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Differential Response to IV Carfentanil in Chronic Cocaine Users and Healthy Controls

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Abstract

Chronic cocaine exposure in both rodents and humans increases regional brain mu-opioid receptor (mOR) binding potential, suggesting that cocaine users might have an altered response to mOR agonists. We evaluated the response to IV carfentanil (a selective mOR agonist) in 23 cocaine users (mean [SD] age 33.8 [4.0] years, 83% men) who underwent PET scanning with [¹¹C]-carfentanil (44.7 [19.5] ng/kg) while housed on a closed research ward and 15 healthy non-drug-using controls (43.9 [14.2] years, 80% men) scanned (49.5 [12.6] ng/kg) as outpatients. Cocaine users had used for 8.7 [4.3] years and on 73 [22] % of days in the two weeks prior to PET scanning. Common adverse effects associated with mOR agonists (nausea, dizziness, headache, vomiting, itchiness) were assessed by self-report (5-point Likert scales) during and for 90 minutes after the scans. Cocaine users were significantly less likely than controls to report any symptom (30.4% vs. 60%) and had fewer total symptoms (0.43 [0.73] vs. 1.1 [1.0]) during scans, even after statistically controlling for age and carfentanil dose. These differences were also present after the scans and at repeat scans done after about one week or 12 weeks of monitored cocaine abstinence. In a larger group of cocaine users and separate controls, there was no significant group difference in carfentanil half-life, suggesting that the observed difference was pharmacodynamically, rather than pharmacokinetically, based. These findings suggest that cocaine users are less responsive than healthy controls to mOR agonist adverse effects, despite having increased regional brain mOR binding potential.

Keywords

agonist; carfentanil; cocaine; mu-opioid receptor; PET scan

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Introduction

Cocaine is a widely abused psychoactive stimulant. Its rewarding effects, including the subjective “high,” are considered to be mediated by increased dopamine availability in the synaptic cleft (Dackis and O’Brien, 2001). However, there is also a relationship between cocaine and the endogenous opioid system of the brain (Unterwald, E. M. et al., 2001). Cocaine and other drugs that enhance brain dopaminergic activity increase mu-opioid receptor (mOR) binding potential (BP) in some regions of both rat brains (Unterwald, E. M., et al., 2001) and human brains (Zubieta, J., et al., 1996; Gorelick et al., 2005; Gorelick et al., 2008). Chronic cocaine users show significantly increased mOR BP in the caudate nucleus, thalamus, anterior cingulate, frontal cortex and temporal cortex, based on PET scanning with the mOR agonist [C-11]-carfentanil (Zubieta, J., et al., 1996; Gorelick, et al., 2005; Gorelick, et al., 2008). The increased mOR BP is associated with increased cocaine craving (Gorelick et al., 2005) and quicker and more intense relapse to cocaine use after discharge from monitored cocaine abstinence (Gorelick et al., 2008). These findings suggest an important functional role for this receptor change.

One possible consequence of the cocaine-associated increase in brain mOR BP is that cocaine users might respond differently to mOR agonists than do non-cocaine-users. We are aware of only one human study that addresses this question. Pregnant women in early labor who had a history of cocaine use (confirmed by a cocaine-positive urine drug screen) had a significantly shorter duration of analgesia (87 min vs. 139 min) from 10 µg of intrathecal sufentanil (a synthetic mOR agonist used as an analgesic) and a lower incidence of nausea and vomiting (0% vs. 25%) than did non-drug-using women (Ross, et al., 2003). This finding suggests that cocaine use is associated with decreased response to a mOR agonist. In contrast, pretreatment of rats with cocaine (30 mg/kg ip daily for three days) had no significant effect on morphine-induced analgesia tested one or seven days later (Lutty and Maidment, 2002).

