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The effects of long-term chronic buprenorphine treatment on the locomotor and nucleus accumbens dopamine response to acute heroin and cocaine in rats

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Abstract

We have previously shown that chronic treatment with the partial mu-opioid receptor agonist, buprenorphine, blocks the nucleus accumbens dopamine response to an acute injection of heroin, whereas it potentiates the response to an acute injection of cocaine after 4–5 days of treatment. Here we studied the effects of chronic exposure to buprenorphine via osmotic minipumps for up to 28 days (1.5 or 3.0 mg/kg/day) on responses to acute injections of heroin and cocaine. Increases in locomotion induced by heroin (0.25 mg/kg, sc), given on the 5th, 15th or 25th day of treatment were unaffected by buprenorphine, whereas increases induced by cocaine (20 mg/kg, ip) were enhanced early in treatment but not on the 15th or 25th days. Using in vivo microdialysis we found that both the suppression of the dopaminergic response in the nucleus accumbens to heroin and the potentiation to cocaine seen early in treatment diminished over the 26–27 days, whereas basal dopamine levels remained elevated throughout. Therefore, although these studies do not explain the mechanism whereby buprenorphine reduces heroin and cocaine intake, they do indicate that there is little tolerance to the presence of chronic buprenorphine.

Keywords: Buprenorphine; Heroin; Cocaine; Dopamine; Locomotion; Microdialysis; Tolerance; Addiction

1. Introduction

The primary drugs used in treatment of opioid addiction are the full mu-opioid receptor agonist, methadone, and the partial mu-opioid receptor agonist buprenorphine, both of which are slow to dissociate from receptors and have long half-lives (Tzschentke, 2002). In studies with opioid addicts there are reports that cocaine use is not significantly affected (Strain et al., 1996; Schottenfeld et al., 1997). In one study, specifically examining concomitant cocaine use in opioid addicts, significant decreases in cocaine use were reported during buprenorphine treatment in a dose-dependent manner (Montoya et al., 2004). Consistent with the latter finding, studies in monkeys have shown that intermittent or daily injections of buprenorphine can reduce cocaine self-administration under complex schedules of reinforcement (Mello et al., 1992), as well as cocaine–heroin "speedball" and heroin self-administration (Mello and Negus, 1998). In fact, in one study it was found that buprenorphine significantly reduced cocaine seeking for more than 120 days (Mello et al., 1992), indicating little tolerance to the effects of repeated acute buprenorphine treatment over time.

We have recently shown that chronic treatment with buprenorphine reduces cocaine, but not heroin, intake in rats trained to self-administer both drugs on an FR1 schedule of reinforcement (Sorge and Stewart, submitted), although it reduces responding in extinction and reinstatement induced by either drug (Sorge et al., 2005). In addition, we found that, in tests performed after less than 10 days of treatment, chronic buprenorphine attenuated the nucleus accumbens (NAc) dopaminergic (DA) response to heroin without affecting heroin-induced locomotor activity. In contrast,

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buprenorphine potentiated the locomotor and NAc DA responses to cocaine (Sorge et al., 2005).

To determine whether these behavioral and neurochemical responses to acute injections of heroin and cocaine would be modified by longer exposure to buprenorphine, we examined the locomotor and NAc DA responses to acute injections of heroin (0.25 mg/kg, sc) or cocaine (20 mg/kg, ip) after either 13–15 or 25–27 days of chronic buprenorphine treatment (sham, BUP1.5: 1.5 mg/kg/day and/or BUP3.0: 3.0 mg/kg/day). In the experiment on locomotion, separate groups of rats were tested on either the 5th, 15th or 25th day of buprenorphine treatment with injections of either heroin or cocaine, and locomotor activity was assessed. In the microdialysis experiment, heroin and cocaine injections were administered on the 13–14th or 26–27th day of buprenorphine exposure (sham, BUP1.5 or BUP3.0) to separate groups of rats.

2. General methods

2.1. Subjects

A total of 107 male Long-Evans rats (5–6 rats per group, Charles River, St. Constant, QC) weighing 325–350 g at the start of the experiments were used. Animals were singly housed in reverse cycle rooms (lights OFF at 0800 h; ON at 2000 h) with food (Rat Chow, Purina Foods) and water *ad libitum*. All experimental procedures followed the guidelines of the Canadian Council on Animal Care and were approved by the Animal Care Committee at Concordia University.

