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Cardiovascular Toxicity of Cocaine: Underlying Mechanisms

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Preface

On August 9-10, 1989, the National Institute on Drug Abuse held a technical review meeting titled "Cardiovascular Toxicity of Cocaine: Underlying Mechanisms" to review the state of knowledge and to identify areas of future research. Biomedical scientists discussed the potential site(s) of cocaine's cardiovascular actions and the possible mechanisms underlying these cardiac events in immature and mature cardiovascular systems in various animal models and in human tissues. A report summarizing the major findings and the future areas of research identified at the meeting was published (Thadani et al. 1990), and included the following summary findings: (1) More than one mechanism is involved with the deleterious effects of cocaine on myocardium; (2) pharmacokinetic investigations indicate that in animals and in humans the elimination of cocaine occurs in a nonlinear fashion, which could cause an unexpected rise in blood cocaine levels in cocaine addicts during a binge period; and (3) a subgroup of the population may be more vulnerable to the cardiotoxic effects of cocaine. Areas of research identified in this field included more investigations at the cellular and subcellular levels, on the central nervous system and respiratory system contributions In these cardiac responses, and on the genetic aspect of cocaine myocardial effects. This monograph consists of the papers presented at the technical review.

REFERENCE

Thadani, P.V., et al.   Cardiovascular toxicity of cocaine: Underlying mechanisms. *J Appl Cardiol* 5:317-320, 1990.

Overview

Pushpa V. Thadanl

Use of cocaine during pregnancy has been associated with increased incidence of miscarriage, rupture of maternal Intracranial aneurysm, abruptio placentae, and delivery of small-for-gestational-age babies. These pregnancy-related complications are thought to result from increasing circulating blood catecholamine levels and vasoconstriction of the regional vascular beds due to cocaine-induced inhibition of catecholamine reuptake at adrenergic nerve terminals.

Dr. James Woods, Jr., and Mark Plessinger describe the impact of these changes on fetal and maternal cardiovascular systems following administration of cocaine to pregnant ewes. Maternal administration of cocaine produced dose-dependent increases in maternal heart rate (HR) and blood pressure (BP). In the fetus, elevations in HR and BP were accompanied by reductions in arterial PO,. Direct administration of cocaine to the fetus caused no change in fetal arterial PO, but produced an increase in BP and HR. These findings indicated that cocaine-induced changes in the fetal cardiovascular system are the result of the drug's direct and Indirect effects. Direct effects are caused via maternal-fetal transfer, whereas indirect actions result from fetal hypoxemia induced by vasoconstrlction of uterine vasculature. Pharmacological studies showed that cocaine-evoked vasoconstriction of uterine vasculature involved stimulation of alpha-adrenergic receptors as well as some other mechanism. Analysis of cocaine levels in maternal and fetal blood indicated that cocaine crosses the placenta rapidly and disappears into two vascular compartments without equilibration.

Because severe cardiopulmonary and neurologic complications also were seen in pregnant ewes following high doses of cocaine, Dr. Woods and Plessinger examined the role of pregnancy-related hormones in cocaine-induced cardiovascular responses. Administration of progesterone to nonpregnant ewes resulted in cocaine-induced cardiovascular responses similar to those seen in pregnant animals, suggesting that this hormone may contribute to the amplified cocaine responses.

Recent reports suggest that cocaine-related, life-threatening cardiac events may not be dependent on the amount of cocaine used. One of the pharmacological actions of cocaine is to cause vasoconstriction and a decrease in blood flow, which could limit the drug's absorption and bioavaiiability-factors that can vary greatly from one individual to another. To assess the variability of these factors, Drs. R. Douglas Wilkerson and John Ambre and their respective colleagues examined, respectively, the pharmacokinetics and time profile of cocaine in animals and in humans.

Dr. Wiikerson and coworkers showed that cocaine elimination in dogs occurred in a linear fashion when the dose was below 2 mg/kg and the peak plasma concentration was below 2 mg/mL. However, at doses above 2 mg/kg, which produced peak plasma concentration greater than 2 mg/mL, elimination reverted to zero order.

Dr. Ambre and colleagues describe a nonlinear elimination kinetics for cocaine in humans over a range of doses, which could lead to disproportionate increases in plasma cocaine levels in a cocaine user during binge episodes. These findings are important in the context of cocaine toxicity among addicts because these unexpected elevations during binge episodes could cause severe morbidity or mortality.

Several cocaine-induced cardiovascular responses, such as elevated BP and HR and associated increases in myocardial oxygen demand, are believed to be mediated through the activation of the sympathetic nervous system. However, there is no information on the relative contribution of the central nervous system (CNS) vs. the peripheral sympathetic nervous system involved in these cocaine-evoked cardiac responses. To delineate the role of these components in cocaine-induced cardiac responses, the next group of speakers described these responses in various animal models.

Dr. Mark Knuepfer and colleagues observed dose-dependent increases in arterial pressure-primarily due to elevated systemic vascular resistance with little change in cardiac output-following cocaine administration in chronically instrumented rats. Pharmacological manipulation at ganglionic site did not affect the cocaine-elicited peripheral vascular response; however, pretreatment with prazosin, an alpha-adrenergic receptor blocker, did inhibit the arterial pressure response. These findings suggest that the cardiovascular effects of cocaine are due primarily to an action on alpha-adrenergic receptors in the peripheral vasculature and not to CNS-mediated sympathoexcitation.

A most interesting finding of these studies is that a few animals showed significant reduction in cardiac output after cocaine injection and a spontaneous

recovery from this response. Pathological findings showed focal aberrations in the myocardium of these animals that were not observed in other animals. These results suggest an increased sensitivity of some individuals to cocaine's adverse effects.

Dr. Tella and associates observed that cocaine elevated HR and BP in conscious squirrel monkeys. These cocaine-induced increases in BP and HR were not abolished by pretreatment with ganglionlc or alpha-adrenergic blockers, suggesting that these responses were due primarily to cocaine's peripheral actions on catecholaminergic systems. They also observed unusual cardiac responses in some monkeys following a cocaine dose. For example, an initial reduction in HR observed in one monkey following cocaine administration was abolished by pharmacological intervention but not in others, again suggesting a genetic difference in the myocardium response to cocaine.

Dr. Richard Gillis and his group also observed dose-dependent increases in HR induced by submaximal stimulation of postgangllonic cardiac sympathetic nerve following cocaine administration in an anesthetized spinal cord-transected cat. These results suggest a role of the peripheral sympathomimetic action of cocaine in these responses. Further studies in cats with intravertebral administration of cocaine revealed no significant effect on BP or HR. Administration of cocaine methiodide, a quaternary derivative, in sedated dogs showed cardiovascular responses similar to those of cocaine, suggesting a lack of CNS involvement in the sympathomimetic action of cocaine.

These findings from various animal models suggesting that the sympathomimetic effects of cocaine are due primarily to a peripheral site of action of cocaine led to further discussions on the earlier findings of Dr. Wilkerson and colleagues, which had shown the involvement of both central and peripheral components of the sympathetic nervous system in these responses in conscious dogs. These discussions can be summarized by stating that the sympathomimetic effects evoked by cocaine depend on the animal model used and could involve one or both components of the sympathetic nervous system in cardiac responses.

Lethal as well as nonlethal cardiac complications associated with cocaine use have been reported in humans. One of the frequent cardiac events reported in young, otherwise healthy persons with angiographically normal coronary arteries following cocaine use is acute myocardial infarction (AMI). Mechanisms thought to be involved in this cardiac complication could be focal vasospasm in a large epicardial coronary artery and/or diffuse increase in coronary vascular resistance leading to a decrease in coronary blood flow in conjunction with an imbalance between myocardial oxygen demand and supply.

Dr. Theodore Fraker and coworkers examined the latter mechanism in both sedated and conscious dogs. Their studies used two-dimensional echocardiography and showed marked, dose-dependent reductions in regional ejection fraction following intravenous (IV) cocaine in both sedated and conscious dogs. However, in conscious dogs the reductions in left ventricular function were accompanied by elevationd in HR, BP, and coronary blood flow, whereas no such hemodynamic changes were observed in pentobarbital-sedated animals. Because the cocaine-elicited depression in the left ventricular function in sedated dogs was observed in the absence of hemodynamic Changes, myocardial ischemia resutting from an imbalance between oxygen supply and demand may not be responsible for the observed decline in the myocardial function. These data also indicate that the primary mechanism most likely involved in this response is the direct local anesthetic action of cocaine.

Dr. Koonlawee Nademanee discusses his electrophysiologicai findings in cocaine addicts undergoing wlthdrawai and speculates on the increased risk of these patients for developing myocardial ischemia or infarction due to possible precipitation of coronary vasospasm during withdrawal. He observed a high incidence of ST elevation episodes and a higher peak exercise BP in these patients during the first week of cocaine withdrawal.

Drs. Jeffrey isner and Saurabh Chokshi examined the potential mechanism of coronary artery vasospasm in cocaine-related AMI in one patient. Under diagnostic coronary arteriography, this patient failed to manifest coronary arterial spasm following cocaine injection. However, *in vitro* studies showed cocaine-induced vasoconstriction in vascular tissues obtained from humans and rabbits. Although these findings suggest an increased coronary vascular resistance, the involvement of coronary vasospasm in cocaine-related AMI is still speculative and tentative.

The other reported life-threatening cardiac disorder associated with cocaine use in humans is cardiac arrhythmia and sudden death. Dr. Peter Temesy-Armos and associates examined the underlying mechanism(s) for arrhythmia in conscious dogs by studying continuous 24-hour ambulatory electrocardiogram (ECG) recordings and electrophysiological changes following IV cocaine injection. Continuous Holter recording revealed cocaine-induced ventricular tachycardia in 5 of 12 dogs; 2 of these arrhythmias were lethal. Electrophysiological changes seen after cocaine use suggest that both direct and indirect actions (i.e., local anesthetic and increased sympathetic tone) of cocaine may be involved in this cardiac complication. Because two of the dogs had lethal arrhythmias, this again raises the question of whether a subgroup of the population is more vulnerable to the deleterious myocardiai effects of cocaine.

Dr. James Morgan and coworkers (Perreault et al., this volume) discuss the role of intracellular calcium in the pathogenesis of cocaine cardiovascular complications. Their *in vitro* studies showed that cocaine elicited both negative and positive inotropic actions in cardiac muscle. The positive inotropic effect appeared to be mediated by catechoiamines, whereas the negative inotropic action probably was due to the drug's direct local anesthetic action on excitation-contraction coupling mechanisms. In vascular smooth muscle, a cocaine-induced relaxant effect appeared to result from changes in myofiiament calcium responsiveness. These physiological findings suggest that a different mechanism may be involved with the depressant effects of cocaine on cardiac and vascular smooth muscle.

Drs. Ronald Langner and Coilette Bement describe cocaine-induced biochemical changes seen in blood vessels in rabbits following diet manipulation. Cocaine administration did not produce a uniform response on blood vessels; aortic injury was observed in some rabbits but not in others. Rabbits sensitive to cocaine-evoked aortic injury also showed elevations in aortic protein synthesis, cyclic adenosine monophosphate, and calcium levels, whereas no such biochemical changes were seen in nonsensitive animals. Diet manipulation studies showed potentiation of atherogenic processes in rabbits fed a high cholesterol diet and cocaine. These important findings suggest that a preexisting condition might increase the risk of premature onset of cardiovascular complications following cocaine use.

Dr. Robert Conlee and his group describe the combined physiological and metabolic responses of cocaine and exercise as a form of stress in an animal model. in an exercising rat model, cocaine had a detrimental effect on endurance and was accompanied by changes in muscle giycogen and in blood lactic acid and catechoiamine levels. In contrast, myocardiai glycogen levels were unaltered in these animals, suggesting that by potentiating the normal sympathetic response during exercise, cocaine can produce adverse consequences on performance as well as on cardiotoxic events.

Dr. Ronald Harper and colleagues discuss cocaine-induced changes on respiratory patterning and the impact of these changes on cardiovascular function. Cocaine administration in conscious cats produced marked elevations in both upper airway and diaphragmatic respiratory musculature activity accompanied by changes in cardiac rhythm, HR, and brain and core temperature. These results suggest interaction among temperature, respiration, and cardiovascular control systems. Another unexpected finding was the conversion of cocaine-induced cardiac and electroencephalogram (EEG) rhythm abnormalities seen in one cat to normal rhythm with diazepam, suggesting that cocaine can modify neural influences on cardiac rhythm.

in the area of pathological findings seen at autopsy following cocaine use, Dr. Margaret Billingham discusses the possible mechanisms for cocaine-associated myocardiai pathological lesions, because many of these lesions have a nonspecific etiology. For instance, the mechanism involved with cocaine-associated myocardiai contraction bands could be increased beta-adrenergic receptor stimulation of myocytes and elevation of intracytocylic calcium or a spasm of small vessels In the myocardium. The cause for other cocaine-associated lesions, such as myocardiai fibrosis, cardiomyopathy, and vascular changes, may be the sympathomlmetic effect of cocaine.

Dr. Renu VIrmani discusses the pathophysiological mechanisms involved with cocaine-associated myocardltis. Because none of the infectious agents associated with myocarditis etiology was found in the 40 deaths associated with cocaine abuse, she reviews the Impact of various factors In the cause of cocaine-related myocarditis, including cocaine-associated vasoconstrlction of small intramyocardial coronary arteries, isolated myocyte necrosis or myocyte death, and changes in lymphocytic activity. Dr. Virmani also discusses the probable endotheiiai disruption and the resultant aiterations in platelet function at the site of coronary atheroscierosis in the pathogenesis of cocaine-associated myocardial ischemia.

Maternal-Fetal Cardiovascular System: A Target of Cocaine

James R. Woods, Jr., and Mark A. Plessinger

INTRODUCTION

The increasing use of cocaine by pregnant women Is affecting medical education, clinical management, and obstetric outcome. Although obstetric resldents In the 1970s learned to manage patients who were abusing heroin, today's residents are discovering firsthand the Impact of prenatal cocaine use on the developing fetus. Hospitals that formerly could accommodate all high-risk obstetric patients In one clinic are developlng specialized high-risk clinics for drug-dependent women to confront the ever-Increasing burdens of patient management created by cocaine and crack abuse.

CLINICAL REPORTS OF COCAINE IN PREGNANCY

Only recently have we become aware of the significance of cocaine use In pregnancy and its effects on the fetus. Nine years ago, a major obstetric textbook stated that "cocaine is not known to have direct deleterious effects upon the fetus" (Lee 1982). Since that publication, the number of case reports concerning perinatal incidents linked to cocaine use has escalated. Acker and coworkers (1983) reported two patients who experienced placental abruption after their self-administration of intranasal cocaine. One of these patlents delivered a stillborn fetus, and the other delivered a newborn that required resuscitation. Later reports have implicated maternal cocaine abuse as the cause of a variety of maternal and fetal complications (tables 1 and 2).

Even breast-fed newborns are not protected from maternal cocaine use, since cocaine found in breast milk (Chasnoff et al. 1987) has been linked to neonatal seizures and apnea (Chaney et al. 1988). Seizures in infants also have been reported to occur when the child passively inhales freebased cocaine from an adult's exhaled crack smoke (Bateman and Heagarty 1980).

MECHANISM OF COCAINE ACTION ON REGIONAL BLOOD FLOW

In part, cocaine produces its cardiovascular effects in adults by blocking reuptake of catecholamines within the synaptic cleft of nerve terminais (Bayorh et al. 1093). This drug effect prolongs the actions of catecholamines at effector terminals and also increases circulating blood levels of catecholamines (Moore et al. 1986). The impact of these changes on the fetus is appreciable. The uterine vasculature supplies oxygen and nutrients to the developing fetus and is dilated throughout most of pregnancy. in the presence of elevated levels of catecholamines, such as norepinephrine, these blood vessels constrict readily and thereby reduce uteroplacental transfer of nutrients to the fetus.

TABLE 1. *Case reports of maternal consequences of cocaine use during pregnancy*

Increased incidence of placental hemorrhage	Chasnoff et al. 1995 Oro and Dixon 1987 Collins et al. 1989
Subarachnoid hemorrhage	Lichtenfeid et al. 1984 Schwartz and Cohen 1984
Intracerebral hemorrhage	Mercado et al. 1989
Premature labor	Chasnoff et al. 1985 MacGregor et al. 1987 Chasnoff et al. 1989
Grand mal seizures	Mercado et al. 1989

Greiss and Van Wilkes (1954) first demonstrated that the pregnant ewe is sensitive to exogenous catecholamines. Using electromagnetic flow probes, these investigators measured reductions in uterine blood flow during infusions of either epinephrine or norepinephrine. Rosenfeld and West (1977) used radiolabeled microspheres to measure a 39.3-percent reduction in uterine blood flow in response to infusion of 0.24 µg/kg/min norepinephrine.

Later, investigators verified that cocaine, by potentiatlng the actions of catechoiamlnes in the uterine circulation, impairs uterine blood flow and interferes with uteroplacentai transfer of oxygen and nutrients to the fetus.

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TABLE 2. *Case reports of fetal consequences of cocaine use during pregnancy*

Prematurity	Oro and Dixon 1987
	MacGregor et al. 1987
	Cherukuri et al. 1988
	Chouteau et al. 1988
	Chasnoff et al. 1989
Low birth weight for gestational age	Oro and Dixon 1987
	MacGregor et al. 1987
	Chouteau et al. 1988
	Chasnoff et al. 1988
intrauterine growth retardation	Oro and Dixon 1987
	MacGregor et al. 1987
	Cherukuri et al. 1988
	Chasnoff et al. 1989
Perinatal cerebral infarct	Chasnoff et at. 1986
	Tenorio et al. 1988
Ischemic infarct of the bowels	Teisey et al. 1998
Genitourinary tract malformations	Chasnoff et al. 1988
Cryptorchidism	Chasnoff et al. 1988
Prune-belly syndrome	Chasnoff et al. 1988
Hydronephrosis	Chasnoff et al. 1988
Intrauterine fetal death	Critchley et al. 1988
Abnormal neonatal electroencephaiogram	Doberczak et al. 1988
Neurobehavioral abnormalities in the newborn	Chasnoff et al. 1985
	Doberczak et al. 1988
	Chasnoff et al. 1989
Sudden infant death syndrome	Chasnoff et al. 1987

Mahalik and coworkers (1984) demonstrated that cocaine, when administered to pregnant mice, reduces the transport of [22]Na to the embryo. These investigators interpreted this finding as evidence that cocaine produces vasoconstriction of uterine blood vessels and restricts uteropiacental transfer of the [22]Na isotope. Moore and coworkers (1986) later reported that cocaine, when glven Intravenously to pregnant ewes, increases maternal plasma noreplnephrine and epinephrine levels and was shown to increase maternal mean arterial blood pressure, decrease uterlne blood flow, and increase fetal mean arterial blood pressure.

in the authors' initial studies, cocaine was administered to pregnant ewes (Woods et al. 1987a) to evaluate effects of intravenous (IV) cocaine on oxygen delivery to the fetus. The results confirmed the conclusion of Mahalik and colleagues (1984) and Moore and coworkers (1986) that cocaine produces vasoconstriction of the uterine vasculature. Following IV administrations of 0.5, 1.0, and 2.0 mg/kg cocaine, maximum reductions of 24, 34, and 47 percent, respectively, were observed in total uterine blood flow (figure 1). Uterine blood flow was measured using electromagnetic flow probes.

Blood flow (Q) to the uterus is dependent on perfusion pressure (blood pressure=BP) and resistance (R) of the uterine vascular bed In the relationship Q=BP/R. An increase in uterine vascular resistance indicates vasoconstriction of resistance arterioles in the uterine vascular bed. Following cocaine administration, maximum increases of 52, 96, and 168 percent in uterine vascular resistance were observed at the above-dose levels, respectively (flgure 1). These findlngs indicate that cocaine produces vasoconstriction in the uterine vasculature, and itt effects this change in a dose-related manner.

The timing of cocaine's cardiovascular actions in the ewe and fetus provides insight into some of the dynamic events occurring at the utero-placental-fetal site. Following maternal cocaine administration, maximum changes in maternal mean arterial pressure, uterine blood flow, and uterine vascular resistance occurred within the first 5 minutes after injection (figure 1). Fetal oxygen levels, as measured by PO_2 and O_2 content, also decreased from baseline levels within 5 minutes of maternal Injection (figure 2). These data demonstrate that cocaine-induced vasoconstriction of the uterine vasculature reduces uteroplacental transfer of oxygen to the fetus.

The fetal cardiovascular response to maternal cocaine injection also proved to be a dose-dependent phenomenon. At 0.5 mg/kg cocaine, no changes in fetal heart rate or mean arterial pressure were detected. However, a significant increase in fetal mean arterial blood pressure was observed at the 1.0 and 2.0 mg/kg dose within 2 to 5 minutes after maternal cocaine injection (figure 3).
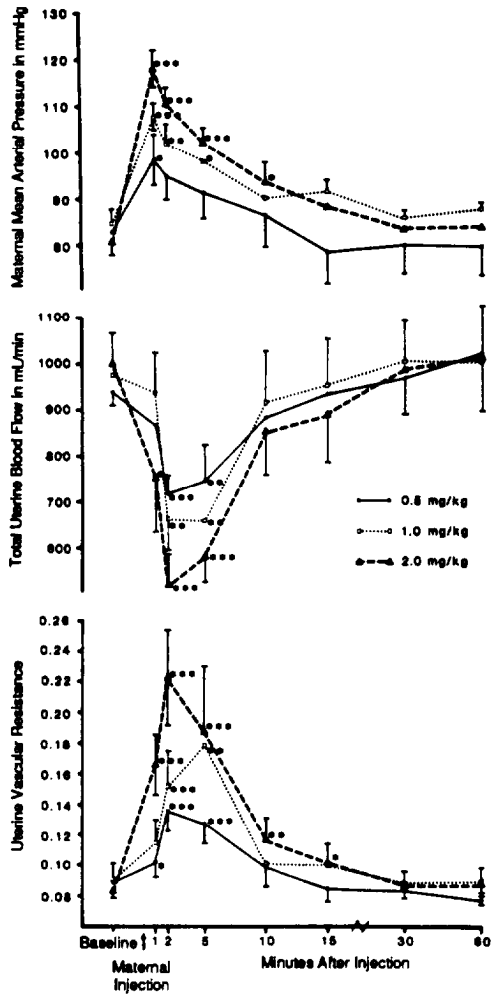
FIGURE 1. *Responses of maternal mean arterial pressure (top), total uterine blood flow (middle), and uterine vascular resistance (bottom) to maternal administration of cocaine*

  *p<0.05
 **p<0.01
***p<0.001

SOURCE: Woods et al. 1987a, copyright 1987, American Medical Association.

FIGURE 2. *Responses of fetal oxygen pressure (PO$_2$)(top) and fetal oxygen (O$_2$) con tent (bottom) to maternal administration of cocaine*

$*p<0.05$
$**p<0.01$

SOURCE: Woods et al. 1987a, copyright 1987, American Medical Association.

FIGURE 3. *Responses of fetal heart rate (top) and fetal mean arterial pressure (bottom) to maternal administration of cocaine*

*p<0.05
**p<0.01
***p<0.001

SOURCE: Woods et al. 1987a, copyright 1987, American Medical Association.

Fetal heart rate did not vary during the initial 5-minute period after maternal injection. By 10 to 15 minutes after injection, however, fetal heart rate increased dramatically in response to 1.0 and 2.0 mg/kg cocaine doses.

FETAL CARDIOVASCULAR RESPONSE TO MATERNAL COCAINE

The elevated fetal blood pressure and heart rate observed after maternal administration of cocaine could be due to (1) the direct actions of cocaine on the fetal cardiovascular system, (2) the resultant fetal hypoxemia from uterine artery vasoconstriction, or (3) cocaine's ability to potentiate the cardiovascular actions of catecholamines released by the fetus during hypoxemia. Hypoxemia in fetal lambs has been demonstrated to produce release of catecholamines by fetal chromatin tissue (Phillippe 1983). Cohen and coworkers (1984) demonstrated in near-term fetal lambs that the adrenal gland secretes primarily norepinephrine and, to a lesser degree, epinephrine in response to hypoxemia. Also, the secretory rates of norepinephrine and epinephrine increased with the degree and duration of hypoxemia. These investigators also observed Increases in fetal blood pressure during the hypoxlc episodes. Therefore, decreases in fetal oxygen levels produce an increase in the release of catecholamines, which elevate fetal blood pressure. Changes in fetal blood pressure and heart rate after maternal injections of cocaine, therefore, may be attributed to fetal hypoxemia.

To separate the indirect fetal effects of hypoxemia, via cocaine-induced uterine artery vasoconstriction, from the direct actions of cocaine on the fetal circulation, cocaine was injected directly into the fetal circulation (Woods et al. 1987a). Following fetal injections of 0.5, 1.0, and 2.0 mg/kg, based on estimated fetal weight, there were no changes in maternal blood pressure, total uterine blood flow, maternal heart rate, or maternal or fetal PO, values. However, fetal mean arterial pressure increased rapidly after fetal administration of cocaine, reaching a maximum value by 1 to 2 minutes after injection. The fetal heart rate decreased during the first 2 minutes after injection, but then increased slowly to reach a peak by 15 minutes after injection (figure 4). These fetal heart rate and blood pressure changes were similar in pattern to those following maternal injections. The magnitude of fetal cardiovascular responses to direct fetal injections, however, were diminished in comparison with those following maternal injections. The increase in fetal heart rate and blood pressure after the maternal cocaine injection and the direct fetal injections strongly suggests that cocaine has direct effects on fetal cardiovascular or cardiac function that are independent of fetal oxygen levels.

