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Phencyclidine and the Dynamics of Mouse Brain Histamine

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ABSTRACT

The effects of phencyclidine (PCP) on the dynamics of brain histamine (HA) were examined in the mouse brain. PCP (2–10 mg/kg i.p.) dose-dependently elevated the level of *tele*-methylhistamine (*t*-MH), a predominant metabolite of brain HA, without altering the HA level. PCP also enhanced the accumulation of *t*-MH after administration of pargyline hydrochloride (80 mg/kg i.p.). PCP at 5 mg/kg facilitated the HA depletion produced by (*S*)-α-fluoromethylhistidine markedly (50 mg/kg i.v.), a specific inhibitor of histidine decarboxylase. Metoprine (10 mg/kg i.p.), an inhibitor of HA-N-methyltransferase, decreased the *t*-MH level and increased the HA level. In the metoprine-treated mice, PCP at 10 mg/kg had no significant effect on the *t*-MH level, whereas it significantly increased the HA level. The increase in the *t*-MH level after administration of PCP (5 mg/kg) was observed in various brain regions except the pons-medulla oblongata. These results suggest that, in mice, PCP increases the brain HA turnover possibly by facilitating the release of HA.

PCP, a widely abused drug, was introduced originally as a dissociative anesthetic agent. However, the clinical application was abandoned because of side effects including delusion and hallucination, reminiscent of paranoid schizophrenia (Domino, 1980; Snyder, 1980). Both pharmacological and biochemical evidence revealed that PCP has broad effects on the dynamics of a variety of neurotransmitters, such as dopamine (Doherty *et al.*, 1980; Johnson, 1983), noradrenaline (Taube *et al.*, 1975), serotonin (Smith *et al.*, 1977; Nabeshima *et al.*, 1985), γ-aminobutyric acid (Nabeshima *et al.*, 1981) and acetylcholine (Maayani *et al.*, 1974). However, the precise mechanism underlying the psychotomimetic action of PCP is poorly understood.

HA is regarded as being a putative neurotransmitter in the brain of several mammalian species (Green *et al.*, 1978; Schwartz *et al.*, 1980). Histochemical studies using fluorescent antibodies against histidine decarboxylase (Watanabe *et al.*, 1984) or HA (Steinbusch and Mulder, 1984) have shown that, in rats, HAergic fibers originating from the cell bodies in the posterior hypothalamus are widely distributed throughout the brain. Brain HA is considered to play physiologically important roles in the regulation of arousal response (Kalivas, 1982), body temperature (Lomax and Green, 1981) and pressor response (Klein and Gertner, 1981).

In the mammalian brain, HA is metabolized predominantly by HA-N-methyltransferase to *t*-MH (Schayer and Reilly, 1973), which is further deaminated by type B MAO to *tele*-methylimidazoleacetic acid (Hough and Domino, 1979). After MAO inhibition by pargyline, *t*-MH accumulates linearly up to 2 to 4 hr in the brain of several mammalian species (Hough *et al.*, 1982; Oishi *et al.*, 1984; Nishibori *et al.*, 1984). Based on the rate of pargyline-induced *t*-MH accumulation, the HA turnover rates in various brain regions have been estimated in rats (Hough *et al.*, 1984; Oishi *et al.*, 1984), mice and guinea pigs (Nishibori *et al.*, 1984). We reported that some psychoactive drugs have marked influences on the brain HA turnover. Δ^9-Tetrahydrocannabinol at sedative doses decreases (Oishi *et al.*, 1985) and morphine at doses effective in behavioral stimulation increases the HA turnover rate (Nishibori *et al.*, 1985). These findings suggest that HAergic neurons are involved in some central effects of psychoactive drugs. Because little is known of the effect of PCP on brain HAergic systems, we investigated the influence of PCP on brain HA dynamics.

