, each striatum or a region of striatum 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 was removed and filtered through 0.2 μM 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 Rheodyne 7125 injector (Rheodyne, Inc., Cotati, CA), a Sipelco Supelcosil LC-18, 3 Mm (7.5 cm × 4.6 mm) analytical column, a LC-4B amperometric detector and LC-17 oxidative flow cell (BAS) consisting of a glassy carbon electrode (TL-5) versus 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 mM 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

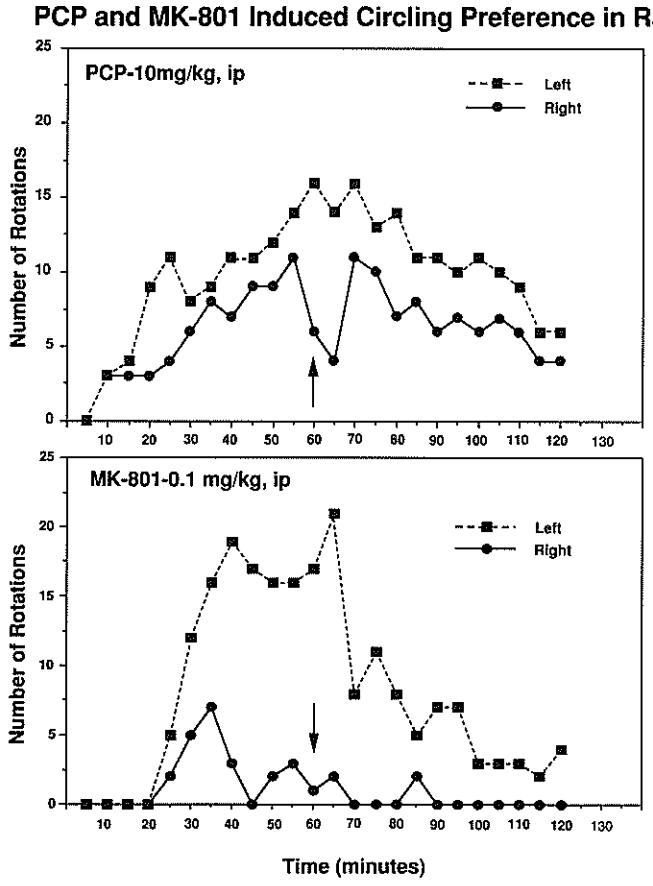

FIG. 3. Effect of a single injection of PCP or (+)-MK-801 on the circling preference presented as number of rotation at each 5-min interval over 2-h period in rats. Arrows indicate the time (1 h) of sacrifice for neurochemical analysis (n = 12 for PCP group and n = 13 for (+)-MK-801 group).

ratio between three different amounts of each amine or its metabolites and a constant amount of internal standard.

Statistical Analysis

Data were analyzed by analysis of variance (ANOVA), followed where appropriate by Duncan's multiple range test (6). A value of $p < 0.05$ was taken as significant.

RESULTS

A single injection of (+)-MK-801 in rats produced a dose-dependent increase of rotation and the highest number of rotations was found at 0.1 mg/kg dose level (Fig. 1). Injection of PCP or (+)-MK-801 at different sites in the rat did not produce any difference in rotational behavior. At doses of 0.5 and 1.0 mg/kg (+)-MK-801 the animals became less active and did not show any motor activity or rotational behavior (Fig. 1). Similar effects were found with different doses of PCP (data not shown). When rotational behavior was analyzed as percent of turning preference, we found that following a single injection of PCP (10 mg/kg) or (+)-MK-801 (0.1 mg/kg) rats showed a preference to turn to the left (65% and 72%, respectively) (Fig. 2). Therefore, these doses were used for the subsequent experiments. The analysis of these rotations at each 5-min interval also demonstrated that rotation preference toward left was highest 1 h after drug administration, then decreased thereafter (Fig. 3). Therefore, in neurochemical studies animals were sacrificed 1 h after the dose of PCP or (+)-MK-801.

Injection of (+)-MK-801 produced an increase of dopamine metabolites (DOPAC and HVA) where as PCP produced an increase of HVA concentration in whole striatum on both sides of the brain. However, these increases tend to be higher in the left than right side of the brain (Fig. 4). In a follow-up experiment, the striatum was further dissected into medioventral, dorsolateral, and globus pallidus from each side of the brain. The neurochemical analysis revealed that the concentration of HVA was increased bilaterally in the medioventral (Fig. 5) and dorsolateral (Fig. 6) region of the striatum. In contrast, in globus pallidus a significant increase in DA, DOPAC, and HVA concentration was found only on the left side after PCP or (+)-MK-801 administration (Fig. 7).

