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The mu opioid receptor is involved in buprenorphine-induced locomotor stimulation and conditioned place preference

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Abstract

The analgesic effect of buprenorphine is mediated via the mu opioid receptor (MOP). In the present study, using mice lacking the MOP and their wild-type littermates, we determined the role of the MOP in buprenorphine-induced locomotor stimulation and conditioned place preference (CPP). Buprenorphine (3 mg/kg) increased motor activity in wild-type but not in MOP knockout mice, showing the motor stimulatory action of buprenorphine is mediated via the MOP. When the mice were given the same treatment once daily for 5 consecutive days and challenged with buprenorphine on day 11, the motor stimulatory action of buprenorphine was enhanced in wild-type but not in MOP knockout mice, showing sensitization developed to the motor stimulatory action of buprenorphine and this phenomenon was mediated via the MOP. Likewise, buprenorphine induced CPP in wild-type mice after four alternate-day saline/buprenorphine (3 mg/kg) injections paired with olfactory and visual cues. However, buprenorphine failed to induce CPP in MOP knockout mice. In contrast, amphetamine (1 mg/kg) induced a comparable CPP in wild-type and MOP knockout mice. Together, the present results suggest that the ability of buprenorphine to increase motor activity and induce locomotor sensitization and CPP is mediated via the MOP.

Keywords: Buprenorphine; Mu opioid receptor (MOP); Knockout mouse; Locomotor sensitization; Conditioned place preference (CPP); Amphetamine

1. Introduction

Opioids and other drugs of abuse exert their rewarding and addictive effects via modulation of the mesolimbic dopaminergic reward circuitry (Di Chiara and Imperato, 1988a; for reviews see Koob and Le Moal, 1997; Koob and Nestler, 1997; Nestler and Malenka, 2004). For example, morphine, a mu opioid receptor (MOP) agonist, increases extracellular dopamine in the nucleus accumbens, a response that is thought to play an important role in its rewarding actions (Di Chiara et al., 2004; Matthes et al., 1996; but see Hnasko et al., 2005). The increase in accumbal dopamine is also important for the motor stimulatory action of morphine (Hnasko et al., 2005). The motor stimulatory action of morphine and other drugs of abuse is enhanced following their repeated intermittent administration, a phenomenon referred to as locomotor sensitization which is thought to play an important role in the development and maintenance of drug dependency, particularly craving (for review see Robinson and Berridge, 1993, 2000).

Buprenorphine, a mixed agonist/antagonist at the opioid receptors, is used clinically as an analgesic and for the management of opiate dependency. Although buprenorphine is described as a partial agonist at the MOP (Martin et al., 1976; for reviews see Cowan, 2003; Lutfy and Cowan, 2004; Ohlsen and Pilowsky, 2005; Robinson, 2002; Tzschentke, 2002), its mechanism of action is not fully understood For example, there is evidence showing its interaction with the kappa and delta opioid receptors as well as with the opioid receptor-like (ORL-1)

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receptor (Bloms-Funke et al., 2000; Hawkinson et al., 2000; Huang et al., 2001; Lutfy et al., 2003; Negus et al., 1989, 2002; Sadee et al., 1982; Wnendt et al., 1999; for review see Lutfy and Cowan, 2004). Thus, buprenorphine represents an opioid with unique and complex pharmacology because it can simultaneously act as an agonist and/or antagonist at different classes of opioid receptors. However, the contribution of each receptor in the actions of buprenorphine remains poorly understood.

There is ample evidence indicating the analgesic effect of buprenorphine to its activity at the MOP. Kamei and colleagues, for example, have demonstrated that the antinociceptive effect of buprenorphine was blocked by naloxonazine (Kamei et al., 1995), a MOP_1 antagonist, as well as in MOP_1 deficient CXBK mice (Kamei et al., 1997). Previously, we have also reported that the antinociceptive effect of buprenorphine was abolished in mice lacking the MOP (Lutfy et al., 2003), raising the possibility that other actions of buprenorphine could also be altered in these mice. Therefore, using mice lacking the MOP and their wild-type littermates, the present study was designed to determine the role of the MOP in locomotor stimulation and conditioned place preference (CPP) induced by buprenorphine.

2. Methods

2.1. Subjects

Male MOP knockout (Matthes et al., 1996) and wild-type offspring (3–6 months) of heterozygous mice were used for all experiments. Mice were housed 2–4 per cage with free access to food and water and maintained under a 12-h light/12-h dark cycle. All experiments were conducted according to the NIH guideline for the proper use of animals in research and approved by the Institutional Animal Care and Use Committee.

