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Effects of the NOP receptor agonist Ro65-6570 on the acquisition of opiate- and psychostimulant-induced conditioned place preference in rats

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ABSTRACT

Activation of the Nociceptin/Orphanin FQ (NOP) receptor may have anti-abuse effects. The present study examined the consequence of NOP receptor activation on the rewarding effect of opiates and psychostimulants in the conditioned place preference task in rats. First, the motivational effect of the NOP receptor agonists Ro64-6198 (0.316–3.16 mg/kg i.p.) and Ro65-6570 (1–10 mg/kg i.p.) when administered alone, was assessed. Ro65-6570 was selected for further drug combination studies since, unlike Ro64-6198, it was devoid of an intrinsic motivational effect. Next, the minimal effective dose to induce reward for the opiates heroin (0.1–3.16 mg/kg i.p.), morphine (1–10 mg/kg i.p.), hydrocodone (0.316–10 mg/kg i.p.), tilidine (1–31.6 mg/kg i.p.), hydromorphone (0.1–10 mg/kg i.p.), and oxycodone (0.0316–10 mg/kg i.p.), as well as for the psychostimulants cocaine (3.16–31.6 mg/kg i.p.) and dexamphetamine (0.316–3.16 mg/kg i.p.) in combination with Ro65-6570 (0 or 3.16 mg/kg i.p.) was determined. All drugs produced conditioned place preference, and for opiates and cocaine, but not for dexamphetamine, the minimal effective dose was higher when combined with Ro65-6570 (3.16 mg/kg i.p.). Attenuation of the rewarding effect of tilidine (3.16 mg/kg i.p.) and oxycodone (1 mg/kg i.p.) by Ro65-6570 (3.16 mg/kg i.p.) could be reversed by pre-treatment with the NOP receptor antagonist J-113397 (4.64 mg/kg i.p.), suggesting that the attenuating effect of Ro65-6570 on opiates is due to activation of the NOP receptor. Taken together, the present study suggests that activation of NOP receptors effectively attenuates the rewarding effect of opiates, but may be less effective in reducing psychostimulant-induced reward.

1. Introduction

The endogenous Nociceptin/Orphanin FQ system, acting via the Nociceptin/Orphanin FQ (NOP; previously known as ORL1 or OP_4) receptor, is widely distributed throughout the brain (Berthele et al., 2003). This system has been implicated in a broad range of central and peripheral effects in animal studies, including drug abuse (for review see Chiou et al., 2007; Lambert, 2008). For example, it was demonstrated that repeated intracerebroventricular (i.c.v.) treatment with the endogenous NOP receptor agonist nociceptin reduced the voluntary intake of alcohol in alcohol-preferring rats (Ciccocioppo et al., 1999, 2004; Economidou et al., 2006, 2008). In addition, systemic (i.p.) administration of the NOP receptor agonist Ro64-6198 (Jenck et al., 2000; Wichmann et al., 2000) reduced alcohol self-administration and prevented relapse-like behaviour in an alcohol-deprivation model in rats (Kuzmin et al., 2007). It was also reported that nociceptin (i.c.v.) attenuated the rewarding effect of various drugs of abuse as measured by the conditioned place preference paradigm. For example, nociceptin (i.c.v.) inhibited acquisition and expression of morphine- and alcohol-induced place preference in mice (Kuzmin et al., 2003; Sakoori and Murphy, 2004; Sakoori and Murphy, 2008b) and acquisition of morphine- and alcohol-induced place preference in rats (Ciccocioppo et al., 2000a,ba; Murphy et al., 1999). Furthermore, nociceptin (i.c.v.) blocked the acquisition and expression of cocaine-induced place preference in rats and mice (Kotlinska et al., 2002; Sakoori and Murphy, 2004), as well as the acquisition of methamphetamine-induced place preference in rats (Kotlinska et al., 2003; Zhao et al., 2003). However, the effect of systemically available non-peptidergic NOP receptor agonists on the acquisition of conditioned place preference has not yet been evaluated in rats.

