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Pharmacology, Biochemistry and Behavior 75 (2003) 289–294
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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Suppression of morphine-induced conditioned place preference by *l*-12-chloroscoulerine, a novel dopamine receptor ligand

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Received 29 November 2002; received in revised form 19 March 2003; accepted 28 March 2003

Abstract

The effect of *l*-12-chloroscoulerine (*l*-CSL), a novel ligand with dual dopamine D_1 receptor agonistic and D_2 receptor antagonistic actions, on the development of morphine-induced conditioned place preference (CPP) was investigated in mice. Morphine (10 mg/kg)-induced place preference was dose dependently suppressed by coadministration of *l*-CSL (5, 10 and 20 mg/kg), which induced neither place preference nor place aversion when administered alone at a dose of 20 mg/kg. The D_1 receptor antagonist SCH23390 (0.1 mg/kg) suppressed, whereas the D_2 receptor agonist (±)-2-(*N*-phenylethyl-*N*-propyl)-amino-5-hydroxytetralin (PPHT) (0.5 mg/kg) had no influence on the development of morphine-induced place preference. However, SCH23390 (0.1 mg/kg) did not affect, whereas PPHT (0.5 mg/kg) reversed the suppressive effect of *l*-CSL on the development of morphine-induced place preference. These results indicate that *l*-CSL suppresses the development of place preference of morphine by blocking D_2 receptors.

Keywords: *l*-12-Chloroscoulerine; Morphine; SCH23390; PPHT; Dopamine receptors; Conditioned place preference

1. Introduction

It has been shown that the dopaminergic system plays a crucial role in the rewarding effect of drugs of abuse (Koob, 1992; Wise, 1998). The conditioned place preference (CPP) paradigm has been widely used as a model to study the rewarding effect of drugs of abuse (Tzschentke, 1998). Numerous studies indicate that morphine-induced CPP depends critically on the dopaminergic system. The D_1 receptors appear to play an important role in the rewarding effect of morphine because the D_1 receptor antagonist could block morphine-induced CPP (Acquas et al., 1989; Leone and Di Chiara, 1987; Manzanedo et al., 2001; Shippenberg and Hertz, 1987, 1988). However, the influence of D_2 receptors is inconsistent because the D_2 antagonists blocked morphine-induced CPP in some studies (Leone and Di Chiara, 1987; Manzanedo et al., 2001; Suzuki and Misawa, 1995), but were without effect in others (Mackey and van der Kooy, 1985; Shippenberg and Hertz, 1988). However, a suppression of the development of morphine-induced CPP in D_2 receptor knockout mice has been reported (Maldonado et al., 1997). More recently, Smith et al. (2002) reported that D_2L receptor (one isoform of the D_2 receptor) knockout mice did not develop place preference to morphine. These results suggest that D_2 receptors also play a crucial role in the rewarding effect of morphine.

l-12-Chloroscoulerine (*l*-CSL) (Fig. 1) is a novel and potent analog of tetrahydroprotoberberines (THPBs) (Chen et al., 1996a,b, 1999). THPBs include three types: non-hydroxy-THPBs, monohydroxy-THPBs and dihydroxy-THPBs. *l*-CSL is one of the dihydroxy-THPBs. Its activities are similar to that of *l*-stepholidine, a leading compound with both D_1 receptor agonistic and D_2 receptor antagonistic actions (Jin, 2001; Jin et al., 2002). The D_1 agonistic action was displayed only in postsynaptic supersensitivity after 6-OHDA lesion of the nigrostriatal dopamine system (Jin et al., 2002). In the normal state, dihydroxy-THPBs displayed D_2 antagonistic action. It has been suggested by behavioral, electrophysiological and biochemical experiments (Chen et al., 1996a,b, 1999; Zhang and Jin, 1996). Previous studies showed that *l*-tetrahydropalmatine (trade name: Rotundine), one of the nonhydroxy-THPBs, could inhibit the development of morphine-induced CPP (Jin et al., 1998) and methamphetamine-induced discrimination (Ren and Zhang,

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doi:10.1016/S0091-3057(03)00089-3

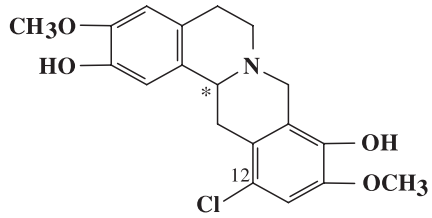

Fig. 1. Chemical structure of 12-chloroscoulerine.

