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The Mu/Kappa Agonist Nalbuphine Attenuates Sensitization to the Behavioral Effects of Cocaine

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Abstract

Sensitization refers to an increase in sensitivity to a drug and is believed to play a role in the etiology of substance use disorders. The purpose of the present study was to evaluate the ability of the mixed mu/kappa agonist nalbuphine to modulate sensitization to the locomotor and positive reinforcing effects of cocaine. Rats were habituated to a locomotor activity chamber and treated with saline (1.0 ml/kg, ip), cocaine (10 mg/kg, ip), or cocaine + nalbuphine (10 mg/kg, ip) every day for 10 days. Following locomotor activity testing, rats were implanted with intravenous catheters and cocaine self-administration was examined on fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement. Rats treated with cocaine exhibited a progressive increase in locomotor activity over the 10-day treatment period, and this effect was significantly reduced in rats treated with cocaine + nalbuphine. In self-administration tests, rats treated with cocaine exhibited significantly higher levels of responding at a threshold dose of cocaine (0.03 mg/kg/infusion) on both FR and PR schedules than rats treated with saline. This increase in responding at a threshold dose of cocaine was blocked completely in rats treated with cocaine + nalbuphine. These data suggest that nalbuphine attenuates the development of sensitization to the behavioral effects of cocaine.

Keywords

cocaine; fixed ratio; locomotor; nalbuphine; progressive ratio; self-administration; sensitization

1. Introduction

Sensitization refers to an increase in sensitivity to a drug following its repeated administration and is believed to be a contributing factor in the development of substance use disorders (Robinson and Berridge, 2000; Morgan and Roberts, 2004). Sensitization has been characterized extensively with psychomotor stimulants, and many studies have described sensitization to the locomotor effects of cocaine (Jackson and Nutt, 1993; Sabeti

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et al., 2003). Both the acute (Beyer and Steketee, 2001) and sensitized (Crombag et al., 2002) locomotor effects of cocaine are due to increases in dopaminergic activity in mesolimbic structures that also mediate cocaine's positive reinforcing effects (Maldonado, 2003; Robinson and Kolb, 2004). Consequently, dosing protocols that produce sensitization to cocaine's locomotor effects frequently produce sensitization to its positive reinforcing effects, resulting in higher rates of self-administration in sensitized animals (Lorrain et al., 2000; Schenk and Partridge, 2000).

Sensitization has also been observed with opioid receptor agonists, and there is evidence that mu and kappa receptors functionally oppose one another in sensitization-related processes. For instance, robust sensitization develops to the locomotor effects of the mu agonist morphine (Vanderschuren et al., 1999; Hofford et al., 2012). Furthermore, rats treated with the mu agonist heroin exhibit cross-sensitization to the locomotor effects of cocaine (Leri et al., 2003), and rats treated with morphine exhibit cross-sensitization to both the locomotor (Lett, 1989; Cunningham et al., 1997) and conditioned rewarding (Shippenberg et al., 1998) effects of cocaine. Similar effects have also been reported at the biochemical level, in that morphinetreated rats show an enhanced response to cocaine-induced increases in *c-fos* expression (Erdtmann-Vourliotis et al., 2000).

Whereas mu opioids positively modulate sensitization-related processes, kappa opioids negatively modulate these processes. For instance, kappa opioids fail to produce sensitization to their own behavioral effects and block the development of sensitization to the locomotor (Heidbreder et al., 1993; Spanagel, 1995) and conditioned rewarding (Shippenberg et al., 1996) effects of cocaine. We previously reported that the kappa agonist spiradoline blocks sensitization to the locomotor effects of morphine (Smith et al., 2009a) and cross-sensitization to the locomotor effects of cocaine in morphine-treated animals (Smith et al., 2009b). The ability of spiradoline to block both sensitization and cross-sensitization in morphine-treated animals is blocked by the kappa-selective antagonist nor-binaltorphimine, indicating that these effects are mediated by kappa receptors and suggesting that kappa agonists functionally oppose mu-mediated sensitization processes (Smith et al., 2009a; 2009b).

