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Short communication

Acute phencyclidine induces aversion, but repeated phencyclidine induces preference in the place conditioning test in rats

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Abstract

Phencyclidine (PCP) is a drug that has been widely abused in the past two decades. PCP produces place aversion, but not preference, in the place conditioning test. The present study examined PCP-induced place conditioning behavior in rats treated with PCP repeatedly. In naive rats, PCP (2–8 mg/kg i.p.) dose dependently produced place aversion, but did not produce any effect in rats treated with PCP (10 mg/kg i.p.) for 14 days, indicating that tolerance developed to PCP-induced place aversion on repeated PCP treatment. In rats treated with PCP (10 mg/kg i.p.) for 28 days, PCP (2–8 mg/kg i.p.) dose dependently produced place preference. These findings suggest that some changes in neuronal function induced by the repeated PCP treatment may play an important role in the addiction to this drug.

Keywords: Phencyclidine; Place conditioning paradigm; Place aversion; Place preference; (Rat)

1. Introduction

Place conditioning is a widely used test for determining the motivational properties of drugs (Schechter and Calcagnetti, 1993). Phencyclidine (1-(1-phenylcyclohexyl)piperidine; PCP) is a drug that has been widely abused during the past two decades (Petersen and Stillman, 1978). PCP has a rewarding effect in rats (Poling et al., 1981); however, it produces place aversion in the place conditioning task in rats (Barr et al., 1985; Iwamoto, 1986; Kitaichi et al., 1995a).

Several previous studies have already demonstrated that repeated PCP treatment produces behavioral sensitization and tolerance; some dopaminergic neuronal system-mediated behaviors (hyperlocomotion, rearing and sniffing) are potentiated, while some serotonergic (5-HTergic) neuronal system-mediated behaviors (head-twitch, head-weaving, backpedaling and turning) are reduced (Nabeshima et al., 1987a; Kitaichi et al., 1995b; Noda et al., 1996). In the present study, we examined whether PCP-induced place conditioning properties are altered in rats pretreated with PCP repeatedly.

2. Materials and methods

All procedures involving animals and their care conformed with the international guidelines that are in compliance with 'Principles of Laboratory Animal Care' (NIH publication No. 85-23, revised 1985).

2.1. Animals and chemicals

Male Wistar rats (Oriental Bio Service, Kyoto, Japan), weighing 200–300 g, were maintained in a temperature- and humidity-regulated room (22–24°C and 55 ± 5%, respectively) with food and water ad libitum under controlled lighting (light on 09:00 to 21:00 h) for at least 3 days before the experiment. Phencyclidine HCl (1-(1-phenylcyclohexyl)piperidine; PCP) was synthesized by the authors according to a report of Maddox et al. (1965) and was checked for purity. PCP was dissolved in saline.

2.2. Experimental schedule

Rats received PCP (10 mg/kg i.p.) repeatedly for 14 and 28 days in accordance with previous reports of PCP-induced changes in behavior (Nabeshima et al., 1987b;

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Kitaichi et al., 1995b). On the day after the repeated PCP treatment, the place conditioning test, including pre-conditioning test, conditioning, and post-conditioning test, was commenced.

The apparatus used for the place conditioning task consisted of three compartments: a black wooden box, a white box (both $30 \times 24 \times 45$ cm high) and a gray wooden box ($10 \times 24 \times 45$ cm high) connecting the two. To enable the rats to distinguish easily the white from the black box, the floor of the white box was covered with steel mesh. The three boxes were divided by sliding doors (10×10 cm). Place conditioning was performed according to the method of Neisewander et al. (1990) with some modifications (Kitaichi et al., 1995a).

In the pre-conditioning test, the sliding doors were opened and the rats were allowed to move freely among the boxes for 15 min once a day for 3 days. On the third day of the pre-conditioning test, we measured the time that rats spent in the black and white boxes. The box in which a rat spent a much longer time than in the other box was called the 'preferred side', and the other box the 'non-preferred side'. Before the start of conditioning, the rats were grouped based on the data from the pre-conditioning test: the number of rats was approximately equal in each group, depending on the differences in time that rats spent in the preferred and non-preferred sides, and the number of animals which preferred the black or white side.

Conditioning was performed during six successive days. the rats were given PCP (2–8 mg/kg i.p.) or saline in the apparatus with the sliding doors closed. That is, a rat was given a drug and put in its preferred side for 15 min. The next day, the rat was given saline, and put in its non-preferred side for 15 min. These treatments were repeated for three cycles (6 days).

In the post-conditioning test, the sliding doors were opened, and we measured the time that rats spent in the black and white boxes over 15 min. Place conditioning behaviors were expressed by 'post − pre', which was calculated as: [(post value) − (pre value)], where post and pre values were the difference in time spent in the preferred and the non-preferred sides in the post-conditioning and pre-conditioning tests, respectively. All data were expressed as means ± S.E.M. The data were analyzed by one-way analysis of variance (ANOVA), followed by the Scheffe test when F ratios were significant ($P < 0.05$).

