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Effects of Labetalol Treatment on the Physiological and Subjective Response to Smoked Cocaine

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SOFUOGLU, M., S. BROWN, D. A. BABB, P. R. PENTEL AND D. K. HATSUKAMI. *Effects of Labetalol treatment on the physiological and subjective response to smoked cocaine.* PHARMACOL BIOCHEM BEHAV **65**(2) 255–259, 2000.—Adrenergic receptors mediate some of the physiological and possibly behavioral effects of cocaine. The purpose of this study was to investigate the effect of treatment with a peripherally acting adrenergic blocking drug labetalol on the cardiovascular and subjective response to repeated deliveries of smoked cocaine. In this double-blind, placebo-controlled, crossover study, 12 cocaine users were treated with a single 100 or 200 mg dose of labetalol, or placebo in each of three experimental sessions. Starting 2 h after the medication treatment, subjects received three doses of 0.4 mg/kg smoked cocaine, 30 min apart. Labetalol treatment significantly attenuated the cocaine-induced increases in heart rate and systolic blood pressure. This effect of labetalol on the cardiovascular response did not decrease with repeated cocaine deliveries. The subjective response to smoked cocaine deliveries was not affected by labetalol treatment. These results suggest that labetalol effectively attenueates the systolic blood pressure and heart rate increases induced by repeated doses of smoked cocaine, but does not alter subjective effects. © 2000 Elsevier Science Inc.

Adrenergic receptors Labetalol Cocaine Crack cocaine

COCAINE activates both central and peripheral adrenergic receptors by its catecholamine reuptake inhibitory effects. Adrenergic blocking agents have been shown to inhibit the effects of cocaine using different experimental models. The alpha-adrenergic blocker prazosin inhibited the increased motor activity in rats (2) and discriminative stimulus effect of cocaine in pigeons (11) and monkeys (17). The beta-adrenergic blocker propranolol inhibited self-administration of cocaine and the anxiety like symptoms after withdrawal from cocaine in rats (8). These findings suggest that both alpha- and beta-adrenergic receptors may be involved in mediating the behavioral and toxic effects of cocaine.

In addition, alpha- and beta-adrenergic blocker attenuate the cardiovascular effects of cocaine. In fact, labetalol, a combined alpha- and beta-adrenergic blocker, has been shown to attenuate the cardiovascular effects of cocaine in dogs more effectively than pure beta or alpha-blockers alone (13). In humans, a number of case reports support the effect of labetalol for the treatment of cocaine-induced hypertension in emergency settings (1,5,7). In addition, the results of two controlled studies suggest that labetalol may be more effective and safer than pure beta-blockers in reversing the cardiovascular effects of intranasal cocaine (3,14). The role of the adrenergic receptors in mediating the subjective response to cocaine in humans has not been studied. There is recent evidence suggesting the role of the adrenergic receptors in higher cognitive functions such as formation of emotional memories. These effects are inhibited by beta-adrenergic blockers (4). Considering the activation of the adrenergic receptors by cocaine, we hypothesized that treatment with adrenergic blocking agents may not only attenuate the physiological response but also decrease the emotional arousal and

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subjective response to cocaine. The study medication labetalol crosses the blood–brain barrier poorly, and its effects are limited to the peripheral adrenergic receptors. Therefore, labetalol provided an opportunity to examine the effects of peripheral adrenergic receptor blockage in physiological and subjective response to cocaine. In this study, we investigated the effects of labetalol treatment on the physiological and subjective effects of repeated doses of smoked cocaine in humans. Because cocaine is commonly used in binge pattern, it was of interest to investigate the effect of labetalol treatment on repeated cocaine deliveries. This study will extend the previous studies on the effect of adrenergic blockers in mediating the cocaine effects in humans.

