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Different Effects of Ethylketocyclazocine on Phencyclidine- and N-Allylnormetazocine-Induced Stereotyped Behaviors in Rats

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HIRAMATSU, M., T. NABESHIMA, H. FURUKAWA AND T. KAMEYAMA. *Different effect of ethylketocyclazocine on phencyclidine- and N-allylnormetazocine-induced stereotyped behaviors in rats.* PHARMACOL BIOCHEM BEHAV **28**(4) 489–494, 1987.—The effects of ethylketocyclazocine (EKC) on the stereotyped behaviors induced by intraperitoneal injection of phencyclidine (PCP) or N-allylnormetazocine (SKF 10,047) were examined. EKC markedly antagonized PCP-induced stereotyped behaviors such as sniffing, head-weaving, turning and backpedalling. On the other hand, EKC failed to antagonize SKF 10,047-induced stereotyped behaviors, which are PCP-like stereotyped behaviors, except sniffing and head-weaving at 0–15 min after the SKF 10,047 injection. PCP-induced turning and backpedalling were potentiated by pretreatment with SKF 10,047, while PCP-induced sniffing and head-weaving were not. EKC failed to affect the enhancing effect of SKF 10,047 on PCP-induced turning and backpedalling. These results suggest that part of the PCP- and SKF 10,047-induced stereotypy may be mediated by different neuronal mechanisms.

Ethylketocyclazocine (EKC) Kappa receptor Phencyclidine (PCP) N-allylnormetazocine (SKF 10,047) Stereotyped behavior

PHENCYCLIDINE (PCP, "angel dust") was first used as a general anesthetic in clinical trials in 1958. However, since it caused postoperative delirium and hallucinations, its use with humans was discontinued [4]. PCP and some of its analogs have appeared as street drugs during the last decade. Administration of PCP to rats induces a complex syndrome of behaviors such as hyperactivity, stereotypy and ataxia [3, 5, 34, 40] and it has been demonstrated that these behaviors are mediated via various neuronal systems [3, 5–8, 15, 18–28].

In studies utilizing the spinal dog, the similarity between the single dose profiles of PCP and N-allylnormetazocine (SKF 10,047) has been reported [38,39]. In addition, several studies have shown specific receptor sites for PCP in brain [29,41] and it has been suggested that sigma opiate receptors and PCP receptors may be the same [45]. Furthermore, the psychotomimetic effects of PCP appear to be mediated by sigma opiate receptors and/or unique PCP receptors, and the effects of opiates such as SKF 10,047 are also produced through PCP/sigma receptors [1, 6, 30]. SKF 10,047 generalizes the effect of PCP in drug-discrimination test [9, 31, 32]. However, Tam *et al.* [36,37] have recently suggested that the previously reported PCP binding sites are different from the (+)-[^{3}H]SKF 10,047 binding sites. This finding has raised additional questions concerning the pharmacological relationship between these two drugs.

It is well known that many opiate drugs interact at multiple receptor sites [16]. The range of neuropharmacological actions of a particular opioid ligand may be indicated by its various potencies when interacting with mu, delta, kappa and sigma receptors [45]. For example, previous reports suggest that SKF 10,047 has not only sigma agonistic activity, but also mu and kappa antagonistic activity [10,32]. Tam [35] has suggested that the highly sedative effect of ethylketocyclazocine (EKC), a kappa opiate agonist, could mask the observable sigma type behavioral responses in animals. If PCP binding sites were different from the SKF 10,047 binding sites, the effects of EKC on PCP- and SKF 10,047-induced behavioral stimulating effects might be different.

