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Phencyclidine-Induced Stereotyped Behaviors After Injection of Morphine and N-Allylnormetazocine (SKF 10,047) in Rats

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NABESHIMA, T., M. HIRAMATSU AND T. KAMEYAMA. *Phencyclidine-induced stereotyped behaviors after injection of morphine and N-allylnormetazocine (SKF 10,047) in rats.* PHARMACOL BIOCHEM BEHAV 24(6) 1629–1634, 1986.—We investigated the effects of N-allylnormetazocine (SKF 10,047) and morphine on the stereotyped behaviors induced by the intraperitoneal injection of phencyclidine (PCP). PCP-induced turning and backpedalling were significantly potentiated by pretreatment with SKF 10,047 (10 mg/kg) but sniffing and head weaving were not. On the other hand, pretreatment with morphine dose-dependently attenuated PCP-induced sniffing and head weaving, but not turning and backpedalling. These results suggest that PCP-induced stereotypy may be mediated by not only a sigma opioid receptor but also some other receptors. In addition, each component of PCP-induced stereotypy may be controlled by different opioid systems and/or neuronal systems.

Morphine Phencyclidine Rat SKF 10,047 (N-allylnormetazocine) Sigma opioid receptor Stereotyped behavior

PHENCYCLIDINE [1-(1-phenylcylclohexyl)-piperidine; PCP], introduced in the 1950's as a general anesthetic, was rejected as an anesthetic for humans, primarily because of its psychotomimetic effects [8,16]. Although it is still considered a useful veterinary anesthetic, its greatest present attraction is as a drug of abuse [6,15]. The ease of synthesis and administration of PCP have contributed to its popularity among illicit users [15,28].

Administration of PCP to rats induces a complex syndrome of behaviors which can be observed and quantified in three relatively distinct categories: locomotor activity, stereotypy and ataxia [32]. Since it has been demonstrated that these behaviors are developed in a dose- and time-dependent manner [25–26, 32] and are mediated via various neuronal systems, it is not surprising that PCP produces a complex syndrome of behaviors.

Furthermore, since stereotyped behavior induced by PCP in animals is regarded as a good model for schizophrenia in humans [16], it is important for understanding schizophrenia to determine the action mechanisms of stereotypy.

During the past few years of opioid receptor research more and more evidence for the concept of multiple subtypes of opioid receptors has accumulated from pharmacological and biochemical experiments. Three classes of opioid receptors have been suggested by Martin *et al.* [19] according to different actions of the prototype drug, morphine (mu), ketocyclazocine (kappa) and SKF 10,047 (sigma). The putative mu opioid agonist, morphine, produced analgesia and stimulated locomotion; the putative kappa opioid agonist, ketocyclazocine, produced analgesia and sedation/ataxia; the putative sigma opioid agonist, SKF 10,047, lacking antinociceptive effects, stimulated locomotor activity and produced psychotomimetic effects in the rat.

In other studies utilizing the spinal dog, the similarity between the single-dose profiles of PCP and SKF 10,047 was reported [13, 33–34]. In addition, several studies have established the existence of specific receptor sites for PCP in the brain [37] and it has been suggested that sigma opioid receptors and PCP receptors may be the same [38]. This finding has raised additional questions concerning the pharmacological relationship between these two drugs. If the central action mechanisms of PCP and SKF 10,047 are the same, their actions should be potentiated by combination of these 2 drugs. At the same time, recent studies suggest that PCP may have important interactions with central mu and/or delta opioid systems: (1) Methadone antagonizes PCP-induced stereotypy in rats [35]; (2) Naloxone decreases PCP-induced stereotypy, ataxia and hyperactivity, but met-enkephalin and morphine increase ataxia in rats [4]; (3) Morphine and enkephalin analogs increase PCP-induced pivoting in mice [9].

