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Morphine- and Cocaine-Induced Conditioned Place Preference: Effects of Quinpirole and Preclamol

TOOMAS KIVASTIK,[1] KATI VUORIKALLAS, T. PETTERI PIEPPONEN, ALEXANDER ZHARKOVSKY[1] AND LIISA AHTEE[2]

University of Helsinki, Department of Pharmacy, Division of Pharmacology and Toxicology, P.O. Box 56, FIN-00014 University of Helsinki, Finland

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KIVASTIK, T., K. VUORIKALLAS, T. P. PIEPPONEN, A. ZHARKOVSKY AND L. AHTEE. *Morphine- and cocaine-induced conditioned place preference: Effects of quinpirole and preclamol.* PHARMACOL BIOCHEM BEHAV **54**(2) 371-375, 1996. - The role of dopamine in opioid reward is unresolved. Furthermore, the issue is somewhat unclear regarding cocaine and the place preference paradigm. In the present study we investigated whether the drugs activating dopamine autoreceptors affect cocaine- and morphine-induced place preference in rats. Neither the dopamine D_2/D_3 receptor agonist, quinpirole (0.05 mg/kg, SC), nor the partial dopamine autoreceptor agonist, preclamol (2 or 8 mg/kg, SC), induced place conditioning by itself. Quinpirole had no significant influence on the place preference induced either by morphine (3 mg/kg, SC) or cocaine (5 mg/kg, IP). Preclamol, when given at the dose of 8 mg/kg SC, significantly attenuated the effect of cocaine but failed to modify the effect of morphine. Our results suggest that the rewarding properties of morphine involve DA-independent mechanisms whereas in the cocaine-induced reward the role of brain DA is critical. Furthermore, as regards place conditioning, we propose that the activation of DA autoreceptors is not sufficient to reliably modify the rewarding effect of cocaine.

Reward Cocaine Morphine DA autoreceptors Quinpirole Preclamol Rats Place preference

MOTIVATIONAL effects of addictive drugs have been attributed to the interaction of exogenous substances with endogenous reward pathways. A great deal of evidence suggests that the mesolimbic dopamine (DA) system could serve as a common neural substrate mediating the appetitive properties of different classes of drugs. Thus, a common feature for many addictive drugs, including opioids and psychomotor stimulants, is their ability to enhance the mesolimbic DA transmission (11).

Behaviourally relevant doses of opioids enhance both the firing of the dopaminergic neurons in the ventral tegmental area (22) and the release of DA in the nucleus accumbens (11). Several studies have demonstrated that DA receptor antagonists and lesions of dopaminergic neurons interfere with the opioid reward (2,30,32). One can find data, however, to indicate that the reinforcing actions of opioids may also involve DA-independent mechanisms. Thus, DA antagonists do not reduce the self-administration of heroin unless given in doses causing motor impairment (12). Furthermore, it has been demonstrated that selective lesions of the DA terminals in the nucleus accumbens significantly attenuate the self-administration of cocaine but not that of heroin (25).

The rewarding properties of cocaine appear to depend on the integrity of the mesolimbic DA system as measured by IV drug self-administration (26). However, the issue is somewhat unclear regarding the place conditioning paradigm because both the neuroleptic drugs and the 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens have failed to influence conditioned place preference (CPP) induced by IP cocaine (23,33). Still, the effect of either ICV- or IV-administered cocaine was blocked by pimozide (23) and haloperidol (34), respectively. In view of these data, it has been questioned

[1] Present address: University of Tartu, Department of Pharmacology, EE2400 Tartu, Estonia.
[2] To whom requests for reprints should be addressed.

whether the effect of IP cocaine truly reflects its central rewarding properties, and alternative explanations have been proposed, including local anaesthetic action of cocaine (33). Drug discrimination studies (9), though, do not support the local anaesthesia hypothesis. Furthermore, according to a recent place conditioning study (17), clozapine impairs the effect of IP-administered cocaine, and another study (14) clearly demonstrates the predominant involvement of central components in the CPP induced by IP cocaine.

The activity of the mesolimbic DA system is regulated by a negative feedback mechanism that involves DA receptors located on the DA cell itself (i.e., autoreceptors). Thus, DA and exogenous DA agonists inhibit the firing of most midbrain dopaminergic neurons by stimulating DA autoreceptors (6). DA autoreceptors exhibit pharmacological characteristics of DA D_2-like receptors (35). It has been demonstrated that D_3 receptors, known to be D_2-like, also act as autoreceptors (31). According to some recent studies, DA autoreceptors could be implicated in the rewarding and discriminative stimulus properties of cocaine (4,5).

