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Rewarding or aversive effects of buprenorphine/naloxone combination (Suboxone) depend on conditioning trial duration

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Abstract

Buprenorphine is used as a sublingual medication in the treatment of opioid dependence. However, its misuse by i.v. injection may limit its acceptability and dissemination. A buprenorphine/naloxone (ratio 4:1) combination has been developed to reduce diversion and abuse. So far, the relevance of this combination has not been investigated in the animal models traditionally used to study the reinforcing effects of drugs of abuse. The aim of this study was to compare the rewarding effects, assessed by conditioned place preference (CPP), of buprenorphine and buprenorphine/naloxone combination following i.v. administration in mice. Animals were treated with different doses of buprenorphine or buprenorphine/naloxone combination (ratio 4:1), and CPP conditioning trial duration was 5 or 30 min. At the longest trial duration, a bell-shaped dose-response curve was obtained with buprenorphine, which was shifted significantly to the right with naloxone combination. At the shortest trial duration, an aversive effect was observed with the buprenorphine/naloxone combination in animals, involving opioid receptor-like 1 (ORL1). These findings may explain the discrepancies reported in the literature as some authors have shown a reduced buprenorphine/naloxone misuse compared to buprenorphine in opioid abusers, while others have not.

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Key words: Buprenorphine, conditioned place preference, naloxone, suboxone.

Introduction

While opioid dependence occurs in only a very small proportion of the world population, addictive behaviours have devastating effects, contributing substantially to morbidity and mortality, especially when opioids are injected intravenously. Public health policy in different countries was to develop opioid substitution treatment (OST), which involves the controlled oral administration of an alternative opioid, to attract opioid users into treatment. Numerous studies have reported the benefits of OST, and their effectiveness is no longer in question with reduction of many adverse health and social harms, fatal overdoses, infectious disease transmission, health care costs, public disorder and crime.

Among the approved medications for OST, buprenorphine is believed to have an advantageous safety profile compared with methadone (Auriacombe et al., 2001)

and its efficacy seems comparable (Mattick et al., 2003a,b). However this safety is compromised by diversion and misuse, usually by injection, leading to significant mortality and morbidity (Neeleman and Farrell, 1997; Sunjic and Zador, 1997; Auriacombe et al., 2001; Parfitt, 2006; Bell et al., 2009).

The combination of buprenorphine with an opioid antagonist, naloxone, should theoretically reduce diversion. When taken sublingually, as prescribed, the bioavailability of naloxone is very low and the therapeutic efficacy and safety of the combination are similar to those of buprenorphine alone (Fudala et al., 2003). In contrast naloxone may precipitate withdrawal in opioid-dependent people when the combination is administered intravenously. Since the development of the buprenorphine/naloxone combination (ratio 4:1) most of the results published are encouraging, but some studies report divergences (Monte et al., 2009; Comer et al., 2010). Strikingly, the effect of this combination has either not been investigated in pre-clinical studies, or the results have not been reported, even though animal models may be used successfully to investigate the rewarding/aversive effects of pharmacological compounds. The purpose of the study was to assess whether buprenorphine/naloxone (4:1) possesses rewarding or aversive properties. This was

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attempted by means of a conditioned place preference (CPP) paradigm, which has proved to be a reliable animal model of drug-induced reward (Tzschentke, 2007). This method has been extensively used to assess the affective properties of a large variety of drugs of abuse, including buprenorphine (Tzschentke, 2004). In order to exclude possible artefacts due to experimental design, we investigated the possibility of the buprenorphine/naloxone combination to induce CPP following i.v. administration (the route of administration used during misuse of OST), using two distinct spatio-temporal associations between treatment and context, with 5 or 30 min conditioning trial duration. Differences were observed between both protocols, with buprenorphine/naloxone combination inducing aversive or rewarding effects with the short or long conditioning trial duration, respectively. We explored this divergence through the complex pharmacology of buprenorphine, which is a mixed opioid receptor agonist-antagonist, with affinities for the different opioid receptors including opioid receptor-like 1 (ORL1) (Bloms-Funke et al., 2000, Huang et al., 2001; Lutfy and Cowan, 2004).

Materials and method

Animals

Male OF1 mice (Charles River, France) weighing 20–22 g at the beginning of the experiment were used. Animals were housed in groups of 6 in a room with a 12 h alternating light/dark cycle and controlled temperature ($21 \pm 2^\circ\text{C}$). Food and water were available *ad libitum*. Behavioural tests and care of the animals were in accordance with guidelines of the European Communities directive 86/609/EEC and under control of the local ethical committee.

