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Short communication

Effects of the 5-HT_3 receptor antagonist ondansetron on the ketamine- and dizocilpine-induced place preferences in mice

Tsutomu Suzuki [a,*], Takeshi Aoki [a], Hideaki Kato [a], Mitsuaki Yamazaki [b], Miwa Misawa [c]

[a] *Department of Toxicology, School of Pharmacy, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*
[b] *Intensive Care Unit, Toyama Medical and Pharmaceutical University, Toyama-shi, Toyama 930-0194, Japan*
[c] *Department of Pharmacology, School of Pharmacy, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*

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Abstract

The effects of the 5-HT_3 receptor antagonist ondansetron on the ketamine- and dizocilpine-induced place preferences in mice were examined. The non-competitive NMDA receptor antagonists ketamine (1.0–10 mg/kg, i.p.) and dizocilpine (0.1 and 0.2 mg/kg, i.p.) each produced a place preference in a dose-dependent manner. The ketamine (10 mg/kg)- and dizocilpine (0.2 mg/kg)-induced place preferences were dose-dependently blocked by pretreatment with ondansetron (0.03–0.1 mg/kg, s.c.). These results suggest that 5-HT_3 receptor may be involved in the development of the place preferences produced by ketamine and dizocilpine.

Keywords: Ketamine; Dizocilpine; Ondansetron; Conditioned place preference

1. Introduction

Since chronic pain impairs a patient's quality of life, the control of pain is very important when treating cancer patients. It has been considered that the non-competitive NMDA receptor antagonist ketamine is useful for treating neuropathic cancer pain which cannot be controlled by morphine alone as an adjunctive medication (Yang et al., 1996). Furthermore, it is known that the chronic administration of the non-competitive NMDA receptor antagonist dizocilpine blocks the development of a conditioned place preference (CPP) by morphine (Tzschentke and Schmidt, 1995; Del Pozo et al., 1996). However, there are some problems with the chronic use of ketamine, since ketamine itself produces some side effects such as a psychotomimetic action (Kamaya and Krishna, 1987) and psychological dependence (Moreton et al., 1977). Although dizocilpine produces a place preference (Tzschentke and Schmidt, 1995; Del Pozo et al., 1996), there has been no report concerning the ketamine-induced place preference.

It has been reported that the conditioned place preferences produced by morphine and nicotine were blocked by the 5-HT_3 receptor antagonists 3-tropanyl-3,5-dichlorobenzoate (ICS 205–930) and 3-tropanyl-indole-3-carboxylate HCl (MDL 72222; tropisetron) (Carboni et al., 1988). We previously reported that ICS 205–930 and MDL 72222 attenuated cocaine- and methamphetamine-induced place preferences (Suzuki et al., 1992). However, it has not been clear whether the place preferences produced by NMDA receptor antagonists are regulated by the 5-HT_3 receptor. The present study was then designed to investigate the effects of the 5-HT_3 receptor antagonist ondansetron on ketamine- and dizocilpine-induced place preferences in mice.

2. Materials and methods

The present study was conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, as adopted by the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture of Japan.

* Corresponding author. Tel.: +81-3-5498-5831; fax: +81-3-5498-5831.
E-mail address: suzuki@hoshi.ac.jp (T. Suzuki)

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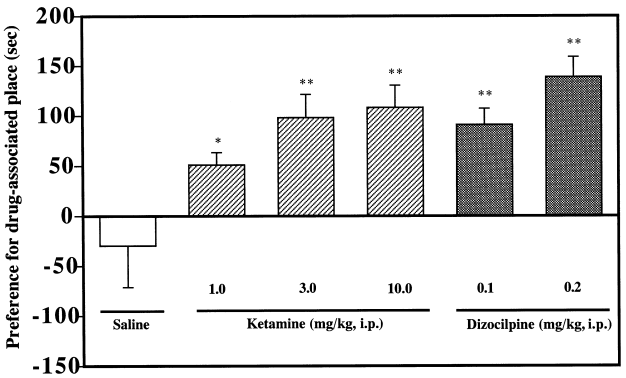

Fig. 1. Place conditioning produced by ketamine (1.0–10 mg/kg, i.p.), dizocilpine (0.1 and 0.2 mg/kg, i.p.) in mice. Ordinate: mean difference between the times spent on the drug- and saline-associated sides of the test box. Each column represents the mean with S.E.M. of 8–12 mice. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. saline (SAL)-treated group.

2.1. Animals

Male ddY mice (17–19 g) were obtained from Tokyo Animal Laboratories (Tokyo, Japan). The animals were housed at a room temperature of 22 ± 1°C with a 12-h light–dark cycle (light on 8:30 AM to 8:30 PM) and were allowed to adapt to this environment for a period of 1 week before the experiments. Food and water were available ad libitum.

