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Reinforcing Properties of Fencamfamine: Involvement of Dopamine and Opioid Receptors

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PLANETA, C. S., M. L. AIZENSTEIN AND R. DeLUCIA. *Reinforcing properties of fencamfamine: Involvement of dopamine and opioid receptors.* PHARMACOL BIOCHEM BEHAV **50**(1) 35-40, 1995.—Fencamfamine (FCF) is a psychostimulant classified as an indirect dopamine agonist. The conditioning place preference (CPP) paradigm was used to investigate the reinforcing properties of FCF. After initial preferences had been determined, animals were conditioned with FCF (1.75, 3.5, or 7.0 mg/kg; IP). Only at the dose of 3.5 mg/kg FCF produced a significant place preference. Pretreatment with SCH23390 (0.05 mg/kg; SC) or naloxone (1.0 mg/kg; SC) 10 min before FCF (3.5 mg/kg; IP) blocked both FCF-induced hyperactivity and CPP. Pretreatment with metoclopramide (10.0 mg/kg; IP) or pimozide (1.0 mg/kg, IP), respectively, 30 min or 4 h before FCF (3.5 mg/kg; IP), which blocked the FCF-induced locomotor activity, failed to influence place conditioning produced by FCF. In conclusion, the present study suggests that dopamine D_1 and opioid receptors are related to FCF reinforcing effect, while dopamine D_2 subtype receptor was ineffective in modifying FCF-induced CPP.

Fencamfamine Place conditioning Reinforcement Dopamine receptors Opioid receptors

FENCAMFAMINE (FCF), 2-ethylamino-3-phenylnorcamphane, is a psychostimulant drug used to be market as an anti-fatigue medication (25). The pharmacological profile of FCF is similar to amphetamine and cocaine. Behavioral studies showed that FCF increases locomotion, rearing, and sniffing and in high doses; it also induces stereotyped behavior (2,24). Neurochemical studies in vivo demonstrated that FCF, like cocaine and amphetamine, increases dopamine levels in both nucleus caudate-putamen and accumbens (18).

In humans, it has been demonstrated that FCF is a psychostimulant with few circulatory effects (11). Abuse of FCF has been reported among students and athletes (7,10,34). Some report that FCF in the USA is a cocaine substitute in the illicit drug market (12,27).

There are some evidence suggesting that FCF could act as a positive reinforcer. In this way, it was demonstrated that FCF induces auto-administration in monkeys and dogs (9,26). In addition, FCF also substitutes for cocaine in drug discrimination paradigms (27).

The conditioning place preference (CPP) is a method extensively used to assess reinforcing actions of drugs. It has been demonstrated that human's abused substances usually induce CPP. For example, CPP has been demonstrated for cocaine, amphetamine, morphine, and ethanol (1,3,13,28-30,32).

The involvement of the dopaminergic mesocorticolimbic system in the rewarding properties of drugs has been clearly demonstrated (8,14). However, only a few studies have investigated the relative participation of dopamine receptors' subtypes on these effects. Nevertheless, it has been shown that both SCH23390 and metoclopramide blocked the amphetamine-induced CPP, suggesting that the reinforcing action of this psychostimulant depend on both dopamine receptors (15). Moreover, pretreatment with SCH23390 blocked the acquisition of CPP by different classes of drugs, such as morphine, diazepam, and nicotine (1,20).

The participation of opioid systems in mediating the reinforcing effects of psychostimulants has been confirmed

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by the fact that naloxone blocks amphetamine-induced CPP (33).

According to Wise and Bozarth (36), the common property of a wide range of addictive substances is their ability to cause psychomotor activation. Moreover, the increase in locomotion induced by drugs could be used as predictive of their abuse liability, and they suggested that both psychomotor activation and the reinforcing effect result from the stimulation of the dopamine mesocorticolimbic system (36).

The present study has been carried out with two main objectives: a) evaluate the reinforcing properties of FCF using the CPP paradigm, b) assess the role of D_1, D_2 and μ receptors on the reinforcing effect of FCF. For this purpose SCH23390, metoclopramide, pimozide, and naloxone were administrated before FCF and conditioning sessions. The degree of dopamine receptors' blockade was assessed by the attenuation of FCF-induced hyperactivity in the open field after the pretreatment with the selective antagonists.

