ELSEVIER

European Journal of Pharmacology 431 (2001) 53–59

ejp

www.elsevier.com/locate/ejphar

Effects of cocaine and cocaine metabolites on cardiovascular function in squirrel monkeys

Charles W. Schindler [a,*], Ji-Wang Zheng [b], Steven R. Goldberg [a]

[a] *Preclinical Pharmacology Section, NIH / NIDA Intramural Research Program, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA*
[b] *National Institute on Drug Dependence, Beijing Medical University, Beijing 100083, China*

Received 3 July 2001; received in revised form 10 September 2001; accepted 17 September 2001

Abstract

The effects of cocaine and the cocaine metabolites norcocaine, ecgonine methyl ester, benzoylecgonine and cocaethylene were evaluated in conscious squirrel monkeys for their effects on blood pressure and heart rate. Norcocaine, ecgonine methyl ester and benzoylecgonine are produced in vivo following cocaine use. Cocaethylene is produced in vivo following concurrent cocaine and alcohol use. Increases in both blood pressure and heart rate were observed following cocaine doses of 0.3–3.0 mg/kg. Ecgonine methyl ester and benzoylecgonine had no effect on either parameter up to doses of 10.0 mg/kg. Norcocaine increased blood pressure, but was less potent than cocaine. Norcocaine did not affect heart rate at doses up to 3.0 mg/kg. In contrast to the other metabolites, cocaethylene increased blood pressure and heart rate similarly to cocaine. These results suggest that ecgonine methyl ester and benzoylecgonine are devoid of cardiovascular effects at doses comparable to cocaine and would not be expected to contribute to cocaine's overall cardiovascular effects. Norcocaine's effect on blood pressure might contribute to the cardiovascular effects of cocaine, but this metabolite is produced only at low levels in vivo. The one metabolite that might be expected to contribute to cocaine's overall cardiovascular effect is cocaethylene, although the degree of this contribution is not clear. Published by Elsevier Science B.V.

Keywords: Cocaine; Cocaine metabolites; Blood pressure; Heart rate; Squirrel monkeys

1. Introduction

Cocaine is metabolized in vivo to ecgonine methyl ester, benzoylecgonine and norcocaine. Norcocaine is a relatively minor metabolite in humans. When cocaine is used concurrently with alcohol, cocaethylene is produced. While a number of reports have pointed to potent cardiovascular effects of norcocaine (Erzouki et al., 1993; Mahlakaarto et al., 1998; Wilson et al., 1978) and cocaethylene (Erzouki et al., 1993; McCance-Katz et al., 1993), it was originally thought that ecgonine methyl ester and benzolyecgonine were inactive. Recent evidence, however, points to a potential role of these metabolites in the cardiovascular effects of cocaine. For example, Pane et al. (1997) report that ecgonine methyl ester produces cerebral vasodilation in neonatal sheep and Madden and Powers (1990) report that benzolyecgonine can mediate potent vasoconstrictor effects. Erzouki et al. (1993) reported effects for both ecgonine methyl ester and benzolyecgonine that tended to be opposite those of cocaine.

The role the metabolites might have in producing cardiovascular effects under typical drug administration situations is less clear. Hollander et al. (1994) reported that chest pain following cocaine administration began a median of 60 min following use and persisted for 120 min. With the half-life of cocaine in humans being approximately 60 min for an i.v. dose, this leaves open the possibility that metabolites may be contributing to these cardiovascular complications. Brogan et al. (1992) reported coronary vasoconstriction in humans 90 min following intranasal cocaine, again suggesting a role of the cocaine metabolites. Recently, Pan and Hedaya (1998) performed a pharmacokinetic/pharmacodynamic analysis of cocaine's cardiovascular effects in rats and also suggested a role for the cocaine metabolites.

The purpose of the current study was to investigate whether the cocaine metabolites ecgonine methyl ester, benzolyecgonine, norcocaine and cocaethylene produce cardiovascular effects when studied in vivo using the

* Corresponding author. Tel.: +1-410-550-1454; fax: +1-410-550-1648.
E-mail address: cschindl@helix.nih.gov (C.W. Schindler).