Biochemical and behavioural investigations indicate that the selective DA D_2/D_3 receptor agonist quinpirole (LY171555) in small doses could act selectively at DA autoreceptors (36,38). Preclamol ([−]3PPP) is a partial DA autoreceptor agonist that also exhibits antagonistic properties at postsynaptic DA receptors [for extensive review see (7,8)].

The present study was devised to further clarify the role of brain DA in cocaine and morphine reward, with an emphasis on DA autoreceptors. Our idea was that drugs activating DA autoreceptors, and hence decreasing DAergic transmission, could interfere with morphine and cocaine reward. To test this hypothesis, a series of experiments was carried out, where we investigated whether quinpirole or preclamol affect cocaine- and morphine-induced place preference.

METHOD

Animals

Male Wistar rats weighing 250–400 g were used. The rats were housed in groups of four to five with food and water available ad lib, under 12 L : 12 D cycle (lights on at 0600 h). The experiments were carried out during the light phase of the cycle.

Drugs

The doses of drugs, except morphine, refer to the salt. The dose of morphine refers to the amount of the free base. All compounds were dissolved in 0.9% NaCl solution and injected in a volume 2 ml/kg. Morphine HCl (Ph. Eur. 2nd ed.) was administered SC into the neck region. Cocaine HCl (Ph. Eur. 2nd ed.) was injected IP. Quinpirole HCl (LY171555; gift of Eli Lilly & Co, Indianapolis, IN) and preclamol HCl ([−]3PPP; RBI, Natick, MO, and gift of Suomen Astra OY) were administered SC into the neck region. The doses of preclamol (2 or 8 mg/kg, SC) used were based on biochemical and behavioural studies where they were found to inhibit DA synthesis in autoreceptor models (7) and cocaine discrimination [(5); for further information about doses and pretreatment intervals see the Experimental Procedure section].

Place Preference Apparatus

An apparatus similar to that described previously (18) was used. It consisted of two square-base compartments (h 40 × 30 × 30 cm), one with white and the other with gray walls and floor. Compartments were separated by a guillotine door and were covered with a transparent Plexiglas ceiling. The apparatus was placed into a dimly lit room with masking noise provided by ventilation fan.

Experimental Procedure

Before starting the experiment the rats were acclimated to experimenter contact for 3 days by handling and weighing in the experiment room.

Each experiment consisted of three phases.

1. Preconditioning: For 3 days (days 1, 2, and 3) rats were given free access to both compartments of the apparatus for 15 min (900 s) each day. On day 3, the time spent by rats in each compartment was recorded and these values served as a baseline.
2. Conditioning was conducted for 4 days (days 4, 5, 6, and 7) and included two sessions each day. The rats were conditioned in the initially nonpreferred chamber after administration of morphine (3 mg/kg, SC) or cocaine (5 mg/kg, IP), and in the preferred one after administration of saline. An interval of 4 h separated the two sessions. The order of drug (i.e., morphine or cocaine) and saline presentation, paired with the given environment, was balanced across treatment groups. Conditioning times of 60 and 45 min were used for morphine and cocaine, respectively. Quinpirole (0.05 mg/kg, SC) was administered 5 and 10 min before morphine and cocaine, respectively. Preclamol (2 or 8 mg/kg) was given 15 min before morphine or cocaine administration. For assessing the conditioning induced by quinpirole and preclamol, separate groups of rats were administered saline immediately, and quinpirole 5 min or preclamol 15 min before placing the rat in the nonpreferred chamber.
3. Postconditioning: On day 8 no injections were given. The rats had free choice in the apparatus for 15 min and the time spent in each chamber was recorded.

Statistics

The data from each drug combination were subjected to two-factor analysis of covariance (ANCOVA) where the time spent in the drug-paired compartment during postconditioning test served as dependent variable, pretreatment (quinpirole or preclamol) and treatment (morphine or cocaine) as categorical variables, and the baseline as covariate. Where necessary, post hoc comparisons were conducted by using the contrast analysis with Bonferroni levels (i.e., the critical level 0.05 was divided by the number of the comparisons made).

RESULTS

Figure 1A shows that neither quinpirole (0.05 mg/kg) nor preclamol (2 or 8 mg/kg) induced a significant place conditioning effect.