METHOD

Subjects

Seven days before the experiments the rats were housed individually in wire mesh cages 15 (width) × 30 (length) × 19 (height) cm. Food and water were freely available.

Behavioral tests were conducted during the light period.

Drugs

Fencamfamine hydrochloride (Merck), SCH23390 hydrochloride (Research Biochemicals), metoclopramide hydrochloride (Laboratorio Americano de Farmacoterapia), and naloxone hydrochloride (Sigma) were dissolved in 0.9% saline and administrated in a volume of 1 ml/kg. All doses are expressed as weight of salt. Pimozide (Janssen Pharmaceutica) was dissolved in boiling tartaric acid and cooled to room temperature before injection.

Open-Field Studies

The open field was constructed as described by Broadhurst (5). Hand-operated counters were used to score locomotor frequency (number of times the animals crossed one quadrant with the four paws). Separate groups of rats (n = 7) were treated with either saline, SCH23390 (0.05 mg/kg, SC), metoclopramide (10.0 mg/kg, SC), pimozide (1.0 mg/kg, IP), or naloxone (1.0 mg/kg, SC) before the injection of FCF (3.5 mg/kg, IP) or saline. The intervals between antagonists and FCF or saline were 10 min for SCH23390 and naloxone, 30 min for metoclopramide, and 4 h for pimozide.

Twenty minutes after FCF or saline injections, rats were placed on the center area of the open field and locomotor activity was recorded for 5 min.

Conditioning Studies

The apparatus used to evaluate the reinforcing properties of FCF consisted of a rectangular shuttle box [90 (length) × 15 (width) × 22 (height) cm] divided in two equal-sized compartments by a guillotine door. One compartment had white walls and grid floor, and the other a black wall and smooth floor. The experimental procedure consisted of three phases:

1. Preconditioning—in this phase, the animals were placed in one side of the shuttle box (initial compartment) for 3 consecutive days and each rat was allowed to explore the two compartments for 15 min. The time spent in each compartment was recorded on the third day.
2. Conditioning phase—during 6 consecutive days the animals were injected with FCF or saline on alternate days and confined for 30 min, respectively, to the white or black compartment. Control groups received saline in both compartments.
3. Postconditioning (test)—on the seventh day doors were opened and the rats were placed in the initial compartment and allowed to freely move inside the apparatus. The time spent in each compartment was recorded for 15 min in a drug-free situation.

To assess FCF reinforcing properties, animals were randomly assigned to groups of seven rats each and were injected (IP) with FCF (1.75, 3.5, or 7.0 mg/kg).

To evaluate the participation of dopamine and opioid receptors on FCF-induced CPP, following the preconditioning phase, separate groups of rats (n = 7) were treated with either saline, SCH23390 (0.05 mg/kg, SC), metoclopramide (10.0 mg/kg, SC), pimozide (1.0 mg/kg, IP), or naloxone (1.0 mg/kg, SC) before the injection of FCF (3.5 mg/kg, IP). The intervals between antagonists and FCF administration were 10 min for SCH23390 and naloxone, 30 min for metoclopramide, and 4 h for pimozide.

Six additional groups (n = 7) were included to determine the effects of the antagonists alone on place conditioning. Thus, on drug-pairing days, saline, SCH23390, metoclopramide, pimozide, or naloxone were injected before saline and conditioning sessions. The intervals, doses, and administration routes were the same described above.

Statistical Analyses

Data from CPP experiments were analyzed by two-way ANOVA with repeated measures on one factor. Time spent in the drug-paired side in pre- and postconditioning phase served as the dependent variable with repeated measures. Drug treatment groups served as the independent variable. Data from open-field experiments were analyzed by Kruskal–Wallis' test.

RESULTS

Fencamfamine Place Conditioning

Figure 1 summarizes the mean time (±SEM) spent in the drug-paired compartment during the pre- and postconditioning phases for animals treated with FCF (1.75, 3.5, or 7.0 mg/kg, IP).