Chemicals

Buprenorphine hydrochloride was purchased from Francopia (France), naloxone hydrochloride from Sigma-Aldrich (France) and J113397 from Tocris (UK). Buprenorphine and naloxone, were dissolved in saline solution [0.9% (m:v) NaCl] and were administered i.v. in the tail vein. J113397 was dissolved in 10% (v:v) DMSO/10% (v:v) Tween-80 and injected i.p. (Redrobe et al., 2002; Sukhtankar et al., 2013). Injection volume was 0.1 ml/10 g of body weight.

Place preference paradigm

A place conditioning methodology was used. The apparatus consisted of two main compartments ($15 \times 15 \times 15$ cm) separated by a neutral triangular central division. Two distinctive sensory cues differentiated the compartments: the wall colouring (black or stripes) and the floor texture (grid or smooth). The combination was as follows: black

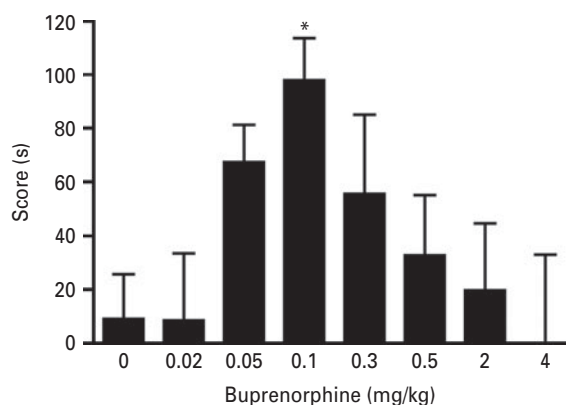


Fig. 1. Buprenorphine dose-response for CPP. Mice were subjected to CPP (30 min conditioning sessions) with different doses of buprenorphine (i.v.). CPP score are expressed as mean \pm S.E.M. * $p < 0.05$ vs. saline-treated group ($n = 14$ to 22 animals/group).

wall-grid floor and striped wall-smooth floor. The movement and location of mice were recorded by computerised monitoring software (Videotrack, Viewpoint, France). Briefly, the protocol was performed in three different phases.

- 1 Pre-conditioning phase: drug naive mice had free access to the 3 compartments for 18 min and the time spent in each compartment was recorded.
- 2 Conditioning phase: this phase consisted of 3 days in which each conditioning chamber was closed. On the morning of the first conditioning day, animals were treated with saline and placed in one of the conditioning environments individually for 5 or 30 min. In the afternoon, the animals were given buprenorphine, naloxone or the combination buprenorphine/naloxone in the opposite compartment and this sequence alternated during the next 2 days. Control animals received saline twice a day and were submitted to the same alternated sequence between the 2 compartments.
- 3 Testing phase. This phase was conducted the day after the last conditioning session and was identical to the preconditioning phase.

Results are expressed in scores (mean \pm S.E.M) calculated as the difference between post-conditioning and pre-conditioning time spent in the compartment associated with the conditioning drug.

Statistical analysis

Data from all the experiments were analysed using a one-way ANOVA followed by Dunnett (Fig. 1) or Bonferroni (other experiments) *post-hoc* test.

Results

Dose-response curve of i.v. injection of buprenorphine in the conditioned place preference

In a first set of experiments we measured the ability of different doses of buprenorphine to promote reward in the CPP paradigm. As shown in Fig. 1, an inverted U shaped dose-response relationship was obtained with one-way ANOVA revealing a significant effect of treatment [$F(7,122)=2.254$, $p<0.05$]. While 0.02 and 0.05 mg/kg buprenorphine were without effect on place conditioning, the dose of 0.1 mg/kg produced a significant CPP ($p<0.05$). When increasing the doses further to 0.3, 0.5, 2 and 4 mg/kg, no CPP effects were observed (Fig. 1).

