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Cross-Sensitization Between Phencyclidine and (−) But Not (+)Pentazocine

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XU, X. AND E. F. DOMINO. *Cross sensitization between phencyclidine and (−) but not (+)pentazocine.* PHARMACOL BIOCHEM BEHAV **56**(2) 205–210, 1997.—Repeated administration of psychomotor stimulants such as amphetamine and cocaine, and psychotomimetics such as phencyclidine, produce progressively enhanced behavioral effects, a phenomenon known as behavioral sensitization. Little is known about the effects of repeated treatment with *sigma* ligands on locomotor activity. The present research determined the psychomotor stimulant effects of the *sigma* ligand (+)pentazocine and its enantiomer; and investigated whether reciprocal cross-sensitization occurs between them and PCP-induced locomotor activity and ambulation. Adult female Sprague–Dawley rats were used. Total locomotor activity and ambulation were assessed with an automated photoelectric system. Acute (+) or (−)pentazocine given IP produced slight but insignificant locomotor stimulant effects. Repeated administration of (+)pentazocine failed to produce behavioral sensitization. However, four repeated injections of (−)pentazocine or PCP produced behavioral sensitization. (−)Pentazocine sensitized rats showed cross-sensitization to PCP-induced locomotion and ambulation. Furthermore, PCP sensitized rats showed cross-sensitization to (−)pentazocine-induced locomotion and ambulation. These findings suggest that (+) and (−)pentazocine act at different receptor sites. (−)Pentazocine is more similar to PCP in producing locomotor stimulant effects. **Copyright © 1997 Elsevier Science Inc.**

Pentazocine Phencyclidine (PCP) Reverse tolerance Behavioral sensitization Locomotor activity Ambulation

ACUTE administration of phencyclidine (PCP) has been shown to produce increases in locomotion, sniffing, repetitive head movements, mouth movements, etc. Chronic daily administration of PCP produces progressively enhanced behavioral stimulant effects, a phenomenon known as sensitization (19,20). Behavioral sensitization is known as an animal model of psychosis (15). Investigating the neural bases of the psychotomimetic effects of PCP may shed some light on the neural basis of psychosis. PCP exerts its effects through several neural mechanisms. It inhibits dopamine (DA) reuptake (11,12), has anticholinergic properties (7,13), affects brain norepinephrine (NE) and serotonin (5-HT; 10), and interacts with sigma (14) and the *N*-methyl-D-aspartate (NMDA) receptors (1,6). PCP may cause behavioral sensitization through any or all of these neural mechanisms. Drugs interacting with DA, sigma, and NMDA receptors have been shown to produce behavioral sensitization (8,10,17,18,20).

Although chronic daily injection of amphetamine (AMPH), a DA agonist, sensitizes animals to the locomotor stimulant effects of PCP, daily PCP treatment does not sensitize animals to a challenge injection of AMPH (8). The asymmetric cross-sensitization between PCP and AMPH suggests significant differences in the mechanisms underlying the effects of chronic PCP and AMPH. Similarly, MK-801, a noncompetitive antagonist of NMDA receptors, sensitizes rats; they show cross-sensitization to PCP. However, PCP sensitized animals do not show cross-sensitization to MK-801 (20). The asymmetric cross-sensitization between PCP and MK-801 suggests that PCP sensitization involves more than simple NMDA receptor blockade. Interestingly, a reciprocal cross-sensitization between PCP and SKF-10,047 (NANM), a PCP as well as sigma ligand, has been observed (9,10). These findings suggest that the neural basis of the psychotomimetic effects of PCP may be the result of its interaction with sigma receptors.

The present study investigated the locomotor stimulant effects of (+)pentazocine, a more potent and selective *sigma*1 ligand that has negligible affinity for PCP receptors, and its enantiomer (−)pentazocine, a nondiscriminant *sigma*1 and *sigma*2 ligand (3). Most importantly, this study also investigated the possible reciprocal cross-sensitization between PCP

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and pentazocine enantiomer-induced locomotor activity and ambulation.