Few studies have examined the ability of mixed mu/kappa agonists (i.e., opioids with agonist activity at both mu and kappa receptors) to modulate sensitization-related processes, but the limited data that exist indicate that their kappa component of action functionally opposes their mu component of action under some conditions. We reported that high, but not low or moderate, doses of the mixed mu/kappa agonist nalbuphine produced sensitization to its effects on locomotor activity (Smith et al., 2009a). When nor-binaltorphimine was given prior to treatment with doses of nalbuphine that did not produce sensitization when administered alone, robust sensitization was seen in all subjects. These data provide additional support for the hypothesis that agonist activity at kappa receptors functionally opposes mu-mediated sensitization processes.

The purpose of the present study was to examine the ability of the mixed mu/kappa agonist nalbuphine to modulate the development of sensitization to the locomotor and positive reinforcing effects of cocaine. To this end, rats were treated with saline, cocaine (10 mg/kg), or cocaine + nalbuphine (10 mg/kg) every day for 10 days and the development of sensitization to the locomotor effects of cocaine was examined. Approximately one week later, all groups were implanted with intravenous catheters and cocaine self-administration was examined on fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement.

2. Methods

2.1. Animals and Apparatus

Male, Long-Evans rats were obtained from Charles Rivers Laboratories (Raleigh, NC, USA) at approximately 230–250 g (young adulthood). Upon arrival, rats were housed individually in polycarbonate cages (interior dimensions: 50 × 28 × 20 cm) on a 12-hr light/dark cycle (lights on 07:00) in a temperature- and humidity-controlled colony room. Except during the brief period of lever-press training, food and drinking water were available *ad libitum* in the home cage. All subjects were maintained in accordance with the guidelines of the *Guide for the Care and Use of Laboratory Animals* (Institute for Laboratory Animal Research, 2011), and all procedures were approved by the Davidson College Animal Care and Use Committee. Two cohorts of rats were obtained at different time points, approximately 3 months apart, and rats from both cohorts were represented in each of the three experimental groups (see below).

All locomotor activity tests were conducted in a single, open-field, locomotor activity chamber (interior dimensions: 43 × 43 × 30 cm) obtained from Med Associates, Inc (St Albans, VT, USA). The chamber consisted of a PVC floor and acrylic sidewalls with aluminum corner supports. Two circuit boards were located on opposite sidewalls 2.5 cm above the floor of the chamber. One board contained 16 infrared photocells spaced 2.5 cm apart; the opposite board contained 16 infrared detectors with identical spacing. Software and interfacing for the chamber were obtained from Med Associates, Inc.

Lever-press training and cocaine self-administration tests were conducted in polycarbonate and aluminum operant conditioning chambers (interior dimensions: 31 × 24 × 21 cm) from Med Associates, Inc. Each chamber was equipped with two response levers on one wall, a food hopper located between the levers, a white stimulus light located above each lever, and a houselight located on the opposite wall. Drug infusions were delivered from an infusion pump mounted outside the chamber via Tygon tubing protected by a stainless steel spring and attached to a counter-balanced swivel suspended above the chamber. Food pellets were delivered via a pellet dispenser located behind the forward wall. The left lever was designated as the active lever in all experimental sessions. All experimental events were programmed and data were collected with software and interfacing from Med Associates, Inc.