Fetal hypoxemia alone produces cardiovascular effects that may provide information regarding the effects of cocaine on the fetus. In previous studies by
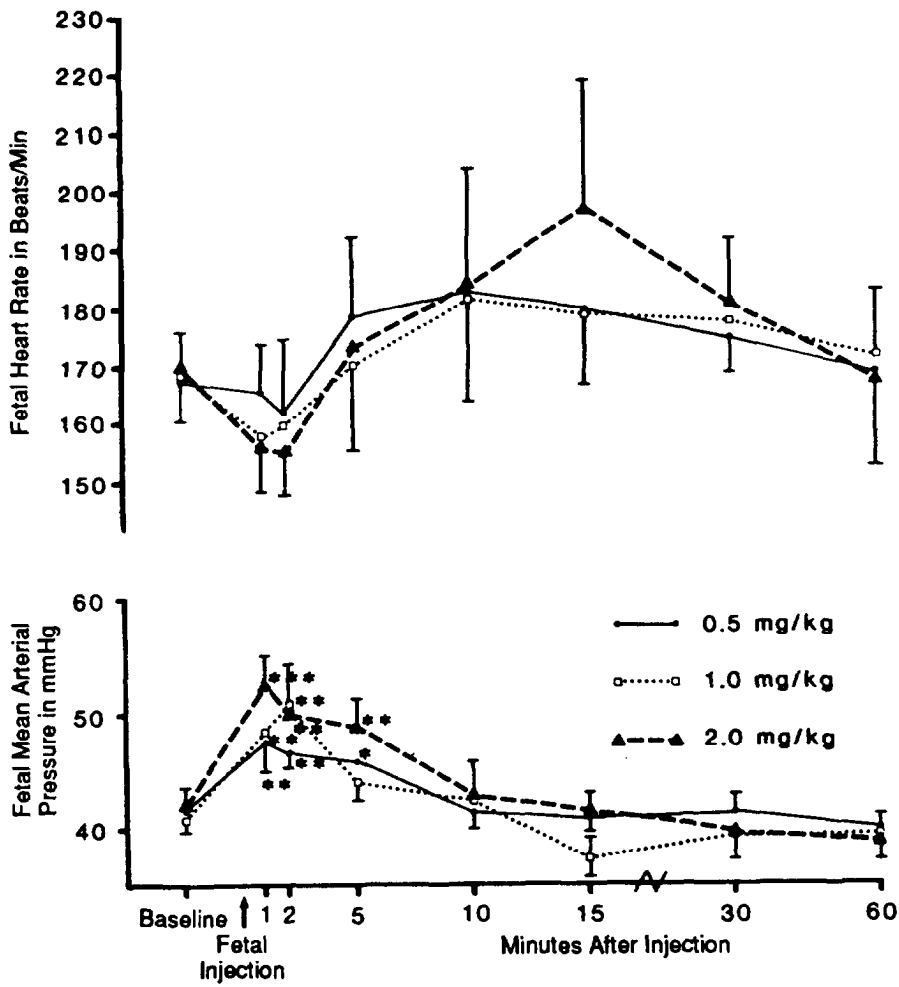
FIGURE 4. *Responses of fetal heart rate (top) and fetal mean arterial pressure (bottom) to fetal administration of cocaine*

*p<0.05
**p<0.01
***p<0.001

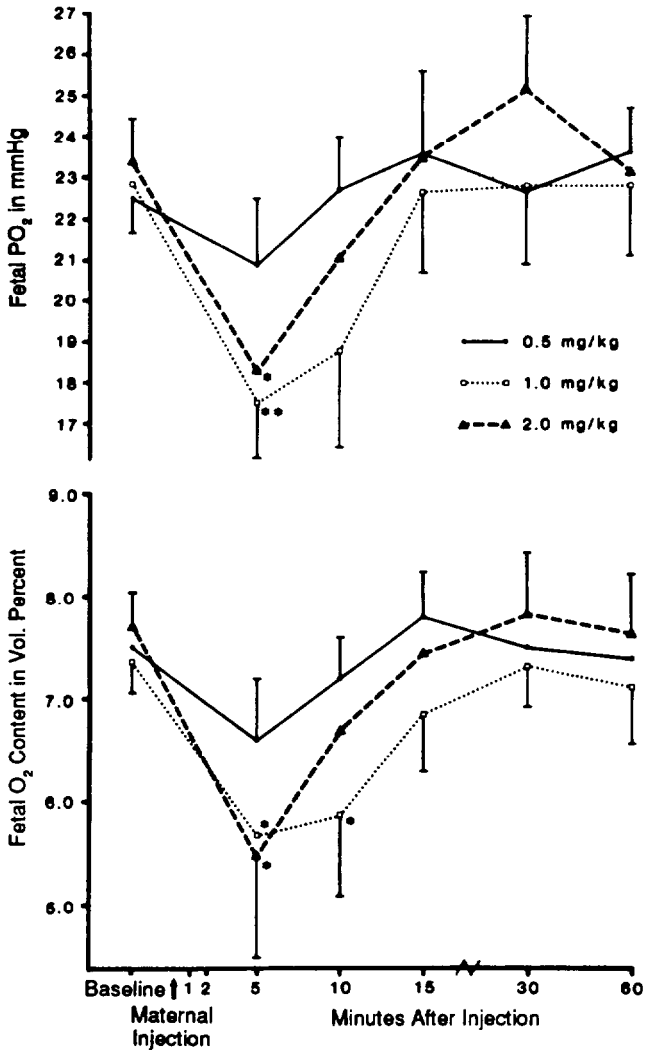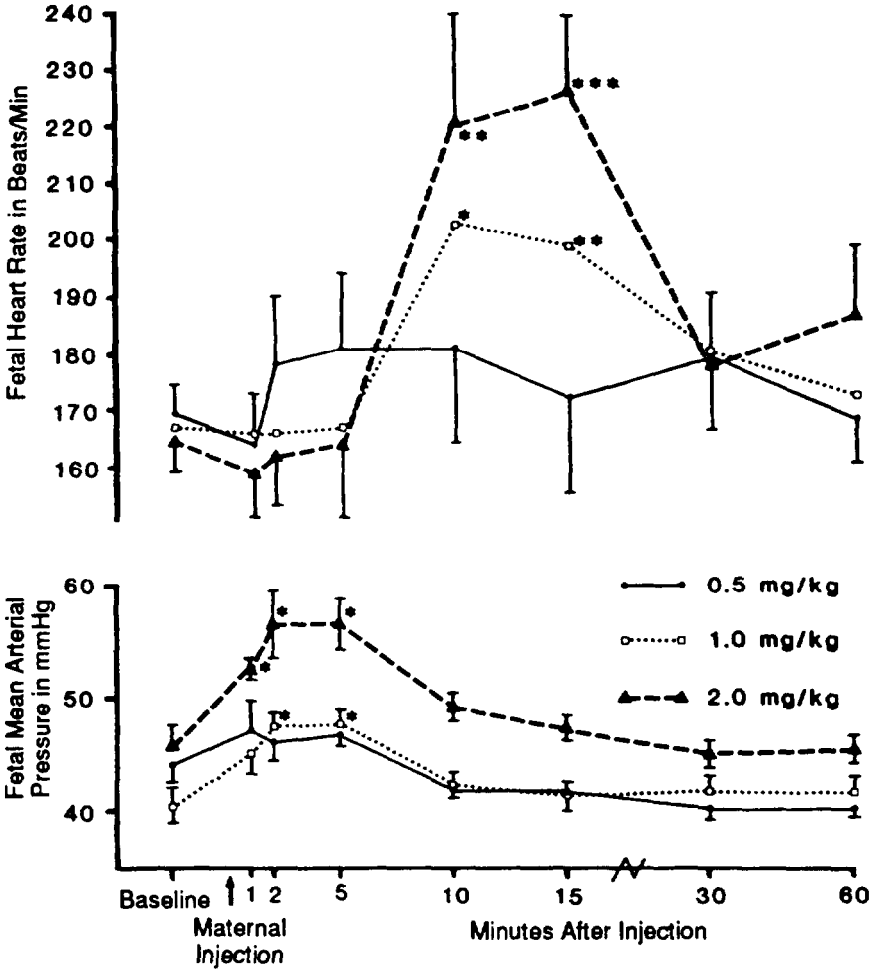SOURCE: Woods et al. 1987a, copyright 1987, American Medical Association.

Skillman and coworkers (1985) hypoxemia was induced in fetal lambs through the use of an externally controlled vascular clamp placed on the uterine arteries. By this method, the authors were able to reduce total uterine blood flow to predetermined levels while monitoring fetal oxygen levels, blood pressure, and heart rate. Reductions in total uterine blood flow of 25 percent produced a small drop in fetal PO_2 levels (-2.4 mmHg) with no associated change in fetal blood pressure. A 50-percent reduction in uterine blood flow produced a drop of 7.9 mmHg in fetal PO_2 and an increase of 5 mmHg in fetal blood pressure. A 83-percent reduction in total uterine blood flow produced a decrease of 8.2 mmHg in fetal PO_2 and an increase of 5 mmHg in fetal blood pressure. Although catecholamine release was not monitored in this study, there appears to be a direct relationship between the degree of fetal hypoxemia and fetal cardiovascular response.

A comparison of fetal cardiovascular changes obtained during mechanical reductions in uterine blood flow with those following maternally administered cocaine provides additional evidence that the two methods for producing reduced uterine blood flow differ in their effects on the fetus. Total uterine blood flow was reduced by 24, 34, and 47 percent when maternal cocaine was given at 0.5, 1.0, and 2.0 mg/kg, respectively. Mechanical reduction in uterine blood flow of 50 percent approximates the 47-percent reduction in uterine blood flow observed after the 2.0 mg/kg cocaine dose. Despite similar drops in fetal PO_2 in response to the two techniques, the increase in fetal blood pressure following maternal cocaine administration was approximately twice that following hypoxemia via vascular clamping (50 percent) of uterine arteries, This difference suggests that cocaine, which crosses the placenta to the fetus, potentiates the cardiovascular actions of fetal catecholamines or increases their release during hypoxemia via uterine vasoconstriction.

PLACENTAL PASSAGE OF COCAINE TO THE FETUS

Drugs such as cocaine that are highly soluble in lipids and aqueous solutions generally pass easily from the maternal to the fetal circulation. Moore and coworkers (1986) measured maternal plasma cocaine levels in response to three doses of cocaine (0.3, 0.5, and 1.0 mg/kg) and fetal plasma cocaine levels in response to one dose of cocaine (0.5 mg/kg). These investigators observed that, within 5 minutes following maternal injection of 0.5 mg/kg, fetal plasma cocaine levels were approximately 12 percent of the maternal plasma cocaine levels. In a later study, Woods and coworkers (1989) examined maternal and fetal serum cocaine levels in response to 1.0 and 2.0 mg/kg maternal cocaine administration. Woods and colleagues (1989) showed fetal serum cocaine levels of 14 and 17 percent of maternal serum levels at 5

minutes following maternal cocaine injection of 1.0 and 2.0 mg/kg, respectively. Although at these two doses, uterine artery vasoconstriction was dose-dependent, these data suggest that placental transfer of cocaine to the fetus is not limited by cocaine-induced uterine artery vasoconstriction.

In a separate experiment, maternal blood samples were taken every 30 seconds for the first 15 minutes and at 30 and 60 minutes following maternal cocaine administration of 2.0 mg/kg. Fetal blood samples also were taken every 30 seconds for the first 5 minutes, then every minute for 15 minutes, and then at 30 and 80 minutes. Maternal cocaine levels were maximum at the first 30-second sample, declined rapidly until 5 minutes (figure 5), then declined
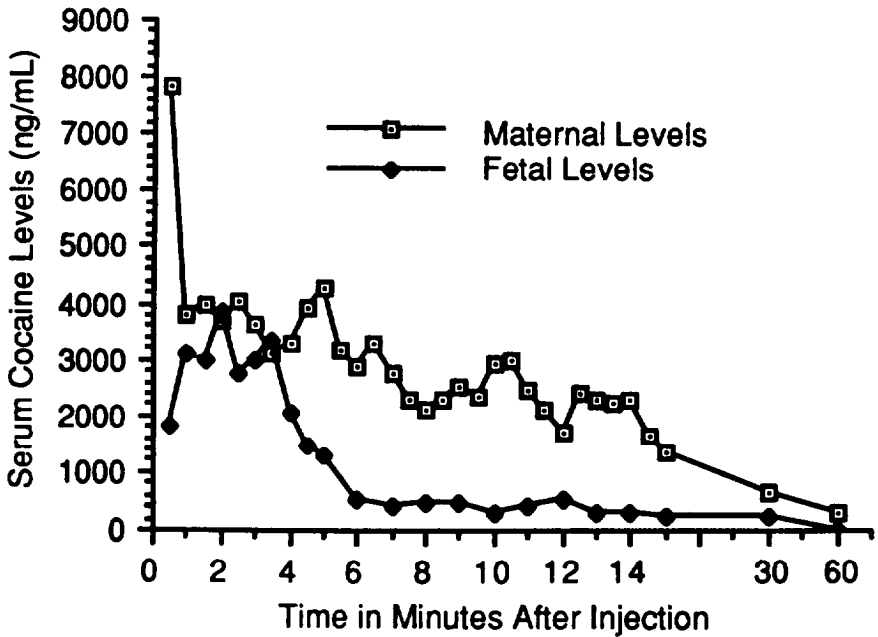
FIGURE 5. *Maternal and fetal serum cocaine levels in one experiment obtained every 30 seconds to 1 minute for 15 minutes and then at 30 and 60 minutes following IV injection of cocaine, 2.0 mg/kg*

SOURCE: Woods et al. 1989, copyright 1989, New York Academy of Sciences.

slowly to near zero levels by 80 minutes after injection. Fetal cocaine levels initially increased to peak by 2 minutes after injection and coincided with maximal increases in fetal mean arterial pressure. Thereafter, the fetal cocaine levels declined rapidly from 4 to 6 minutes after injection, remained at low levels to 30 minutes, and were undetectable by 60 minutes. These data demonstrate that cocaine neither equilibrates nor accumulates in the fetal blood compartment. Moreover, the fetus appears to have the capacity to metabolize cocaine, or the cocaine is distributed into other fetal tissues. It is noteworthy that fetal cocaine levels remained relatively constant from 6 to 30 minutes after maternal administration, despite recovery of uterine blood flow to approximate control values by 10 minutes after cocaine injection. That there was no increase in fetal cocaine levels during this period of uterine blood flow restoration suggests either that once maternal cocaine concentrations drop below a certain level, there is no further placental transfer of cocaine to the fetus or that the fetus has the capacity to metabolize or redistribute to its tissues the additional cocaine transferred during uterine blood flow restoration.

ROLE OF ALPHA-ADRENERGIC RECEPTORS IN COCAINE-INDUCED UTERINE ARTERY VASOCONSTRICTION

Blood vessel vasoconstriction occurs primarily by the interaction of norepinephrine with alpha-1-adrenergic receptors. The uterine resistance arterioles possess alpha-receptors that produce vasownstriction of the uterine vasculature when stimulated. If the primary mechanism by which cocaine produces its vasoconstrictlve action on the uterine vasculature is mediated by alpha receptors, then the vasoconstrictive effects of cocaine should be blocked by an alpha-l receptor blocking agent.

Phenoxybenzamine, a noncompetitive alpha-1 receptor blocking agent, was employed to determine whether uterine vasoconstrictive actions of cocaine could be blocked (Dolkart et al. 1990). Pretreatment with phenoxybenzamlne 5.0 µg/kg blocked increases in blood pressure or uterine blood flow following IV doses of norepinephrine, 30 mg, in pregnant ewes. Administration of 2.0 mg/kg cocaine in pregnant ewes before phenoxybenzamine produced a 53-percent increase in maternal mean arterial pressure, a 50-percent reduction in uterine blood flow, and a 191 -percent increase in uterine vascular resistance. After phenoxybenzamine administration, there was no increase in maternal mean arterial pressure in response to a second dose of cocaine. However, there was a 44-percent reduction in uterine blood flow and a 59-percent increase in uterine vascular resistance. These data indicate that vasoconstriction of the uterine vascular bed occurs in response to cocaine despite complete uterine and systemic alpha-1 receptor blockade. Thus, cocaine acts on the uterine vasculature by other mechanisms in addition to alpha-adrenergic receptor stimulation.

The fetal response to maternal cocaine injection during alpha-adrenerglc blockade confirmed that uterine artery vasownstriction had occurred. Before phenoxybenzamine administration, cocaine produced a 24-percent increase in fetal mean arterial pressure, a 51 -percent increase in fetal heart rate, and a 29-percent reduction in fetal PO_2 levels. After phenoxybenzamine, there was no increase in fetal mean arterial pressure; however, fetal heart rate increased 38 percent, and fetal PO_2 decreased 18 percent. Not only did the reductions in fetal PO_2 levels in response to cocaine after phenoxybenzamine confirm that uterine artery vasoconstriction had occurred, but also the lack of increase in fetal mean arterial pressure indicated that phenoxybenzamine had crossed the placenta to block fetal alpha-1 receptors as well.

COMPARISON OF COCAINE'S CARDIOVASCULAR ACTION IN THE PREGNANT AND NONPREGNANT EWE

Changes in cardiac output, blood volume, receptor function, and hormonal levels are known to occur during pregnancy. To evaluate the influence of these pregnancy-related changes on cocaine's actions, the responses of blood pressure and heart rate to cocaine were measured in nonpregnant oophorectomized ewes and pregnant ewes. In response to cocaine in doses of 1.0 and 2.0 mg/kg, pregnant ewes exhibited a twofold greater increase in systolic blood pressure, diastolic blood pressure, and mean arterial pressure (Woods and Plessinger 1990) than did nonpregnant ewes. These results were surprising, because many drugs produce lesser cardiovascular effects during pregnancy (Perucca 1987). This increased sensitivity of pregnant ewes Is attributed to possible changes in cocaine metabolism, increases in peripheral adrenergic sensitivity to norepinephrine, or differences in cocaine-induced cardiac responsiveness.

Cocaine (benzoylmethylecgonine) is a methyl ester that is metabolized by liver and plasma esterases and cytochrome P_{450} enzymes. In a study by Stewart and coworkers (1978), cocaine given to rats was found to be metabolized by N-demethylation to norcocaine at a rate of 20 percent of the cocaine dose. Norcocaine is a potent local anesthetic agent that inhibits norepinephrine reuptake by the presynaptic membrane to a greater degree than does cocaine (Hawks et al. 1974). The remaining metabolism (80 percent) of cocaine appears to be mediated by plasma and liver esterases and microsomal monooxygenase (Stewart et al. 1979). The increased sensitivity of the pregnant ewe to cocaine may be due to a reduced metabolism of cocaine or to an increase in bioactivation of cocaine to norcocaine. Reports have indicated that there are reductions in liver cytochrome P_{450} concentrations (-25 percent) and reduced activities of glucuronyl transferase (Neale and Parke 1973) and monooxygenase (Dean and Stock 1975) in pregnant rats and rabbits.

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Aminopyrine is an agent that is commonly used as a substrate in studies of microsomal monooxygenases, most notably N-demethylation reactions. Because progesterone treatment of nonpregnant rats is known to produce an increase in N-demethylation of aminopyrine (Ochs et al. 1986), high levels of progesterone in the pregnant ewes also may produce an increase In N-demethylation of cocaine to norcocaine. This hypothesis is especially plausible since Stewart and coworkers (1978) demonstrated that N-demethylation of cocaine to norcocaine has kinetics that are nearly identical to those for N-demethylation of aminopyrine.

Alpha-adrenergic receptor sensitivity also may increase during pregnancy, producing the observed increase in blood pressure response to cocaine in pregnant ewes. if, during pregnancy, alpha-1 receptor sensitivity to norepinephrine increased, this change could explain the greater increase in blood pressure observed in pregnant ewes than in nonpregnant ewes. McLaughlin and coworkers (1985) used phenylephrine, an alpha-1 agonist, to demonstrate that vascular reactivity of the hind limb to this agent increased following treatment of nonpregnant ewes with progesterone. In this study, the vascular reactivity of the hind limb of pregnant ewes also was found to increase in comparison with that observed in untreated nonpregnant ewes. Other investigators have reported that estrogens increase the number of adrenergic receptors (Peters et al. 1979). Collectively, these observations indicate that pregnancy produces an increased peripheral reactivity to exogenous or endogenous norepinephrine, and pregnancy hormones may explain the increased cardiovascular responsiveness seen in pregnant ewes exposed to cocaine.

HORMONAL ROLE IN PREGNANCY-RELATED COCAINE ACTION

To determine whether pregnancy-related alterations in hormonal levels are responsible for increased sensitivity of pregnant ewes to cocaine, responses of blood pressure and heart rate in nonpregnant oophorectomized ewes to cocaine were examined before and during 3 days of treatment with progesterone (Woods et al. 1987b, 1988; Plessinger and Woods 1990). in addition, blood pressure responses to norepinephrine were examined In these animals to determine whether alpha-adrenergic receptor sensitivity was influenced by progesterone. Responses of systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, and heart rate to norepinephrine were similar before and during 3 days of progesterone treatment. These consistent responses Indicated that progesterone has no influence on and does not alter alpha-1 receptor sensitivity to norepinephrine. in contrast, blood pressure increases in response to cocaine at either 1.0 or 2.0 mg/kg were approximately two times greater during each day of progesterone

treatment when compared with the responses of nonpregnant ewes to the same dose of cocaine before progesterone. Increased sensitivity to cocaine was consistent throughout all 3 days of progesterone treatment. These data indicate that progesterone increases cardiovascular responses to cocaine. Alterations in alpha-1 receptor sensitivity, however, do not seem to explain this phenomenon.

Progesterone may produce an increased cardiac sensitivity to cocaine, leading to increased cardiac output as an explanation for the elevated blood pressure seen in pregnant ewes and progesterone-treated nonpregnant ewes. If so, progesterone may potentiate the action of cocaine to increase heart rate or cardiac contractility. From *in vivo* preparations, there is evidence that cocaine may act directly on the heart. Mugge and coworkers (1984) used isolated cat papillary muscle strips to examine the force of cardiac contraction in response to phenylephrine in the presence of cocaine and hydrocortisone, a corticosteroid. Cocaine alone increased the force of contraction, and pretreatment with hydrocortisone increased this cocaine effect even further. Although these investigators were interested mainly in extraneuronal uptake of phenylephrlne, which is inhibited by hydrocortisone, their data illustrate that steroids have an influence on cardiac contractility and can potentiate effects of cocaine.

COCAINE EFFECTS ON NEUROBEHAVIOR AND CARDIOPULMONARY FUNCTION

Although most of the authors' studies to date have used 1.0 and 2.0 mg/kg doses in pregnant ewes, they have expanded the dosage regimen to include 3.0 and 5.0 mg/kg. At these doses, cocaine in pregnant ewes produced placental abruptions, cardiac arrhythmias, respiratory distress, seizures, and death (Woods et al. 1989) (table 3). in the nonpregnant ewe, increasing the dose of cocaine to 3.0 or 5.0 mg/kg only increased the hypertensive response in a dose-dependent manner. Not until doses of 10.0 to 15.0 mg/kg were administered to nonpregnant ewes were the sequelae of cardiac arrhythmias, respiratory distress, seizures, and death observed. These results indicate that there is a shift to the left in the cocaine dose-response curve for cardiovascular as well as neurobehaviorai and lethal sequelae in the pregnant ewe. These data strongly suggest that pregnancy increases the risk of cocaine-induced cardiovascular and neurologic complications and death.

The seizure activity exhibited by pregnant and nonpregnant ewes is characterized by extension of the extremities, collapse, opisthotonos, and respiratory distress. These observations indicate that cocaine, at least in the ewe, produces strychnine-type seizures. The convulsive actions of strychnine

reportedly result from alterations in glycine metabolism. As a result, inhibitory influences on nerve impulses are blocked and movement at any given joint is manifested by contraction of the strongest muscle at that joint. This results in dramatic arching of the back and neck (opisthotonos), extension of all extremities, and spasm of the diaphragmatic muscles leading to respiratory distress (Franz 1985). That cocaine produces strychnine-like seizures suggests that cocaine in high doses may selectively block inhibitory neurons.

TABLE 3. *Cocaine responses in the pregnant ewe*

IV Dose (mg/kg)	N	Responses
0.5	5	No restlessness, no arrhythmias
1.0-2.0	15	Increased restlessness, vocalization (15/1 5); increased attentiveness (15/15); mild arrhythmias
3.0	5	Acute myocarditis (1); pulmonary artery rupture (1); abruptio placenta (1)
5.0	3	Seizure activity and opisthotonos (3/3); death by arrhythmias (1/3); respiratory distress (3/3)

SOURCE: Woods et al. 1989, copyright 1989, New York Academy of Sciences.

USING ANIMAL STUDIES TO EXAMINE DRUG CONSEQUENCES IN HUMANS

One of the difficulties with using animal models for the study of any drug is the extrapolation of these results to humans. Few controlled studies of effects of cocaine on humans have been reported in the literature. Furthermore, uncertain purity of "street" cocaine and estimation of amount of cocaine consumed make it impossible to establish a relationship between dose and clinical complication. Based on autopsy results of cocaine overdose victims, the lethal dose of cocaine in the human is estimated to be 1.4 g (Smart and Anglin 1987), which is approximately 20 mg/kg for a 70 kg individual. This estimation of human lethal cocaine dose approximates the lethal dose that the authors have observed for nonpregnant ewes. Sheep, therefore, appear to be dose-appropriate animal models for cardiovascular studies when compared with

rodent models. The lethal dose of cocaine in rats by intraarterial injection is 148 mg/kg (Nahas et al. 1985). Selection of an appropriate animal model for studies of cocaine is crucial if we are to understand the effects of cocaine on the fetus.

CONCLUSION

Collective data generated in animal models help explain some of the clinical consequences of cocaine use by pregnant women. The rapid onset of maternal hypertension following IV administration of cocaine may be responsible for placental abruptions, subarachnoid hemorrhage, intracerebrai hemorrhage, and onset of premature labor. Uterine artery vasoconstriction may interfere with placental transfer of oxygen and essential nutrients necessary for fetal growth and development. The observation that cocaine produces reduced uterine blood flow and increased uterine vascular resistance (vasoconstriction) may help explain the observed incidence of fetal growth retardation and low birth weights in babies exposed to prenatal cocaine. The fetal hypertensive effects of cocaine observed following direct fetal injectlons of cocaine were, In part, independent of hypoxia and may explain cocaine-related intrauterine cerebral and bowel infarcts. Abnormal neurobehavioral effects seen in newborns may be the result of cocaine-induced fetal hypoxia, or they may be secondary to direct effects of cocaine and its metabolites.

One of the most confounding variables in linking human and animal studies of cocaine is that typical cocaine abusers use several other drugs in conjunction with cocaine. Some of the cocaine-related events observed in pregnant cocaine addicts may result from interactions of cocaine with other abused drugs. Nevertheless, animal studies certainly indicate that cocaine has the potential to be damaging to the woman and her fetus.

A second reason for cautiously extrapolating animal data to humans is the possibility that interspecies differences in cocaine responses may exist. Among case reports that have been published to date, there are no reports that indicate that pregnant women are more sensitive to cocaine than are nonpregnant women, even though the authors' results in pregnant and nonpregnant ewes clearly demonstrate this phenomenon. In addition, the data reported in their studies were generated from pregnant and nonpregnant ewes exposed to cocaine for the first time. The typical abuser has used cocaine repeatedly before conception and, in many cases, continues to use the drug repeatedly throughout pregnancy. The effects of long-term chronic cocaine exposure on the pregnant ewe and her fetus therefore remain to be investigated.

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Pharmacokinetics and Time-Action Profile of Cocaine in Dogs

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INTRODUCTION

A fundamental principle of drug action is that the magnitude of the drug response is a function of its concentration at its site(s) of action. Although tolerance (Fischman et al. 1985; Chow et al. 1985) and sensitization (Downs and Eddy 1932a, 1932b) have been reported after cocaine treatment, these phenomena modify the relationship between drug concentration and effect; they do not negate the above principle. Many drugs exert more than one pharmacologic action and generally exhibit different concentration-response relationships for individual actions. For example, cocaine exerts at least two pharmacologic actions-inhibition of neuronal monoamine transport (Trendelenburg 1959) and local anesthesia (Ritchie and Greene 1990)—and these two actions have different concentration-response relationships, with the former occurring at much lower concentrations than the latter (Yasuda et al. 1984).

Because the concentration of a drug at its active site(s) rarely can be determined, the concentration of drugs in plasma or serum generally is employed in attempts to define concentration-response relationships. Although not ideal, this approach has several advantages over the use of the dose administered to infer relationships between the quantity of drug and its effect (Neubig 1990). indeed, it is only that fraction of the quantity administered that exists unbound in arterial plasma perfusing the area in which a drug acts that is available to diffuse out of the circulation and possibly reach its site of action. The dose of a drug is one of the major determinants of plasma drug concentration. Indeed, it is the only determinant that can be selected by the investigator. Probably for this reason and to avoid the necessity for difficult and expensive analytical procedures, it is used frequently instead of plasma drug concentration in quantitative expressions of the relationship between the effect of a drug and the amount of the drug available to produce that action. In fact, the plasma drug concentration, or more precisely, the plasma concentration of

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unbound drug, is a much better indicator of the drug concentration at its site of action than is the total dose administered. This is because unless a drug Is administered intravenously, several factors in addition to the dose influence its concentration in plasma and, thus, at its site of action.