EXPERIMENTAL PROCEDURES

Subjects

Adult female Sprague–Dawley rats, weighing 200–250 g, were allowed at least one week of acclimatization to the animal facilities. During this time, as well as during the subsequent experimental period, the rats were housed two or three per cage with unlimited access to food and water in a rodent room with constant temperature, humidity, and a 12 h light-dark cycle (0700-1900 light).

Apparatus

The locomotor activity of each animal was measured with the Digiscan "Micro" system consisting of four mounting frames and one analyzer (Omnitech Electronics, Columbus, OH 43228). A mounting frame contained two parallel panels, one photocell panel with 16 infrared light beams spaced 2.54 cm apart, and one light beam detector panel. Each rat was placed in a transparent plexiglas cage (46 cm × 24 cm × 18 cm) within a mounting frame located in a sound dampened chamber. The Digiscan system detected total locomotor activity by counting light beam interruptions. Ambulation is defined as interruptions of consecutive light beams caused by the animal moving from one location to another. Thus, ambulation is separate from the total locomotor activity which also contains repetitive interruptions of the same light beams produced by stereotyped movements. Data were automatically recorded and processed by the analyzer, and further transferred to and stored on a Macintosh IIsi computer.

Drugs

PCP (National Institute on Drug Abuse, Rockville, MD 20857) was dissolved in a dilute HCl and saline (0.9 % NaCl) solution. The drug was then neutralized with NaOH to give a final pH of approximately 6.4. (+) and (−)Pentazocine were dissolved in saline. The two enantiomers were obtained through the kindness of Dr. S.W. Tam, Dupont Merck Pharmaceutical Company, Wilmington, DE 19880-0400. All drugs were given IP

Experiment 1. Psychomotor Stimulant Effects of a Single Dose of (+) and (−)Pentazocine

This experiment investigated the possible psychomotor stimulant effects of a single injection of (+) and (−)pentazocine. Rats were randomly divided into seven groups. Groups were injected IP with either saline, one dose of (+)pentazocine (10, 17.8, or 32 mg/kg), or one dose of (−)pentazocine (10, 17.8, or 32 mg/kg). Total locomotor activity and ambulation were assessed immediately following injections. The animals' activity was monitored continuously for the next 120 min. Data were accumulated in 10 min blocks throughout the 120 min period.

Results

Acute administration of (+)pentazocine produced slight changes in total locomotor activity and ambulation (see Fig. 1a). The dose of 10 mg/kg (+)pentazocine produced a slight decrease in both total locomotor activity and ambulation, while the 17.8 and 32 mg/kg doses produced slight increases.

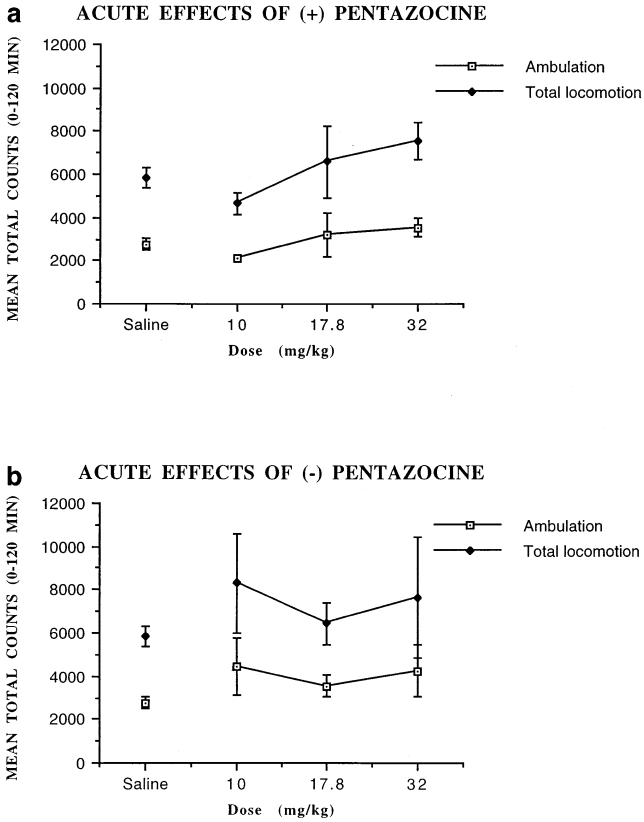

FIG. 1. Total locomotor activity and ambulation of rats treated with single doses of either (+)pentazocine (a) or (−)pentazocine (b). Each point represents the mean total counts in 120 min ± SE for 3 to 12 rats.

