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Effects of the NOP agonist SCH221510 on producing and attenuating reinforcing effects as measured by drug self-administration in rats

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Abstract

Nociceptin/orphanin FQ peptide (NOP) receptor agonists attenuate morphine-induced conditioned place preference in rodents. However, it is not known whether NOP agonists have reinforcing properties or can inhibit mu opioid receptor (MOP)-mediated reinforcement as measured by drug self-administration in rodents. Further understanding the behavioral effects of NOP agonists could suggest them as having potential in attenuating reinforcing effects of opioids. In the first part of the study, reinforcing properties of selective NOP agonist SCH221510 were determined and compared with the full MOP agonist remifentanyl under fixed-ratio 5 (FR5) and progressive-ratio (PR) schedules of drug self-administration. In the second part, effects of systemic and intracisternal pretreatment of SCH221510 were determined and compared with MOP antagonist naltrexone in attenuating reinforcing effects of remifentanyl and a non-drug reinforcer (sucrose pellets). Remifentanyl self-administration (0.3-10 µg/kg/infusion) generated a biphasic dose-response curve, characteristic of drugs with reinforcing properties. SCH221510 (3-300 µg/kg/infusion) self-administration resulted in flat dose-response curves and early break-points under the PR, indicative of drugs lacking reinforcing value. Intracisternally, but not systemically, administered SCH221510 (0.3-3 µg) attenuated remifentanyl self-administration, comparable with systemic naltrexone (0.03-0.3 mg/kg). SCH221510 (1-3 µg), unlike naltrexone (0.03-1 mg/kg), attenuated responding for sucrose pellets. Both effects of SCH221510 were reversed by the NOP antagonist J-113397 (0.3-3 µg). These results suggest that SCH221510 does not function as a reinforcer in rats, and that it can attenuate the reinforcing value of MOP agonists; therefore, the potential utility of NOP agonists for the treatment of drug addiction warrants further evaluation.

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Keywords

Drug self-administration; nociceptin/orphanin FQ; NOP receptor; SCH221510; remifentanyl; opioids

1. Introduction

Nonprescription use of mu-opioid (MOP) receptor agonists has been a longstanding public health concern due to the mortality and economic loss resulting from their excessive consumption (Dodds, 2013; Wightman et al., 2012). It is therefore critical to develop analgesic drugs that are devoid of the detrimental side effects and abuse liability (Mogali and Comer, 2013). Agonists selective for the nociceptin/orphanin FQ (NOP) receptor have a promising analgesic profile (Lin and Ko, 2013; Schroder et al., 2014; Sukhtankar and Ko, 2013). In rodent models of neuropathic and inflammatory pain, NOP agonists have antihypersensitive effects (Linz et al., 2013; Obara et al., 2005; Sukhtankar et al., 2013); and they potently produce analgesia in nonhuman primates under both acute and inflammatory pain (Cremeans et al., 2012; Ko et al., 2009; Sukhtankar et al., 2014). Importantly, NOP agonist-induced analgesia is not accompanied by MOP-associated side effects such as respiratory depression and pruritus (Ko et al., 2009). Given their promising analgesic potential, more preclinical research is warranted to better predict abuse liability in humans.

N/OFQ and NOP receptors are widely distributed in the mesolimbic pathways associated with reward and motivation (Calo and Guerrini, 2013; Lambert, 2008). Despite this, NOP agonists do not produce conditioned place preference (CPP) in rodents, suggesting a lack of rewarding properties (Devine et al., 1996; Le Pen et al., 2002). However, it is not yet known whether NOP agonists produce reinforcing effects in rats as measured by intravenous drug self-administration. Drugs producing CPP may not have reinforcing properties and *vice versa* (Bardo and Bevins, 2000); therefore, predictive strength of abuse liability can be maximized from using both assays to examine novel compounds. Moreover, understanding self-administration by rodents in particular offers additional information for neurochemical investigations and has other advantages not limited to species cost, care and availability. Therefore, potential reinforcing properties of NOP agonists needs further examination in rats to strengthen the notion that NOP agonists are not likely to have addictive properties.

