

## Effects of naltrexone and isradipine, alone or in combination, on cocaine responses in humans

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### Abstract

Preclinical studies suggested that combination of naltrexone and isradipine may be useful for the treatment of cocaine addiction. This study examined whether naltrexone and isradipine, alone or in combination, would attenuate the subjective and physiological effects of cocaine in humans. Seven cocaine users participated in a randomized, double-blind, placebo-controlled inpatient study. Before each of the seven experimental sessions, subjects were treated orally with naltrexone (50 mg or placebo), isradipine (10 mg or placebo), or naltrexone plus isradipine. Subjects then received a single dose of intranasal cocaine (4 mg or 100 mg/70 kg). Isradipine alone attenuated the systolic blood pressure response to cocaine. In contrast, isradipine plus naltrexone treatment attenuated both the systolic and diastolic blood pressure responses. Naltrexone alone did not affect the blood pressure response to cocaine. For subjective response to cocaine, isradipine, alone or in combination with naltrexone, did not have significant effects. Naltrexone treatment alone attenuated the rating of “good effects” from cocaine without affecting other subjective responses. These results suggest that isradipine alone or in combination with naltrexone attenuates some of the physiological effects of cocaine.

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### 1. Introduction

The brain opioid system may mediate the rewarding effects of drugs of abuse including cocaine (van Ree et al., 1999). For instance, the opioid antagonist naloxone reduced cocaine self-administration in rats (Corrigall and Coen, 1991), blocked cocaine place preference in rats (Bilsky et al., 1992; Suzuki et al., 1992), and attenuated the threshold lowering effects of cocaine for intracranial stimulation in rats (Bain and Kornetsky, 1987). Another opioid antagonist naltrexone reduced cocaine self-administration in monkeys (Mello et al., 1990). Other studies, however, contradicted these findings. Naltrexone treatment did not change cocaine self-administration in monkeys (Rowlett et al., 1998) and it

increased cocaine self-administration in rats (Carroll et al., 1986). In a human study, naltrexone treatment attenuated the cocaine-induced increases in self-reported value of cocaine and unpleasant sensations that follow intravenous cocaine “crash” (Kosten et al., 1992). In contrast, with cocaine- and opioid-using men, Walsh et al. (1996) reported that naltrexone treatment did not affect the subjective or physiological effects of ascending doses of intravenous cocaine. In addition to these human laboratory studies, the utility of naltrexone for cocaine dependence was also investigated in outpatient studies (Hersh et al., 1998; Oslin et al., 1999). In a recent outpatient clinical trial, the combination of naltrexone and relapse prevention treatment was more effective than the control treatments in reducing cocaine use (Schmitz et al., 2001). Although not consistent, these results suggest that naltrexone may have value as a treatment for cocaine dependence.

Calcium ion channels have also been proposed to mediate the effects of cocaine. In preclinical studies, isradipine, a

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dihydropyridine derivative calcium channel blocker, blocked calcium-dependent dopamine release in the mesolimbic system (Pani et al., 1990), suppressed cocaine self-administration (Martellotta et al., 1994), and blocked cocaine place preference (Pani et al., 1991) in rats. In human studies, isradipine treatment prevented the cocaine-induced changes in brain blood flow using single photon emission computerized tomography (Johnson et al., 1998). Isradipine treatment also attenuated the subjective effects of oral methamphetamine in humans (Johnson et al., 1999). These findings suggest that isradipine may attenuate both the behavioral and physiological effects of cocaine.

Interestingly, the combination of naltrexone and isradipine, in doses that are not effective alone, blocked the threshold lowering effects of cocaine for intracranial stimulation in rats, suggesting that combining these medications may be valuable for the treatment of cocaine addiction (Pabello et al., 1998; Reid et al., 1997). Considering these promising findings, the purpose of this study was to investigate the effects of naltrexone alone and isradipine alone on acute cocaine responses in humans. In addition, we also examined the effects of isradipine plus naltrexone treatment on the subjective response to cocaine.