On the other hand, it was reported that systemic administration of the NOP receptor antagonist J-113397 (Kawamoto et al., 1999; Ozaki et al., 2000) enhanced the acquisition of cocaine-induced conditioned place preference in mice (Marquez et al., 2008a) and the peptide NOP receptor antagonist UFP-101 (i.c.v.) enhanced the acquisition of methamphetamine-induced place preference in mice (Sakoori and Murphy, 2008a). Moreover, studies with genetically modified mice lacking the NOP receptor showed that these mice were more susceptible to the rewarding effect of cocaine (Marquez et al., 2008a), methamphetamine and alcohol (Sakoori and Murphy, 2008a).

Given the paucity of conditioned place preference studies with non-peptidergic NOP receptor agonists, and in order to further

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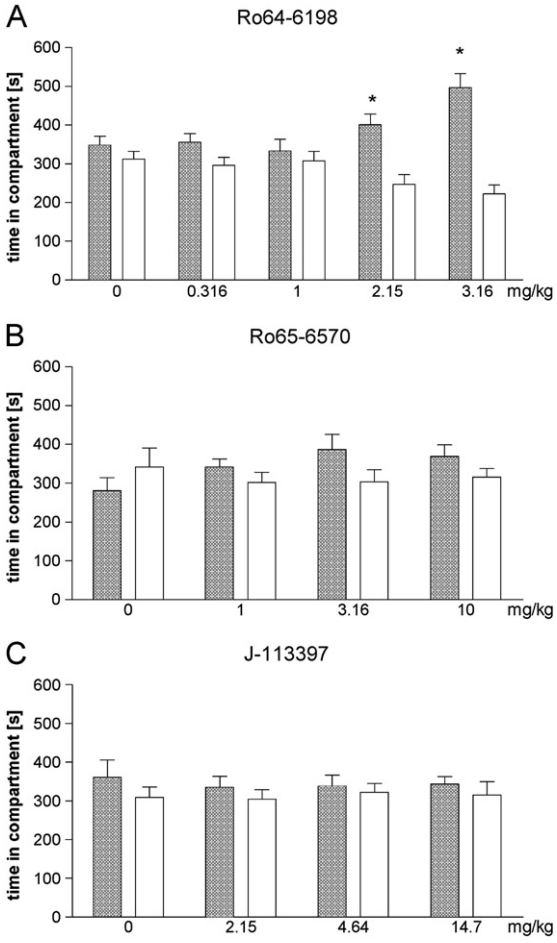

Fig. 1. Effect of the NOP receptor agonists Ro64-6198 and Ro65-6570, and the NOP receptor antagonist J-113397 in CPP. Rats were injected (i.p.) with (A) Ro64-6198, (B) Ro65-6570, or (C) J-113397 and conditioned for 40 min (for each dose condition n = 7–8/group). *$p < 0.05$ time spent in drug-paired compartment (grey bars) compared to vehicle-paired compartment (white bars).

investigate the behavioural mechanism underlying the attenuating effect of the Nociceptin/Orphanin FQ system, we systematically investigated the effect of the non-peptidergic NOP receptor agonist Ro65-6570 (= compound 1a; Rover et al., 2000; Wichmann et al., 1999) on the acquisition of conditioned place preference induced by the opiates heroin, morphine, hydrocodone, tilidine, hydromorphone, and oxycodone, and by the psychostimulants cocaine and dexamphetamine, using a standard, unbiased conditioning protocol. In addition, we investigated whether the effect of Ro65-6570 on tilidine- and oxycodone-induced place preference could be reversed by co-administration of the NOP receptor antagonist J-113397, to strengthen the suggestion that the observed effects of Ro65-6570 were mediated by NOP receptor activation.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats (180–200 g) were obtained from Janvier Laboratories (Le Genest St. Isle, France). Rats were housed four per cage (Macrolon® type IV) with a 12/12-h day/night cycle (lights on at 6:00 am) in temperature-controlled rooms (22 ± 2 °C) and food and water available *ad libitum*. After arrival, rats were allowed to acclimatize for at least 5 days before the start of the experiment. Rats were always tested during the light phase of the day–night cycle. All experiments were performed in accordance with company, national and international regulations and laws for animal care and welfare.