DISCUSSION

There have been consistent reports of PCP-induced psychotic behavior in humans (5,20) and circling behavior in rats (12,14,28), however, this is one of the first studies to report that PCP and a noncompetitive NMDA receptor antagonist, (+)-MK-801, produces left-turning preference in rats, a finding similar to that found in human psychosis. There are reports in the literature that other drugs of abuse such as amphetamine and cocaine along with PCP produces circling behavior (4,12,13,14). However, in this study we report that

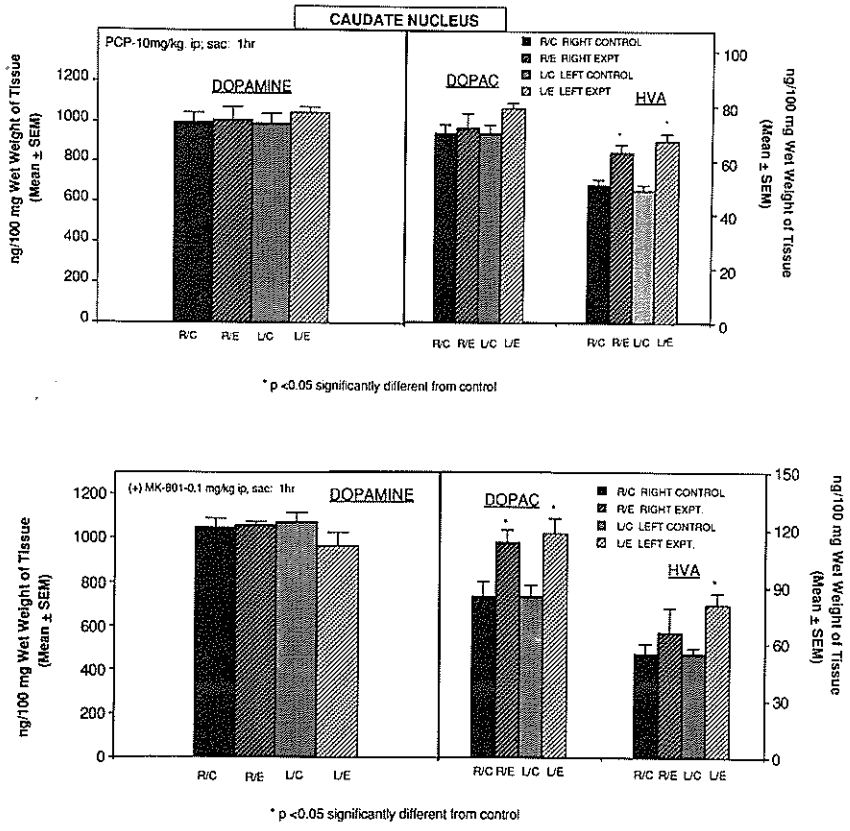

FIG. 4. Effect of a single injection of PCP or (+)-MK-801 on the concentration of dopamine and its metabolites DOPAC and HVA in rat striatum. Each value represented as ng/100 mg wet weight of tissue, Mean ± SEM (n = 6–8).

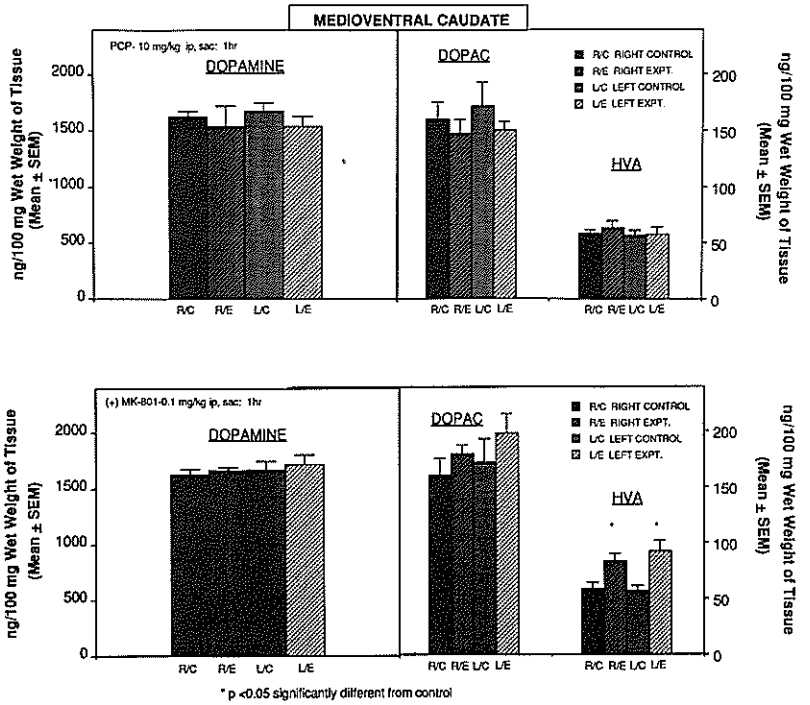

FIG. 5. Effect of a single injection of PCP or (+)-MK-801 on the concentration of dopamine and its metabolites DOPAC and HVA in medioventral caudate of rat. Each value is represented as ng/100 mg wet weight of tissue, Mean ± SEM (n = 6–8).