Therefore, our purpose in the present study was to investigate whether the mechanisms of action of PCP and SKF 10,047 for producing stereotypy were similar or not by com-

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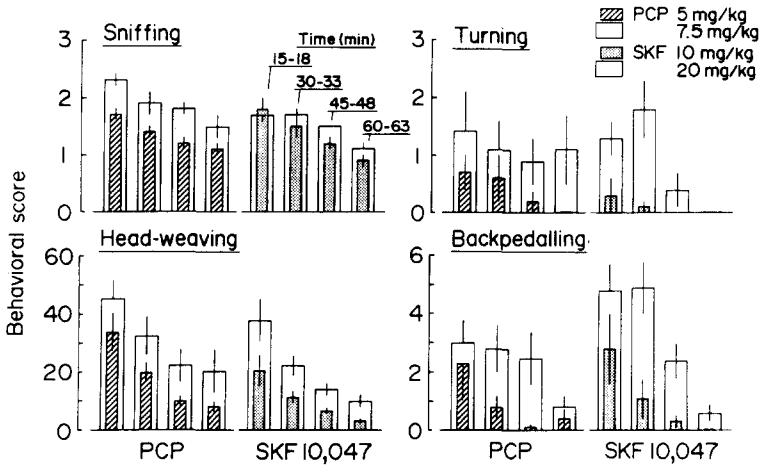

FIG. 1. Comparison of stereotyped behaviors induced by phencyclidine (PCP) and N-allylnormetazocine (SKF 10,047) in rats. Stereotyped behaviors were observed during a 3-min period at 15, 30, 45 and 60 min after the injection of test drugs. Values are the mean±S.E.M. of 7–9 animals.

paring the effect of EKC on PCP- and SKF 10,047-produced stereotypy.

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 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 us, identified by NMR and IR), N-allylnormetazocine-HCl (SKF 10,047; NIDA), ethylketocyclazocine methanesulfonate (EKC; Sterling Winthrop). PCP and SKF 10,047 were dissolved in 0.9% NaCl solution. EKC was dissolved in distilled water with a small amount of lactic acid, and sodium bicarbonate was used to bring the pH of the solution up to about 4. Control experiments were performed by the injection of 0.9% NaCl solution instead of drug solutions. Drugs were injected in a volume of 2 ml/kg body weight. PCP (7.5 mg/kg) and SKF 10,047 (10 mg/kg) were administered (IP) 15 min after treatment with EKC (4 mg/kg, SC). In the next experiments, PCP (5 or 7.5 mg/kg) was administered (IP) 21 and 15 min after EKC (2 or 4 mg/kg, SC) and SKF 10,047 (10 mg/kg, SC) treatment, respectively. Doses of drugs were based on previous experiments [22,23]. Doses of these drugs were expressed in terms of the above-mentioned salts.

Measurement of Stereotyped Behaviors in Rats

To evaluate PCP- or SKF 10,047-induced stereotyped behaviors, the behavioral scoring system developed by us [25] was employed and behavioral scores were recorded for four periods (1 time-period=3 min or 15 min) as follows: sniffing (0: absent, 1: occasional, 2: frequent, 3: constant); backpedalling (the number of times the animal made back-