One of these factors is the bioavailability of the drug, which is defined as that fraction of the dose administered that reaches the arterial side of the circulation and, thus, may reach the site of action. Only Intravenous (IV) administration guarantees 100 percent bioavailability. Any route of administration that exposes cocaine to the action of esterases before reaching the arterial side of the circulation may result in low and/or unpredictable bioavailablllty (Stewart et al. 1977, 1979). Although cocaine is effective after oral administration (Jatlow 1988; Van Dyke et al. 1978), it virtually never is administered orally because of the potential for poor bioavailability by this route. The intraperitoneal (IP) route of administration, however, is used frequently in rodent species. Unfortunately, even though this is a parenteral route that provides a large absorptive surface allowing relatively rapid absorption, the absorption is largely into the hepatic portal circulation, which exposes cocaine to the same hepatic clearance mechanisms as after oral administration (Benet et al. 1990). Another factor that influences the plasma concentration of a drug is its rate of absorption. Although the IV route provides instantaneous absorption into the vascular compartment, all other routes impose barriers that the drug must cross to reach the circulation. Two major factors that Influence the rate of absorption from any site of administration are the rate of blood flow to that site and the surface area over which absorption may occur. Because of its action to cause peripheral vasoconstriction, cocaine may reduce its own rate of absorption when administered by non-IV parenteral routes. Finally, the rate of elimination of active drug is probably the major factor determining the plasma concentration-time relationship for any drug. Thus, because of the complex factors involved in the absorptive process after non-IV administration, it is probably not appropriate to assume that the same relationship always exists between the dose administered and cocaine plasma concentration. There is undoubtedly considerable variation between animals and possibly even from one dose to the next in the same animal.

Even when cocaine is administered intravenously, one cannot assume that the same dose always will result in the same plasma cocaine concentration-time profile. The rate of IV administration is a major determinant of the plasma cocaine concentration-time relationship. Thus, the same IV cocaine dose administered over a 10- to 15-second period will result in a much higher peak plasma cocaine concentration than when administered over a 1 -minute period, even though the areas under the plasma concentration-time curves may be equivalent. A continuous IV infusion will result in an even slower approach to a

maximum (and in this case steady-state) plasma concentration, which will be achieved after a time equivalent to 4- to 5-elimination half-lives, if cocaine does not accumulate to a lethal level before reaching the plateau concentration dictated by the infusion rate chosen and its rate of clearance from the animal. Consequently, the time-action profile of the same IV cocaine dose may vary considerably, depending on the rate of IV administration. Thus, it is important to understand the influence of these factors if research in laboratory animals is to produce findings relevant to Its effects in humans.

EXPERIMENTAL MODEL

To gain a better understanding of the plasma concentration-time relationship and the plasma concentration-effect relationship for cocaine after IV administration, we administered cocaine to chronically instrumented conscious dogs, a model we have described elsewhere (Wilkerson 1988). Briefly, dogs were trained to stand quietly in a nylon sling during cardiovascular monitoring. After training, cardiovascular monitoring devices were implanted in each animal. These devices included a doppier blood flow transducer that was implanted around the left circumflex coronary artery and an electromagnetic blood flow transducer that was implanted around the root of the aorta. Wires from these devices and subcutaneous electrocardiogram (ECG) electrodes were exteriorized to the animal's back. In addition, catheters were implanted in an omocervical artery and an omocervicai vein for blood pressure recording and drug administration or blood withdrawal, respectively. These catheters also were exteriorized to the back of the animal's neck. All surgical procedures were performed under sterile conditions, and animals received preoperative and postoperative prophylactic antibiotic treatment. In addition, morphine was administered postoperatively to prevent pain or discomfort.

Throughout an animal's participation in these studies, all cutaneous incisions were treated daily with antibiotic ointment and covered with sterile bandages, except when standing in the nylon sling during an experiment. A soft leather collar was utilized to protect the catheters, and a cotton body stocking covered by a nylon jacket was utilized to protect flow transducer and ECG wires. Dressings were changed dally, and catheters were flushed and filled with heparinized saline daily. Sterile procedures were observed for drug injections and blood withdrawal during ail experiments. in all experiments, cocaine was administered intravenously with the entire dose being given over a 10- to 15-second period. With the exception of six animals that received chronic cocaine treatment for a 4-week period, no animal received more than one dose of cocaine during each experiment, and the interval between experiments was at least 48 hours. The six animals receiving chronic cocaine treatment were given 2 mg/kg twice daily for 4 weeks. On the last day of chronic cocaine treatment, 4

mg/kg was administered as a single dose to determine the plasma concentration-time profile for cocaine.

PHARMACOKINETICS OF COCAINE IN THE DOG

The plasma concentration-time profile for cocaine was studied after IV administration of three doses of cocaine in chronically instrumented, conscious dogs. Animals that previously had not received cocaine treatment were given either 1, 2, or 4 mg/kg doses of cocaine intravenously as described above. Blood samples (5 mL) were obtained 1, 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, and 160 minutes after each dose. Samples were placed immediately into tubes containing sodium fluoride (to Inhibit plasma esterase activity) and heparin and centrifuged. After centrifugation, plasma was collected and frozen at -40°C until assayed. Plasma cocaine concentration was determined by the Medical College Hospital Toxicology Laboratory using a modification of the gas chromatography-mass spectroscopic procedure described previously (Foltz et al. 1980). Deuterated cocaine (0.25 mg/L) and deuterated benzoylecgonine (0.25 mg/L) were added to each sample as internal standards. The sensitivity of this assay for cocaine is 0.02 mg/L, and it is linear over a range of 0.02 to 10.0 mg/L.

Figure 1 illustrates the plasma concentration-time relationship for each of the three doses of cocaine in this experimental model. The peak plasma cocaine concentrations, observed 1 minute after administration of 1, 2, and 4 mg/kg of cocaine, were 0.92±0.07 mg/L, 2.1±0.6 mg/L, and 3.48±0.26 mg/L, respectively. Plasma cocaine concentrations 1 hour after administration of the above doses were 0.097±0.013 mg/L, 0.21±0.02 mg/L, and 0.44±0.03 mg/L, respectively. Pharmacokinetic analysis of the data presented in figure 1 was performed using PCNONLIN (Statistical Consultants, Inc., Lexington, KY), a software package designed for statistical analysis of general nonlinear models, including pharmacokinetic models. Although distribution of cocaine after a single IV dose is rapid, a two-compartment open model was employed for the pharmacokinetlc analysis of the cocaine plasma concentration-time data obtained in these experiments (Neubig 1990). Although a one-compartment model has been used to analyze cocaine pharmacoklnetics (Wilkinson et al. 1980), a two-compartment model provides a more rigorous analysis and has been shown to better fit cocaine disposition in humans (Chow et al. 1985; Ambre 1986).

The pharmacokinetic parameters calculated for the three cocaine doses are shown in table 1. No significant differences were noted between the 1 and 2
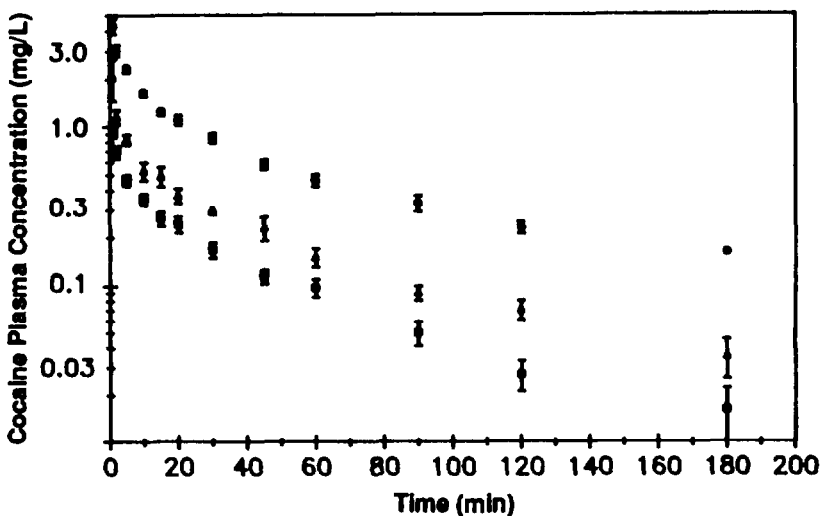
FIGURE 1. *Plasma concentration of cocaine as a function of time after administration for IV doses of 1 mg/kg (squares), 2 mg/kg (triangles), and 4 mg/kg (circles) in chronically instrumented conscious dogs*

NOTE: Points represent the mean±SEM for seven animals at the 1 mg/kg dose and nine animals each at the 2 mg/kg and 4 mg/kg doses.

mg/kg doses except that the area under the plasma concentration vs. time curve increased as a function of dose after the 2 mg/kg dose. Cocaine distribution was rapid and occurred with a half-life of less than 3 minutes. The elimination half-life for cocaine was approximately 29 minutes after administration of each dose. Previous studies have reported that the elimination half-life of cocaine in humans ranged from 15 minutes to approximately 1.5 hours (Chow et al. 1985; Wilkinson et al. 1980; Javaid et al. 1976; Inaba 1989; Barnett et al. 1981); it was reported to be 18 minutes in rats (Misra 1976) and 16 minutes in mice (Benuck et al. 1987).

Thus, the rate of elimination of cocaine in the dog appears to be quantitatively similar to humans. Although several studies have reported elimination half-lives for cocaine that were different for different routes of administration (e.g., subcutaneous vs. IP), these differences probably resulted from methodological problems rather than differences in the rate of elimination of cocaine from plasma. Although, as stated above, the character of the plasma concentration-

time relationship may be markedly different for the same dose given by different routes of administration, the elimination half-life for any drug is independent of absorptive processes when correctly determined. Undoubtedly, studies that report elimination half-lives for cocaine that are different for various routes of administration have not restricted their analysis to the slope of the terminal phase of the plasma concentration-time curve but have incorrectly mixed data from the absorption and elimination phases in their analysis.

TABLE 1.   *Cocaine pharmacokinetics*

Acute Cocaine Treatment Only	Intravenous Cocaine Dose (mg/kg)		
	1 (N=7)	2 (N=9)	4 (N=9)
Distribution half-life (min)	2.52±0.76	2.40±0.56	3.81±0.65
Elimination half-life (min)	29.29±5.20	29.23±2.38	47.02±4.74
Apparent volume of distribution (L/kg)	0.78±0.18	1.22±0.21	1.07±0.11
Area under plasma concentration vs. time curve (mg/L*min)	17.89±1.63	30.53±3.04	97.09±7.24
Total body clearance (mL/min/kg)	60.35±7.10	71.73±7.35	33.85±4.50

These relationships between the 1 and 2 mg/kg doses would be expected for a drug that is eliminated by first-order processes. On the other hand, there were significant differences in the pharmacoklnetics of cocaine after the 4 mg/kg dose. The total body clearance of cocaine was decreased by approximately 50 percent after the 4 mg/kg dose compared with the 1 and 2 mg/kg doses, This resulted in a significant increase in the elimination half-life after the 4 mg/kg dose. Similarly, the area under the plasma concentration vs. time curve, which should be linearly related to dose if cocaine elimination continued to be by a first-order process, was significantly more than doubled when the dose was increased from 2 mg/kg to 4 mg/kg. These data clearly indicate that cocaine elimination in the dog becomes saturable somewhere between 2 mg/kg and 4 mg/kg, that is, between peak plasma cocaine concentrations of approximately 2 mg/L and 3.5 mg/L. At this higher concentration of cocaine, additional increments in cocaine dose would be expected to result in much greater than anticipated increments in plasma concentration. Most studies of the pharmacokinetics of cocaine in humans have reported a linear relationship

between cocaine dose and cocaine plasma concentration, suggesting elimination solely by processes that were independent of cocaine plasma concentration (Wilkinson et al. 1980; Van Dyke et al. 1977); however, Barnett and colleagues (1981) reported two patients who exhibited concentration-dependent elimination kinetics for cocaine. Similarly, concentration-dependent elimination kinetics recently have been reported for cocaine in sheep (Khan et al. 1987).

The paucity of reports of concentration-dependent elimination kinetics for cocaine in human subjects may be the result of prudent selection of cocaine doses in human study subjects to minimize risk in those individuals. At the relatively low doses employed in these studies, the plasma concentration of cocaine may be well below that required to begin to saturate elimination processes, which must occur before concentration-dependent elimination kinetics can be detected. On the other hand, individuals who abuse cocaine frequently administer multiple doses of cocaine at intervals that should result in cocaine plasma concentrations far in excess of those obtained during studies on human volunteers where cocaine doses are controlled by the investigator.

A concern with any drug such as cocaine that is used chronically is whether chronic use leads to changes in the way the drug is handled by the body. To address this question in our animal model, we compared the plasma concentration-time relationships for single 4 mg/kg IV doses of cocaine in dogs that had received no previous cocaine treatment and dogs that had received chronic cocaine treatment for 4 weeks (2 mg/kg twice daily). Figure 2 shows the plasma cocaine concentration-time relationships for these two groups of animals, No significant effect of chronic cocaine treatment was observed in these studies,

TIME-ACTION PROFILE FOR COCAINE IN CONSCIOUS DOGS

Nine chronically instrumented conscious dogs that had been trained to stand quietly in a nylon mesh sling for extended periods were treated with cocaine, 2 mg/kg IV, during continuous recording of blood pressure, heart rate, left circumflex coronary artery blood flow, and cardiac output (aortic blood flow). At times corresponding to those employed in pharmacokinetic studies described above, blood samples were obtained for determination of plasma cocaine concentration. Before cocaine administration and 5, 30, 60, and 120 minutes after cocaine treatment, norepinephrine, 0.25 µg/kg IV, was administered. The duration of the increase in blood pressure was determined after each norepinephrine treatment and was employed as an index of neuronal monoamine transport function. Because neuronal monoamine uptake is the major mechanism by which the action of norepinephrine is terminated (Iversen
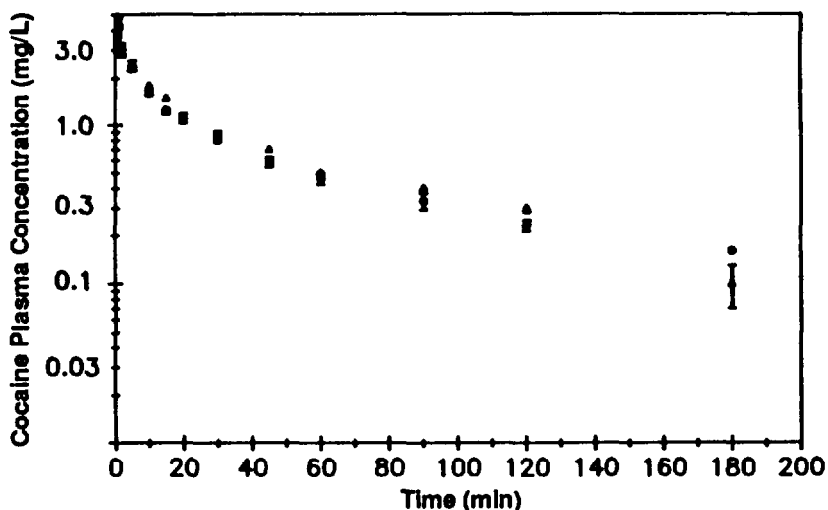
FIGURE 2. *Effect of chronic cocaine treatment on the pharmacokinetics of a single 4 mg/kg IV cocaine dose in chronically instrumented conscious dogs. Plasma cocaine concentrations after the 4 mg/ kg IV bolus of cocaine in 17 naive animals are shown by circles, and those concentrations after the same cocaine dose given to 6 animals on the 28th day of chronic cocaine treatment (2 mg/kg IV twice daiiy) are shown by triangles.*

NOTE: Each point represents the mean±SEM.

1975), inhibition of that transport increases the duration of action of norepinephrine.

Figure 3 illustrates the effects of cocaine on the above cardiovascular parameters. Immediately after administration of cocaine, blood pressure, heart rate, and coronary blood flow are significantly increased. Although the change in heart rate ceases to be significant within 5 minutes after cocaine treatment, blood pressure and coronary blood flow remaln significantly elevated for an hour after this single dose of cocaine. Cardiac output was not changed significantly at any time after cocaine treatment. It is interesting to note that the effects of cocaine on blood pressure roughly parallel plasma cocaine concentration; it is undoubtedly the increase in myocardial oxygen demand imposed by this increase in blood pressure that keeps coronary blood flow elevated along with blood pressure. Of particular interest is the relationship

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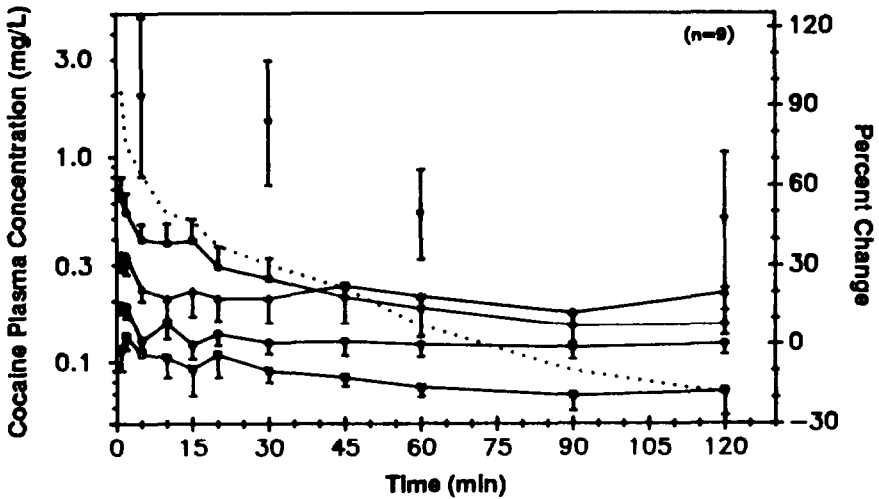
FIGURE 3. *Time-action profile for cocaine after a 2 mg/kg IV dose in chronically instrumented conscious dogs. The dotted curve represents the mean cocaine plasma concentration at each time that is plotted against the left ordinate. Cardiovascular responses to cocaine are plotted as percent change from their pretreatment value against the right ordinate. Mean arterial blood pressure is shown as open circles; heart rate is shown as closed circles; coronary blood flow is shown as closed, upward pointing triangles; cardiac output is shown as open squares; and the duration of the pressor response to norepinephrine, 0.25 mg/kg IV, is shown as the closed, downward pointing triangles.*

NOTE: All points represent the mean±SEM for nine animals.

between the cardiovascular effects of cocaine and its action to inhibit neuronal monoamine transport. Although the cardiovascular changes elicited by the 2 mg/kg dose of cocaine dissipated within 60 to 90 minutes after treatment, neuronal monoamine transport appears to be significantly inhibited 120 minutes after cocaine treatment. This is indicated by our finding that the duration of the pressor response to 0.25 µg/kg of norepinephrine remained significantly longer than that observed before to cocaine treatment.

POTENTIAL IMPLICATIONS OF THESE FINDINGS

A major complicating factor in any attempt to relate cocaine dose to plasma concentration and pharmacologic effect is the flndlng that, at high plasma concentrations, cocaine elimination processes become saturated and its elimination ceases to be a first-order process. Thus, additional dose increments result in much larger than expected increments in plasma concentration. This fact alone may be a major contributing factor to cocaine toxicity among users. When cocaine is used in binges, individual doses that produce modest increments in the plasma cocaine concentration at the beginning of the binge may result in much larger increments at a time when the plasma cocaine concentration is still elevated from previous doses. Thus, if tolerance develops to the central stimulant actions of cocaine, the added dose increments required to maintain the desired high may push the plasma cocaine concentration into the range where its elimination processes become saturated, thus setting the stage for subsequent doses to produce unexpectedly large increments in plasma concentration and lead to toxicity. This is an especially dangerous situation with cocaine, because tolerance probably does not develop to its local anesthetic actions, which are characterized by a concentration-response relationship that is approximately one log unit higher on the concentration axis than the actions of cocaine to inhibit monoamine uptake (Yasuda et al. 1984). it also is not clear whether tolerance develops to the other cardiovascular actions of cocaine. Although tolerance to the increase in heart rate elicited by cocaine has been reported to occur (Fischman et al. 1985; Chow et al. 1985; Ambre et al. 1988), this finding has not been universal (Kumor et al. 1988). No tolerance has been observed to the actions of cocaine that result in increased blood pressure (Kumor et al. 1988; Foltin et al. 1988). Thus, cardiovascular toxicity associated with these adrenerglc actions of cocaine as well as its local anesthetic effects may be a direct result of nonlinear pharmacokinetic behavior at relatively high plasma cocaine concentrations. A major concern is depression of left ventricular function, which is probably the result of the local anesthetic actions of cocaine. Depression of left ventricular function induced by cocaine has been described in isolated hearts (Abel et al. 1989) as well as in anesthetized dogs (Hale et al. 1989). More recently, severe, translent depression of left ventricular function has been demonstrated in conscious dogs that received cocaine, 4 mg/kg IV (Fraker et al. 1990).

Although most studies involving human volunteers report peak plasma cocaine concentrations of less than 1 mg/L, plasma cocaine concentrations determined at autopsy of individuals who died shortly after cocaine use have been much higher. In one recent study, the average cocaine plasma concentration found at autopsy was 6.2 mg/L with a range of 0.1 mg/L to 17 mg/L (Wetli and Wright 1979). Thus, abnormalities in cardiac electrophysiology as well as convulsions

also may result from the local anesthetic actions of cocaine. Any or all these effects associated with extremely high cocaine plasma concentrations may lead to severe morbidity or mortality.

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Acute Tolerance to the Chronotropic Effect of Cocaine in Humans

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INTRODUCTION

Acute tolerance develops to the cardiac chronotropic and subjective effects of cocaine in humans (Chow et al. 1985). In previous studies Ambre and colleagues (1988) showed that tolerance to the chronotroplc effect is incomplete; that is, heart rate decline in the presence of stable plasma cocaine concentrations approaches a plateau that is still higher than the baseline heart rate. They also found that tolerance development can be described as an exponential process with a half-time averaging 28 minutes and that by producing steady-state cocaine concentrations, the extent of tolerance development also can be determined (Ambre et al. 1988). The studies described here aim at full specification of a pharmawkinetic and dynamic model by determining the rate of tolerance loss (return of cocaine responsiveness). A quantitative description of tolerance may help us understand patterns of drug use and provide a basis for developing testable hypotheses about the mechanisms involved in the tolerance process.

METHODS

Acute tolerance to cocaine was induced by two procedures: long- and short-term cocaine exposures. Loading doses followed by steady-state cocaine infusions (long-term exposure) were used, as in our previous studies, to induce a full or maximal state of tolerance. The Identical injectlon or loading dose producing similar peak plasma levels, but with no further infusion (short-term exposure), was given in separate study sessions. Cocaine challenge injections then were given at various Intervals after tolerance induction to determine the rate of tolerance loss.

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Dosage Regimens

Subjects received an intravenous (IV) dose of approximately 100 mg cocaine delivered by a constant-rate syringe pump over 10 minutes (loading dose) followed by an infusion designed to maintain stable plasma concentrations in the range of 1,000 ng/mL. Cocaine infusions were continued for 3 hours to allow full tolerance development (long-term exposure). in other sessions, an identical loading dose was given without the infusion (short-term). A 50 or 100 mg challenge dose was administered over 10 minutes in each subject at an interval of 2, 4, and/or 20 hours from the end of the induction dose, depending on the study. Placebo studies consisted of saline infusion.

Investigational Drug

Vials containing a sterile, nonpyrogenic, 10 mg/mL (33.0 µmol/L as the base) solution of cocaine hydrochloride (HCI) in water was prepared In the Pharmacy Department of Northwestern Memorial Hospital (cocaine HCI USP-flakes, Mallinckrodt Inc., St. Louis, MO). The required infusion solutions were prepared from this solution under sterile conditions by the hospital pharmacy IV admixture service. A portion of each dose solution used in each study was taken for quantitative analysis as described below to verify calculation of the administered dose and demonstrate stability of the dose solution. (Dr. Ambre holds an Investigational New Drug application from the Food and Drug Administration for the cocaine HCI preparation used in these studies.)

Subjects

The subjects were healthy adult male volunteers, 32 to 42 years of age, with a history of IV cocaine use at least once a week for 2 years. Prior cocaine use was determined (Chow et al. 1985; Ambre et al. 1988) to ensure that subjects were experienced, confirmed cocaine users. Each had used a variety of other drugs in the past but was using only alcohol and/or marijuana around the time of the study. Subject characteristics are shown in table 1. Each subject was informed of the nature of the study and its potential hazards and signed a written consent form that had been approved by the Institutional Review Board of Northwestern University. Subjects underwent a medical history evaluation, a complete physical and psychiatric examination, chest x-ray, electrocardiogram (ECG), 25-test blood chemistry panel, urine drug screen, and serum cholinesterase determination, The subjects were clinically well nourished and weighed within 10 percent of ideal weight as estimated for their height and build (Hamwi 1964).

TABLE 1. *Subject   characteristics*

Subject	Age (yr)	Sex	Height (cm)	Weight (kg)
20	32	M	183	77
21	32	M	173	73
22	35	M	165	61
23	42	M	175	77
24	40	M	177	75
25	37	M	183	90
26	41	M	178	84
27	25	M	175	76
28	42	M	175	77
29	27	M	182	86
30	34	M	167	65

Conduct of Study

Subjects were asked to abstain from cocaine use for at least 2 days before the study. On the night before the study they were admitted to the Clinical Research Center at Northwestern University Medical School. Urine was taken for drug screening to detect recent drug use, including thin-layer chromatography by the commercially available TOXI-LAB system (Analytical Systems, Laguna Hills, CA), and a battery of immunoassay tests for drugs of abuse in urine (Abbott TDx tests for cocaine, amphetamines, opioids, phencyciidine, cannabinoids, methaqualone, barbiturates, and benzodiazepines (Abbott Laboratories, North Chicago, IL). The use of a single 15 to 30 mg (49.5 to 99.0 µmol) dose of cocaine can be detected by urine testing for at least 48 hours afterwards (Ambre 1985).

On the study day a heparin lock was placed in a forearm vein for blood sampling, and an IV line was established in the other arm for drug administration. The electrodes for a continuous ECG monitor and a blood pressure cuff were put in place. Subjects were continuously monitored by the physician investigators. The cardiovascular monitoring system is a Marquette Series 7000 ECG Telemetry Unit (Marquette Electronics inc, Milwaukee, WI) that provides real-time display at the bedside of a high-resolution ECG tracing, six-beat average heart rate record, and ST segment position. Subjects were sitting or semireclining in bed throughout the study. The urinary bladder was emptied, and the urine was analyzed again for drugs of abuse. After these

preparations baseline measurements were taken for at least 30 minutes while the subject was undisturbed.

Laboratory Methods

Blood samples were drawn into Vacutainer tubes (Becton-Dickinson, Rutherford, NJ) containing sodium fluoride and potassium oxalate (Chow et al. 1985; Ambre et al. 1988). Plasma was separated immediately and stored at -20°C until analyzed. Plasma cocaine concentrations were determined by gas chromatography/mass spectrometry on a Hewlett-Packard MSD system as described previously (Chow et al. 1985). The method has a detection limit of approximately 5 ng/mL (.016 µmol/L) using a 0.5 mL sample. Sample extracts were injected twice. The coefficient of variation was less than 10 percent for samples between 100 and 5,000 ng/mL (0.33 and 18.5 µmol/L).

Pharmacokinetic Analysis

Kinetic analyses were made with CONSAM 30, an interactive version of the SAAM 27 modeling program (Berman and Weiss 1978) and implemented on a VAX 11/785 computer (Digital Equipment Corporation, Boston, MA) and more recently on an 80388 microcomputer. Curve fitting and data analysis were done on data obtained from an individual subject. Cocaine disposition was appropriately modeled with a one- or two-compartment open system with elimination from the central compartment. Parameter values for this model were adjusted iteratively by the computer program to optimize the fit of the theoretic plasma level curve to the experimental data. The parameter estimates of the disposition model then were used to fit the pharmacodynamic model to the effect data in each subject by nonlinear least squares regression.