2.2. Induction of Sensitization

Approximately one week after arrival, all rats were habituated to the locomotor activity chamber for 5 min/day for two consecutive days. On the following day, a 5-min baseline control test was conducted in which all rats received an injection of saline (1.0 ml/kg, ip), 15 min prior to placement in the chamber. Following this test, rats were assigned randomly to one of three experimental groups (saline, cocaine, or cocaine + nalbuphine) and locomotor activity was examined over the next 10 consecutive days. On each of these days, rats were removed from their home cage and administered an intraperitoneal injection based on their group assignment: saline (1.0 mg/kg), cocaine (10 mg/kg), or cocaine (10 mg/kg) + nalbuphine (10 mg/kg). Saline and cocaine were always administered 15 min prior to testing; nalbuphine was administered 5 min before cocaine and 20 min prior to testing. During the locomotor activity test, each rat was placed individually into the locomotor activity chamber, and distance traveled was measured over the next 5 min. Immediately after the test, the rat was returned to its home cage and left undisturbed until the next testing day. The 15 min pretreatment interval and the 5 min testing period were selected to coincide with the time and duration of cocaine's peak effects on locomotor activity (Smith et al., 2003).

2.3. Lever Press Training

Beginning on the day immediately following the final locomotor activity test, all rats were lightly food restricted to no less than 90% of their free feeding body weight and trained to lever press using food reinforcement in the operant conditioning chambers. In these sessions, each lever press was reinforced with a 45 mg Noyes grain pellet (Lancaster, NH, USA) on a fixed ratio (FR1) schedule of food reinforcement. Each training session lasted 2 hr or until 40 reinforcers had been delivered, whichever occurred first. If any rat failed to acquire the lever press response by the third day of training, the response was shaped by the experimenter using manually delivered food pellets. Training continued until rats acquired the maximum number of 40 reinforcers in any three training sessions. All rats met this criterion within 7 days, and no differences were observed between groups. Rats returned to unrestricted feed once they met the acquisition criterion.

2.4. Surgery

Eight days after the final locomotor activity test, rats were anesthetized with a combination of ketamine (100 mg/kg, ip) and xylazine (8.0 mg/kg, ip) and surgically implanted with intravenous catheters (CamCaths, Cambridge, UK) according to previously described methods (Smith et al., 2008). Each catheter was inserted into the right jugular vein, routed subcutaneously over the shoulder, and exited the body on the dorsal surface of the scapulae. Butorphanol (1.0 mg/kg, sc) was administered immediately after surgery as an analgesic, and a solution of heparinized saline and ticarcillin (20 mg/kg, iv) was infused through the catheter daily to maintain patency and prevent infection. After 7 days, ticarcillin was discontinued and only heparinized saline was used to maintain catheter patency. All rats were given two days to recover before beginning self-administration training.

2.5. Self-Administration Training

Two days after surgery, and 10 days after the final locomotor activity test, rats were placed in the operant conditioning chambers and connected to an infusion pump via Tygon tubing. All self-administration sessions began with illumination of the house light and illumination of the white stimulus light above the active response lever. During the initial training sessions, each response on the active response lever delivered a 1.0 mg/kg infusion of cocaine lasting between 3.0 and 4.0 s, based on body weight. During these and all subsequent self-administration sessions, a tone sounded for 5 s coincident with each infusion and the stimulus light above the lever turned off for 20 s to signal a timeout period during which cocaine was not available. A total of three training sessions were conducted over three consecutive days. During the first two training sessions, responding was reinforced on an FR1 schedule of reinforcement; during the third and final training session, responding was reinforced on an FR2 schedule of reinforcement. All three training sessions terminated automatically after 10 infusions were obtained. The number of infusions was limited in this manner to minimize any sensitization that may have developed from contingent infusions of self-administered cocaine (see Morgan et al., 2006).