METHOD

Subjects

Subjects were nine male and three female crack-cocaine users. Ten subjects were African-American, 2 were white, and the average (SD) years of cocaine use was 10.7 (4.8) years. The average (SD) frequency and amount of cocaine use were 4.2 (1.9) days/week and 3 (0.9) g/day, respectively. Drug use was confirmed with urine analysis before the study participation. Other drugs used within the past month were cigarettes (n = 10), alcohol (n = 9), and marijuana (n = 5). Subjects had normal physical, laboratory, and psychiatric examinations and were not dependent on drugs other than cocaine and nicotine. Subjects were told that the goal of the study was to investigate whether labetalol will reverse their response to cocaine. Subjects were encouraged not to use drugs other than the ones provided during the sessions, and were asked to provide urine samples before each session for urine drug screening. Randomly selected urine samples were tested for compliance. Prior to their participation, subjects signed an informed consent. This study was approved by the Institutional Review Board of the University of Minnesota. Experimental sessions were carried out in the General Clinical Research Center, and subjects were paid for participation.

Study Procedure

In this outpatient, double-blind, placebo-controlled crossover study there were one adaptation and three experimental sessions. All sessions started at 1100 h and were 2 to 7 days apart to minimize the carryover effects from labetalol or cocaine. Subjects had an indwelling intravenous catheter placed in an antecubital vein before the sessions for blood drawing and safety reasons. Subjects were oriented to the laboratory procedures on the adaptation session, and received a single dose of smoked cocaine to familiarize with the dose that they would receive during the experimental sessions. During each of the experimental sessions, subjects received the study medication followed by a light meal. Starting 2 h after medication administration, when peak levels of labetalol were attained, subjects received three doses of 0.4 mg/kg of smoked cocaine, 30 min apart. Several physiological and subjective measures were taken before and after each dose. Cardiac rhythm was monitored continuously during sessions. Twelve-lead EKGs 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. At the end of the session, subjects were examined and were discharged home.

Cocaine and Labetalol Administration

The device used to deliver smoked cocaine base was described previously (9), and shown to deliver precise and reliable doses of cocaine. Briefly, specific amounts of cocaine base were applied to wire coil devices at least 24 h prior to experimental sessions. After weighing, a coil device was inserted into a glass mouthpiece, and connected through a smoking chamber to a power supply. When the subject inhaled using the mouthpiece, it caused a change in air flow across the coil device that triggered the electrical heating of the coil. This process led to rapid volatilization of cocaine. Our previous analysis showed that the smoke produced consisted of more than 96% cocaine (Thompson and Hatsukami, unpublished). Subjects were told to inhale for 10 s, and then hold the vapor for an additional 15 s. After the delivery, coils were reweighed to verify the amount of cocaine that was volatilized.

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse and converted to cocaine base. The cocaine dose was 0.4 mg/kg, a dose that is reliably self-administered and considered safe (9,10). On each of three experimental sessions, subjects were given a single low (100-mg) or high (200-mg) dose of labetalol (Trandate,® Glaxo Wellcome Inc., NC) or placebo, orally. Labetalol has a half-life of 3 to 7 h, and the duration of its blood pressure lowering effects lasts 8 to 12 h after a single oral 200-mg dose (15). To minimize any possible adverse events, the labetalol doses were given in ascending order, and the placebo treatment was randomly inserted into the sequence.

Data Analysis

The main dependent variables were the physiological and subjective measures. Physiological measures included heart rate and systolic and diastolic blood pressure, which were taken 2 min before and every 5 min, for 30 min, after each dose. Peak- change scores (maximum postdose minus predose) and area under the curve (AUC) scores were evaluated as dependent variables for the physiological responses of heart rate, systolic, and diastolic blood pressure. To incorporate baseline information, peak change score was chosen as a measure for the magnitude of response with each delivery of cocaine. AUC was chosen as a summary measure for the magnitude and time course of the response to cocaine deliveries.

Subjective drug effects were measured by the cocaine effects questionnaire (CEQ), a computerized visual analog scale (VAS) derived from a similar scale (6). The craving questionnaire was given 4.5 min before and 2.5 min after each dose. Additional measures were also obtained at 10 and 15 min after the first dose. Peak change scores were used for the analysis of the subjective measures. Samples for plasma cocaine concentrations were taken just before and 6 min after the first dose.