Based on preclinical findings, we hypothesized that treatment with a combination of isradipine and naltrexone would be more effective than either treatment alone in attenuating the subjective and physiological effects of cocaine. This hypothesis was tested in non-treatment-seeking cocaine users using a randomized, double-blind, placebo-controlled study design.

## 2. Methods

### 2.1. Subjects

Subjects were five males and two females, non-treatment-seeking, crack cocaine users with an average (S.D.) age of 38.0 (4.5) years. Three additional subjects were enrolled but dropped out of the study for personal reasons and lack of compliance with study procedures and were not included in the analyses. Each participant had to meet the following inclusion criteria: (1) history of cocaine use, with street cocaine use by history being a minimum of 7 g during the preceding 3 months, with at least one previous episode of using at least 1 g within a 5-day period and (2) laboratory confirmation of cocaine use (positive urine for cocaine or benzoylecgonine) during the 3 weeks prior to entry. Subjects were excluded from participation if they (1) had ill health (major cardiovascular, renal, endocrine, hepatic disorder, or acute hepatitis); (2) present use of narcotic analgesics either by history or by urine drug screening; (3) showed signs and symptoms of acute opioid withdrawal; (4) had a diagnosis of drug (e.g. opioids) or alcohol dependence (other than cocaine or tobacco) as defined by DSM-IV (American Psychiatric Association [APA], 1994); (5) had hypersensitivity to isradipine

or other calcium antagonists; (6) had symptomatic hypotension with systolic blood pressure less than 90 mmHg; (7) had sick sinus syndrome or any degree of AV block detected with ECG or physical examination; (8) had a history of major psychiatric disorder (psychosis, schizophrenia, bipolar, depression) or significant psychiatric symptoms at the time of evaluation for study participation, including suicidal ideation; (9) were pregnant (positive urine pregnancy test), or planning to become pregnant or using inadequate birth control; (10) had medical contraindication to, or prior serious adverse effects from, cocaine or stimulants (i.e. seizures, cardiac arrest); and (11) were currently seeking treatment for cocaine dependence. Each subject's eligibility was ascertained through a comprehensive evaluation including a physical, psychiatric, and laboratory examination. Psychiatric and drug use diagnoses were determined by a research psychiatrist based on clinical examination and urine drug screening.

Five subjects were African American, one was Hispanic, and one was Caucasian with an average (S.D.) schooling of 12.7 (1.5) years. All the subjects were cocaine dependent as defined by the DSM-IV (APA, 1994). Subjects weighed an average of 76.5 (15.8) kg. Within the month before admission, the average frequency of cocaine use was 5.0 (1.8) days/week and the amount of use was 6.6 (4.3) g/week. The average duration of cocaine use was 9.6 (7.3) years. Other drugs used currently were cigarettes ( $n=6$ ), alcohol ( $n=3$ ), marijuana ( $n=2$ ), and opioids ( $n=1$ ). Drug use history was confirmed with urine toxicology screening before study participation. Before study participation, subjects signed an informed consent. Subjects were paid for study participation. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee.

### 2.2. Study procedure

This inpatient, randomized, double-blind, placebo-controlled, within-subjects study was carried out at the VA Connecticut Healthcare System while subjects were housed in a hospital ward with around the clock nursing staff. The study had one adaptation and seven experimental sessions. Before the first experimental session, subjects underwent an adaptation session to orient them to the laboratory procedures. During each experimental session, subjects were administered one of the following treatments according to a randomized, double-blind design: (1) placebo: placebo plus placebo–cocaine (cocaine at 4 mg), (2) cocaine alone: placebo plus cocaine (100 mg/70 kg), (3) naltrexone alone: naltrexone (50 mg) plus placebo–cocaine, (4) isradipine alone: isradipine (10 mg) plus placebo–cocaine, (5) cocaine–naltrexone: naltrexone (50 mg) plus cocaine, (6) cocaine–isradipine: isradipine (10 mg) plus cocaine, and (7) cocaine–naltrexone plus isradipine: naltrexone and isradipine plus cocaine. The experimental sessions were completed over a 2–3 week period with a