2.2. Drugs

Chronic buprenorphine (3.0 mg/kg/day, buprenorphine HCl purchased from Reckitt Benckiser Healthcare Limited, Hull, UK) treatment was achieved via subcutaneous (sc) implantation of osmotic, buprenorphine-filled, minipumps (Alzet model 2ML2, Durect Corp., Cupertino, CA). Surgical procedures, using Isoflurane anesthesia (Vetoquinol N.A. Inc, Lavaltrie, QC) have been previously described (Sorge et al., 2005). No pump was implanted in the sham rats, though the same surgical procedures were employed. (Preliminary results in our lab showed no significant behavioral effects of saline-filled osmotic minipumps on self-administration behavior so, to reduce experimental costs, the practice was discontinued.) Heroin (0.25 mg/kg, sc, diacetylmorphine HCl) was purchased from Almat Pharmachem Inc (Concord, ON) and cocaine (20 mg/kg, ip, cocaine HCl) from Medisca Pharmaceutique (Montreal, QC). The doses of heroin and cocaine chosen were those previously used in our laboratory to elicit both locomotor activity (without sedation or stereotypy) and a significant NAc DA response (Sorge et al., 2005).

2.3. Apparatus

Locomotor activity and microdialysis chambers have been described elsewhere (Sorge et al., 2005). Briefly locomotor activity was monitored in a bank of 12 activity chambers by dual infrared beams located on each of the long sides of the rectangular chamber, positioned 3.5 cm from the stainless steel bar floor and 10 cm from each other. Microdialysis chambers were custom made hexagonal chambers with Plexiglas walls, wooden ceilings and stainless steel bar floors. The microdialysis probe, also described previously (Sorge et al., 2005), consisted of a 2.5 mm length of semi-permeable dialysis membrane (Fisher Scientific, 240 μm OD, 13,000 MW cutoff) connected to a 21 mm long, 26 gauge piece of stainless steel tubing. This tubing was connected to a variable speed electric syringe infusion pump (Harvard Apparatus, South Natick, MA) that delivered artificial cerebrospinal fluid (aCSF: 145 mM Na^+, 2.7 mM K^+, 1.2 mM Ca^{2+}, 1.0 mM Mg^{2+}, 150 mM Cl^-, 0.2 mM ascorbate, 2 mM Na_2HPO_4, pH, 7.4±0.1) to the system. Small diameter fused silica tubing extended internally through the probe. The probes were inserted the day before the start of microdialysis testing and, to prevent occlusion, aCSF was perfused overnight at a rate of 1.0 μl/min.

2.4. Procedures

Microdialysis guide cannulae (Plastics One, Roanoke, VA) were implanted under sodium pentobarbital (Somnotol™, MTC Pharmaceuticals, Cambridge, ON; 65 mg/kg intraperitoneally [ip]) anesthesia for rats in the microdialysis experiment. Cannulae were targeted above the NAc (NAc: AP +1.6 mm, ML +2.8 mm, DV −5.5 mm from bregma) at an angle of 10° (Paxinos and Watson, 1986) and were fixed in place with dental acrylic. Rats were placed in recovery following an injection of penicillin (Pen G, Vetoquinol, Lavaltrie, QC; intramuscularly [im]).

For the experiment on locomotion, rats were given a baseline test at day 0 for 120 min at either 0900 h or 1200 h. Groups were matched on the basis of locomotor activity on this test and rats received osmotic minipumps or sham surgery. The rats were left in their home cages until testing on either day 5, 15 or 25. Different groups of rats were tested at each time point such that each rat had its exposure to heroin or cocaine at the time of test.

Microdialysis testing was begun 13 or 26 days following intracranial cannulation and buprenorphine minipump or sham surgery. Probes were inserted on days 12 or 25 and rats were taken to the microdialysis chambers where they were connected to the infusion pumps overnight. The next day (starting at 0900 h) samples were collected at 20-min intervals and 10 μl of dialysate was injected and analyzed using one of two similar HPLC systems with electrochemical detection (HPLC-EC). Once baseline levels were stable (less than 10% variability in three consecutive samples) rats were injected (between 1100 h and 1300 h) with either heroin (0.25 mg/kg, sc) or cocaine (20 mg/kg, ip) and samples were taken for another 120 min. Rats remained connected overnight and were tested the following day with the opposite drug in a counterbalanced fashion such that each rat was tested with both heroin and cocaine, but at only one time point.