Two-way ANOVA (phase and group factors) with repeated measure on one factor (phase) revealed significant interaction between phase and dose, $F(3, 24) = 9.28$, $p < 0.01$. Thus, the phase factor could be analyzed independently for each treatment group (35).

Comparing post- to preconditioning phase, the time spent in the drug-paired compartment was significant higher for the group injected with 3.5 mg/kg of FCF, $F(1, 24) = 26.2$, $p < 0.01$. None of the other doses showed statistically significant changes considering the phase factor.

Control groups showed a decrease in the time spent in the white compartment, but it was not statistically significant, $F(1, 24) = 1.82$).

Open-Field Experiments

As depicted in Fig. 2A–D, Kruskal–Wallis' test showed statistically significant differences in the three experimental de-

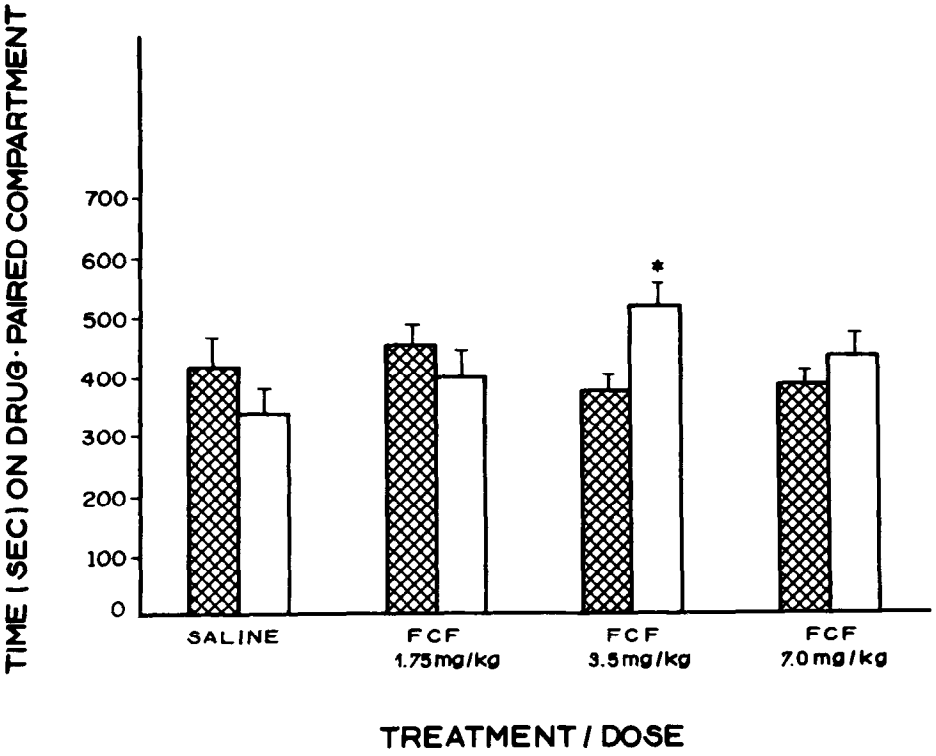

FIG. 1. Time (s) spent on the drug-paired compartment during the preconditioning phase and after conditioning with FCF (1.75, 3.5, or 7.0 mg/kg). Histograms represent mean ± SEM of rats (n = 7) observed during 15 min in the shuttle box. *$p < 0.05$ pre vs. postconditioning: crosshatched column—preconditioning; open column—postconditioning.

signs carried out to evaluate the effect of pretreatment with dopamine and opiod antagonists on FCF-induced locomotor activity. The comparison of pairs of means showed that treatment with FCF plus saline (3.5 mg/kg; IP) significantly increased locomotor activity as compared to saline plus saline groups in the three experiments. The dopamine antagonists SCH23390, metoclopramide, and pimozide significantly reduced locomotion, while naloxone alone had no effects on this behavioral parameter. The pretreatment with SCH23390, metoclopramide, pimozide, or naloxone decreased the FCF-induced locomotor activity.