RESULTS AND DISCUSSION

Figures 1 and 2 show plasma cocaine levels and chronotropic response in a cocaine infusion experiment. Plasma levels rise during the 10-minute loading injection and then are maintained relatively constant during the infusion. Heart rate reaches a peak at the end of the 10-minute injection, declines toward a plateau, and finally declines with concentrations when the infusion is stopped. The data were evaluated as plots of effect vs. concentration at each plasma sampling point in temporal sequence (phase plots). On an idealized effect-vs-concentration plot, when no distributional lag, tolerance, or other phenomenon distorts the relationship, intensity of effects follow drug concentrations, and rising and falling limbs of the phase plot are superimposed. Acute tolerance development is associated with clockwise opening (hysteresis) of the phase loop.
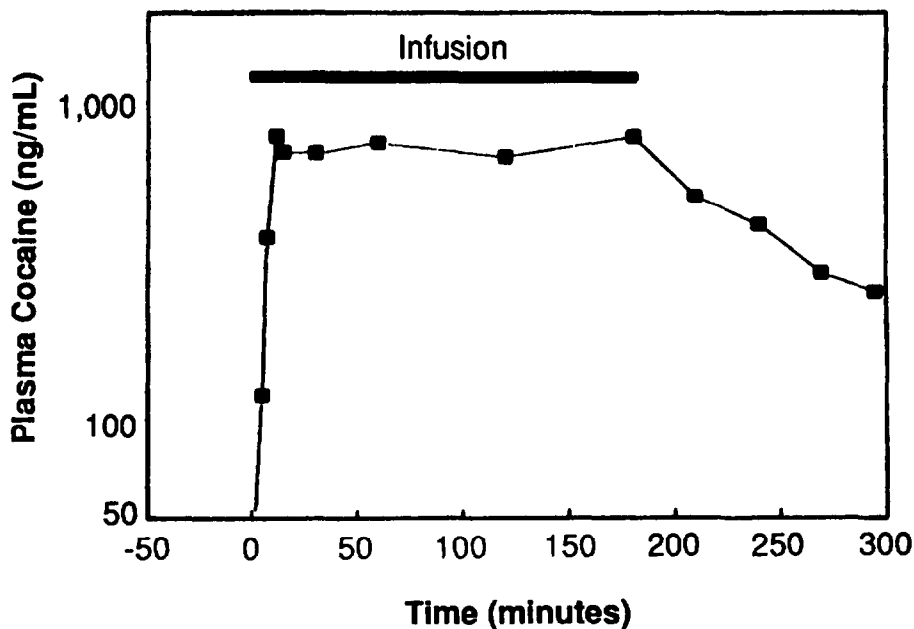
FIGURE 1. *Plasma cocaine concentrations during an infusion of "long-term, cocaine exposure" experiment. Cocaine concentrations rise during the 10-minute constant rate injection and then remain relatively constant during the infusion.*

Figures 3 and 4 show typical phase plots for tolerance-inducing infusions in individual subjects. Heart rate rises sharply during the injection and then begins to fall even as concentrations continue to rise slightly to the appropriate steady state. The vertical segment of the loop represents the infusion period when concentrations are stable but heart rate is falling due to tolerance development. Full tolerance development is indicated by clustering at one coordinate. When the infusion is stopped, heart rate declines with concentration. Data from an early 4-hour challenge dose show that tolerance is still maximal. The plot shows the characteristics of a phase plot without the distortion produced by varying degrees of increasing tolerance. The slope of the initial response is decreased and the limbs of the phase plot are nearly superimposed on each other as well as the declining limb of the induction plot. Response also is shown to be linearly related to concentration in the presence of tolerance (up to 1,200 ng/ml). Data from challenge doses at 20 hours indicate that tolerance has been lost (or sensitivity restored). Phase plots show initial slopes identical to the original response, and some clockwise opening of the loop may be

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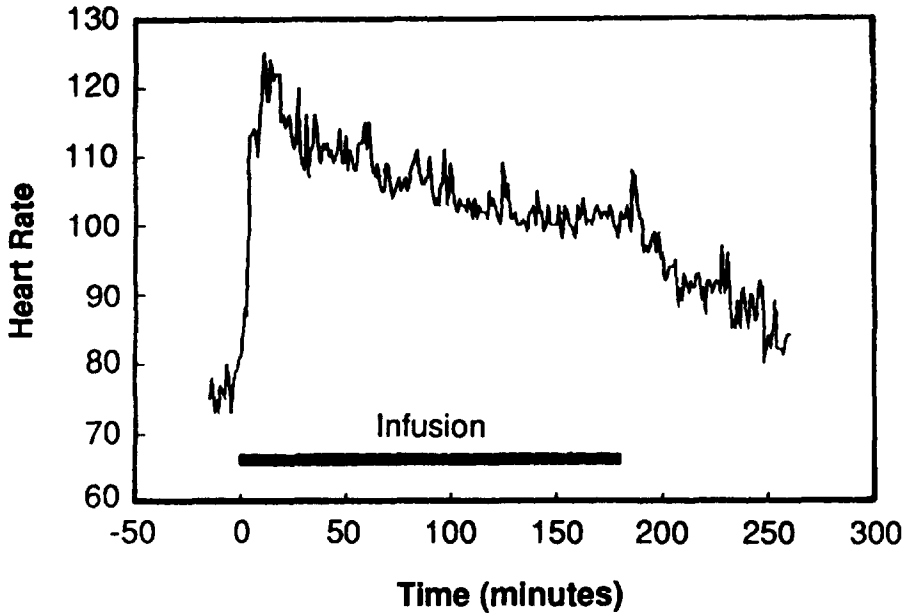
FIGURE 2. *Heart rate (beats per minute) in response to the cocaine infusion described in figure 1. Heart rate reaches a peak at the end of the injection dose and then declines toward a plateau despite the constant level of cocaine. Heart rate then declines with the decline in cocaine concentration when the infusion is stopped.*

evident. Phase plots from all subjects show the identical characteristics. A challenge dose administered when sensitivity is partially restored gives the expected Intermediate result. Results show that maximal tolerance persists at 4 hours after the induction infusion and that tolerance disappears at 20 hours.

The studies at challenge intervals between 4 and 20 hours are still in progress; these results will be required to fully define the rate of tolerance loss. Existing results, however, allow some conclusions about the design of a pharmacodynamic model. In earlier studies we used a model that mainly allowed data description and calculation of the tolerance development rate without mechanistic assumptions. Other investigators have proposed tolerance models. A model used for nicotine but proposed to be generally applicable to other abused drugs is the "antagonist-force" model of Porchet and coworkers (1988). This model postulates the generation of a hypothetical substance (or
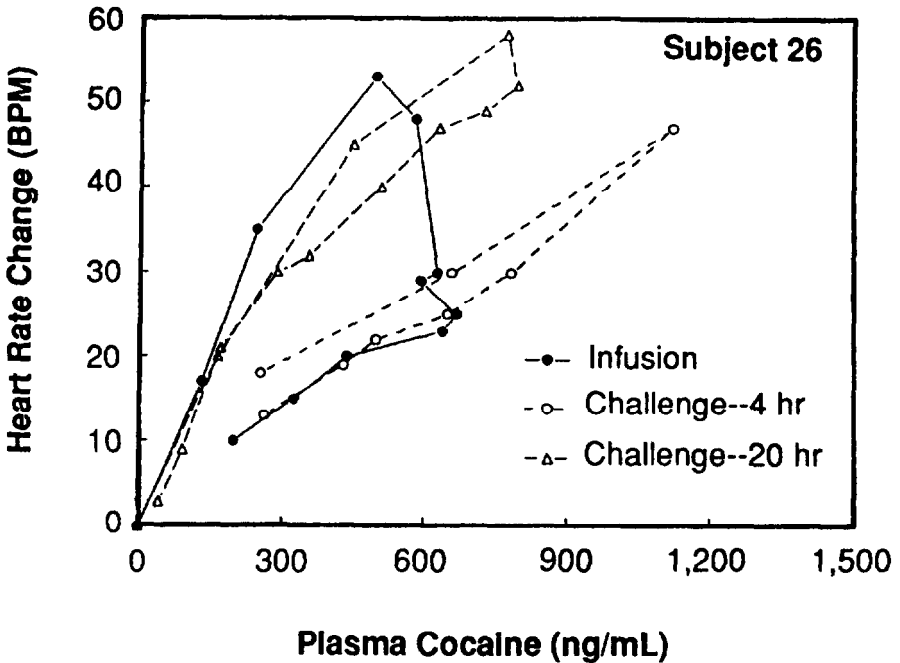
FIGURE 3. *Phase plots of data obtained during a tolerance-inducing (3 hours long) infusion and challenge injections at 4 hours and 20 hours after the end of the infusion. As described in the text, the position and contour of the 4-hour plot indicate that tolerance is still present. Data from the 20-hour challenge dose indicate that tolerance has been lost (or sensitivity restored).*

alternatively a "force") that acts as a noncompetitive antagonist of the chronotropic effects of nicotine. Generation of the antagonist is driven by nicotine concentrations in the central kinetic compartment. A limitation of the model is the requirement that the rates of development and disappearance of tolerance be identical. With a half-time for cocaine acute tolerance development of about 30 minutes, the Porchet model would predict return of full sensitivity within 3 hours (five or six half-lives). Our results show that this clearly is not the case for cocaine, under conditions of our study, simulating typical exposure. Figure 5 shows heart rate data from one subject that were fitted to the Porchet model and then plotted with the model-predicted response to a 4-hour challenge dose.
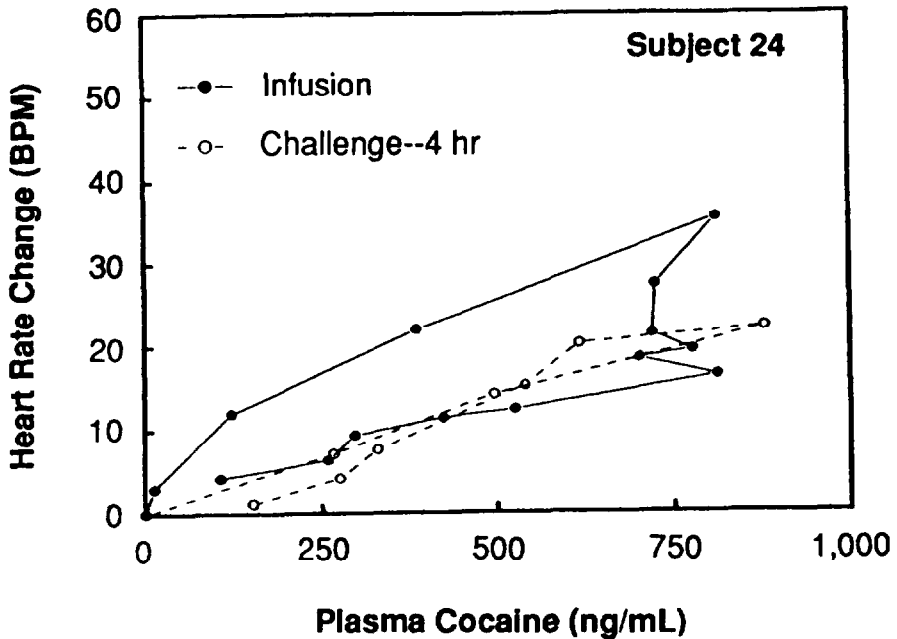
FIGURE 4. *Phase plots of data obtained during a tolerance-inducing infusion and challenge injection at 4 hours after the end of the infusion in subject 24. As described in the text, the position of the 4-hour challenge dose plot indicates the continued presence of tolerance.*

Porchet and colleagues applied their model to data collected during short infusions of nicotine. Data for our short-term cocaine exposure studies are shown in figures 6 and 7. In these studies, 100 mg of cocaine was given by constant injection pump over 10 minutes without further infusion of cocaine. Challenge doses of cocaine (50 to 100 mg) were given over 10 minutes at intervals of 2 and 4 hours. Phase plots of the results (figures 6 and 7) show that tolerance present at 2 hours was reversed at 4 hours. These results suggest that the duration or intensity of cocaine exposure influences the rate of tolerance reversal. Although the rate of tolerance onset is similar after single-injection (short-term) or steady-state infusion (long-term induction) (Ambre et al. 1988), after prolonged exposure the time constant for regression is longer than that for tolerance development.

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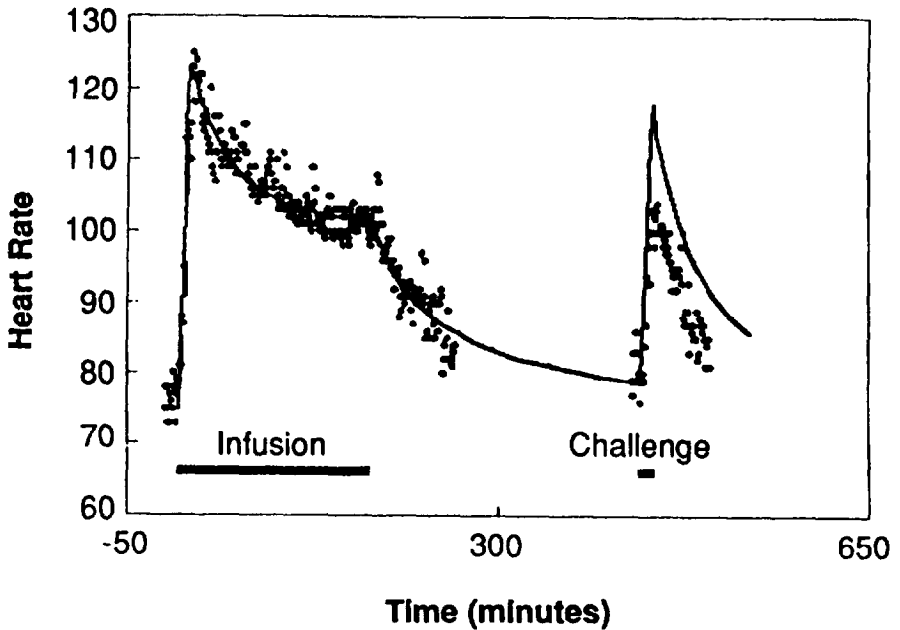
FIGURE 5. *Data from a study involving cocaine injection/infusion followed by a 4-hour challenge dose were fitted to the model of Porchet and colleagues. The closed circles are measured heart rate data, and the solid line indicates model-predicted response. The model clearly predicts the return of initial sensitivity at 4 hours, whereas the actual response is blunted, indicating persistent tolerance.*

Although the Porchet model may be applicable for short-term exposure, it clearly is not adequate to describe our infusion data. The kinetic behavior and magnitude of the tolerance factors for the cardiac chronotropic effect of cocaine suggest a relation to rate constants for events in adrenergic receptor systems (Porchet et al. 1988). According to a common concept of adrenergic receptor systems (Levitzki 1988), agonists interact with beta-adrenergic receptors; adenylate cyclase is activated; and cyclic adenosine monophosphate is produced within the cell. If agonist exposure continues, cellular response decreases (desensitization) as a result of component processes with different time courses: (1) Receptors are uncoupled from adenylate cyclase and/or redistributed from the cell surface (internalized); this process has a short time course and is reversible. (2) The number of (detectable) receptors decreases; this process has a longer time course and is less readily reversible.

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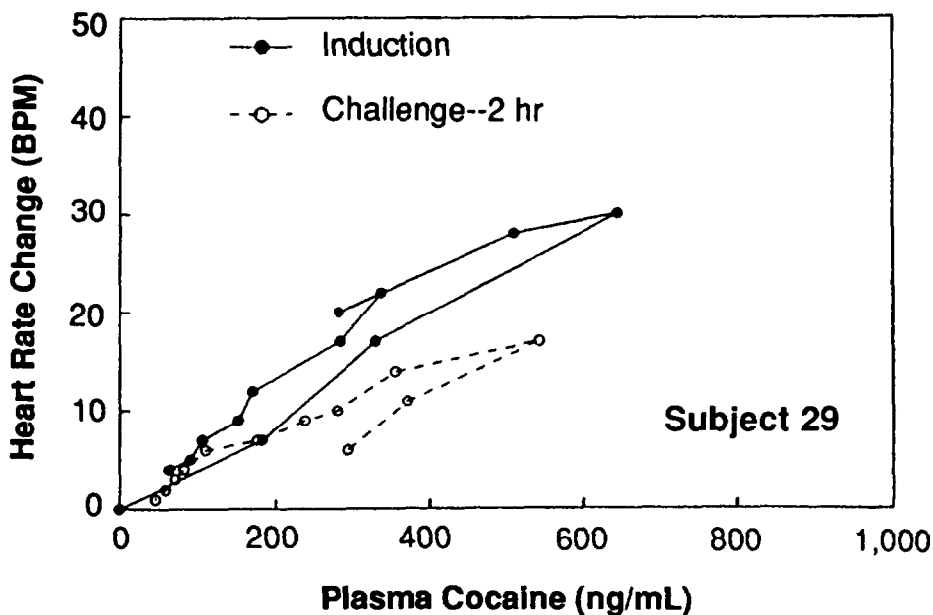
FIGURE 6. *Phase plots of a study in subject 29 involving short-term exposure to cocaine (100 mg of cocaine by constant injection pump over 10 minutes) and a challenge dose 2 hours later. The slope and position of the challenge dose plot indicate the presence of tolerance.*

Our results indicate that tolerance induced by short-term (single injection) cocaine exposure is more rapidly reversible than that induced by more prolonged (cocaine infusion) exposure. Based on the above concept, these results suggest that the apparent tolerance is related to receptor alteration and that rapidly reversible processes (e.g., receptor uncoupling and/or internalization) may predominate in tolerance induced by short-term cocaine exposure, and more slowly reversible processes (e.g., receptor catabolism) may become significant when cocaine exposure is prolonged.

We propose a model of acute tolerance that is based on receptor pharmacology (figure 8) and incorporates rapidly reversible and more slowly reversible processes. Such a model should allow description of cocaine response and tolerance regardless of exposure conditions. In this model, the receptor is synthesized (process 1) and activated but is also subject to inactivation and/or unavailability (reversible process 3) and can be degraded or catabolized (process 2). Computer simulations, using the CONSAM 30 program, of brief
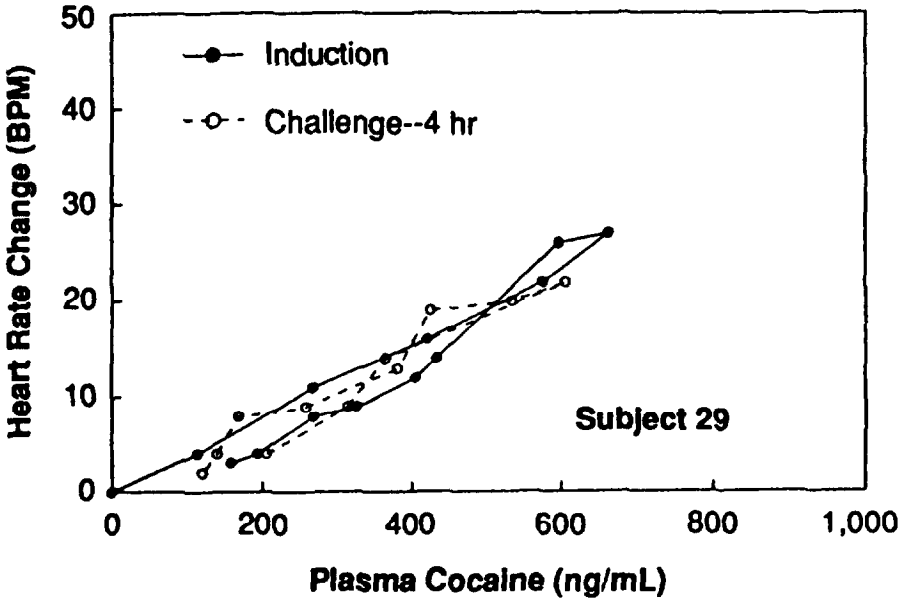
FIGURE 7. *Phase plots of a study in subject 29 involving short-term, exposure to cocaine (100 mg of cocaine by constant infusion pump over 10 minutes) and a challenge dose 4 hours later. The two plots are superimposed, indicating identical responsiveness or loss of tolerance.*

(figure 9) and prolonged (figure 10) exposure to cocaine and subsequent challenge, show their effects on the population of active receptors. Studies of the two exposure conditions, both in terms of *in vivo* responsiveness to beta agonists and *in vitro* receptor status, should allow characterization of the rates of the component processes of the model. Current studies are aiming at verification of this model.
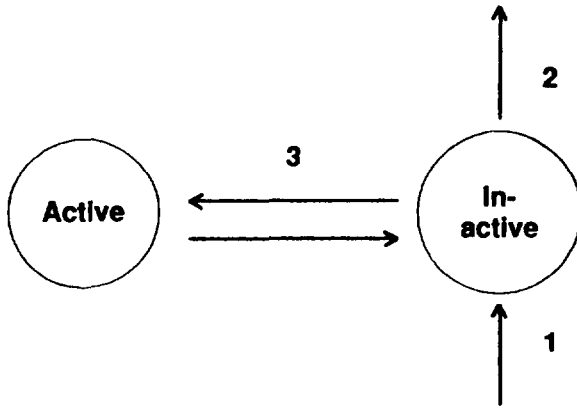
FIGURE 8. *Proposed model of a receptor system subject to tolerance induction. In this model, receptor is synthesized (process 1) and then activated but is a/so subject to inactivation and/or unavailability (reversible process 3). The inactive receptor can be degraded or cataboiized (process 2).*

FIGURE 9. *Computer simulation of the response of the heart rate and proposed receptor system to brief exposure to cocaine and subsequent cocaine challenge. The population of responsive receptors declines with exposure and returns to baseline levels quickly.*
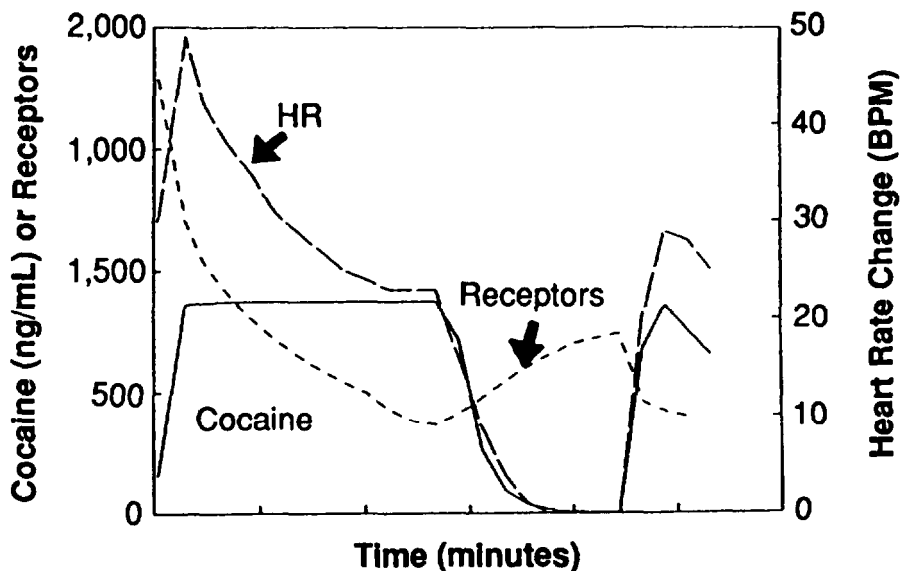
FIGURE 10. *Computer simulation of the response of heart rate and the proposed receptor system to prolonged exposure to cocaine and subsequent cocaine challenge. Responsive receptors decline during exposure and return slowly to baseline levels.*

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Mechanisms of Cardiac and Vascular Responses to Cocaine

Mark M. Knuepfer, Carrie A. Branch, and Vernon W. Fischer

INTRODUCTION

Cocaine is a potent central nervous system (CNS) stimulant and local anesthetic with limited clinical usefulness that has become one of the most widely abused drugs in the United States. Cocaine's high abuse potential is due to its ability to produce euphoria within minutes and central arousal for up to an hour in humans (Fischman et al. 1976; Fischman 1984; Van Dyke et al. 1979). Behavioral models of addictive and hedonistic potential and self-stimulation studies have demonstrated that cocaine also is a powerful reinforcing agent in nonhuman animals (Johanson and Balster 1978; Kornetsky et al. 1979; Wise 1984). in addition to its euphoric effects, cocaine produces cardiovascular responses usually described as modest pressor response and tachycardia in conscious animals and humans. Although the mechanisms eliciting these cardiovascular responses are as yet unclear, the responses presumably are due to direct potentiation of catecholaminergic activity and indirect (CNS-mediated) sympathoexcltation. Within the past decade, there has been a dramatic increase in the number of clinical reports associating cardiac abnormalities and cocaine use. Life-threatening and sometimes fatal cardiac toxicity by unknown mechanisms reportedly has occurred after inhalation or infusion of cocaine in otherwise asymptomatic patients. Our studies have attempted to identify the mechanisms whereby cocaine produces its vascular and cardiac effects in conscious animals, with particular interest in studying cardiotoxic reactions and elucidating appropriate therapeutic interventions for these responses.

EFFECTS OF COCAINE ON HEMODYNAMICS

Several studies on the effects of cocaine have examined the physiological effects on arterial pressure (AP) and heart rate (HR) and the behavioral effects in conscious animals; related studies also have been performed in humans (Fischman et al. 1976; Fischman 1984; Van Dyke et al. 1979; Chow et al. 1985; Resnick et al. 1977). Studies in anesthetized animals have examined in detail

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the effects on adrenergic systems (Gunne and Jonsson 1964; Hadfield et al. 1980; Masuda and Levy 1984; Tariuo and Rubio 1985); however, recent studies show that anesthesia alters cardiovascular responses to cocaine (Wilkerson 1988; Knuepfer et al. 1987). Little is known concerning the effects of cocaine on the heart and vasculature in conscious animals.

Several observations have been made while examining cocaine's actions on cells and tissues. Cocaine is a competitive antagonist for neuronal uptake of catecholamines *via* the energy-dependent, uptake I pump (Gilman et al. 1985; Wise 1984); it also binds to other cellular sites (Kuhar et al. 1988; Reith 1988). Studies performed in vitro have demonstrated that cocaine causes increases in norepinephrine release and contractility of smooth muscle in response to electrical stimulation (Langer and Enero 1974) or to exogenous sympathomimetics (Kalsner and Nickerson 1969). Chronotropic and lnotropic responses to sympathetic nerve stimulation were potentiated by cocaine in isolated heart muscle (McCulloch et al. 1974) but not in intact, anesthetized animals (Masuda and Levy 1984; Inoue and Zipes 1988). However, recently, Gillis and coworkers (this volume) observed potentiated responses to sympathetic nerve stimulation when low doses of cocaine were injected into anesthetized cats. Exogenous sympathomimetics elicit positive chronotropic and inotropic effects on the myocardium and a pressor response that is potentiated by cocaine in anesthetized dogs (Levy and Blattberg 1978; lnoue and Zipes 1988). Cocaine caused a decrease In the positive chronotropic effect of norepinephrine in excised atria that was interpreted to be due to a rapidly induced, lowered sensitivity of beta-adrenergic receptors to sympathomimetics (Tarizzo and Rubio 1985). Data describing the cardiovascular effects of cocaine in conscious animals are limited almost entirely to analyses of AP and HR responses. Our studies have examined regional vascular and cardiac responses to cocaine to describe more completely the mechanisms by which cocaine produces its complex effects and to determine how drugs antagonize specific responses to cocaine.