In addition, NOP agonists may hold potential to dampen reinforcing effects of opioids with high abuse liability. They have been shown to inhibit morphine-induced dopamine release in the mesolimbic pathway (Di Giannuario et al., 1999), and enhanced rewarding effects of morphine have been observed in NOP receptor knockout rats (Rutten et al., 2011). In addition, NOP agonists can block CPP induced by opioids and psychostimulants (Zaveri, 2011). However, it is not yet known if NOP agonists can attenuate the reinforcing effects of MOP agonists. Together with understanding rate of self-administration, these studies will determine whether NOP agonists also hold potential as anti-addiction treatment options.

The first aim of the present study was to investigate the reinforcing properties of selective NOP agonist SCH221510 (Varty et al., 2008) using fixed- and progressive-ratio schedules of reinforcement. These effects were compared with MOP agonist remifentanyl (Servin and

Billard, 2008). The second aim was to determine the effectiveness of SCH221510 and MOP antagonist naltrexone in attenuating the reinforcing effects of remifentanyl and a non-drug reinforcer (sucrose pellets).

2. Materials and Methods

2.1 Subjects

Adult male Sprague-Dawley rats (325-350 g) were obtained from Harlan (Indianapolis, IN) and maintained on a 12-h light/dark cycle with lights on at 7:00 AM. Rats had free access to water and ~ 20 g of standard laboratory chow (Purina, St. Louis, MO) per day to maintain 80-90% of the free-feeding body weight. Rats with chronic indwelling catheters were housed individually whereas the rats trained to respond for sucrose pellets were group-housed (three per cage); all were tested during the light cycle (between 8:00 am-1:00 pm). All studies were conducted in accordance with the University Committee on the Use and Care of Animals at the University of Michigan (Ann Arbor, MI) and Wake Forest University (Winston-Salem, NC), and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the U.S. National Institutes of Health (Bethesda, MD).

2.2 Drugs

Remifentanyl (Hospira, Lake Forest, IL) and naltrexone (National Institute on Drug Abuse, Bethesda, MD) were dissolved in sterile water. SCH221510 and J-113397 (Tocris Bioscience, Minneapolis, MN) were dissolved in a 1:1:8 ratio of dimethyl sulfoxide, Tween 80 and sterile water. For drug self-administration, remifentanyl and SCH221510 were intravenously delivered in the volume of 0.1 ml/kg. SCH221510 and J-113397 were administered centrally by intracisternal injection. Briefly, the rat was lightly anesthetized with isoflurane and placed in a stereotaxic device. The head of the rat was held perpendicular to the body axis and the drug was administered through a 26G, ½ g needle inserted in the cisterna magna to a depth of 5mm. The position of the needle was confirmed by a flow of clean cerebrospinal fluid. A solution of 100 µl was infused over 20 s and the needle was held in place for an additional 10 s before being withdrawn (Lee et al., 2003; Shannon and Lutz, 2002).

2.3 Procedures

2.3.1 Surgery—Surgery was performed to implant chronic indwelling catheters in the femoral vein to allow for intravenous drug self-administration as previously described (Bertz and Woods, 2013). Experimental sessions began one week post-surgery. Catheters were flushed daily with 0.25 ml of heparinized saline (50U/ml) during recovery as well as before and after experimental sessions to ensure patency.

2.3.2 Apparatus—Experimental sessions were conducted in standard operant conditioning chambers (Med Associates, St. Albans, VT) that were located inside light- and sound-attenuating cubicles. The chambers were equipped with a white house light, left and right nose poke apertures (2.5 cm) with yellow lights, and a pellet dispenser delivering 45 mg sucrose pellets (PJ Noyes Company Inc., Lancaster, NH). The beginning of a session was signaled by illumination of the house light. Responses in the active nose poke aperture

resulted in delivery of a single drug infusion or sucrose pellet, which was accompanied by illumination of the nose poke light. Nose pokes in the inactive aperture were recorded but had no programmed consequences. There was a 5 s time-out period after each reinforcer delivery during which responses did not have programmed consequences.

2.3.3 Acquisition of responding—Different groups of rats were trained to respond for either one 45 mg sucrose pellet or 3 µg/kg/infusion remifentanyl under a fixed-ratio 1 (FR1) schedule of reinforcement in daily 1 h sessions. This dose of remifentanyl is shown to maintain high rates of responding in rats (Collins and Woods, 2007; Cooper et al., 2008). During the FR1 schedule, each active nose poke response resulted in a single reinforcer delivery (drug infusion or sucrose pellet). Once stable responding was established at the FR1, the response requirement was increased to FR2, and subsequently to FR5. The criterion for stable responding was defined as three consecutive sessions with less than 20% variation in the number of active responses. A minimum of 5 sessions was completed at each ratio value. Sessions terminated after 60 min (or 60 sucrose pellet deliveries, whichever came first).