Acute administration of (−)pentazocine produced increases in total locomotor activity and ambulation (Fig. 1b). However, the increases were not dose-related. A one-way MANOVA with univarite F-tests was used to evaluate the differences in total locomotor activity and in ambulation between the seven groups. The one-way MANOVA revealed no significant drug effects on total locomotor activity [$F(6, 32) = 0.8815, p < 0.5$] nor on ambulation [$F(6, 32) = 1.3571, p < 0.5$].

Experiment 2. Effects of Repeated Administration of (+) or (−)Pentazocine

Experiment 2a. Repeated Administration of (+)Pentazocine

Although Experiment 1 showed that an acute single dose of (+)pentazocine did not produce significant locomotor stimulant effects, the data also showed slight increases in locomotor activity produced by 17.8 and 32 mg/kg of (+)pentazocine. Thus, the present experiment investigated whether repeated injections of 17.8 and 32 mg/kg (+)pentazocine produced progressively increased locomotor activity. Rats were randomly divided into four groups. Groups 1 and 2 received a daily IP injection of either saline or 17.8 mg/kg(+)pentazocine for four days. Groups 3 and 4 received repeated injections of saline or 32 mg/kg (+)pentazocine four days apart for a total of four injections. Total locomotor activity and ambulation were assessed immediately following each injection. The animals' activity was monitored continuously for the next 120 min.

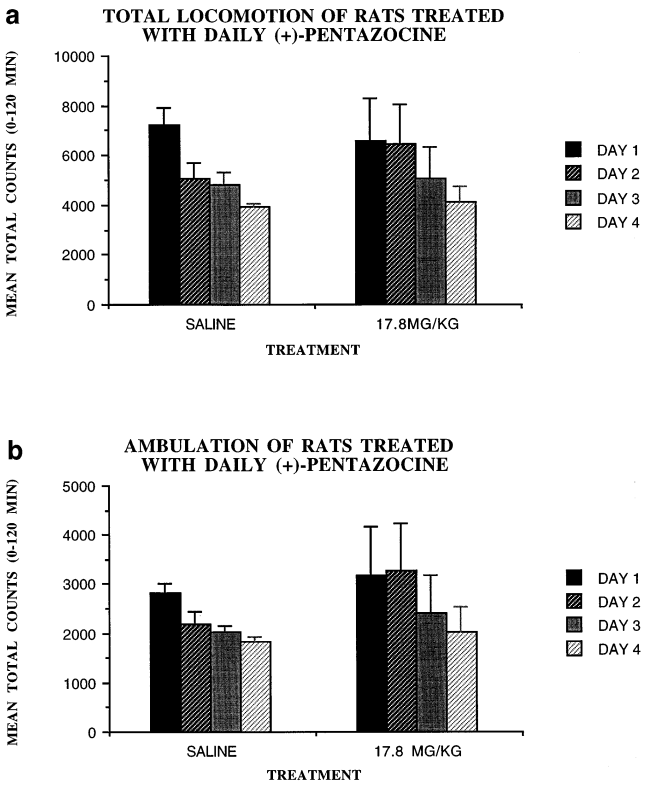

FIG. 2. Total locomotor (a) and ambulatory (b) activity of rats treated with (+)pentazocine over 4 consecutive days. Each bar represents the mean total activity counts in 120 min ± SE for 3 to 6 rats.