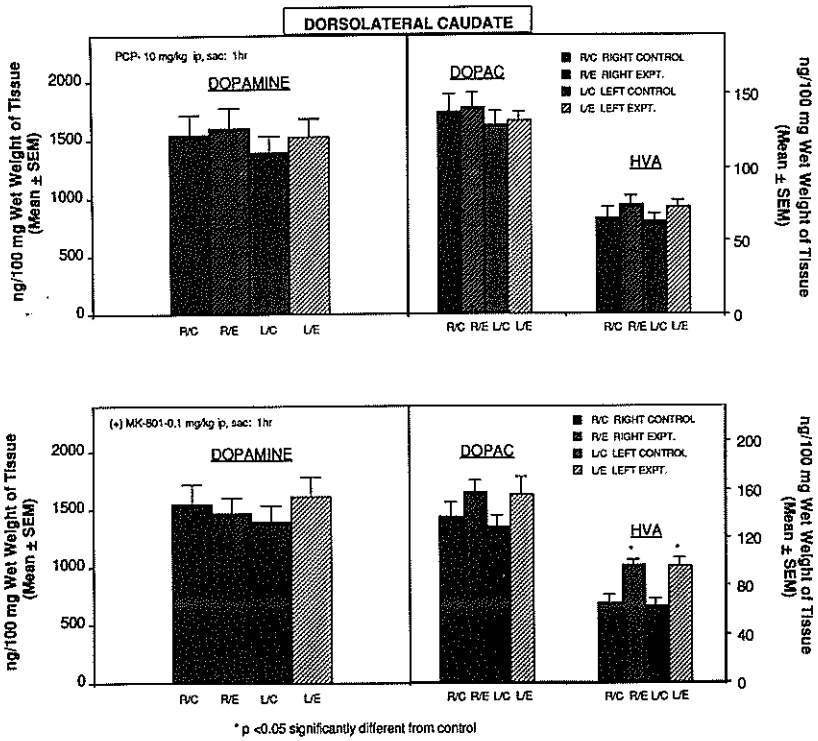

FIG. 6. Effect of a single injection of PCP or (+)-MK-801 on dopamine and its metabolites DOPAC and HVA concentrations in dorsolateral caudate of rat. Each value is represented as ng/100 mg wet weight of tissue, Mean ± SEM (n = 6–8).