minimum of 2 days between sessions, to minimize the carryover effects from the study medications. Subjects were asked not to use any illicit drugs or alcohol during the study and their compliance was checked with urine drug screening using immunoassay method and breathalyzer (Alco-Sensor III) before the sessions. Subjects were not permitted to eat solid food and drink beverages with caffeine for 4 h before the sessions and during the sessions. This procedure was implemented for safety reasons in case of a severe adverse reaction to study medications and to minimize the interaction between the acute effects from caffeine and study medications. Subjects were provided with noncaffeinated beverages every 2 h during each experimental session.

### 2.3. Drugs

The orally administered study medications and their placebo (i.e. lactose) were prepared in blue opaque capsules (size 00). Isradipine (Dynacir, Novartis) was administered 90 min before postdrug assessment as a single 10 mg oral dose, since this dose has been reported to reverse some of the physiological effects of cocaine in humans and is below the maximum recommended daily dose of 20 mg of isradipine (Johnson et al., 1998). Following oral administration, peak levels of isradipine are reached in 1.5–3 h and it has an elimination half-life of 5–11 h (PDR, 2002).

Naltrexone HCl (ReVia, DuPont) was administered 60 min before postdrug assessment as a single 50 mg oral dose, since peak plasma levels of naltrexone are reached within 1 h and it has an elimination half-life of 4 h (PDR, 2002).

Cocaine hydrochloride was administered by nasal insufflation. Cocaine powder was given on a tray with a straw. Subjects were instructed to make their own line and ensure that all the cocaine was insufflated. For placebo cocaine, 4 mg of cocaine was added to lactose to provide peripheral cues of cocaine without producing measurable cocaine levels (Javaid et al., 1978). The active dose of cocaine was 100 mg/70 kg, which reliably elicits physiological and subjective responses (Oliveto et al., 2001). Following intranasal delivery, peak plasma levels of cocaine are reached within 30 to 120 min while the peak subjective effects of cocaine are observed 30 min following cocaine administration (Jones, 1990).

### 2.4. Medical monitoring and safety

For cardiac rhythm monitoring and heart rate and blood pressure measurements, an automated equipment (Hewlett-Packard 43200A) was used. Twelve-lead ECGs were obtained prior to cocaine administration and at the end of each session. Subjects remained in the laboratory until all vital signs returned to baseline levels. A research nurse administered all medications and was present for the entire

session. During the sessions, subjects had an indwelling catheter for blood drawing and safety reasons.

### 2.5. Outcome variables

The outcome variables were the physiological, subjective, and biochemical measures.

Physiological measures included heart rate, systolic and diastolic blood pressure, which were taken at –90, –30, –15, 15, 30, 60, 90, 120, 150, 180, 210, and 240 min in relation to the cocaine delivery.

The subjective measures were the Adjective Rating Questionnaire, Visual Analog Scales, and Addiction Research Center Inventory—short form (ARCI), administered in that order. Subjective measures were administered at –90, –30, 30, 60, and 90 min in relation to the cocaine delivery.

The Adjective Rating Questionnaire includes 27 items, which are rated on a five-point scale from 0 (*not at all*) to 4 (*extremely*). The items in the list were grouped into three subscales as follows: (1) a stimulant-good effects scale, consisting of the adjectives: active, alert, energetic, excited, euphoric, and talkative; (2) a stimulant-bad effects scale, consisting of the adjectives: irritable/angry, muscle twitches, nervous/afraid, racing heart, restless, shaky, stomach ache, and sweating; and (3) a sedative scale, consisting of adjectives: clumsy, confused, dazed, depressed, difficulty walking, dizzy, drowsy/sleepy, drunken, lazy, relaxed, sluggish, spaced out, and tired (Oliveto et al., 1995). The Visual Analog Scale consisted of nine items: drug strength, cocaine high, any high, drug-liking, “good” drug effects, “bad” drug effects, desire for cocaine, rush, and anxious/nervous. Subjects indicated how they felt on a scale from 0 (*not at all*) to 100 (*extremely*). The ARCI consists of 49 true or false questions that are scored as five subscales: MBG, a measure of “euphoria”; PCAG, a measure of “sedation”; LSD, a measure of “dysphoria”; and BG and A scales, which are sensitive to amphetamine-like effects (Martin et al., 1971).