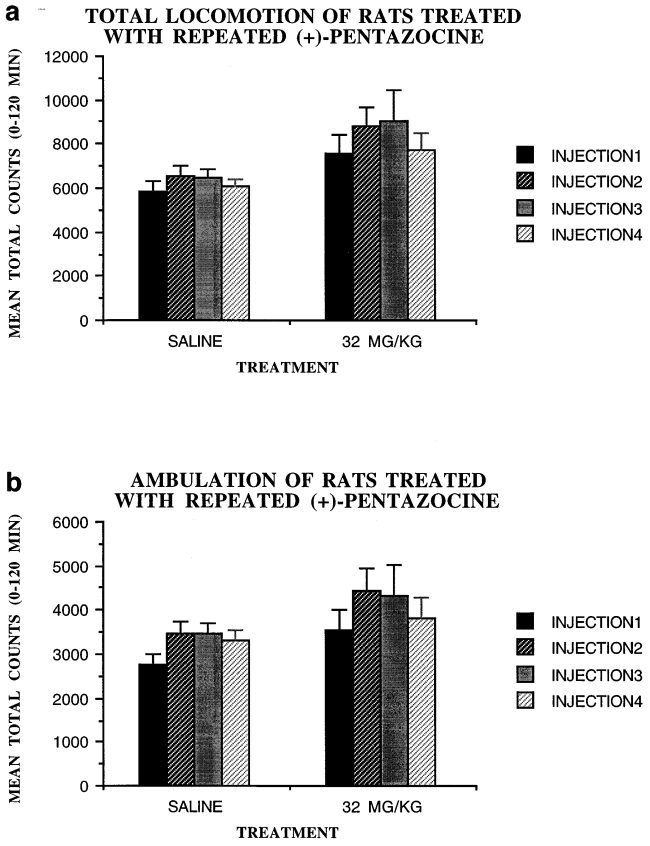

FIG. 3. Total locomotor (a) and ambulatory (b) activity of rats treated with (+)pentazocine 4 days apart. Each bar represents the mean total activity counts in 120 min ± SE for 6 to 12 rats.

Data were accumulated in 10 min blocks throughout the 120 min period.

Results

Repeated injections of (+)pentazocine did not produce any significant change in total locomotor activity and ambulation over time whether the injection was daily or four days apart. Daily administration of 17.8 mg/kg (+)pentazocine produced decreases in total locomotor activity (Fig. 2a) and in ambulation (Fig. 2b) as did daily saline injections. Repeated injections of 32 mg/kg (+)pentazocine four days apart produced slight increases in total locomotor activity (Fig. 3a) and in ambulation (Fig. 3b). However, these increases were not statistically significant compared with respective Day 1 levels.

Experiment 2b. Repeated Administration of (−)Pentazocine

Experiment 2a showed that (+)pentazocine did not produce behavioral sensitization. However, Experiment 2a suggested that when repeated injections were four days apart, the drug produced a slight increase in total locomotor activity and ambulation. The present experiment employed a moderate dose of 17.8 mg/kg (−)pentazocine to investigate whether (−)pentazocine produced behavioral sensitization. The injections were made four days apart for a total of four injections. Total locomotor activity and ambulation were assessed immediately following each injection. The animals' activity was monitored continuously for the next 120 min. Data were accumulated in 10 min blocks throughout the 120 min period. Data from Group 3 in Experiment 2a were used as saline controls.

Results

A two way ANOVA with one between factor (saline/(−)pentazocine) and one within factor (Injection 1/ Injection 4) on total locomotor activity (Fig. 4a) indicated significant effects of treatment [$F(1, 19) = 7.355$, $p < 0.01$], injection [$F(1, 19) = 6.529$, $p < 0.05$], and interaction [$F(1, 19) = 5.129$, $p < 0.05$]. Further correlated t-tests showed while repeated saline injections did not change total locomotor activity, repeated injections of 17.8 mg/kg (−)pentazocine produced a significant increase in total locomotor activity [$t(8) = 4.737$, $p < 0.05$].