0014-2999/01/$ - see front matter. Published by Elsevier Science B.V.
PII: S0014-2999(01)01406-6

conscious squirrel monkey model. Comparisons were made directly to the parent compound, cocaine. While a number of previous studies have investigated the cardiovascular effects of the cocaine metabolites, few have directly compared more than one or two of the metabolites with cocaine. Further, most of those studies have looked at rats (e.g., Erzouki et al., 1993), where the cardiovascular response is much different from that of humans. The few monkey studies have looked at only a single metabolite (e.g., Wilson et al., 1978). An evaluation of multiple metabolites within a single species whose cardiovascular response is similar to humans should provide a clearer picture of the relative contribution of the metabolites to cocaine's cardiovascular effects. The squirrel monkey model has proven useful in past studies, as the squirrel monkey's cardiovascular responses to cocaine, both in terms of size and duration, are similar to those of humans (Schindler, 1996). Also, following systemic cocaine administration, moderate levels of both ecgonine methyl ester and benzolyecgonine are observed in squirrel monkeys (Carmona et al., 2000), suggesting a similar metabolic pathway for cocaine in squirrel monkeys and humans.

2. Materials and methods

2.1. Subjects

The subjects were 11 adult male squirrel monkeys (*Saimiri sciureus*) housed in individual cages in rooms in which light, temperature and humidity were controlled. Fresh water was continuously available. The monkey's daily food intake was restricted to maintain their body weights between 800 and 1000 g. A venous catheter for the delivery of drug and an arterial catheter for the measurement of blood pressure were implanted during a single sterile surgery. The general surgical procedure has been described in detail elsewhere (Herd et al., 1969). In brief, polyvinyl chloride catheters were implanted in the external iliac vein and the internal iliac artery during anesthesia with halothane–oxygen or flurothane–oxygen mixtures. The distal ends of the catheters were passed s.c. out through the skin in the middle of the back. Monkeys wore nylon jackets at all times to protect the catheters. Following a 2-week recovery period, experiments were begun. Catheters were flushed with heparinized saline at least twice weekly and sealed with stainless steel obturators when not in use.

All animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). All procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the NIDA/IRP and the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

The monkeys sat in Plexiglas chairs similar to the one described by Hake and Azrin (1953) and were loosely restrained in the seated position by a waist lock during experimental sessions. The monkeys were fully adapted to these chairs prior to experimentation. The chairs were enclosed in ventilated, sound-attenuating chambers (model AC-3; Industrial Acoustics, Bronx, NY) that were provided with continuous white noise to mask extraneous sounds. The distal end of the arterial catheter was connected via polyethylene tubing to a blood pressure transducer (no. T42-20, Coulbourn Instruments, Lehigh Valley, PA).

The arterial catheter was continuously flushed with saline at a rate of 1.8 ml/h. The transducer was connected to an associated amplifier (no. S72-25, Coulbourn Instruments) and blood pressure processor (no. S77-34, Coulbourn Instruments) outside the experimental chamber. The blood pressure processor analyzed the raw transducer signal, giving analog outputs of systolic (SP), diastolic (DP) and mean pressure ($DP + [(SP - DP)/3]$) after each cardiac cycle. The signal for the end of the cardiac cycle was fed into an Apple II or Macintosh computer. For each cycle, the computer measured the time between cycles with a resolution of 1 ms and read the analog signals for pressure from the blood pressure processor with a resolution of 1 mm Hg. These values were summed and averaged over periods of 30 s for subsequent analysis. Only mean blood pressure and heart rate were used for statistical analysis. The distal end of the venous catheter was passed outside the experimental chamber via polyethylene tubing and connected to a syringe for the injection of either saline or drug.

2.3. Procedure

The monkeys were fully adapted to the restraint chair and chamber prior to surgery. Following recovery from surgery, the monkeys were placed in the experimental chamber each weekday, with injections of drug typically occurring on Tuesdays and Fridays with saline administered on Thursdays. When they were administered, drug or saline were given i.v. 30 min into the 90-min session. On any given test day, only one dose of a test drug was administered. In general, animals were tested with two to five of the test drugs over a period of 3–6 months. The order of drugs and doses was unsystematic.

2.4. Drugs

Cocaine hydrochloride (NIDA, Baltimore), cocaethylene hydrochloride, norcocaine hydrochloride, ecognine methyl ester mesylate and benzoylecgonine (RBI, Natick, MA) were dissolved in sterile saline. Doses are expressed as the salt.

2.5. Data analysis

Five-minute means were determined from the 30-s means stored by the computer. Peak changes in blood pressure and heart rate after were calculated from these 5-min means from the 30-min period after saline or cocaine administration, by subtracting the value from the 5-min period just prior to the saline or drug injection as the baseline. The area-under-the-curve (AUC) was calculated from the 5-min change scores over the first 30 min following the injection, the time at which peak effects were typically observed. All data were subjected to a least squares analysis-of-variance with Fisher follow-up tests to determine individual effects (Wilkinson, 1992). A $P < 0.05$ was considered significant.