3. Results

As shown in Fig. 1, PCP (4 and 8 mg/kg i.p.) significantly produced place aversion in a dose-dependent manner in naive rats. In rats pretreated with PCP (10 mg/kg i.p.) for 14 days, however, PCP (2–8 mg/kg i.p.) produced neither place preference nor place aversion. On the other hand, PCP (4 and 8 mg/kg) significantly induced place preference in a dose-dependent manner in rats pre-

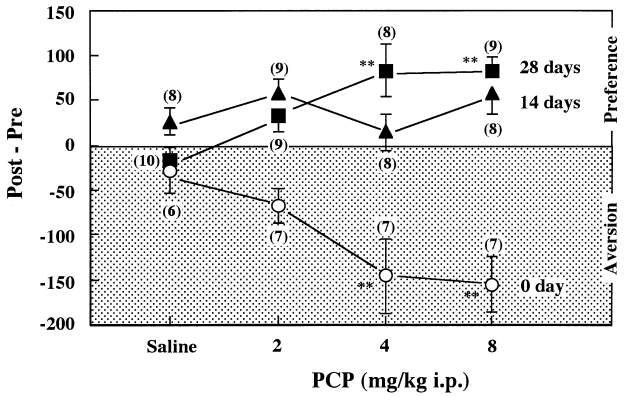

Fig. 1. Effects of repeated PCP treatment on the motivational properties induced by PCP. Experimental protocol is described in detail in the text. Post − Pre = Post value (the difference in time between the preferred and non-preferred side in the post-conditioning test) − Pre value (the difference in time between the preferred and non-preferred side in the pre-conditioning test). Each value represents the mean ± S.E.M. Numbers in parentheses show the number of animals used. ** $P < 0.01$ vs. corresponding saline-treated group.

treated with PCP (10 mg/kg i.p.) for 28 days ($P < 0.015$, $F(3,32) = 6.845$).

4. Discussion

Several previous studies have demonstrated that repeated PCP treatment produces various behavioral and neurochemical changes (Nabeshima et al., 1987a; Kitaichi et al., 1995b; Noda et al., 1996) and that both behavioral sensitization and tolerance depend on different neuronal systems, as described in Section 1. In the present study, we investigated whether effects of PCP on place conditioning behaviors in rats could be altered by repeated PCP treatment, because PCP produces place aversion, although it has a rewarding effect in both humans and animals.

PCP-induced place aversion was not observed in rats treated with PCP for 14 days, whereas surprisingly, it was seen in rats treated with PCP for 28 days. It has been reported that PCP treatment repeated for 14 days produces changes in the function of 5-HT_{2A} receptors, that is, (1) head-twitch behavior, which may be mediated by 5-HT_{2A} receptors since it is blocked by 5-HT_{2A} receptor antagonists (Nabeshima et al., 1987b), is diminished (Nabeshima et al., 1987a), and (2) the number of 5-HT_{2A} receptors is reduced (Nabeshima et al., 1985). Further, PCP-induced place aversion is blocked by a 5-HT_{2A} receptor antagonist, ritanserin (Kitaichi et al., 1995a). Taken together, these findings suggest that the development of tolerance to PCP-induced place aversion may depend on the down-regulation of 5-HT_{2A} receptors induced by PCP treatment repeated for 14 days.

The findings from the 28-day administration of PCP

suggest that some functional changes induced by repeated PCP treatment play a role in PCP-induced place preference. PCP is self-administered by animals (Marquis and Moreton, 1987) and has drug-discriminative properties (Beardsley et al., 1990). Whether such effects are expressed or not depends on the number of times and the duration of drug training and test trials. Further, long-term treatment with PCP produces the development of sensitization to PCP-induced hyperlocomotion, rearing and sniffing (Nabeshima et al., 1987a; Kitaichi et al., 1995b), and these behaviors are inhibited by dopamine receptor antagonists (Kitaichi et al., 1994), suggesting that behavioral sensitization may develop in dopaminergic neuronal systems. It is well established that many drugs which can stimulate the dopaminergic neuronal systems are capable of producing rewarding effects (Schechter and Calcagnetti, 1993). Our preliminary findings showed that PCP-induced place preference in mice treated with PCP for 28 days was reversed by coadministration of a dopamine synthesis inhibitor, α-methyl-ρ-tyrosine (100 mg/kg i.p.), but not by a 5-HT_{2A} receptor antagonist, ritanserin (data not shown). Thus, in view of the repeated PCP-induced behavioral sensitization in the dopaminergic neuronal systems, together with the critical importance of the dopaminergic neuronal systems to the rewarding properties of drugs, it is suggested that the place preference induced by repeated administration of PCP for 28 days may be due to functional changes in the dopaminergic neuronal systems.

In summary, the present results indicated that, depending on duration, the repeated administration of PCP produces not only the development of tolerance to PCP-induced place aversion, but also place preference. These results suggest that the changes in neuronal function induced by repeated administration of PCP may be involved in the changes in PCP-induced place conditioning behaviors. Further studies, using receptor-selective ligands and sensitive probes that could associate with the pharmacological actions of PCP, should be done to elucidate the mechanisms of these behavioral changes and of PCP abuse.

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