The biochemical measure was plasma cocaine levels, which were obtained 30 min before and 30, 60, and 90 min after cocaine administration. Blood samples were collected in tubes, which contained sodium fluoride to prevent breakdown of cocaine by pseudocholine esterase. Immediately after collection, samples were centrifuged and frozen at –70° until the time of analysis. The analysis of plasma cocaine concentrations was done using reverse-phase high-performance liquid chromatography with ion pairing as described previously (Jatlow et al., 1991).

### 2.6. Statistical analysis

The physiological, subjective, and plasma cocaine measures were analyzed using repeated-measures analysis of variance. For the analysis of heart rate, systolic and diastolic blood pressure, and Visual Analog Scale, two different

analysis were conducted using area under the curve (AUC) and peak change score—maximum postcocaine dose score minus predose baseline—as outcome measures. While peak change score was chosen as a measure for the magnitude of response to cocaine, AUC was chosen as a summary measure for the magnitude and time course of the response. These analyses showed almost identical results and only the results of analysis using AUC will be shown. In these analyses, the within-subject factor was treatment with seven levels. These were (1) placebo, (2) cocaine alone, (3) naltrexone alone, (4) cocaine–naltrexone, (5) isradipine alone, (6) cocaine–isradipine, and (7) cocaine–naltrexone plus isradipine. Two sets of post hoc comparisons were performed using Fisher’s LSD: (1) placebo condition was compared to naltrexone alone and isradipine alone to ad-

dress whether these drugs alone produced behavioral effects that differed from placebo and (2) cocaine alone was compared to cocaine–naltrexone, cocaine–isradipine, and cocaine–naltrexone plus isradipine treatments to examine whether cocaine responses were altered by the different study medications. To examine possible baseline differences among treatment groups, subjective and physiological measures obtained before and after medication treatment were also analyzed. For all these analyses, a significance level of .05 was used with Huynh–Feldt adjustments to correct for possible violations of sphericity assumptions. Given the small sample size, no adjustments were made for multiple comparisons to avoid a Type II error. All analyses were conducted in Statistical Package for the Social Sciences (SPSS), version 11.0 (Norušis and SPSS, 2002).