3. Results

Prior to saline administration, mean blood pressure was 91.6 ± 4.7 mm Hg. Heart rate was 219.3 ± 7.7 beats/min. The baseline blood pressure and heart rate prior to drug administration did not differ significantly from these values for any of the drugs tested.

Fig. 1 shows the peak effects of each drug compared to saline control. The peak effect was calculated as the maximum 5-min change score over the first 30 min following the injection of saline or drug. Cocaine ($n = 5$–7/dose), cocaethylene ($n = 5$–8/dose) and norcocaine ($n = 4$–5/dose) produced significant increases in blood pressure (Fig. 1, top panel). The effects for cocaine and cocaethylene were comparable. For cocaine, $F(5,36) = 11.6$, $P < 0.001$, doses of 0.3 mg/kg and above were significantly different from saline, while for cocaethylene, $F(5,38) = 16.2$, $P < 0.001$, doses of 0.1 mg/kg and above were different from saline. Norcocaine, $F(4,34) = 13.9$, $P < 0.001$, was clearly less potent than either cocaine or cocaethylene, with significant effects observed only at the 1.0 and 3.0 mg/kg doses.

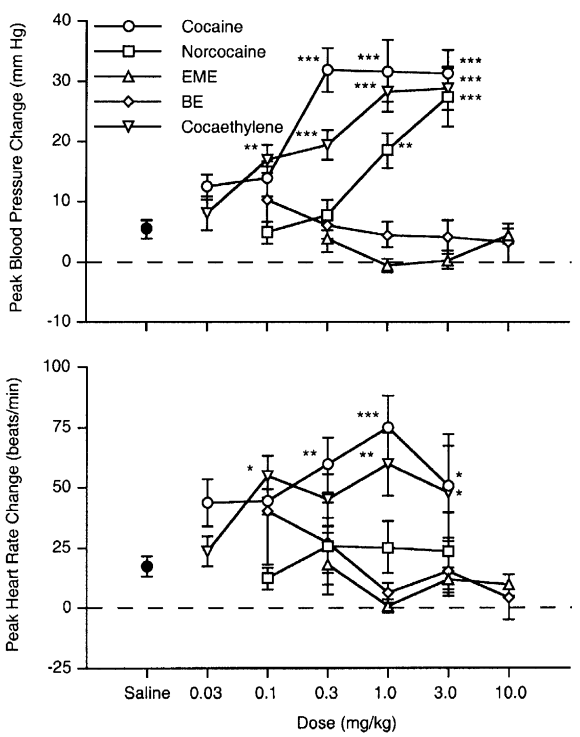

Fig. 1. Peak effects of cocaine and the metabolites on blood pressure (upper panel) and heart rate (lower panel). Peak effects were calculated from 5-min means over the first 30 min following the injection. The 5-min period prior to the injection was used as the control. Values are mean ± S.E.M. All injections were i.v. Significantly different from saline control: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Cocaine, $F(5,36) = 4.4$, $P < 0.01$, and cocaethylene, $F(5,38) = 2.6$, $P < 0.05$, also produced significant increases in heart rate (Fig. 1, bottom panel). As with blood pressure, cocaine produced significant increases in heart rate at the 0.3 mg/kg and higher doses ($P < 0.05$). For cocaethylene, the effects of the 0.1, 1.0 and 3.0 mg/kg doses were significantly different from the saline control. Norcocaine did not produce significant effects on heart rate, and ecgonine methyl ester ($n = 4$–6/dose) and benzolyecgonine ($n = 4$–6/dose) did not produce changes in either blood pressure or heart rate.

Since a 5-min mean was used to calculate the peak pressor effect, pressor effects of a shorter duration might have been obscured. Table 1 shows the peak blood pressure change for cocaine and the metabolites calculated from 30-s mean values for the first 10 min following drug administration. The 5 min prior to the drug injection was still used as the baseline. For comparison, the peak 30-s change for saline was 12.1 ± 2.8 mm Hg. As with the 5-min mean values, cocaine and cocaethylene produced the largest effects and were both approximately equipotent. Norcocaine also produced a pressor effect similar to cocaine at the highest dose tested, but was clearly less potent than cocaine. Benzoylecgonine and ecgonine methyl ester did not produce effects that were different from saline. Also shown in Table 1 are the mean times at which the peak effect was observed. For cocaine, cocaethylene and norcocaine, the peak effect was typically observed within 2 min of drug administration. There was a tendency for the highest dose of each drug to peak after 2 min. For both benzoylecgonine and ecgonine methyl ester, for which no significant increases were observed, there was less consistency on when the peak effect was observed. Nevertheless, the peak was often observed within 2 min of administration. This may reflect the monkey's ability to detect the injection, which results in a slight increase in blood pressure. In fact, even for saline the peak effect occurred soon after the injection (2.4 ± 0.4 min).