2000). The present study was designed to determine the effect of *l*-CSL on the development of morphine-induced CPP in mice. The D_1 receptor antagonist SCH23390 (Iorio et al., 1983) and the D_2 receptor agonist (±)-2-(*N*-phenylethyl-*N*-propyl)-amino-5-hydroxytetralin (PPHT) (Seeman et al., 1985; Seiler et al., 1986) were used to investigate the dopaminergic mechanism of the effect of *l*-CSL.

2. Materials and methods

2.1. Animals

Male Kunming albino mice (18–22 g) were supplied by the Department of Experimental Animal, Medical Center of Fudan University, Shanghai, China. All animals were kept on a 12:12-h light–dark cycle in temperature and humidity controlled rooms. The animals were fed with standard laboratory chow and water ad libitum. All animal experiments were in compliance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Drugs

l-CSL was synthesized by the Department of Synthesis, Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. Morphine hydrochloride was purchased from Qinghai Pharmaceutical Factory, China. SCH23390 and PPHT were purchased from RBI, USA.

2.3. Conditioned place preference apparatus

The plastic apparatus similar to that described previously was used (Guo et al., 2001). It consisted of two compartments (15 × 15 × 15 cm) equal in size. One compartment was white with a textured floor and the other was black with a smooth floor. Compartments were separated by a guillotine door. The apparatus was placed in a soundproof room with ventilation and dim illumination.

2.4. Experimental procedure

The experimental procedure consisted of preconditioning, conditioning and postconditioning phases. The preconditioning phase lasted 3 days. On the first day, mice were placed in the apparatus with an open guillotine door (6 × 6 cm) allowing them to explore both compartments for 40 min. On the second and third days, the time spent in each compartment was recorded for 15 min. Under these conditions, most animals preferred the black compartment. Therefore, a biased procedure was used. The white compartment served as the drug-paired side. Only mice staying in the white compartment between 240 and 420 s were chosen for further studies.

During the conditioning phase (the fourth to eighth day), the guillotine door was closed. Mice were immediately confined 40 min to the white compartment after injection of morphine (10 mg/kg ip) and to the black compartment after saline administration. The alternate injections of morphine or saline were conducted twice daily (one for morphine and one for saline) for 5 days. The order of treatment was counterbalanced. Half of animals within a group received drugs in the morning and the other half in the afternoon.

To determine the effect of *l*-CSL on the place preference of morphine, *l*-CSL (5, 10 and 20 mg/kg sc) was administered 10 min before morphine injection. To investigate the dopaminergic mechanism of the effect of *l*-CSL on the development of morphine-induced CPP, SCH23390 (0.1 mg/kg ip) and PPHT (0.5 mg/kg ip) were administered 5 min before *l*-CSL (20 mg/kg sc). To study the effect of SCH23390 and PPHT on the place preference of morphine, SCH23390 (0.1 mg/kg ip) and PPHT (0.5 mg/kg ip) were administered 15 min before morphine. To evaluate the place conditioning effect induced by SCH23390 plus *l*-CSL and PPHT plus *l*-CSL, SHC23390 (0.1 mg/kg ip) and PPHT (0.5 mg/kg ip) were administered, respectively, 5 min before *l*-CSL (20 mg/kg sc). The place conditioning effect induced by *l*-CSL (20 mg/kg sc), SCH23390 (0.1 mg/kg ip) or PPHT (0.5 mg/kg ip) alone was also evaluated, respectively.

During the postconditioning phase (the ninth day), mice received no injections. Place conditioning was reexamined using the preconditioning phase protocol. The change in the amount of time spent in the drug-paired side during the postconditioning versus preconditioning test served as a measure of drug-induced place conditioning.

2.5. Statistics

The results were expressed as mean ± S.E.M. and were analyzed using one-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls test. Statistical analysis was performed using the computer program SPSS10.0 (SPSS, USA). The significant level was set at $P < .05$.