2.6. Progressive Ratio Testing

On the day immediately following the third training session, operant contingencies changed, and responding was reinforced on a PR schedule of reinforcement. On this schedule, the number of responses required for each infusion of cocaine increased progressively over the course of the session according to the following ratio values: 1, 3, 6, 9, 12, 17, 24, 32, 42, 56, 73, 95, 124, 161, 208, 268, 346, 445, and 573 (for complete algorithm, see Suto et al., 2002). Each session continued until a breakpoint was reached, with breakpoint defined as the number of infusions obtained before 1 hr elapsed with no infusions. Daily test sessions were conducted for each dose of cocaine until breakpoints were stable (i.e., three consecutive

days during which breakpoint varied by no more than three increments with no increasing or decreasing trends). In the first cohort of rats tested, breakpoints were determined for 0.0 (saline), 0.3, and 1.0 mg/kg/infusion cocaine. The second cohort was tested with an additional dose of cocaine (0.03 mg/kg/infusion), because selective effects were observed at this dose during FR testing in the first cohort (see Results). All doses were tested in an irregular order with the stipulation that no more than two ascending or descending doses could be tested consecutively.

2.7. Fixed Ratio Testing

On the day immediately following the final test session on the PR schedule, operant contingencies changed again, and responding was reinforced on an FR1 schedule of reinforcement. Testing on the FR1 schedule was conducted during five test sessions conducted over five consecutive days. Each session lasted 120 min, and a different dose of cocaine (or saline) was tested during each session. No limit was placed on the maximum number of infusions that could be earned, other than those set by the session length and post-infusion timeout. Each dose was tested once, and the order in which doses were tested varied in an irregular order with the stipulation that no more than two ascending or descending doses could be tested consecutively. All rats were tested with 0.0 (saline), 0.03, 0.1, 0.3, and 1.0 mg/kg/infusion cocaine.

2.8. Data Analysis

Locomotor activity was measured as distance traveled in cm. Data from each of the 10 test days were normalized across subjects by subtracting the distance traveled from each of the 10 test sessions from the distance traveled during the baseline control test in which saline was administered. These data were analyzed via a mixed-factor, repeated-measures ANOVA using group as a between-subjects factor and time (day) as a within-subjects factor. To examine changes in locomotor activity across the 10 days of testing, a regression line was then fitted to the data from each individual rat and the slope of this line was determined. The slopes of these lines were then analyzed via one-way ANOVA to compare the development of sensitization across groups. Post hoc analyses were conducted using Dunnett's *t* tests with cocaine-treated rats serving as the reference comparison group. Slope estimates from individual animals were normally distributed and homogeneity of variance testing revealed no significant heterogeneity across groups.

Self-administration data were initially analyzed via a mixed-factor ANOVA that included the variable "cohort" as a between-subjects factor. No main effects or interactions were observed for the cohort variable; consequently, data from both cohorts were collapsed and considered collectively. Data for the PR and FR schedules of reinforcement were analyzed via two-way, mixed-factor ANOVA using group as a between-subjects factor and dose as a within-subjects factor. Because only a subset of rats were tested with the lowest dose of cocaine on the PR schedule of reinforcement (see Self-Administration Testing above), data from that dose were analyzed separately via one-way ANOVA. For both the FR and PR schedules, data obtained with saline were analyzed separately from the dose-response data via one-way ANOVA. For the FR schedule, area under the curve (AUC) estimates were calculated for each rat by applying the Trapezoidal Rule to the dose-response data. AUC estimates provide a measure of reinforcing efficacy in drug self-administration procedures, and are helpful when a dose-effect curve has both an ascending and descending limb (Cooper et al. 2008). These AUC estimates were then analyzed via one-way ANOVA. Post hoc analyses were conducted using Dunnett's *t* tests with cocaine-treated rats serving as the reference comparison group. AUC estimates from individual animals were normally distributed and homogeneity of variance testing revealed no significant heterogeneity across groups.

3. Results

3.1. Locomotor Activity Testing

The three groups differed significantly in baseline rates of locomotor activity during the saline control test and prior to drug administration [main effect of group: $F(2, 33) = 3.549$; $p = .041$]. Specifically, the group randomly assigned to receive nalbuphine + cocaine traveled approximately 35% further than the other two groups. The mean (SE) distance traveled of the three groups were 1242 (117), 1244 (118), and 1677 (108) cm in the saline, cocaine, and nalbuphine + cocaine groups, respectively. Because of these differences, locomotor activity data over the 10 days of drug treatment were normalized across groups by expressing distance traveled as a difference from these baseline values.