Buprenorphine/naloxone combination is rewarding with the 30-min conditioning sessions

We then tested the effect of buprenorphine/naloxone combination in the CPP paradigm with 30-min conditioning sessions. Five experiments have been performed with different doses of buprenorphine (0.02, 0.05, 0.1, 1 and 4 mg/kg) and naloxone (0.005, 0.0125, 0.025, 0.25 and 1 mg/kg), corresponding to the ratio 4:1 (buprenorphine/naloxone). Statistical analyses have been performed for each experiment. One-way ANOVA revealed no significant effect with the lower doses of buprenorphine [0.02 and 0.05 mg/kg; $F(3,27)=0.097$, $p=0.96$ and $F(3,50)=1.58$, $p=0.205$, respectively] (Fig. 2a, b). As shown on Fig. 2c, the one-way ANOVA revealed a significant conditioned place preference [$F(3,49)=3.307$, $p<0.05$] with buprenorphine alone (0.1 mg/kg) as compared to the control group ($p<0.05$). No significant effect was observed with naloxone and the buprenorphine/naloxone combination. Regarding the two experiments with the higher doses of buprenorphine (1 and 4 mg/kg) (Fig. 2d, e), one-way ANOVA revealed significant effects [$F(3,52)=6.602$, $p<0.001$ and $F(3,55)=3.971$, $p<0.05$, respectively]. *Post-hoc* analysis demonstrated significant differences between the buprenorphine/naloxone combination (1/0.25 mg/kg) as compared to control ($p<0.05$), buprenorphine ($p<0.01$) or naloxone ($p<0.01$) groups (Fig. 2d). Similar results were obtained with the highest dose of buprenorphine (Fig. 2e), with a significant CPP induced by the buprenorphine/naloxone combination as compared to the control ($p<0.05$) and naloxone ($p<0.01$) groups.

Buprenorphine/naloxone combination is aversive with the 5-min conditioning sessions

Two CPP experiments with the 5-min conditioning sessions were performed with different doses of buprenorphine (0.1 and 1 mg/kg) and naloxone (0.025 and 0.25 mg/kg) alone or in combination. The one-way ANOVA revealed a significant effect in both experiments [$F(3,54)=3.796$, $p<0.05$ and $F(3,52)=5.216$, $p<0.01$,

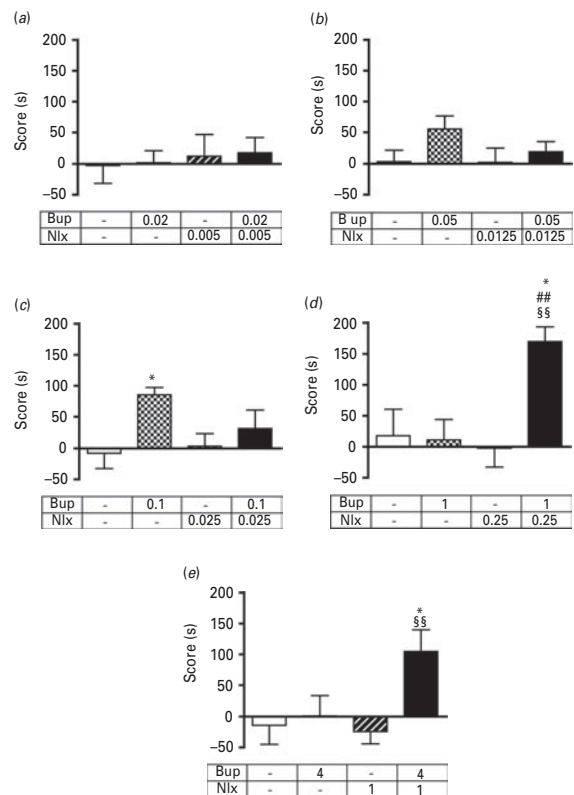


Fig. 2. Rewarding effects of buprenorphine and naloxone alone or in combination with 30-min conditioning sessions. CPP (30-min conditioning sessions) was induced in mice with different doses (mg/kg) of buprenorphine, naloxone or buprenorphine/naloxone (i.v.). Scores are expressed as mean \pm s.e.m. * $p<0.05$ vs. saline-treated animals; ## $p<0.01$ vs. buprenorphine-treated animals; §§ $p<0.01$ vs. naloxone-treated animals ($n=7$ to 16 animals/group).

respectively]. *Post-hoc* analyses revealed no significant effect with buprenorphine or naloxone alone (Fig. 3a, b), while a significant difference was observed between the buprenorphine/naloxone combination (0.1/0.025 mg/kg) and buprenorphine group ($p<0.05$) (Fig. 3a). A similar result was observed with the highest dose of buprenorphine (Fig. 3b), with a significant effect observed following i.v. administration of the buprenorphine/naloxone combination as compared to control ($p<0.01$) and naloxone ($p<0.01$) groups.

