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Naltrindole, a selective δ-opioid receptor antagonist, potentiates the lethal effects of cocaine by a central mechanism of action

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Abstract

The potentiation of the toxic and lethal effects of cocaine by the selective δ-opioid receptor antagonist naltrindole was explored in unrestrained, unanesthetized rats that received a continuous intravenous infusion of cocaine until death. The lethal dose of cocaine was lowered dose dependently in animals administered naltrindole intracisternally (3.0–30 μg), but not intravenously (30–300 μg). There was also a decrease in the lethal dose of cocaine following an injection of the nonselective opioid antagonist naltrexone, but not naloxone. However, the seizure-producing dose of cocaine was decreased dose dependently in rats that received naltrindole, regardless of the route of administration, naloxone, or naltrexone. In contrast, the effect of cocaine on heart rate was altered only by centrally administered naltrindole or intravenous naltrexone, with a dose of 30 μg naltrindole and 10 mg/kg naltrexone abolishing the bradycardic effect of cocaine. Despite this, neither naltrindole nor naltrexone changed the hypertensive effect of cocaine. Higher doses of naltrindole (100 μg i.c.) produced significant increases in heart rate and mean arterial pressure and were not tested in combination with cocaine. Because the lethal dose of cocaine was reduced only when naltrindole was administered intracisternally, the potentiation of the lethal effects of cocaine by naltrindole is through a central mechanism of action that may involve changes in cardiovascular function. © 1997 Elsevier Science B.V.

Keywords: Opioid; Cocaine; Lethality; Cardiovascular; Blood pressure; Seizure

1. Introduction

Abuse of cocaine is a major health care problem in the United States. In the first six months of 1991, 47 000 people were admitted for emergency care due to cocaine intoxication or acute cocaine toxicity (Randall, 1992). The cause(s) of cocaine-induced death in humans remains unclear because death is usually rapid and heath care providers rarely have the opportunity to treat victims (Jonsson et al., 1983).

It is not clear to what extent animal models can be extrapolated to all cocaine-induced deaths in humans given the variety of abuse patterns, pre-existing medical conditions, multi-drug abuse and proximal causes of death following cocaine use. However, studies in unanesthetized animals have provided useful information regarding potential cause(s) of death resulting from cocaine overdose and have suggested possible therapeutic interventions. In rats, seizures (Tella et al., 1992b) or the synergistic actions of seizures and respiratory depression (Tseng et al., 1992) are the major cause(s) of cocaine-induced death. Seizures also contribute to death following cocaine infusion in nonhuman primates (Guinn et al., 1980), while hyperthermia is an important factor in dogs (Catravas and Waters, 1981). Despite these findings, the neurotransmitter/neuromodulator systems responsible for seizure induction, respiratory depression and hyperthermia have not been defined clearly.

Cocaine also produces profound and potentially life threatening effects upon the cardiovascular system. In fact, direct local anesthetic effects upon the myocardium or induction of arrhythmias are potential causes of death in humans (Lathers et al., 1988). In unanesthetized rats, cocaine causes a rapid increase in mean arterial pressure (Pitts et al., 1987; Smith et al., 1993; Tella et al., 1992b) and tachycardia (Smith et al., 1993; Tella et al., 1992b, 1993). However, it is not clear how these cardiovascular effects contribute, if at all, to cocaine-induced sudden death in rats receiving a slow, continuous i.v. drug infu-

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sion. For example, Tella et al. (1992a) used this model of cocaine-induced lethality and reported no reliable correspondence between attenuation of the cardiovascular effects of cocaine with adrenergic antagonists or calcium channel blockers and reduction in the lethality of cocaine.

Administration of opioids also produce changes in blood pressure and heart rate. However, the magnitude and direction of change are dependent upon a number of factors including, but not limited to, species, route of administration and dose (Holaday, 1983). Agonists selective for all three major subtypes of opioid receptors (μ, δ, κ) produce negative inotropic effects in the isolated rat heart or isolated myocytes. Agonists selective for μ- and δ-opioid receptors produce negative chronotropic effects as well (Clo et al., 1985; Ventura et al., 1992). Centrally administered opioids also have profound effects on the cardiovascular system. For example, μ-, δ- and κ-selective opioid agonists all produce a hypertensive effect when administered intracerebroventricularly to unanesthetized rats (Glatt et al., 1987; Kiritsy-Roy et al., 1989).

