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Effects of $\alpha_4\beta_2$ and α_7 nicotinic acetylcholine receptor antagonists on place aversion induced by naloxone in single-dose morphine-treated rats

Seiki Motoshima [a], Katsuya Suemaru [b,*], Youichi Kawasaki [c], Chunyu Jin [d], Hiromu Kawasaki [d], Yutaka Gomita [c], Hiroaki Araki [b]

[a] *Onomichi Municipal Hospital Hiroshima, 3-1170-177 Shintakayama, Onomichi, Hiroshima 722-8503, Japan*
[b] *Division of Pharmacy, Ehime University Hospital, Shitsukawa, Toon, Ehime 791-0295, Japan*
[c] *Department of Hospital Pharmacy, Okayama University Medical School, 2-5-1, Shikata-cho, Okayama 700-8558, Japan*
[d] *Department of Clinical Pharmaceutical Science, Graduate School of Natural Science and Technology, Okayama University, 1-1-1, Tsushima-naka, Okayama 700-8530, Japan*

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Abstract

Acute dependence can be observed when naloxone is administered 24 h after even a single dose of morphine, and nicotine attenuates this naloxone-precipitated withdrawal syndrome. This acute dependence has been hypothesized to be associated with a dopaminergic mechanism. In the present study, the role of nicotinic acetylcholine receptor subtypes in the place aversion induced by naloxone in single-dose morphine-treated rats was investigated. Methyllycaconitine (1, 2 and 5 mg/kg), an α_7 nicotinic acetylcholine receptor subtype inhibitor, significantly and dose dependently inhibited the attenuating effect of nicotine on naloxone-induced place aversion. In contrast, dihydroxy-β-erithroidine (1, 2 and 5 mg/kg), an $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype inhibitor, did not have any effect on the attenuating effect of nicotine on naloxone-induced place aversion. These findings suggested that the α_7 nicotinic acetylcholine receptor subtype is associated with the place aversion induced by naloxone in single-dose morphine-treated rats. Nicotinic acetylcholine receptor subtype inhibitors warrant further study as possible treatment for acute dependence.

Keywords: Morphine; Naloxone; Place aversion; α_7 Nicotinic acetylcholine receptor subtype; $\alpha_4\beta_2$ Nicotinic acetylcholine receptor subtype

1. Introduction

Both animal and human studies indicate that the symptoms of withdrawal from acute physical dependence are qualitatively similar to those seen following long-term opioid exposure (Martin and Eades, 1977; Heishman et al., 1990; June et al., 1995). Acute dependence can be observed not only when naloxone is administered several hours after even a single dose of morphine (Martin and Eades, 1977; Eiserberg, 1982; Heishman et al., 1990; June et al., 1995) but also by the ability of such withdrawal to serve as an aversion motivational stimulus (McDonald et al., 1997). Parker and Joshi (1998) reported that naloxone (24-h interval) precipitated withdrawal from acutely administered morphine and produced an aversive motivational state that became associated with place cues in a place-conditioning paradigm.

In a previous study, we also confirmed conditioned place aversion using naloxone in rats subjected to a single exposure to morphine 24 h previously following a one-trial conditioning procedure, and found that nicotine, when it was administered prior to naloxone administration, attenuated the naloxone-precipitated withdrawal syndrome when used to produce an aversive state in a place-conditioning paradigm (Araki et al., 2004). This nicotine-induced attenuation of the naloxone-precipitated withdrawal syn-

* Corresponding author. Tel.: +81 89 960 5731; fax: +81 89 960 5745.
E-mail address: suemaru@m.ehime-u.ac.jp (K. Suemaru).

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drome was completely blocked by mecamylamine but not by hexamethonium. Therefore, it is conceivable that the place aversion induced by naloxone-precipitated morphine withdrawal is associated with nicotinic receptors in the central nervous system.