The purpose of the present investigation is to determine if

TABLE 1

COMPARISON OF STEREOTYPED BEHAVIORS INDUCED BY PHENCYCLIDINE (PCP) AND N-ALLYLNORMETAZOCINE (SKF) IN RATS

Treatments (mg/kg)	N	Time after administration (min) 0–15	15–30	30–45	45–60
Sniffing					
Saline	7	1.6 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.1 ± 0.2
PCP 5	9	2.0 ± 0.1	1.7 ± 0.1	1.5 ± 0.1	1.3 ± 0.1
PCP 7.5	8	2.3 ± 0.1	2.1 ± 0.1	1.8 ± 0.2	1.8 ± 0.2
SKF 10	8	1.9 ± 0.1	1.6 ± 0.2	1.3 ± 0.1	1.1 ± 0.1
SKF 20	8	1.5 ± 0.0	1.8 ± 0.1	1.6 ± 0.1	1.4 ± 0.1
Head weaving					
Saline	7	0	0	0	0
PCP 5	9	159.1 ± 44.5	128.8 ± 18.8	79.6 ± 13.5	40.1 ± 7.5
PCP 7.5	8	274.6 ± 35.3	183.3 ± 24.4	132.9 ± 25.0	105.0 ± 26.4
SKF 10	8	89.3 ± 25.4	74.1 ± 15.3	40.6 ± 6.4	21.4 ± 3.3
SKF 20	8	172.9 ± 28.9	143.5 ± 28.0	80.3 ± 15.3	59.8 ± 11.3
Turning					
Saline	7	0	0	0	0
PCP 5	9	1.4 ± 1.3	4.1 ± 2.2	1.3 ± 0.9	0.7 ± 0.6
PCP 7.5	8	4.4 ± 1.5	6.9 ± 1.6	6.1 ± 2.3	7.5 ± 3.2
SKF 10	8	1.6 ± 0.4	1.1 ± 0.4	0.1 ± 0.1	0.3 ± 0.2
SKF 20	8	2.5 ± 0.7	8.3 ± 1.4	3.6 ± 1.0	1.4 ± 0.4
Backpedalling					
Saline	7	0	0	0	0
PCP 5	9	7.7 ± 4.4	5.8 ± 3.1	2.8 ± 1.7	1.1 ± 1.1
PCP 7.5	8	7.4 ± 1.9	14.5 ± 3.9	12.3 ± 3.6	10.0 ± 3.1
SKF 10	8	3.6 ± 1.1	7.9 ± 2.5	3.3 ± 1.3	1.0 ± 0.6
SKF 20	8	9.8 ± 2.1	21.1 ± 3.7	14.8 ± 3.7	6.4 ± 1.4

putative sigma and mu opioid agonists affect PCP-induced stereotypy in rats.

METHOD

Animals

Male Wistar rats (Kyoto Inst. Kitayama Labo. Co., Japan), weighing 200 to 300 g at the time of the stereotypy experiments, were housed in a temperature (23±1°C)- and humidity (55±5%)-regulated room with a 12 hr light/dark cycle; the room was lit between 8 a.m.–8 p.m. for at least 7 days before the start of experiments. The animals were given free access to food and water.

Drugs

The drugs used were phencyclidine-HCl (PCP; synthesized by Dr. Furukawa), morphine-HCl (Shionogi Pharmaceutical Co., Japan), N-allylnormetazocine-HCl (SKF 10,047; gift from NIDA, MD). PCP was administered IP 15 min after morphine or SKF 10,047 SC treatment. Control experiments were performed by the injection of 0.9% saline solution, both alone and in combination with the test drugs. Doses of these drugs were expressed in terms of the salt. Drugs were injected in a volume of 2 ml/kg body weight.

Measurement of PCP-Induced Behaviors

To evaluate the PCP-induced stereotyped behaviors, the behavioral scoring systems developed by us [25] were employed and behavioral scores were recorded for four periods of 15 min each as follows: sniffing (0: absent, 1: occasional, 2: frequent, 3: constant); backpedalling (the number of times the animal made backward locomotion); head weaving (the number of times the animal made slow, side-to-side or lateral head movements); turning (the number of times the animal circled laterally to left or right over 360° within a relatively small area). The PCP-induced stereotyped behaviors were observed in a cage with dimensions of 30×35×17 cm.

The experiments were conducted between 10:00 a.m. and 6 p.m. in a quiet laboratory.

Analysis of Data

All tests for statistical significance were performed using a two-tailed Mann-Whitney U-test for non-parametric data.