2.4 Dose-response curves for remifentanyl and SCH221510 self-administration

2.4.1 Fixed-ratio schedule of reinforcement—Following acquisition of stable nose-poke responding for remifentanyl, 10 rats were divided into two groups to self-administer different doses of remifentanyl (0, 0.3, 1, 3 and 10 µg/kg/infusion) or SCH221510 (3, 10, 30, 100 and 300 µg/kg/infusion) under a FR5 schedule during 1 h sessions. Each dose was tested until stable responding was observed, defined as three consecutive sessions with less than 20% variation in number of active responses.

2.4.2 Progressive-ratio schedule of reinforcement—Following acquisition of stable nose poke responding for remifentanyl, two groups of 4 rats self-administered different doses of remifentanyl (0, 0.3, 1, 3 and 10 µg/kg/infusion) or SCH221510 (3, 10, 30, 100 and 300 µg/kg/infusion) under a progressive ratio (PR) schedule of reinforcement. Within a session, the response requirement to obtain a single drug infusion increased after each injection according to the following sequence of ratios: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, and 268. Sessions were terminated after a 30 min period (break-point) in which no infusions were obtained. Total number of responses, number of infusions and final ratio completed were recorded. Each dose was tested until stable responding was observed, defined as two consecutive sessions with less than 15% variation in the number of infusions. For both FR and PR schedules, all dose-response effects were determined by presenting the doses in a counterbalanced order across subjects in each drug group and a minimum of 5 sessions were required at each dose. After determining the dose-response curves, responding for remifentanyl was re-established and catheter patency was tested with methohexital sodium in all rats.

2.5 Effect of SCH221510 and naltrexone on remifentanyl- and sucrose pellet-maintained behavior

In a separate group of 12 rats trained to self-administer remifentanyl, either naltrexone (0.03–0.3 mg/kg, s.c.) or SCH221510 (1–30 mg/kg, s.c.) were systemically administered 20 min

prior to experimental sessions to assess potential effects on remifentanyl self-administration. At 30 mg/kg, SCH221510 caused adverse behavioral abnormalities in rats indicated by flattened postures, unresponsiveness and loss of righting reflex. Therefore, in this and subsequent analyses, SCH221510 (0.3-3 µg) was centrally administered by intracisternal (i.c.) injection as a 20 min pretreatment as previously described.

To determine the effects on sucrose pellet-maintained responding, naltrexone (0.03–1 mg/kg, s.c.) or SCH221510 (0.3-3 µg, i.c.) were administered 20 min prior to sessions in 12 subjects trained to respond for sucrose pellets. To assess whether the effects of SCH221510 were NOP-mediated, a NOP antagonist J-113397 (0.3-3 µg) was intracisternally co-administered with SCH221510. All doses of naltrexone, SCH221510, or J-113397 were presented in a randomized order. Doses of 0.3 and 1 µg SCH221510 were selected for the antagonist studies, as it was determined that 3 µg produced high levels of sedation (score: 1.8 ± 0.2). Washout periods of 3-4 days were experienced between doses.

Sedative effects of the pretreatment drugs were monitored, as adapted from a sedation rating scale (Chuck et al., 2006). Scores were assigned as follows: 0 = alert; 1 = minimal spontaneous movement; 2 = no spontaneous movement, but responsive to touch; 3 = flattened posture but responsive to touch; 4 = no response to touch; 5 = loss of righting reflex. After being administered a pretreatment drug, each subject was assigned a sedation score before initiation of experimental sessions by an individual blinded to the dosing conditions.

2.6 Data analysis

Data from the final three sessions in the FR schedule, final two sessions in the PR schedule, and a single session in the pretreatment studies were used. All data are presented as mean values (mean $\pm$ S.E.M.) calculated from individual animals for all stable behavioral endpoints. Comparisons of data across different dosing conditions were made using repeated measures one-way analysis of variance followed by the Dunnett test. $P < 0.05$ was considered statistically significant for all tests.