The HPLC-EC apparatus has been previously described (Sorge et al., 2005). The currents for DA were measured independently of those for DOPAC and HVA using separate channels and were quantified by EZChrom Chromatography

Data System (Scientific Software Inc, San Ramon, CA) such that two rats were analyzed simultaneously on two identical systems.

Following microdialysis sampling, rats were anesthetized and perfused intracardially with saline and formaldehyde (Formalin 10%V/V, Anachemia, Montreal, QC) before brain removal. To identify placements of the cannula tract and probes, coronal frozen sections were taken using a cryostat, mounted and stained with cresyl violet.

2.5. Data analysis

All data were analyzed using the analysis of variance (ANOVA) with Fisher's LSD comparisons conducted as post-hoc analysis. The alpha level was set to 0.05.

3. Results

Fig. 1a shows the effect of chronic buprenorphine treatment on the locomotor response to an acute injection of heroin for the different groups of rats ($n=5$–6) tested for the first time at one of the three time points after buprenorphine treatment. It can be seen that heroin increased locomotion over baseline (dotted line) in buprenorphine-treated and untreated rats to a similar magnitude. An ANOVA conducted on the activity counts during the Baseline and Heroin Tests revealed a significant effect of Test (i.e. Baseline vs. Heroin Test) ($F(1, 29)=216.67$, $p<0.001$), but no effect of Buprenorphine treatment ($F(2, 29)=0.001$, ns) and no Buprenorphine treatment by Time of Test interaction ($F(2, 29)=0.27$, ns).

Fig. 1b shows the locomotor response to an acute injection of cocaine in different groups of rats ($n=5$–6). It can be seen that buprenorphine enhanced the response to cocaine only on day 5;

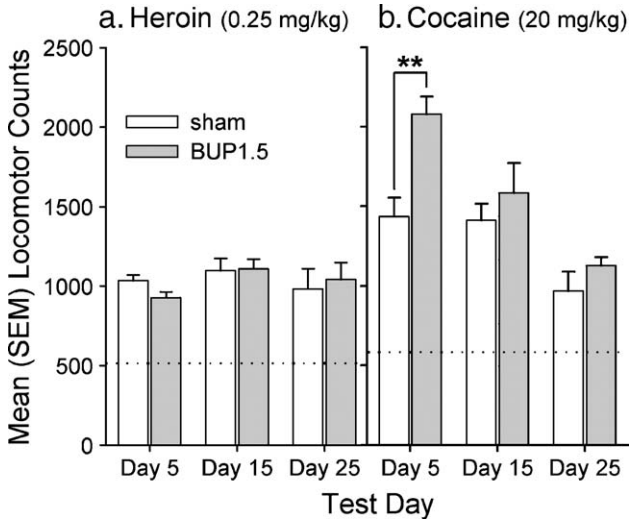

Fig. 1. The effect of chronic buprenorphine on the locomotor response to an acute injection of (a) heroin (0.25 mg/kg, sc) or (b) cocaine (20 mg/kg, ip) after 5, 15 or 25 days of treatment. The graphs display the mean (±sem) locomotor counts with the baseline locomotion indicated by the dotted line (heroin: sham; Day 5, $n=6$, Day 15, $n=6$, Day 25, $n=6$; BUP1.5, Day 5, $n=6$, Day 15, $n=6$. Day 25, $n=5$; Cocaine; sham; Day 5, $n=5$, Day 15, $n=6$, Day 25, $n=6$; BUP1.5, Day 5, $n=6$, Day 15, $n=6$. Day 25, $n=6$). $^{**}p<0.01$.