Fig. 2 shows the AUC measures for cocaine and the metabolites. For blood pressure, the statistical results for AUC essentially replicated those of the peak blood pressure measure for each drug [cocaine $F(5,36) = 10.0$, $P < 0.001$; cocaethylene $F(5,38) = 12.7$, $P < 0.001$; norco-

Table 1
Peak effect of cocaine and metabolites on blood pressure over 30-s intervals

Dose (mg/kg)	Cocaine	Cocaethylene	Norcocaine	Benzoyl-ecgonine	Ecgonine methyl ester
0.03	25.8 ± 6.2 (1.7 ± 0.2)[a]	25.2 ± 6.1 (1.5 ± 0.2)			
0.1	23.8 ± 4.3 (1.4 ± 0.1)	33.0 ± 8.0[b] (2.0 ± 0)	10.5 ± 1.5 (1.8 ± 0.3)	11.7 ± 2.4 (5.7 ± 1.4)	
0.3	63.9 ± 15.1[b] (1.9 ± 0.2)	25.0 ± 5.7[b] (2.2 ± 0.6)	12.5 ± 1.7 (1.2 ± 0.3)	9.9 ± 3.0 (2.5 ± 1.5)	9.3 ± 3.3 (2.7 ± 1.0)
1.0	37.8 ± 4.9[b] (1.6 ± 0.1)	41.3 ± 3.1[b] (1.6 ± 0.2)	27.2 ± 4.5[b] (1.6 ± 0.1)	14.0 ± 4.2 (3.8 ± 4.2)	8.2 ± 2.2 (1.1 ± 0.1)
3.0	45.0 ± 6.6[b] (2.9 ± 0.2)	45.2 ± 8.2[b] (3.0 ± 0.4)	37.4 ± 4.3[b] (2.3 ± 0.4)	8.7 ± 2.9 (2.4 ± 1.0)	6.6 ± 1.0 (1.1 ± 0.2)
10.0				7.8 ± 3.7 (1.1 ± 0.5)	8.0 ± 0.7 (2.8 ± 1.9)

[a] Values in parentheses are time of the peak response in min following the injection of drug.
[b] Significantly ($P < 0.05$) different from saline (12.1 ± 2.8), values are mean mm Hg ± S.E.M.

caine $F(4,24) = 4.5$, $P < 0.01$]. However, it appears that norcocaine was not just less potent than cocaine, but that the maximal effect on the blood pressure AUC was reduced. Again, benzolyecgonine and ecgonine methyl ester had no significant effect on the blood pressure AUC, and norcocaine, as well as benzolyecgonine and ecgonine methyl ester did not affect the heart rate AUC measure. Cocaine, $F(5,36) = 2.6$, $P < 0.05$, again produced significant increases in the heart rate AUC at the 0.3 mg/kg and higher doses. The effects of cocaethylene, $F(5,38) = 2.5$, $P < 0.05$, on heart rate AUC were more variable than for cocaine, as only the effect at 1.0 mg/kg dose reached significance.

Because it has been suggested that cocaethylene may have prolonged effects when compared to cocaine (McCance-Katz et al., 1998), Fig. 3 shows a time-effect function for doses of cocaine, cocaethylene and norcocaine that produced comparable peak increases in blood pressure. For the first 10 min following the injection, 30-s change scores are shown, while 5-min change scores are shown for the rest of the session. The effect of cocaethylene is slightly above that of cocaine, although this difference was not significant. When an exponential decay function was fitted to these curves, there were no significant differences observed in the decay parameters between cocaine and cocaethylene. The effect of norcocaine on blood pressure, however, clearly returned to baseline more quickly than the other drugs. This accounts for the lower AUC measures seen for norcocaine in Fig. 2.