Many behavioral effects of nicotine result from activation of nigrostriatal and mesolimbic dopaminergic systems (Corrigall et al., 1992; Louis and Clarke, 1998). Nicotine regulates dopamine release not only by stimulation of nicotinic acetylcholine receptors on dopamine cell bodies within the substantia nigra and ventral tegmental area (Imperato et al., 1986; Merreu et al., 1987; Benwell and Balfour, 1997) but also by stimulation of presynaptic nicotinic acetylcholine receptors located on striatal terminals (Azam et al., 2002). It has proven difficult to identify the specific subtypes of nicotinic acetylcholine receptors on the cell bodies and terminals of dopamine neurons. However, recently some specific ligands became available and possible receptor subtypes located on dopaminergic terminals were identified (Kulak et al., 1997; Kaiser et al., 1998; Clarke and Pert, 1985; Clarke and Reuben, 1996; Sorenson et al., 1998). The heterogeneity in the expression of nicotinic acetylcholine receptor subtypes within the midbrain dopaminergic nuclei may be associated with different behaviors. Behavioral withdrawal signs also can be precipitated by the acute administration of mechamylamine, a non-competitive nicotine receptor antagonist, and dihydroxy-β-erythroidine, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor antagonist (Williams and Robinson, 1984), in nicotine-dependent rats (Malin et al., 1994, 1998). Previous studies have shown a critical role for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (Malin et al., 1993), and dopaminergic (Heidebrand et al., 1998, 1999) and opiate (Malin et al., 1993) mechanisms in the nicotine withdrawal syndrome. However, the specific neuronal nicotinic acetylcholine receptor subtypes responsible for the place aversion induced by naloxone-precipitated morphine withdrawal are not clearly understood. In the present study, we examined the effects of $\alpha_4\beta_2$ and α_7 nicotinic acetylcholine receptor antagonists on the place aversion induced by naloxone in single-dose morphine-treated rats.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River, Japan; initial weight 205–235 g) were housed two or three per cage. The room temperature was kept at 23±1 °C, and a 12-h light–dark cycle (lights on at 7:00 a.m.) was used throughout the experimental period. Food and water were available ad libitum. The experimental protocol was conducted according to the Guidelines of the Ethics Review Committee for Animal Experimentation of Okayama University Medical School. The rats were handled daily from the time of their arrival in the laboratory up to one week prior to the initiation of conditioning trial.

2.2. Drugs

Morphine hydrochloride was purchased from Takeda Pharmaceutical Co., Ltd. (Tokyo, Japan). (−)-Nicotine tartrate and naloxone hydrochloride were purchased from Sigma Chemical (St. Louis, MO, USA). Dihydroxy-β-erithroidine and methyllycaconitine were purchased from Research Biochemicals (Natick, MA, USA). All drugs were dissolved in physiological saline (0.9% sodium chloride) and were administered s.c. in an injection volume of 0.1 ml per 100 g body weight. The nicotine solution was further adjusted to pH 7.0 with NaOH solution. Drug doses are expressed in terms of the free base.

2.3. Drug treatment and conditioning paradigm

The place-conditioning apparatus was similar to that previously described by Parker and Rennie (1992) and included 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 floor was covered with sandpaper squares forming a checkered pattern. Place aversion testing was performed according to the method of Parker and Joshi (1998). On the day before the conditioning procedure, the animals were allowed to freely explore the entire apparatus for 15 min. 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-floor chamber or the sandpaper-floor chamber in a counterbalanced manner, for 30 min. This chamber is 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 the morphine administration), the 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 is 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 and the amount of time spent in the treatment-paired chamber minus the time spent in the non-treatment-paired chamber during the place preference test was recorded.