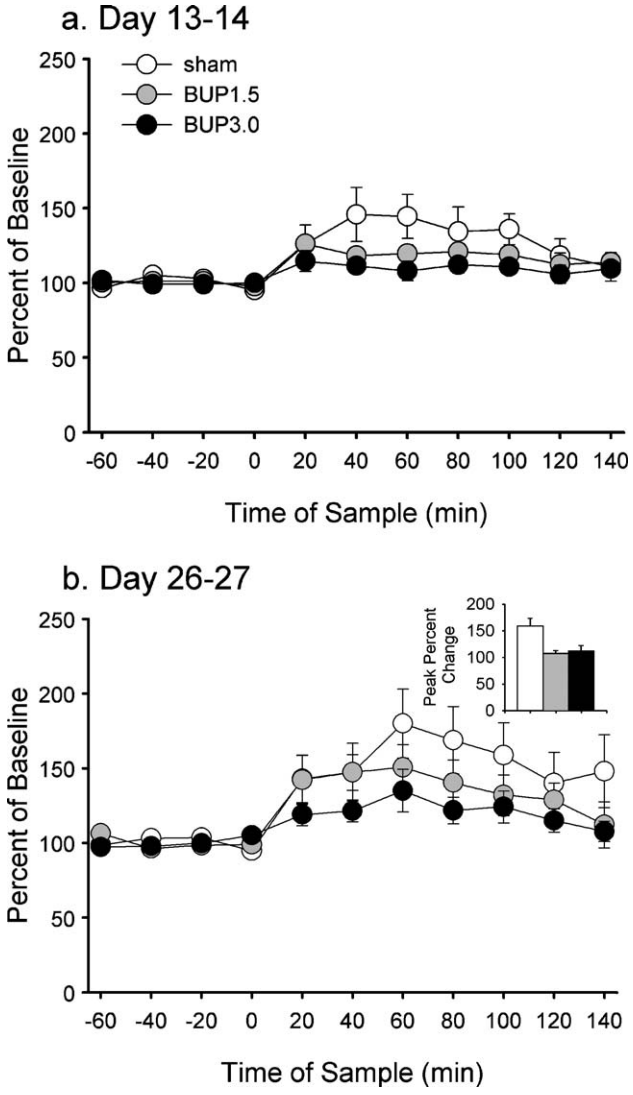

Fig. 2. The mean (±sem) percent change from baseline in extracellular DA in the NAc following an acute injection of heroin (0.25 mg/kg, sc) after (a) 13–14 or (b) 26–27 days of chronic buprenorphine treatment. Insert in b shows the peak values for rats tested at days 4–5 of treatment from an earlier report (Sorge et al., 2005) (Day 13–14: sham, $n=4$, BUP1.5, $n=5$, BUP3.0, $n=5$; Day 26–27: sham, $n=6$, BUP1.5, $n=4$, BUP3.0, $n=6$).

although cocaine increased activity above baseline on days 15 and 25, the groups did not differ. The ANOVA revealed significant effects of Test (Baseline vs. Cocaine) ($F(1, 29)=279.21$, $p<0.001$), Buprenorphine treatment ($F(1, 29)=7.75$, $p<0.01$), and Time of Test ($F(2, 29)=15.24$, $p<0.001$) as well as a significant Test by Buprenorphine treatment interaction ($F(1, 29)=9.00$, $p<0.01$). Post-hoc analysis revealed that BUP1.5 rats differed from sham rats only at Day 5 ($p<0.01$). These findings show that cocaine significantly increased locomotion in both buprenorphine-treated and untreated rats and that buprenorphine treatment significantly enhanced the locomotor response to cocaine but only early in treatment. In addition, the ANOVA revealed a significant Test by Time of Test interaction ($F(2, 29)=11.23$, $p<0.001$). Groups tested for the first time at the late time point (day 25) were less responsive to cocaine regardless of buprenorphine treatment. We cannot explain the