Exposure to synthetic stimulants such as amphetamines appears to enhance the response to mOR agonists in rats. Pretreatment with amphetamine (2.5 µg into the ventral tegmental area bilaterally daily for two days) significantly enhanced the locomotor response one day later to morphine (1 mg/kg ip) (Vezina & Stewart, 1990). Similarly, pretreatment with methamphetamine (6 mg/kg ip daily for 9 days) significantly enhanced the effect of DAGO (a mOR agonist enkephalin analogue) 9 days later in increasing extracellular dopamine levels in the nucleus accumbens (Yokoo et al., 1994). We are not aware of any published studies in humans on the effects of amphetamine exposure on the response to a mOR agonist.

The use of [C-11] carfentanil as a PET scan radiotracer provided an opportunity to evaluate the response of cocaine users to a mOR agonist in terms of adverse effects. The present study compared the response to [C-11] carfentanil in chronic cocaine users and healthy controls. Because cocaine exposure has been reported to increase the activity of the liver enzyme that metabolizes carfentanil (Pellinen et al., 1996), we also compared the plasma half-life of carfentanil in the two groups.

Materials and Methods

Participants

Participants were recruited by the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP) Recruiting Unit using newspaper, television and radio ads, flyers, and word of mouth. Eligibility criteria for cocaine-using subjects included 1) 21–40 years of age; 2) within 10% of ideal weight (based on the 1983 Metropolitan Life Insurance

Company tables) (University of Washington, 1997); 3) current cocaine abuse or dependence, but no current dependence on other psychoactive substances, except for caffeine or tobacco (DSM-IV criteria); 4) history of cocaine use averaging 1 gram per week over the prior 3 months; 5) cocaine use within 24 hours of admission; 6) urine toxicology positive for cocaine, negative for other drugs; 7) no more than 3 uses in the prior three months of opiates, antidepressants, neuroleptics, lithium, isoniazid, glucocorticoids, or psychostimulants other than cocaine; 8) no clinically significant CNS disorder or cognitive impairment; 9) no current primary DSM-IV Axis 1 psychiatric disorder (other than substance-use disorder, adjustment disorder, phobia, or posttraumatic stress disorder); 10) no current serious medical condition that would impair ability to participate safely in the study; 11) no history of adverse reactions to opioids; and 12) no seizure disorder or history of head injury with loss of consciousness for more than three minutes. Healthy controls were recruited at the Johns Hopkins Hospital to participate in other brain imaging studies using [C-11] carfentanil. The healthy controls, primarily hospital employees, had no current medical or psychiatric disorders (including substance use disorders) based on self-report.

All subjects gave written informed consent and were paid for their participation. The study was approved by the institutional review boards of the NIDA IRP and the Johns Hopkins School of Medicine and was conducted in accordance with US federal regulations on the protection of human research subjects (45 CFR part 46).

Procedures

Carfentanil is a synthetic, selective mOR agonist that is, with an in vitro K_D of 0.08 nM (Titeler et al., 1989). It is a 4-anilinopiperidine structurally similar to fentanyl, alfentanil, and sufentanil, which are used clinically for analgesia and anesthesia (Gutstein and Akil 2006). Carfentanil is about 7000 times more potent than morphine and 10–20 times more potent than sufentanil, which is typically given at 5–20 $\mu\text{g/kg}$ IV for anesthesia (Gutstein and Akil 2006). Because of its extreme potency, carfentanil is not approved for clinical use in humans, except as a radioligand for PET imaging, where only very low doses are required.

All PET scans were done at the Johns Hopkins Hospital PET Center with [11-C] carfentanil as the radioligand. Subjects received an intravenous injection of carfentanil while lying supine with their head in the PET scanner. The carfentanil dose was not pre-specified, but varied depending on the specific activity achieved by [C-11] carfentanil synthesis at the time of the scan (see Table 1). The goal was to inject enough [C-11] carfentanil to have sufficient radioactivity in the brain to generate interpretable brain images. Each PET session lasted about 90 minutes after bolus carfentanil injection. During this interval, subjects remained supine in the scanner. They were periodically asked to report whether they experienced any of five physical symptoms commonly reported during clinical use of mu-opioid agonists (opioid analgesics): itching, nausea, headache, vomiting, and dizziness (Gutstein and Akil 2006). Subjects were also asked about these symptoms 90 minutes after completion of the scan, during which time they remained seated in the scanner area. The total symptom count for a subject was the number of symptoms reported by that subject during the indicated time period (possible range 0 to 5 symptoms).