Aversive effects of buprenorphine/naloxone combination is blocked by the ORL-1 antagonist

In this experiment, we investigated the effect of the ORL-1 antagonist, J113397 (20 mg/kg, i.p.), on the aversion promoted by the buprenorphine/naloxone combination (1/0.25 mg/kg) in 5-min conditioning sessions protocol. The one-way ANOVA revealed a significant effect [$F(3,63)=5.742$, $p<0.0015$]. *Post-hoc* analyses revealed that buprenorphine/naloxone combination induced place aversion ($p<0.01$) that is blocked with the ORL-1 antagonist, which has no effect by itself (Fig. 4).

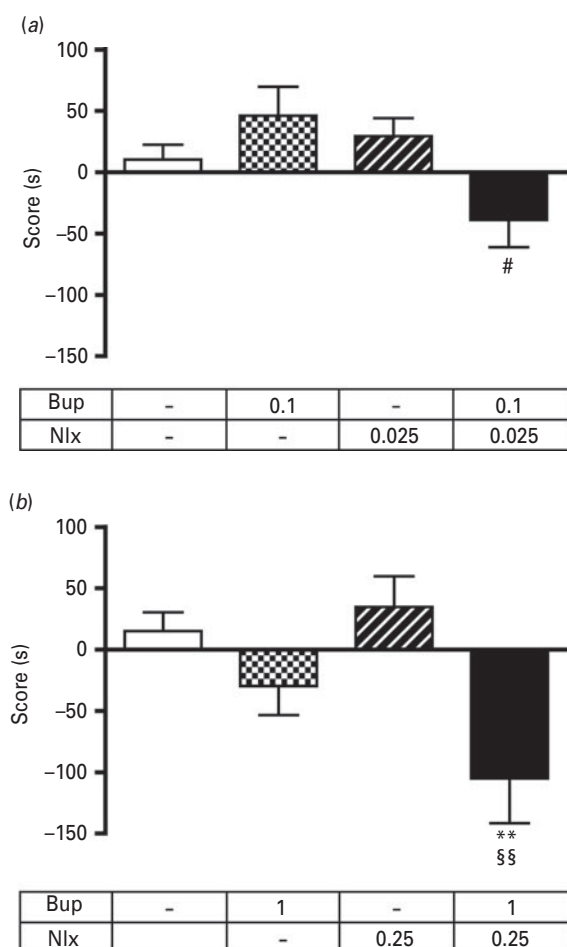


Fig. 3. Effects of buprenorphine and naloxone alone or in combination in CPP with short conditioning sessions. CPP (5-min conditioning sessions) was induced in mice with different doses (mg/kg) of buprenorphine, naloxone or buprenorphine/naloxone (i.v.). Scores are expressed as mean \pm S.E.M. $**p < 0.01$ vs. saline-treated animals; $\#p < 0.01$ vs. buprenorphine-treated animals; $\S\S p < 0.01$ vs. naloxone-treated animals ($n = 12$ to 16 animals/group).

Discussion

Buprenorphine is an oripavine derivative with mixed agonist-antagonist activity at classical opioid receptors, mu, delta, kappa and ORL-1. In this way, buprenorphine is a unique drug with a complex pharmacology (Lutfy and Cowan, 2004).

It is now well established that mu opioid receptor (MOR) plays a key role in the development of opioid addiction (Matthes et al., 1996). Buprenorphine is a potent partial MOR agonist with a very high affinity (0.08 nM), and with a long duration of action related to a very slow receptor kinetics/receptor dissociation rates (Villiger, 1984; Huang et al., 2001; Yassen et al., 2005; Megarbane et al., 2006). Previous reports have shown that the rewarding effects of buprenorphine as determined in the conditioned place preference (CPP) follow an inverted U-shaped dose-response function (Rowlett et al., 1994;

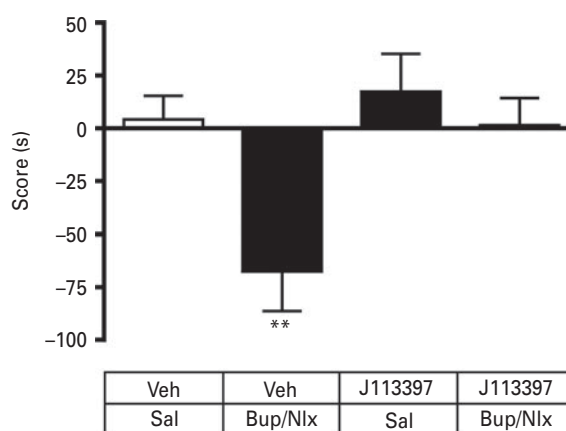


Fig. 4. Effects of J113397, the ORL-1 antagonist, on buprenorphine/naloxone induced aversion in CPP. CPP (5-min conditioning sessions) was induced in mice with buprenorphine/naloxone (1/0.25 mg/kg, i.v.) in the absence (Veh) or presence of J113397 (20 mg/kg, i.p., injected 30 min before afternoon conditioning sessions). Scores are expressed as mean \pm S.E.M. $**p < 0.01$, vs. saline-treated animals ($n = 15$ to 20 animals/group).