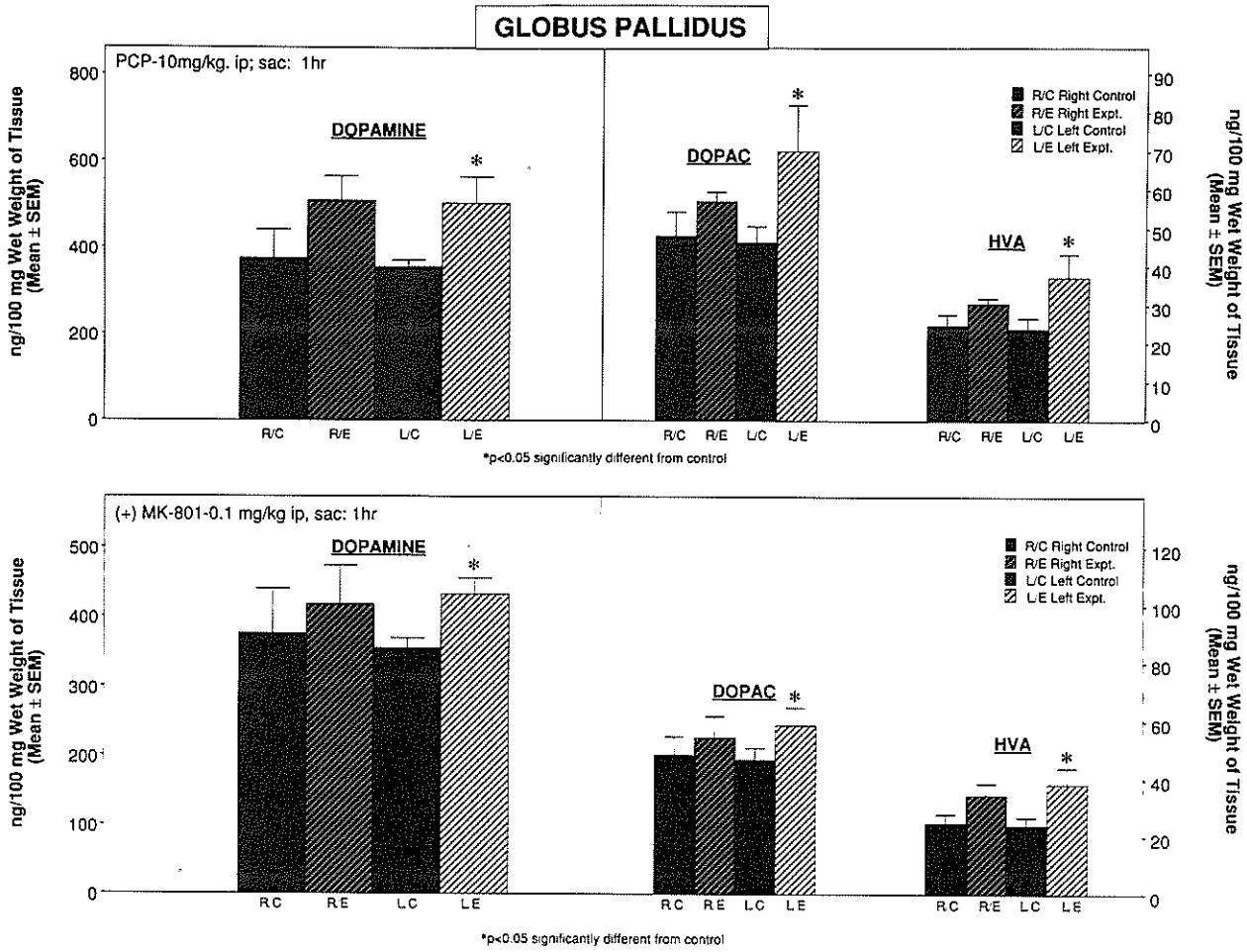

FIG. 7. Effects of a single injection of PCP or (+)-MK-801 on the concentration of dopamine and its metabolites DOPAC and HVA in the globus pallidus of rat. Each value is represented as ng/100 mg wet weight of tissue, Mean ± SEM (n = 8–10).

PCP and (+)-MK-801 produced predominately left circling in rats. Recent review by Javitt and Zukin (20) clearly summarized that 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. As opposed to amphetamine-induced psychosis, PCP induced psychosis incorporated both positive (e.g., hallucinations, paranoia) and negative (e.g., emotional withdrawal, flat affect) schizophrenic symptoms. PCP-induced psychosis also uniquely incorporated the formal thought disorder and neuropsychological deficit associated with schizophrenia (20). Recently, Bracha et al. (3) also demonstrated a correlation between the severity of unmedicated schizophrenic patient's delusions and the severity of their left turning behavior bias. They attributed the "spontaneous, subtle preference for turning toward the left hemispace while moving around" which they monitored with a device worn by the patient's during walking hours for several days, to "inattention to the right hemispace".

Here, we clearly demonstrate that PCP and a similar compound, (+)-MK-801, can produce a similar turning preference towards the left, and therefore these behaviors in rats may be used as a model to further study the etiology of schizophrenia in humans. Our neurochemical data also demonstrate that single injections of PCP or (+)-MK-801 increased the turnover of DA on both sides of striatum by increasing the concentrations of metabolites. However, further dissection of striatum revealed that PCP and (+)-MK-801 produced significant increases of dopamine and its metabolites, DOPAC, and HVA, on the left side of the globus pallidus. There are some reports suggesting left hemispheric dysfunction in patients with schizophrenia. These studies used evoked potentials, auditory threshold, electroencephalograph, performance on psychometric tests, signals from computerized tomography, and hemispheric blood flow (7,8,17). Early et al. (8) used positron emission tomography (PET) to identify abnormalities in regional cerebral blood flow in newly diagnosed, never medicated patients with schizophrenia. It is interesting to note that Early et al. (8) found no other abnormalities except that patients had abnormally high blood flow in the left globus pallidus. This study correlated with our neurochemical finding of increased of dopamine and metabolites on the left side of the globus pallidus. Further studies are underway to evaluate if these drugs also produce the same effects after chronic administration of low doses.

The neurochemical data in these rodents (higher concentrations of dopamine and metabolites in the left GP after PCP or MK-801) may look contradictory because the direction of turning in previous studies was, as a rule, toward the hemisphere with low dopamine activity. We would like to suggest that high concentrations of dopamine and metabolites may actually be a manifestation of impaired release of dopamine from the presynaptic neuron as has also been suggested by Reynolds (27). In summary, these data suggest that PCP and similar compounds produce a greater preference to turn toward the left hemispace. This finding is remarkably similar to that reported in two recent studies of human patients with severe psychotic symptoms (2,3).

ACKNOWLEDGEMENT

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