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Methods

Male ddY mice weighing 25 to 30 g (Shizuoka Laboratory Animal Center, Hamamatsu, Japan) were housed in groups and given free access to food and water. All experiments were performed between 11:00 A.M. and 2:00 P.M.

The chemicals and drugs used in this study were: HA dihydrochloride (Wako Chemicals, Osaka, Japan), *t*-MH dihydrochloride and *pros*-methylhistamine dihydrochloride (Calbiochem-Behring Corp., San Diego, CA) and pargyline hydrochloride (Sigma Chemical Co., St. Louis, MO). PCP hydrochloride was a generous gift from Dr. T. Nabeshima (Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya, Japan). α-FMH monohydrochloride hemihydrate and metoprine were kindly donated by Dr. J. Kollonitsch (Merck Sharp & Dohme Research Laboratories,

ABBREVIATIONS: PCP, phencyclidine; HA, histamine; HAergic, histaminergic; *t*-MH, *tele*-methylhistamine; MAO, monoamine oxidase; α-FMH, (*S*)-α-fluoromethylhistidine; CMC, carboxymethylcellulose.

Rahway, NJ) and Dr. C. A. Nichol (Burroughs Wellcome Research Laboratories, Research Triangle Park, NC), respectively. All drugs except metoprine were dissolved in 0.9% saline. Metoprine was emulsified in 0.5% CMC. All drugs were injected in a volume of 0.1 ml/10 g b.wt. Pargyline and metoprine were injected i.p. 15 min before the i.p. injection of PCP. α-FMH was administered i.v. simultaneously with PCP.

Determination of HA and *t*-MH. Mice were decapitated and the brain excluding the cerebellum was removed rapidly. For the study of regional effects of PCP, the brain was dissected on ice into six regions including the cerebral cortex, hippocampus, striatum, hypothalamus, midbrain and pons-medulla oblongata, according to the method of Glowinski and Iversen (1966) with a modification (Oishi *et al.*, 1983). The tissue of the whole brain or the various regions was homogenized in 2 to 5 ml of 0.4 N perchloric acid containing an appropriate amount of *pros*-methylhistamine as an internal standard. The homogenate was centrifuged at 1000 × *g* for 20 min. The HA and *t*-MH contents of the supernatant were determined simultaneously by a slight modification (Oishi *et al.*, 1985) of the method of Tsuruta *et al.* (1981), using high-performance liquid chromatography with fluorescence detection. The system used was composed of a pump (LC-3A, Shimadzu, Kyoto, Japan), a fluorescence spectromonitor (RF-530, Shimadzu) and a reverse-phase column (150 × 4 mm inside diameter) packed with Chemcosorb ODS-H (5 μm, spherical form; Chemco Scientific Co., Osaka, Japan).

Statistical analysis. Data were analyzed by the two-tailed Student's *t* test. P values of less than .05 were considered statistically significant.

Results

Effect of PCP on brain levels of HA and *t*-MH. As shown in table 1, PCP (2–10 mg/kg) produced a dose-dependent elevation of *t*-MH level in the brain of the saline-pretreated mice 75 min after the injection. However, the HA level was not significantly altered by any dose of PCP tested. Pargyline hydrochloride (80 mg/kg) increased the *t*-MH level by 66.9% during 90 min after the injection in the control mice. PCP significantly increased the *t*-MH level in the pargyline-pretreated animals, in a dose-dependent manner, with no influence on the HA level. The *t*-MH accumulation (difference in the *t*-MH level between the pargyline- and saline-pretreated groups) was also increased markedly by 2 to 10 mg/kg of PCP (table 1). The increase in the *t*-MH level was observed at 30 min, reached the maximum at 60 min and was still evident 240 min after administration of 10 mg/kg of PCP (fig. 1). The HA level did not change at any time tested.

