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Tropisetron attenuates naloxone-induced place aversion in single-dose morphine-treated rats: Role of α7 nicotinic receptors

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ABSTRACT

We have previously reported that acute dependence can occur when naloxone is administered 24 h after even a single dose of morphine, and that nicotine attenuates this naloxone-precipitated withdrawal syndrome. In the present study, we studied the effect of tropisetron, an α7 nicotinic receptor agonist and 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist, on place aversion induced by naloxone in morphine-treated rats. Place aversion was significantly attenuated by pre-administered tropisetron (1.0 and 2.0 mg/kg, i.p.) in a dose-dependent manner, however tropisetron alone had no effect in a place-conditioning paradigm. This attenuation was completely antagonized by mecamylamine (1.0 mg/kg, s.c.), which is a central nicotinic receptor antagonist, but not by ondansetron (0.3 and 1.0 mg/kg, s.c.), a 5-HT_3 receptor antagonist. Furthermore, methyllycaconitine (1.0 and 2.0 mg/kg, s.c.), an α7 nicotinic acetylcholine receptor antagonist, but not dihydroxy-β-erithroidine (1.0 and 2.0 mg/kg, s.c.), an α4β2 nicotinic acetylcholine receptor antagonist, also antagonized the inhibitory effect of tropisetron. These findings suggest that tropisetron attenuates place aversion induced by naloxone in single-dose morphine-treated rats via α7 nicotinic receptors.

1. Introduction

Recently, there has been renewed interest in the phenomenon of acute opioid dependence, defined as "a state in which abstinence withdrawal can be demonstrated or precipitated following either a single dose or a short-term infusion of an opioid" (Martin and Eades, 1964; Bickel et al., 1988). In animals, administration of a single dose of a morphine-like agent followed by an opioid antagonist can result in a number of physiological and behavioural changes (Schulteis et al., 1997, 1999), which are indicative of opiate withdrawal syndrome. Furthermore, the ability of such withdrawal serves as an aversion motivational stimulus (McDonald et al., 1997). It has been reported that naloxone precipitated (at 24 or even up to 48 h) withdrawal after acutely administrated morphine and produced an aversive motivational state that became associated with place cues in a place-conditioning paradigm (Parker and Joshi 1998; Parker et al., 2002). Therefore, it is well known that a conditioned place aversion paradigm is a highly sensitive measure, which is reflective of the negative motivational aspect of opiate withdrawal, and an index of conditioned affective withdrawal from opioid dependence (Araki et al., 2004; Jin et al., 2005). In our previous study, pre-treatment with a single dose of morphine (10 mg/kg), 24 h previously, enabled naloxone to induce conditioned place aversion at a dose of 0.5 mg/kg, which was not aversive itself (Araki et al., 2004). Moreover, we have reported that the centromedial amygdala of rats receiving a single morphine exposure displays increased c-Fos expression following naloxone-precipitated withdrawal (Jin et al., 2004, 2005).

Opioid receptor blockade is thought to be principally involved in place aversion induced by naloxone (Araki et al., 2004). Several studies have demonstrated the involvement of the central dopamine system in the expression of opiate dependence, and reduction of extracellular dopamine level in mesolimbic areas is associated with both spontaneous (Acquas and Di Chiara, 1992) and opiate-receptor-antagonist-induced withdrawal (Pothos et al., 1991; Rossetti et al., 1992). We have also reported that the release of dopamine, facilitated by nicotine administration, contributes to the inhibitory effect of nicotine on place aversion induced by naloxone-precipitated withdrawal from acutely administered morphine (Araki et al., 2004). Dopamine agonist apomorphine can reverse place aversion induced by withdrawal of rats from a single exposure to morphine (Araki et al., 2004). In addition, we have shown that nicotine attenuates naloxone-induced place aversion in morphine-treated rats, without inducing place conditioning itself (Araki et al., 2004). We have also shown that methyllycaconitine, an α7 nicotinic acetylcholine receptor inhibitor, but not dihydroxy-β-erithroidine, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor inhibitor, significantly and dose-dependently inhibits the attenuating effect of nicotine on naloxone-induced place aversion (Motoshima et al., 2005). Therefore, it is possible that the α7 nicotinic acetylcholine receptor subtype is closely associated with the place aversion induced by naloxone in rats treated with single-dose morphine. However, the effects of α7 nicotinic acetylcholine receptor

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agonists on place aversion induced by naloxone in rats treated with single-dose morphine are not clearly understood.

