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BRIEF COMMUNICATION

Cardiovascular and Plasma Prolactin Responses to Stereoisomers of Phencyclidine

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BAYORH, M. A., D. LOZOVSKY, K. C. RICE, T. R. BURKE, JR., AND I. J. KOPIN. *Cardiovascular and plasma prolactin responses to stereoisomers of phencyclidine.* PHARMACOL BIOCHEM BEHAV **19**(2) 365–367, 1983.—The effect of phencyclidine (PCP) and dextro- and levorotatory isomers of its derivatives 1-(l-phenylcyclohexyl)-3-methylpiperidine [(+)-PCMP and (−)-PCMP] (5 mg/kg, SC) on blood pressure (BP), heart rate (HR) and plasma prolactin (PRL) were examined. PCP and (+)-PCMP but not (−)-PCMP increased BP and HR and suppressed plasma PRL.

Phencyclidine (+)-PCMP (−)-PCMP Plasma prolactin Blood pressure Heart rate

PHENCYCLIDINE is a psychotomimetic drug that is widely abused in the United States. Enhancement of central dopaminergic transmission through stimulation of dopamine (DA) release and/or inhibition of DA uptake is considered as one of the major mechanisms involved in the behavioral effects of PCP [3,10]. The results of our recent study [9] demonstrating suppressive effect of PCP on plasma PRL are in agreement with this hypothesis. Sympathetically mediated hypertension is one of the major complications that attend PCP intoxication in man [7]. Increase in BP after administration of PCP has been also reported in rats [1,4]. These effects of PCP, however, are more likely a result of adrenergic rather than dopaminergic stimulation [1]. It has been shown recently that some effects of PCP are stereospecific and a good correlation has been demonstrated between relative potencies of the optically active derivatives of PCP in their ability to displace [^{3}H]-PCP binding to brain membranes [8] and in their electrophysiological and behavioral effects [6].

In the present study we examined the stereospecificity of the effects of PCP on the cardiovascular system (BP and HR) responses and plasma PRL levels which are probably mediated by adrenergic and dopaminergic systems, respectively. Effects of dextro- and levorotatory isomers of 1-(l-phenylcyclohexyl)-3-methylpiperidine (PCMP) were compared to the effects of PCP.

METHOD

Male Sprague-Dawley rats, 250–300 g (Zivic-Miller Laboratories, Inc., Allison Park, PA) were maintained in a room with 12 hr light-dark cycle for 5–6 days before use, with rat chow and water available ad lib.

In the cardiovascular study, indwelling tail artery catheters were inserted in rats under halothane anesthesia (2% oxygen) one day prior to the experiment as previously described [2]. On the day of the experiment, the arterial catheter of each rat was attached to a blood pressure transducer (Type 4-327-C, Beckman Dynograph 511A) and BP and HR (computed from the QRS components of the EKG signals by a Beckman cardiotachometer coupler type 9587B) were recorded for 10–15 minutes before and two hours after SC injection of either saline or PCP HCl, (+)-PCMP HCl and (−)-PCMP HCl (5 mg/kg).

In the PRL study, rats were decapitated three hours after SC injection of either saline or PCP HCl, (+)-PCMP HCl and (−)-PCMP HCl (5 mg/kg). Plasma was separated from heparanized trunk blood by centrifugation and stored at −20°C until assayed.

Plasma PRL Assay

Rat plasma PRL levels were measured by radioimmunoassay using antibodies and standard (RP-2) obtained from the National Institute of Arthritis, Metabolism and Digestive Diseases. Final assay dilution of the antibodies was 1:20,000. [^{125}I] rat PRL was obtained from New England Nuclear (Boston, MA) and 10,000 CPM per tube were used. Bound material was precipitated with polyethylene glycol after 24 hours incubation at room temperature. The sensitivity of the assay was approximately 25 pg PRL/ml plasma.