RESULTS

Effects of Pretreatment With SKF 10,047 on the PCP-Induced Stereotyped Behaviors in Rats

Gross observation of behavioral changes in Wistar rats treated with PCP IP indicated hyperactivity, ataxia and some stereotyped behaviors consisting of sniffing, turning, head weaving and backpedalling, and these effects were dose-dependent in agreement with results reported in a previous

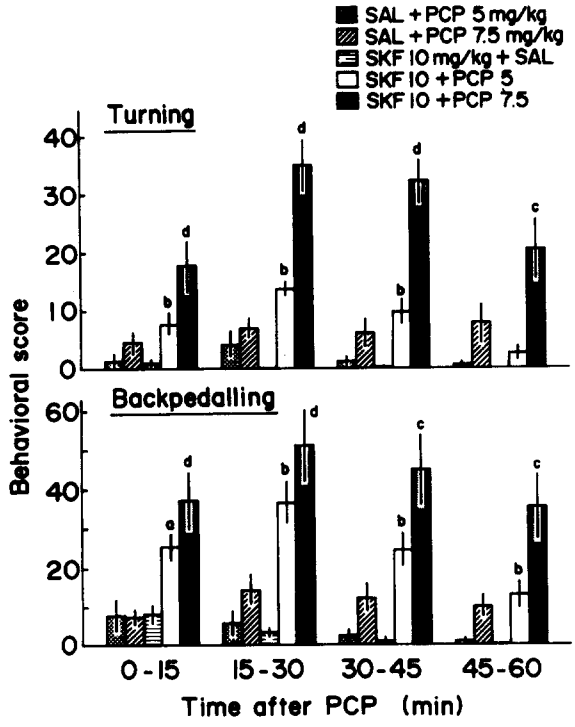

FIG. 1. Effects of SKF 10,047 (SKF) on the phencyclidine (PCP)-induced turning and backpedalling. SKF 10,047 was administered SC 15 min before the PCP injection. Each bar shows the mean± S.E.M. of 8–10 animals. $^{a}p<0.05$, $^{b}p<0.01$ vs. SAL + PCP 5 mg/kg; $^{c}p<0.05$, $^{d}p<0.01$ vs. SAL + PCP 7.5 mg/kg (Mann-Whitney's U-test).

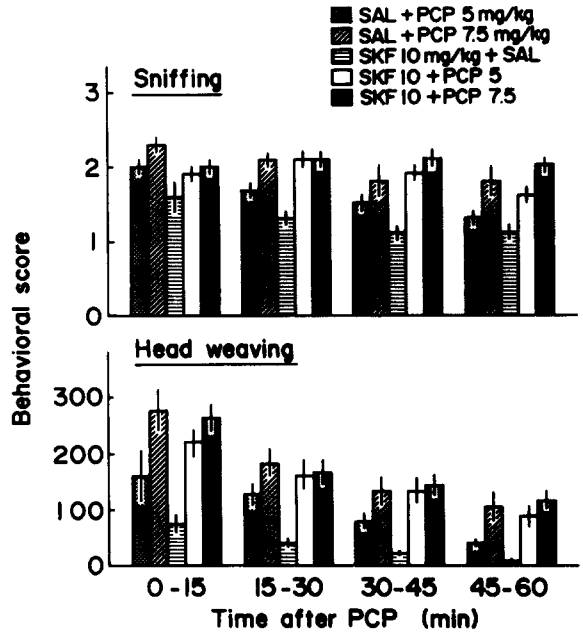

FIG. 2. Effects of SKF 10,047 (SKF) on the phencyclidine (PCP)-induced sniffing and head weaving. SKF 10,047 was administered SC 15 min before the PCP injection. Each bar shows the mean± S.E.M. of 8–10 animals.

paper [26]. SKF 10,047, which acts as a sigma opioid receptor agonist, also produced hyperactivity (data not shown) and PCP-like stereotyped behaviors. SKF 10,047-induced stereotypy was also dose-dependent. The higher dose of SKF 10,047 (20 mg/kg) produced stereotypy ratings greater than those of the 5 mg/kg dose and, in the case of backpedalling, even greater than those of the 7.5 mg/kg dose of PCP (Table 1). If the stereotyped behaviors induced by SKF 10,047 were produced through some mechanisms similar to PCP, the PCP-induced behavioral changes should be potentiated additively when SKF 10,047 is administered before the PCP injection.