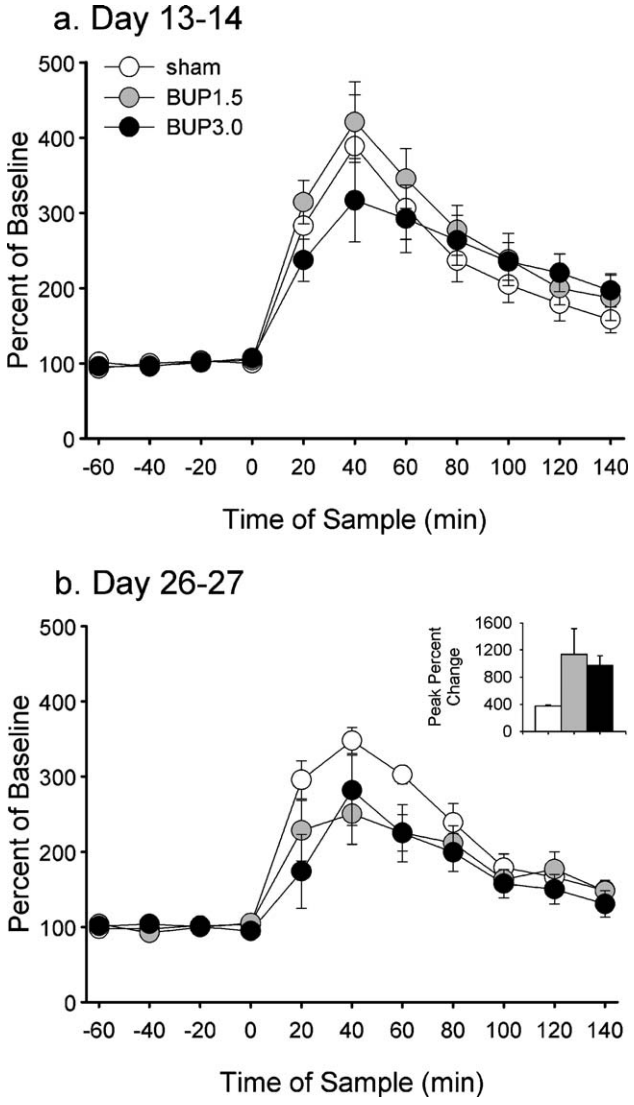

Fig. 3. The mean (±sem) percent change from baseline in extracellular DA in the NAc following an acute injection of cocaine (20 mg/kg, ip) after (a) 13–14 or (b) 26–27 days of chronic buprenorphine treatment. Insert in b shows the peak values for rats tested at day 4–5 of treatment from an earlier report (Sorge et al., 2005) (Day 13–14: sham, $n=5$, BUP1.5, $n=5$, BUP3.0, $n=5$; Day 26–27: sham, $n=4$, BUP1.5, $n=2$, BUP3.0, $n=4$).

reduced responsiveness to the locomotor stimulatory effect of cocaine, however, this reduction was consistent in rats in both treatment conditions.

Fig. 2(a and b) shows the change in extracellular DA levels in the NAc following an acute injection of heroin after 13–14 (Fig. 2a) or 26–27 (Fig. 2b) days of chronic BUP treatment ($n=5$–7/group). The mean of four baseline samples was used to calculate the percent change in DA around the mean before and following the injection of heroin. It can be seen that although heroin caused an increase in DA levels over baseline in all groups, this increase was less in buprenorphine-treated groups at both time points. This effect of buprenorphine is reflected in the significant Post-Injection Time by Buprenorphine treatment interaction ($F(12, 174)=1.92$, $p<0.05$) in the ANOVA carried out on the post-injection scores. There was also an unexpected Post-Injection Time by Time of Test interaction ($F(6, 174)=2.25$, $p<0.05$) reflecting the greater DA response in all groups at the later time point. The main effect of Buprenorphine treatment was marginally significant ($p=0.06$). Thus after 13–14 and 26–27 days of chronic buprenorphine, the blockade seen previously (Sorge et al., 2005) was attenuated though buprenorphine continued to elevate basal levels of DA at day 26 (see Fig. 4b).

Fig. 3 shows the effects of chronic buprenorphine on the NAc DA response to acute injections of cocaine after 13–14 (Fig. 3a) or 26–27 days of treatment (Fig. 3b). It can be seen that cocaine enhanced DA levels in all groups. The ANOVA revealed significant main effects of Post-Injection Time ($F(6, 156)=30.69$, $p<0.001$) and Time of Test ($F(1, 26)=4.37$, $p<0.05$), but no effect of Buprenorphine treatment ($F(2, 26)=0.41$, ns). Subsequent analyses of buprenorphine-treated groups alone, revealed a significant effect of Time of Test ($F(1, 17)=5.03$, $p<0.05$), whereas there was no difference in the response of the untreated groups at the two time points ($F(1, 9)=0.09$, ns). These data reveal that the ability of buprenorphine treatment to potentiate the NAc DA response to acute cocaine reported previously (Sorge et al., 2005) is absent and slightly attenuated after long-term chronic treatment.