3. Results

3.1 Assessment of remifentanyl and SCH221510 self-administration under fixed and progressive ratio schedules of reinforcement

Fig. 1 illustrates the dose-response curves for the primary reinforcing effects of remifentanyl and SCH221510 under the FR5 schedule. As anticipated from previous research, all rats readily acquired responding for 3 µg/kg/infusion remifentanyl. Starting at FR1, by the last three stable sessions rats displayed near-exclusive preference for the active nose poke (responses/session: 30.8 ± 1) as compared to the inactive nose poke (responses/session: 4 ± 0.12). When rats were presented with different doses of remifentanyl, the number of responses and infusions were significantly greater than the vehicle condition at all doses [$F(4,16)=18$, $P<0.05$]. Remifentanyl self-administration resulted in a biphasic dose-response curve. By contrast, SCH221510 did not maintain responding significantly different from the

vehicle condition at any doses tested [$F(5,20)=0.5$; $P>0.05$], resulting in a flat dose-response curve.

Fig. 2 illustrates the dose-response curves for remifentanyl and SCH221510 under the PR schedule. When rats were presented with different doses of remifentanyl, the number of responses [$F(4,12)=8.6$, $P<0.05$], infusions [$F(4,12)=27.8$, $P<0.05$] and final ratio completed [$F(4,12)=4.3$, $P<0.05$] were significantly greater than the vehicle condition at all doses. By contrast, SCH221510 did not maintain responding at any doses, which resulted in lower break-points not differing significantly from the vehicle condition [responses: $F(5,15)=0.2$, infusions: $F(5,15)=0.2$ and final ratio completed: $F(5,15)=2.1$].

3.2 Effect of naltrexone pretreatment on remifentanyl and sucrose pellet-maintained responding

Fig. 3 illustrates the effects of naltrexone on responding maintained by remifentanyl (panels A and B) or sucrose pellets (panels C and D). Prior to these determinations, all rats acquired stable responding for either 3 $\mu\text{g/kg}$ /infusion remifentanyl or sucrose pellets under a FR5 schedule. Pretreatment with systemically administered naltrexone produced dose-dependent decreases in remifentanyl self-administration [$F(3,15)=19.7$, $P<0.05$]. Post-hoc analyses revealed that the attenuation was significantly greater than the vehicle pretreatment at all doses of naltrexone (0.03–0.3 mg/kg). By contrast, tested doses of naltrexone (0.03 – 1 mg/kg) did not alter responses or the rate of responding for sucrose pellets [$F(4,20)=0.2$, $P>0.05$], indicating that while naltrexone dampens remifentanyl self-administration, it may not alter the value of other reinforcers such as sucrose pellets.

3.3 Effect of centrally and systemically administered SCH221510 on remifentanyl-maintained responding

Fig. 4 illustrates the effects of systemically (panels A and B) and centrally (panels C and D) administered SCH221510 on remifentanyl-maintained responding. Pretreatment with systemically-administered SCH221510 (1–10 mg/kg) did not alter remifentanyl self-administration [$F(3,15)=1$, $P>0.05$]. At 30 mg/kg SCH221510, all four rats tested displayed flattened postures, unresponsiveness and loss of righting reflex (sedation score: 5). When administered centrally, however, SCH221510 attenuated remifentanyl self-administration in a dose-dependent manner [$F(3,15)=51$, $P<0.05$]; producing significantly greater decreases than vehicle pretreatment. At 3 μg , some degree of sedation was observed (score: 1.8 ± 0.2), manifested by minimal or no spontaneous movement. Therefore, that dose was not used in subsequent antagonist examinations.

3.4 Effect of SCH221510 on sucrose pellet-maintained responding

Fig. 5 illustrates the effects of centrally administered SCH221510 on sucrose pellet-maintained responding. Pretreatment with SCH221510 dose-dependently attenuated the responding for sucrose pellets [$F(3,15)=14.8$, $P<0.05$] as well as rate of responding [$F(3,15)=27.4$, $P<0.05$]. Post-hoc analyses revealed that the responding for sucrose pellets was significantly reduced at 1 and 3 μg (but not at 0.3 μg), whereas decreases in rate of responding were significant at all doses of SCH221510 as compared to vehicle pretreatment.