Both α7 nicotinic receptors and 5-hydroxytryptamine-3 (5-HT_3) receptors are members of the superfamily of ligand-gated ion channels. These two receptors demonstrate the greatest similarity within the family, and display approximately 30% sequence homology (Maricq et al., 1991). Tropisetron, which is widely used in the treatment of patients with chemotherapy-induced nausea and vomiting (Simpson et al., 2000), is a 5-HT_3 receptor antagonist and α7 nicotinic receptor agonist (Ki = 5.3 nM for 5-HT_3 receptors, Ki = 6.9 nM for α7 nicotinic receptors) (Macor et al., 2001). In addition, tropisetron has been reported to reduce morphine self-administration in rats (Hui et al., 1993). A previous study has shown that place aversion induced by naloxone is antagonized by pre-treatment with 5-HT_3 receptor antagonists, ondansetron and MDL 72222, in rats administered morphine by chronic subcutaneous implantation of a 75 mg pellet (Higgins et al., 1991). These findings indicate the involvement of α7 nicotinic and 5-HT_3 receptors in place aversion induced by naloxone in morphine-treated rats. Therefore, the present study was undertaken to examine whether tropisetron affected naloxone-induced place aversion in rats treated with single-dose morphine.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats at 8–10 weeks of age were obtained from Charles River Laboratories (Yokohama, Japan). All animals were housed as two rats/cage (42 × 26 × 15 cm). The animal room was maintained at 22 ± 1 °C under a 12 h/12 h light/dark cycle with lights on from 07:00 h. Food and water were available *ad libitum*. Animal experiments were performed in compliance with the Guidelines for Animal Experimentation and with the approval of the Committee of Animal Experimentation, Ehime University School of Medicine, Japan. Every effort was made to minimize the number of animals used and their suffering.

2.2. Drugs

Tropisetron hydrochloride was provided by Novartis Pharma AG (Basel, Switzerland). Morphine hydrochloride and ondansetron hydrochloride were purchased from Takeda Pharmaceutical Co. (Osaka, Japan) and Glaxo Smith Kline (Tokyo, Japan), respectively. (−)-Nicotine tartrate, naloxone hydrochloride, dihydroxy-β-erithroidine, methyllycaconitine and mecamylamine hydrochloride were purchased from Sigma-Aldrich (St. Louis, MO, USA). All drugs were dissolved in physiological saline (0.9% sodium chloride). The nicotine solution was further adjusted to pH 7.0 with NaOH solution.

2.3. Conditioned place aversion

The method to establish conditioned place aversion has been described elsewhere (Araki et al., 2004). Briefly, the apparatus consisted of two chambers separated during the conditioning trials by a wooden divider. The wooden walls of each chamber (42 × 30 × 29 cm) were painted black. One floor was covered with wire mesh (0.65 × 0.65 cm) and the other was covered with sandpaper squares that formed a chequered pattern. The distinctive tactile stimuli served as the conditioning cues. On the day before the conditioning procedure, the animals were allowed to freely explore the entire apparatus for 15 min. When animals displayed a preference of over 250 s for either compartment, the rats were eliminated from the study (Jin et al., 2004). However, the rats showed no initial bias for either compartment. On the first day of the conditioning procedure, all rats were injected with saline (1 ml/kg, s.c.), and 5 min later, were confined to one side of the apparatus, either the mesh- or sandpaper-floor chamber, in a counterbalanced manner for 30 min. This chamber was referred to as the "non-treatment-paired chamber". On the second day, the rats were injected with either morphine (10 mg/kg, s.c.) or saline and then returned to their home cages. On the third day (24 h after morphine administration), rats were injected with either naloxone (0.5 mg/kg, s.c.) or saline, and 5 min later, were confined to the chamber opposite to that on the first day for 30 min. This chamber was referred to as the "treatment-paired chamber". Forty-eight hours after the conditioning trial, all rats were given free access to the entire apparatus for 15 min. The length of time spent in the treatment-paired chamber minus that spent in the non-treatment-paired chamber during the place preference test was recorded.