Tzschentke, 2004). The results of the present study agree with these data. For the 30-min period of conditioning, i.v. administration induced CPP with an inverted U-shaped curve. It is interesting to note that a long conditioning session is mandatory to induce reward as the dose of 0.1 mg/kg of buprenorphine, which give a significant CPP in the 30-min conditioning session, is ineffective in the shortest conditioning session. There is evidence that for obtaining a CPP effect, the peak drug effect should occur within the conditioning session. Our results are fully consistent with these observations, as following i.v. administration of buprenorphine, the peak concentration into the brain is observed after 10 min (Ohtani et al., 1995).

The rewarding effects of buprenorphine following i.v. administration observed in CPP may explain the abuse liability and the diversion and injection of buprenorphine. Several strategies have been developed to reduce this misuse, such as implantable formulations (Lanier et al., 2007), or a formulation combining buprenorphine with the opioid antagonist, naloxone. Interestingly, the results obtained in the present study show that i.v. injection of the buprenorphine/naloxone combinations are able to induce rewarding effects when long periods of conditioning are used in naïve animals. However, the U-shaped dose-response curve of buprenorphine alone was shifted to the right with naloxone combination. This may explain the clinical observation of Bruce and collaborators (Bruce et al., 2009) reporting that half of the buprenorphine injectors increased the amount of buprenorphine/naloxone injected.

The inverted U-shaped dose-response curve observed following i.v. administration of buprenorphine alone with a 30-min conditioning trial duration, might be due

to pharmacokinetic factors, as previously suggested (Tzschentke, 2004). It is well known that buprenorphine dissociates from MOR very slowly, and increasing the delay between two conditioning sessions lead to a clear tendency towards CPP even with higher doses of buprenorphine (Tzschentke, 2004).

However, very interestingly, even with short periods between two conditioning sessions, the results obtained clearly show a significant CPP with buprenorphine/naloxone combination. A possible hypothesis could be dissociation of bound buprenorphine from the MOR (previous conditioning session) by naloxone, which reaches the brain very quickly, followed a few minutes later by the competitive displacement of naloxone by buprenorphine, which is the ligand with the higher affinity [K_i buprenorphine = 0.08 nM *vs.* K_i naloxone = 0.93 nM (Raynor et al., 1994; Huang et al., 2001)]. The consequences of this sequence of events are a significant CPP. Based on all these observations, a longer time delay between conditioning sessions should not dramatically modify the results observed, naloxone is the first to bind to MOR, but very rapidly a competitive displacement by buprenorphine occurred resulting in activation of MOR by buprenorphine that induces significant CPP.

Whatever the molecular or cellular explanation, the results obtained with the 30-min period of conditioning clearly showed that buprenorphine/naloxone did not induce any aversive effect. This result appears consistent with clinical observations showing that buprenorphine/naloxone combination has i.v. abuse potential (Comer et al., 2010). Nevertheless, in their paper Alho and colleagues (Alho et al., 2007) mentioned that 80% of i.v. users of the buprenorphine/naloxone combination reported a 'bad' experience, while less than 20% reported an effect 'similar' to experiences with i.v. buprenorphine alone. As the dissociation kinetics of buprenorphine on MOR is very low, it could be speculated that the 'bad' experience reported might be due to an effect of naloxone immediately following i.v. injection (before the buprenorphine binding) (Fig. 5). This hypothesis is in agreement with the pharmacokinetic parameters of buprenorphine and naloxone. In humans, the bio-phase equilibration rate constant for buprenorphine (k_{e0}) was 0.004 min⁻¹, which corresponds to $t_{1/2, ke0}$ = 173.2 min, and for naloxone the k_{e0} was estimated at 0.106 min⁻¹, which corresponds to $t_{1/2, ke0}$ = 6.5 min (Yassen et al., 2007). This is in agreement with the peak concentrations observed in the brain following i.v. injection of the drugs. This peak is observed immediately following i.v. injection of naloxone and delayed with buprenorphine (Ohtani et al., 1995). Thus to investigate whether the 'bad' experience reported by i.v. drug users with the combination buprenorphine/naloxone could be due to a binding of naloxone to MOR before the binding of buprenorphine to the same receptors, we used a short conditioning trial duration (5-min).