Effect of PCP on α-FMH-induced HA depletion. In order to confirm that PCP facilitates the HA turnover, we examined the effect of this drug on the HA depletion produced by α-FMH, a specific inhibitor of histidine decarboxylase (Kollonitsch *et al.*, 1978). The HA level decreased by 21 and 38%, respectively, 30 and 60 min after i.v. administration of α-FMH (50 mg/kg) (table 2). The *t*-MH level also decreased to about the same extent. The simultaneous administration of 5 mg/kg of PCP facilitated the α-FMH-induced HA depletion markedly. The HA level in the PCP plus α-FMH-treated group was significantly lower than the value in the saline plus α-FMH-treated group 30 and 60 min after injection. On the other hand, PCP did not affect the *t*-MH depletion.

TABLE 1

Effect of PCP on the levels of HA and *t*-MH in the brain of mice pretreated with pargyline

Pargyline hydrochloride (80 mg/kg) or saline was injected i.p. 15 min before the i.p. administration of PCP. Mice were decapitated 90 min after the injection of pargyline or saline. Each value represents the mean ± S.E.M. of five to six animals.

Drugs	Dose	Amine Contents			
		Saline-pretreated		Pargyline-pretreated	
		HA	*t*-MH	HA	*t*-MH
	mg/kg	*ng/g*			
Saline		37.7 ± 1.5	88.4 ± 3.4	34.9 ± 2.1	147.5 ± 8.7
PCP	2	39.9 ± 2.5	92.5 ± 7.7	34.7 ± 0.8	177.6 ± 9.7*
	5	41.8 ± 2.9	109.8 ± 3.6**	34.8 ± 2.1	197.2 ± 6.6**
	10	43.4 ± 3.8	119.0 ± 6.7**	38.6 ± 2.2	210.4 ± 8.0***

* P < .05; ** P < .01; *** P < .001 as compared with the corresponding values in the saline-injected control group.

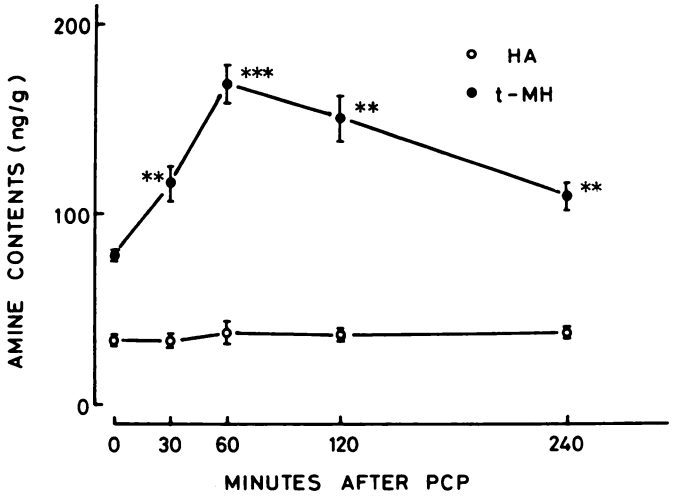

Fig. 1. Time course of the effect of PCP (10 mg/kg) on the levels of HA and *t*-MH in the mouse brain. Each point represents the mean ± S.E.M. of five to six animals. **P < .01; ***P < .001 as compared with 0 time value.

TABLE 2

Effect of PCP (5 mg/kg) on HA depletion induced by α-FMH

α-FMH (50 mg/kg) was injected i.v. simultaneously with the i.p. injection of PCP or saline. Numbers in parentheses, percentage of 0 time values. Each value represents the mean ± S.E.M. of five to six animals.

Drugs	Time after α-FMH	Amine Contents	
		HA	*t*-MH
	min	*ng/g*	
Saline	0	40.8 ± 3.7 (100)	94.0 ± 5.8 (100)
PCP	30	32.4 ± 2.8 (79)	81.8 ± 8.8 (87)
Saline	30	22.6 ± 3.2 (55)**·†	82.4 ± 5.9 (88)
PCP	60	25.3 ± 1.5 (62)**	57.4 ± 6.5 (61)**
	60	16.2 ± 1.7 (40)***·‡	59.3 ± 5.3 (63)**

** P < .01; *** P < .001 as compared with 0 time values; † P < .05; †† P < .01 as compared with the corresponding values in the saline-injected control groups.