2.4. Experimental procedure and drug treatment

To investigate the effects of nicotinic receptor agonist and 5-HT_3 receptor antagonist, rats were administered nicotine, tropisetron, ondansetron or saline before the naloxone injection on the third day of the conditioning procedure. Nicotine (0.1 and 0.2 mg/kg, i.p.) was administered 15 min prior to naloxone, and tropisetron (0.5, 1.0 and 2.0 mg/kg, i.p.) and ondansetron (0.3 and 1.0 mg/kg, s.c.) were administered 30 min prior to naloxone. To investigate the effect of tropisetron alone, rats were administered saline on the second day of the conditioning procedure and tropisetron (2.0 mg/kg, i.p.) or saline on the third day. To determine the involvement of nicotinic acetylcholine receptor subtype on the effects of tropisetron, rats were administered mecamylamine (1.0 mg/kg, s.c.), dihydroxy-β-erithroidine (1.0 or 2.0 mg/kg, s.c.) or methyllycaconitine (1.0 and 2.0 mg/kg, s.c.) 30 min prior to tropisetron (2.0 mg/kg, i.p.). There were six to eight rats in each group.

2.5. Statistical analysis

The dwell time (mean ± SEM) was calculated as the time spent in the treatment-paired chamber minus that spent in the non-treatment-paired chamber during place aversion testing. Data were statistically analyzed using one-way ANOVA followed by Dunnett's test. In the case of comparisons between two groups, Student's t test was carried out. The significance level was set at $P<0.05$.

3. Results

3.1. Effect of nicotine on place aversion

As presented in Fig. 1, nicotine (0.1 and 0.2 mg/kg, i.p.) dose-dependently attenuated place aversion induced by naloxone in

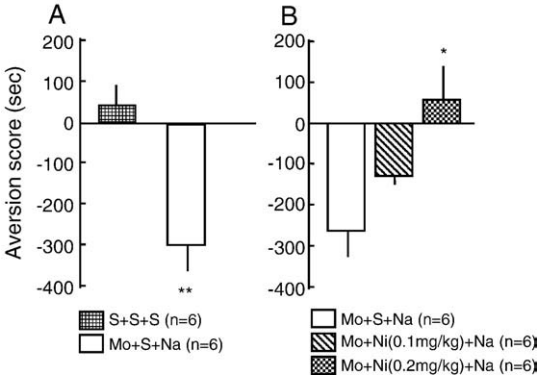

Fig. 1. Effect of nicotine on naloxone-induced place aversion in morphine-treated rats. (A) Morphine (10 mg/kg, s.c.) or saline was administered on day 2, and saline was administered 15 min prior to naloxone (0.5 mg/kg, s.c.) or saline injection on day 3. (B) Morphine (10 mg/kg, s.c.) was administered on day 2, and nicotine (0.1 and 0.2 mg/kg, i.p) or saline was administered 15 min prior to naloxone (0.5 mg/kg, s.c.) injection on day 3. Each value represents the mean ± SEM, ($n = 6$), *$P<0.05$. Mo, morphine; Na, naloxone; Ni, nicotine; S, saline.

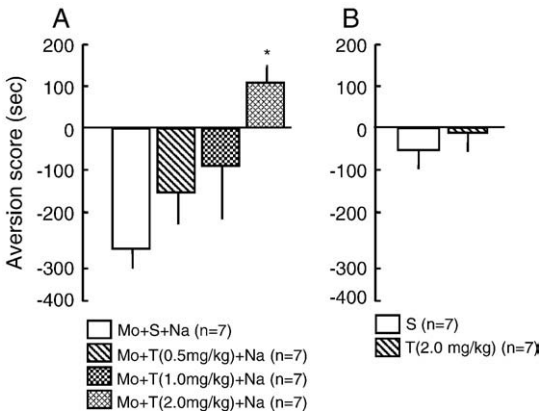

Fig. 2. Effect of tropisetron on naloxone-induced place aversion in morphine-treated rats. (A) Morphine (10 mg/kg, s.c.) was administered on day 2, and tropisetron (0.5, 1.0 and 2.0 mg/kg, i.p.) or saline was administered 30 min prior to naloxone (0.5 mg/kg, s.c.) injection on day 3. (B) Saline was administered on day 2, and tropisetron (2.0 mg/kg, i.p.) or saline was administered 15 min prior to saline injection on day 3. Each value represents the mean ± SEM, ($n = 7$), *$P<0.05$. T, tropisetron.