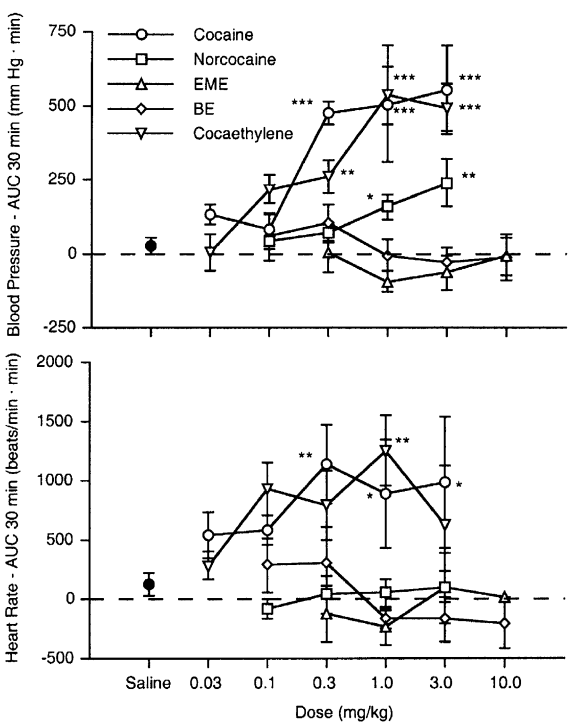

Fig. 2. Area-under-the-curve (AUC) for the effects of cocaine and the metabolites on blood pressure (upper panel) and heart rate (lower panel). The AUC was calculated from 5-min mean change scores over the first 30 min following the injection. The 5-min period prior to the injection was used as the control. Values are mean ± S.E.M. All injections were i.v. Significantly different from saline control: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

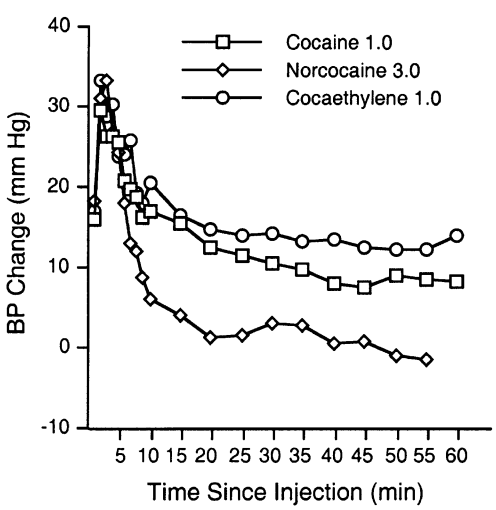

Fig. 3. Time course for the effects of cocaine, norcocaine and cocaethylene on blood pressure. The doses are in mg/kg. The measure presented is the blood pressure change score using the 5 min prior to drug injection as the control. For the first 10 min following the injection, 30-s change scores are shown. After 10 min, 5-min change scores are presented.

4. Discussion

In general, cocaine produced increases in blood pressure that were highest at the highest doses tested. In contrast, the effects of cocaine on heart rate peaked at 1.0 mg/kg, with smaller effects seen at the higher 3.0 mg/kg dose. These effects of cocaine were similar to previous results reported for squirrel monkeys (Gonzalez and Byrd, 1977; Tella et al., 1990; Schindler et al., 1992).

Like cocaine, norcocaine increased blood pressure, although norcocaine was less potent than cocaine and had a shorter duration of action. Blood pressure increases with norcocaine were clearly dose-dependent. Norcocaine did not increase heart rate. This last result was surprising as a number of investigators have reported that norcocaine has cardiovascular effects similar to cocaine (Barber and Tackett, 1992). However, many of these studies involved rats where the predominant effect of cocaine was a heart rate decrease (Erzouki et al., 1993; Mahlakaarto et al., 1998; Pan and Hedaya, 1999). Norcocaine has been shown to produce tachycardia in rhesus monkeys, but no change in heart rate for cynomolgus monkeys (Wilson et al., 1978). These results suggest that the effects of norcocaine may vary across species. Like cocaine, norcocaine binds potently to monoamine transporters in the brain and also has local anesthetic effects. However, norcocaine is less potent than cocaine at the dopamine transporter, and is much more potent than cocaine at the serotonin transporter (Ritz et al., 1990). Norcocaine also produces a use-dependent block of sodium channels like cocaine, but recovery from the block is much quicker with norcocaine (Crumb and Clarkson, 1992). One would expect that norcocaine's potency in blocking sodium channels would work against increases in heart rate. Therefore, the present results, suggest that norcocaine would contribute little to the overall toxicity of cocaine. The effects observed here were clearly less than for cocaine and of a shorter duration. Further, norcocaine represents a small fraction of the overall metabolic product from cocaine.