Precursors of opioid peptides are localized in sympathetic, parasympathetic, and sensory neurons in the heart (Steele et al., 1996), and cardiac opioid levels are increased following sympathetic nerve stimulation (Xiang et al., 1984). The presence of opioid receptors in cardiac tissue and endogenous opioid peptide precursors in surrounding neurons suggest a role for endogenous opioids in cardiovascular function; however, further research is needed to elucidate their exact role.

Opioid antagonists modify the effects of cocaine in a number of paradigms. These include, but are not limited to, cocaine self-administration (Carroll et al., 1986), conditioned place preference (Shippenberg and Heidbreder, 1995), locomotor activity (Jones and Holtzman, 1994) and cocaine-induced behavioral sensitization (Sala et al., 1995). The results of these studies imply a role for endogenous opioids in the development and/or expression of some actions of cocaine.

This laboratory recently reported an increase in the signs of cocaine-induced toxicity in rats following intracisternal (i.c.) administration of the selective δ-opioid receptor antagonist naltrindole (Jones et al., 1993); there was an increased incidence of respiratory depression, death, and evidence of cardiovascular trauma evaluated during autopsy. The purpose of the present study was to clarify further the relationship between δ-opioid receptor blockade and cocaine-induced toxicity in the unanesthetized rat. Experiments were performed to determine (1) if the interaction between naltrindole and cocaine is dependent upon the dose of naltrindole, (2) if the site of action of naltrindole is central or peripheral and (3) if the nonselective opioid antagonists naloxone and naltrexone produce effects similar to those of naltrindole. Mean arterial pressure, heart rate, seizure threshold and lethal dose of cocaine were recorded in unanesthetized rats while cocaine was administered by continuous i.v. infusion.

2. Materials and methods

2.1. Subjects

Male Sprague Dawley rats (Charles River, Raleigh, NC, USA) weighing 325–450 g were housed three per cage in a temperature controlled room prior to surgery. Animals had constant access to food and water. A twelve hour light–dark cycle was maintained, with lights on between 7.00 a.m. and 7.00 p.m. All animals were used once and were tested between 10.00 a.m. and 4.00 p.m. The procedures used in this study were approved by the Institutional Animal Care and Use Committee of Emory University.

2.2. Surgery

Animals were weighed, anesthetized with sodium pentobarbital (50 mg/kg i.p.), and given atropine methyl nitrate (2.0 mg/kg i.p.) to minimize pulmonary secretions. Indwelling arterial (Tygon i.d. 0.02 inches and silastic i.d. 0.012 inches; soaked in 30 units/ml heparin for at least 24 h) and venous (Tygon i.d. 0.01 inches and silastic i.d. 0.012 inches) femoral catheters were inserted and then brought subcutaneously up the back and exteriorized between the scapulae. Ticracillin (6 mg) and tobramycin sulfate (8 mg) were administered i.m. to reduce the probability of infection. The venous line was flushed with heparinized isotonic saline (20 units/ml) to prevent clotting. The arterial catheter was filled with heparinized (5 units/ml) sucrose solution (5 mg/ml dH_2O), to provide increased resistance against blood flow into the catheter. Both catheters were plugged with 23 gauge wire and flushed daily with heparinized isotonic saline (20 units/ml) and refilled as indicated above. Animals were housed individually with free access to food and water and allowed to recover for at least 48 h before testing.