As shown in Fig. 1, the behavioral scores for PCP-induced turning and backpedalling were significantly increased when SKF 10,047 (10 mg/kg) was injected before the PCP (5 and 7.5 mg/kg) injection. In addition, the duration of the PCP effect was prolonged in combination with SKF 10,047, compared with the duration of the PCP effect alone. However, pretreatment with SKF 10,047 (10 mg/kg) failed to potentiate PCP-induced head weaving and sniffing (Fig. 2).

Effects of Pretreatment With Morphine on the PCP-Induced Stereotyped Behaviors in Rats

As shown in Table 2, pretreatment with morphine at the dose range of 1.25–3.75 mg/kg dose-dependently attenuated PCP-induced sniffing and head weaving. Morphine showed a tendency to suppress PCP-induced turning and backpedalling, but not significantly. Morphine alone did not produce any stereotyped behaviors in the dose range used.

DISCUSSION

We have shown that opioid agonists such as morphine and enkephalin analogs enhance the pharmacological effects of PCP in mice [8, 22–24]. In addition, the combination with enkephalinase inhibitors, thiorphan + bestatin, produces a naloxone-reversible increase in PCP-induced turning and sniffing in rats [10]. Verebey *et al.* [35], however, have reported that methadone antagonizes PCP-induced stereotypy in rats. Although PCP interacts at opioid receptor sites such as mu and sigma receptors [36,38], there are few reports that PCP-induced stereotypy is concerned with sigma and/or mu opioid receptors. Therefore, in the present work, we have tried to examine whether SKF 10,047 as a sigma opioid agonist can enhance PCP-induced stereotypy and whether morphine also affects PCP-induced stereotypy.

SKF 10,047 alone produced PCP-like stereotyped behavior in a dose-dependent manner. Although there is some controversy regarding the relative activity of (+)- and (−)-SKF 10,047 [2, 30–31], the racemic mixture of SKF 10,047 is about one-half to one-sixth as potent as PCP [11, 17, 29]. In agreement with the findings in previous reports, the stereotypy-producing potency of SKF 10,047 (10.0 mg/kg=34.0 μmol/kg) was weak compared with that of a similar dose of PCP (7.5 mg/kg=26.8 μmol/kg).

TABLE 2

EFFECTS OF MORPHINE (MOR) ON THE PHENCYCLIDINE (PCP)-INDUCED STEREOTYPED BEHAVIORS IN RATS

Treatments (mg/kg)	N	Time after administration (min) 0–15	15–30	30–45	45–60
Sniffing					
SAL + PCP 7.5	8	2.3 ± 0.1	2.1 ± 0.1	1.8 ± 0.2	1.8 ± 0.2
MOR 1.25 + PCP 7.5	9	1.8 ± 0.1*	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
MOR 2.5 + PCP 7.5	10	1.6 ± 0.1†	1.4 ± 0.1*	1.4 ± 0.1	1.3 ± 0.1*
MOR 3.75 + PCP 7.5	9	1.1 ± 0.2†	1.2 ± 0.2†	1.2 ± 0.1*	1.2 ± 0.2*
MOR 2.5 + SAL	8	0.8 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	1.1 ± 0.2
Head weaving					
SAL + PCP 7.5	8	274.6 ± 35.3	183.3 ± 24.4	132.9 ± 25.0	105.0 ± 26.4
MOR 1.25 + PCP 7.5	9	204.3 ± 22.6	172.9 ± 17.5	120.4 ± 16.7	85.4 ± 8.7
MOR 2.5 + PCP 7.5	10	191.0 ± 23.1	196.5 ± 16.7	148.4 ± 15.8	122.1 ± 20.2
MOR 3.75 + PCP 7.5	9	106.6 ± 29.3†	119.9 ± 21.2	108.3 ± 22.4	65.7 ± 13.4
MOR 2.5 + SAL	8	0	0	0	0
Turning					
SAL + PCP 7.5	8	4.4 ± 1.5	6.9 ± 1.6	6.1 ± 2.3	7.5 ± 3.2
MOR 1.25 + PCP 7.5	9	3.4 ± 2.8	6.1 ± 3.0	5.0 ± 3.1	3.3 ± 1.9
MOR 2.5 + PCP 7.5	10	1.2 ± 0.6	2.6 ± 1.0	2.1 ± 1.1	1.3 ± 0.4
MOR 3.75 + PCP 7.5	9	3.7 ± 2.1	4.4 ± 1.6	3.7 ± 1.9	3.0 ± 1.2
MOR 2.5 + SAL	8	0	0	0	0
Backpedalling					
SAL + PCP 7.5	8	7.4 ± 1.9	14.5 ± 3.9	12.3 ± 3.6	10.0 ± 3.1
MOR 1.25 + PCP 7.5	9	6.4 ± 2.7	10.4 ± 2.8	7.0 ± 2.6	5.9 ± 2.0
MOR 2.5 + PCP 7.5	10	4.1 ± 1.4	6.8 ± 2.0	5.7 ± 2.3	4.3 ± 1.7
MOR 3.75 + PCP 7.5	9	6.1 ± 3.0	6.7 ± 2.7	6.7 ± 3.0	4.0 ± 1.8
MOR 2.5 + SAL	8	0	0	0	0