The regional vascular effects of acute cocaine administration were examined in unanesthetized, freely moving rats, which were surgically prepared using sterile technique 3 to 5 days in advance. Rats were Instrumented for measurement of AP, HR, and regional vascular blood flows. Miniaturized pulsed Doppler flow probes were implanted on the abdominal aorta and the superior mesenteric artery for estimates of hindquarters (skeletal muscle) and mesenteric (visceral) blood flows, as described by Haywood and coworkers (1981).

Before drug administration, mean AP was 111 +/-3 mmHg and HR was 470+/-1 3 beats/min (n=19). Responses to cocaine (0.25-10 mg/kg IV[intravenous]) were variable, but dose-related increases in AP and mesenteric vascular resistance

and decreases in HR and, occasionally, vascular resistance in hindquarters were observed (data not shown). Administration of 5 mg/kg cocaine produced changes as shown in figure 1. The AP response is characterized by an acute pressor response lasting less than 1 minute, hereafter referred to as the peak response, followed by a sustained modest pressor response. Although the data confirm these peak responses, as described in previous studies, they are short lived. These data also demonstrate that cocaine does not produce a generalized vasoconstrlctor response, but it does elicit a response characterized by visceral vasoconstrictlon and, in some cases, skeletal muscle vasodilation. Occasionally, there was a modest, Initial increase in HR occurring within the first 30 seconds after cocaine administration that preceded a profound, long-lasting bradycardia. These responses were reproducible when rats were given cocaine twice daily for up to 2 weeks. Behaviorally, rats appeared aroused and often had an apparent increase in locomotor activity, repetitive head movements, and, in a few cases at high doses, tonic-clonic seizure activity. Data from rats demonstrating seizure activity were not included In these analyses.

MECHANISMS MEDIATING CARDIOVASCULAR EFFECTS OF COCAINE

These studies examined several mechanisms by which cocaine may produce its cardiovascular effects. Because cocaine has a local anesthetic action that may contribute to its cardiovascular effects, the cardiovascular effects of procaine were compared with those of cocaine in conscious rats (figure 2). Due to the difference in magnitude or direction of the peak and sustained responses, these were analyzed independently using a paired Student's t-test and a two-way, split-plot, two-way analysis of variance, respectively. Procaine (10 mg/kg) produced a significantly smaller peak pressor response (PEAK) and a somewhat smaller sustained pressor response than that of cocaine (figure 2, panel A). The reduced pressor response apparently was dependent on a significantly smaller mesenteric vascoconstrictor response. A tachycardiac response after procaine, instead of a bradycardiac response, contributed to the pressor response. Equivalent doses of procaine have been reported to partially mimic the cardiovascular effects of cocaine in rats (Pitts et al. 1987). Because cocaine is at least twice as potent in blocking neuronal conduction (Skou 1954), it is likely that the higher dose of procaine more aptly mimics the local anesthetic effects of cocaine. These results suggest that cocaine's vascular effects are not likely to be mediated by its local anesthetic actions.

Because it generally is thought that CNS-mediated sympathoexcitation and baroreflex-mediated vagal activity contribute to the responses elicited by cocaine (Gilman et al. 1985; Wilkerson 1988), the roles of the sympathetic and parasympathetic nervous systems were investigated. Ganglionic blockade
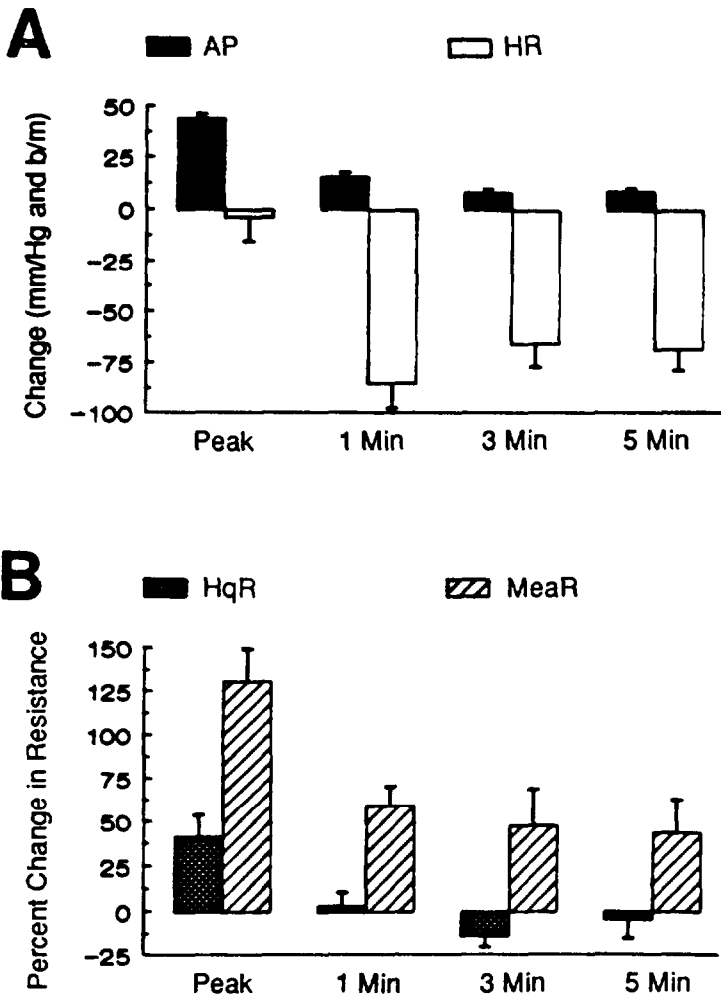
FIGURE 1. *Effects of cocaine (5 mg/kg IV) on arterial pressure (AP in mmHg) and heart rate (HR in beats/min) in panel A and on hindquarters and mesenteric vascular resistance (HqR and MesR, respectively) in panel B. Changes and percent changes are shown at the time of the PEAK and at 1, 3, and 5 minutes after cocaine administration. Note the large magnitude of the peak responses in comparison to the modest, sustained responses.*
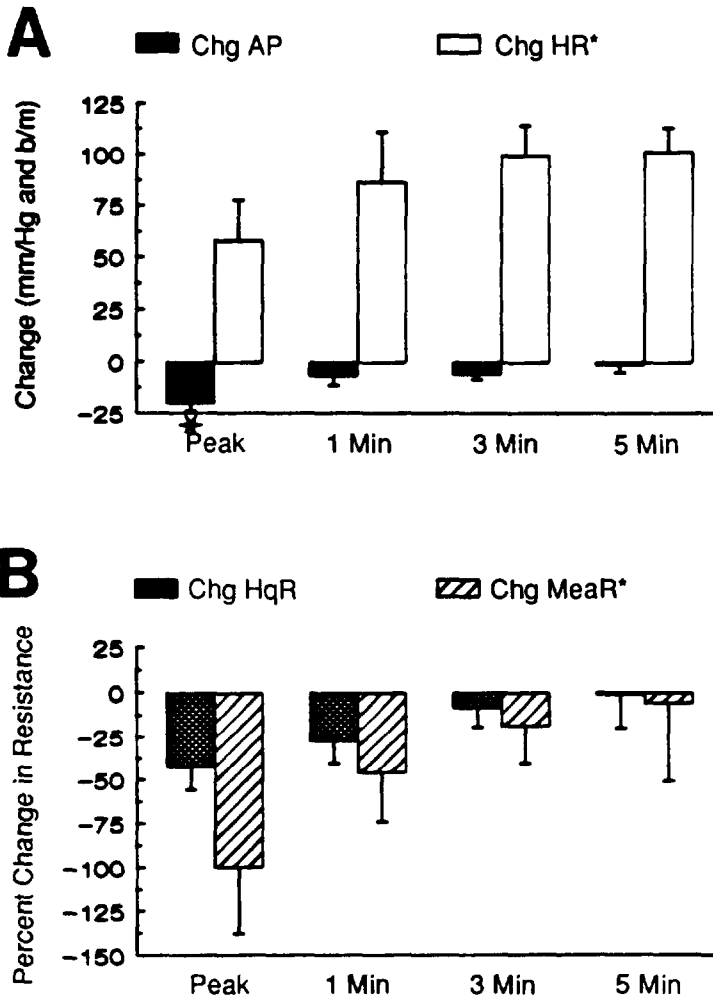
FIGURE 2. *A comparison of the effects of cocaine (5 mg/kg IV) with those of procaine (10 mg/kg IV). The differences in each response (denoted as in figure 1) were obtained by subtracting changes elicited by procaine from those elicited by cocaine at different periods after drug administration. Responses were analyzed using a split-plot, two-way analysis of variance. Peak responses also were analyzed independently using Student's t-test. Significant differences (p<0.05) are denoted by an asterisk for analysis of variance and a star for Student's t-test.*

using pentolinium (7.5 mg/kg) elicited falls in AP, HR, and regional vascular resistances (table 1). Subsequent cocaine administration (5 mg/kg IV) demonstrated an attenuated PEAK with no effect on the sustained pressor response (figure 3, panel A). The reduced PEAK was coincident with a reduction in mesenteric vasoconstriction (figure 3, panel B). Therefore, the early initial pressor response may be due to a CNS-mediated sympatho-excitation, but the sustained responses (after 30 seconds) appear to be mediated primarily by peripheral actions of cocaine. These data are consistent with those of Wilkerson (1988), who reported an attenuation of the PEAK after ganglionic blockade in conscious dogs, although it is not clear from this report whether the sustained modest pressor response also was attenuated in dogs.

The bradycardiac response to cocaine was blocked by pentolinium without affecting the regional vascular responses (figure 3, panel A). Similarly, peripheral muscarinic receptor blockade with methylatropine (0.5-1 mg/kg) resulted In an Increase in HR. Subsequent administration of cocaine (5 mg/kg IV) revealed a significant decrease in the bradycardiac response (data not shown). These results suggest that the bradycardiac response is dependent on an increase in vagal tone, presumably due to activation of the baroreceptors.

TABLE 1. *Effects of receptor antagonists on cardiovascular parameters*

	Pentolinium	Propranolol
Arterial pressure (mmHg)	-36 ± 2*	3 ± 1
Heart rate (beats/min)	-83 ± 11*	-65 ± 8*
Hindquarter resistance (percent change)	-28 ± 6*	6 ± 3
Mesenteric resistance (percent change)	-17 ± 4*	8 ± 3*

*Significantly different from control ($p<0.05$) using paired Student's t-test

Although nonspecific beta-adrenergic receptor antagonists, such as propranolol, have been proposed by one group of investigators to be effective in the treatment of cocaine-induced cardiotoxic responses (Rappolt et al. 1977, 1979; Gay 1982) few data are available suggesting that such effects are pharmacologically indicated. The effects of propranoiol on hemodynamic responses to cocaine were examined. Propranolol (1 mg/kg) alone produced a significant decrease in HR and a slight increase in mesenteric vascular
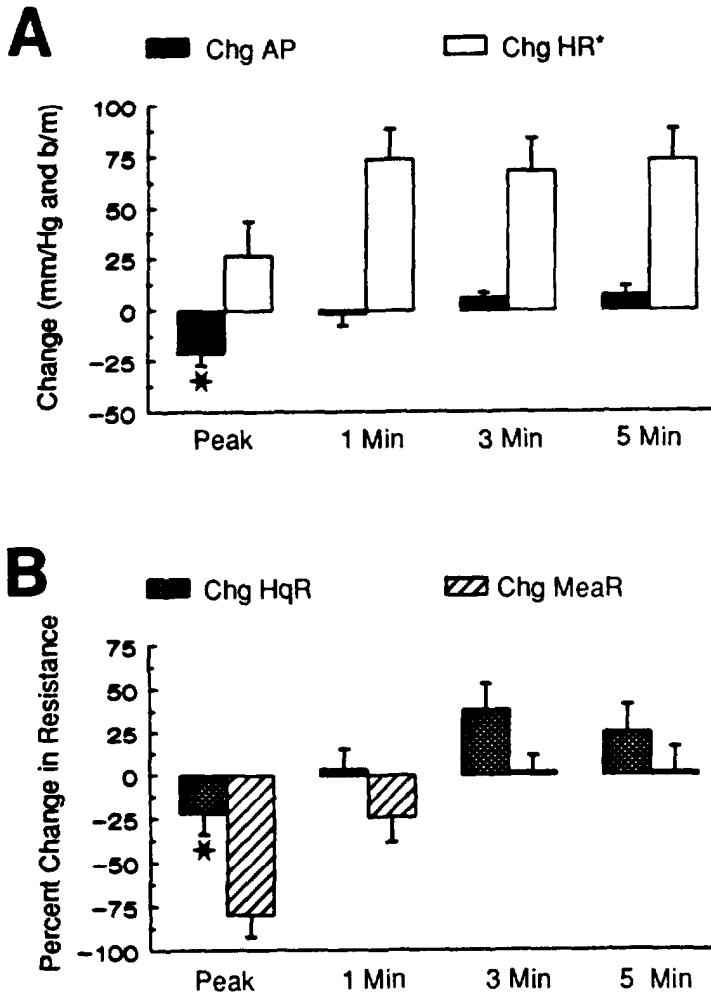
FIGURE 3. *The effects of ganglionic blockade with pentolinium (7.5 mg/kg IV) on responses to cocaine (5 mg/kg IV are depicted. Pentolinium was administered 10 minutes before cocaine and compared with responses obtained with cocaine alone. The changes in responses caused by gang/ionic blockade are shown and analyzed as described in figure 2.*

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resistance without affecting other parameters (table 1). Pressor responses to cocaine were exacerbated due to a reversal of the vascular response In hindquarters from a vasodiiation to a vasoconstrlction (figure 4). Interestingly, selective beta,-adrenergic receptor blockade with metoprolol had no effect on responses to cocaine (data not shown). Therefore, $beta_2$-adrenergic receptors appear to have a beneficial effect on cocaine intoxication, at least with respect to attenuating the pressor responses and, presumably, the increase in myocardial oxygen demand. This observation may raise concerns with regard to the rationale for using propranolol clinically in cocaine-related cardiotoxicity. Reports have shown that propranolol does not protect dogs or monkeys from the lethal effects of cocaine (Catravas and Waters 1981; Guinn et al. 1980), and at least two clinical reports also have suggested that propranolol may be detrimental due to unopposed alpha-adrenergic-mediated vasoconstriction (Ramoska and Sacchetti 1985; Olson et al. 1983).

CARDIOTOXIC EFFECTS OF COCAINE-FUNCTIONAL STUDIES

There are a growing number of clinical reports relating cocaine use to the occurrence of serious and sometimes fatal ischemic heart disease (Isner et al. 1986; Kossowsky and Lyon 1984; Mathias 1986; Pasterneck et al. 1985; Schachne et al. 1984; Simpson and Edwards 1986; Tazelaar et al. 1987; Wetli and Wright 1979: Zimmerman et al. 1987). Typically, patients had symptoms of angina pectoris or ventricular fibrillation within an hour after intranasal or IV cocaine administration, and electrocardiograms and/or serum creatine phosphokinase levels indicated substantial to severe myocardiai infarction. In 6 of 14 patients who underwent angiography, normal coronary arteries were observed. Many patients had coronary obstructive disease, usually without any other signs of atherosclerosis or occlusive disease and with minimal risk factors, Three hypotheses have been used to describe the transient myocardial ischemia observed after cocaine use: (1) local occlusive spasm of a major coronary artery with resultant transmural ischemia leading to infarction (Kossowsky and Lyon 1984; Pasternack et al. 1985; Schachne et al. 1984; Zimmerman et al. 1987); (2) induction of platelet aggregation by alpha-adrenergic stimulation leading to thrombotic occlusion of a coronary artery (Isner et al. 1986; Simpson and Edwards 1986); and/or (3) extreme elevations in HR and AP resulting in subendocardial ischemia due to excessive myocardial oxygen demand (Pasterneck et al. 1985). Our studies were undertaken in a rat model to elucidate the mechanisms by which cocaine induces cardiomyopathies as the data from these studies might provide an insight for potential therapeutic intervention and to examine the rationale for the commonly prescribed treatment of cocaine-related cardiotoxlcity with propranolol (Rappolt et al. 1977; Rappolt et al. 1979; Gay 1982).
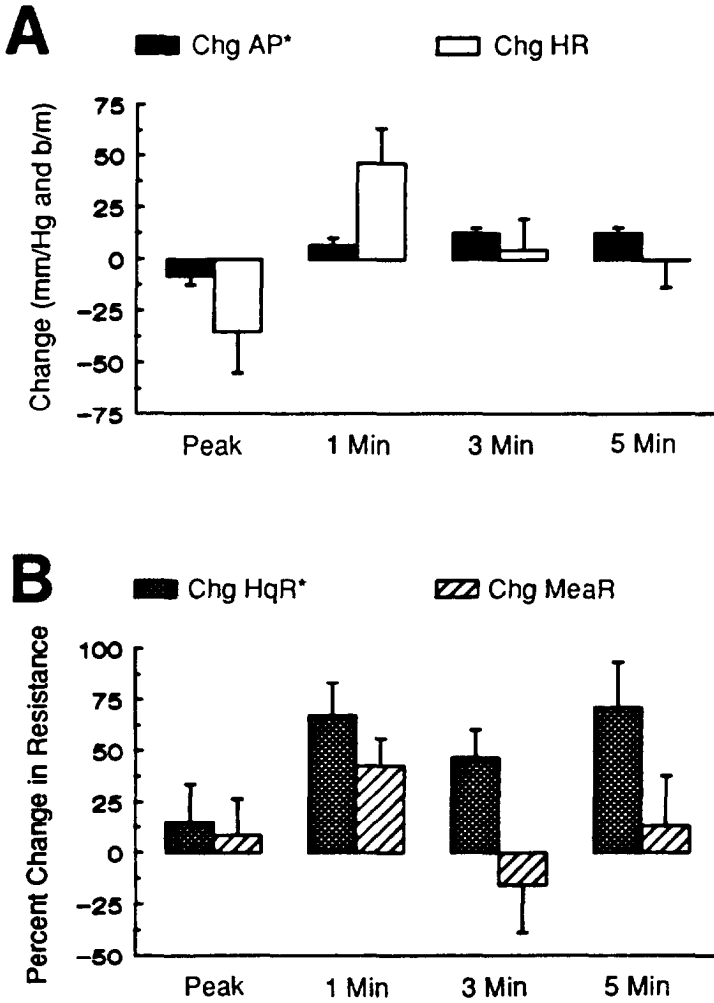
FIGURE 4. *The effects of beta-adrenergic receptor blockade with propranolol (1 mg/kg IV on responses to cocaine (5 mg/kg IV) are depicted as described in figure 3 and analyzed as described in figure 2.*
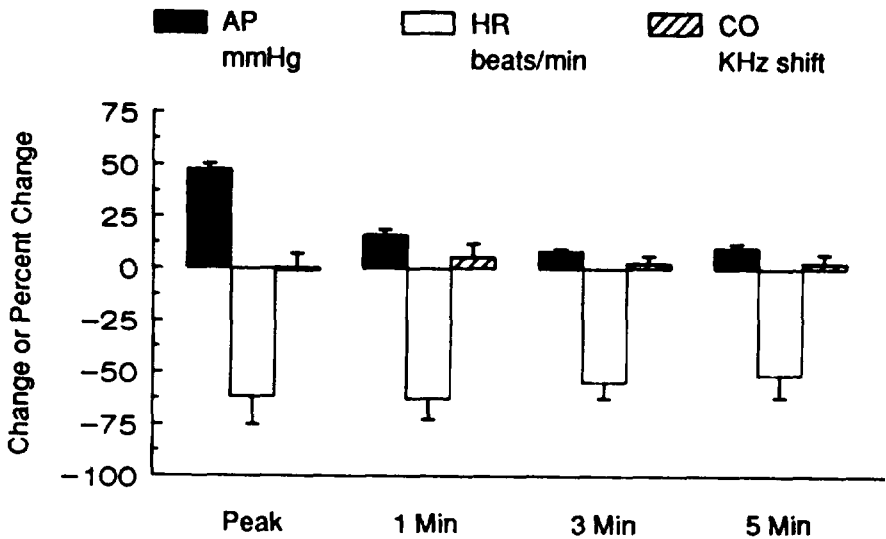
FIGURE 5. *Effects of cocaine (5 mg/kg IV on AP, HR, and CO at times after cocaine administration described in figure 1. Note the minimal effect of cocaine on CO.*

Using functional and anatomical techniques, the effects of cocaine on the myocardium in conscious, freely moving rats were examined. Rats were instrumented for AP and HR determination and for continuous measurement of ascending aortic blood flow as a measure of cardiac output (CO) using miniaturized pulsed Doppler flow probes as described by Werber and coworkers (1984). Estimates of total peripheral resistance and stroke volume also were made using these variables. After 5 to 7 days for recovery, rats were treated with cocaine (0.5-5 mg/kg IV) for analysis of the cardiac and vascular components of cocaine's action in conscious, freely moving rats. Cocaine elicited increases in total peripheral resistance with little effect on stroke volume (figure 5). Therefore, the data suggest that cocaine-induced cardiomyopathies in rats are not dependent on a sustained increase in afterload or direct cardiac stimulation but may be dependent on local ischemia resulting from vasospasm or thrombotic occlusion. These studies supported the observations described earlier with beta-adrenerglc antagonists, suggesting that cocaine's stimulatory effects on the heart may be minimal. Indeed, recent observations in humans also have suggested that propranolol may exacerbate cocaine-related cardiac abnormalities (Ramoska and Sacchetti 1985; Olson et al. 1983).

During the analysis of these data, it became apparent that changes In CO elicited by cocaine were not similar in all rats. In approximately two-thirds of the rats, cocaine produced little or no change in CO, whereas in one-third of the animals, a profound, acute drop in cardiac output of varying magnitude (20 to 80 percent) was observed (figure 6). These functional deficits in myocardial
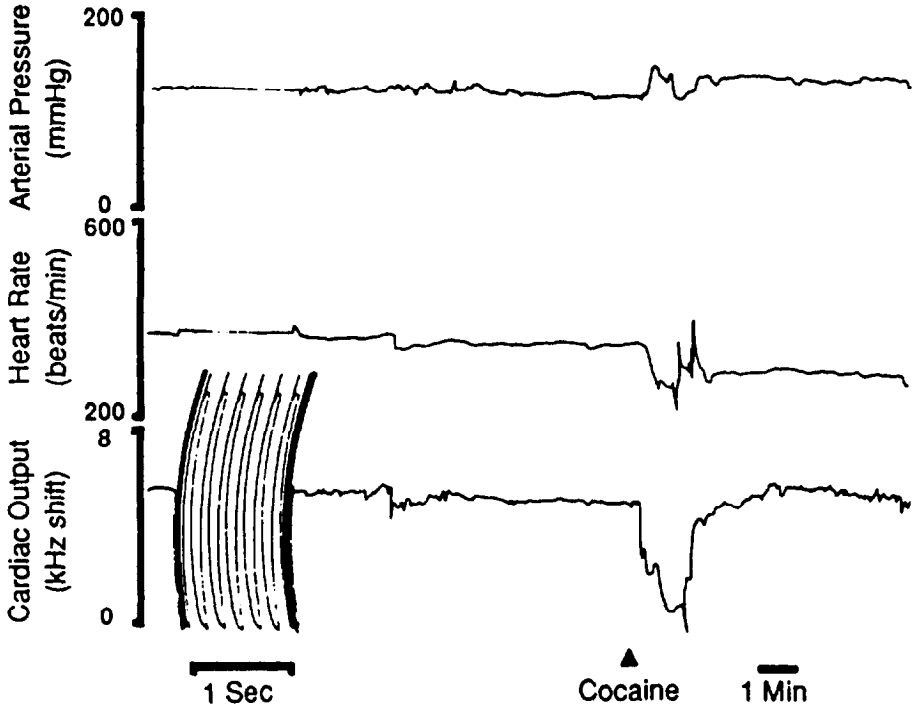
FIGURE 6. *An example of responses to cocaine (5 mg/kg IV) in a rat that apparently experienced a cardiotoxic response. The AP and HR responses did not appear different than responses observed in other rats (see mean responses in figures 1 and 5) yet were severely compromised. This response followed pretreatment with propranolol (1 mg/kg) but also was observed without any pretreatment. The time scale, shown at bottom, includes a period showing phasic blood flow in the ascending aorta without electronic filtering.*

activity were observed either relatively consistently in Individual rats or not at all, despite the total number of trials with cocaine. Acute impairment of cardiac function was observed In rats with normal pressor and bradycardiac responses to cocaine, indicating that earlier studies measuring only AP and HR probably missed identifying this higher sensitivity. Again, propranoloi pretreatment did not prevent this cardiotoxic response in "responding" rats; yet, prazosin appeared to prevent the toxicity (data not shown). Furthermore, significant elevations in CO did not precede the profound fall, further supporting the findings described herein that cocaine does not elicit cardiac stimulation either directly or indirectly.

CARDIOTOXIC EFFECTS OF COCAINE-ANATOMICAL STUDIES

Two studies have reported the presence of contraction bands in myocardiai tissue on postmortem analyses in cocaine users, a cardinal sign of myocardiai dysfunction (Simpson and Edwards 1986; Tazelaar et al. 1987). These observations are described further in this volume by Drs. Billingham and Virmani. Recently, the appearance of myocardial contraction bands has been considered as an anatomical basis for arrhythmias associated with cocaine administration (Karch and Billingham 1988). It also has been suggested that their presence, although not conclusive, may provide evidence for the cause of death in cases of cocaine abuse without other demonstrable abnormalities (Simpson and Edwards 1986; Tazelaar et al. 1987).

Limited experiments have been performed that attempt to correlate functional deficits in the myocardlum elicited by cocaine administration with structural alterations of myocardiai tissue. At the completion of experiments measuring cardiac function, 14 rats were sacrificed, and their hearts were removed rapidly. One-millimeter cubes of ventricular myocardiai tissue were placed immediately in 3 percent giutaraidehyde in Sorensen's phosphate buffer at pH 7.2, postfixed with osmium tetroxide (1 percent at pH 7.2), and processed routinely for viewing in a JEOL 100 CX electron microscope. For light microscopic orientation, plastic embedded sections, 1 µm thick, were stained with alkaline methylene blue. The remainder of the heart was fixed In 10 percent neutral, buffered formalin and was dehydrated, embedded in paraffin, and examined by light microscopy. Myocardiai tissues from similarly instrumented rats that did not receive cocaine were examined in a similar manner. The myocardiai tissues were examined by an investigator who was unaware of the functional data obtained (double blind).

Examination of the myocardiai tissues revealed specific alterations that appeared to be related to the functional sensitivity to cocaine as well as changes that were present in all rats regardless of their exposure and

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responsiveness to cocaine. Figure 7 is an electron micrograph of cardiac tissue from the rat whose cardiovascular responses to cocaine are shown in figure 6. Figure 8 is a micrograph from another rat with a similar cardiotoxic reaction to cocaine. These micrographs demonstrate a marked translucency of mitochondrial matrices with disruption of the cristae, hypercontraction of myofibrils, and subsarcolemmal and intramyocytic dilations of the sarcoplasmic reticulum. Minimal, highly focal changes were seen in myocardiai tissue of control and "nonresponding" rats. These included large numbers of pinocytotic vesicles within endothelial ceils, patches of interstitial fibrosis, and widening of intermyocytic spaces. Although these changes may be a consequence of the surgical and experimental interventions, they appeared to be exacerbated in "responding" rats. Interestingly, specific alterations in the myocardium using the protocol were not identifiable at the light microscopic level with the exception of an epicarditis, which most likely resulted from damage and irritation of this tissue associated with the operative procedures and foci of fibrosis. Although additional detailed studies of the correlation between functional and anatomical changes induced by cocaine are necessary to verify these observations, the changes observed in these preliminary studies suggest that cocaine may cause substantial cardiac damage in a subset of the population, even with limited exposure.