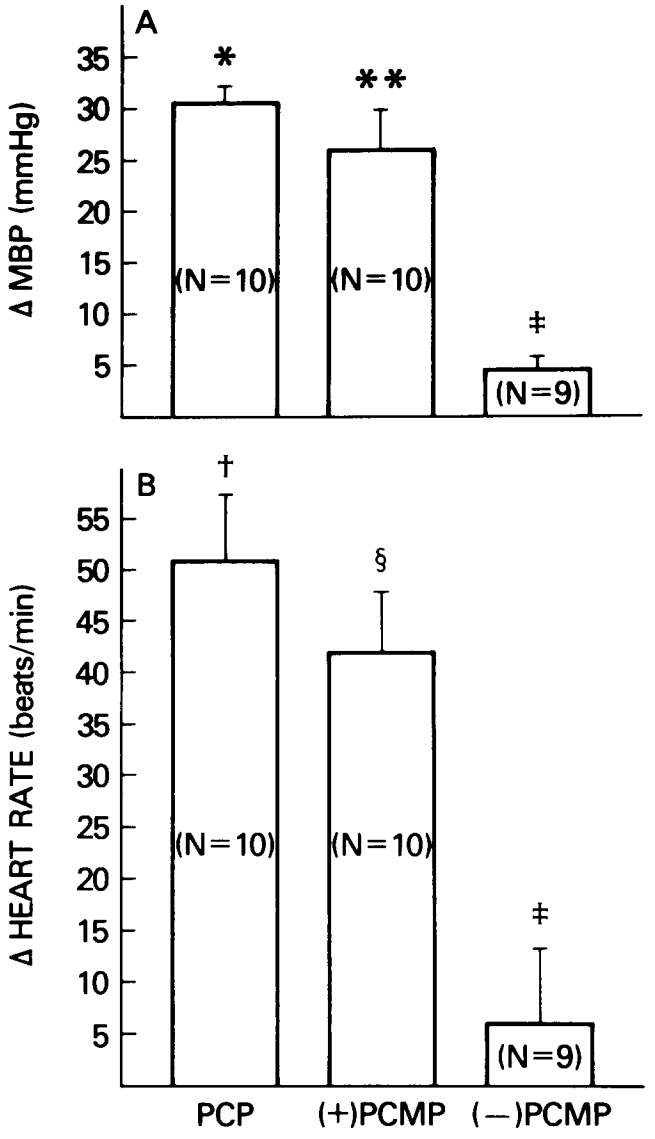

FIG. 1. Changes in BP (A) and HR (B) two hours after SC injection of PCP, (+)-PCMP and (−)-PCMP (5 mg/kg). Number of rats in each group is shown in parentheses. Statistical significance using Student's two-tailed *t*-test is as follows: *, **, † and § significantly different from the saline group value at $p<0.005$, $p<0.01$, $p<0.02$ and $p<0.05$ respectively. ‡Significantly different from PCP and (+)-PCMP values at $p<0.002$.