2.3. Testing

On the day of testing, the bottom part of the rat's home cage was placed in a $20 \times 30 \times 45$ cm ($L \times W \times H$) opaque Plexiglas box. The arterial catheter of unanesthetized, unrestrained rats was connected to a blood pressure transducer for continuous recording of pulsatile arterial pressure, mean arterial pressure and heart rate. Once stable baseline readings were obtained, animals were injected intracisternally (i.c.) over 30 s with either distilled water, or naltrindole hydrochloride (3.0, 10, 30, 100 μg/10 μl), or injected intravenously (i.v.) with either distilled water (0.1 ml), naltrindole hydrochloride (30, 100, 300 μg/0.1 ml), naloxone hydrochloride (10 mg/kg per 0.1 ml), or naltrexone hydrochloride (1, 3, 10 mg/kg per 0.1 ml) over 30 s. Animals were lightly anesthetized with isoflurane while i.c. injections were made percutaneously. This route of administration was used in previous studies from this laboratory (Jones et al., 1993) and therefore was chosen

for these experiments. Subjects remained connected to the pressure transducer during the pretreatment injection. Thirty minutes after discontinuing anesthesia, a continuous i.v. infusion of cocaine hydrochloride (1.0 mg/kg per min) was started and continued until the rat died. In addition to monitoring heart rate and blood pressure, the dose of cocaine causing the first observable tonic–clonic seizure (seizure threshold) and the dose causing death (lethal dose) were recorded. The lethal dose of cocaine was operationally defined as the dose producing a fall in mean arterial pressure below 40 mmHg without subsequent recovery within 30 s.

2.4. Data analysis

Lethality and seizure threshold data were analyzed by a one-way analysis of variance (ANOVA). Heart rate and mean arterial pressure data are presented as change from baseline, which was determined just prior to the start of cocaine infusion. Animals died at different times after initiating the cocaine infusion (10.0–121.5 min). For this reason, data were normalized by conversion to a percentage time course (i.e., data were plotted at 5%, 10%, 20%, etc. of the total experiment time for each subject). These data were then analyzed with a two-factor (dose of pretreatment drug × %time) analysis of variance. Post hoc comparisons were performed using Tukey's test for multiple comparisons when indicated by results of the ANOVA. The two vehicle groups were compared using a *t*-test for unrelated means. For all analyses, the significance level was chosen, a priori, as $\alpha = 0.05$.

2.5. Drugs

Naltrindole hydrochloride was purchased from Research Biochemicals International (Natick, MA, USA), cocaine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD, USA), naloxone hydrochloride and naltrexone hydrochloride were purchased from Sigma (St. Louis, MO, USA). Naltrindole was dissolved in distilled water, and cocaine, naloxone and naltrexone were dissolved in saline. Doses of all drugs used in the naltrindole and naloxone experiments are expressed as the salt. Doses of drugs used in the naltrexone experiment are expressed as free base.

3. Results

3.1. Lethal and seizure-producing doses of cocaine

There was no difference in the lethal or seizure-producing doses of cocaine between groups of rats that were given vehicle centrally or peripherally. The lethal dose of cocaine was 60.2 ± 10.3 mg/kg in rats receiving distilled water i.c. and 51.4 ± 7.9 mg/kg in rats pretreated with vehicle i.v. Seizure threshold was 33.9 ± 1.7 mg/kg cocaine (i.c. vehicle) and 35.0 ± 3.2 mg/kg cocaine (i.v. vehicle). Isoflurane, which was administered only to rats receiving i.c. injections, did not affect the lethal or seizure-producing dose of cocaine when compared to animals receiving vehicle intravenously without anesthesia. In addition, animals that received isoflurane and i.v. vehicle (lethal dose cocaine 38.4 ± 4.9 mg/kg; seizure threshold 28.2 ± 5.4 mg/kg; $n = 4$) were compared to the animals receiving i.v. vehicle and no anesthesia. There was no difference between these two groups.