CONCLUSIONS

Our data demonstrate that, in the majority of rats, cocaine produces a dose-dependent, short-lasting pressor response, followed by a modest pressor response dependent on an increase in total peripheral resistance with little effect on stroke volume or CO. The increase in peripheral resistance was due in part to mesenteric vasoconstrictlon and counteracted in part by a modest vasodiiation in the vascular bed of the hindquarters. The vasoconstrictor responses were due to alpha,-adrenergic receptor activation, whereas the vasodiiator responses appeared to be due to activation of beta$_2$-adrenergic receptors. The authors suggest that these responses are mediated indirectly by cocaine's ability to potentiate the effects of catechoiamines in plasma and at the neuroeffector junction. We found no evidence for a central component of cocaine's vasoconstrictor effects. Approximately one-third of the rats appeared to have moderately to severely acute decrements in CO after cocaine administration. This higher sensitivity to cocaine's functional cardiotoxic effects was mirrored in more severe alterations in myocardiai cells, including an apparently greater incidence of contraction bands, mitochondriai and myofibrillar disruption, and foci of fibrosis in "sensitive" rats. The functional deficits In the myocardiai responses could not be prevented with propranoloi, but they may be attenuated by prazosin.

FIGURE 7. *An electron micrograph from the myocardium of a rat after cocaine administration (physiologic data shown in figure 6). Note the hypercon tracted, electron-dense myocardiocyte (top half of picture) in contrast to the electron-lucent cell in the lower half. The latter cell shows widely dilated sarcoplasmic reticular profiles and foci of interfibrillar and intrafibrillar lucency. In addition, a few mitochondria exhibit loss of matrical density. Original magnification x 12,500.*

FIGURE 8. *An electron micrograph demonstrating changes in myocardiocytes from another rat with a cardiotoxic response to cocaine. Note focal electron-lucency within myocyte in the center of the picture with derangement and loss of contractile elements, In addition, the pericapillary space is filled with fluid resembling that present within the capillary lumen. A profusion of transcytotic vesicles also can be seen in the capillary endothelium. Original magnification x 5,000.*

Many studies have described the local anesthetic actions, the potentiation of central and peripheral monoamine action, and the behavioral stimulation elicited by cocaine. The studies described here and in this volume present the first comprehensive description of the effects of cocaine on the cardiovascular system. These observations are important in understanding the mechanisms of cocaine's actions and In treating deleterious effects of cocaine in humans.

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Cardiovascular Effects of Cocaine in Squirrel Monkeys

Sriharl R. Tella, Charles W. Schindler, and Steven R. Goldberg

INTRODUCTION

The latest National Institute on Drug Abuse surveys indicate that toxic consequences of cocaine abuse are on the rise. Although occasional use of cocaine may be down, long-term use and Its consequences are up, as Indicated by hospital emergency room admissions. However, the precise mechanism of cocaine toxicity is not well understood.

Cocaine is a central nervous system (CNS) stimulant with local anesthetic and sympathomimetic properties. The serious toxic manifestations reported appear to be of central and cardiovascular origin. Recent clinical reports show the potential of cocaine to cause cardiovascular complications such as angina and acute myocardial ischemia resulting in infarction, cardiac arrhythmias, myocarditis, and dilated cardiomyopathy (Duke 1986; Mathlas 1986; Frishman et al. 1989). Among the cocaine-associated cardiovascular complications, acute myocardial infarction can lead to sudden death due to cardiac pump failure or accompanying cardiac arrhythmias. The pharmacological basis of cocaine-related myocardial infarction is uncertain. Various possibilities Include coronary artery spasm, thrombosis, or an increased workload on the myocardium due to the pressor and tachycardiac effects of cocaine (Frishman et al. 1989). In subjects with underlying coronary artery disease, the simultaneous increase in blood pressure (BP) and heart rate (HR) can evoke myocardial ischemla via an increase in myocardial oxygen demand. Persistent increases in BP and HR also can lead to other serious clinical conditions such as pulmonary and cerebral edema and hemorrhage. Therefore, understanding the nature and mechanism of the pressor and tachycardiac effects of cocaine is clinically Important.

Cocaine is thought to produce Its excitatory effects on the cardiovascular system by inhibiting the neuronal reuptake of norepinephrine at sympathetic nerve terminals (MacMillan 1959; Whitby et al. 1960; Muscholl 1961; Matsuda et al. 1980). However, there Is an efficient negative feedback mechanism

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regulating synaptic *or* junctional levels of norepinephrine within the physiological range (Langer 1981; Starke 1987) that makes it difficult to implicate this property of cocaine in its prolonged cardiovascular effects. Furthermore, other uptake inhibitors such as desipramine do not produce cardiovascular responses comparable to those produced by cocaine (Wilkerson 1978). These findings suggest that, in addition to the inhibition of neuronal reuptake of norepinephrlne, other mechanisms also might be operative in eliciting the prolonged pressor and tachycardiac effects of cocaine. Possible mechanisms include central nervous stimulation leading to an increase in peripheral sympathetic tone (Wilkerson 1988) and/or direct action of cocaine on sympathetic nerve terminals causing the release of norepinephrine (Campos et al. 1963; Maengwyn-Davies and Koppanyi 1966; Trendelenburg 1968; Tessel et al. 1978; Palaty 1988).

Most earlier studies have examined the cardiovascular effects of cocaine In anesthetized animals, ignoring the possible mediation of its intense central actions. To examine the importance of some of the above-mentioned mechanisms, this chapter reviews the cardiovascular effects of cocaine in intact conscious squirrel monkeys and in monkeys under halothane or pentobarbital anesthesia.

GENERAL METHODS

The monkeys were surgically prepared with chronic catheters In the abdominal aorta and in the right atrium. Catheters were implanted under halothane anesthesia via the right internal iliac artery and vein and were used for recording BP and for intravenous (IV) injection of drugs. The free ends of the catheters were passed under the skin to the monkey's back where they exited the skin.   Catheters were filled with heparinized saline (20 units/mL) and closed with stainless steel obturators. Animals wore nylon mesh jackets to protect the catheters. A postoperative recovery period of 2 to 3 weeks was allowed before any experimentation.

During experimental sessions, chronically catheterized monkeys were seated in Plexiglas chairs within illuminated, sound-attenuating chambers 5 days a week for a period of 90 minutes per day. Pressure signals from the arterial catheter were processed via a pressure transducer, an amplifier, and a BP processor (Coulbourn Instruments, Allentown, PA). The output from the BP processor was analyzed online by an Apple IIe computer for recording systolic, diastolic, and mean arterial BP and HR. The computer averaged the above parameters over a period of 30 seconds. A lead II electrocardiogram was recorded on a chart recorder using needle electrodes to monitor cardiac rhythm and to further verify HR changes. Cocaine hydrochloride (0.01-3.0 mg/kg) was administered as an IV bolus injection over a period of 15 seconds on Tuesdays and Fridays,

and saline was administered on Thursdays. Only one dose of cocaine was tested on each day of drug intervention. Cocaine or saline was administered 30 minutes after the start of the experimental session. Parts of these results have been reported elsewhere (Tella et al. 1990).

EFFECTS OF COCAINE ALONE

Cocaine alone produced a dose-dependent increase in BP that was linear over the dose range tested (figure 1). At 3.0 mg/kg, cocaine produced approximately a 30-percent increase in BP. Cocaine's effects on HR were not as clearly dose dependent. Figure 1 shows a linear increase in HR up to 0.3 mg/kg; above this dose HR plateaued, which may be due to a tendency for the higher doses of cocaine to produce decreases in HR immediately after administration. Figure 2 compares the effects of 0.3 and 3.0 mg/kg injections of cocaine on HR as a function of time since injection. At the 0.3 mg/kg dose of cocaine, HR was increased by approximately 26 percent, with the peak effect occurring approximately 20 to 30 minutes following the injection. At the higher dose of 3.0 mg/kg, however, the peak increase in HR was delayed. At this dose there was also an initial bradycardia followed by tachycardia approximately 15 to 20 minutes following the injection of cocaine, and the peak tachycardiac effect occurred 50 minutes following the injection.

EFFECTS OF ANESTHESIA AND GANGLIONIC BLOCKADE

Table 1 presents the baseline BP and HR values for the various experimental conditions. Pentobarbital, halothane, and hexamethonium treatments all reduced BP, whereas pentobarbttal and halothane reduced HR. When monkeys were anesthetized wlth either pentobarbitai (25 mg/kg IV) or halothane (1.75 percent), the pressor ($p<0.05$ to 0.01) and tachycardiac ($p<0.01$) responses to cocaine were reduced markedly (table 2). Antagonism of the pressor response to cocaine by halothane was significantly greater ($p<0.01$) than that by pentobarbital. Haiothane, but not pentobarbitai, significantly reduced ($p<0.01$) the pressor response to exogenously administered norepinephrine (data not shown). The IV administration of 15 mg/kg hexamethonium, 10 minutes before an IV dose of 3 mg/kg cocaine, together with a slow intra-arterial infusion of hexamethonium (0.1 mg/kg/min) throughout the session, failed to antagonize the pressor or tachycardiac effects of cocaine (figure 3). As cocaine-induced cardiovascular responses were not abolished by hexamethonium pretreatment in conscious animals and were reduced differently by the two anesthetic agents, the primary mechanism involved in cocaine's actions may not be the activation of the CNS-sympathoadrenai neural axis but the drug's peripheral effects on neuronal release and function.
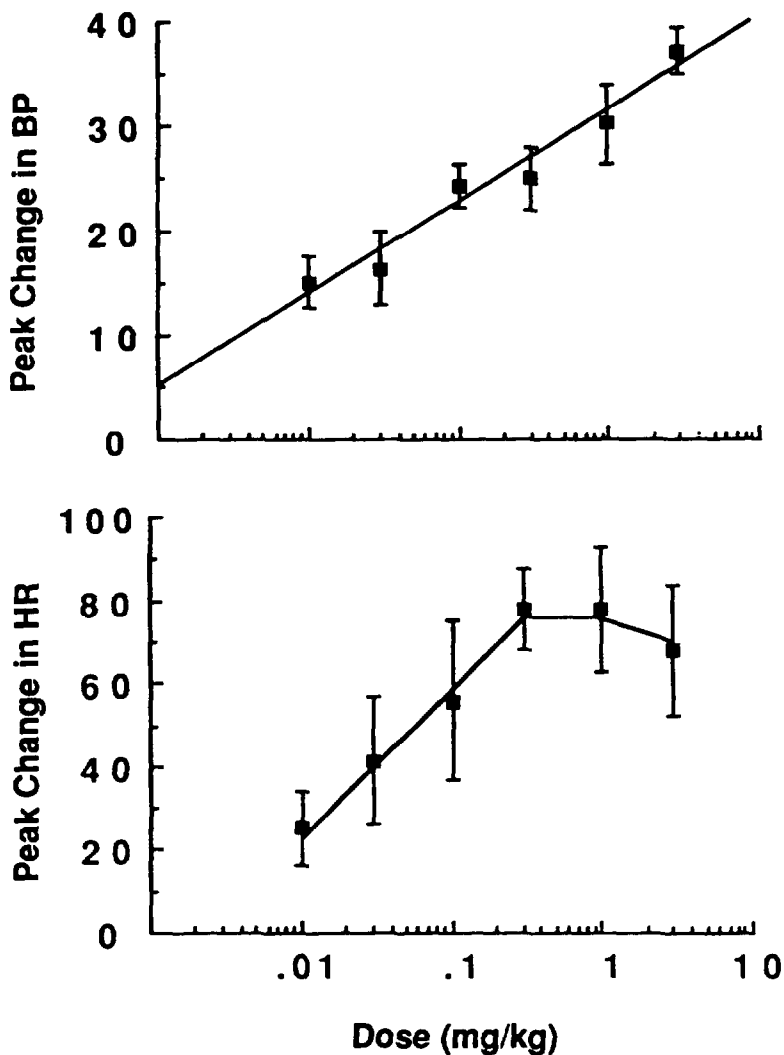
FIGURE 1. *Effects of cocaine on peak changes in BP (mmHg) and HR (beats per min) in six conscious squirrel monkeys. Error bars are +1 SE. Baseline BP was 113.2+7.9 mmHg, and baseline heart rate was 266+6 bears per minute.*

SOURCE: Tella et al. 1990, copyright 1990, American Society for Pharmacology and Experimental Therapeutics.
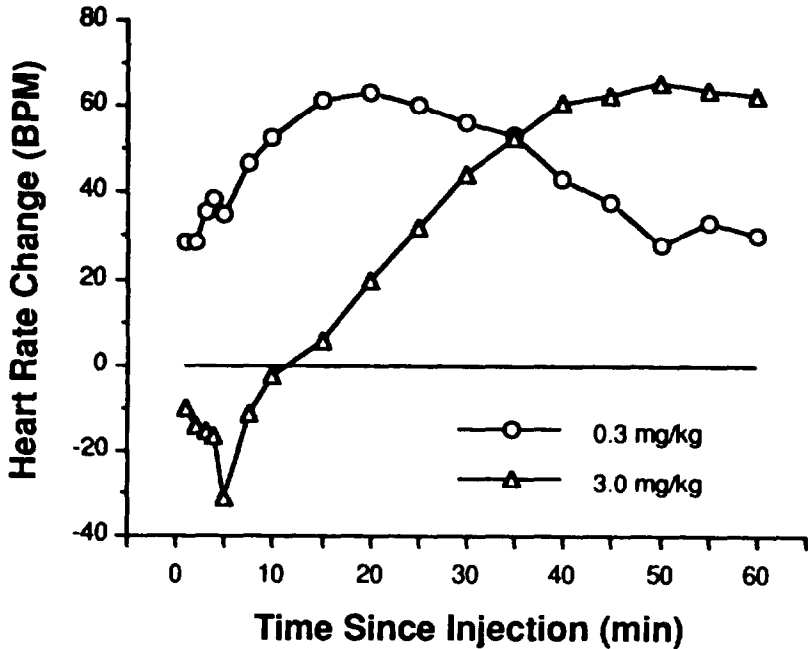
FIGURE 2. *Time course for the effects of two doses of cocaine (0.3 and 3.0 mg/kg) on HR for those subjects presented in figure 1 (n=6). Note the delayed occurrence of tachycardia to 3 mg/kg cocaine as opposed to 0.3 mg/kg cocaine. Note also the initial bradycardia with the 3 mg/kg dose.*

SOURCE: Tella et al. 1990, copyright 1990, American Society for Pharmacology and Experimental Therapeutics.

These results do not agree with an earlier study demonstrating the predominant role of a centrally mediated increase in sympathoadrenal discharge in the cardiovascular effects of cocaine in conscious dogs (Wilkerson 1988). There appear to be several other qualitative and quantitative differences in the cardiovascular effects of cocaine in conscious dogs and squirrel monkeys. First, the HR response to cocaine, unlike BP, reached the plateau of the log-dose response curve at 0.3 mg/kg dose In squirrel monkeys; in dogs the HR and BP responses continued to increase up to the highest dose of 8 mg/kg tested. Second, the peak pressor responses observed with cocaine in dogs are much larger than those in squirrel monkeys (Tella et al. 1990). For example, a dose of 0.3 mg/kg cocaine produced a 21-percent increase in BP in squirrel

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TABLE 1.   *Effects of pharmacological pretreatments on baseline BP and HR*

Drug	BP (mmHg)		HR (Beats/Min)	
	Control	Postdrug	Control	Postdrug
Control	113.2 + 7.9	————	266.0 + 0.0	————
Pentobarbital	104.3+ 10	73.2 + 13.3*	263.8 + 7.9	167.2 + 10.1*
Halothane	104.3+ 10	65.3 + 5.8*	263.8 + 7.9	220.4 + 24.8*
Hexamethonium	110.4 + 10.5	95.2 + 10.3*	203.8 + 7.9	266.2 + 19.8
Phentolamine	104.3+ 10	56.8 + 5.8*	258.5 + 6.9	301.3 + 16.3*
Propranolol	104.3 + 10	111.3 + 4.4	258.5 + 6.9	195.2 + 13.1*

NOTE: Each value is the mean of 4 to 5 subjects.

*$p < .05$.

SOURCE: Tella et al. 1990, copyright 1990, Williams and Wilkins.

TABLE 2.   *Effects of anesthesia on the cardiovascular effects of 3.0 mg/kg cocaine injections*

	Peak Change After Cocaine		
	Conscious	Halothane	Pentobarbitai
Blood Pressure (mmHg)	39.0+ 5.3	9.3+2.4	28.7+5.7
Heart Rate (beats/min)	70.4+19.0	18.2 + 6.9	12.6 + 4.6

NOTE: N=4 to 5 per cell. For baseline values, see table 1.

SOURCE: Tella et al. 1990, copyright 1990, Williams and Wilkins.

monkeys, which is comparable to the 15- to 20-percent increase seen in human subjects (Resnick et al. 1977; Fischman and Schuster 1982). In contrast, a comparable dose of cocaine produced approximately a 40-percent increase in BP in conscious dogs, and increases as large as 70 to 100 percent were produced by 4 to 8 mg/kg doses of cocaine, Third, there are differences in the duration of cardiovascular effects of cocaine in monkeys and dogs. The BP and HR response to a 3 mg/kg dose of cocaine lasted more than 1 hour in squirrel monkeys (Tella et al. 1990), whereas in dogs these responses lasted for a maximum of 20 minutes with the highest dose tested of 8 mg/kg (Wilkerson 1988).
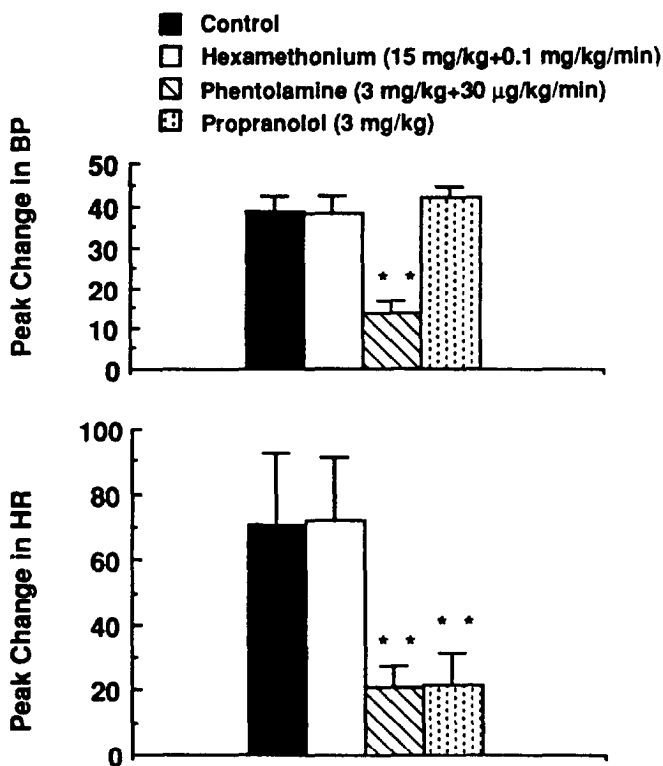
FIGURE 3. *Effects of hexamethonium (n=5), phentolamine (n=4), or propranolol (n=4) on the peak pressor (mmHg) and tachycardiac (beats/min) effects of a 3 mg/kg IV dose of cocaine in conscious squirrel monkeys. Cocaine was administered at 30 minutes after the start of the experimental session. Hexamethonium was administered as an initial IV loading dose of 75 mg/kg given 10 minutes before the administration of cocaine, followed by a slow intra-arterial infusion at a rate of 0.1 mg/kg/min throughout the experimental period of 90 minutes. Phentolamine was administered as an initial IV loading dose of 3 mg/kg 5 minutes before the start of the session followed by a slow intra-arterial infusion of 30 µg/kg/min throughout the session. Propranolol was administered as a 3 mg/kg IV dose 5 minutes before the start of the experimental session. Control (n=5) represents the effects of cocaine obtained in normal conscious monkeys on a different day. Data are expressed as mean + 1 SE. See table 2 for baseline values.*

SOURCE: Tella et al. 1990, copyright 1990, American Society for Pharmacology and Experimental Therapeutics.

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These differences in duration are probably of pharmacodynamlc rather than pharmacokinetic origin, as the plasma half-lives of cocaine in dogs (72 min) and monkeys (72-78 min) are comparable (Misra 1976). Differences in the actions of cocaine in dogs and squirrel monkeys do not appear to be due to different doses or routes of administration because these also were comparable. Also, the mean baseline BP of conscious monkeys averaged about 110 mmHg, which was comparable to 109 mmHg reported In conscious dogs. The doses of cocaine employed in both series of experiments were within the range of the steeper portion of their corresponding log-dose pressure-response curves. The doses of hexamethonium employed In the present work were sufficient to completely antagonize the reflex reduction in HR caused by norepinephrlne (1 mg/kg IV), thus indicating the presence of an adequate blockade of autonomic ganglia.

Other evidence favoring the mediation of the CNS-sympathoadrenal neural axis in the cardiovascular effects of cocaine includes the fact that cocaine causes the release of catecholamines at least in part via this pathway in conscious rats (Chiueh and Kopin 1978). However, these catechoiamine levels were measured 15 minutes after the administration of cocaine; the cardiovascular effects of cocaine in this species have a mean duration of about 15 seconds (Pitts et al. 1987). The above data indicate possible species differences In the mechanisms of cocaine's cardiovascular effects. increases In activity of the CNS-sympathoadrenal neural axis do not seem to be the primary mechanism in the pressor and tachycardiac actions of cocaine in conscious squirrel monkeys.

Failure to antagonize the cardiovascular effects of cocaine by prior blockade of autonomic ganglia suggests that these effects are not due to potentiation of tonically released norepinephrine from sympathetic nerve terminals. Presynaptic inhibitory mechanisms theoretically would tend to counteract any increase in synaptic norepinephrine levels resulting from cocaine-induced inhibition of neuronal uptake mechanisms. Thus, the inhibition of neuronal uptake of norepinephrine by cocaine does not explain completely the prolonged cardiovascular effects of cocaine.

EFFECTS OF ADRENERGIC BLOCKADE

We also have studied the effects of alpha and beta adrenoceptor blockade on the cardiovascular effects of cocaine. Pretreatment with phentolamine prevented the pressor effect of cocaine, whereas propranolol blocked the cocaine-induced increase in HR (figure 3). The decrease in the magnitude of the cocaine-induced HR increase by phentoiamine may be due to the dramatic increase in baseline HR produced by phentolamine (table 1). These results suggest that the cardiovascular effects of cocaine in squirrel monkeys are

mediated primarily by the peripheral adrenergic nervous system. The results, however, do not rule out another possible mechanism of centrally mediated cardiovascular effects of cocaine; that is, cocaine may act centrally to cause the release of some pituitary hormones that subsequently act peripherally on the sympathoadrenal system (Gothert 1981) to elicit, or at least contribute to, the sustained excitatory cardiovascular effects.

The source of catecholamines mediating cocaine's pressor and tachycardiac effects in conscious squirrel monkeys remains in question. It is possible that cocaine may have a direct effect on the adrenal medulla causing release of catecholamines. However, recent *in vitro* evidence obtained from adrenal medullary chromaffin cell culture studies has shown that cocaine has no direct effects on catecholamine release but, on the contrary, inhibits the release of catecholamines evoked by nicotine, veratroldine, and ouabain, but not potassium (Powis et al. 1989). It Is also possible that cocaine causes release of norepinephrine from sympathetic nerve terminals, similar to indirectly acting sympathomimetic agents, and subsequently inhibits neuronal reuptake of the released noreplnephrine. Experimental evidence obtained from intact animals and *in vitro* organ preparations suggests that cocaine, like indirect sympathomimetic agents, releases norepinephrine from sympathetic nerve terminals (Campos et al. 1963; Maengwyn-Davies and Koppanyi 1966; Trendelenburg 1968; Tessel et al. 1978; Palaty 1988). It has been shown that depletion of norepinephrine stores from peripheral sympathetic nerve terminals by repeated injection of ephedrine blocks the pressor effects of cocaine in spinal cats. This suggests the importance of peripheral sites of norepinephrine release (Teeters et al. 1963).

INDIVIDUAL EFFECTS

in squirrel monkeys higher doses of cocaine tended to produce an initlal bradycardia, followed by increases in HR 20 to 60 minutes following the injection. However, this tendency to produce bradycardia is not evident in all monkeys. Although all the monkeys showed a delayed tachycardiac response to cocaine, the tachycardia was not always preceded by bradycardia. These intriguing, individual differences in HR effects of cocaine led to a search for an explanation.

For the six monkeys whose results are presented in figures 1 and 2, the 1 and 3 mg/kg bolus doses of cocaine caused an initial bradycardia ranging from 10 to 30 beats/minute in three monkeys and a large reduction of 90 and 110 beats/ minute in one of six monkeys tested in this study. None of the pharmacological interventions discussed above prevented the moderate bradycardia caused by cocaine in three monkeys. However, when cocaine was administered as a slow

infusion over a 10-minute period, no bradycardia occurred. Thus, this moderate bradycardia produced by cocaine may be due to cocaine's direct depressant effect on the pacemaker function of the heart (Trendelenburg 1968; Tessel et al. 1978). Contrary to this, the large bradycardia caused by cocaine in one monkey was not prevented by slow infusion but was completely blocked by hexamethonium (15 mg/kg IV+0.1 mg/kg/min slow intra-arterial infusion) and was attenuated by atropine (1 mg/kg intramuscular) or propranolol (1 mg/kg IV). The pronounced bradycardia produced by cocaine in this one monkey may have been due to a baroreceptor reflex response secondary to cocaine's pressor effects. Pharmacological interventions that reduced the pressor response to cocaine, such as the use of general anesthesia and phentolamine treatment, prevented this large bradycardia (figure 4).

Figure 5 shows a further analysis of the time course for the 3.0 mg/kg dose of cocaine. The subjects for this analysis were broken down according to subspecies. The Guyanan subspecies of squirrel monkeys showed clear bradycardia following cocaine, whereas "other" monkeys, which were primarily Peruvian, did not ($p<.001$). Figure 5 also shows the study results of Gonzalez and Byrd (1977) who reported that cocaine produced only tachycardia in squirrel monkeys; their results are clearly comparable to our results for the "other" monkeys. These results clearly indicate that even subtle genetic differences may produce large differences in the effects of cocaine and that these differences may account for much of the variability observed following cocaine. An appreciation of these potential genetic differences in cocaine's effects has gained considerable recognition lately (George and Goldberg 1989; ishizuka et al. 1989).

Although our recent studies never have noted cocaine-produced arrhythmias, cocaine could potentiate a preexisting arrhythmia. For example, one subject showed a low level of ectopic beats following saline injections. As shown in figure 8, a cocaine dose of 3.0 mg/kg potentiated that arrhythmia. Following saline in this monkey, ectopic beats rarely occurred at a rate exceeding 10 per minute. Following cocaine, however, an average of more than 20 beats/minute was observed. The large standard error following cocaine suggests some caution in the interpretation of these results; nevertheless, it does suggest the possibility that cocaine may influence the electrical rhythm of the heart if an abnormal rhythm preexists.