Fig. 4 shows the mean basal levels of DA as determined from the last four samples before heroin or cocaine injections in buprenorphine-treated and untreated groups on the first day of microdialysis sampling (Fig. 4a, day 13; Fig. 4b, day 26). It can be seen that basal DA levels, at each of the locations anterior to bregma, were higher in buprenorphine-treated groups on both days 13 and 26. The ANOVA revealed a significant main effect of BUP treatment ($F(2, 19)=10.08$, $p<0.01$) and post-hoc analysis confirmed that the sham group was significantly different from the BUP1.5 ($p<0.01$) and BUP3.0 groups ($p<0.001$) when the groups were collapsed across probe location. At each location there were significant differences seen between the BUP3.0 and sham rats at +1.6 mm from Bregma on Day 13 ($p<0.05$) and at +1.6 mm and +1.7 mm on Day 26 ($p<0.05$). There was no effect of Length of Treatment ($F(1, 19)=2.95$, ns), although there appeared to be a trend towards higher levels later in treatment.

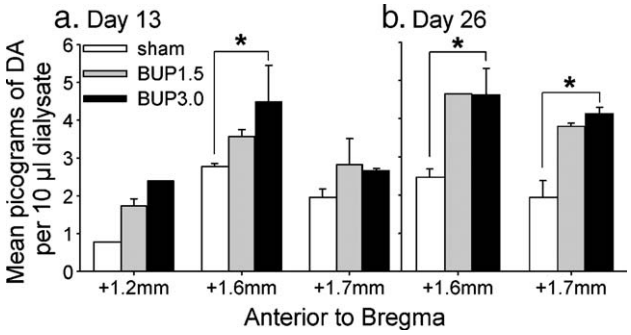

Fig. 4. Mean (±sem) basal levels of DA in the NAc at various levels anterior to bregma for rats with similar probe placements after (a) 13 or (b) 26 days of chronic buprenorphine treatment (Day 13: +1.2 mm; sham, $n=1$, BUP1.5, $n=2$, BUP3.0, $n=1$; +1.6 mm; sham, $n=2$, BUP1.5, $n=2$, BUP3.0, $n=2$; +1.7 mm; sham, $n=3$, BUP1.5, $n=3$, BUP3.0, $n=3$; Day 26; +1.6 mm; sham, $n=2$, BUP1.5, $n=1$, BUP3.0, $n=4$; +1.7 mm; sham, $n=4$, BUP1.5, $n=2$, BUP3.0, $n=2$). $^{*}p<0.05$.

4. Discussion

These experiments were carried out to determine whether responses to acute injections of heroin and cocaine would change as a function of duration of exposure to buprenorphine delivered chronically via osmotic minipump. In the case of heroin, it was found that the locomotor response was elevated at all time points in treatment and that buprenorphine neither enhanced nor reduced this response. There was, however, a change in the effect of heroin on the NAc DA response such that the complete blockade of the response seen previously (Sorge et al., 2005) was diminished in tests made after 13–14 or 26–27 days of treatment. In the case of cocaine, it was found that the locomotor response was consistently elevated and that buprenorphine enhanced this response only at the early time point (Day 5). Similarly, the enhanced NAc DA response seen previously (Sorge et al., 2005) was no longer evident at 13–14 days and was below the control levels after 26–27 days. Despite these changes in response to heroin and cocaine, buprenorphine continued to elevate basal levels of DA in the NAc throughout treatment. Furthermore, we have recently found that the level of buprenorphine in plasma, in rats with osmotic minipumps (3.0 mg/kg/day), is stable (approximately 10 ng/ml) over the course of 28 days of chronic treatment (Sorge and Stewart, submitted). Thus, although aspects of these data suggest modest tolerance to some of the effects of buprenorphine, others were unaffected by long-term exposure.