3.5 Effect of J-113397 on SCH221510-induced attenuation of remifentanyl and sucrose pellet-maintained responding

Fig. 6 illustrates the effects of NOP antagonist J-113397 on SCH221510-induced attenuation of remifentanyl- and sucrose pellet- maintained responding. Following central co-administration, J-113397 (0.3-3 μ g) dose-dependently attenuated the SCH221510 (0.3 and 1 μ g)-induced suppression of remifentanyl self-administration [$F(3,15)=9.2$ and $F(3,15)=19.2$, $P<0.05$]. Similarly, J-113397 (0.3-3 μ g) dose-dependently reversed SCH221510 (1 μ g)-induced decreased responding for sucrose pellets [$F(3,15)=8.4$, $P<0.05$] and SCH221510 (0.3 and 1 μ g)-induced decreases in rate of responding [$F(3,15)=10.4$ and $F(3,15)=13$, $P<0.05$]. Post-hoc analyses indicated that the reversal of SCH221510-induced attenuation of remifentanyl- and sucrose pellet-maintained responding was significant at doses of J-113397 (1 and 3 μ g) as compared to pretreatment with SCH221510 alone.

4. Discussion

The present study is the first to examine the primary and relative reinforcing effects of NOP agonist SCH221510 in rats using intravenous drug self-administration. Drug self-administration is considered a standard model for assessing reinforcing properties, given its high predictive validity and correlation between drugs that are self-administered by animals and those that function as reinforcers in humans (Carter and Griffiths, 2009; Haney and Spealman, 2008; O'Connor et al., 2011). In the present study, rats maintained high responding when self-administering the MOP agonist remifentanyl, consistent with its addictive properties in humans and as seen in other animal models (Baylton et al., 2000; O'Connor and Mead, 2010). Remifentanyl self-administration (0.3-10 μ g/kg/infusion) generated a biphasic dose-response curve under both fixed and progressive ratio schedules of reinforcement (Fig. 1 & 2), characteristic of a compound with reinforcing effects. By contrast, SCH221510 (3-300 μ g/kg/infusion) failed to maintain responding over the wide range of tested doses. This resulted in a flat dose-response curve under both schedule types; indicative of a compound lacking reinforcing properties.

Lack of reinforcing effects by NOP agonists is supported by previous studies in other animal models. For example, monkeys do not self-administer the NOP agonist Ro 64-6198 over a wide dose range (0.03-30 μ g/kg/infusion) (Ko et al., 2009). Ro 64-6198 has produced no change in the threshold for intracranial self-stimulation in rats implanted with electrodes in the ventral tegmental area (VTA) implicated in drug reward (Jenck et al., 2000). In rodents, NOP agonists do not produce CPP, indicating a lack of rewarding properties (Devine et al., 1996; Le Pen et al., 2002; Whiteside and Kyle, 2013). Therefore, our present findings, together with the previous reports utilizing different assays or species, strengthen the notion that NOP agonists are not likely to have abuse potential in humans.

N/OFQ and NOP receptors are widely distributed in moderate to high density in the mesolimbic areas, including the nucleus accumbens and VTA, which have been shown to play an important role in the modulation of reward and motivation pathways (Whiteside and Kyle, 2013; Witkin et al., 2014). Interestingly, centrally- but not systemically-administered SCH221510 attenuated remifentanyl self-administration in a dose-dependent manner (Fig. 4). These differences could be due to differential pharmacokinetics of centrally- versus

systemically-administered SCH221510, and distribution into brain areas required to impact MOP-mediated reinforcement. In monkeys, systemically administered Ro 64-6198 attenuated remifentanyl self-administration but only at a large dose (0.32 mg/kg, IV), which also caused sedation (Podlesnik et al., 2011). This, together with the present data, suggests that large systemic doses of NOP agonists may be required to modulate operant responding in both monkeys and rodents as compared to doses regulating other behavioral attributes. The centrally-administered SCH221510-induced suppression of remifentanyl self-administration provides functional support of previous studies suggesting that NOP agonists inhibit MOP-mediated dopamine release in the mesolimbic pathway (Di Giannuario and Pieretti, 2000; Di Giannuario et al., 1999). These findings indicate that NOP agonists may have the potential to dampen reinforcing effects mediated by MOP receptors.