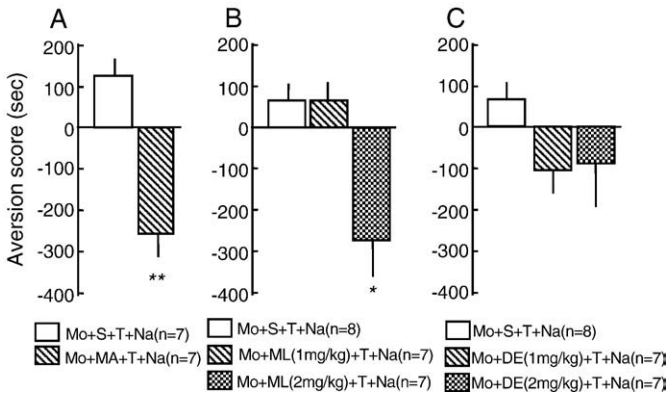

Fig. 4. Effect of nicotinic receptor antagonists on tropisetron-induced attenuation of naloxone-induced place aversion in morphine-treated rats. Morphine (10 mg/kg, s.c.) was administered on day 2, and mecamylamine (1.0 mg/kg, s.c.), methyllycaconitine (1.0 and 2.0 mg/kg, s.c.), dihydroxy-β-erithroidine (1.0 and 2.0 mg/kg, s.c.) or saline were administered 30 min prior to tropisetron (2.0 mg/kg, i.p.) injection on day 3. Naloxone (0.5 mg/kg s.c.) was administered 30 min after the tropisetron treatment. Each value represents the mean ± SEM, ($n = 7$–8), *$P<0.05$, **$P<0.01$. DE, dihydroxy-β-erithroidine; MA, mecamylamine; ML, methyllycaconitine.

morphine-treated rats [$F_{(2,18)} = 3.632$, $P<0.05$]. The *post hoc* comparison showed a significant difference ($P<0.05$) between the nicotine (0.5 mg/kg) and saline-treated control groups.

3.2. Effect of tropisetron or ondansetron on place aversion

Figs. 2 and 3 show the effect of tropisetron or ondansetron on place aversion induced by naloxone in morphine-treated rats. Tropisetron (0.5, 1.0 and 2.0 mg/kg, i.p.), a 5-HT_3 receptor antagonist and α7 nicotinic receptor agonist, showed a dose-dependent inhibitory effect on naloxone-induced place aversion in rats treated with a single dose of morphine [$F_{(3,24)} = 3.733$, $P<0.05$] (Fig. 4). The *post hoc* comparison demonstrated a significant difference ($P<0.05$) between the tropisetron (2.0 mg/kg) and saline-treated control groups. However, tropisetron (2 mg/kg, i.p.) itself produced no place bias in either chamber (Fig. 2). Ondansetron (0.3 and 1.0 mg/kg, s.c.), a 5-HT_3 receptor antagonist, had no effect on place aversion [$F_{(2,18)} = 0.972$, $P>0.05$] (Fig. 3).

3.3. Effect of methyllycaconitine or dihydroxy-β-erithroidine on tropisetron-induced attenuation place aversion

The attenuating effect of tropisetron (2.0 mg/kg, i.p.) on naloxone-induced place aversion in morphine-injected rats was significantly ($P<0.01$) antagonized by mecamylamine (1.0 mg/kg, s.c.), which is a non-specific central nicotinic receptor antagonist. Methyllycaconitine (1.0 and 2.0 mg/kg, s.c.), an α7 nicotinic receptor antagonist, also blocked the inhibitory effect of tropisetron [$F_{(2,19)} = 9.326$, $P<0.01$]. The *post hoc* comparison revealed a significant difference ($P<0.05$) between the methyllycaconitine (2.0 mg/kg) and saline-treated control groups. However, dihydroxy-β-erithroidine (1.0 or 2.0 mg/kg, s.c.), an $\alpha4\beta2$ nicotinic receptor antagonist, had no effect [$F_{(2,19)} = 1.883$, $P>0.05$].