2.4. Effect of nicotinic acetylcholine receptor subtype antagonists on naloxone-induced place aversion in morphine-pretreated rats

According to drug treatments on day 2 and day 3, the rats were divided into the following groups: (morphine, day 2)+(saline+naloxone, day 3), (morphine, day 2)+(nicotine+naloxone, day 3), (morphine, day 2)+(saline+nicotine+naloxone, day 3), (morphine, day 2)+(methyllycaconitine+nicotine+naloxone, day 3), (morphine, day 2)+(dihydroxy-β-erithroidine+nicotine+naloxone, day 3), with individual group numbers of five to six animals. Rats received saline or drugs (dihydroxy-β-erithroidine; 1, 2, 5 mg/kg and methyllycaconitine; 1, 2, 5 mg/kg, s.c., respectively) 30 min prior to naloxone (0.5 mg/kg, s.c.) injection on day 3. Nicotine (0.2 mg/kg, i.p.) was administered 15 min before naloxone injection.

The effects of nicotinic acetylcholine receptor antagonists alone on place preference or place aversion were also investigated. Rats were administered saline on day 2 and were administered methylly-

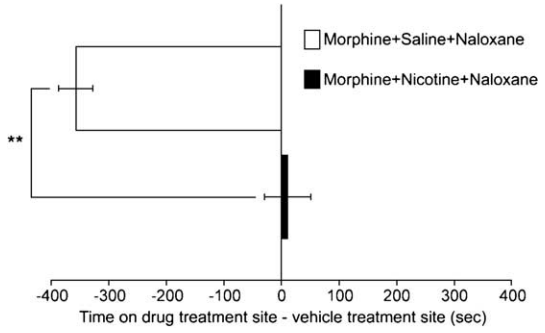

Fig. 1. Effect of nicotine on naloxone-induced place aversion in morphine-injected rats. Morphine (10 mg/kg) was administered s.c. on day 2, and nicotine (0.2 mg/kg) was administered i.p. 15 min prior to naloxone (0.5 mg/kg, s.c.) injection on day 3. Each value represents the mean±S.E.M. for 6 rats. $^{**}p<0.01$ vs. saline instead of nicotine-injected group.

caconitine (5 mg/kg, s.c.), dihydroxy-β-erithroidine (5 mg/kg, s.c.) or saline on day 3.

2.5. Statistical analysis

The dwell time (mean ±S.E.M.) was calculated as the time spent in the treatment-paired chamber minus the time spent in the non-treatment-paired chamber during place aversion testing. Most of the data were statistically analyzed using the Student's *t*-test or one-way analysis of variance (ANOVA) followed by Dunnett's test. The significance level was set at $P<0.05$.

3. Results

3.1. Effect of nicotine on naloxone-induced place aversion in morphine-pretreated rats

Nicotine alone (0.2 mg/kg, i.p.) did not have an effect on the preference of rats for either chamber (data not shown). When nicotine at a dose of 0.2 mg/kg was administered 15 min prior to naloxone injection, the place aversion in morphine-pretreated rats was significantly abolished ($P<0.01$ vs. saline group) (Fig. 1).

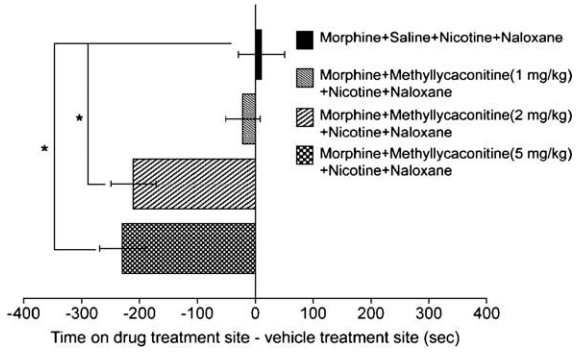

Fig. 2. Effect of methyllycaconitine on nicotine-induced attenuation of naloxone-induced place aversion in morphine-injected rats. Morphine (10 mg/kg) was administered s.c. on day 2, and nicotine (0.2 mg/kg) was administered i.p. 15 min prior to naloxone (0.5 mg/kg, s.c.) injection on day 3. Methyllycaconitine (1, 2 or 5 mg/kg s.c.) was administered s.c. 30 min prior to nicotine (0.2 mg/kg, i.p.) injection. Each value represents the mean±S.E.M. for 6 rats. $^{*}p<0.05$ vs. nicotine+saline injected group.