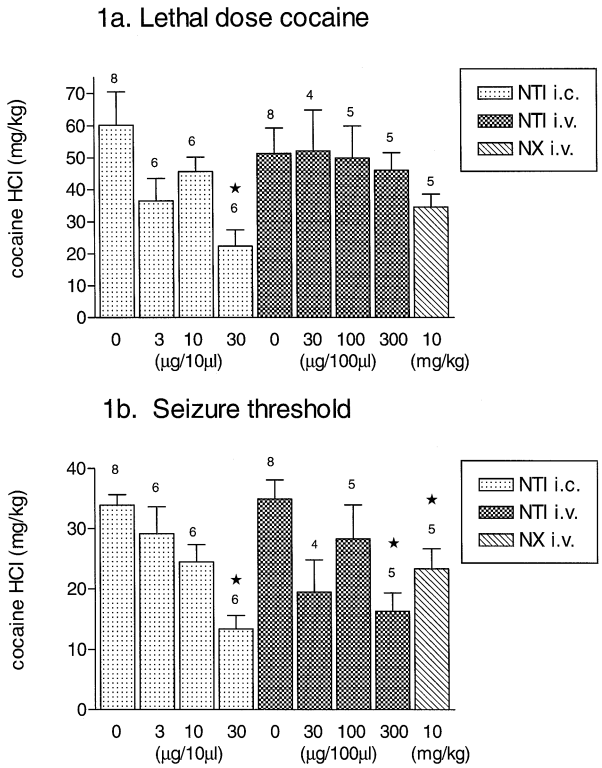

Fig. 1. (a) Lethal dose and (b) seizure producing dose of cocaine hydrochloride following pretreatment with naltrindole (NTI) i.c., NTI i.v., or naloxone (NX) i.v. Numbers above bars is *n*. ★ = $P < 0.05$ compared to respective vehicle. Error bars = S.E.M.

Naltrindole, administered centrally, dose dependently reduced the lethal dose of cocaine (Fig. 1a), with 30 μg naltrindole i.c. reducing the lethal dose of cocaine by 63% to 22.5 ± 5.0 mg/kg. In contrast, as much as 300 μg naltrindole given peripherally had no effect on the lethality of cocaine. Both i.c. and i.v. naltrindole, at the highest doses used in this study, reduced the seizure threshold of cocaine, by 60% and 53% respectively (Fig. 1b). Naloxone (10 mg/kg i.v.) did not change the lethal dose of cocaine (Fig. 1a), but did reduce the seizure producing dose of cocaine to 67% of control (Fig. 1b). Naltrexone dose dependently reduced both the lethal dose (Fig. 2a) and seizure threshold (Fig. 2b).

3.2. Effects of cocaine on arterial pressure

Baseline mean arterial pressure did not differ between any of the pretreatment groups versus the appropriate

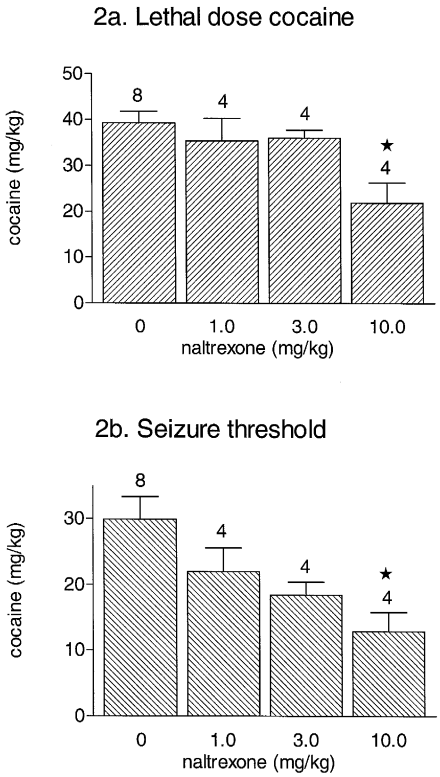

Fig. 2. (a) Lethal dose and (b) seizure producing dose of cocaine following pretreatment with naltrexone (NTX) i.v. Numbers above bars is *n*. ★ = $P < 0.05$ compared to vehicle. Error bars = S.E.M.

control group (Table 1). In all groups, initiation of cocaine infusion produced a transient increase in mean arterial pressure (46 ± 6 mmHg i.c. group; 40 ± 5 mmHg i.v. group; Fig. 3a and b) that lasted less than 5% of the total experiment time (1.5–6.0 min). This was followed by a slow increase in mean arterial pressure over the duration of the experiment, reaching 50–80 mmHg greater than baseline prior to death (Fig. 3). The effect of cocaine on blood pressure was not different between any of the groups (Fig. 3).