2.2. Drugs

Morphine hydrochloride trihydrate (1, 2.15, 4.64 or 10 mg/kg), cocaine hydrochloride (3.16, 10 or 31.6 mg/kg) (Merck, Frankfurt, Germany), tilidine hydrochloride (1, 2.15, 3.16, 10 or 31.6 mg/kg) (Gödecke, Freiburg, Germany), heroin hydrochloride-monohydrate (0.1, 0.316, 1 or 3.16 mg/kg), oxycodone hydrochloride (0.0316, 0.1, 0.316, 1, 3.16 or 10 mg/kg), hydrocodone bitartrate (0.316, 1, 3.16 or 10 mg/kg), hydromorphone hydrochloride (0.1, 0.316, 1, 3.16 or 10 mg/kg) (Macfarlan Smith Ltd., Edinburgh, UK), and dexamphetamine hydrochloride (0.316, 1 or 3.16 mg/kg) (Knoll, Ludwigshafen, Germany) were dissolved in saline (0.9% NaCl in H_2O). Tilidine, although not available as an analgesic in many countries, was chosen because of its lower potency compared to the other strong opiates, in order to cover a range of opiates with different potencies.

Ro64-6198 (0.316, 1, 2.15 or 3.16 mg/kg; (1*S*,3a*S*)-8-(2,3,3*a*,4,5,6-Hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one hydrochloride; synthesised by the Chemistry Department of Grünenthal GmbH, Aachen, Germany) was dissolved in 5% DMSO in a 5% glucose solution, Ro65-6570 (1, 3.16 or 10 mg/kg; 8-acenaphthen-1-yl-phenyl-1,3,8-triaza-spiro[4,5]decan-4-one hydrochloride; synthesised by the Chemistry Department of Grünenthal GmbH, Aachen, Germany) was dissolved in 2% cremophor in a 5% glucose solution, and J-113397 (2.15, 4.64, or 14.7 mg/kg; 1-[(3R,4R)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1, 3-dihydro-2H-benzimidazol-2-one hydrochloride; Merck, Frankfurt, Germany) was dissolved in a 5% glucose solution. All substances were administered intraperitoneally (i.p.) in a volume of 1 ml/kg.

2.3. Conditioned place preference paradigm

A standard apparatus for conditioned place preference was used (TSE, Bad Homburg, Germany). The apparatus consisted of three compartments and was enclosed in a sound attenuating cubicle. A ventilation fan provided background noise. The outer compartments (25 × 30 × 30 cm [length × width × height]) were visually (black and white stripes versus grey) and structurally (grid floor versus smooth floor) different and separated by a smaller white middle compartment (25 × 10 × 30 cm). Time spent and activity in each compartment were automatically recorded during the sessions by means of infrared beam interruptions (infrared light beams were 3 cm apart).

Experiments were performed as described in Tzschentke et al. (2002) and consisted of three phases. During preconditioning, rats were allowed to explore the whole box for 15 min. If a rat showed an initial preference for one of the outer compartments (>65% of time), it was discarded from the experiment (in total 5% of all rats tested). After the preconditioning session, rats were randomly assigned to their respective treatment group. During conditioning (6 sessions of 40 min) rats received their respective treatment and were restricted to one of the outer compartments during the odd-numbered sessions, and received their control treatment and were restricted to the respective other outer compartment during the even-numbered

Fig. 2. Effect of co-treatment with the NOP receptor agonist Ro65-6570 versus vehicle on opioid-induced CPP. Rats were injected (i.p.) with vehicle or 3.16 mg/kg Ro65-6570 followed directly (i.e. 30 s) by an injection (i.p.) of heroin (a), morphine (b), hydrocodone (c), tilidine (d), hydromorphone (e), or oxycodone (f), and conditioned for 40 min (for each dose condition n = 8–16/group). The minimal effective dose to induce CPP after co-treatment with Ro65-6570 is compared to the minimal effect dose after co-treatment with vehicle (i.e. upper panel: co-treatment with vehicle; lower panel: co-treatment with Ro65-6570).*$p < 0.05$ time spent in drug-paired compartment (grey bars) compared to vehicle-paired compartment (white bars). § not tested. Shaded bars depict a replication experiment for 0.316 mg/kg heroin and 2.15 mg/kg morphine.