Another two way ANOVA with one between factor and one within factor on ambulation (Fig. 4b) indicated significant effects of treatment [$F(1, 19) = 11.076$, $p < 0.01$] and injection [$F(1, 19) = 10.103$, $p < 0.01$], but not interaction [$F(1, 19) = 4.153$, $p > 0.05$]. Further correlated t-tests revealed while repeated saline injections did not produce significant change in ambulation, repeated injections of 17.8 mg/kg (−)pentazocine produced a significant increase in ambulation [$t(8) = 5.562$, $p < 0.05$].

Experiment 3. Effects of Repeated (−)Pentazocine and PCP: Cross-Sensitization

This experiment investigated whether (−)pentazocine and PCP showed cross-sensitization. Because acute 1 mg/kg of

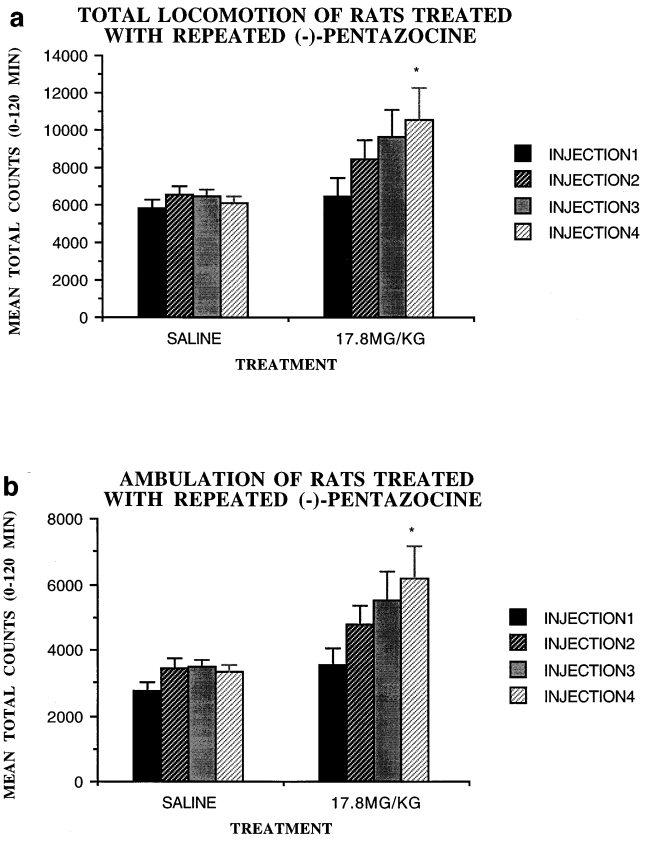

FIG. 4. Total locomotor (a) and ambulatory (b) activity of rats treated with (−)pentazocine 4 days apart. Each bar represents the mean total activity counts in 120 min ± SE for 9 to 12 rats. $*p < 0.05$ compared with Day 1 level.