Table 1
Baseline mean arterial pressure (MAP) and heart rate (HR) after 30 min pretreatment with naltrindole (NTI), naloxone (NX) or naltrexone (NTX)

Pretreatment	*n*	MAP (mmHg)	HR (beats/min)
i.c. NTI (μg)			
0	8	117 ± 3	334 ± 5
3	6	110 ± 3	310 ± 10
10	6	115 ± 4	357 ± 5
30	6	131 ± 6	374 ± 18
i.v. NTI (μg)			
0	8	103 ± 1	314 ± 32
30	4	115 ± 4	348 ± 5
100	5	110 ± 2	289 ± 58
300	5	108 ± 2	353 ± 10
i.v. NX (mg/kg)			
10	5	108 ± 1	335 ± 9
i.v. NTX (mg/kg)			
0	8	101 ± 1	342 ± 9
1	4	97 ± 4	369 ± 8
3	4	102 ± 4	341 ± 8
10	4	107 ± 3	308 ± 8

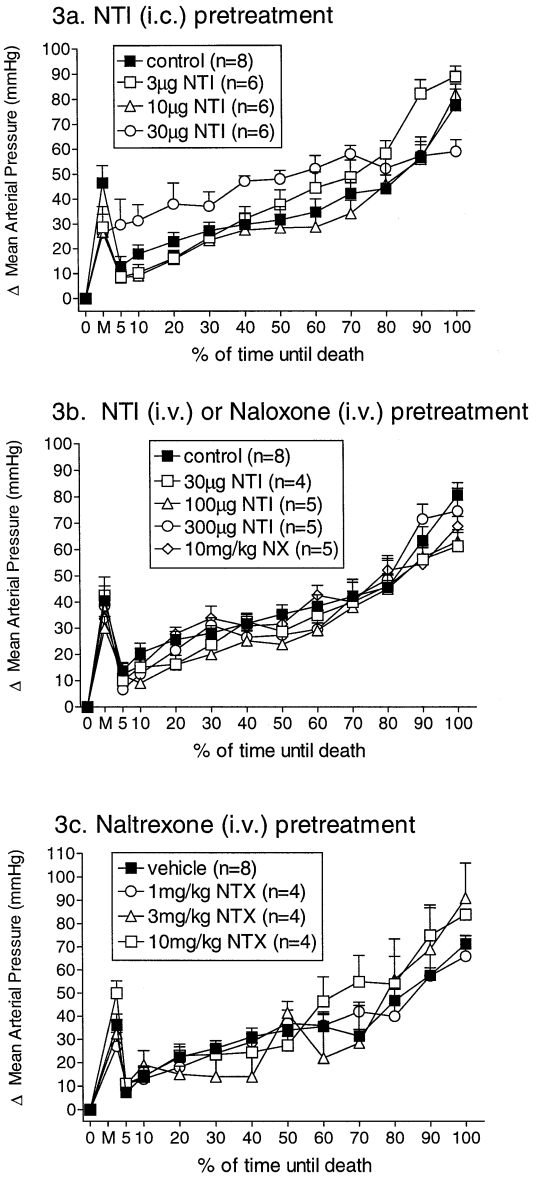

Fig. 3. Changes in mean arterial pressure during cocaine administration (1 mg/kg per min i.v.) following pretreatment with (a) naltrindole (NTI) i.c. (b) NTI i.v. or naloxone (NX) i.v. (c) Naltrexone (NTX) i.v. Data is presented as the mean arterial pressure recorded at points representing the percent elapsed time for each experiment. '*M*' on the abscissa represents the maximum change in mean arterial pressure during the first 5% of the total experiment time. Error bars = S.E.M.