TOLERANCE

It has been reported that in human subjects acute tolerance develops to the effects of successive doses of cocaine on HR (Fischman et al. 1985; Foltin et al. 1988) but not on BP (Foltin et al. 1988). However, in these studies the BP
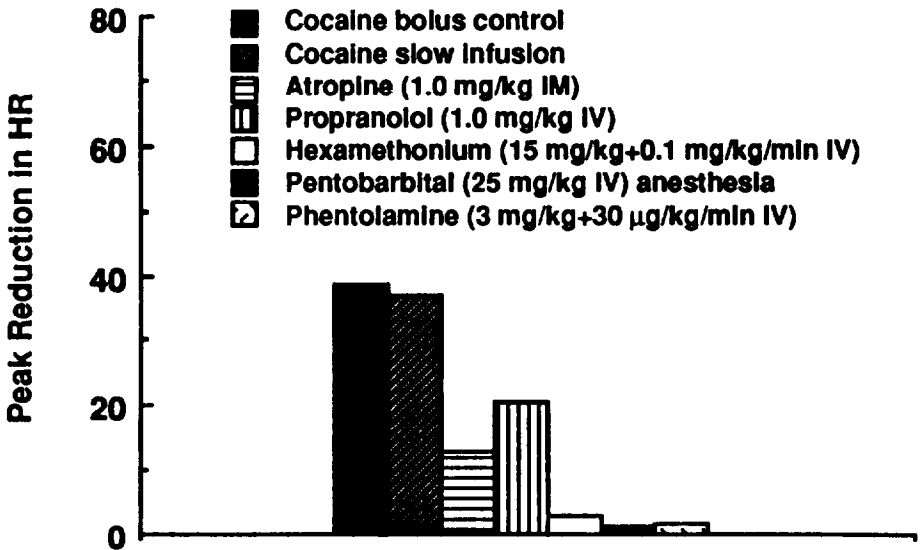
FIGURE 4. *Effects of various pharmacological interventions on the peak bradycardiac effect of a 3 mg/kg IV bolus injection of cocaine in one monkey (S1086). Note the partial antagonism of the bradycardia by atropine and propranolol. These drugs were administered 5 minutes before the start of the experimental session. Pentobarbltal anesthesia, phentolamine treatment, or hexamethonium interventions completely prevented the bradycardiac effect of cocaine. Time and mode of administration of these three drugs were the same as those described in figure 3.*

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and HR increases caused by the first dose of cocaine had not subsided completely before administration of the second dose. it remains to be determined whether tolerance still occurs if the doses of cocaine are spaced at intervals allowing responses to the first dose of cocaine to completely subside before administration of a second dose. in this study with squirrel monkeys, the
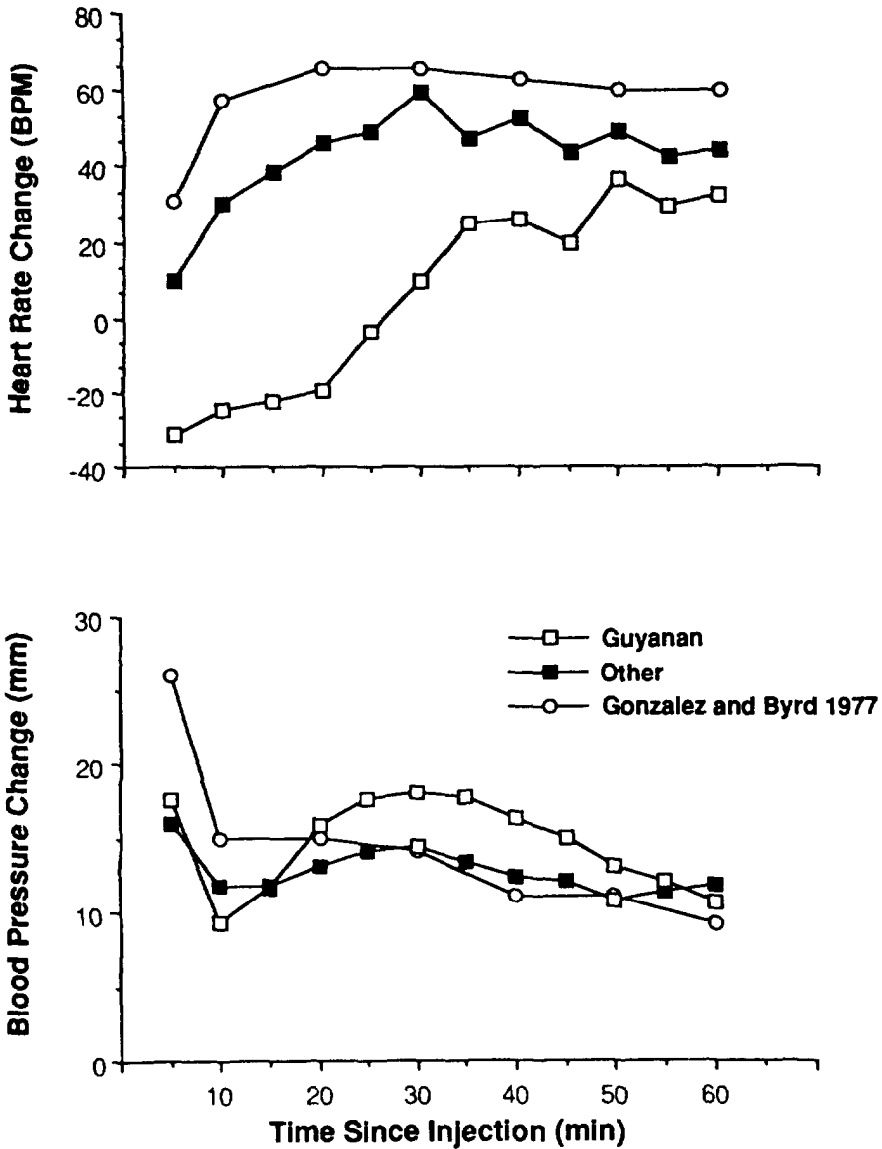
FIGURE 5. *Time course for the effects of 3.0 mg/kg cocaine in various groups of monkeys. Monkeys were divided into two groups according to subspecies (Guyanan n=4, all "others" n=3). Also plotted are the results from Gonzalez and Byrd (1977) for 3.0 mg/kg cocaine. BPM=beats/min; MM=mmHg.*
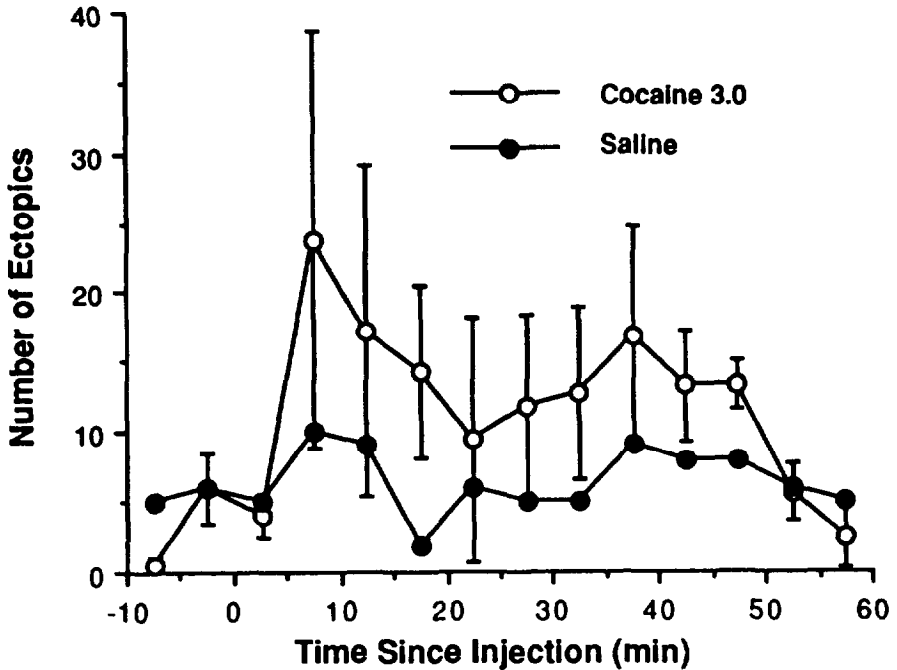
FIGURE 8. *Frequency of ectopic beats following IV injection of 3.0 mg/kg cocaine or saline for one monkey (S-1-87). The cocaine curve represents the mean of four sessions. The saline curve is a single representative session. Error bars are + 1 SE.*

HR response to cocaine reached a maximum at the 0.3 mg/kg dose. In contrast, the BP response to cocaine continued to rise with increasing doses up to the highest dose tested (3.0 mg/kg). The possible occurrence of such a plateau phase to the HR response to cocaine also should be considered when evaluating the possible development of tolerance to the HR effects of cocaine in humans. Due to ethical reasons a systematic human dose response study using higher doses of cocaine could not be conducted. However, careful examination of the data of Fischman and colleagues (1976) indicates that such a plateau phase to HR response, as seen in squirrel monkeys, might occur in humans. It also has been reported that acute tolerance to the HR effects of cocaine occurs in rhesus monkeys (Matsuzaki et al. 1976). Administration of cocaine (2-4 mg/kg IV) at 24-hour intervals resulted in reduced HR and respiratory rate responses to cocaine, suggesting development of acute tolerance lasting at least 24 hours. These data should be viewed with some
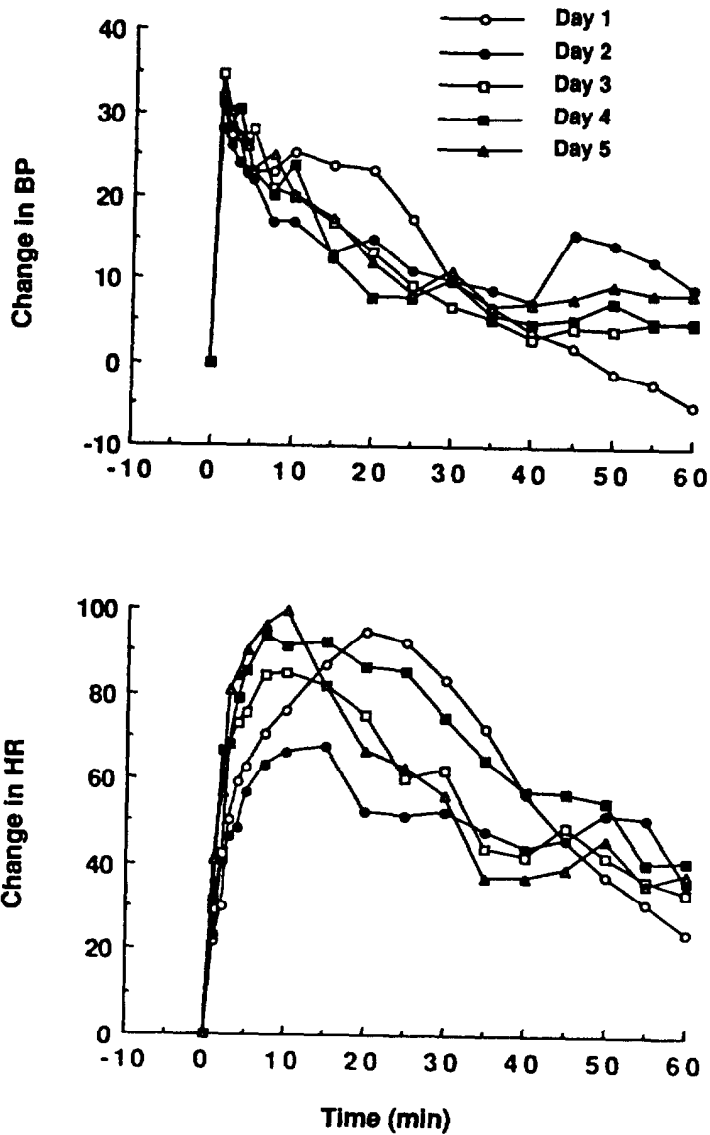
FIGURE 7. *Changes in HR (beats/min) and BP (mmHg) following IV administration of a 0.3 mg/kg dose of cocaine on 5 consecutive days in three monkeys. Monkeys were allowed to remain drug free for 10 days before the start of this protocol. Cocaine was administered once per day for 5 consecutive days.*

caution as HR is a particularly complex parameter to measure because it is susceptible to changes due to baroreceptor reflex control secondary to the pressor effects of cocaine. Unfortunately, BP was not measured in the study by Matsuzaki and coworkers. In contrast, our experiments with squirrel monkeys failed to show such tolerance to either the pressor or the tachycardiac effects of a 0.3 mg/kg IV dose of cocaine administered at 24-hour intervals for 5 consecutive days (figure 7). Development of tolerance to the cardiovascular effects of cocaine needs further exploration using a wider range of doses.

CONCLUSIONS

Cocaine elicits pressor and tachycardiac effects in conscious squirrel monkeys, and in some monkeys higher doses of cocaine also cause an initial bradycardia before tachycardia. The mechanism of cocaine's cardiovascular effects appears to be complex in nature. Stimulation of the CNS-sympathoadrenal neural axis, unlike in dogs, does not appear to be the main pathway in eliciting the pressor and tachycardlac effects of cocaine in conscious squirrel monkeys. Possible mechanisms include peripheral effects on the sympathoadrenal system and/or central neuroendocrine effects of cocaine. Higher doses of cocaine appear to elicit bradycardia by a direct depressant action on the pacemaker function of the heart or by baroreceptor reflex in response to cocaine's pressor effects. In addition, study data show that certain animals are more sensitive to cocaine's cardiotoxlc effects than others. No clear tolerance development to the effects of repeated cocaine administration was observed. However, because limited doses were studied, this area of investigation requires further analysis.

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Role of the Sympathetic Nervous System in the Cardiovascular Effects of Cocaine

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INTRODUCTION

Many of the cardiovascular effects of cocaine have been attributed to sympathomimetic actions of the drug. The peripheral nervous system and the brain have been studied as potential sites for the sympathomimetic actions of cocaine. In terms of the peripheral nervous system, one of cocaine's important actions is to block the uptake of catecholamines such as norepinephrine into sympathetic postganglionic nerve terminals, thereby allowing higher concentrations of norepinephrine to interact with the physiological postsynaptic receptor site. In terms of the central nervous system (CNS), it has been proposed that cocaine increases sympathetic nerve activity and that the site of this action is in the brain (Chiueh and Kopin 1978; Wilkerson 1988). Our study had three purposes: The first was to determine whether cocaine potentiates sympathetic neural effects on the heart. Interestingly, previous data from experiments in which cocaine was tested on cardiac responses elicited by cardiac sympathetic nerve stimulation generally indicate an inability of cocaine to potentiate the responses to cardiac sympathetic nerve stimulation (Pappas et al. 1965; Johnson and Kahn 1966; Koerker and Moran 1971; Levy and Blattberg 1976, 1978; Matsuda et al. 1980; lnoue and Zipes 1988). The second was to determine whether cocaine increases central sympathetic outflow. In this regard, a careful review of published papers on cocaine fails to provide direct evidence that cocaine stimulates sympathetic centers. The third was to determine whether any observed changes in sympathetic nervous system activity produced by cocaine contribute to the cardiovascular effects elicited by the drug.

METHODS

Experiments were performed on adult cats and dogs of both sexes. Cats were anesthetized either with intravenous (IV) alpha-chloralose, 70 to 80 mg/kg (for the majority of the experiments), or pentobarbital sodium, 35 mg/kg IV (for the experiments in which sympathetic neural activity was recorded). Dogs were anesthetized with thiopental sodium (25 µg/kg IV) followed by intubation with a cuffed endotracheal tube. Sufentanil was given as an IV bolus (2 µg/kg) followed by a continuous IV infusion (1 mg/kg/hr) to achieve a constant level of sedation throughout the experiment. Pancuronium bromide (0.1 mg/kg IV) was given as needed to provide continuous skeletal muscle relaxation. In the cat experiments, the trachea was cannulated, and the animals were allowed to breathe spontaneously, except in the sympathetic nerve recording studies in which the cats were artificially ventilated with room air. A femoral artery and vein were routinely cannulated for measurement of arterial blood pressure and systemic administration of drugs, respectively. Rectal temperature was monitored and maintained between 37°C and 38°C by an infrared lamp. For the sympathetic nerve recording experiments, vecuronium bromide was administered (initial IV bolus of 0.02 mg/kg followed by a continuous infusion of 0.15 mg/kg/hr) to produce skeletal muscle paralysis: respirator settings were adjusted to maintain end-tidal CO, between 4.0 and 5.0 percent (CO, monitor [IL 200]).

In the dog studies, the following indices of cardiovascular function were measured and/or derived: heart rate by Lead II of the electrocardiogram (ECG), arterial blood pressure (catheter in the aortic root), transmural myocardial blood flow (colored microsphere technique, Hale et al. 1988) coronary vascular resistance (derived by dividing mean arterial pressure by myocardial blood flow), left anterior descending epicardial coronary vessel diameter (coronary angiography), and cardiac output (thermodilution technique). Details of the techniques are described by Kuhn and colleagues (1990).

In the cat studies, measurements were made of heart rate (standard limb leads of the ECG plus augmented leads and a chest lead for analysis of sinus rate, ST segment changes, conduction changes, and cardiac rhythm changes) and arterial blood pressure (catheter in the femoral artery).

In cat studies in which the postganglionic cardioaccelerator nerve was electrically stimulated, the animals were subjected to bilateral cervical vagotomy and to spinal cord transection at the atlanto-occipital junction to eliminate all cardiovascular reflexes.

The technique for electrical stimulation of the postganglionic cardioaccelerator nerve was the same as that described by Aiken and Reit (1968). To gain access to this nerve, the right chest was opened in the first intercostal space. The stellate ganglion and its neural connections were exposed by bluntly dissecting away the surrounding fat and connective tissue. The cardioaccelerator nerve was dissected free and placed on bipolar stimulating electrodes. The sympathetic trunk containing preganglionic fibers synapsing at the stellate ganglion was exposed and cut.

Electrical stimulation of the cardioaccelerator nerves was applied with a conventional stimulator (Grass). Supramaximal square-wave impulses of 0.5 msec in duration were used. The frequency of stimulation was set in each experiment to elicit a heart rate response that was about 40 percent of the maximal response attainable. This increase was approximately 30 to 35 beats/min and was elicited with a frequency of stimulation ranging between 0.5 and 3 Hz. Each train of stimulation was applied for 30 to 45 seconds, a duration long enough to give a steady-state effect. The basis for selecting a 40-percent maximal response and the corresponding low frequency of stimulation is that cocaine has been demonstrated to potentiate submaximal responses but not maximal responses elicited by sympathetic nerve stimulation (Trendelenburg 1959). Atropine methylbromide, 0.5 mg/kg IV, was administered routinely to each animal to eliminate effects that might arise from activation of any cholinergic fibers, which have been described as coursing with the cardioaccelerator nerve (Juhasz-Nagy and Szentivanyi 1961).

The following experimental protocol was used: (1) Supramaximal voltage was determined by increasing voltage while maintaining constant impulse duration (0.5 msec) and frequency of stimulation (usually 1 to 3 Hz). Supramaximal voltage was set at a value approximately 5 V in excess of the voltage required to produce a maximal increase in heart rate. (2) Maximal heart rate obtainable in each animal was determined by increasing the frequency of stimulation (up to 20 to 25 Hz). (3) The frequency of stimulation then was adjusted to produce a heart rate increase that was about 40 percent of the maximal increase attainable. (4) Electrical stimulation was performed at 6-minute intervals. (5) Once three to four reproducible responses to sympathetic nerve stimulation were obtained, cocaine was administered and sympathetic nerve stimulation was repeated. In some experiments, norepinephrine was administered intravenously. The dose chosen was one that would produce approximately the same increase in heart rate as sympathetic nerve stimulation (i.e., in the range of 0.7 to 1.5 µg/kg). Again, three reproducible responses were obtained using a 6-minute interval between dosing before testing the effect of IV cocaine. In all cases, a value was calculated that indicated the degree of potentiation

produced by cocaine. This value is designated as magnitude of potentiation and is calculated as follows:

$$\text{Magnitude of Potentiation (\%)} = \frac{\text{additional heart rate increase observed above control response after cocaine}}{\text{heart rate increase observed during the control period}} \times 100$$

For the purpose of injecting drugs into the vertebral artery of cats, retrograde cannulation of the right axillary artery was performed. The tip of the cannula was positioned at the bifurcation of this vessel with the vertebral artery after ligating costocervical, thyrocervical, and internal mammary arteries (Van Zwieten 1975). During periods of intra-arterial drug administration, the vertebral artery was clamped between the bifurcation and the heart. The clamp was removed after injection of a bolus of drug, thus allowing the flow of blood to deliver the drug to the hindbrain. Cocaine was administered in a total volume of 0.1 mL followed by a saline flush of 0.3 mL, which represented cannula dead space.

For the purpose of recording cardiac sympathetic nerve activity In anesthetized cats, the right stellate ganglion was exposed by excising the first three ribs on the right side from the sternum to the midaxillary line. The postganglionic sympathetic cardiac nerve emerging from the stellate ganglion was dissected free, sectioned distally, and desheathed. The nerve then was placed on bipolar platinum-iridium recording electrodes and covered with mineral oil. Sympathetic nerve discharges were amplified using a differential amplifier (Tektronix) with low- and high-frequency filters set at 10 and 3,000 Hz, respectively. The amplified signal was displayed on an oscilloscope and recorded on magnetic tape.

Sympathetic nerve activity was quantified using a technique similar to that employed by Eldridge (1971). The amplified pulses were halfway rectified and fed into a voltage-frequency converter (Sample/Hold Integrator; BAK, Inc.), the output pulse frequency of which is proportional to applied voltage. Integration was accomplished by counting the voltage-to-frequency output pulses. The output pulses were counted electronically in intervals of 10 msec. The digital count, representing the electrical activity, was recorded on a recorder (Gould) following digital-to-analog conversion. The data were analyzed directly from the recorded tracing by averaging the amplitude of the peaks in the segment immediately preceding drug administration and comparing this value to the mean peak amplitude at the time of maximum drug response. Drug effects were expressed as percent of control values.

The values stated in the text are mean±SEM. For most of the data calculations in this study, statistical significance was determined by use of the Student's f-test for paired data and by use of Scheffe's test when multiple comparisons were made (Steel and Torrie 1980). The criterion for statistical significance was p<=0.05.

RESULTS

The initial focus of the study was to examine cocaine for its ability to potentiate the cardiac rate responses produced by electrical stimulation of postganglionlc sympathetic nerves. A dose of 0.25 mg/kg was selected for study, because this falls into the range of IV cocaine doses reported by Fischman and coworkers (1985) to produce behavioral effects in humans that are similar to those experienced when the drug is used on an illicit basis (i.e., doses of 18 to 49 mg, equivalent to 0.23 to 0.89 mg/kg in a 70-kg subject). Figure 1 depicts the results of a typical experiment in which a single dose of 0.25 mg/kg of IV cocaine was tested for its effect on heart rate responses produced by electrical stimulation of the cardiac accelerator nerves In an anesthetized cat. Reproducible positive chronotropic control responses to nerve stimulation were obtained at 0 and 6 minutes before cocaine administration. A bolus IV Injection of 0.25 mg/kg of cocaine was administered; neural stimulation was repeated within 1 minute after the IV injection was given. As can be noted, a marked potentiation of the neurally evoked cardioaccelerator response was obtained that was maximal at 1 minute after the injection.

A decline in the response was observed about 12 minutes after injection, and the effect lasted for about 1 hour. Responses similar to this were observed in each of 12 animals studied; the data are summarized in table 1 and indicate that the magnitude of the potentiation of cardioaccelerator nerve stimulation by 0.25 mg/kg IV cocaine averaged 80 percent over control values. We were unable to accurately evaluate the effect of cocaine on neurally evoked pressor responses because of variations in the response during the control stimulation periods and because the 30- to 40-second stimulation period was not long enough to obtain a steady-state blood pressure response. The baseline values for heart rate and mean arterial blood pressure in the animals studied were 143±9 beats/min and 47±2 mmHg, respectively. Cocaine administration alone resulted in maximal changes in heart rate and mean arterial blood pressure of +5±1.3 beats/min (p<0.05) and +11.2±4.3 mmHg (p<0.05) respectively.

We next studied the effect of repeated IV injections of 0.25 mg/kg of cocaine on heart rate increases elicited by electrical stimulation of postganglionic cardiac sympathetic nerves. The impetus for this was the clinical finding of Fischman and coworkers (1985) that tachyphylaxis develops to the positive
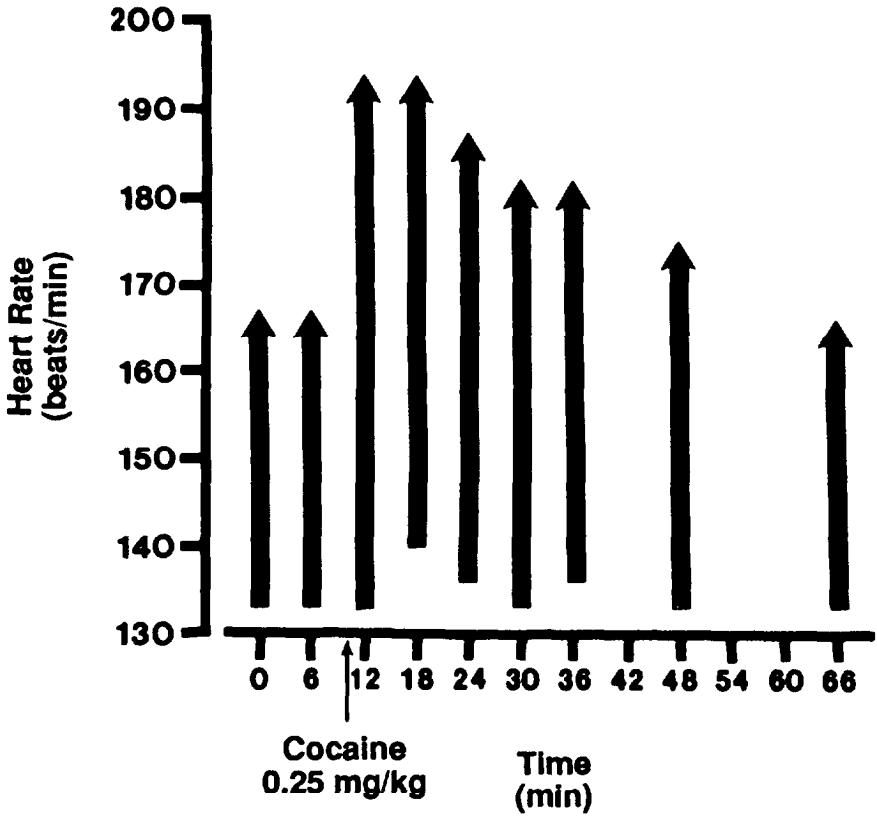
FIGURE 1. *Effect of cocaine on heart rate increases produced by electrical stimulation of cardiac accelerator nerves in an anesthetized, spinal cord transected cat. Control responses were obtained at 0 and 6 minutes before cocaine administration. Note the enhanced response approximately 1 minute after cocaine (i.e., at 12 minutes) and restoration of the normal response at 66 minutes. Columns depict the baseline levels (fiat end) immediately before nerve stimulation; tips of arrows depict maximal increase in heart rate during accelerator nerve stimulation.*

SOURCE: Jain et al. 1990, copyright 1990, Williams and Wilkins.

TABLE 1. *Effect of cocaine administration on heart rate increases induced by electrical stimulation of postgangiionic cardiac sympathetic nerves*

Dose of Cocaine	Number of Animals studied	HR Increase Before Cocaine (beats/min)	Additional HR Increase Observed		
			HR Increase After Cocaine (beats/min)	Above Control Response (beats/min)	Magnltude of Potentiation (percent)
0.25 mg/kg	12	31±2	55±2	24±2[a]	80±10[a]

HR=Heart rate

*p≤0.05 ι using Student's *t*-test for paired data

SOURCE: Jain et al. 1990, copyright 1990, Williams and Wilkins.

chronotropic effect of cocaine when human subjects were given IV doses of 16 to 40 mg of the drug 1 hour after using 94 mg of cocaine by the intranasal route. Figure 2 shows a representative experiment in an anesthetized cat in which an initial IV dose of 0.25 mg/kg of cocaine produced the expected enhancement in the neurally evoked heart rate responses. That is, the heart rate increase elicited by stimulation 1 minute after cocaine was 60 beats/min compared with a 36-beats/min increase before cocaine was given. When the tachycardiac response to nerve stimulation returned to baseline level 2 hours later (plus 35 beats/min), a second IV dose of 0.25 mg/kg cocaine was given and was found to produce a potentiating response *of* 50 beats/min that lasted 30 minutes. A third dose of cocaine produced a potentiating response of only 45 beats/min, suggesting the appearance of tachyphylaxis. The data obtained from five such experiments are shown in table 2; the magnitude of potentiation of neurally evoked tachycardia was 66±5, 19±6, and 24±4 percent after three successive IV doses of cocaine.