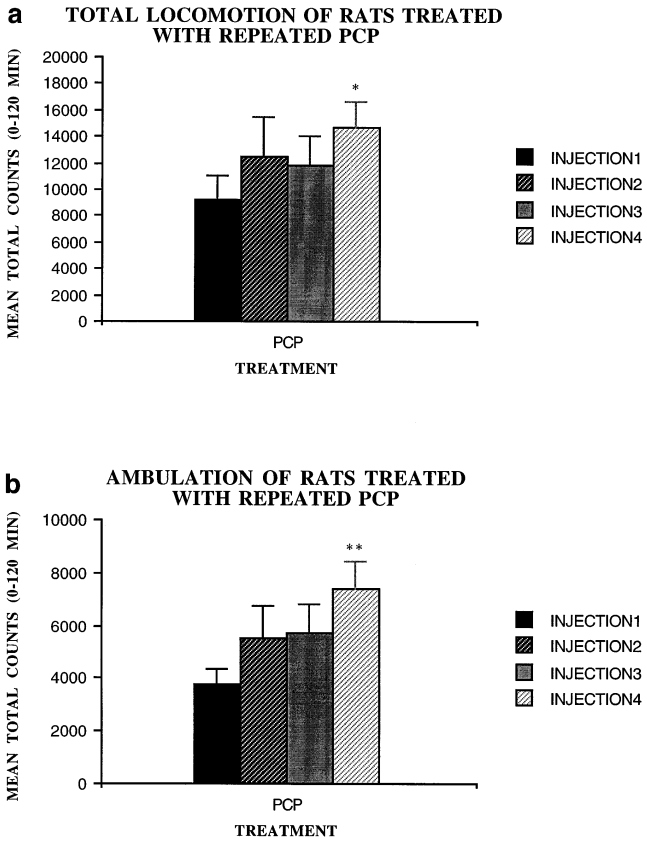

FIG. 5. Total locomotor (a) and ambulatory (b) activity of rats treated with PCP 4 days apart. Each bar represents the mean total activity counts in 120 min ± SE for 6 rats. $*p < 0.05$ and $**p < 0.01$ compared with Day 1 level.

PCP and 17.8 mg/kg of (−)pentazocine produced the same level of psychomotor stimulant effects, these doses were used to study the possible reciprocal cross-sensitization of the two drugs. Rats were randomly assigned into three groups. Groups received repeated injections of either saline, PCP (1 mg/kg), or (−)pentazocine (17.8 mg/kg) four days apart for a total of four injections. On Day 20, half of the chronic saline-treated rats received PCP and the other half received (−)pentazocine. Chronic PCP-treated rats received (−)pentazocine while chronic (−)pentazocine-treated rats received PCP. Activity was assessed immediately following each injection, as described in Experiment 2.

Results

Consistent with previous findings (3, 15, 18, 19), repeated administration of PCP increased the locomotor responses to the drug. The difference in total locomotor activity between the first and fourth injections of PCP was subjected to a correlated t-test, which indicated a statistically significant increase [$t(5) = 7.516, p < 0.05$; Fig. 5a]. The difference in ambulation between the first and fourth injections of PCP also showed a statistically significant increase [$t(5) = 13.81$, $p < 0.01$; Fig. 5b]. Furthermore, reciprocal cross-sensitization between PCP and (−)pentazocine induced ambulation (Fig. 6a) and total locomotor activity (Fig. 6b) occurred. The PCP-induced ambulation and total locomotor activity were significantly enhanced after four repeated (−)pentazocine injections when compared to those after four repeated saline injections [$t(19) = 8.4$, $p < 0.01$ for ambulation; $t(19) = 5.006$, $p < 0.05$ for total locomotor activity]. The (−)pentazocine-induced ambulation and total locomotor activity were also significantly enhanced after four repeated PCP injections [$t(17) = 10.414$, $p < 0.01$ for ambulation; $t(17) = 7.951$, $p < 0.01$ for total locomotor activity].

DISCUSSION

Both (+) and (−)pentazocine produced insignificant locomotor stimulant effects following acute single injections in doses ranging from 10 to 32 mg/kg, IP Repeated injections of the high-affinity *sigma*1 ligand (+)pentazocine failed to produce behavioral sensitization. However, repeated injections of the nonselective *sigma*1 and *sigma*2 ligand (−)pentazocine produced progressively enhanced locomotor activity. Furthermore, reciprocal cross-sensitization occurred between PCP and (−)pentazocine induced locomotor activity.

It has been shown that treatment with (+)pentazocine does not induce any obvious overt behaviors (2). The fact that acute administration of (+)pentazocine did not produce significant changes in locomotor activity in the present study confirms this earlier finding. Chronic constant-dose treatment with pentazocine lactate, a mixture of (+) and (−)pentazocine, produces a considerable increase in locomotor activity over the initial acute response (5). Behavioral sensitization produced by repeated treatment of (−)pentazocine in our study suggests