All groups, including the saline control group, exhibited an increase in locomotor activity over the 10 days of testing (Figure 1). A mixed-factor, repeated-measures ANOVA revealed a main effect of day [$F(9, 279) = 10.779$; $p < .001$] and a main effect of group [$F(2, 31) = 15.021$; $p < .001$]. In the group treated with cocaine, locomotor activity was significantly greater on Days 5–10 than on Day 1 ($p < .05$). As noted above (see Methods), regression lines were fitted to the individual data and the slopes of these lines were used to compare changes in locomotor activity over the 10 days of testing. The slopes of all regression lines were positive, indicating a progressive increase in locomotor activity over the testing period. Importantly, the degree to which locomotor activity increased differed significantly across groups [$F(2, 33) = 4.545$; $p = .019$]. Locomotor activity increased significantly more in the cocaine-treated group than in the saline-treated group ($p = .009$), and this effect was apparent within the first few days of testing. Nalbuphine attenuated the increase in locomotor activity observed with cocaine ($p = .032$), such that the increase in activity observed in nalbuphine-treated rats was similar to that observed in saline-treated rats.

3.2 Self-Administration Training

All rats responded on the first day of training and received the maximum number of 10 infusions during all three training sessions. All training sessions terminated automatically after 10 infusions had been obtained, and the duration of these training sessions was similar across the three days of training and the three groups of rats (Table 1). A two-way, mixed factor ANOVA revealed no significant effects of group or day, and no significant group $\times$ day interaction.

3.3 Progressive Ratio Testing

All rats were tested with saline and the two highest doses of cocaine on the PR schedule of reinforcement (Figure 2). As expected, breakpoints were greater at the high dose of cocaine than at the low dose [$F(1, 29) = 15.810$; $p < .001$], but no significant differences were observed across the three groups. A subset of rats from each group was tested with a lower dose of cocaine (0.03 mg/kg/infusion; see Methods above), and breakpoints differed significantly at this dose [$F(2, 15) = 4.507$; $p = .033$]. In this subset of rats (see Figure 2, insert), breakpoints were greater in the cocaine-treated group than in the saline-treated group ($p = .030$) and cocaine + nalbuphine group ($p = .017$); however, breakpoints did not differ at the two higher doses of cocaine in this subgroup (data not shown). Breakpoints maintained by saline did not differ across groups when data from the total population of rats were considered or when data from only the subset of rats tested at the lowest dose were considered.

3.3. Fixed Ratio Testing

In most rats, responding on the FR schedule was characterized by an inverted U-shaped dose-effect curve with a short ascending limb and a long descending limb (Figure 3). A two-

way, mixed-factor ANOVA revealed a main effect of dose [$F(3, 75) = 46.444$; $p < .001$], a main effect of group [$F(2, 25) = 5.418$; $p = .011$], and a dose $\times$ group interaction [$F(6, 75) = 2.931$; $p = .013$]. Although minimal differences were observed at higher doses of cocaine, cocaine-treated rats self-administered more of the lowest dose of cocaine (0.03 mg/kg/infusion) than either saline-treated rats or rats treated with cocaine + nalbuphine. An AUC analysis also revealed significant differences across the three groups [$F(2, 27) = 5.009$; $p = .015$], and post hoc tests revealed that rats treated with cocaine self-administered more cocaine than rats treated with saline ($p = .007$) or cocaine + nalbuphine ($p = .025$). Responding maintained by saline was low (generally less than 25 responses/session) and did not differ across groups. Similar effects were observed when only data from the rats tested with the lowest dose of cocaine on the PR schedule were considered. Specifically, in this subgroup, a repeated-measures ANOVA revealed main effect of dose [$F(3, 33) = 44.277$; $p < .001$], a main effect of group [$F(2, 11) = 7.932$; $p = .007$], and a dose $\times$ group interaction [$F(6, 33) = 6.281$; $p < .001$], and these effects were attributed to significant differences at the lowest dose of cocaine tested (data not shown).