Twenty-three cocaine users had a PET scan within two days of admission to the closed research unit of the NIDA IRP. Thirteen of these had additional PET scans about one week and 12 weeks later while remaining on the research unit. These scans used similar carfentanil parameters as the first scan. Subjects received no opiates or other psychoactive medications and had no access to alcohol or illegal drugs while on the research unit. As expected from the study eligibility criteria, none of the cocaine users was depressed at the

time of PET scanning, based on clinical interview and scores on the Beck Depression Inventory and SCL-90R. Fifteen healthy controls had a single PET scan done as outpatients.

Carfentanil Half-life

Blood samples were collected into heparinized tubes from an indwelling peripheral venous catheter at 0, 5, 10, 15, 20, 30, 40, 45, 60, and 90 minutes after bolus IV carfentanil administration. Plasma was promptly separated by centrifugation and stored frozen until later analysis for parent carfentanil and carfentanil metabolites by column-switch HPLC (Hilton, et. al, 2000). Carfentanil half-life was calculated by linear intercalation between the two time points bracketing the interval during which the proportion of parent carfentanil remaining in the blood declined to 50% of the initial total administered carfentanil dose

Carfentanil data were available for 13 of the 23 cocaine users (mean [SD] age 33.1 years, 100% male, 85% African-American, 8% white, weight 164.5 [17.2] lbs, carfentanil dose .037 [.033] $\mu\text{g/kg}$) and for a separate group of 13 healthy controls (age 25.0 [3.2] years, 46% male, 80% white, 0% African-American, weight 155.6 [29.6] lbs., carfentanil dose .019 [.019] $\mu\text{g/kg}$) drawn from other PET imaging studies conducted at the Johns Hopkins PET Center.

Statistical analysis

Comparisons of subject characteristics, carfentanil-associated symptoms, and carfentanil half-life between cocaine users and controls used the chi-square test for categorical variables and the t-test for continuous variables. The association between subject age or carfentanil dose and total symptom count was evaluated using the Pearson correlation coefficient. Because the cocaine users and healthy controls were not prospectively matched for age or carfentanil dose, which may influence response to carfentanil, these variables were controlled for statistically in group comparisons of total symptom counts by using analysis of covariance. In addition, the group comparisons of categorical variables (symptom presence or absence) were repeated excluding the 7 healthy controls older than 40 years.

All analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL). The two-tailed alpha level was 0.05.

Results

Baseline characteristics of 23 cocaine users and 15 non-drug-using healthy controls are given in Table 1. The two groups differed significantly in race (chi-square = 8.10, $df = 1$, $p = 0.004$) and age ($t = 3.25$, $df = 36$, $p = 0.002$), but not in carfentanil dose (chi-square = 0.83, $df = 36$, $p = 0.41$), weight (chi-square = 1.88, $df = 36$, $p = 0.07$), or sex (chi-square = 0.04, $df = 1$, $p = 0.84$). There were no significant correlations between subject age or carfentanil dose and total symptom count either during the scan, after the scan, or for the entire interval, either in the 38 subjects overall or in the cocaine user and healthy control groups separately (data not shown). Cocaine users reported significantly fewer total symptoms during their first PET scan (mean [SD] of 0.43 [0.73]) than the healthy control subjects (1.1 [1.0]) ($t = 2.22$, $df = 36$, $p = 0.05$). Almost one-third of cocaine users reported experiencing any symptoms during PET scans, whereas almost two-thirds of healthy controls did so (chi-square = 3.26, $df = 1$, $p = 0.07$) (Table 2). Among specific symptoms, only dizziness was reported by significantly fewer cocaine users than controls (chi-square = 5.71, $df = 1$, $p = 0.002$) (Table 2). These symptom differences persisted during the 90 minutes after the PET scan, when subjects were sitting up, for total symptom count ($t = 2.86$, $df = 36$, $p = .02$), any symptom (chi-square = 9.27, $df = 1$, $p = 0.002$), and dizziness (chi-square = 11.62, $df = 1$, $p = 0.001$) (Table 2).