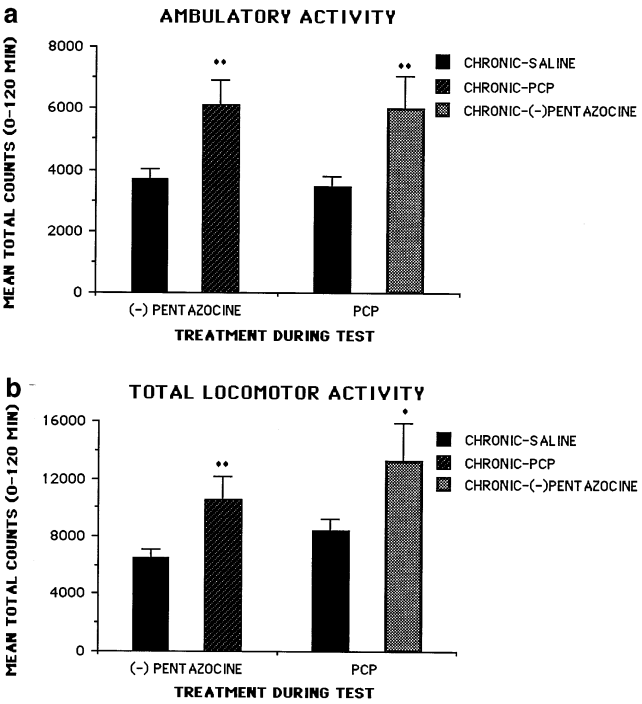

FIG. 6. Phencyclidine and (−)pentazocine induced ambulatory (a) and total locomotor (b) activity after chronic pretreatment with saline, phencyclidine or (−)pentazocine respectively. Each bar represents the mean total activity counts in 120 min ± SE for 6–15 rats. $*p < 0.05$ and $**p < 0.01$ compared with activity of chronic-saline rats.

that behavioral sensitization produced by pentazocine lactate may be due to the effects of (−)pentazocine.

The present study measuring ambulation and total locomotor activity confirms previous reports that chronic administration of PCP results in an enhanced locomotor stimulant effect or sensitization (4,9,10,16). In the present study, (−)pentazocine sensitized rats showed cross-sensitization to PCP, and PCP-sensitized rats showed cross-sensitization to (−)pentazocine. These results suggest that there are important similarities in the neuronal mechanisms underlying repeated administration of both drugs.

Reciprocal cross-sensitization of locomotion occurs between PCP and racemic as well as (+) and (−) NANM (9,10). The (+) and (−) NANM enantiomers are ligands for multiple receptors. (±)NANM, in particular, has moderate to high affinity for *sigma*1 and low to moderate affinity for *sigma*2 receptors (14). Thus it is possible that some types of sigma receptors play a major role in the development of PCP sensitization. However, (+)pentazocine, which has high affinity for *sigma*1 receptors and low affinity for *sigma*2 receptors, produces neither significant locomotor stimulant effects nor behavioral sensitization. In contrast, (−)pentazocine, which has low to moderate affinity for *sigma*1 and *sigma*2 receptors and is a kappa opioid agonist, showed the reciprocal cross-sensitization with PCP. Therefore, the *sigma*2 receptors may be involved in behavioral sensitization of PCP, but not *sigma*1 receptors. Both (±)NANM and (−)pentazocine have dual affinities for the PCP receptor and the sigma receptors (3). Since PCP and MK-801 showed an asymmetric cross-sensitization, behavioral sensitization of PCP may not be totally medicated by PCP sites associated with NMDA receptors. (+)Pentazocine has high affinity for *sigma*1 receptors and negligible affinity for PCP receptors (3). Therefore, (+)pentazocine was thought to be ideal to study the involvement of sigma receptors in PCP behavioral sensitization. Because (+)pentazocine did not produce behavioral sensitization, further studies with a more selective *sigma*2 ligand may shed light on the mechanisms of PCP behavioral sensitization.

In sum, acute administration of either (+) or (−)pentazocine produced insignificant locomotor stimulant effects in doses ranging from 10 to 32 mg/kg, IP Repeated injections of (+)pentazocine did not produce behavioral sensitization, whereas repeated injections of (−)pentazocine produced behavioral sensitization. Moreover, reciprocal cross-sensitization occurred between PCP and (−) pentazocine induced locomotion and ambulation.

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