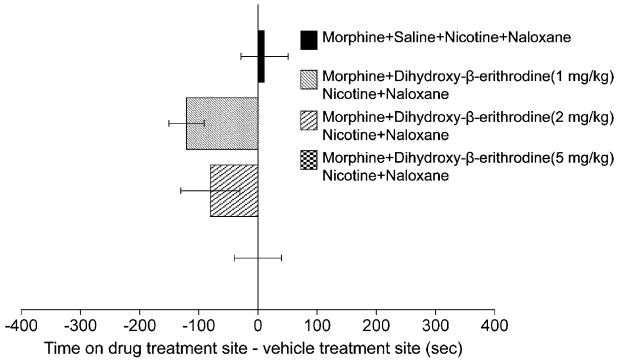

Fig. 3. Effect of dihydroxy-β-erithroidine on nicotine-induced attenuation of naloxone-induced place aversion in morphine-injected rats. Morphine (10 mg/kg) was administered s.c. on day 2, and nicotine (0.2 mg/kg) was administered i.p. 15 min prior to naloxone (0.5 mg/kg, s.c.) injection on day 3. Dihydroxy-β-erithroidine (1, 2 or 5 mg/kg, s.c.) was administered s.c. 30 min prior to nicotine (0.2 mg/kg, i.p.) injection. Each value represents the mean±S.E.M. for 6 rats.

3.2. Effects of α4β2 and α7 nicotinic acetylcholine receptor antagonists on nicotine-induced attenuation of place aversion produced by naloxone in morphine-pretreated rats

The attenuating effect of nicotine on naloxone-induced place aversion in morphine-injected rats was blocked by the α_7 nicotinic acetylcholine receptor antagonist, methyllycaconitine, at a dose of 2 and 5 mg/kg (s.c.) administered 15 min prior to nicotine [$F_{(3,\ 20)}=5.042$, $P<0.01$] (Fig. 2). In contrast to this finding, the $\alpha_4\beta_2$ nicotinic acetylcholine receptor antagonist, dihydroxy-β-erithroidine (1–5 mg/kg, s.c.), did not have an effect on the ameliorating effect of nicotine on place aversion induced by naloxone-precipitated morphine withdrawal [$F_{(3,\ 20)}=0.654$, not significant] (Fig. 3). Additionally, methyllycaconitine (5 mg/kg, s.c.) and dihydroxy-β-erithroidine (5 mg/kg, s.c.) had no effect on the preference of rats for either chamber [$F_{(2,\ 12)}=1.196$, not significant] (Fig. 4).

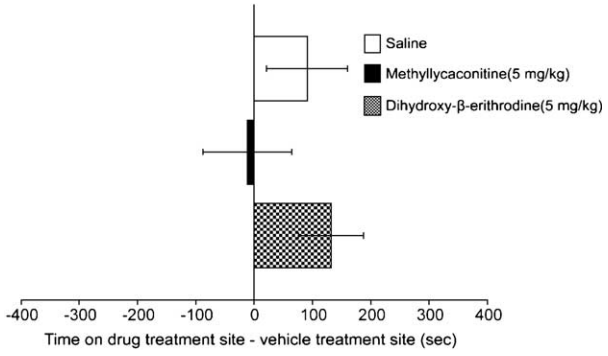

Fig. 4. Effect of methyllycaconitine and dihydroxy-β-erithroidine on the preference of rats for either chamber. Rats were administered saline on day 2 and methyllycaconitine (5 mg/kg, s.c.), dihydroxy-β-erithroidine (5 mg/kg, s.c.) or saline on day 3. Each value represents the mean±S.E.M. for 5 rats.