4. Discussion

The primary finding of this study is that the mixed μ/κ agonist nalbuphine attenuates the development of sensitization to the behavioral effects of cocaine. The progressive increase in locomotor activity observed in cocaine-treated rats was significantly attenuated in rats that were co-administered nalbuphine throughout the dosing regimen. Perhaps more importantly, nalbuphine completely blocked the development of sensitization to the positive reinforcing effects of a threshold dose of cocaine. Data from cocaine-treated rats that were co-administered nalbuphine were almost identical to those of rats treated with only saline on both FR and PR schedules of reinforcement. These effects are consistent with nalbuphine's agonist activity at κ opioid receptors and suggest that the κ receptor may be a useful target in the development of therapeutics for cocaine abuse.

In the locomotor activity test, all rats exhibited a progressive increase in locomotor activity over the 10 days of testing, but this effect was significantly greater in rats treated with cocaine. One caveat about the locomotor activity data is that significant differences were observed across the three groups under baseline conditions and prior to any drug administration. Groups were assigned randomly and were not matched based on locomotor activity scores, and rats assigned to the nalbuphine + cocaine group traveled approximately 35% further than the other two groups during baseline control tests. Although all locomotor activity data after drug administration were normalized by expressing distance traveled as a difference from these baseline control values, the higher baseline values for the nalbuphine + cocaine group may have limited the degree to which locomotor activity could be expressed if a ceiling effect was observed. A second caveat about the locomotor activity data is that a numeric increase in locomotion was observed over the 10 days of testing in rats treated with saline. In this group, locomotor activity was numerically suppressed relative to baseline during the first four days of treatment and then returned to baseline during the last six days of treatment. The reason for the initial suppression of locomotor activity and subsequent return to baseline is not known, but it may be due to the minimal amount of habituation to the locomotor activity chamber prior to testing (only two exposures of 5 min each). Indeed, locomotor activity stabilized in the saline group after the initial few days of testing. Because neither of these caveats was predicted *a priori*, the locomotor activity data should be considered exploratory until these effects can be replicated.

By normalizing the data as a difference from baseline, we were able to examine changes in locomotor activity over the 10 days of testing by comparing the slopes of the regression lines fitted to individual data collected over the testing period. The slopes of all regression

lines were positive, indicating an increase in locomotor activity over the 10 days of testing. Importantly, the slopes of the regression lines for the cocaine-only group were significantly steeper than the slopes for the other two groups, indicating that locomotor activity increased to a significantly greater degree in rats treated with cocaine. The slopes for the saline group and the nalbuphine + cocaine group were nearly identical, indicating that the increases in locomotor activity were similar between these two groups. Because increases in locomotor activity are indicative of sensitization to the behavioral effects of cocaine, these data suggest that sensitization was observed in rats treated with cocaine, and that this effect was significantly attenuated in rats treated with nalbuphine. If correct, this would represent one of the first demonstrations that an opioid with agonist activity at both mu and kappa receptors attenuates the development of sensitization to the behavioral effects of cocaine.

Sensitization to the positive reinforcing and incentive motivational properties of drugs is believed to contribute to the etiology of substance use disorders (Robinson and Berridge, 2000; Morgan and Roberts, 2004), so it is notable that nalbuphine completely blocked sensitization to the positive reinforcing effects of a threshold dose of cocaine. On both FR and PR schedules of reinforcement, rats treated with cocaine + nalbuphine did not differ from rats treated with saline. In contrast, cocaine-only rats exhibited higher levels of responding for a low dose of cocaine on both FR and PR schedules of reinforcement. Although only a subset of rats was tested with the lowest dose of cocaine on the PR schedule, all rats were tested with the lowest dose of cocaine on the FR schedule. The effects observed on the FR schedule were apparent when only those rats tested with all three doses on the PR schedule were used in the analysis (i.e., the second cohort) or when all the rats were used in the analysis (i.e., both cohorts). Consequently, the effects observed on the FR schedule cannot be explained by differences in the behavioral history of the rats when tested on the PR schedule.