Previous reports have suggested that both ecgonine methyl ester and benzolyecgonine might have cardiovascular effects on their own (Erzouki et al., 1993; Madden and Powers, 1990; Pane et al., 1997). In conscious squirrel monkeys, neither benzolyecgonine nor ecgonine methyl ester produced any significant changes in blood pressure and heart rate at doses up to 10 mg/kg. This confirms results from a number of labs that very large doses of these drugs are required to produce toxicity (Mets and Virag, 1995; Morishima et al., 1999; Pan and Hedaya, 1999). In general, these results suggest that neither benzolyecgonine nor ecgonine methyl ester contribute to the toxicity associated with cocaine. However, it is possible the these drugs have more prominent central nervous system effects, which are obscured by their poor penetration to the central nervous system. When cocaine is administered, these metabolites might be produced once cocaine reaches the brain. However, ecgonine methyl ester is produced almost exclusively by plasma esterases (Warner and Norman, 2000). Benzoylecgonine can be produced both spontaneously and enzymatically (Warner and Norman, 2000), but little benzolyecgonine is found in the brain of mice following systemic cocaine administration (Benuck et al., 1987). Therefore, one would expect benzolyecgonine and ecgonine methyl ester to have their greatest effects in the periphery. Given that no changes were observed in either heart rate or blood pressure following doses up to 10 mg/kg (30 times the dose required for cocaine to produce significant effects), it would appear than these metabolites do not contribute to the overall cardiovascular toxicity of cocaine.

In contrast to the other metabolites, cocaethylene produced clear increases in blood pressure and heart rate that were comparable to cocaine. These results confirm those of other investigators who have reported that cocaethylene has potent effects on the cardiovascular system (e.g., Henning and Wilson, 1996; McCance-Katz et al., 1998; Morishima et al., 1999; Perez-Reyes, 1993). A number of authors have reported that cocaethylene has a slower elimination half-life than cocaine (McCance et al., 1995; Perez-Reyes et al., 1994), however, it is not clear that this longer half-life leads to larger effects. Pan and Hedaya (1999) report that cocaethylene had more potent and prolonged effects on heart rate than did cocaine. In the current study, the time-course for the blood pressure effect was not significantly longer than for cocaine and some investigators have reported that cocaethylene produces smaller effects than cocaine (Hart et al., 2000; Perez-Reyes et al., 1994). In humans, when cocaine and alcohol are used concurrently, cocaethylene levels reach a peak concentration of about 1/5 those of cocaine (McCance-Katz et al., 1993; Perez-Reyes et al., 1994). Therefore, even the small increases in effect size and duration of action that have been reported would be unlikely to greatly contribute to cocaine's overall cardiovascular toxicity. Nevertheless, cocaethylene was the one compound studied which did produce effects comparable to cocaine alone. Therefore, with repeated administrations, as might occur during "bingeing", the role of cocaethylene in producing cardiovascular toxicity might become more prevalent. A complicating factor in the effects of cocaethylene in humans is the interaction that can occur between cocaine and alcohol independent of cocaethylene (Henning and Wilson, 1996). That is, the cardiovascular effects of cocaine and alcohol in combination can be greater than either alone even in the absence of significant cocaethylene.

It might be argued that effects observed for some of the metabolites have been underestimated because of the use of mg doses rather than molar doses. However, cocaine, cocaethylene and norcocaine, the only compounds to produce significant cardiovascular effects, have very similar molecular weights (339.82, 353.85 and 325.79, respectively). Therefore, the mg/kg doses approximate equiva-

lent molar doses. Benzoylecgonine (289.33) and ecgonine methyl ester (235.71) have lower molecular weights than cocaine, which would translate into larger doses on a molar basis for the equivalent mg dose. They were also tested at doses higher than cocaine. Therefore, the failure of benzolyecgonine and ecgonine methyl ester to produce cardiovascular effects cannot be attributed to differences in molecular weights.

The toxicity of cocaine in humans is probably related to a variety of factors including the pre-existing condition of the individual involved and cocaine's potent local anesthetic effects, which may induce arrhythmias or be proarrhythmic. However, the sympathomimetic effect of cocaine is also thought to be an important factor in cocaine's toxicity (Bauman et al., 1994; Billman, 1995; Hollander, 1996; Mouhaffel et al., 1995). The increases in blood pressure and heart rate following cocaine increase the workload on the heart and myocardical oxygen demand. Coupled with cocaine's ability to constrict coronary arteries (Lange et al., 1989), myocardial infarction and arrhythmias can result. Therefore the increases in blood pressure and heart rate produced by cocaine can be an important part of its overall toxicity. To the degree that the metabolites also increase blood pressure and heart rate, they may contribute to cocaine's toxicity via these same mechanisms. Other factors not studied here (i.e., sodium channel blockade) are almost certainly involved in cocaine's overall cardiovascular toxicity. In addition, we cannot rule out the possibility that interactions between cocaine and the metabolites, or between the metabolites themselves, may also increase toxicity. That is, while benzolyecgoine and ecgonine methyl ester alone may not increase blood pressure, when given together they might. As both are seen in blood following cocaine administration, there is the possibility of this type of interaction. Nevertheless, the changes in blood pressure and heart rate observed in the current study are important aspects of cocaine's overall toxicity.