4. Discussion

In a previous study, we found that nicotine, when administered prior to naloxone administration, attenuated the place aversion induced by naloxone in single-dose morphine-treated rats. The inhibitory effect of nicotine on place aversion induced by naloxone-precipitated morphine withdrawal may be associated with the dopaminergic system, because the effect of nicotine was completely blocked by the dopamine receptor antagonists (Araki et al., 2004). Although the relationship between place aversion and nicotinic acetylcholine receptor subtypes is unclear, Klink et al. (2001) reported that neurons in the dopamine nuclei, substantia nigra and ventral tegmental area, that exhibit a diversity of nicotinic acetylcholine receptors might differentially modulate reinforcement and motor behavior. Within the ventral tegmental area, there is expression of α_2, α_4, α_5, α_6, β_2 and β_3 nicotinic acetylcholine receptor subunit mRNA (Azam et al., 2002). Within the substantia nigra, $\alpha_4\beta_2$, α_7 and β_4 mRNAs are also expressed in a significant number of nondopaminergic neurons, and in the ventral tegmental area for only β_4 mRNA is expressed. Sharples et al. (2000) reported that presynaptic nicotinic acetylcholine receptors on striatal synaptosomes, especially presynaptic $\alpha_4\beta_2$ nicotinic acetylcholine receptors, stimulate dopamine release.

In the present experiment, the attenuating effect of nicotine on naloxone-induce place aversion in morphine-injected rats was blocked by the α_7 nicotinic acetylcholine receptor subtype blocker, but not by the $\alpha_4\beta_2$ subtype blocker. In general, the $\alpha_4\beta_2$ subtype is closely associated with animal behavior. Kempsill and Pratt (2000) reported that nicotine receptors of the $\alpha_4\beta_2$ subtype rather than the α_7 subtype are important in mediating the expression of the locomotor stimulant effects of nicotine. Schreiber et al. (2002) reported that the effects of nicotinic acetylcholine receptor agonists on prepulse inhibition are species dependent and suggested that stimulation of heteromeric nicotinic acetylcholine receptors containing both alpha and beta subunits, and possibly of the $\alpha_4\beta_2$ subtype, affects sensorimotor gating. Cohen et al. (2003) confirmed the importance of $\alpha_4\beta_2$ nicotinic acetylcholine receptors in mediating nicotine dependence. It is reported that the role of α_7 receptors in nicotine-induced hyperlocomotion and reward in the rat is negligible, which supports the involvement of a member of the high-affinity nicotinic receptor subclass, possibly $\alpha_4\beta_2$ (Grottick et al., 2000). We also reported that a $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype antagonist precipitated 5-HT_2 receptor agonist and (±)-1-(2, 5-dimethoxy-4-iodophenyl)-2-amino-propane induced head twitch response in mice repeatedly treated with nicotine but not with saline (Yasuda et al., 2002).

The anxiolytic and anxiogenic effects of nicotine can be distinguished in terms of the nicotinic acetylcholine receptor subtype involved. Methyllycaconitine blocks the nicotine-evoked anxiogenic effect and 5-HT release in the dorsal hippocampus. This means that the α_7 subtype also has a possible role in the anxiogenic effects (Tucci et al., 2003). Stevens et al. (1998) reported that the anabaseine compounds increase sensory inhibition by acting through α_7 nicotinic acetylcholine receptors. The distribution of the α_7 nicotinic acetylcholine receptor subtype has been clarified in the mouse brain. The highest density of [^{3}H]-methyllycaconitine was found in the dorsal tegmental nucleus of the pons, colliculi and hippocampus (Whiteaker et al., 1999).

Thus, the results from the present study suggest that the α_7 nicotinic acetylcholine receptor subtype, but not the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes, may have an important role in the attenuating effect of nicotine on naloxone-induced place aversion in morphine-injected rats. Although the relationship between this aversive effect and nicotinic acetylcholine receptors, and the associated brain region involved in this behavioral aversion are still unclear, nicotinic acetylcholine receptors warrant further study with a view to a possible treatment for in acute dependence.

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