Similar results were observed when the comparisons of total symptom counts were statistically controlled for age and carfentanil dose using analysis of covariance (during scan $F = 2.62$, $df = 3$, $p = .07$; after scan $F = 3.33$, $df = 3$, $p = .03$, during plus after scan $F = 3.75$, $df = 3$, $p = .02$) and when the analysis excluded the seven controls older than 40 years, bringing their mean [SD] age close to that of the cocaine users (34.3 [5.5] years vs. 33.8 [4.0] years) ($t = 0.26$, $df = 29$, $p = 0.80$). The 23 cocaine users again had significantly fewer total symptoms during ($t = 2.33$, $df = 29$, $p = 0.03$) and after the scan ($t = 2.61$, $df = 29$, $p = 0.01$) and overall ($t = 2.78$, $df = 29$, $p = 0.01$), a lower incidence of reporting any symptom (chi-square = 4.84, $df = 1$, $p = 0.04$), and significantly less dizziness (chi-square = 4.51, $df = 1$, $p = 0.04$ during the scan; chi-square = 9.83, $df = 1$, $p = 0.002$ after the scan) than the 8 controls (Table 2).

The pattern of differences between cocaine users and controls remained similar, although no longer statistically significant, during the second (after one week of abstinence) and third (after 12 weeks of abstinence) PET scans in 13 cocaine users: lower incidence of reporting any symptoms (46% vs. 67% [chi-square = 1.20, $df = 1$, $p = 0.27$] and 39% vs. 67% [chi-square = 2.23, $df = 1$, $p = 0.14$], respectively) and significantly fewer total symptoms (1.0 [1.6] vs. 2.1 [2.1] [$t = 1.54$, $df = 26$, $p = 0.14$] and 0.94 [1.31] vs. 2.1 [2.1] [$t = 1.72$, $df = 26$, $p = .10$], respectively).

There was no significant difference in carfentanil half-life between the 13 cocaine users and 13 non-drug using controls (51.4 [16.2] minutes vs. 41.8 [17.5] minutes, $t = 1.45$, $df = 24$, $p = 0.16$).

Discussion

The present study compared the incidence of several mOR agonist-associated adverse effects in chronic cocaine users and in non-drug-using healthy controls after IV administration of very low doses of carfentanil (a mOR agonist). Cocaine users reported significantly fewer total symptoms than the controls, and significantly fewer cocaine users reported any symptoms. These differences occurred after about 1–2 days, one week, or 12 weeks of cocaine abstinence. These findings suggest that cocaine users experience fewer acute adverse effects than do controls when exposed to a mOR agonist. They are consistent with the prior published human study, which found cocaine-using women less responsive to the nausea-inducing effects of sufentanil (Ross et al., 2003).

Rat studies show a different effect of stimulant exposure on the acute response to mOR agonists. Three days of cocaine exposure (30 mg/kg ip daily) had no significant effect on morphine-induced analgesia tested one or seven days later (Lutfy and Maidment, 2002). Pretreatment with amphetamine or methamphetamine significantly enhanced the locomotor response to morphine and the effect of DAGO in increasing extracellular dopamine levels in the nucleus accumbens, respectively (Vezina & Stewart, 1990; Yokoo et al., 1994). The reasons for these differences are unclear, but could relate to species differences or differences in stimulant exposure. Subjects in the two human studies had been using cocaine for years (about one-quarter of lifespan at time of study, on average), while cocaine or other stimulant exposure in the rat studies was limited to several days (5% or less of lifespan at time of study). It is also possible that stimulant exposure differentially affects various mOR agonist-associated effects, e.g., analgesia or locomotor activity vs. nausea, itching, and headache.