In conclusion, cocaine produced significant effects on both blood pressure and heart rate in the conscious squirrel monkey. Of the four cocaine metabolites studied, only cocaethylene produced effects that were comparable to cocaine. However, cocaethylene blood levels approximating those of cocaine would be required to produce similar effects, negating cocaethylene's overall contribution to cocaine toxicity. With repeated doses, this metabolite might become a factor. Norcocaine also produced increases in blood pressure, but not heart rate. Norcocaine was clearly less potent than cocaine and its duration of action was less than cocaine. Because norcocaine represents a relatively minor metabolite in vivo, these factors would suggest that norcocaine does not contribute to cocaine's overall cardiovascular effects. Finally, benzolyecgonine and ecgonine methyl ester had no effects on either blood pressure or heart rate, even at doses well above those for cocaine that produced significant effects. Therefore, these metabolites would not be expected to contribute to any cardiovascular changes following cocaine use.

Acknowledgements

NIDA Intramural Research Funds supported this work. We would like to thank Joanne Gilman and Zofi Graczyk for their technical assistance. A preliminary report of this work appeared in L. Harris (Ed.), Problems of Drug Dependence 1992, NIDA Monograph Series 132, p. 367.

References

Barber, D.A., Tackett, R.L., 1992. Hemodynamic effects of centrally administered norcocaine in the rat. Life Sci. 51, 1269–1276.

Bauman, J.L., Grawe, J.J., Winecoff, A.P., Hariman, R.J., 1994. Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. J. Clin. Pharmacol. 34, 902–911.

Benuck, M., Lajtha, A., Reith, M.E., 1987. Pharmacokinetics of systemically administered cocaine and locomotor stimulation in mice. J. Pharmacol. Exp. Ther. 243, 144–149.

Billman, G.E., 1995. Cocaine: a review of its toxic actions on cardiac function. Crit. Rev. Toxicol. 25, 113–132.

Brogan, W.C., Lange, R.A., Glamann, D.B., Hillis, L.D., 1992. Recurrent coronary vasoconstriction caused by intranasal cocaine: possible role for metabolites. Ann. Intern. Med. 116, 556–561.

Carmona, G.N., Jufer, R.A., Goldberg, S.R., Gorelick, D.A., Greig, N.H., Yu, Q.-S., Cone, E.J., Schindler, C.W., 2000. Butyrylcholinesterase accelerates cocaine metabolism: in vitro and in vivo effects in nonhuman primates and humans. Drug Metab. Dispos. 28, 367–371.

Crumb Jr., W.J., Clarkson, C.W., 1992. Characterization of the sodium channel blocking properties of the major metabolites of cocaine in single cardiac myocytes. J. Pharmacol. Exp. Ther. 261, 910–917.

Erzouki, H.K., Baum, I., Goldberg, S.R., Schindler, C.W., 1993. Comparison of the effects of cocaine and its metabolites on cardiovascular function in anesthetized rats. J. Cardiovasc. Pharmacol. 22, 557–563.

Gonzalez, F.A., Byrd, L.D., 1977. Physiological effects of cocaine in the squirrel monkey. Life Sci. 21, 1417–1424.

Hake, D.F., Azrin, N., 1953. An apparatus for delivering pain shock to monkeys. J. Exp. Anal. Behav. 6, 297–298.

Hart, C.L., Jatlow, P., Sevarino, K.A., McCance-Katz, E.F., 2000. Comparison of intravenous cocaethylene and cocaine in humans. Psychopharmacology 149, 153–162.

Henning, R.J., Wilson, L.D., 1996. Cocaethylene is as cardiotoxic as cocaine but is less toxic than cocaine plus ethanol. Life Sci. 59, 615–627.

Herd, J.A., Morse, W.H., Kelleher, R.T., Jones, L.G., 1969. Arterial hypertension in the squirrel monkey during behavioral experiments. Am. J. Physiol. 217, 24–29.

Hollander, J.E., 1996. Cocaine-associated myocardial infarction. J. R. Soc. Med. 89, 443–447.

Hollander, J.E., Hoffman, R.S., Gennis, P., Fairweather, P., DiSano, M.J., Schumb, D.A., Feldman, J.A., Fish, S.S., Dyer, S., Wax, P., Whelan, C., Schwarzwald, E., 1994. Prospective multicenter evaluation of cocaine-associated chest pain. Acad. Emerg. Med. 1, 330–339.