3. Results

3.1. Effect of l-CSL on the development of morphine-induced CPP

The time spent in the drug-paired side during pre- and postconditioning phases in the saline group was 314.8 ±

20.1 and 322.1 ± 28.3 s, respectively. Saline was ineffective in producing place conditioning. Fig. 2 shows the results of the place conditioning induced by morphine (10 mg/kg) and the effect of *l*-CSL (5, 10 and 20 mg/kg) on the development of morphine-induced CPP. Data were analyzed by one-way ANOVA. The results revealed a significant main effect of treatment [$F(5,50) = 9.469$, $P < .01$]. Post hoc comparisons using the Student–Newman–Keuls test showed that morphine induced a significant place preference effect ($P < .01$). Pretreatment with *l*-CSL suppressed the development of morphine-induced CPP in a dose-dependent manner. The suppressive effect of *l*-CSL was statistically significant at doses of 10 mg/kg ($P < .05$) and 20 mg/kg ($P < .01$), but not at 5 mg/kg ($P > .05$). *l*-CSL (20 mg/kg) by itself did not induce any place conditioning effect as compared with the saline group ($P > .05$).

3.2. Effect of SCH23390 on the suppression of the development of morphine-induced CPP by l-CSL

Fig. 3 shows the effect of *l*-CSL (20 mg/kg) in the presence or absence of SCH23390 (0.1 mg/kg) on the development of morphine (10 mg/kg)-induced CPP. One-way ANOVA indicated a significant treatment effect [$F(6,59) = 7.302$, $P < .01$]. Post hoc analysis revealed that SCH23390 alone or with *l*-CSL induced a slight but statistically insignificant place aversion as compared with the saline control group ($P > .05$). SCH23390 did not influence the suppression of *l*-CSL on the development of morphine-induced CPP ($P > .05$), whereas SCH23390 by itself inhibited the development of morphine-induced CPP ($P < .01$).

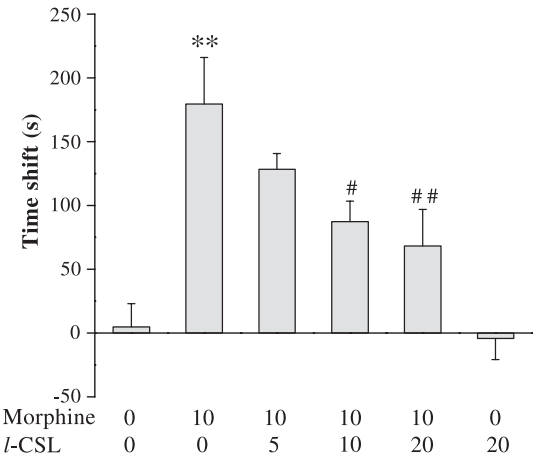

Fig. 2. Effect of *l*-CSL (5, 10 and 20 mg/kg sc) on the development of morphine (10 mg/kg ip)-induced place preference. Data were expressed as mean ± S.E.M. of the time shift (s) in the drug-paired side during postconditioning vs. preconditioning. ** $P < .01$ compared with the saline control; # $P < .05$, ## $P < .01$ compared with morphine by one-way ANOVA followed by the Student–Newman–Keuls test.

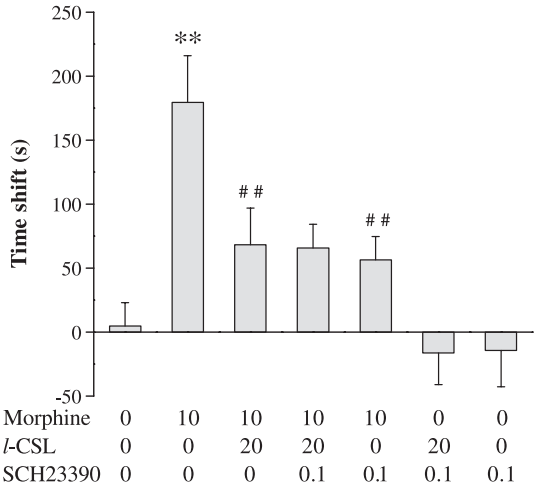

Fig. 3. Effect of SCH23390 (0.1 mg/kg ip) on the suppression of the development of morphine (10 mg/kg ip)-induced place preference by *l*-CSL (20 mg/kg sc). Data were expressed as mean ± S.E.M. of the time shift (s) in the drug-paired side during postconditioning vs. preconditioning. ** $P < .01$ compared with the saline control; ## $P < .01$ compared with morphine by one-way ANOVA followed by the Student–Newman–Keuls test.