A mixed-effects repeated-measures analysis of the primary physiological and subjective responses was conducted to assess treatment effects. In these analyses, effects for treatment (placebo, low, or high), dose of cocaine (1, 2, and 3), time from cocaine delivery and the interaction of these effects were included.

RESULTS

The heart rate, systolic, and diastolic blood pressure response to cocaine deliveries under three treatment conditions are shown in Fig. 1 and 2. For three deliveries of cocaine, the analyses of the peak changes revealed significant treatment effects for systolic blood pressure, $F(2, 85) = 3.41$, $p < 0.05$, and for heart rate, $F(2, 85) = 8.99$, $p < 0.001$. Similarly, the analyses of the AUC measure showed significant treatment effects for systolic blood pressure, $F(2,85) = 6.84$, $p < 0.05$,

and heart rate, $F(2,85) = 8.86$, $p < 0.001$). The treatment effect on diastolic blood pressure was not significant ($p > 0.05$) for either peak change or AUC analyses. For peak change scores, post hoc comparisons revealed significant contrast for high dose vs. placebo for systolic blood pressure ($p < 0.05$) and heart rate ($p < 0.001$). Low dose and placebo were significantly different for heart rate ($p < 0.001$).

For AUC scores, post hoc comparisons revealed significant contrasts between the high dose vs. placebo for systolic blood pressure and heart rate (both p-values < 0.001). In addition, there were significant differences between high dose vs. low dose for systolic blood pressure ($p < 0.05$) and between low dose vs. placebo for heart rate ($p < 0.001$).

Over three cocaine deliveries, there was a statistically significant decrease in peak change and AUC measures in heart rate response to cocaine ($p < 0.001$). For systolic and diastolic blood pressure, the change in peak and AUC measures over three cocaine deliveries were not significant. None of the measures showed treatment by delivery interaction that would suggest a decreasing effect of labetalol with repeated cocaine deliveries.

Subjective Response

Two summary measures were created from the CEQ scores items related to craving (want, need, crave, and desire for cocaine) and items related to the effects of cocaine (high, stimulated, heart racing/pounding, paranoid, feel the effect of last dose). For both measures, there was a decrease in re-