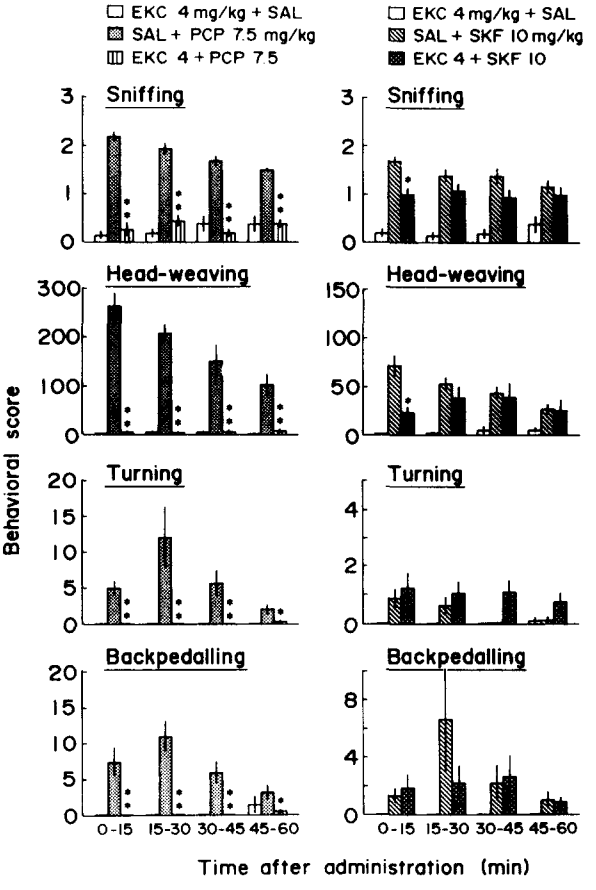

FIG. 2. Effects of ethylketocyclazocine (EKC) on the PCP- or SKF 10,047 (SKF)-induced stereotyped behaviors in rats. EKC (4 mg/kg) was administered SC 15 min before the PCP (7.5 mg/kg) or SKF (10 mg/kg) injection. Each bar is the mean±S.E.M. of 7–9 animals. $*p<0.05$, $**p<0.01$ vs. SAL + PCP or SAL + SKF (Mann-Whitney U-test).

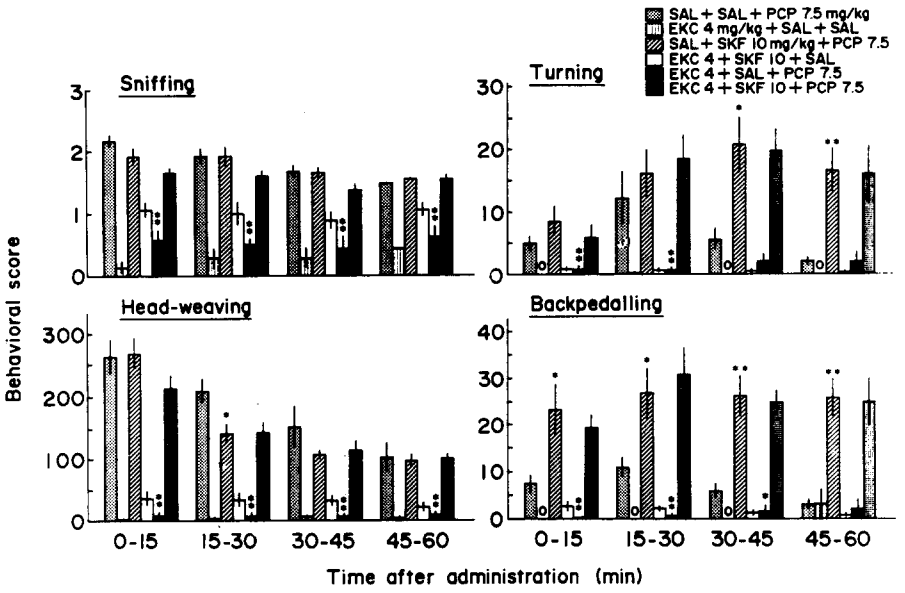

FIG. 3. Effects of ethylketocyclazocine (EKC 4 mg/kg) on the stereotyped behaviors induced by PCP (7.5 mg/kg) in combination with SKF 10,047. EKC (4 mg/kg) and SKF 10,047 (SKF 10 mg/kg) were administered SC 21 and 15 min before the PCP (7.5 mg/kg) injection, respectively. Each bar is the mean±S.E.M. of 7–9 animals. *$p<0.05$, **$p<0.01$ vs. SAL + SAL + PCP (Mann-Whitney U-test).

ward 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 360° within a relatively small area). The PCP- or SKF 10,047-induced stereotyped behaviors were observed in a cage with dimensions of 30×35×17 cm. Rating of behavior was made by one of the authors who was blind to the treatments that the animals had received. The experiments were conducted between 10:00 a.m. and 6:00 p.m. in a quiet laboratory.

Analysis of Data

Comparisons of three or more treatments were made using the Kruskal-Wallis test and where tests were positive, post-hoc comparisons of selected pairs of groups were made using the two-tailed Mann-Whitney U-test.