3.3. Naltrindole i.c. blocks the bradycardic effect of cocaine

The baseline heart rate was not different between groups (Table 1). Cocaine produced significant changes in heart rate in both vehicle groups, which consisted of an initial,

brief tachycardia ($+31 \pm 8$ beats/min i.c.; $+22 \pm 7$ beats/min i.v.) lasting less than 5% of the total experiment time (1.5–6.0 min), followed by a period of bradycardia lasting 60%–70% (18–72 min) of the total experiment time, with maximum decreases of 34 ± 14 (i.c.) and 40 ± 7 (i.v.) beats/min. There was a final tachycardia that coincided with the onset of tonic–clonic seizures, with values reaching $+60 \pm 26$ beats/min (i.c.) and $+62 \pm 10$ beats/min (i.v.) greater than baseline. Changes in heart rate did not differ between the two vehicle groups at any of the time points measured.

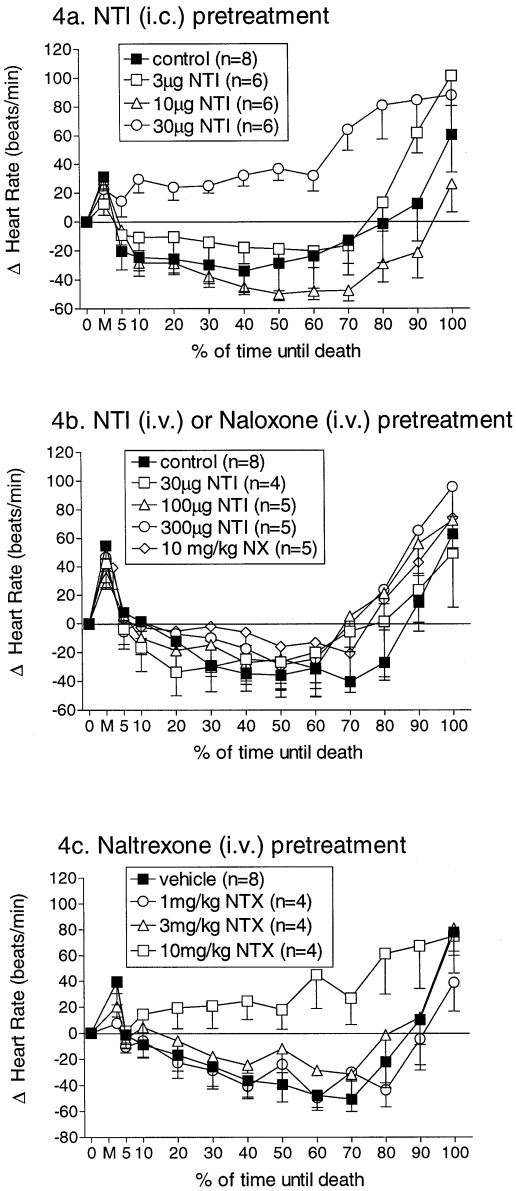

Fig. 4. (a) Changes in heart rate from precocaine levels during cocaine administration (1 mg/kg per min) following pretreatment with naltrindole (NTI) i.c. The bradycardic effect is significantly attenuated ($P < 0.01$) following pretreatment with 30 μg NTI i.c. (b) The heart rate effects of cocaine are not significantly altered by NTI i.v. or naloxone (NX). (c) Naltrexone (NTX), at 10 mg/kg (open squares), also attenuates the bradycardic effect of cocaine ($P < 0.05$). 'M' on the abscissa represents the maximum change in heart rate during the first 5% of the total experiment time. Error bars = S.E.M.