Acute administration of heroin or cocaine results in an increase in extracellular DA within the NAc (Di Chiara and Imperato, 1988). Heroin is thought to increase DA cell firing by acting primarily at mu-opioid receptors located on GABA interneurons in the ventral tegmental area (VTA) (Johnson and North, 1992), whereas cocaine blocks the DA transporter (DAT) preventing reuptake of DA (Heikkila et al., 1975). Buprenorphine would be expected to enhance extracellular levels of DA in the NAc (Brown et al., 1991) by acting in a manner similar to heroin at mu-opioid receptors in the VTA and, indeed, we found that chronic treatment with buprenorphine raised basal DA levels in NAc. Such chronic elevation of DA might in turn increase or up-regulate the functioning of the DAT in a manner similar to that seen after repeated infusions of cocaine (Letchworth et al., 2001), thereby attenuating the effect of cocaine on extracellular DA. Furthermore, the chronic presence of buprenorphine would be expected to compete with heroin for the mu-opioid receptor as it has been shown to induce withdrawal from morphine (Gmerek, 1984). Combined, these two effects could help account for the reduction of heroin-induced DA release and the reduction of the enhanced DA response to cocaine under prolonged buprenorphine treatment.

Another possibility is a down-regulation of mu-opioid receptor over time in rats treated chronically with buprenorphine. Acute or chronic administration of buprenorphine has been shown to reduce mu-opioid receptor number in the frontal cortex, thalamus, hippocampus striatum and brainstem (Belcheva et al., 1996; Debruyne et al., 2005). A reduction in mu-opioid receptor number and/or affinity might explain the attenuated NAc DA response to the acute injection of heroin during buprenorphine treatment. This reduction in binding would not, however, explain why the locomotor response to heroin was unaffected during buprenorphine treatment.

Chronic buprenorphine would be expected to lead to adaptations within other opioid receptor systems. It has been shown that chronic treatment with morphine (Rady et al., 2000) or methadone (Rady et al., 2002) pellets shifts the mediation of the antinociceptive effect of heroin from mu to delta-opioid receptors, where heroin is a potent agonist. Interestingly, delta-opioid agonists are self-infused into the VTA (Devine and Wise, 1994), lead to increases in extracellular DA in the NAc (Devine et al., 1993) and, importantly, increase locomotion (Michael-Titus et al., 1989). Thus, heroin may have retained its stimulatory and DA-elevating effects through delta-opioid receptor activation during chronic buprenorphine treatment. If this were the case, it would be relevant that intra-VTA infusions of the mu-opioid receptor agonist, DAMGO, have been found to induce greater DA release in the NAc than similar infusions of the delta-opioid receptor agonist, DPDPE (Devine et al., 1993). This might account for the change in the NAc DA response to heroin over the duration of BUP treatment. Initially buprenorphine completely blocked the DA response (Sorge et al., 2005), whereas after long-term chronic treatment acute injections of heroin induced a modest, but lower, rise in DA in the buprenorphine-treated groups possibly due to delta-opioid receptor activation.

Finally, concerning the interaction between cocaine and buprenorphine, additive effects of opioids and psychostimulants have been demonstrated using different experimental procedures. For example, synergistic effects have been seen on acquisition of a conditioned place preference (Brown et al., 1991) and in enhanced locomotor activity (Smith et al., 2003). Therefore, it was expected that treatment with buprenorphine would potentiate the locomotor activity to an acute injection of cocaine. As discussed above, however, there was an attenuation of this response with chronic buprenorphine treatment that might be accounted for by up-regulation of the DAT.

In summary, for up to 25–27 days of chronic administration of buprenorphine there was no change in the locomotor activity induced by acute injections of heroin, whereas the blockade of the heroin-induced increase in extracellular DA in the NAc seen in a previous experiment (Sorge et al., 2005) was reduced. These data were discussed in terms of increased activity at the delta-opioid receptor and reduced activity at the mu-opioid receptor. In the case of cocaine, the potentiation of the locomotor and NAc DA responses seen early in treatment was no longer evident during prolonged chronic treatment. In addition, although these data suggest that after acute injections or early chronic exposure to buprenorphine responses to cocaine may be enhanced (Brown et al., 1991), with chronic treatment this enhancement is no longer evident. Paradoxically, however, rats treated chronically with buprenorphine maintained significantly elevated basal extracellular DA levels in the NAc throughout long-term treatment. Although these studies do not shed direct light on how buprenorphine acts to reduce self-administration of heroin and cocaine, they are consistent with findings in monkeys that there is little tolerance to the suppressant effect of buprenorphine on self-administration (Mello et al., 1992). Thus, from the perspective

treatment drug abuse, it is encouraging that there seems little reason to be concerned that the useful effects of buprenorphine will show tolerance.