RESULTS

Comparison of Stereotyped Behaviors Induced by PCP and SKF 10,047 in Rats

Gross observation of behavioral changes in Wistar rats treated with PCP indicated hyperactivity, ataxia and some stereotyped behaviors consisting of sniffing, turning, head-weaving and backpedalling, and these effects were dose-dependent [22]. SKF 10,047, acting as a sigma receptor agonist, also produced hyperactivity (data not shown) and PCP-like stereotyped behaviors (Fig. 1). SKF 10,047-induced stereotypy was also dose-dependent. The higher dose of SKF 10,047 (20 mg/kg) produced the greater intensity of stereotypy than the 5 mg/kg dose and in the case of backpedalling the intensity was even greater than 7.5 mg/kg dose of PCP (Fig. 1).

Effects of Pretreatment With Ethylketocyclazocine on PCP- or SKF 10,047-Induced Stereotyped Behaviors

As shown in Fig. 2, all of the PCP- (7.5 mg/kg) induced stereotyped behaviors indicated in the present study were completely antagonized by pretreatment with EKC (4 mg/kg) at almost all observation periods. On the other hand, SKF 10,047- (10 mg/kg) induced turning and backpedalling were not antagonized by EKC (4 mg/kg). SKF 10,047-induced sniffing and head-weaving were significantly antagonized by EKC at 0–15 min after the SKF 10,047 injection (first observation period). However, after this period, the antagonizing effects of EKC were not observed. The antagonistic effects of EKC on SKF 10,047-induced stereotyped behaviors were weak compared with those on PCP-induced stereotypy (Fig. 2). EKC alone did not produce stereotypy at all observation periods (Fig. 2).

In previous experiments, we have found that the behavioral scores of PCP-induced turning and backpedalling are significantly increased when SKF 10,047 (10 mg/kg) is injected before the PCP (5 and 7.5 mg/kg) injection [22]. In following experiments, therefore, we used the doses of PCP (5 and 7.5 mg/kg) and SKF 10,047 (10 mg/kg) to evaluate whether the increase in the intensity of PCP-induced stereotyped behaviors produced by SKF 10,047 was antagonized by EKC.

Effects of Ethylketocyclazocine on the Stereotyped Behaviors Induced by PCP in Combination With SKF 10,047

Frequency and duration of turning and backpedalling induced by PCP (5 and 7.5 mg/kg) were significantly increased by pretreatment with SKF 10,047 (10 mg/kg) (Figs. 3 and 4). However, the pretreatment with SKF 10,047 failed to potentiate PCP-induced sniffing and head-weaving. On the con-