Attenuation of remifentanyl self-administration at non-sedative doses of SCH221510 was reversed by the NOP antagonist J-113397, indicating a NOP-mediated effect (Fig. 6, panels A and B). Importantly, the SCH221510-induced attenuation of remifentanyl self-administration was comparable to that of naltrexone (Fig. 3, panels A and B) – a drug clinically prescribed to help treat opioid addiction. However, the clinical benefit of naltrexone has been limited due to its dysphoric effects and lack of patient compliance (Aklin et al., 2012). In recent preclinical studies, NOP agonists were shown to possess potent anxiolytic and anti-stress actions, but did not appear to have adverse dysphoric effects (Andero et al., 2013; Witkin et al., 2014). Such properties of NOP agonists, together with our data indicating their ability to block MOP-mediated reinforcing value, suggest their further evaluation for the treatment of opioid addiction.

To assess whether NOP agonists specifically modulate MOP agonist-induced reinforcement, effects of SCH221510 on a non-drug reinforcer (sucrose pellets) were examined. Centrally administered SCH221510 dose-dependently attenuated responding for sucrose pellets, and this effect was mediated by NOP receptors. At the low dose of SCH221510 (0.3 µg), reduction in rate of responding was observed, but the number of sucrose pellets consumed in a session remained the same (Fig. 5). Although the pattern of responding was altered at the lowest dose, the maximum number of reinforcers was still earned indicating that NOP agonists may not alter the hedonic value of other reinforcers. It is possible that this dose of SCH221510 could cause decreased consumption of sucrose pellets in comparison to vehicle had there been no limit to sucrose pellet consumption; future work might further examine these parameters. Sedation is thought to be the side effect of NOP agonists that could potentially disrupt operant behavior (Varty et al., 2005). However, sedative behavior was absent at 0.3 and 1 µg of SCH221510 in the present studies.

Previous studies in rats have shown that palatable food causes increased dopamine release in the nucleus accumbens (Kawahara et al., 2013). It is possible that the mechanism by which NOP agonists attenuate responding for sucrose pellets is by modulating dopamine release in nucleus accumbens. It has also been speculated that food-induced increases in dopamine levels in the nucleus accumbens results from activation of MOP receptors in VTA (Kawahara et al., 2013). Therefore, SCH221510-induced attenuation of responding for sucrose pellets could be due to such anti-opioid mechanisms. However, since naltrexone did not suppress responding for sucrose pellets (Fig. 3 B) over a wide dose-range (0.03-1 mg/

kg), it is more likely that opioid receptors were specifically involved in remifentanyl but not sucrose pellet-reinforced responding. The present data indicated a slight potency difference in the doses of SCH221510 effective in attenuating responding for sucrose pellets (0.3-1 μ g) versus remifentanyl (1-3 μ g). Nevertheless, further studies by using diverse drug and non-drug reinforcers in subjects under different operant schedules are required to determine whether low doses of NOP agonists can specifically modulate drug seeking and taking behaviors. While the basic mechanism of drug and sucrose pellet-maintained behavior is thought to be similar (i.e., increased dopamine release in the mesolimbic pathway); several differences have been reported. For example, remifentanyl- but not food-reinforced behavior is specifically accompanied by increases in the release of neurotransmitter acetylcholine in the nucleus accumbens core (Crespo et al., 2008). Moreover, in the VTA, glutamate receptors regulate feeding behavior whereas opioid receptors regulate drug-maintained behavior (Taber et al., 1998). Further research, such as in microdialysis studies showing more specific effects of NOP agonists on neurotransmitter release, could improve the understanding of how NOP receptors regulate drug versus food-maintained reward and reinforcement.

Conclusion

The present study is the first to use intravenous drug self-administration to provide functional evidence that NOP agonists are devoid of reinforcing effects in rats, as assessed under both fixed and progressive ratio schedules of reinforcement. These findings are in coherence with those from multiple addiction models and species, strongly suggesting that the NOP agonists are less likely to have addictive properties in humans as compared to the opioid analgesics. In addition, these findings demonstrated that NOP agonists attenuated reinforcing effects of the MOP agonist remifentanyl as well as the nondrug reinforcer sucrose pellets. NOP and MOP agonists have opposite effects on the mesolimbic system in modulating reward and reinforcement, i.e., MOP agonists stimulate whereas the NOP agonists inhibit the release of dopamine in the nucleus accumbens (Whiteside and Kyle, 2013). However, NOP agonists do not alter basal dopamine levels in the nucleus accumbens, which may be responsible for the purported lack of dysphoric or adverse effects of such agonists in animal models (Di Giannuario et al., 1999; Le Pen et al., 2002). The anxiolytic and anti-stress actions of NOP agonists are important aspects of these compounds in serving as potential anti-addiction medications - as anxiety and stress-related behaviors are implicated in drug addiction (Andero et al., 2013; Witkin et al., 2014). Since NOP agonists also attenuate rewarding effects of psychostimulants in rodents (Zaveri 2011), it will be important to further investigate whether NOP agonists have the potential to block reinforcing effects of psychostimulants like cocaine or can assist in the treatment of polydrug addiction. Overall, future research should address whether NOP agonists generally or more specifically modulate MOP-mediated reinforcement, and continue to explore their therapeutic potential for the treatment of drug abuse in humans.