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References

Belcheva MM, Ho MT, Ignatova EG, Jefcoat LB, Barg J, Vogel Z, et al. Buprenorphine differentially alters opioid receptor adaptation in rat brain regions. J Pharmacol Exp Ther 1996;277:1322–7.

Brown EE, Finlay JM, Wong JT, Damsma G, Fibiger HC. Behavioral and neurochemical interactions between cocaine and buprenorphine: implications for the pharmacotherapy of cocaine abuse. J Pharmacol Exp Ther 1991;256:119–26.

Debruyne D, Quentin T, Poisnel G, Lelong-Boulouard V, Barre L, Coquerel A. Acute and chronic administration of clorazepate modifies the cell surface regulation of mu opioid receptors induced by buprenorphine in specific regions of the rat brain. Brain Res 2005;1052:222–31.

Devine DP, Wise RA. Self-administration of morphine, DAMGO, and DPDPE into the ventral tegmental area of rats. J Neurosci 1994;14:1978–84.

Devine DP, Leone P, Pocock D, Wise RA. Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. J Pharmacol Exp Ther 1993;266:1236–46.

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 1988;85:5274–8.

Gmerek DE. The suppression of deprivation and antagonist-induced withdrawal in morphine-dependent rhesus monkeys. Neuropeptides 1984;5:19–22.

Heikkila RE, Orlansky H, Cohen G. Studies on the distinction between uptake inhibition and release of (3H)dopamine in rat brain tissue slices. Biochem Pharmacol 1975;24:847–52.

Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci 1992;12:483–8.

Letchworth SR, Nader MA, Smith HR, Friedman DP, Porrino LJ. Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. J Neurosci 2001;21:2799–807.

Mello NK, Negus SS. The effects of buprenorphine on self-administration of cocaine and heroin "speedball" combinations and heroin alone by rhesus monkeys. J Pharmacol Exp Ther 1998;285:444–56.

Mello NK, Lukas SE, Kamien JB, Mendelson JH, Drieze J, Cone EJ. The effects of chronic buprenorphine treatment on cocaine and food self-administration by rhesus monkeys. J Pharmacol Exp Ther 1992;260:1185–93.

Michael-Titus A, Dourmap N, Costentin J. MU and delta opioid receptors control differently the horizontal and vertical components of locomotor activity in mice. Neuropeptides 1989;13:235–42.

Montoya ID, Gorelick DA, Preston KL, Schroeder JR, Umbricht A, Cheskin LJ, et al. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. Clin Pharmacol Ther 2004;75:34–48.

Paxinos G, Watson C. The rat brain in stereotaxic coordinates. San Diego: Academic Press; 1986.

Rady JJ, Holmes BB, Portoghese PS, Fujimoto JM. Morphine tolerance in mice changes response of heroin from mu to delta opioid receptors. Proc Soc Exp Biol Med 2000;224:93–101.

Rady JJ, Portoghese PS, Fujimo JM. Methadone and heroin antinociception: predominant delta-opioid-receptor responses in methadone-tolerant mice. Jpn J Pharmacol 2002;88:319–31.

Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry 1997;54:713–20.

Smith MA, Gordon KA, Craig CK, Bryant PA, Ferguson ME, French AM, et al. Interactions between opioids and cocaine on locomotor activity in rats: influence of an opioid's relative efficacy at the mu receptor. Psychopharmacology 2003;167:265–73.

Sorge RE, Stewart J. The effects of chronic buprenorphine on intake of heroin and cocaine in rats and its effects on nucleus accumbens dopamine levels during self-administration. Psychopharmacology, submitted.

Sorge RE, Rajabi H, Stewart J. Rats maintained chronically on buprenorphine show reduced heroin and cocaine seeking in tests of extinction and drug-induced reinstatement. Neuropsychopharmacology 2005;30:1681–92.

Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid dependence: self-reports, urinalysis, and addiction severity index. J Clin Psychopharmacol 1996;16:58–67.

Tzschentke TM. Behavioral pharmacology of buprenorphine, with a focus on preclinical models of reward and addiction. Psychopharmacology 2002;161:1–16.