2.2. Experimental procedure

2.2.1. Buprenorphine-induced motor stimulation and locomotor sensitization

Mice were habituated to activity testing chambers (3.8 L Plexiglas cylinders) for 1 h, injected with buprenorphine (3 mg/kg, s.c.) and distance traveled (cm), used as a measure of motor activity, was recorded for 1 h (4 × 15-min sessions). The Videomex-V system (Columbus Instruments Inc., Columbus, OH, USA) was used to measure motor activity. Mice were given the same treatment for 4 additional days and then left untreated until day 11 (test day). On the test day, mice were habituated for 1 h, then injected with buprenorphine (3 mg/kg, s.c.) and motor activity recorded for 1 h (4 × 15-min sessions).

2.2.2. Buprenorphine-induced conditioned place preference (CPP)

The CPP apparatus and paradigm were as described previously (Marquez et al., 2006). Mice lacking the MOP and their wild-type littermates were tested for baseline preference toward the CPP chambers on day 1. On this day, each mouse was individually placed in the neutral (central gray) chamber of a three-chambered CPP apparatus and allowed to freely explore all three chambers of the CPP apparatus for 15 min. The amount of time that the mice spent in each chamber was recorded. On days 2–9, mice received alternate-day saline/buprenorphine (3 mg/kg, s.c.) conditioning sessions. During the conditioning sessions, mice were daily injected with saline or buprenorphine and confined to the vehicle-paired or drug-paired conditioning chambers for 1 h. The conditioning chambers were distinguishable by the presence of olfactory (almond or orange scent) or visual (decorated with 1-inch horizontal or vertical black and white stripes). Every attempt was made to balance the exposure of the mice to the treatments and conditioning chambers including the olfactory and visual cues. On day 10, mice were tested for post-conditioning preference in which each mouse was placed in the neutral chamber and allowed to freely explore all the CPP chambers for 15 min. The amount of time that the mice spent in each chamber was recorded and used for data analysis. For comparison, we also assessed amphetamine-induced CPP in mice lacking the MOP and their wild-type littermates. A separate group of naïve mice were used for this experiment. Mice were tested for baseline preference on day 1, received alternate-day saline/amphetamine (1 mg/kg, i.p.) conditioning sessions on days 2–9 and then tested for post-conditioning preference on day 10, as described above for buprenorphine-induced CPP.

2.2.3. Data analysis

Data are expressed as mean ± S.E.M. The motor activity data were analyzed using a two-way randomized block analysis of variance (ANOVA). The CPP data were analyzed using two-factor ANOVA. The two factors were CPP chambers [vehicle-paired chamber (VPCh) versus drug-paired chamber (DPCh) and genotype (wild-type mice versus MOP knockout mice)]. Wherever it was appropriate, the post-hoc Student-Newman–Keuls test or the Least Squares of Means analysis was used to reveal significant differences between various groups. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Buprenorphine induced motor stimulation and locomotor sensitization in wild-type but not in MOP knockout mice

Fig. 1 illustrates the motor stimulatory action of buprenorphine in mice lacking the MOP and their wild-type littermates. A two-way randomized block ANOVA revealed a significant effect of time with regards to buprenorphine administration ($F_{7,70} = 48.46$; $p < 0.001$), a significant effect of genotype ($F_{1,10} = 108.48$; $p < 0.0001$) and a significant interaction between time and genotype ($F_{7,70} = 105.21$; $p < 0.0001$), showing that buprenorphine stimulated motor activity in wild-type but not in MOP knockout mice. Fig. 2 illustrates the development of locomotor sensitization in wild-type but not in MOP knockout mice. The motor stimulatory action of buprenorphine was enhanced upon its repeated intermittent

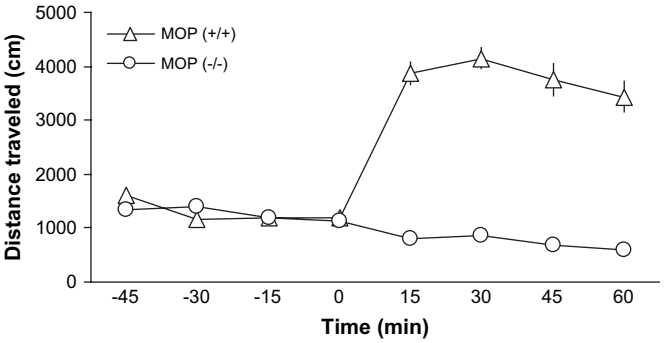

Fig. 1. Buprenorphine failed to increase motor activity in mice lacking the MOP. Mice lacking the MOP [MOP (−/−)] and their wild-type littermates [MOP (+/+)] were habituated to motor activity chambers for 1 h, then injected with buprenorphine (3 mg/kg, s.c.) and motor activity recorded for an additional 1 h (4 × 15-min sessions). Data are presented as mean (±S.E.M.) of 6 mice per genotype.