TABLE 3

Effect of PCP (10 mg/kg) on the levels of HA and *t*-MH in the brain of mice pretreated with metoprine

Metoprine (10 mg/kg) or CMC was injected i.p. 15 min before the i.p. administration of PCP or saline. Mice were decapitated 90 min after the injection of metoprine or CMC. Each value represents the mean ± S.E.M. of five to six animals. Numbers in parentheses, percentage of respective control values.

Drugs	Amine Contents	
	HA	*t*-MH
	ng/g	
CMC and saline	38.6 ± 2.2 (100)	82.4 ± 3.7 (100)
CMC and PCP	40.2 ± 3.3 (104)	115.8 ± 8.5 (141)**
Metoprine and saline	52.9 ± 3.0 (137)**	60.1 ± 4.7 (73)**
Metoprine and PCP	64.4 ± 3.2 (167)***·†	66.3 ± 1.4 (80)**

** P < .01; *** P < .001 as compared with the CMC and saline-treated group; † P < .05 as compared with the metoprine and saline-treated group.

Effect of PCP on brain HA and *t*-MH levels in metoprine-treated mice. In an attempt to explain the increase in the steady-state *t*-MH level after PCP injection, the effect of PCP was examined in mice treated with metoprine, a potent inhibitor of HA-N-methyltransferase (Duch *et al.*, 1978). Metoprine (10 mg/kg i.p.) decreased the *t*-MH level by 27% and increased the HA level by 37% 90 min after injection, these effects being statistically significant (table 3). Although PCP at 10 mg/kg increased the *t*-MH level in the CMC control group, it did not significantly affect the level in the metoprine-treated mice, when administered 15 min after metoprine treatment. In addition, PCP significantly increased the HA level in the metoprine-treated mice.

Effect of PCP on the levels of HA and *t*-MH in various brain regions. The above results appeared to indicate that the increase in the *t*-MH level in the whole brain after PCP treatment reflects the enhancement of HA turnover. To get additional information concerning regional effects of PCP, we measured the steady-state levels of HA and *t*-MH in six brain regions including the cerebral cortex, hippocampus, striatum, hypothalamus, midbrain and pons-medulla oblongata, 60 min after the administration of PCP (5 mg/kg). As shown in table 4, PCP produced a significant rise in the *t*-MH level in all the brain regions except the pons-medulla oblongata. The increase was the most marked in the hippocampus. In other regions about the same extent of increases in the *t*-MH level were observed. No alteration in the HA level occurred in any region.

Discussion

Brain HA exists in at least two different pools: neuronal and non-neuronal. Mast cells are thought to be the major source of non-neuronal HA (Garbarg *et al.*, 1976). Neuronal HA has a half-life of less than 1 hr, in contrast to mast-cell HA with a half-life of more than several days (Martres *et al.*, 1975). After injection of α-FMH, a specific inhibitor of histidine decarboxylase, the brain HA concentration decreases to a minimum of about 30 to 50% of the control level within 4 hr and remains at this low level for 24 hr (Garbarg *et al.*, 1980; Maeyama *et al.*, 1982). This indicates that about 50 to 70% of brain HA is contained in a pool(s) with a rapid turnover (presumably neuronal pool). The presence in the brain of plural HA pools with different turnover rates poses problems when attempting to analyze drug action on the dynamics of neuronal HA. Drug-induced changes in the steady-state HA level may often be poor indices of the changes in the dynamics of neuronal HA and changes in the turnover of neuronal HA may occur with no change in the steady-state HA level.