Cocaine induced significant CPP, $F(1, 69) = 18.9$, $p < 0.01$. This effect was significantly impaired by 8 mg/kg of preclamol but was unaffected by quinpirole and preclamol at the dose 2 mg/kg (Fig. 1B). In fact, the ANCOVA revealed a nonsignificant quinpirole × cocaine interaction, $F(1, 69) = 0.44$, $p = 0.5$, whereas the preclamol × cocaine interaction was significant, $F(2, 70) = 5.1$, $p = 0.009$. Post hoc comparisons showed that there was no significant difference between the treatment groups preclamol 2 mg/kg + cocaine and saline + cocaine, whereas the difference between the groups precla-

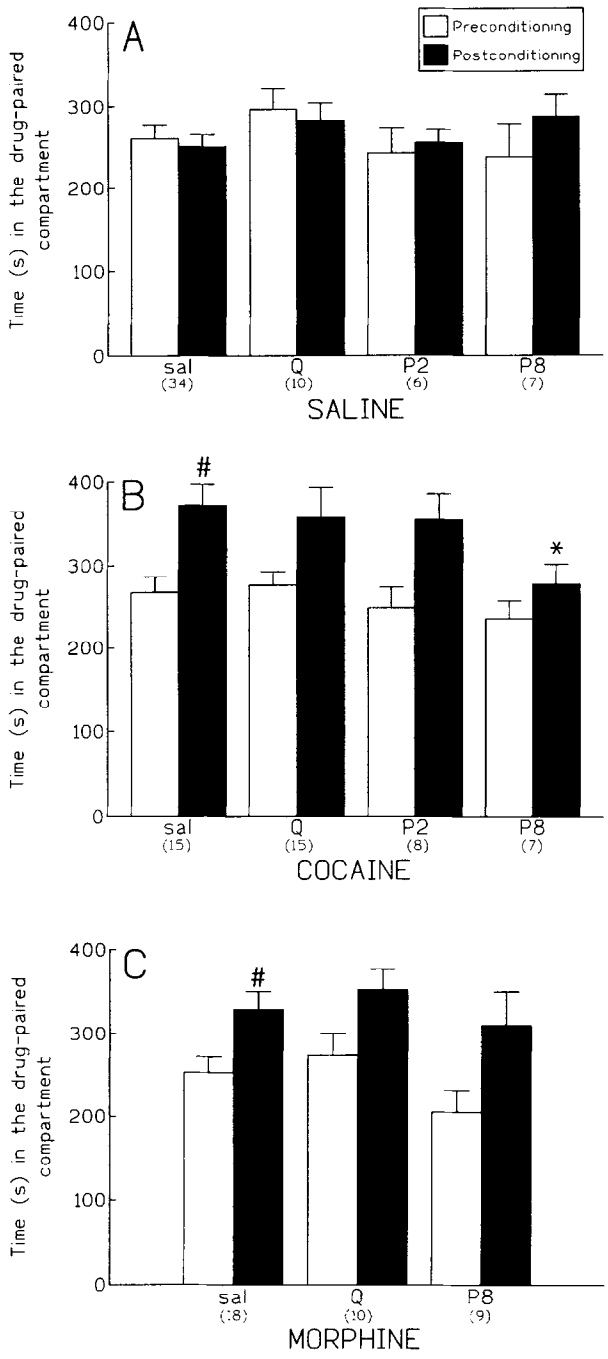

FIG. 1. Effect of quinpirole and preclamol on conditioned place preference (CPP) induced by morphine or cocaine in rats. (A) The effect of quinpirole and preclamol in saline-treated control rats. (B) The effect of drugs on CPP induced by cocaine (5 mg/kg, IP). (C) The effect of drugs on CPP induced by morphine (3 mg/kg, SC). The columns depict the mean ± SE time spent in the initially nonpreferred (i.e., drug-paired) compartment during preconditioning (open columns) and postconditioning (filled columns) tests. Abbreviations under columns indicate the pretreatment during conditioning: sal—saline, Q—quinpirole (0.05 mg/kg, SC), P2—preclamol (2 mg/kg, SC), P8—preclamol (8 mg/kg, SC). Number of animals in parentheses. #$p < 0.01$ compared with control (saline + saline) group; *$p < 0.05$ compared with saline-pretreated cocaine group (contrast analysis with Bonferroni adjustment).

mol 8 mg/kg + cocaine and saline + cocaine was significant, $F(1, 70) = 6.45, p = 0.013$.

Morphine also induced significant CPP, $F(1, 67) = 14.56$, $p < 0.01$, but neither quinpirole nor preclamol (8 mg/kg) had significant influence on this effect (Fig. 1C).

DISCUSSION

In our study conditioned place preference induced by cocaine was significantly attenuated by the partial DA autoreceptor agonist, preclamol (8 mg/kg), but not by the DA D_2/D_3 receptor agonist, quinpirole. Neither preclamol nor quinpirole significantly influenced the CPP induced by morphine. Quinpirole and preclamol by themselves had no place conditioning effect. The finding that quinpirole lacked the effect on place conditioning at a dose of 0.05 mg/kg agrees with the earlier results, indicating that quinpirole can induce CPP within the limited dose range (0.1–1.0 mg/kg), whereas smaller and larger doses are ineffective (15,37).