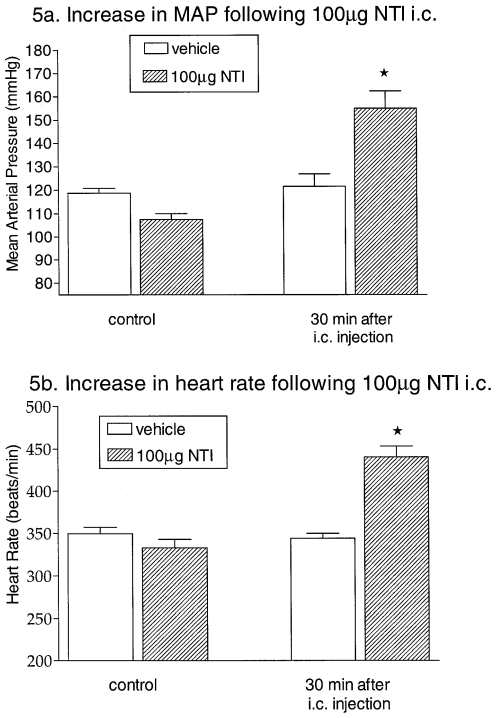

Fig. 5. (a) Mean arterial pressure and (b) heart rate were significantly increased by 100 μg naltrindole (NTI) i.c. ($P < 0.01$). Control, pre-drug baseline; open bars, control ($n = 8$); cross-hatched bars, 100 μg NTI i.c. ($n = 6$); error bars, S.E.M. ★ = $P < 0.05$ versus vehicle control.

Naltrindole administered centrally, but not peripherally, altered the effect of cocaine on heart rate. At a dose of 30 μg, naltrindole i.c. abolished the bradycardic effect of cocaine (Fig. 4a). The bradycardic effect was also antagonized by 10 mg/kg naltrexone (Fig. 4c), but was not affected by 10 mg/kg naloxone (Fig. 4b).

3.4. Increases in baseline mean arterial pressure and heart rate by a high dose of naltrindole i.c.

Mean arterial pressure and heart rate were both increased by central administration of 100 μg naltrindole (Fig. 5a and b). Since these elevations in mean arterial pressure and heart rate persisted longer than the 30 min pretreatment time and were significantly higher than prenaltrindole levels, cocaine was not tested in these animals. Transient increases in these measures were also seen in three out of six animals receiving 30 μg naltrindole i.c. However, both heart rate and mean arterial pressure had returned to levels not significantly different from initial baseline levels in less than 30 min. Consequentially, these animals were tested with cocaine and included in the data presented. In contrast, neither blood pressure nor heart rate was affected by any of the other doses of naltrindole administered centrally or peripherally. Neither naltrexone nor naloxone affected either measure at any of the doses tested.

4. Discussion

Naltrindole, a highly selective δ-opioid receptor antagonist, lowered the lethal dose of cocaine in a dose dependent manner when administered centrally. However, when administered peripherally, naltrindole did not alter the lethal dose of cocaine in doses up to 10-times greater than the effective centrally administered dose. Therefore, the potentiation of cocaine-induced lethality by naltrindole is through a central mechanism of action.

In contrast, the seizure-producing dose of cocaine was decreased in a dose dependent manner by both centrally and peripherally administered naltrindole as well as by 10 mg/kg naloxone and naltrexone. Although seizures have been cited as the primary cause of cocaine-induced death in a number of studies involving both rats (Tella et al., 1992a; Tseng et al., 1992) and nonhuman primates (Guinn et al., 1980), there was no correspondence between the potentiation of lethality and seizure-induction by naltrindole in this study. For example, 300 μg naltrindole (i.v.) lowered the seizure threshold of cocaine from 35.0 ± 3.2 to 16.3 ± 3.0 mg/kg cocaine without significantly affecting the lethal dose of cocaine. A quicker onset of tonic–clonic seizures following naltrindole administration, which is indicated by a lower dose of cocaine producing seizures, did not necessarily result in an increase in the lethality of cocaine. Therefore, the potentiation of the lethal effects of cocaine by naltrindole is probably not due to changes in seizure threshold.