On the other hand, *t*-MH, a predominant metabolite of brain HA, is thought to be a good index of the activity of HAergic neurons (Bischoff and Korf, 1978). We also reported that an increase in the *t*-MH level (but not in the HA level) after treatment with L-histidine paralleled the behavioral effect of this amino acid (Itoh *et al.*, 1984). Inasmuch as *t*-MH is metabolized further by type B MAO to *tele*-methylimidazoleacetic acid (Hough and Domino, 1979) and an almost linear accumulation of *t*-MH occurs after pargyline injection, the HA turnover rate has been estimated from the rate of the pargyline-induced *t*-MH accumulation in the brain of several mammalian species (Hough *et al.*, 1982, 1984; Nishibori *et al.*, 1984; Oishi *et al.*, 1984). We found no significant increase in the *t*-MH level by pargyline in mice pretreated with α-FMH (Oishi *et al.*, 1984). Therefore, the HA turnover calculated from the *t*-MH accumulation appears to reflect the HAergic activity (Oishi *et al.*, 1984).

In the present study, PCP at 2 mg/kg had no significant effect on the *t*-MH level in the saline-pretreated mice, whereas it significantly elevated the *t*-MH level in the pargyline-pretreated group (table 1). Thus, the HA turnover rate in the PCP-treated group estimated from the pargyline-induced *t*-MH accumulation (85 ng/g/90 min) was 0.45 nmol/g/hr. This value is about 1.5 times as high as the value in the control group (0.31 nmol/g/hr). These results support the idea described above. However, PCP at 5 and 10 mg/kg significantly increased the *t*-MH level, both in the saline- and pargyline-pretreated groups. The HA turnover rates in the groups treated with 5 and 10 mg/kg of PCP were estimated to be 0.47 and 0.49 nmol/g/hr respectively. These findings were much the same as the group treated with 2 mg/kg of PCP. The values may even be underestimated due to an increase in the steady-state *t*-MH level. It was subsequently shown that PCP at 5 mg/kg significantly facilitated the HA depletion both at 30 and 60 min after administration of α-FMH (table 2). Furthermore, in the metoprine-treated mice, the *t*-MH increase by PCP was not observed. These results strongly suggest that PCP enhances the HA turnover with the resultant increased steady-state level of *t*-MH.

The steady-state *t*-MH level in the mouse brain also increases when the *t*-MH elimination (transport and/or metabolism of *t*-MH) is inhibited by high doses of ethanol (Itoh *et al.*, 1985). However, such a mechanism does not seem to underlie the PCP-induced increase in the steady-state *t*-MH level, for the

TABLE 4

Effect of PCP on the levels of HA and *t*-MH in various regions of the mouse brain

PCP (5 mg/kg) was injected i.p. Mice were decapitated 60 min after the PCP injection. Each value represents the mean ± S.E.M. of six animals. Numbers in parentheses indicate percentage of the respective control values.

Brain Regions	Amine Contents			
	Saline-treated		PCP-treated	
	HA	*t*-MH	HA	*t*-MH
	ng/g			
Cerebral cortex	41.3 ± 4.2	57.1 ± 2.6	41.0 ± 1.8 (99)	73.1 ± 4.7 (128)*
Hippocampus	32.9 ± 3.9	135.4 ± 12.5	37.4 ± 2.7 (114)	198.6 ± 23.0 (147)*
Striatum	40.1 ± 4.7	83.9 ± 5.6	36.1 ± 1.6 (90)	111.8 ± 10.6 (133)*
Hypothalamus	126.0 ± 5.3	215.0 ± 13.8	149.5 ± 12.3 (119)	266.1 ± 18.3 (124)*
Midbrain	41.2 ± 4.5	63.6 ± 4.2	46.1 ± 3.5 (112)	85.9 ± 4.2 (135)**
Pons-medulla oblongata	16.4 ± 1.6	22.4 ± 2.7	16.7 ± 1.5 (102)	22.7 ± 1.4 (101)

* $P < .05$; ** $P < .01$ as compared with the corresponding values in the saline-treated group.

following reasons: first, because PCP increased the *t*-MH level even after 80 mg/kg of pargyline, it is unlikely that PCP affects the *t*-MH level by an action on MAO. Second, PCP at 10 mg/kg, a dose which produces the most marked increase in the *t*-MH level in the control mice (table 1; fig. 1), had no effect on the *t*-MH level in the metoprine-treated mice (table 3).