Lange, R.A., Cigarroa, R.G., Yancy Jr., C.W., Willard, J.E., Popma, J.J., Sills, M.N., McBride, W., Kim, A.S., Hillis, L.D., 1989. Cocaine-induced coronary–artery vasoconstriction. N. Engl. J. Med. 321, 1557–1562.

Madden, J.A., Powers, R.H., 1990. Effect of cocaine and cocaine metabolites on cerebral arteries in vitro. Life Sci. 47, 1109–1114.

Mahlakaarto, J., Ruskoaho, H., Huttunen, P., MacDonald, E., Pasanen, M., 1998. Norcocaine is a potent modulator of haemodynamic responses, plasma catecholamines and cardiac hormone release in conscious rats. Toxicology 128, 101–111.

McCance, E.F., Price, L.H., Kosten, T.R., Jatlow, P.I., 1995. Cocaethylene: pharmacology, physiology and behavioral effects in humans. J. Pharmacol. Exp. Ther. 274, 215–223.

McCance-Katz, E.F., Price, L.H., McDougle, C.J., Kosten, T.R., Black, J.E., Jatlow, P.I., 1993. Concurrent cocaine-ethanol ingestion in humans: pharmacology, physiology, behavior, and the role of cocaethylene. Psychopharmacology 111, 39–46.

McCance-Katz, E.F., Kosten, T.R., Jatlow, P., 1998. Concurrent use of cocaine and alcohol is more potent and potentially more toxic than use of either alone—a multiple-dose study. Biol. Psychiatry 44, 250–259.

Mets, B., Virag, L., 1995. Lethal toxicity from equimolar infusions of cocaine and cocaine metabolites in conscious and anesthetized rats. Anesth. Analg. 81, 1033–1038.

Morishima, H.O., Whittington, R.A., Iso, A., Cooper, T.B., 1999. The comparative toxicity of cocaine and its metabolites in conscious rats. Anesthesiology 90, 1684–1690.

Mouhaffel, A.H., Madu, E.C., Satmary, W.A., Fraker Jr., T.D., 1995. Cardiovascular complications of cocaine. Chest, 107, 1426–1434.

National Research Council, 1996. Guide for the Care and Use of Laboratory Animals. National Academy Press, Washington, DC.

Pan, W.J., Hedaya, M.A., 1998. An animal model for simultaneous pharmacokinetic/pharmacodynamic investigations: application to cocaine. J. Pharmacol. Toxicol. Methods 39, 1–8.

Pan, W.J., Hedaya, M.A., 1999. Cocaine and alcohol interactions in the rat: contribution of cocaine metabolites to the pharmacological effects. J. Pharm. Sci. 88, 468–476.

Pane, M.A., Traystman, R.J., Gleason, C.A., 1997. Ecgonine methyl ester, a major cocaine metabolite, causes cerebral vasodilation in neonatal sheep. Pediatr. Res. 41, 815–821.

Perez-Reyes, M., 1993. Subjective and cardiovascular effects of cocaethylene in humans. Psychopharmacology 113, 144–147.

Perez-Reyes, M., Jeffcoat, A.R., Myers, M., Sihler, K., Cook, C.E., 1994. Comparison in humans of the potency and pharmacokinetics of intravenously injected cocaethylene and cocaine. Psychopharmacology 116, 428–432.

Ritz, M.C., Cone, E.J., Kuhar, M.J., 1990. Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure activity study. Life Sci. 46, 635–645.

Schindler, C.W., 1996. Cocaine and cardiovascular toxicity. Addict. Biol. 1, 31–47.

Schindler, C.W., Tella, S.R., Katz, J.L., Goldberg, S.R., 1992. Effects of cocaine and its quaternary derivative cocaine methiodide on cardiovascular function in squirrel monkeys. Eur. J. Pharmacol. 213, 99–105.

Tella, S.R., Schindler, C.W., Goldberg, S.R., 1990. The role of central and autonomic nerural mechanisms in the cardiovascular effects of cocaine in conscious squirrel monkeys. J. Pharmacol. Exp. Ther. 252, 491–499.

Warner, A., Norman, A.B., 2000. Mechanisms of cocaine hydrolysis and metabolism in vitro and in vivo: a clarification. Ther. Drug Monit. 22, 266–270.

Wilkinson, L., 1992. SYSTAT: Statistics, Version 5.2. SYSTAT, Evanston, IL.

Wilson, M.C., Bedford, J.A., Kibbe, A.H., Sam, J.A., 1978. Comparative pharmacology of norcocaine in *M. mulatta* and *M. fascicularis*. Pharmacol. Biochem. Behav. 9, 141–145.