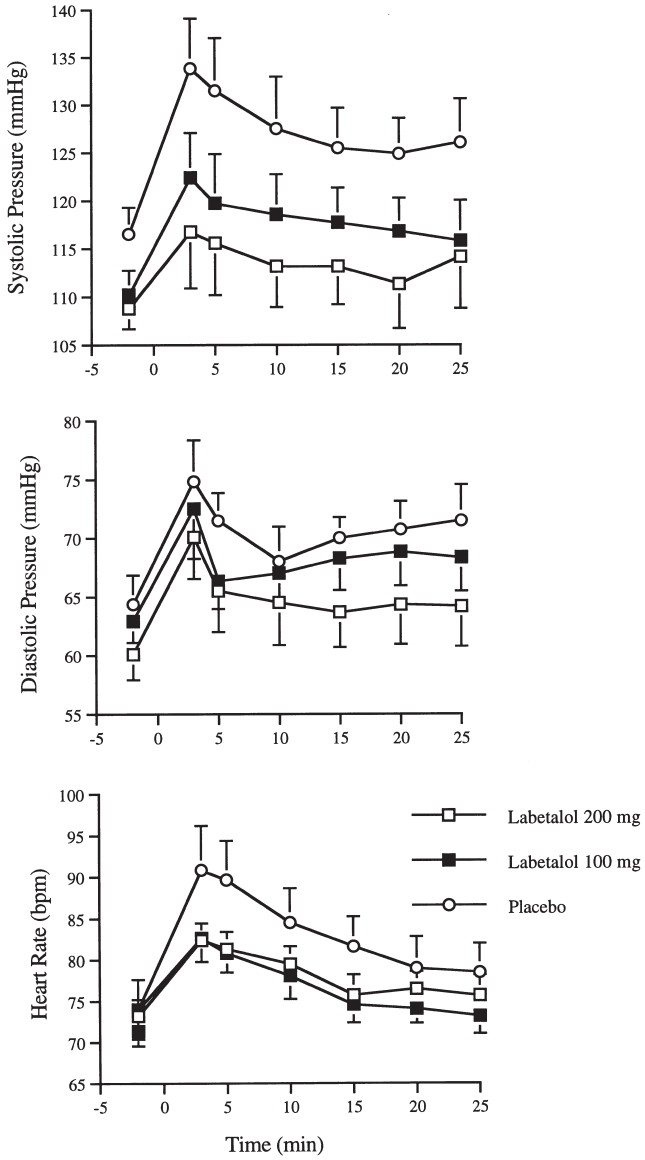

FIG. 1. The average (±SEM) systolic pressure, diastolic pressure, and heart rate response to the first smoked cocaine administration under different treatment conditions. Measurement were taken at 2 min before and 2.5, 4.5, 9.5, 14.5, and 19.5 min after a 0.4 mg/kg of cocaine delivery.

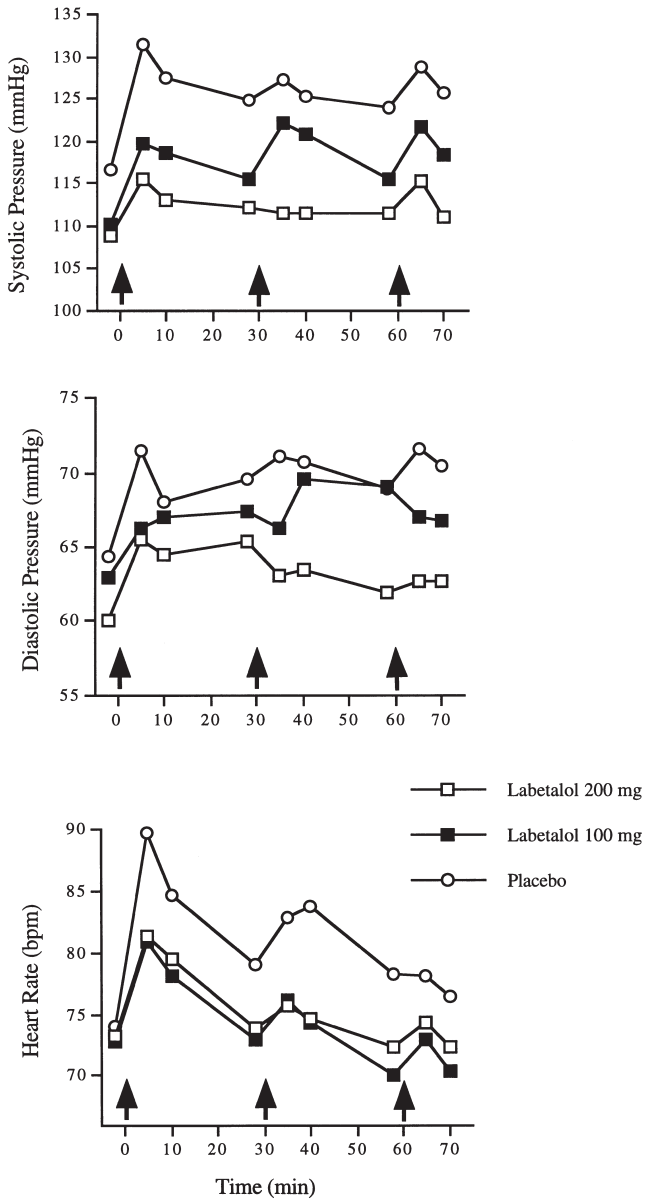

FIG. 2. The average systolic, diastolic blood pressure, and heart rate response to three deliveries of cocaine under different treatment conditions. Subjects received cocaine deliveries at 0, 30, and 60 min (indicated by arrows). For clarity, measurements only taken 2 min before, 4.5 and 9.5 min after each dose are shown.

sponse with the second and third dose delivery of each day ($p < 0.01$). There was no treatment effect of labetalol for the subjective response to cocaine deliveries (Fig. 3).