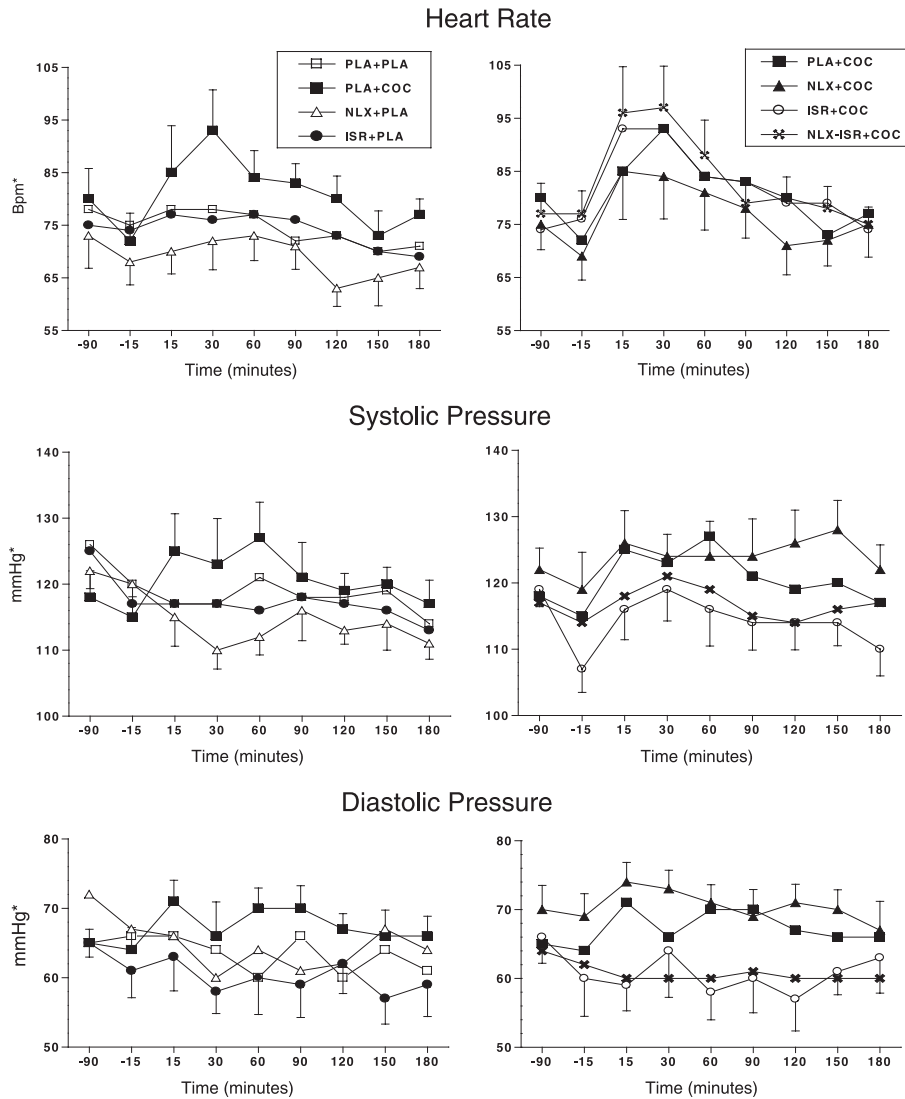


Fig. 1. Treatment effects on the mean systolic pressure, diastolic pressure, and heart rate values in response to 100 mg/70 kg intranasal cocaine as a function of time. For easier comparison, the seven treatment conditions were divided in two separate figures and the cocaine-alone treatment was included in both figures. Bars represent S.E. of the mean. For clarity, some of the error bars are not shown. Measures which show significant group difference ( $P < .05$ ) are indicated by an asterisk (\*).

### 3. Results

#### 3.1. Physiological response

For AUC scores of heart rate response, there was no overall treatment effect [ $F(6,36)=2.3, P=.15$ ; Fig. 1]. For systolic blood pressure, the analyses of the AUC scores showed significant overall treatment effect [ $F(6,36)=3.7, P<.05$ ; Fig. 1]. In post hoc analysis, the effects of isradipine alone or naltrexone alone were not different from placebo treatment in response to placebo–cocaine administration. Both cocaine–isradipine ( $P<.05$ ) and cocaine–isradipine plus naltrexone ( $P<.05$ ) treatments attenuated the cocaine-induced increases in systolic blood pressure. For diastolic

blood pressure, the analyses of the AUC scores showed significant overall treatment effect [ $F(6,36)=5.5, P=.001$ ; Fig. 1]. In post hoc analysis, treatment with isradipine alone attenuated the AUC scores for diastolic blood pressure response ( $P<.01$ ) following placebo–cocaine administration. For the cocaine-induced increases in diastolic blood pressure, cocaine–isradipine plus naltrexone treatment attenuated the response ( $P<.05$ ), while cocaine–isradipine alone showed a trend ( $P=.076$ ) for attenuation.

#### 3.2. Subjective response

The AUC scores showed overall treatment effects for all the Visual Analog Scale items except bad effects (Fig. 2).