Rats were given SC saline (SAL) or MOR 15 min before the administration of PCP, IP.
*$p<0.05$, †$p<0.01$ vs. SAL + PCP 7.5 mg/kg (Mann-Whitney's U-test).

SKF 10,047 produces some psychotomimetic effects which may be mediated through the sigma receptor [19,33]. If PCP-induced stereotypy is mediated via the sigma opioid receptor, the PCP-induced stereotypy should be potentiated additively when SKF 10,047 is administered before the PCP injection. Although SKF 10,047 is a prototype sigma receptor agonist, the enhancing effect of SKF 10,047 on the PCP-induced stereotypy was not additive. SKF 10,047 potentiated synergistically the PCP-induced turning and backpedalling, but not head weaving and sniffing, Therefore, the enhancing effect of SKF 10,047 may be due to not only the sigma opioid receptor but also some other mechanisms.

Previous reports have shown that both morphine and SKF 10,047 enhance horizontal locomotor activity in rats [3, 7, 12]. However, morphine suppressed the PCP-induced sniffing and head weaving and showed a tendency to attenuate PCP-induced turning and backpedalling. Verebey *et al.* [35] have reported that methadone antagonizes PCP-induced stereotypy in rats. Furthermore, Castellani *et al.* [4] have also reported that naloxone decreased PCP-induced stereotypy in rats, and the effects of the opiate agonists (morphine, metenkephalin) on PCP-induced stereotypy were unclear but these agents clearly enhanced PCP-induced ataxia. This raises the question of whether the morphine-induced suppression of PCP-induced stereotyped behaviors in the current study may be due at least in part to the enhancing effects of morphine on PCP ataxia. However, morphine attenuated PCP-induced sniffing and head weaving, but not turning and backpedalling. In addition, previous investigators have used only a single rating scale for measuring stereotyped behavior in spite of the fact that this consists of many different components of behavior. As we have suggested, different components of stereotyped behaviors are mediated by different neuronal systems [25–27]. Indeed, PCP-induced turning and backpedalling were potentiated by SKF 10,047, but not stereotyped sniffing and head weaving. Therefore, it appears that each component of stereotypy should be assessed by using an individual rating scale to evaluate the mechanism of action of PCP in more detail.

It has been suggested that the sigma receptor is linked in some manner to the central dopaminergic system [19]. In addition, morphine also activates the dopaminergic system in the brain [1, 3, 5]. Evidence from several laboratories has demonstrated unequivocally that PCP enhances locomotor activity, stereotypy and turning behavior, which, in the rodent, are known to be strongly influenced by dopaminergic systems [14, 20–21]. In addition, the central serotonergic neuronal system is also apparently important in mediating stereotyped behavior [18, 25–27]. Therefore, interpretation of present results is difficult in view of the possible involvement of several central neuronal systems. The results of this study point to the need for further research into the effects of

opiate/opioid drugs, in combination with agents modifying other neuronal systems, on PCP-induced behaviors.

In conclusion, the present data show that SKF 10,047, a sigma agonist, markedly enhances PCP-induced turning and backpedalling, but not sniffing and head weaving, while morphine, a mu agonist, suppresses PCP-induced sniffing and head weaving, but not turning and backpedalling. It is speculated that the various components of PCP-induced stereotypy are controlled by different opioid systems and/or neuronal systems.

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