3.3. Effect of PPHT on the suppression of the development of morphine-induced CPP by l-CSL

Fig. 4 indicates the effect of the D_2 receptor agonist PPHT (0.5 mg/kg) on the suppression of the development of morphine (10 mg/kg)-induced CPP by *l*-CSL (20 mg/kg). There was a significant overall treatment effect [$F(6,58) = 8.913$, $P < .01$]. Further post hoc analysis showed that PPHT

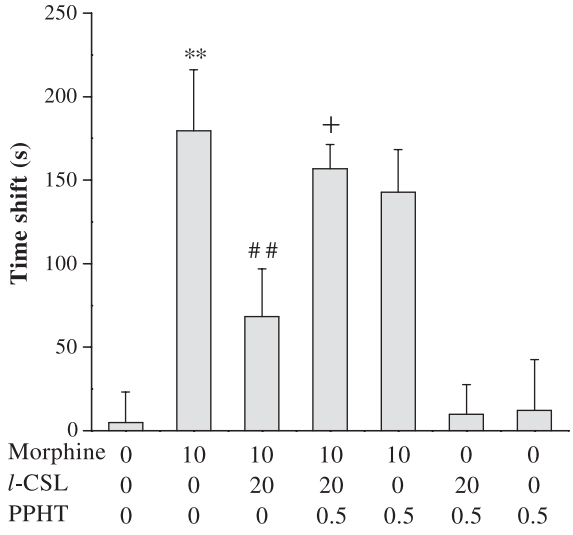

Fig. 4. Effect of PPHT (0.5 mg/kg ip) on the suppression of the development of morphine (10 mg/kg ip)-induced place preference by *l*-CSL (20 mg/kg sc). Data were expressed as mean ± S.E.M. of the time shift (s) in the drug-paired side during postconditioning vs. preconditioning. ** $P < .01$ compared with the saline control; ## $P < .01$ compared with morphine; + $P < .05$ compared with *l*-CSL plus morphine by one-way ANOVA followed by the Student–Newman–Keuls test.

alone or with *l*-CSL did not induce place preference as compared with the saline group ($P>.05$). PPHT by itself was ineffective to influence the development of morphine-induced CPP ($P>.05$), but reversed the suppressive effect of *l*-CSL on the development of morphine-induced CPP ($P<.05$).

4. Discussion

The present results showed that as previously reported (Guo et al., 2001), morphine induced significant place preference for the drug-paired side in male mice. *l*-CSL, a novel ligand with both dopamine D_1 receptor agonistic and D_2 receptor antagonistic actions, produced neither place preference nor place aversion at a high dose. However, *l*-CSL dose dependently suppressed the development of morphine-induced CPP. The D_1 receptor antagonist SCH23390 did not influence, whereas the D_2 receptor agonist PPHT reversed the suppression of the development of morphine-induced CPP by *l*-CSL. These results suggest a crucial role of D_2 receptors in the suppression of the development of morphine-induced CPP by *l*-CSL.

The CPP paradigm is considered a useful model to study the rewarding properties of drugs of abuse (Tzschentke, 1998). In the present study, a biased procedure was used because most animals preferred the black compartment under the experimental conditions. Such a procedure may affect the interpretation of data. The shift in preference to the initial nonpreferred side may be regarded as the anti-aversive property of a given drug. An unbiased design has been proposed to circumvent this problem. With morphine, however, the experiment comparing the biased and unbiased procedures has provided consistent results (Blander et al., 1984). In the place conditioning, associative learning is involved. The animals must associate the rewarding effect of drugs with environmental cues. Accordingly, the influence of the "state-dependency effect" on the observation of an effect in CPP was considered by researchers (Nomikos and Spyraki, 1988; Tzschentke and Schmidt, 1997; Laviola and Adriani, 1998; Tzschentke, 1998). Nomikos and Spyraki (1988) have tested cocaine-induced CPP in the drugged and undrugged states and found no difference. Spyraki et al. (1985), however, reported that picrotoxin-induced place aversion was state dependent. In the present study, animals were conditioned in the drugged state, but were tested for CPP in drug-free state. It cannot exclude the possibility that the blockade of the development of morphine-induced CPP was due to a state-dependency effect.