The mechanism of the decreased incidence of acute adverse effects in cocaine users is unclear. The cocaine-using subjects in this study had 10–50% increases in mOR BP, compared to non-drug-using controls, in several brain regions, including thalamus, anterior

cingulate, frontal cortex, and temporal cortex (Gorelick et al., 2005)(Zubieta et al., 1996). The PET analysis used cannot distinguish among increased mOR number, increased mOR affinity, or decreased levels of endogenous mOR ligands (which would leave more receptors available for occupancy by the radiotracer) as the mechanism. Animal studies suggest that subacute (up to 14 days) cocaine exposure increases mOR receptor number (Hammer 1989; Izenwasser et al., 1996; Unterwald et al., 1994) and decreases levels of enkephalin (an endogenous mOR ligand) (Daunais et al., 1997; Laforge et al., 2003; Przewlocka and Lason, 1995). Either of these changes might result in decreased fractional mOR occupancy by carfentanil in the cocaine users compared with the healthy controls, resulting in decreased mOR agonist effects. This hypothesis is speculative in the absence of data on the mOR occupancy levels needed for carfentanil to exert various agonist effects. Furthermore, the brain regions observed to have increased mOR BP in cocaine users are not those considered to mediate the mOR agonist effects that were assessed in this study. For example, opioid-associated pruritus is mediated in part by mOR in the dorsal horn of the spinal cord (Reich and Szepietowski 2010), and opioid-associated nausea and vomiting in part by mOR in the medulla oblongata and area postrema (Porreca and Ossipov 2009).

Another possible mechanism is desensitization of the mu-opioid receptor due to chronic cocaine use. Two rodent studies found that binge pattern cocaine exposure for 14 days either had no effect on (Unterwald et al., 1993) or increased (Schroeder et al., 2003) the in vitro mOR response to a selective mOR agonist. Therefore, mOR desensitization appears an unlikely mechanism for our finding.

Another possible explanation is that the cocaine users had a higher tolerance for adverse symptoms or were less likely than the controls to report them. We are not aware of any direct evidence bearing on this possibility. Response bias was minimized by periodically asking subjects about each symptom, rather than relying on subject initiation of a response. Current cocaine users have been reported to have lower pain tolerance than abstinent (at least 6 weeks) users and healthy controls (Compton, 1994). This factor, if operating in our subjects, would have tended to increase reporting of adverse symptoms, the opposite of what was observed. We are not aware of any data bearing on the possibility that the lower pain tolerance in cocaine users, which is also found in opiate addicts (Compton, 1994), might be related to altered endogenous opioid tone. Thus, it remains unclear whether our subjects had altered endogenous opioid tone which might help explain our findings.

A third possible explanation is that chronic cocaine use alters carfentanil metabolism such that the effective dose is reduced. Synthetic mOR agonists such as fentanyl and sufentanil (and presumably carfentanil) are metabolized primarily by liver cytochrome P450 3A4 (Scholz et al., 1996; Yun et al., 1992). Cocaine is a substrate for this enzyme, although with relatively low affinity compared to other substrates (Ladona et al., 2000). Seven to 14 days of cocaine exposure (60 mg/kg/day ip) in mice increased liver microsomal 3A4 protein levels 2- to 6-fold and enzyme activity (with cocaine as substrate) 2-fold (Pellinen et al., 1996). Enhanced carfentanil metabolism in the cocaine users might significantly reduce carfentanil concentrations in the brain, thus accounting for the reduced mOR agonist response compared to controls. This explanation appears unlikely given that the cocaine users and a separate group of controls had similar carfentanil plasma half-lives.

It is possible, but unlikely, that some group difference in subject characteristics other than cocaine use could account for the observed difference in carfentanil adverse effects. Age is known to influence brain mOR BP (Zubieta, et al., 1999) and the cocaine users were significantly younger than the controls (Table 1). However, the same group differences in carfentanil response were observed after statistically controlling for age with analysis of covariance, or after restricting the comparison to controls aged ≤ 40 years. Patients with

depression have lower regional brain mOR BP (Kennedy et al., 2006) and a decreased subjective response to an IV mOR agonist (fentanyl) (Matussek and Hoehe, 1989) than do healthy controls. However, the cocaine users in this study were not depressed at the time of PET scanning.