Sensitization to the positive reinforcing effects of drugs may be expressed in multiple ways. For instance, sensitization may increase the effectiveness of a drug, thereby shifting the curve upward, or it may increase the potency of a drug, thereby shifting the curve leftward. In the present investigation, responding maintained by moderate and high doses of cocaine were unaffected by cocaine treatment, indicating that the treatment regimen did not produce a parallel upward or a parallel leftward shift of the dose-effect curve. Rather, cocaine treatment increased the salience of a very low dose of cocaine, thereby lowering the threshold dose needed to maintain responding (see Oleson and Roberts, 2009 for examples of dosing regimens that selectively increase cocaine self-administration at threshold doses). It is unclear how these different manifestations of sensitization impact drug use in human populations, but responding maintained by a threshold dose of cocaine is positively correlated with other measures of drug-seeking behavior (Smith et al., 2004; España et al., 2010). At the very least, an increase in the reinforcing efficacy of a low dose of cocaine expands the conditions under which the drug will be self-administered, particularly under conditions in which unit price is high or drug purity is low.

The pharmacological mechanisms responsible for the locomotor and positive reinforcing effects of cocaine are well understood. Cocaine binds to dopamine transporters on the terminal buttons of dopamine A10 neurons that originate in the ventral tegmental area (VTA) and project to the nucleus accumbens (NAc). Cocaine blocks the reuptake of dopamine in this structure, thus increasing synaptic concentrations of dopamine and prolonging its activity at postsynaptic receptors. The release of dopamine from A10 neurons is under tonic inhibitory and excitatory control by endogenous opioid peptides acting in both the VTA and NAc. For instance, dopamine-releasing neurons projecting to the NAc are under inhibitory control by GABAergic interneurons located in the VTA. Endogenous mu opioid peptides inhibit these GABAergic neurons, thus releasing dopamine cell bodies from

inhibition and inducing the release of dopamine in the NAc (Spanagel et al., 1992). When administered acutely, selective mu agonists increase central dopamine concentrations (Wise et al., 1995; Lecca et al., 2007) and synergistically enhance the elevations of extracellular dopamine induced by cocaine (Smith et al., 2006). In the NAc, the endogenous opioid peptide dynorphin inhibits dopamine release by binding to kappa opioid receptors on the terminal buttons of dopamine neurons. Selective agonists at kappa receptors decrease mesolimbic dopamine concentrations (Di Chiara and Imperato 1988; Heijna et al. 1990; Spanagel et al. 1990; Donzanti et al. 1992) and attenuate the increases in mesolimbic dopamine concentrations induced by cocaine administration (Maisonneuve et al. 1994; Thompson et al. 2000). In the present study, the ability of nalbuphine to attenuate sensitization to the behavioral effects of cocaine is consistent with its activity at kappa receptors.