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Fig. 1.

Dose-response curves for self-administration of remifentanyl and SCH221510 under a fixed ratio 5 schedule of reinforcement. Results are expressed as the mean $\pm$ S.E.M. number of active nose-poke responses (A) and number of infusions obtained (B) in a 1 h session. Each data point represents mean data from the final 3 sessions at each dose of both drugs. Asterisks (*) denote significant differences from the respective vehicle ($P<0.05$).

Fig. 2.

Dose-response curves for self-administration of remifentanyl and SCH221510 under the progressive ratio schedule of reinforcement. Results are expressed as the mean $\pm$ S.E.M. number of active nose-poke responses (A), number of infusions (B) and final ratio completed (C) per session. Each value represents mean data from the final 2 sessions at each dose of remifentanyl or SCH221510. Asterisks (*) denote significant differences from the respective vehicle ($P<0.05$).

Fig. 3. Effects of naltrexone on remifentanyl- and sucrose pellet-maintained responding under a fixed ratio 5 schedule of reinforcement. Naltrexone was administered subcutaneously as a 20 min pretreatment to determine its effects on remifentanyl (left panels) or sucrose pellet-maintained responding (right panels) in a single session. Results are expressed as the mean $\pm$ S.E.M. (n=6) number of active nose-poke responses (A) and rate of responding (responses/sec) (B) for remifentanyl and number of active nose-poke responses (C) and rate of responding (responses/sec) (D) for sucrose pellets at each dose of naltrexone. 'BL' denotes mean data across-subject at the end of remifentanyl acquisition. 'Pre-' denotes mean data across-subjects from a session without a naltrexone pretreatment. Asterisks (*) denote significant differences from the vehicle pretreatment ($P < 0.05$).

Fig. 4.

Effect of SCH221510 on remifentanyl self-administration under a fixed ratio 5 schedule of reinforcement. SCH221510 was administered subcutaneously (left panels) or intracisternally (right panels) as a 20 min pretreatment. Results are expressed as the mean $\pm$ S.E.M. (n=6) number of active nose-poke responses (A & C) and rate of responding (responses/sec) (B & C) in a single 1 h remifentanyl self-administration session at each dose of SCH221510. 'BL' denotes mean data across-subject at the end of remifentanyl acquisition 'Pre-' denotes data from a session without a SCH221510 pretreatment. Asterisks (*) denote significant differences from the vehicle pretreatment ($P<0.05$).

Fig. 5.

Effect of SCH221510 on sucrose pellet-maintained responding under a fixed ratio 5 schedule of reinforcement. SCH221510 was intracisternally administered as a 20 min pretreatment. Results are expressed as the mean $\pm$ S.E.M. (n=6) number of active nose-poke responses (A) and rate of responding (responses/sec) (B) for sucrose pellets in a single session at each dose of SCH221510. 'Pre-' denotes data from a session without a SCH221510 pretreatment. Asterisks (*) denote significant differences from the vehicle pretreatment ($P<0.05$).

Fig. 6.

Effect of J-113397 on SCH221510-induced attenuation of remifentaniil- and sucrose pellet-maintained responding under a fixed ratio 5 schedule of reinforcement. J-113397 and SCH221510 were intracisternally co-administered as a 20 min pretreatment. Results are expressed as the mean $\pm$ S.E.M (n=6) number of active nose-poke responses (A) and rate of responding (responses/sec) (B) for remifentaniil and number of active nose-poke responses (C) and rate of responding (responses/sec) (D) for sucrose pellets in a single session. Asterisks (*) denote significant differences from the J-113397 vehicle co-administered with 0.3 µg (grey bars) or 1 µg (black bars) of SCH221510 ($P < 0.05$).