Cardiovascular changes produced by cocaine did not contribute to it's lethal effects in a previous study using a continuous infusion of cocaine to cause death (Tella et al., 1992b). However, cardiovascular complications do contribute to cocaine-related death in humans (Lathers et al., 1988). In the present study, naltrindole abolished the bradycardic effect of cocaine when it was given intracisternally, but not intravenously. Naltrexone also antagonized the bradycardic effect of cocaine, while naloxone did not affect it. Naltrindole and naltrexone could have influenced the chronotropic effects of cocaine via several different mechanisms. Cocaine depresses baroreflex function (Andresen et al., 1990; Trouve et al., 1992; Knuepfer et al., 1993), and produces a prolonged decrease in central sympathetic outflow (Raczkowski et al., 1990; Gantenberg and Hageman, 1991; Knuepfer and Branch, 1992). The results of this study would be consistent with a further decreases in baroreflex function or opposition of the decreases in sympathetic outflow. However, further experiments are needed to establish if naltrindole and naltrexone produced their effects through one of these mechanisms. The decrease in the bradycardic effect of cocaine following naltrindole i.c. was probably not due to direct effects on the heart, because peripherally administered naltrindole did not produce any changes in the chronotropic effects of cocaine. Significant changes in heart rate only occurred in the same group of animals in which the lethality of cocaine was potentiated (30 μg naltrindole i.c. and 10 mg/kg naltrexone i.v.). Therefore, the blockade of the bradycardic effect of cocaine may have contributed to the increased lethality of cocaine.

Although the effects of endogenous opioids upon the cardiovascular system are complex, there is evidence for a role of endogenous opioid systems in modulating cardiovascular function during states of extreme physiologic stress. For example, depressed circulatory function during shock, spinal injury, and orthostatic hypotension is attenuated by administration of naloxone (for review, see Holaday (1983)). Endogenous opioids are apparently released in these situations, and may potentiate the cardiovascular system depression seen under these circumstances. Additionally, opioid antagonists can potentiate or attenuate effects of cocaine in several experimental paradigms (Carroll et al., 1986; Shippenberg and Heidbreder, 1995; Jones and Holtzman, 1994; Sala et al., 1995), indicating a role for endogenous opioids in modulating these effects of cocaine. Endogenous opioids may also change the cardiovascular effects of cocaine. If this is the case, then blockade of opioid receptors could alter the cardiovascular effects of cocaine in a way that increases it's lethality, as was shown in this study.

Naltrindole is highly selective for δ-opioid receptors versus μ- or κ-opioid receptors: its affinity for δ-opioid receptors is more than 100-fold greater than its affinity for the other opioid receptors (Portoghese et al., 1988). In addition, naltrindole, in doses up to 20 mg/kg subcutaneously or 30 μg intrathecally, selectively blocks analgesia induced by δ-opioid agonists, but not that induced by μ- or κ-opioid receptor agonists (Portoghese et al., 1988; Calcagnetti and Holtzman, 1991; Drower et al., 1991). Given its selectivity for δ-opioid receptors versus other opioid receptor subtypes, naltrindole is probably not producing its effects on the lethality of cocaine through μ- or κ-opioid receptors.

The nonselective opioid receptor antagonist naloxone, at a dose of 10 mg/kg, did not produce the same effects as naltrindole on cocaine-induced lethality or on the cardiovascular actions of cocaine, whereas naltrexone did. It is not clear why naloxone and naltrexone are producing different effects, given the similarities in the opioid receptor binding profiles of the two drugs (Wood et al., 1981). The dose of naloxone used in this study was at least ten times greater than the dose needed to block δ-opioid receptor mediated effects. For example, 1.0 mg/kg naloxone administered subcutaneously is sufficient to decrease the locomotor stimulant effects (Chang et al., 1993) and antinociceptive effects (Tiseo et al., 1988) of δ-opioid receptor agonists. Because different results were seen with naloxone, at a dose shown to block δ-opioid receptors in vivo, versus naltrexone and naltrindole, it is not clear if the latter two are exerting their effects by blocking δ-opioid receptors. In addition, 100 μg naltrindole i.c. produced profound and long-lasting increases in baseline heart rate

and blood pressure. This suggests high doses of naltrindole may have significant pharmacological actions that are not mediated by opioid receptors. Further study is needed to determine conclusively if the effect of naltrindole upon cocaine-induced lethality seen in this study was mediated by blockade of δ-opioid receptors, and if other factors not measured in this study, such as respiratory depression, contributed to it.

In summary, this is the first study to show that the selective δ-opioid antagonist, naltrindole, increases the lethal effect of cocaine. This effect was accompanied by a potentiation of cocaine-induced seizures and an abolition of the bradycardic effect of cocaine, all of which were produced via a central mechanism of action.

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