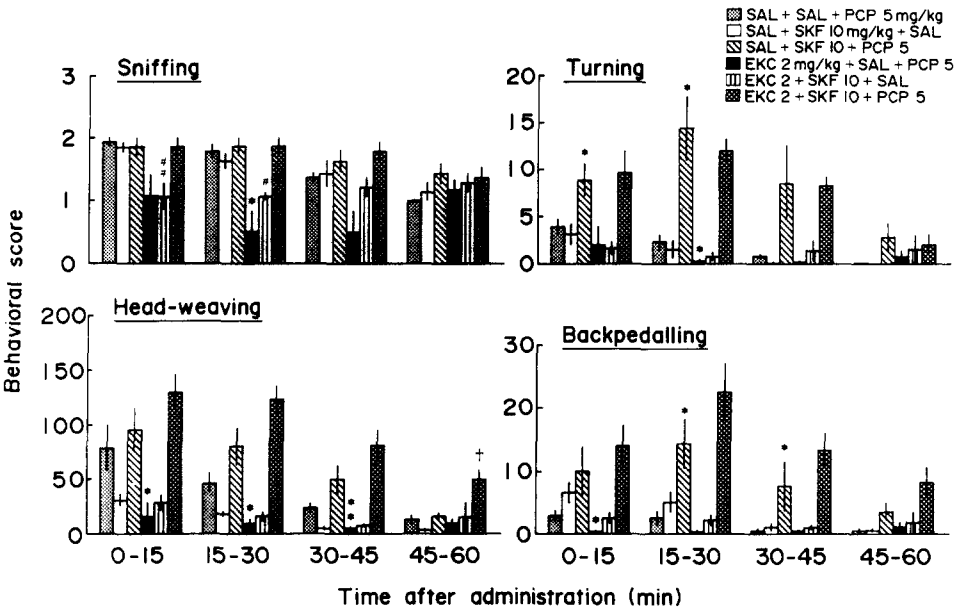

FIG. 4. Effects of ethylketocyclazocine (EKC 2 mg/kg) on the stereotyped behaviors induced by PCP (5 mg/kg) in combination with SKF 10,047. EKC (2 mg/kg) and SKF 10,047 (SKF 10 mg/kg) were administered SC 21 and 15 min before the PCP (5 mg/kg) injection, respectively. Each bar is the mean±S.E.M. of 7–9 animals. $^{*}p<0.05$, $^{**}p<0.01$ vs. SAL + SAL + PCP; $\#p<0.05$, $\#\#p<0.01$ vs. SAL + SKF + SAL; $\dagger p<0.01$ vs. SAL + SKF + PCP (Mann-Whitney U-test).

trary, PCP- (7.5 mg/kg) induced head-weaving was antagonized by SKF 10,047 but not PCP- (5 mg/kg) induced head-weaving at 15–30 min after the PCP injection (Figs. 3 and 4). Interestingly, although EKC was able to completely suppress PCP-induced turning and backpedalling, the increase in the intensity of PCP-induced turning and backpedalling produced by SKF 10,047 was not affected by pretreatment with EKC. In addition, the pretreatment with EKC antagonized PCP-induced sniffing and head-weaving (Figs. 3 and 4) and SKF 10,047-induced sniffing (Fig. 4), but EKC unaffected or enhanced (SKF 10,047 + PCP)-induced sniffing and/or head-weaving (Figs. 3 and 4).

DISCUSSION

SKF 10,047, which is considered to be a prototypic sigma opiate receptor agonist [16], has been determined to be pharmacologically very similar to PCP. In the chronic spinal dog, the single-dose profile of the two drugs is virtually indistinguishable [38,39]. SKF 10,047 produces discriminative stimuli in the rat which are generalized to those of PCP [9, 31, 32]. Also, the dose response curves for the two drugs for producing ataxia on the rotarod are parallel. Furthermore, SKF 10,047 displaces specifically [^{3}H]PCP-binding [19]. In man, SKF 10,047, as well as cyclazocine and other drugs considered to have sigma-receptor activity [16], produces a broad spectrum of effects which includes tiredness, drunkenness and psychotomimetic phenomena [11,13]. Thus, in man, PCP and drugs with sigma-receptor activity appear to produce many similar effects. Therefore, PCP and SKF 10,047 have been demonstrated to produce similar spectra of action in a variety of situations.

In the present study, SKF 10,047 alone produced PCP-like stereotyped behaviors in a dose-dependent manner (Fig. 1) consistent with previous reports [6,22]. Although there is some controversy regarding the relative activity of (+)- and (−)-SKF 10,047 [1], with a (+) isomer that has activity like that of PCP and a (−) isomer that probably has activity like that of EKC, the racemic mixture of SKF 10,047 is about one-half to one-sixth as potent as PCP [17,31]. In agreement with previous reports, the potency of SKF 10,047 (10 mg/kg=34.0 μmol/kg) to produce stereotypy was weak compared with a similar dose of PCP (7.5 mg/kg=26.8 μmol/kg). Very recently, Greenberg and Segal [6] have reported that PCP and SKF 10,047 appear to exert many of their effects on unconditioned behavior through common mechanisms, including interaction with sigma receptors. However, our results indicated that SKF 10,047 potentiated the intensity of PCP-induced turning and backpedalling more than the sum of their behavioral responses. Therefore, the enhancing effects of SKF 10,047 may be due to not only sigma receptors but also some other mechanisms.