Plasma Cocaine Measurements

There was no treatment effect on changes in plasma cocaine concentrations with cocaine delivery. The average (SD) cocaine concentrations after the first cocaine delivery were 290 (138) ng/ml for the high dose, 245 (123) ng/ml for the low dose labetalol, and 258 (95) ng/ml for the placebo group.

DISCUSSION

The main finding of this study was the attenuation of cocaine-induced heart rate and systolic blood pressure changes by labetalol treatment. Our results are similar to previous reports on labetalol effects on the cardiovascular response to single doses of cocaine. In dogs, the increased heart rate, mean arterial pressure, and decreased coronary blood flow induced by 1.5 mg/kg of intravenous cocaine was attenuated by 5 mg/kg of labetalol pretreatment (13). In another study with patients undergoing cardiac catheterization for chest pain, 0.25 mg/kg of intravenous labetalol attenuated the mean arterial pressure increase induced by 2 mg/kg of intranasal cocaine (3). In our study, the effect of labetalol on cocaine-induced changes in diastolic blood pressure was not statistically significant. We cannot compare our results with the previous ones, because only mean arterial pressure was reported in these two reports. The lack of effect of labetalol on diastolic blood pressure increase may be due to a three- to sevenfold higher affinity of labetalol to beta compared to alpha-adrenergic receptors (15), which resulted in a greater effect on cardiac output than on vascular resistance. Labetalol doses higher then employed in our study may be needed to block the alpha-adrenergic receptors and decrease the diastolic pressure. Altogether, these results further support the effect of labetalol in attenuating the cardiovascular effects of cocaine.

Previous studies on the effects of labetalol on the cardiovascular response to cocaine have used a single dose of cocaine administration. Because cocaine is commonly used in a binge pattern, it was of clinical interest to investigate whether repeated doses of cocaine overcome the blocking effects of labetalol on the cardiovascular response. Our results suggest that the effects of labetalol in attenuating the blood pressure and heart rate changes do not diminish with up to three repeated cocaine deliveries. In this study, the dose dependency for labetalol effects were observed for systolic blood pressure AUC measure but not for other cardiovascular measures. These results suggest that both 100 and 200 mg of labetalol doses were equally effective in attenuating the blood pressure and heart rate change induced by repeated doses of smoked cocaine. However, cocaine users report an interdose interval much shorter than 30 min between cocaine doses during cocaine binges. Whether labetalol treatment will attenuate the physiological effects of cocaine under those circumstances is not known.

Based on several case reports, labetalol has been recommended for the treatment of cocaine induced hypertensive emergencies (1,5,7,12). The proposed advantage of labetalol over pure beta-blockers is the additional alpha-adrenergic blockage with labetalol. Treatment with pure beta-adrenergic blockers like propranolol has been shown to enhance some of the cardiovascular effects of cocaine (13,14,16). This enhancement of cocaine effects by pure beta-blockers may be mediated by the stimulation of unopposed alpha-adrenergic receptors. Although it may be more effective than propranolol, labetalol may not attenuate all the cardiovascular effects of cocaine. In a previous study, labetalol treatment failed to reverse the coronary vasoconstriction induced by intranasal cocaine in subjects undergoing cardiac catheterization (3). As mentioned earlier, in our study labetalol did not significantly reduce the diastolic pressure increases induced by cocaine. These results may be due to lower potency of labetalol for alpha-adrenergic receptors that may mediate vasoconstriction. Labetalol may act like a beta-adrenergic blocker in lower doses, and higher doses may be needed to block the effects of cocaine that are mediated by alpha-adrenergic receptors.