2.2. Place conditioning

Place conditioning was conducted as previously described (Suzuki et al., 1990). The apparatus consisted of a shuttle box ($15 \times 30 \times 15$ cm, $w \times l \times h$) which was made of acrylic resin board and divided into two equal-sized compartments. One compartment was white with a textured floor, and the other was black with a smooth floor. For conditioning, mice were confined to one compartment after drug injection and to the other compartment after saline injection. The order of injection (drug or saline) and compartment (white or black) was counter-balanced (unbiased) across the subjects. Conditioning sessions (three days for drug: three days for saline) were conducted for a 60-min period once daily. On day 7, tests of conditioning were performed as follows: the partition separating the two compartments was raised to 7 cm above the floor, and a neutral platform was inserted along the seam separating the compartments. After the conditioning sessions, on day 7, mice were not treated with either drugs or saline, and were then placed on the platform. The time spent in each compartment during a 900-s session was then recorded automatically using an infrared beam sensor (KN-80, Natsume Seisakusyo, Tokyo, Japan). All sessions were conducted dim illumination (28-lx lamp) and white masking noise. Ketamine (1.0–10 mg/kg) or dizocilpine (0.1, 0.2 mg/kg) and saline or vehicle (10 ml/kg) were injected i.p. on alternate days. In the combination study, ondansetron (0.03–0.3 mg/kg) was injected s.c. 30 min before treatment with ketamine or dizocilpine. Each group consisted of 8–12 mice.

2.3. Drugs

The drugs used in the present study were ketamine hydrochloride (Sigma, St. Louis, MO, USA), dizocilpine maleate ((+)-5-methyl-10, 11-dihydro-5*H*-dibenzo (*a*, *d*) cycloheptan-5, 10-imine maleate; Merck/Banyu, Tokyo, Japan) and ondansetron hydrochloride (Nisshin Flour Milling, Saitama, Japan). These drugs were dissolved in saline.

2.4. Statistical analysis

Conditioning scores represent the time spent in the drug-associated place minus the time spent in the vehicle-associated place, and are expressed as the mean with S.E.M. Each score was evaluated statistically using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test.

3. Results

The saline-control mice exhibited no place preference for either place: the mean conditioning score was -29.6 ± 41.6 s ($n = 8$). Ondansetron (0.03–0.3 mg/kg) alone induced neither significant place preference nor place aversion in mice; the mean conditioning scores were -4.4 ± 26.3 s (0.03 mg/kg: $n = 8$), -55.0 ± 58.9 s (0.1 mg/kg: $n = 8$), -55.3 ± 55.4 s (0.3 mg/kg: $n = 8$). As shown in Fig. 1, the non-competitive NMDA receptor antagonists ketamine (1.0–10 mg/kg, i.p.) and dizocilpine (0.1 and 0.2 mg/kg, i.p.) each produced a significant and dose-dependent preference for the drug-associated place

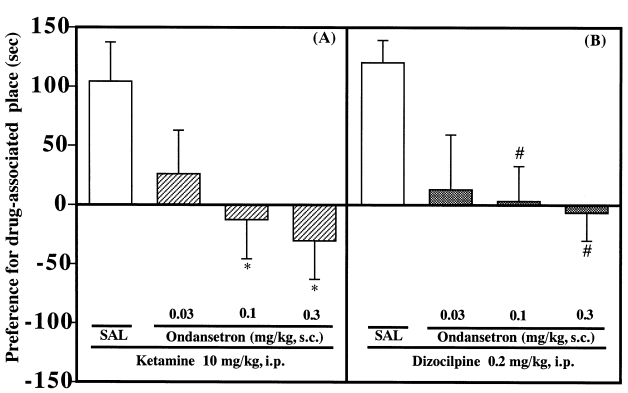

Fig. 2. Effect of ondansetron (0.03–0.3 mg/kg, s.c.) on the place conditioning produced by (A) ketamine (10 mg/kg) and (B) dizocilpine (0.2 mg/kg) in mice. Each column represents the mean with S.E.M. of 8–12 mice. $^{*}P < 0.05$ vs. ketamine with saline (SAL)-treated group. $\#P < 0.05$ vs. dizocilpine with SAL-treated group.