Participation of Dopamine and Opioid Receptors on FCF-Induced Conditioning Place Preference

As observed above two-way ANOVA (phase and group factors) with one repeated measure on one factor (phase) revealed significant interaction between phase and treatment group, $F(3, 24) = 6.45, p < 0.01$, for SCH23390, $F(3, 24) = 5.65, p < 0.05$, for metoclopramide, pimozide, $F(3, 24) = 4.89, p < 0.01$, and $F(3, 24) = 7.65, p < 0.01$, for naloxone. Thus, the phase factor could be analyzed independently for each treatment group.

When SCH23390 was directly tested for place conditioning it did not modify the time spent in the drug-paired compartment, $F(1, 24) = 0.87$, NS. FCF-treated animals spent a significantly higher amount of time in the postconditioning phase compared to preconditioning, $F(1, 24) = 9.1, p < 0.01$. The group that received SCH23390 plus FCF showed no difference in the time spent in the drug-paired side after conditioning trials, $F(1, 24) = 3.8$, NS (Fig. 3A). Thus, the reinforcing effects of FCF were not detected in animals pretreated with D_1 antagonist.

Metoclopramide plus saline did not change place preference after conditioning trials, $F(1, 24) = 0.02$, NS. While both groups saline plus FCF, $F(1,24) = 19.1, p < 0.01$, and metoclopramide plus FCF, $F(1,24) = 17.4, p < 0.01$, showed a significant increase in the time spent in the drug-paired compartment (Fig. 3B). Thus, the pretreatment with this D_2 antagonist did not affect FCF-induced CPP.

Pimozide plus saline did not change place preference after conditioning trials, $F(1, 24) = 0.04$, NS. While both groups saline plus FCF, $F(1, 24) = 4.7, p < 0.05$, and pimozide plus FCF, $F(1, 24) = 9.5, p < 0.01$, showed a significant increase in the time spent in the drug-paired compartment (Fig. 3C). Thus, the pretreatment with this D_2 antagonist did not affect FCF-induced CPP.

Naloxone plus saline significantly reduced the time spent on the drug-paired side, $F(1, 24) = 8.20, p < 0.01$, comparing the post- to preconditioning phase. The group that received naloxone plus FCF showed no difference in the time spent in the drug-paired side after conditioning trials, $F(1, 24) = 0.42$, NS (Fig. 3D). Thus, the reinforcing effects of FCF were not detected in animals pretreated with the opioid antagonist.

DISCUSSION

The present experiments, by using the place-conditioning technique, showed that FCF can produce significant place

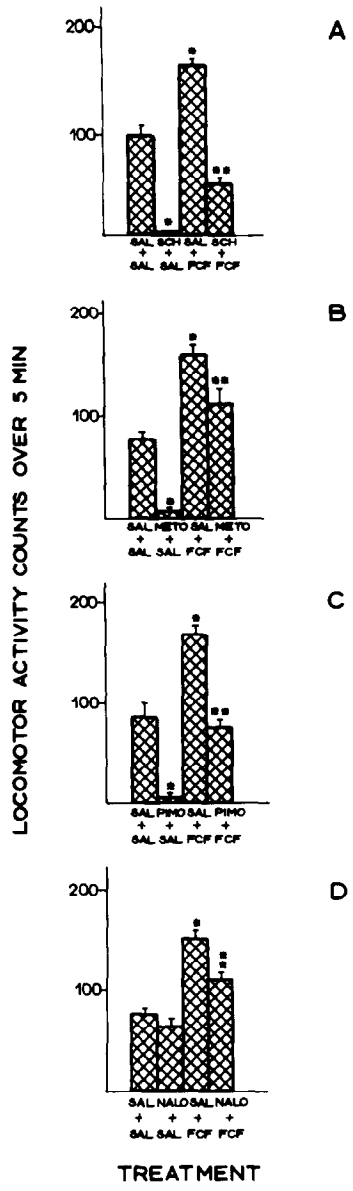

FIG. 2. Effect of antagonists' pretreatment (A) SCH23390; (B) metoclopramide; (C) pimozide, and (D) naloxome on FCF-induced locomotor activity. Histograms represent mean ± SEM of rats (n = 7) observed in the open field during 5 min. *$p < 0.05$ compared to sal + sal; **$p < 0.05$ compared to sal + FCF post hoc comparisons after Kruskall-Wallis.

preference in rats at the dose of 3.5 mg/kg. As it has been previously demonstrated with self-administration studies in monkeys and dogs (9,26), our data confirm that FCF acts as a positive reinforcer.