At doses where animals showed CPP with a 30-min conditioning trial duration with buprenorphine alone

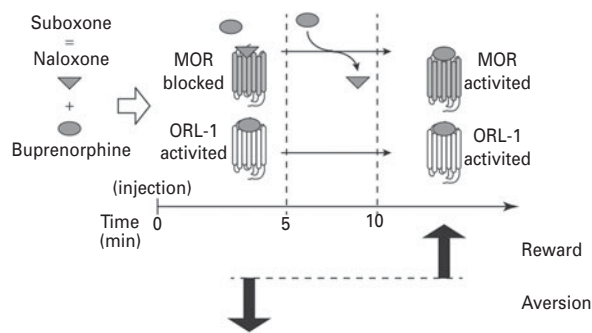


Fig. 5. Proposed model of rewarding and aversive effects of suboxone. Immediately after i.v. injection (0–5 min) of suboxone, naloxone will bind to mu opioid receptors (MOR) and buprenorphine to opioid-receptor like 1 (ORL-1) resulting in place aversion. Then, rapidly, naloxone will be replaced by buprenorphine (10 min is the brain peak of buprenorphine) and MOR will be activated and counteract ORL-1 to promote reward.

or with the combination buprenorphine/naloxone, the mice that spent 5-min in the conditioning compartment did not show preference or aversion to buprenorphine-paired compartment, but showed significant aversion to the buprenorphine/naloxone-paired compartment whatever the doses used. Several hypotheses could explain these results. These effects could be due to withdrawal syndrome provoked by naloxone following administration of buprenorphine/naloxone combination. Another possibility is that blockade of MOR by naloxone may reveal the effects of buprenorphine on other opioid receptors. This hypothesis is consistent with the complex pharmacology of buprenorphine. Previous studies have shown that buprenorphine interacts with the opioid receptor-like 1 (ORL1) receptor (Wnendt et al., 1999). Interestingly, orphanin FQ/nociceptin (OFQ/N), the endogenous ligand of the ORL1 receptor is considered an anti-opioid peptide in the brain (Grisel and Mogil, 2000). Moreover while activation of MOR increases the extracellular dopamine levels in the nucleus accumbens, it has been demonstrated that stimulation of ORL1 receptor reduces dopamine levels in this brain region (Murphy et al., 1996), and that nociceptin/ORL1 administration induces place aversion (Sakoori and Murphy, 2004). Thus, the behaviour observed in this study with the 5-min conditioning trial duration with the buprenorphine/naloxone combination could be the consequence of the MOR blockade by naloxone, and the activation of ORL1 receptor by buprenorphine resulting in a reduction of dopamine release in the nucleus accumbens that overshadow the rewarding drug effects, and may lead to an aversive response (Fig. 5). This hypothesis was validated using the potent ORL-1 antagonist, J113397 (Ozaki et al., 2000a,b), during conditioning. Indeed, we found that J113397 blocked aversion promoted by buprenorphine/naloxone in 5-min conditioning sessions. Our data are emphasized by the results obtained in mice lacking the

ORL1 receptor, showing that the rewarding action of buprenorphine is compromised by its ability to interact with the ORL1 receptor (Marquez et al., 2008). However, in our experimental design, the ORL1 antagonist in the drug-free test blocked acquisition of buprenorphine/naloxone place aversion. We did not perform the experiment in the drugged state. We, therefore, cannot exclude that the ORL1 antagonist did not block the buprenorphine/naloxone place aversion in the drug-free test by a pharmacological antagonism but rather rendered the expression of place aversion dependent upon its presence during the test (state-dependency effects).

In conclusion, while a negative effect may be observed immediately following i.v. administration of the buprenorphine/naloxone combination (only observed with a 5-min conditioning trial duration), it clearly appears that this effect remains below the rewarding effect, as with a 30-min conditioning trial duration, the global effect is a conditioned place preference. These results are in agreement with the clinical literature reporting 'bad' experiences following i.v. administration of the combination, but with a very weak decrease in the self-administered buprenorphine/naloxone combination (Bruce et al., 2009).

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Interest Statement

None.

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