($F(3, 36) = 4.38$, $P < 0.01$, $F(2, 29) = 5.42$, $P < 0.01$). Preferences induced by 3 and 10 mg/kg of ketamine was dose-dependently and significantly antagonized by pretreatment with ondansetron (0.03–0.3 mg/kg, s.c.) (3 mg/kg; $F(3, 36) = 2.87$, $P < 0.05$, figure not shown/10 mg/kg; $F(3, 44) = 2.82$, $P < 0.05$, Fig. 2A). Place preferences induced by 0.1 and 0.2 mg/kg of dizocilpine was also significantly suppressed by ondansetron (0.1 mg/kg; $F(3, 48) = 2.80$, $P < 0.05$, figure not shown/0.2 mg/kg; $F(3, 44) = 2.82$, $P < 0.05$, Fig. 2B).

4. Discussion

The conditioned place preference paradigm is widely used to examine the rewarding effects of drugs. Using the conditioned place preference paradigm, it has been shown that the place preference produced by morphine is blocked by the NMDA receptor antagonists dizocilpine (Tzschentke and Schmidt, 1995; Del Pozo et al., 1996) and ifenprodil (Suzuki et al., 1999). In the present study, we, however, found that dizocilpine itself significantly produced a conditioned place preference in a dose-dependent manner. The present finding was consistent with the reports by Tzschentke and Schmidt (1995) and Del Pozo et al. (1996). It is well known that the rewarding properties of various abused drugs are mediated by mesolimbic dopaminergic neurons that terminate into the nucleus accumbens (Di Chiara and Imperato, 1988). Dizocilpine has been shown to increase dopamine release in the nucleus accumbens (Steinpreis and Salamone, 1993). These findings suggest that the blockade of NMDA receptors may produce the rewarding effect through the activation of mesolimbic dopaminergic system. However, it is unclear at this point why the blockade of NMDA receptors attenuate the morphine-induced place preference.

A variety of NMDA receptor subunits have been identified by molecular cloning studies. There are two families of NMDA receptor subunits, NR1 and NR2 (A, B, C and D), and the expression of NR1 along with different NR2 subunits yields receptors with distinct pharmacological characteristics (Monyer et al., 1992). Several neurochemical studies have demonstrated that the non-specific NMDA receptor antagonist ketamine as well as dizocilpine (Verney et al., 1996; Avenet et al., 1997) increases dopamine release in the nucleus accumbens (Steinpreis and Salamone, 1993; Irifune et al., 1997). In the present study, we demonstrated for the first time that ketamine produced a significant rewarding effect in the conditioned place preference paradigm. In contrast, the selective NR2B subunit-containing NMDA receptor antagonist ifenprodil (Williams, 1993) and the NR2B-preferred antagonist eliprodil (Verney et al., 1996) at least produce no place preference (Sukhotina et al., 1998; Suzuki et al., 1999). These results suggest that the NR2A subunit may be involved in the expression of rewarding effects induced by several non-specific NMDA receptor antagonists. Additionally, although further investigation is necessary to clarify the neuronal interaction of opioidnergic systems and NMDA receptors in the brain, the blockade of NR2B subunits appears to contribute to the attenuation of the morphine-induced place preference.

It is known that 5-HT_3 receptor antagonists, ICS 205–930 and MDL 72222, block morphine-, nicotine-, cocaine- and methamphetamine-induced place preferences (Carboni et al., 1988; Suzuki et al., 1992). It has also been shown that ondansetron attenuates cocaine-induced hyperlocomotion (Van der Hoek and Cooper, 1990), and that ICS 205–930 and/or MDL 72222 inhibit dopamine release in the nucleus accumbens produced by various narcotics and psychostimulants using in vivo microdialysis (Carboni et al., 1989; Kankaanpää et al., 1996). However, it was not demonstrated whether the place preference produced by NMDA receptor antagonists can be regulated by the 5-HT_3 receptor. In the present study, we report here that the 5-HT_3 receptor antagonist ondansetron attenuates both ketamine- and dizocilpine-induced place preferences. Based on the anatomical study, mesolimbic dopamine neurons receive 5-HT nerve input from raphe nuclei, and there is a high density of 5-HT_3 receptors in presynaptic dopaminergic neurons in the nucleus accumbens (Imperato and Angelucci, 1989). These findings provide the evidence that ondansetron blocks the rewarding effect induced by ketamine and dizocilpine through preventing the enhancement of dopamine release in the nucleus accumbens.

In conclusion, we found that the non-specific NMDA receptor antagonists ketamine and dizocilpine produce a clear rewarding effect in the conditioned place preference paradigm, and these effects were blocked by the 5-HT_3 receptor antagonist ondansetron. These findings indicate that the treatment of 5-HT_3 receptor antagonists with ketamine may prevent the ketamine-induced undesirable side effects, such as psychological dependence.

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