In contrast to the *t*-MH level, the HA level was not changed by PCP, at any dose (table 1) and at any time (fig. 1) tested, despite the marked increase in HA turnover. This may be due to an increased HA synthesis counterbalancing an increased HA release. Such a view is supported by the finding that PCP at 10 mg/kg significantly increased the HA level in the metoprine-treated mice (table 3).

The regional differences in the biochemical actions of PCP on opioid (Nabeshima *et al.*, 1983a) and cholinergic (Murray and Cheney, 1981) systems have been demonstrated. Because, as discussed above, the changes in the *t*-MH level after the administration of PCP seem to serve as a good index of the activity of HAergic neurons, we investigated the effect of PCP on the steady-state *t*-MH level in various brain regions. PCP produced a rise in the *t*-MH level in all regions except the pons-medulla oblongata. In the hypothalamus HA turnover rate is the highest among various regions (Nishibori *et al.*, 1984). However, the PCP-induced increase in the *t*-MH level in this region was not so marked as compared with other regions. Therefore, it is likely that PCP increases HA turnover by acting directly or indirectly on nerve terminals rather than on cell bodies of HAergic neurons. The lack of influence of PCP on the *t*-MH level in the pons-medulla oblongata may be due to the fact that the percentage of neuronal HA, as measured by the HA depletion 4 hr after α-FMH injection, is the lowest (33.1%) among all the brain regions tested (Nishibori *et al.*, 1984).

Specific binding sites for PCP have been demonstrated in various regions of the mammalian brain, and the highest densities of these sites are found in the hippocampus and the cerebral cortex (Zukin and Zukin, 1979; Quirion *et al.*, 1981). In the present experiment, the effect of PCP on the *t*-MH level was the most marked in the hippocampus among the brain resions tested. Therefore, it is suggested that the action of PCP on the HA dynamics may be mediated by the specific PCP binding sites.

PCP is a potent blocker of K^+ channels at the neuromuscular junction of the frog skeletal muscle and rat brain synaptosomes, and the relationship between the decreased K^+ conductance and behavioral effects of this drug has been discussed (Albuquerque *et al.*, 1981). The inhibition of K^+ conductance may result in the prolongation of the presynaptic action potential, which in turn leads to an increased inward Ca^{++} current and an enhanced transmitter release (Albuquerque *et al.*, 1981). The present data suggest that PCP enhances HA release from HAergic nerve terminals, but the precise mechanism of HA releasing action of PCP remains to be clarified.

Although the functional roles of brain HA are not fully understood, intracerebral injection of this amine produces hypothermia (Lomax and Green, 1981), arousal responses (Kalivas, 1982), analgesia (Glick and Crane, 1978) and pressor response (Klein and Gertner, 1981), thereby suggesting the involvement of HA in the regulation of such functions. These functions are modified by PCP administration (Nabeshima *et al.*, 1983b; Johnson, 1983; Bayorh *et al.*, 1984). Further studies are under way to determine the possible involvement of HAergic neurons in the pharmacological actions of PCP.

In conclusion, PCP at doses of 2 to 10 mg/kg produced a dose-dependent elevation of the *t*-MH level without altering the HA level in the mouse brain. The *t*-MH increase was observed in various brain regions except the pons-medulla oblongata. The HA turnover seems to be increased by this drug, as evidenced by the enhancement of pargyline-induced accumulation of *t*-MH, the facilitation of the HA depletion after α-FMH injection and the potentiation of the metoprine-induced increase in the HA level.

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