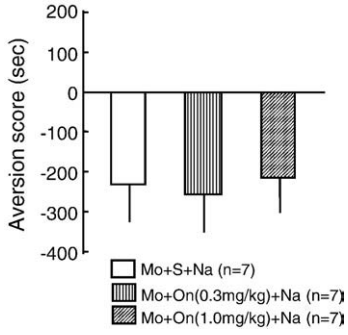

Fig. 3. Effect of ondansetron on naloxone-induced place aversion in morphine-treated rats. Morphine (10 mg/kg, s.c.) was administered on day 2, and ondansetron (0.1, 0.3 and 1.0 mg/kg, s.c.) was administered 30 min prior to naloxone (0.5 mg/kg s.c.) or saline injection on day 3. Each value represents the mean ± SEM, ($n = 7$). On, ondansetron.

4. Discussion

Previously, we have found that nicotine attenuates naloxone-induced place aversion in morphine-treated rats without producing place conditioning itself (Araki et al., 2004). Furthermore, the attenuating effect of nicotine on naloxone-induced place aversion was significantly and dose-dependently inhibited by methyllycaconitine, an α7 nicotinic receptor antagonist, but not by dihydroxy-β-erithroidine, an $\alpha_4\beta_2$ nicotinic receptor antagonist (Motoshima et al., 2005). The major findings of the present study were that tropisetron attenuated place aversion induced by naloxone in rats treated with a single dose of morphine, and that methyllycaconitine, but not dihydroxy-β-erithroidine, fully reversed the inhibitory effect of tropisetron. These findings indicated that the central α7 nicotinic receptors play an important role in the inhibitory effect of tropisetron on naloxone-induced place aversion in single-dose morphine-injected rats.

Previous studies have demonstrated the role of the dopamine system in the conditioned aversive effects of opiate withdrawal. Raclopride, a dopamine receptor antagonist, has been shown to induce place aversion in rats treated with morphine pellets (Funada and Shippenberg, 1996). We have reported that apomorphine, a dopamine receptor agonist, reverses place aversion induced by withdrawal of rats from a single morphine exposure (Araki et al., 2004). Ventral tegmental area dopamine neurons send projections to many brain areas, including nucleus accumbens, prefrontal cortex and basolateral amygdala, and dopamine release from these neurons has been correlated with the rewarding effects of many addictive drugs, including opiates (Narita et al., 2001). α7 nicotine receptors are present in the ventral tegmental area, where they control dopamine release (Klink et al., 2001; Schilström et al., 1998). In addition, it has been reported that intrategmental injection of methyllycaconitine, an α7 nicotinic acetylcholine receptor antagonist, reduces dopamine output in the ipsilateral nucleus accumbens of nicotine-treated rats (Nomikos et al., 1999; Schilström et al., 1998). In the present study, methyllycaconitine antagonized the inhibitory effect of tropisetron.

Therefore, it is possible that the inhibitory effect of tropisetron on the current place aversion behaviour via α7 nicotinic receptors is related to the dopaminergic system.

It is known that 5-HT_3 receptor antagonists ondansetron and MDL 72222 block place preference conditioning induced by repeated administration of morphine, nicotine, ketamine and dizocilpine in mice (Carboni et al., 1988; Suzuki et al., 1997, 1999). It has also been reported that the place aversion induced by naloxone is antagonized by pre-treatment with ondansetron and MDL 72222 in rats administered morphine by chronic subcutaneous implantation of a 75 mg pellet for 3 or 4 days (Higgins et al., 1991). These results indicate that 5-HT_3 receptors play a role in naloxone-induced place aversion during repeated morphine treatment. However, in the present study, ondansetron did not have any effect on place aversion induced by naloxone in single-dose morphine-treated rats. It has reported that ondansetron partially inhibits, with low potency, morphine-induced stimulation of dopamine release in the nucleus accumbens (Pei et al., 1993). Therefore, the inhibitory effect of tropisetron on place aversion in single-dose morphine-treated rats may be unrelated to 5-HT_3 receptors directly.

Accumulating evidence has shown that dysfunction of α7 nicotinic receptors is associated with a number of neurological diseases, including schizophrenia (Hashimoto et al., 2005, 2006; Koike et al., 2005)and Alzheimer's disease (Hogg and Bertrand, 2007), and these receptors have become important therapeutic targets. The findings of the present study suggest that tropisetron attenuates naloxone-induced place aversion in single-dose morphine-treated rats, through activation of α7 nicotinic receptors. Moreover, the facilitation of α7 nicotinic receptors may be related to dopaminergic neurotransmission (Klink et al., 2001; Schilström et al., 1998). Therefore, these results suggest that α7 nicotinic receptors are therapeutic targets for opiate withdrawal syndrome.

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