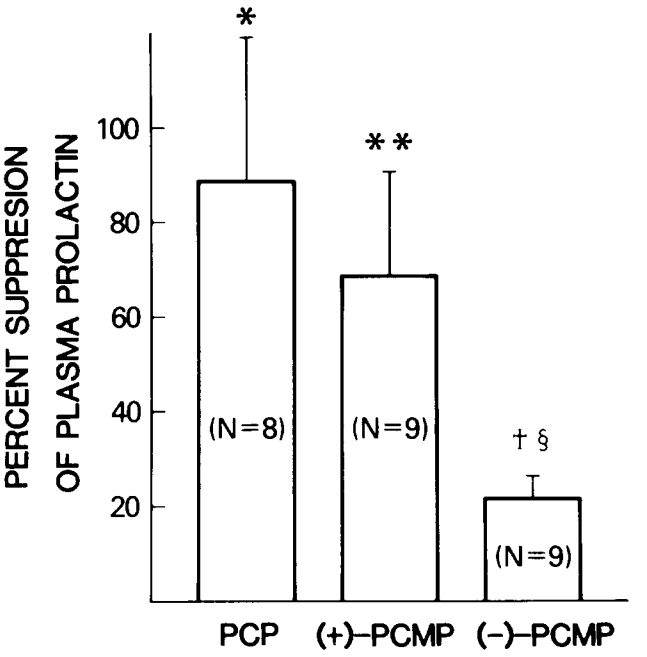

FIG. 2. Changes in plasma PRL levels three hours after SC injection of PCP, (+)-PCMP, (−)-PCMP (5 mg/kg) or saline. Each column represents % of suppression as compared to the plasma PRL in saline treated rats (13.2±4.0 ng/ml). Number of rats in each group is shown in parentheses. Statistical significance utilizing Student's two-tailed *t* test is as follows: *Significantly different from the saline group value at $p<0.005$, **significantly different from the saline group value at $p<0.05$, † significantly different from the PCP group value at $p<0.001$ and § significantly different from the (+)-PCMP group value at $p<0.05$.

RESULTS

The basal mean of BPs of the different groups of rats were similar before drug administration (93±2, 98±3 and 95±2 mm Hg for the PCP, (+)-PCMP and (−)-PCMP groups, respectively). Two hours following the administration of the drugs, mean BPs increased to 121±3, 123±4 and 99±3 mm Hg, respectively. The increases in BP after both PCP and (+)-PCMP were significant. Blood pressure, however, was not increased after injection of (−)-PCMP (Fig. 1A).

The pattern of the HR responses was similar to that of the BP responses. Basal mean HRs were 290±6, 289±12 and 283±11 beats/minute for the PCP, (+)-PCMP and (−)-PCMP groups, respectively. Two hours after the administration of the drugs, the HRs increased to 340±11, 324±13 and 290±9 beats/minute, respectively. PCP and (+)-PCMP but not (−)-PCMP significantly increased HRs (Fig. 1B).

Plasma PRL levels three hours after SC injection of PCP, (+)-PCMP, (−)-PCMP (5 mg/kg) or saline were 1.4±1.0, 4.10±1.0, 10.2±2.0 and 13.2±4.0 ng/ml respectively. PCP and (+)-PCMP significantly suppressed plasma PRL. Plasma PRL, however, was not changed in rats injected with (−)-PCMP (Fig. 2).

DISCUSSION

Equal doses of PCP and (+)-PCMP evoked equal cardiovascular effects and similarly suppressed plasma PRL whereas (−)-PCMP had no significant effect on either of the above parameters. These results suggest that there is a good correlation between the ability of PCP derivatives to increase BP and HR and their suppressive effect on plasma PRL. The stereospecificity of the effects of the PCP derivatives on plasma PRL and the cardiovascular system reported in this study is in agreement with their previously reported effects on [^{3}H] PCP binding [8] and electrophysiological and behavioral indices [6]. The implications of the present report is of significance when one considers the fact that the effect of various PCP derivatives on plasma PRL may be due to facilitation of DA release and/or inhibition of its uptake whereas the cardiovascular effects may be mediated via a different mechanism. As has been reported earlier, the

pressor effect of PCP is markedly reduced by α-adrenergic blockade [6] whereas the PRL-suppressive effect of PCP is antagonized by a dopamine receptor blocker haloperidol [9]. There is also evidence that PCP may alter noradrenergic transmission by causing norepinephrine (NE) release through a presynaptic mechanism [1,5]. Also, we have recently shown that the pressor effect of PCP is associated with a significant activation of the sympathoadrenal medullary system as evidenced by striking increases in plasma NE and epinephrine but not DA [1]. Thus, the same stereospecific effects of PCP derivatives on the cardiovascular system and plasma PRL, as evidenced from the present study, indicate that the stimulatory action of PCP on both the dopaminergic and adrenergic systems may be attributed to the same active conformation of the PCP molecule.

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