It has been hypothesized that addictive substances such as psychostimulants and opioids derive their reinforcing effects by stimulating the dopaminergic mesocorticolimbic system that also mediates psychomotor activity (36). Thus, to evaluate the involvement of dopamine receptors' subtypes in FCF-induced CPP, animals were pretreated with selective D_1 or D_2 antagonists, SCH23390, metoclopramide, and pimozide, in doses that blocked the increase in locomotor activity induced by FCF (3.5 mg/kg). As observed in the open-field experiments SCH23390 (0.05 mg/kg), metoclopramide (10.0 mg/kg), and pimozide (1.0 mg/kg) were effective in blocking the hyperactivity induced by FCF.

The results of the present experiment show that SCH23390 blocked both hyperactivity and CPP induced by FCF. Otherwise, the pretreatment with metoclopramide or pimozide did not modify FCF-induced CPP, although the same doses of these D_2 antagonists blocked FCF-induced locomotion.

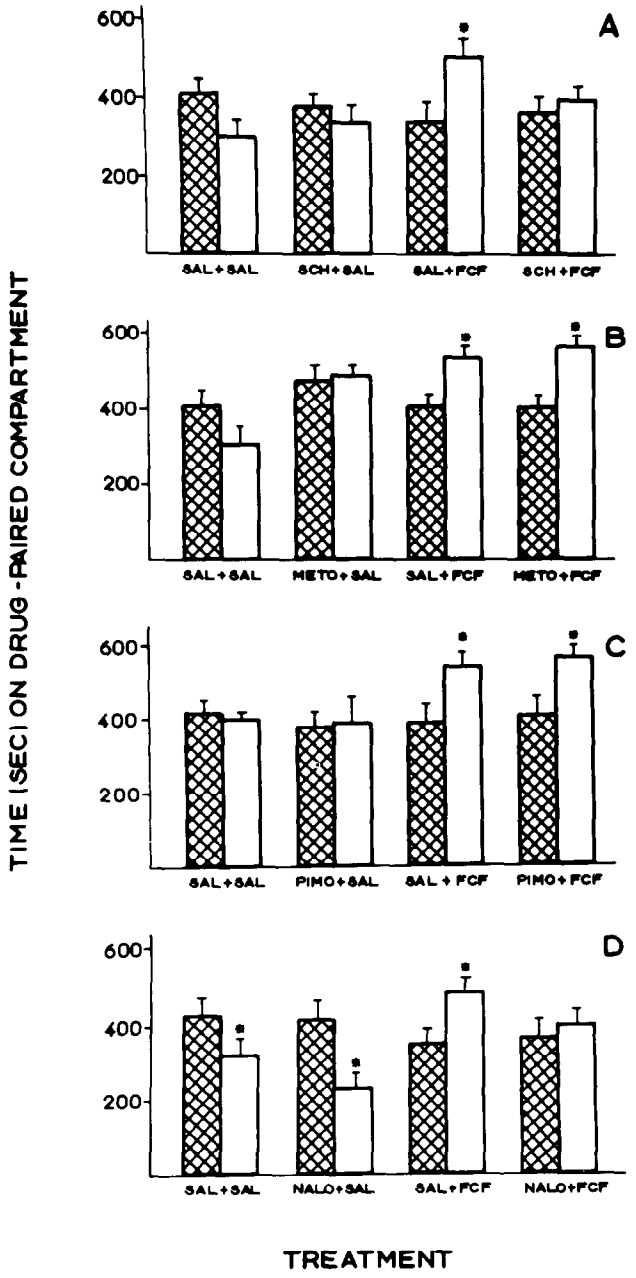

FIG. 3. Effect of antagonists' pretreatment (A) SCH23390; (B) metoclopramide, (C) pimozide, and (D) naloxone on FCF-induced conditioning place preference. Histograms represent mean ± SEM of rats (n = 7) observed in the shuttle box during 15 min. *p = 0.05 pre vs. postconditioning: crosshatched column—preconditioning; open column—postconditioning.