In contrast to the cardiovascular response, labetalol had no significant effect on subjective response to cocaine administration. Interestingly, subjects rated the item "heart racing/pounding" similarly under different treatment conditions, al-

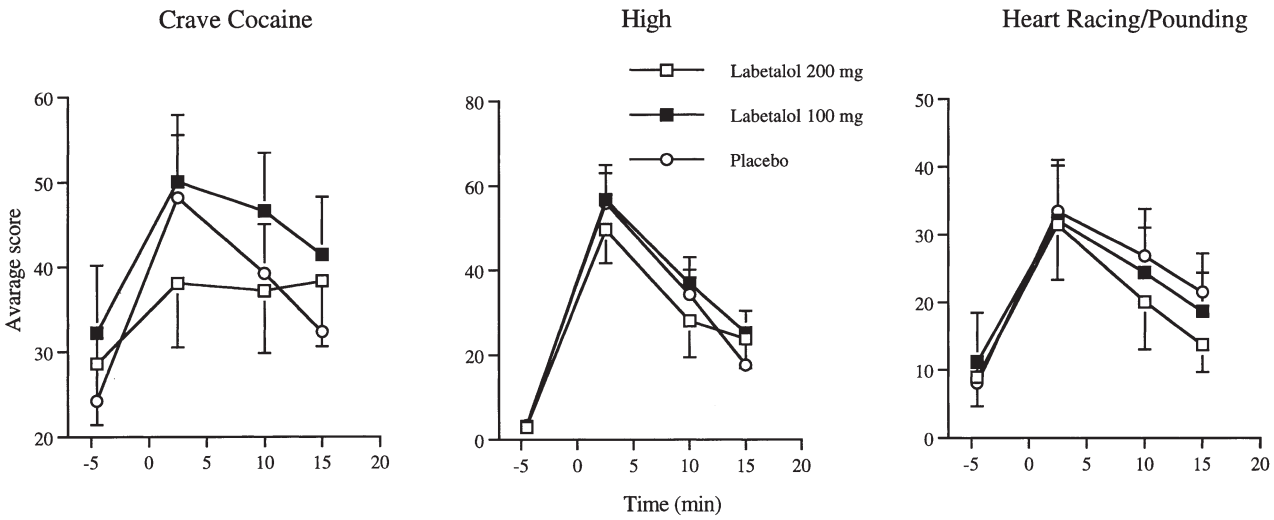

FIG. 3. The average scores (±SEM) on selected subjective measures in response to the first smoked cocaine administration under different treatment conditions. Subjective measures were taken at −4.5, 2.5, 10, and 15 min in relation to 0.4 mg/kg of cocaine delivery.

though labetalol significantly attenuated the cocaine-induced increases in heart rate. The reason for this discrepancy between the physiological effects and subjective ratings are unknown. These results do not support the role of adrenergic receptors activation in mediating the subjective response to cocaine. However, this conclusion based on this present study, may need to be amplified with future research for the following reasons. First, labetalol effects are limited to the periphery because it does not cross the blood–brain barrier effectively. In a recent study, recall of emotional memories has been shown not to be blocked by peripherally acting beta-adrenergic blockers (18) in contrast to the effects of the centrally acting beta-blocker propranolol (4). It will be of interest to investigate the effects of lipophilic alpha- and beta-blockers on cocaine effects, especially subjective effects. Second, this study was limited to the acute effects of cocaine in laboratory conditions. Other aspects of cocaine addiction including the reactivity to cocaine-related cues may be mediated by the activation of the adrenergic receptors.

There are several limitations of this study. First, only acute effects of labetalol on physiological and subjective response to cocaine were studied. It is possible that the full effects of labetalol treatment may need treatment longer than a single exposure. Second, the plasma levels of labetalol was not measured. However, clear-but baseline cardiovascular effects demonstrate that an effective adrenergic blocking dose of labetalol had been observed. Third, for safety reasons, subjects received the low dose of labetalol treatment before high dose. This treatment sequence has the potential to confound the results, and may be a reason for the lack of differences between the high and low dose of the labetalol treatment. Fourth, because our sample size was based on the expected cardiovascular effects of labetalol, the study may not have enough power to detect the labetalol effects on the subjective response to cocaine.

To summarize, this is the first controlled human study showing that labetalol treatment reduces the systolic blood pressure and heart rate increases induced by repeated doses of smoked cocaine. Further studies are needed to explore the role of adrenergic receptors in cocaine addiction.

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