It is generally agreed that the dopaminergic system is critical in the rewarding effect of opiates. Drugs of abuse, including opiates and psychomotor stimulants, could enhance mesolimbic DA transmission (Di Chiara and Imperato, 1988). 6-OHDA lesions of the nucleus accumbens (Shippenberg et al., 1993; Spyraki et al., 1983) or pretreatment with DA receptor antagonists (Acquas et al., 1989; Leone and Di Chiara, 1987; Manzanedo et al., 2001; Shippenberg and Hertz, 1987, 1988; Suzuki and Misawa, 1995) blocked the place preference of opiates. In the subtypes of DA receptors, the essential role of D_1 receptors in the rewarding effect of opiates is widely accepted. Much evidence indicated that the blockade of D_1 receptors with SCH23390 inhibited the place preference of morphine (Acquas et al., 1989; Leone and Di Chiara, 1987; Manzanedo et al., 2001; Shippenberg and Hertz, 1987, 1988; Suzuki et al., 1995). In agreement with previous studies, the present results also suggested the suppressive effect of SCH23390 on the development of morphine-induced CPP. It further demonstrated the important role of D_1 receptors in the rewarding properties of morphine. SCH23390 by itself produced place aversion in some studies (Shippenberg and Hertz, 1987, 1988) or had no effect in others (Acquas et al., 1989; Leone and Di Chiara, 1987; Manzanedo et al., 2001). This discrepancy might be due to the differences in the doses selected, animal species or experimental procedure. Generally, SCH23390 might induce place aversion at high doses, and be without effect at lower doses (Manzanedo et al., 2001). Under the present experimental conditions, SCH23390 at a dose of 0.1 mg/kg induced a slight but statistically insignificant aversion for the drug-paired side.

Although *l*-CSL exhibited D_1 agonistic properties only in postsynaptic DA receptor supersensitivity, the D_1 receptor antagonist SCH23390 was still used in the present study to investigate the role of D_1 receptors in the suppression of *l*-CSL on the development of morphine-induced CPP. The results showed that SCH23390 did not influence the suppressive effect of *l*-CSL. This is not surprising because the D_1 agonistic action of *l*-CSL could not be exhibited under the present conditions. Therefore, the suppression of *l*-CSL on the development of morphine-induced CPP was not due to D_1 agonism.

The blockade of D_2 receptors seems to have no motivational effects because administration of the D_2 antagonists did not produce place preference or place aversion in most studies (Hoffman and Donovan, 1995; Manzanedo et al., 2001; Shippenberg and Hertz, 1988; Suzuki and Misawa, 1995). On the contrary, there was controversy about the role of D_2 receptors in opiates' rewarding properties. Some studies indicated that the D_2 antagonists blocked the place preference of morphine (Leone and Di Chiara, 1987; Manzanedo et al., 2001; Suzuki and Misawa, 1995), but others did not find such an effect (Mackey and van der Kooy, 1985; Shippenberg and Hertz, 1988). However, recent studies using the D_2 antagonists (Manzanedo et al., 2001) or D_2 receptor knockout mice (Maldonado et al., 1997; Smith et al., 2002) revealed that D_2 receptors could be as important as D_1 receptors in the development of morphine-induced CPP. In the present study, *l*-CSL by itself had no motivational effect but dose dependently suppressed the development of morphine-induced CPP. Combined with the D_2 antagonistic properties of *l*-CSL, it was assumed that the suppressive effect of *l*-CSL was through blocking

D_2 receptors. This hypothesis was demonstrated by the abolition of the suppression of *l*-CSL on the development of morphine-induced CPP when pretreated with the D_2 agonist PPHT. The present study also showed that PPHT at a dose of 0.5 mg/kg did not induce place conditioning and was ineffective to influence the place preference induced by morphine. These results were similar to a previous report that the D_2 agonist quinpirole by itself produced no place conditioning and had no influence on the place preference induced by morphine (Kivastik et al., 1996). However, Rezayof et al. (2002) has reported that intra-central amygdala injection of quinpirole potentiated the development of place preference induced by the lower doses of morphine. Therefore, it cannot exclude the possibility that PPHT may influence the place preference induced by morphine at the lower doses. Further experiments are necessary to clarify this point.

A previous study has showed that *l*-CSL could decrease locomotor activity in mice (Chen et al., 1999). Although some studies suggested that there was only a very weak or no correlation between place preference and locomotor activity (Rademacher et al., 2000; Rademacher and Steinpreis, 2002; Tzschentke, 1998), the possibility exists that *l*-CSL might interfere with the effect of morphine as a result of the inhibition of locomotor activity. It will be of interest to address this question in future works.

In conclusion, the present study indicated that the suppression of the development of morphine-induced place preference by *l*-CSL, a novel dopamine receptor ligand with both D_1 receptor agonistic and D_2 receptor antagonistic actions, was due to D_2 antagonism but not D_1 agonism.

Acknowledgements

This work was supported by Grant G (1998) 051126 from the Ministry of Science and Technology of China and Grant No. 01EA14074 from the Shanghai Natural Science Foundation of China. We thank Dr. Patrick S. Mangan for revision of the manuscript.

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