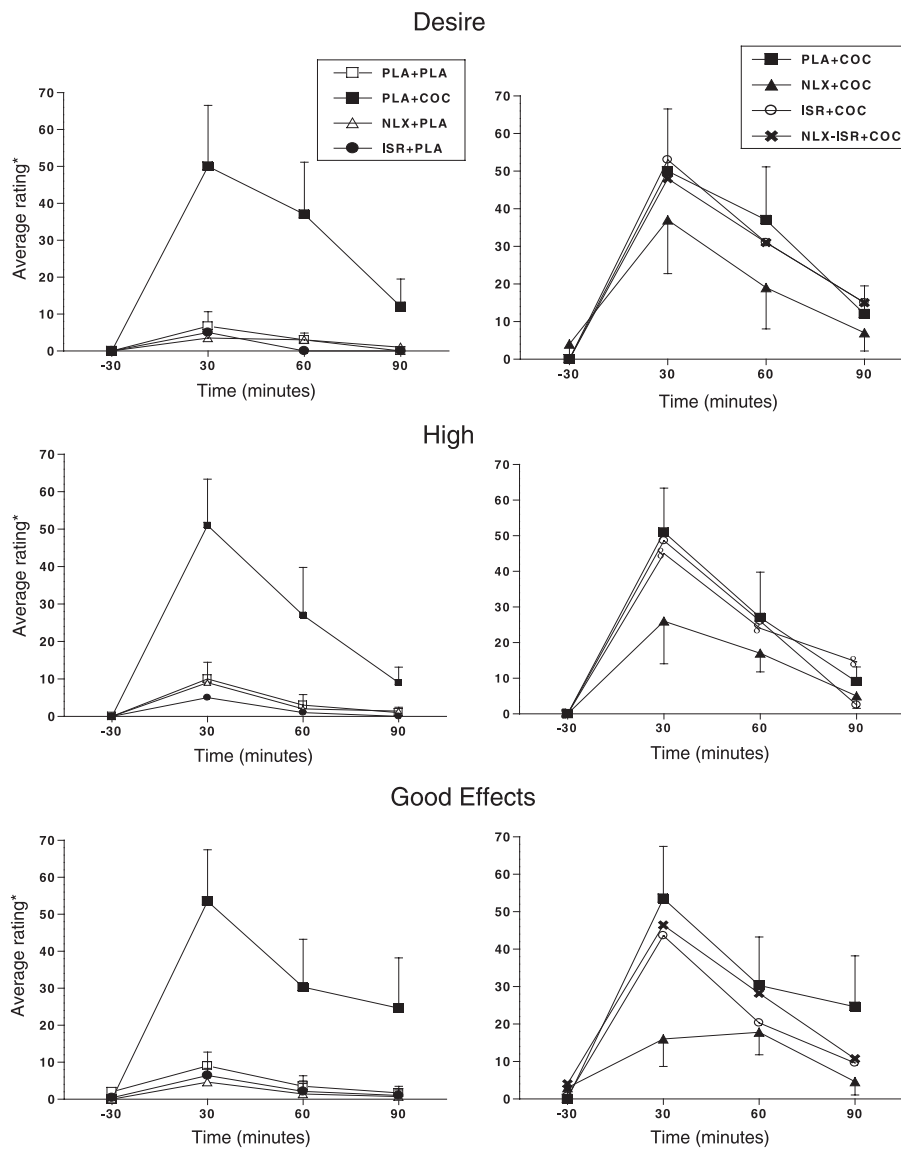


Fig. 2. Treatment effects on the average ratings for selected Visual Analog Scale items in response to intranasal 100 mg/70 kg cocaine or placebo cocaine. For easier comparison, the seven treatment conditions were divided in two separate figures and the cocaine-alone treatment was included in both figures. Bars represent S.E. of the mean. For clarity, some of the error bars are not shown. Measures which show significant group difference ( $P<.05$ ) are indicated by an asterisk (\*).