Our data agree with the recent results demonstrating that preclamol dose-dependently (0.625–10 mg/kg) reduces the discriminative stimulus properties of cocaine (5). However, it appears that the activation of DA autoreceptors is not sufficient to antagonize cocaine reward, because quinpirole and the smaller dose of preclamol that was shown to activate the autoreceptors (1) were ineffective. Quinpirole, acting upon DA autoreceptors, reduces the release of DA both in vivo (28) and in vitro (3), yet it does not block it entirely. It has been shown, furthermore, that only extensive lesions (>90%) with 6-OHDA could effectively reduce psychomotor stimulant reward (26,27). Martin-Iverson et al. (21), proceeding from their work with indirect DA agonists, methylphenidate and nomifensine, proposed that " . . . even a slight increase in activation of DA receptors could be sufficient to produce a rewarding effect." Such an explanation also seems to be appropriate in our case, to interpret the lack of quinpirole's effect. It is also unclear to what extent quinpirole at such a small dose (0.05 mg/kg) activates the postsynaptic DA receptors. However, the discriminative stimulus properties of 0.05 mg/kg SC of quinpirole were shown to be mediated via DA autoreceptors (38). Preclamol, besides being a partial DA autoreceptor agonist, has antagonistic properties on postsynaptic DA receptors (7,8). Therefore, the effect of the larger dose of preclamol could be due to either its postsynaptic action or to the combination of its pre- and postsynaptic actions.

A recent self-administration study (4) demonstrated that the D_3 receptor agonists quinpirole and 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetraline (7-OH-DPAT), when coadministered with cocaine (at doses that were not self-administered by themselves), reduced cocaine intake by increasing the intervals between injections without disrupting self-administration. The same effect occurs when the dose of cocaine is increased (39). Because 7-OH-DPAT did not alter self-administration of a direct DA agonist, apomorphine, the authors suggested that " . . . D_3 selective dopamine agonists may interact presynaptically to enhance cocaine's reinforcing properties." The results of our study, however, do not agree with this proposal, for quinpirole neither potentiated nor inhibited the effect of cocaine. One of the reasons for this discrepancy could be the difference in paradigms used: IV self-administration vs. CPP. As far as IV self-administration is concerned, the animals are tested under direct influence of drugs (that is not the case in CPP). Thus, besides the changes in reinforcing effects, the changes in motor behaviour may be underlying: a decrease or increase in response rate may result from an inhibition or

stimulation of motor behaviour, respectively (39). Because both 7-OH-DPAT and quinpirole in "autoreceptor-selective" doses reduce locomotor activity (10,16), their direct influence on test performance may serve as a confounding factor. However, the fact that 7-OH-DPAT did not alter self-administration of apomorphine (4) could possibly rule it out. An alternative explanation for the inconsistency in ours vs. Caine and Koob's results is that CPP and IV self-administration, due to some fundamental differences, reflect different aspects of cocaine reward (e.g., in the case of the former paradigm the acquisition phase is routinely studied whereas the latter one considers usually the maintenance). This view is further sustained by the discrepancy in results concerning clozapine's effect on cocaine self-administration and CPP (17,19).

A substantial body of evidence refers to the central role of the dopaminergic substrate in opioid reward (2,30,32). Moreover, a recent place conditioning study (29) suggests the significance of DA D_1 receptor in the nucleus accumbens [but see below and (13)]. It was also demonstrated that selective DA D_1 receptor antagonist, SCH23390, over a large dose range increases the responding for heroin, which was interpreted as a decrease in heroin reward (24). On the other hand, several studies do not agree with such a DA hypothesis (12,20,25). Thus, DA receptor antagonist, α-flupentixol, although eliminating IV self-administration of cocaine, did not reduce self-administration of heroin, unless given in doses impairing locomotor activity (12). Neither did small doses of α-flupentixol cause a compensatory increase in responding for heroin (12). Likewise, SCH23390 affects the initiation of heroin self-administration only in doses that inhibit motor behaviour as well (13). In our study preclamol, at the dose that impaired the effect of cocaine, did not affect significantly place preference induced by morphine. Hence, our data agree with the earlier reports indicating the existence of different endogenous substrates in opioid and psychomotor stimulant reward.

In conclusion, the results of the present study confirm the involvement of the central DAergic substrate in CPP induced by IP cocaine. Furthermore, our data suggest that the endogenous pathways mediating rewarding effects of morphine and cocaine differ. Rewarding properties of morphine appear to also involve DA-independent mechanisms, whereas in the case of cocaine the role of brain DA is critical. However, the role of DA autoreceptors remains fairly unclear. Thus, cocaine-induced CPP was impaired by preclamol at a dose that may have antagonistic properties at postsynaptic DA receptors, whereas a small dose of preclamol as well as quinpirole in an "autoreceptor-selective" dose lacked the effect. We propose that, as far as the place preference paradigm is concerned, the activation of DA autoreceptors is not sufficient to reliably modify the rewarding effect of cocaine.

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