Considering the effect of antagonists apart, neither D_1 nor D_2 antagonist changed place preference, suggesting that SCH23390, metoclopramide, and pimozide are neutral reinforcers in CPP paradigms. Similar results with SCH23390 were found by others that used the D_1 antagonist in the same dose and route of administration (1,20). On the other hand, results with metoclopramide are a matter of controversy. While, some authors' results (29) are in the same directions as ours, others show that metoclopramide produced a significant increase in the amount of time spent on the drug-paired compartment, suggesting the establishment of a place conditioning (15). Moreover, place conditioning has not been demonstrated for pimozide or other D_2 selective or nonselective dopamine antagonists such as haloperidol, sulpiride, and flupentixol (4,20-22,29,31).

The observation that metoclopramide and pimozide blocked FCF-induced hyperactivity in the open field but did not prevented acquisition of place preference could suggest that the degree of dopaminergic activation by FCF could be different producing hyperactivity or reinforcement. Although this interpretation is based on the effect of only one dose of the D_2 antagonists, similar results were obtained by other authors with haloperidol pretreatment (22,23), which is a nonselective dopamine antagonist, but acts preferentially at D_2 receptors (6). In fact, haloperidol has been observed to block amphetamine- but not methylphenidate or nomifensine-induced CPP, although the doses of the antagonist were effective in blocking the hyperactivity produced by both stimulants (22,23). In addition, pretreatment with the D_2 antagonists (−)-sulpiride or spiperone were ineffective in modifying the reinforcing effect of opioid agonists as measured by CPP (29).

The results described above suggest that the reinforcing effect of FCF depend on the activation of dopamine D_1 receptors. Likewise, it has been demonstrated that pretreatment with SCH23390 (0.05 mg/kg; SC) blocked the establishment of place conditioning induced by different addictive drugs, such as amphetamine, morphine, nicotine, and diazepam (1,20). In fact, attempts have been made to identify a common mechanism to explain drug reinforcement. An interesting hypothesis consider that the dopamine receptor subtype D_1 could be critical for both stimulants and opioid reinforcing effects (20,28). It is important noticing that some authors suggest a more general role for dopamine on conditioned behavior. For example, Acquas et al. (1) showed that pretreatment with SCH23390 blocked motivational properties of both rewarding and aversive drugs, suggesting that dopaminergic transmission mediates motivational effects independently of their aversive or rewarding property.

Another convergent idea is that opioid receptors mediate the reinforcing effects of stimulant drugs (33). In this way, it was of interest to evaluate the participation of these receptors in FCF-induced CPP.

As in the previous experiments, we firsts studied the effect of opioid receptor antagonism on FCF-induced hyperactivity. Our results showed that naloxone, at the dose of 1.0 mg/kg, blocked the increase in locomotor activity induced by FCF. Corroborating this finding is the observation that naloxone also blocked cocaine-induce hyperactivity (16). Because naloxone per se had no effect on locomotion, the blockade of FCF-induced hyperactivity is probably related to the specific action of this opioid antagonist on dopaminergic systems (17,19).

Although naloxone pretreatment (1.0 mg/kg) prevented acquisition of place conditioning by FCF, the former drug also produced a significant decrease in time spent on the drug-paired side, suggesting that naloxone induces place aversion. However, in our experimental conditions, the control group also showed a significant decrease in time spent in the drug-paired side. Other data showed that the pretreatment with naloxone blocked the amphetamine-induced CPP (33). Taken together, all these results suggest that the blockade of opioid receptors attenuate the reinforcing effects of stimulant drugs. In fact, it has been demonstrated that opioid peptides modulate mesocorticolimbic dopaminergic pathways (17,19). In this way, naloxone might prevent FCF reinforcement by blocking opiate receptors on dopamine neurons in the ventral tegmental area.

In conclusion, the present study suggests that dopamine D_1 and opioid μ receptors are related to FCF reinforcing effect, while dopamine D_2 receptor blockade was ineffective in modifying FCF-induced CPP.

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