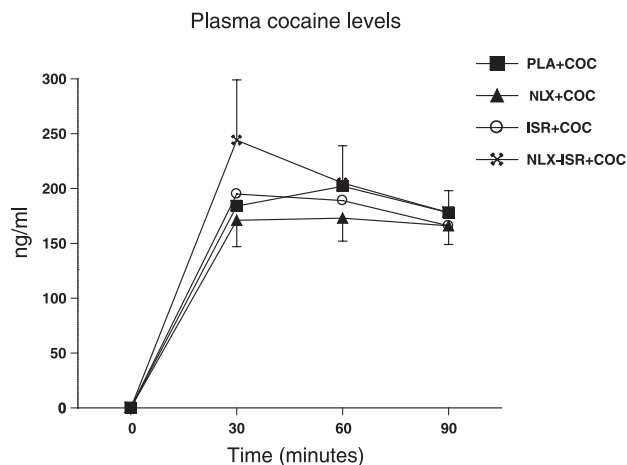


Fig. 3. Treatment effects on the plasma cocaine levels following intranasal 100 mg/70 kg cocaine administration. The treatment conditions which used placebo cocaine were excluded. Bars represent S.E. of the mean. For clarity, some of the error bars are not shown.

Neither naltrexone nor isradipine alone altered the ratings on these measures compared to placebo in response to placebo–cocaine. In response to cocaine administration, cocaine–naltrexone treatment significantly attenuated AUC measures of ratings of “good effects” ( $P < .05$ ) and marginally attenuated ratings of anxious/nervous ( $P = .06$ ), compared to cocaine alone treatment.

On the Adjective Rating Questionnaire, peak ratings on the stimulant good effects [ $F(6,36) = 4.7$ ,  $P < .05$ ], and stimulant bad effects [ $F(6,36) = 3.7$ ,  $P < .05$ ], subscales showed significant treatment effects. In post hoc comparisons, the effects of neither isradipine alone nor naltrexone alone differed from placebo treatments for placebo–cocaine response. Similarly, isradipine and naltrexone, alone or combined, did not alter cocaine’s effects. Ratings on the sedative subscale showed no overall treatment effect. For the ARCI, none of the subscales showed any treatment effects (data not shown).

### 3.3. Plasma cocaine measurements

Peak plasma cocaine levels were reached at 30 to 60 min following cocaine administration (Fig. 3). The average (S.D.) for the peak plasma levels were 202 (51) ng/ml for cocaine alone, 195 (132) ng/ml for cocaine–naltrexone, 173 (56) ng/ml for cocaine–isradipine, and 244 (146) ng/ml for cocaine–naltrexone plus isradipine treatment. There were no treatment effects on cocaine plasma concentrations.

## 4. Discussion

Isradipine attenuated the systolic blood pressure changes induced by cocaine without affecting the subjective responses to cocaine. These results are in agreement with

preclinical studies showing that calcium channel blockers attenuate the cocaine-induced blood pressure but not heart rate increases (Schindler et al., 1995b). Cocaine effects on the heart rate and blood pressure are likely mediated by the activation of  $\alpha$ - and  $\beta$ -adrenergic receptors (Schindler et al., 1995a). Calcium channel blockers such as isradipine may counteract the effects of cocaine on blood pressure by inhibiting the entry of calcium into vascular smooth muscle (Schindler et al., 1995a). These findings suggest that isradipine may be clinically useful to attenuate the cocaine-induced blood pressure increases. However, previous studies examining the calcium channel antagonists on physiological responses to cocaine have yielded mixed findings. For instance, treatment with 60 mg of nimodipine, a dihydropyridine type calcium channel antagonist like isradipine, attenuated the systolic but not diastolic blood pressure changes in response to intranasal cocaine (Kosten et al., 1999). Moreover, neither 60 mg diltiazem (Rowbotham et al., 1987), nor 10 mg nifedipine (Muntaner et al., 1991), affected the blood pressure changes induced by intravenous cocaine. The reason for these mixed findings with different calcium channel antagonists on cocaine-induced physiological changes is not clear. Possible explanations include the differences in the doses and pharmacological effects of calcium antagonists used in these studies.