There are currently no FDA-approved pharmacotherapies for cocaine abuse. Kappa agonists block the positive reinforcing effects of cocaine (Mello and Negus, 1998; Cosgrove and Carroll, 2002, Morani et al., 2009), and block the development of sensitization to cocaine's behavioral effects (Heidbreder et al., 1993; Shippenberg et al., 1996; Puig-Ramos et al., 2008); however, kappa agonists do not represent viable options in human populations because they produce dysphoria and hallucinations, which limit their clinical utility (Wadenberg, 2003; Dortch-Carnes and Potter, 2005). Mixed mu/kappa agonists, in contrast, have a long history of being well tolerated in clinical populations (Schmidt et al., 1985; Vogelsang and Hayes, 1991). Furthermore, they have less abuse liability than traditional mu agonists (Peachey, 1987; Hoskin and Hanks, 1991), and reports of their misuse are uncommon. In animal models, nalbuphine blocks the positive reinforcing effects of cocaine (Negus and Mello, 2002; but also see Mello et al., 1993), fails to produce cross-sensitization to cocaine when administered repeatedly (Smith et al., 2009b), and attenuates the development of sensitization to the behavioral effects of cocaine (present study). Unfortunately, the limited data with nalbuphine in human subjects have been less promising. In one of the very few studies that examined nalbuphine in a stimulant-abusing population, it failed to attenuate the positive affective states produced by cocaine (Mello et al., 2005). Although nalbuphine probably lacks utility as a monotherapy for cocaine abuse, it may have utility as an adjunctive treatment in combination with other medications. For instance, clinical trials examining the efficacy of agonist substitution therapies have reported positive findings with amphetamine and other stimulants (Grabowski et al., 2004; Dackis et al., 2005; Mooney et al., 2009); however, amphetamine-like drugs carry significant abuse liability and produce sensitization and cross-sensitization when administered repeatedly (Lett, 1989; Vanderschuren et al., 1999). Nalbuphine and other mixed mu/kappa agonists may be particularly useful with these therapies because their kappa component of action may serve both to decrease their abuse liability and to reduce their ability to produce sensitization and cross-sensitization during repeated treatment.

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Research Highlights

- Nalbuphine's ability to reduce cocaine-induced sensitization was examined.
- Nalbuphine attenuated the progressive increase in locomotor activity induced by cocaine.
- Nalbuphine blocked the development of sensitization to the positive reinforcing effects of a threshold dose of cocaine.

Figure 1.

Locomotor effects produced by daily injections of saline, 10 mg/kg cocaine, and 10 mg/kg cocaine + 10 mg/kg nalbuphine across 10 consecutive days of testing. Left panel depicts distance traveled (cm) relative to a baseline control session conducted one day prior to beginning drug treatment. Asterisks (*) indicate significant differences from Day 1 ($p < .05$). Right panel depicts slopes of regression lines fitted to the data of individual rats from each group. Asterisks (*) indicate significant differences between groups ($p < .05$). Vertical lines represent the SEM. $n = 7-12$ per group.

Figure 2. Cocaine self-administration on a PR schedule of reinforcement in rats treated with saline, 10 mg/kg cocaine, and 10 mg/kg cocaine + 10 mg/kg nalbuphine over 10 consecutive days. Left axis depicts breakpoints as number of infusions obtained; right axis depicts breakpoints as final ratio value completed. Inset: Breakpoints maintained by the lowest dose of cocaine. Asterisks (*) indicate significant differences between groups ($p < .05$). Vertical lines represent the SEM. $n = 7-12$ per group (inset: $n = 5-6$ per group).

Figure 3.

Cocaine self-administration on an FR1 schedule of reinforcement in rats treated with saline, 10 mg/kg cocaine, and 10 mg/kg cocaine + 10 mg/kg nalbuphine over 10 consecutive days. Left panel depicts number of infusions obtained during 2-hr test sessions. Right panel depicts area under the curve (AUC) estimates for each group. Asterisks (*) indicate significant differences between groups ($p < .05$). Vertical lines represent the SEM. $n = 7-11$ per group.

Table 1

Mean (SEM) duration ^a of each training session for rats treated with saline, cocaine, and cocaine + nalbuphine.

Group	Day 1 (FR1)	Day 2 (FR1)	Day 3 (FR2)
Saline	31.6 (6.4)	37.7 (8.5)	45.9 (9.1)
Cocaine	39.0 (5.5)	40.4 (6.8)	43.3 (8.4)
Cocaine + Nalbuphine	32.1 (12.8)	35.8 (12.1)	43.0 (11.7)

^a All values expressed in min.