The method used to measure carfentanil response was self-report on a 5-point Likert scale. It is possible that this method lacked adequate sensitivity or reliability in this setting. However, it is not clear why the method would have different characteristics in the cocaine-using and control subjects that might generate the observed group differences.

The finding that chronic cocaine use reduced the incidence of acute adverse effects associated with a mOR agonist has clinical implications. The agonist used in this study, carfentanil, while not itself used clinically, is closely related structurally to several that are, e.g., fentanyl and sufentanil. Decreased sufentanil-induced analgesia and decreased incidence of side-effects (nausea and vomiting) in cocaine users have been reported in a clinical setting (women in labor) (Ross et al., 2003). Cocaine use could affect analgesia in other clinical settings such as dentistry and surgery. This suggests the importance of evaluating cocaine (and other stimulant) use history as part of routine clinical examinations. Stimulants (other than cocaine) are widely prescribed for attention deficit disorder and, to some extent, for weight loss (Drug Store News, January 19, 2009 issue, p. 4; accessed at www.drugstorenews.com on June 7, 2010). We are not aware of any studies evaluating the influence of stimulant treatment on such patients' responsiveness to opioid analgesics. Further research is needed to evaluate these possibilities.

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Table 1

Demographic, Cocaine Use, and First PET Scan Characteristics of 23 Cocaine Users and 15 Non-Drug-Using Healthy Controls

	Cocaine Users (n = 23)	Healthy Controls (n = 15)	Cocaine Users vs. Controls <i>P</i>
Gender (% men)	83%	80%	0.58
Race (% AA, % C)	87%, 13%	40%, 53.3%	0.007
Age (years)	33.8 [4.0]	43.9 [14.2]	0.02
Age range	24 – 39	23 – 74	-----
Weight (lbs)	167.9 [30.0]	186.7 [30.2]	0.07
Carfentanil Dose (µg/kg)	.045 [.020]	.049 [.013]	0.37
Dose Range	.011–.075	.025–.069	-----
Specific Activity (mCi/µmole)	3089.9 [2306.1] *	2203.5 [816.3]	0.17
Lifetime Cocaine Use (years)	8.8 [5.4]	0	-----
Days with Cocaine Use in Month Before First PET Scan	24 [4.5]	0	-----

Values are means and standard deviations, except where otherwise indicated

*
n = 19

Table 2

Mu-Opioid Agonist Symptoms in Response to IV Carfentanil in Cocaine Users (First PET Scan) and Non-Drug-Using Healthy Controls

	Cocaine Users	Healthy Controls		P value Comparing All Subject s
<i>During Scan (0–90mins)</i>	<i>(n = 23)</i>	<i>All Subjects (n=15)</i>	<i>Subjects ≤40 (n = 8)</i>	
Itching	0%	6.7%	12.5%	0.21
Nausea	17.4%	33.3%	37.5%	0.26
Vomiting	0%	6.7%	12.5%	0.21
Dizziness	21.7%	60.0%	62.5%	0.02
Headache	4.3%	0%	0%	.41
Any Symptom	30.4%	60%	62.5%	.07
Total Symptom Count *	.43 [.73]	1.1 [1.0]	1.0 [1.0]	.05
<i>After Scan (90–180mins)</i>	<i>(n = 23)</i>	<i>(n = 15)</i>	<i>(n = 8)</i>	
Itching	0%	0%	0%	-----
Nausea	4.3%	26.7%	25.0%	0.05
Vomiting	4.3%	20.0%	25.0%	0.12
Dizziness	8.7%	60.0%	62.5%	0.001
Headache	4.3%	0%	0%	0.41
Any Symptom	13.0%	60.0%	62.5%	.002
Total Symptom Count *	.22 [.67]	1.1 [1.2]	.83 [.94]	.02
Total Symptom Count Before and After Scan *	.61 [1.3]	2.1 [2.1]		.02

* mean [standard deviation]

All cocaine users were ≤ 40 years old.

Comparisons between cocaine users and healthy controls used chi-square test for categorical variables (symptom presence or absence) and t-test for continuous variables (total symptom count).