In our study, isradipine did not affect the subjective responses to cocaine. These results are consistent with previous human studies which showed no interaction of calcium antagonists nimodipine (Kosten et al., 1999) and diltiazem (Rowbotham et al., 1987) with the subjective effects of cocaine. In contrast, another study found attenuation of the subjective effects of cocaine with nifedipine treatment (Muntaner et al., 1991). Similarly, isradipine treatment was reported to attenuate the subjective effects of methamphetamine (Johnson et al., 1999), a psychostimulant with actions similar to cocaine. These mixed results from human studies on cocaine effects of different calcium channel antagonists are similar to the results of preclinical studies. In a systematic study using cocaine self-administration procedure in monkeys, Schindler et al. (1995b) reported that three calcium channel antagonists, diltiazem, nimodipine, and verapamil, did not affect cocaine self-administration. In contrast, other studies found isradipine and nimodipine effective in attenuating cocaine self-administration in rats and mice (Kuzmin et al., 1996, 1992; Martellotta et al., 1994). As stated before, differences in the pharmacological effects of calcium channel blockers and the doses used may contribute to these mixed findings. Future studies comparing various calcium channel blockers using the same behavioral paradigm may help to understand these conflicting findings.

Naltrexone treatment did not change the subjective effects of cocaine, except the rating of “good effects” was attenuated by naltrexone. These results suggest minimal effects of naltrexone on the subjective effects of cocaine. The previous human studies on naltrexone effects

on cocaine responses have yielded mixed results (Kosten et al., 1992; Walsh et al., 1996). In Kosten et al.'s (1992) study, naltrexone treatment attenuated the cocaine-induced increases in self-reported value of cocaine and unpleasant sensations that follow intravenous cocaine "crash," suggesting attenuation of some of the subjective effects of cocaine by naltrexone. In another study, naltrexone treatment did not affect the subjective or physiological effects of intravenous cocaine (Walsh et al., 1996) in heroin- and cocaine-using men. Altogether these previous human laboratory studies suggest minimal or no effect of naltrexone on the subjective effects of cocaine.

The combination of isradipine and naltrexone had different effects on the subjective and physiological responses to cocaine. Isradipine plus naltrexone was more effective than either medication alone in attenuating the systolic and diastolic blood pressure response to cocaine. In contrast, isradipine plus naltrexone treatment did not affect the subjective response to cocaine. In fact, the attenuation of cocaine's subjective effects by naltrexone seemed to be reversed by the addition of isradipine to the treatment. These results are in contrast to the preclinical studies in which treatment with a combination of isradipine and naltrexone, in doses that are not effective alone, blocked the rewarding effects of cocaine (Pabello et al., 1998; Reid et al., 1997). The reason for this finding is also unclear, but may be due to several limitations of our study. First, only a single dose size of active naltrexone and isradipine was used. It is possible that higher doses of isradipine and naltrexone may have a different affect on cocaine response. Second, the treatment duration was brief, only acute effects of isradipine and naltrexone were investigated. It is possible that longer treatment duration may be needed for the emergence of the proposed isradipine and naltrexone synergism on cocaine responses. Third, the sample size of the study was small, but was clearly sufficient to allow us to show treatment effects on several physiological variables. Fourth, we did not include a naltrexone–isradipine control session, which may have helped to clarify the interaction between these two compounds in the absence of cocaine. Lastly, the study did not include cocaine self-administration behavior as a measure of cocaine reinforcement but rather relied on the self-reported subjective effects of cocaine. However, subjective effects of drugs of abuse, especially drug liking and euphoria, predict their reinforcing effects in humans (Fischman and Foltin, 1991). Nonetheless, these findings suggest that at the doses employed, combined naltrexone–isradipine treatment attenuates the physiological but not the subjective effects of cocaine.

To summarize, isradipine alone attenuated the systolic blood response to cocaine while naltrexone plus isradipine attenuated both the systolic and diastolic blood pressure response to cocaine. These results suggest the efficacy of isradipine alone or in combination with naltrexone in attenuating the physiological effects of cocaine.

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