In our present results, EKC antagonized PCP-induced hyperactivity and stereotyped behaviors. If the mechanisms of actions of PCP and SKF 10,047 are the same, the stereotypy produced by SKF 10,047 should also be antagonized by EKC pretreatment. However, SKF 10,047-induced stereotyped behaviors were not antagonized effectively by pretreatment with EKC in contrast with PCP-induced stereotypy. Furthermore, the enhancing effects of SKF 10,047 on PCP-induced turning and backpedalling also were not antagonized by EKC. These results suggest that PCP- and SKF 10,047-induced stereotyped behaviors are not mediated via only common mechanisms of action.

PCP binding sites [29, 41, 44] have been identified as accounting for the pharmacological action of PCP and its derivatives. It has been proposed that the sigma (SKF 10,047) binding sites are the same as the PCP binding sites, since both SKF 10,047 and PCP produce psychotomimetic effect and bind to the PCP binding sites [45]. The finding that PCP

binds to the (+)-[^{3}H]SKF 10,047 binding site with similar affinity may account for some of the similar pharmacological properties of PCP and SKF 10,047. However, Tam [36] has suggested that the PCP binding sites are different from the (+)-[^{3}H]SKF 10,047 binding sites. The reasons are: (1) [^{3}H]PCP binding [44] but not (+)-[^{3}H]SKF 10,047 binding is decreased in the presence of sodium ions [36]; (2) the two binding sites have different drug selectivity; (3) the PCP binding sites show low affinity and little stereoselectivity towards SKF 10,047 and EKC, whereas these drugs are highly stereoselective towards the (+)-[^{3}H]SKF 10,047 binding sites; and (4) the regional distribution of (+)-[^{3}H]SKF 10,047 and PCP binding sites in the rat central nervous system is different [14,35].

SKF 10,047 antagonizes ketocyclazocine-induced analgesia in rats [10] and also antagonizes the EKC discriminative stimulus [32]. These data suggest that in addition to its previously known mu antagonistic activity, SKF 10,047 also has kappa antagonistic properties. Furthermore, we have shown that pretreatment with Mr 2266 (2.5 mg/kg), a selective kappa antagonist, completely antagonized the effect of EKC on PCP-induced stereotypy [23]. Therefore, another possible explanation for the results obtained in the present study could be that the kappa antagonistic activity of SKF 10,047 masks the kappa properties of EKC, and as a result EKC fails to antagonize SKF 10,047 alone- and (SKF 10,047 + PCP)-induced stereotypy. Furthermore, Tam [35] has suggested that the sedative effect of EKC could mask the sigma opiate mediated behavioral responses. Therefore, the sedative effect of EKC may mask PCP-induced sigma type behavioral responses in rats, because PCP does not appear to have kappa antagonistic activity.

Previous studies have emphasized that many of the behavioral and biochemical effects of PCP can be attributed to its indirect dopamine agonist properties [5, 12, 18, 25, 27, 33, 34], and that an enhancement of the dopaminergic system is important for producing PCP-induced stereotypy [5, 12, 18, 25, 27]. An opiate agonist/antagonist, cyclazocine, which also produces PCP-like stereotypy, increases the levels of striatal DOPAC and HVA [2]. Although EKC alone does not alter the striatal dopamine metabolism in the rat [43], pretreatment with EKC can antagonize the cyclazocine-induced increase of dopamine turnover [42]. Furthermore, Wood *et al.* [43] have suggested that the mu_2 receptor is responsible for the regulation of nigrostriatal dopaminergic neurones and that EKC is a specific mu_2 receptor antagonist. Taken together, it is possible to speculate that EKC antagonizes the PCP-induced increase of dopamine turnover, as a result PCP-induced stereotypy is antagonized.

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