The relationship between the amount of cocaine administered and the magnitude of potentiation observed with nerve stimulation was examined by testing IV doses of cocaine over the range of 0.0625 to 2.0 mg/kg. The results are shown in table 3. Significant potentiation occurred with as little as 0.0625 mg/kg of cocaine, and linear dose-related increases in the magnitude of potentiation were observed when the dose was doubled to 0.125 mg/kg and again to 0.25 mg/kg. However, a significant dropoff in the magnitude of potentiation occurred when larger doses of cocaine (0.5 mg/kg and 2.0 mg/kg) were tested. An interesting point that emerged from these dose-response studies was that tachyphylaxis did not occur to the potentiating effect of the lowest dose of cocaine that was tested. An example of the

FIGURE 2. *Effect of repeated injections of cocaine on heart rate increases produced by electrical stimulation of cardiac accelerator nerves in an anesthetized, spinal wtd transected cat. Control responses were obtained at 0 and 6 minutes before cocaine administration. Note the enhanced response approximately 1 minute afler cocaine (i.e., at 12 minutes) and restoration of the normal response at 132 minutes. Note the occurrenoe of tachyphyiaxis developing toward the enhancing effect of repeated doses of cocaine on heart rate increases ewked by nerve stimulation. Columns depict baseline levels (flat end) immediately before nerve stimulation, and tips of arrows depict maximal increase in heart rate during accelerator nerve stimulation.*

TABLE 2. *Magnitude of potentiation of sympathetic nerve stimulation response produced by cocaine on repeated dosing of 0.25 mg/kg (n=5)*

Dose Number	HR Increase Before Cocaine (beats/min) (control)	HR Increase After Cocaine (beats/min)	HR Increase Observed Above Control Response	Magnitude of Potentiation (percent)
1	39±1	57±1	23±[a]	55±5[a]
2	39±1	47±2	8±2[a,b]	19±6[a,b]
3	37±2	45±2	8±1[a,b]	24+4[a,b]

HR=Heart rate

[a]$p<0.05$ using Student's *t*-test for paired data
[b]$p<0.06$ when data are compared to data obtained with Dose No. 1 using Scheffe's test

SOURCE: Jain et al. 1990, copyright 1990, Williams and Wilkins

tachyphylaxis development with the 0.0625 mg/kg dose is shown as figure 3. As can be seen, before the first dose of cocaine, nerve stimulation increased the heart rate by 35 beats/min. After the first dose of cocaine, this response was increased to 46 beats/min. About an hour later nerve stimulation effects were similar to the original response. The dose of cocaine was repeated and produced a 54-beats/min increase in heart rate.

Additional studies were performed to evaluate the ability of cocaine (0.25 and 2.0 mg/kg IV) to potentiate the positive chronotropic effects of IV norepinephrine. The doses of norepinephrine used in these studies ranged from 0.25 to 1.4 μg/kg and were selected to produce chronotropic responses similar to those obtained with nerve stimulation. The results obtained are shown in table 3. With the 0.25 mg/kg cocaine dose, potentiation of norepinephrine-induced increases in heart rate was observed, and the magnitude of potentiation was similar to that observed with 0.25 mg/kg of cocaine tested on neurally induced increases in heart rate. Interestingly, the administration of 2.0 mg/kg of cocaine to animals resulted in a magnitude of potentiation of norepinephrine-induced increase in heart rate that was approximately four times greater than the magnitude of potentiation observed when 2.0 mg/kg of cocaine was tested on neurally induced increases in heart rate.

To determine the effect of cocaine on CNS structures that mediate sympathetic nervous system outflow, three types of experiments were performed using

TABLE 3. *Effects of cocaine administration on heart rate increases induced by electrical stimulation of postganglionic cardiac sympathetic nerves and by IV norepinephrine*

Experimental Procedure	Cocaine Dose (mg/kg)	HR Increase Before Cocaine (beats/min) (Control)	Additional HR Increase After Cocaine	Additional HR Increase Observed Above Control Response (beats/min)	Magnitude of Potentiation (Percent)
SNS (N=3)	0.0625	34±2	45±2	11±1[a]	32± 5[a]
SNS (N=3)	0.125	31±2	48±6	17±3[a]	54± 7[a]
SNS (N=12)[b]	0.25	31±2	55±2	24±2[a]	80±10[a]
SNS (N=3)	0.5	36±1	51±1	16±2[a]	45± 8[a]
SNS (N=8)	2.0	32±3	37±5	7±3[a]	23± 9[a]
NE (N=5)	0.25	29±6	48±6	21±3[a]	83±17[a]
NE (N=4)	2.0	30±5	54±1	24±4[a]	90±28[a]

HR=Heart rate
SNS=Sympathetic nerve stimulation
NE=Exogenous norepinephrine administration

Numbers in parentheses indicate number of animals studied.

[a]p<0.05 using Student's *t*-test for paired data
[b]Data taken from table 1

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anesthetized cats and dogs. The first was to administer cocaine into the vertebral artery of anesthetized cats while monitoring mean arterial blood pressure and heart rate. The second was to administer IV cocaine to anesthetized cats while monitoring spontaneous discharge from postganglionic cardiac sympathetic nerve fibers. The third was to compare in sedated dogs the cardiovascular effects of IV cocaine to those elicited by an equimolar IV dose of cocaine methiodide (a derivative of cocaine that does not cross the blood-brain barrier).

Intravertebral administration of drugs results in their delivery primarily to hindbrain structures (Van Zwieten 1975). Vertebral artery injection of 0.1, 0.3, and 1.0 mg cocaine in anesthetized cats resulted in decreases in mean arterial blood pressure of -24±7, -16±6, and -32±13 mmHg, respectively. Corresponding changes in heart rate were -4±1, -17±5, and -66±21 beats/min, respectively. To test the possibility that cocaine injected into the vertebral artery might have produced hypotension and bradycardia by crossing from the CNS into the peripheral circulation, the largest dose (1.0 mg) was administered by the IV route; no significant effect on either blood pressure or heart rate occurred.
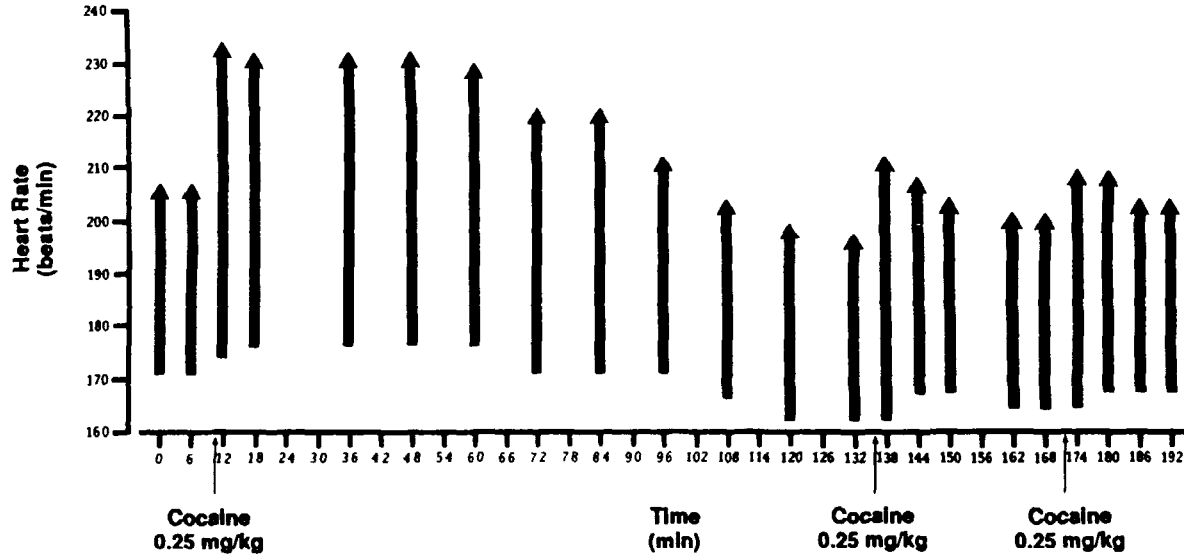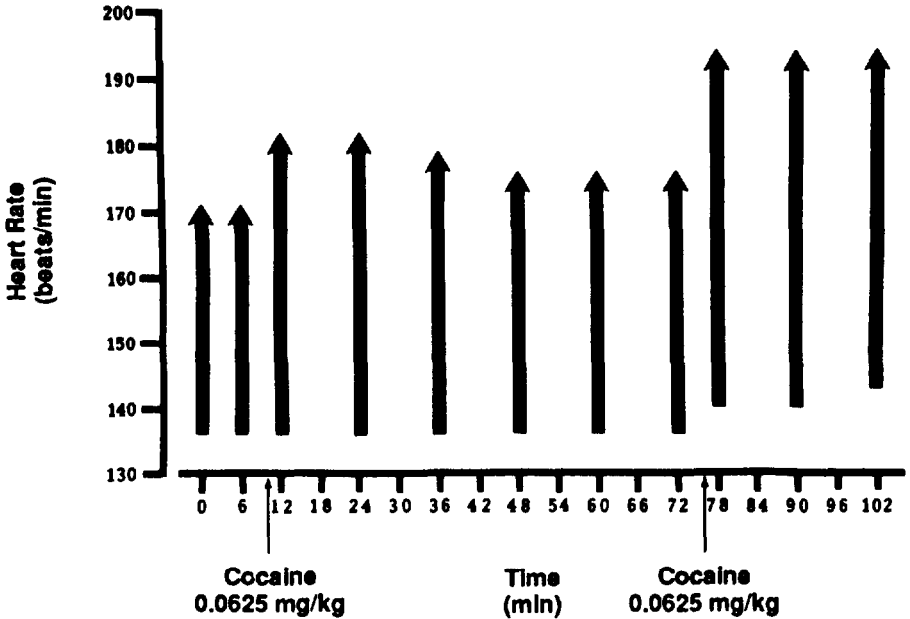
FIGURE 3. *Effect of repeated injection of cocaine on heart rate increases produced by electrical stimulation of cardiac accelerator nerves in an anesthetized, spinal cord transected cat. Control responses were obtained at 0 and 6 minutes before cocaine administration. Note enhanced response approximately 1 minute after cocaine (i.e., at 12 minutes). The cocaine dose was repeated about 77 minutes, and no evidence of tachyphylaxis was noted with the low dose of cocaine tested. Columns depict baseline levels (flat end) immediately before nerve stimulation, and tips of arrows depict maximal increase in heart rate during accelerator nerve stimulation.*

SOURCE: Jain et al. 1990, copyright 1990, Williams and Wilkins.

More direct evidence indicating an inhibitory effect of cocaine on central sympathetic centers was obtained from five experiments in anesthetized cats in which postganglionic sympathetic nerve activity was monitored during IV administration of 2 mg/kg of cocaine. Mean arterial blood pressure and heart rate also were monitored in these studies. IV injection of cocaine produced an

immediate reduction in integrated sympathetic nerve activity; the mean reduction obtained in the five animals was 52±7 percent (p<0.05). However, there were no accompanying significant decreases in either arterial blood pressure (-7±8 mmHg) or heart rate (-11±10 beats/min).

Table 4 indicates the cardiovascular responses that were obtained in sedated dogs when an IV dose of 2 mg/kg of cocaine and an equimolar IV dose of its quaternary derivative, cocaine methiodide, were studied. Both compounds produced essentially similar increases in blood pressure, heart rate, and cardiac output; neither compound altered coronary blood flow. The qualitative and quantitative similarities in the cardiovascular responses produced by these agents, one of which does not penetrate the blood-brain barrier, provide further evidence against an action of cocaine in the CNS to produce stimulation of sympathetic centers.

TABLE 4.   *Comparative effects of cocaine and cocaine methiodide on several indices of cardiovascular function in dogs*

			Indices of Cardiovascular Function Measured		
Drug Tested and Number of Animals Studied (mL/min/g)	Experimental Conditions	Heart Rate (beats/min)	Mean Arterial Blood Pressure (mmHg)	Cardiac Output (L/min)	Coronary Blood Flow
Cocaine (N=7) (2 mg/kg)	Before cocaine	76±9	106±6	3.7±0.7	1.2±0.3
	Maximum effect of cocaine	117±24[a]	160±17[a]	6.1±2.0	2.6±0.9
Cocaine methiodide (N=6) (2.65 mg/kg)	Before cocaine methiodide	82±8	109± 2	3.4±0.4	0.6±0.0
	Maximum effect of cocaine methiodide	136±11[a]	152±12[a]	4.6+0.3[a]	1.0+0.3

Values=meane±SEM
[a]p<0.05 using the Student's *t*-test for paired data

SOURCE: Kuhn et al. 1988, copyright 1988, American Heart Association.

The role of the sympathetic nervous system effects of cocaine in the cardiovascular responses produced by the drug was studied using anesthetized dogs and cats. In the dog studies, the effect of alpha-adrenoceptor blockage with phentolamine on the coronary circulatory changes produced by IV cocaine (0.5, 1.0, and 2.0 mg/kg) was evaluated. In control dogs, the largest IV dose of cocaine (2 mg/kg IV) was found to produce a decrease in the diameter of the left anterior descending coronary artery of 19±3 percent (p<0.05) and an increase in coronary vascular resistance of 55±20 percent (p<0.05). The effects were noted 2 minutes after cocaine administration and were accompanied by significant (p<0.05) increases in heart rate (from 76±9 to 100+14 beats/min), mean arterial blood pressure (from 106±6 to 128±10 mmHg), and cardiac output (from 3.7±0.7 to 5.4±1.7 L/min). The two lower doses of cocaine (0.5 and 1.0 mg/kg IV) produced similar changes that were of lesser magnitude. The deleterious effects of cocaine (2 mg/kg IV) on the coronary circulation appeared to be due to alpha-adrenoceptor stimulation. Evidence for this was that phentolamine pretreatment (2.5 mg/kg) prevented cocaine-induced narrowing of the left anterior descending coronary artery and increase in coronary vascular resistance. In addition, phentolamine-pretreatment also counteracted the pressor effect of cocaine (Kuhn et al. 1990).

In the cat studies, the effect of blockade of alpha- and beta-adrenoceptors, using phentolamine (5 mg/kg) and propranolol (0.75 mg/kg), respectively, was evaluated on the blood pressure and myocardial conduction changes produced by IV cocaine (0.25-4.0 mg/kg). In control cats, these doses of cocaine produced increases in blood pressure and increases in the PR interval and the QRS duration of the ECG (Bachenheimer et al. 1988). Doses of 2 and 4 mg/kg resulted in intraventricular conduction defects, secondary and tertiary heart block, and isolated premature ventricular contractions (Bachenheimer et al. 1988). The rhythm disturbances and the prolongation of the ECG intervals were dose-related (Bachenheimer et al. 1988). Tachyphylaxis was observed to occur to the pressor effect of cocaine, 2 mg/kg IV. Initial administration of this dose increased the mean arterial blood pressure by 24±6 percent (p<0.05). Upon repeating the 2 mg/kg dose five times, the mean arterial blood pressure response for the fifth administration of cocaine was 0±10 percent. Furthermore, the pressor response observed with the initial 2.0 mg/kg dose was absent in animals pretreated with a combination of phentolamine and propranolol. Indeed, 2 mg/kg cocaine IV, administered after adrenergic blockade, produced a decrease in arterial blood pressure of 34±19 percent.

In terms of the effect of cocaine on QRS duration, tachyphylaxis was not observed to cocaine-induced prolongation of this interval (QRS duration increased by +83±15 percent with 2 mg/kg given as a first dose vs. an increase

of +92±31 percent after administration of a fifth dose), and pretreatment with adrenergic blocking agents did not counteract cocaine-induced prolongation of the QRS duration. In control animals, cocaine 2 mg/kg IV prolonged QRS duration by +83±15 percent as indicated above. The corresponding value after adrenergic blockade was +156±17 percent.

DISCUSSION

Data from our studies provide the following evidence that sympathomimetic effects of cocaine are only due to a peripheral site of action of the drug: (1) cocaine given IV to cats with transacted spinal cord potentiates the chronotropic response to sympathetic nerve stimulation; (2) cocaine methiodide, a quaternary analog of cocaine, produces cardiovascular effects in dogs similar to those evoked by cocaine; (3) cocaine does not produce increases in heart rate or blood pressure after vertebral artery administration; and (4) cocaine does not increase spontaneously occurring sympathetic nerve discharge after IV administration. Presumably, this peripheral sympathomimetic effect of cocaine was due to the well-known action of this agent to inhibit the neuronal uptake of norepinephrine.

Focusing on these peripheral effects of cocaine, the degree of potentiation was related linearly to dose over the range of 0.0625 to 0.25 mg/kg and then began to decline as the dose was increased further. The time course for potentiation followed a consistent pattern, with maximal enhancement in response occurring immediately after cocaine administration; the enhanced response then dissipated rapidly and was usually gone within 1 hour after cocaine administration. Tachyphylaxis developed to the cocaine-induced potentiation of the response to cardiac sympathetic nerve stimulation.

These findings also indicate that cocaine can potentiate cardiovascular responses to injected norepinephrine. Potentiation occurred with low and high doses of cocaine tested. Unlike the situation with neurally released norepinephrine, no falloff in cocaine-induced potentiation of injected norepinephrine was observed, which suggests that the falloff in the potentiated response with nerve stimulation was due to a local anesthetic effect of cocaine. Consistent with this notion are the findings of Yasuda and colleagues (1984), which demonstrate that local anesthetic effects of cocaine become manifest at dose levels about 10 times higher than the dose required *for* inhibition of norepinephrine at nerve terminals. That is, we observed maximal potentiation with 0.25 mg/kg, and this "potentiation" was canceled out with the 2.0 mg/kg dose of cocaine.

In terms of the role of the peripheral sympathomimetic action of cocaine on the cardiovascular responses seen with this drug, it is clear from our studies that

the following responses evoked by cocaine are mediated by the sympathetic nervous system: (1) narrowing of the lumen of the coronary epicardial vessels in dogs, (2) increase in resistance of the coronary arterioles in dogs, and (3) increase in systemic arterial pressure in dogs and cats. All these effects were blocked by pharmacological agents that competitively antagonize norepinephrine on postsynaptic receptors. Since tachyphylaxis was observed with cocaine-induced inhibition of norepinephrine uptake, it was not unexpected that this effect would be observed with the pressor effect of IV cocaine. As pointed out In the results section, repeated administration of cocaine to anesthetized cats resulted in diminishing effects on blood pressure. This was in contrast to cocaine-induced increases in the PR interval and the QRS duration of the ECG. Tachyphylaxis was not observed to occur to this effect (Bachenheimer et al. 1988).

With regard to cocaine's action in the CNS, we observed only sympathoinhibitory effects on blood pressure, heart rate, and spontaneously occurring sympathetic nerve discharge. Preliminary experiments performed in our laboratory on decerebrate unanesthetized cats also indicate an effect of cocaine to depress spontaneously occurring sympathetic nerve discharge (Raczkowski et al., In press). A possible reason for this inhibitory effect on sympathetic nerve discharge may be that, as in the periphery, cocaine is inhibiting the uptake of catecholamines at CNS sites controlling sympathetic outflow. Central administration of catecholamines is known to inhibit sympathetic outflow (De Jong 1974). Thus, blockade of catecholamine uptake in the periphery and in the CNS produce opposing effects on sympathetic nervous system function, with the peripheral sympathomimetic effects of cocaine predominating on administration of doses of cocaine used initially for recreational purposes. Since tachyphylaxis occurs to the peripheral sympathomimetic effects of cocaine and since the pattern of use of this drug involves repeated administration of increasing doses, the serious cardiovascular complications associated with cocaine may be due to the direct effects of the drug on cardiac conduction and contractility. The peripheral sympathomimetic effects of cocaine initially may counteract the direct deleterious effects of cocaine on cardiac conduction (conduction is slowed) and force of contraction (force is decreased). However, once tachyphylaxis occurs to the sympathomimetic effects, the direct effects on the heart, to which tachyphylaxis does not occur, ultimately may prevail and result in death. Finally, at this point during cocaine administration, cocaine-induced central sympathoinhibition would be manifested fully as well since it would not be offset by the peripheral potentiating effects of cocaine. Thus, once tachyphylaxis occurs to cocaine, the direct myocardial effects of the drug as well as centrally mediated inhibition of sympathetic outflow could lead to cardiovascular collapse and death.

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Cocaine-Induced Myocardial Depression

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INTRODUCTION

The cardiovascular effects of cocaine are complex, diverse, and sometimes divergent in their biologic activity. Because cocaine is a local anesthetic, it shares the membrane-depressant effects, and hence negative inotropic effects, of other local anesthetics (e.g., procainamide). Unlike other local anesthetic agents, however, cocaine has the unique ability to block neuronal reuptake of biogenic amines, including norepinephrine. This latter effect leads to adrenergic stimulation and activation of cardiac beta receptors, producing an augmented inotropic state. Which of these two effects—the local anesthetic/negative inotropic effect or the adrenergic stimulation/positive inotropic effect—predominates in humans after recreational cocaine use is unknown, Adding to the complexity of the myocardial function issue is the possibility that cocaine may cause focal coronary artery spasm or diffuse coronary artery vasoconstriction. Either effect could result in depressed regional myocardial function indirectly via myocardial ischemia. This chapter focuses on negative inotropism caused by cocaine in isolated muscle preparations, in sedated but intact dogs, in conscious dogs, and in humans.

ISOLATED MUSCLE PREPARATIONS

Herman and Vick (1987) studied the direct effect of cocaine on isolated, blood-perfused Langendorff dog hearts. Doses of less than 1 mg of cocaine injected directly into a 500 mL coronary circulation produced variable effects on heart rate and force of contraction. Doses of 2 to 25 mg of cocaine thus injected decreased both heart rate and force of contraction. A dose of 50 mg of cocaine resulted in cardiac arrest. Morcos and coworkers (1988) studied the direct effect of cocaine on isolated rabbit ventricular septa maintained in an oxygenated Krebs solution. Perfusion of these septa with 10^{-5}, 10^{-4}, and 10^{-3} molar cocaine concentrations resulted in progressively increased depression of developed tension, rate of tension development, and rate of tension relaxation.

Excitation-contraction decoupling, occurring at all doses, was seen in 100 percent of paced beats at the 10^{-3} molar concentration. These effects were rapidly reversed after washout of cocaine. Although these two reports were preliminary, both are consistent with a direct negative inotropic effect of cocaine on the myocardium.

SEDATED DOG PREPARATIONS

Bedotto and colleagues (1988) have done extensive studies in mongrel dogs during diazepam and hydromorphone sedation. These animals were instrumented previously with pulmonary artery, aortic, and left ventricular catheters. During a cocaine infusion of 0.5 mg/kg per minute, hemodynamic variables were measured. Cocaine caused significant increases in mean aortic pressure and systemic vascular resistance. Heart rate and pulmonary artery pressure rose modestly but not significantly. A negative inotropic effect of cocaine was suggested by a modest but nonsignificant fall in left ventricular dp/dt. A significant decrease occurred in cardiac index (measured by thermodilution) and in left ventricular ejection fraction from 0.61 to 0.49 (determined by contrast angiography). Proximal and distal coronary artery diameters (left anterior descending artery) were unchanged by cocaine: thus, it seemed unlikely that the negative inotropic effect was due to an ischemic mechanism. Wilson and colleagues (1988) studied eight pentobarbital-anesthetized, open-chest dogs subjected to contrast arterial pressure and heart rate. Large doses of cocaine (>100 mg) caused significant depression of dp/dt and an increase in left ventricular end-diastolic pressure. Coronary sinus blood flow, circumflex artery flow, and myocardial atrioventricular oxygen difference were measured and found to be unaffected by cocaine. These data also suggest a direct depressant effect of cocaine on the myocardium. Other data (Hale et al. 1989) differ somewhat from that described above. Pentobarbital-anesthetized dogs were studied after a bolus injection of 10 mg/kg of cocaine; 15 minutes later, heart rate and left ventricular dp/dt were significantly reduced compared with baseline. Left ventricular size (by echocardiography) was significantly increased, and subepicardial blood flow was reduced by more than 25 percent. Another group of animals was studied 3 to 5 minutes after injection of 10 mg/kg of cocaine. Angiographic coronary artery diameters were decreased by 15±4 percent, and regional epicardial blood flow again fell by about 25 percent. These data suggest that myocardial ischemia caused by coronary artery vasoconstriction may play a role in cocaine-induced left ventricular depression.

CONSCIOUS DOGS

Studies on the effects of cocaine in conscious dogs have been reported only from our laboratory (Fraker et al. 1989). Our model uses conditioned mongrel

dogs that are trained to lie quietly on a raised nylon mesh support stand. This stand allows access to the dog's right parasternal chest with an echocardiographic transducer while the animal is lying on its right side. Animals that cooperate with the echo examination become the subjects of study. Each animal undergoes implantation of a Doppler coronary blood flow probe (on the circumflex coronary artery), an arterial catheter, and a left atrial catheter during general anesthesia. This technique has been shown to preserve the innervation of the circumflex vascular bed (Knight et al. 1987). After a P-week recovery and training period, the animals are ready for study.

We evaluated left ventricular function by measuring the systolic/diastolic change in the area of the short axis view of the midleft ventricle obtained by two-dimensional echocardiography. In this study, the left ventricle looks roughly like a donut. The circumference of the left ventricle is split almost equally between the distribution of the circumflex coronary artery and the left anterior descending coronary artery. Measurement of the change in the area of the left ventricular cavity from systole to diastole is called the regional (i.e., mid left ventricular) ejection fraction and is roughly equivalent to an ejection fraction obtained by contrast left ventricular angiography, presuming that the mid left ventricle behaves in a way representative of the whole left ventricle.

The animal is positioned without sedation on the nylon mesh support, and the echo transducer is positioned at the right parasternal edge below the support, Baseline echocardiographic imaging is recorded continuously on videotape. Simultaneous measurements of circumflex artery blood flow, heart rate, and blood pressure also are recorded. After a period of stable baseline recording, the animal is given cocaine as a bolus injection into the left atrial catheter. The echocardiographic imaging and hemodynamic recordings are continued for the next 10 to 15 minutes.

At doses of 1 mg/kg of cocaine (four dogs), very little effect on regional ejection fraction was observed by echo. As expected, heart rate and blood pressure rose acutely, peaking at 1 to 2 minutes after cocaine. The rate pressure product (heart rate x systolic blood pressure) was increased by 20 percent at 1 minute, and coronary blood flow was increased by 23 percent. At a dose of 4 mg/kg of cocaine (eight dogs), the cardiovascular responses were very different. Midleft ventricular ejection fraction fell by 47 percent at 1 minute after cocaine. By 10 minutes, the ejection fraction was only 15 percent below baseline values. At 1 minute after cocaine, the rate-pressure product was 93 percent above baseline values, while coronary blood flow was increased by 38 percent. Calculated coronary resistance actually rose despite the high metabolic demand imposed by the dramatic increase in heart rate and blood pressure. At 10 minutes after cocaine, the rate-pressure product was still 70

percent above baseline: coronary blood flow was 23 percent above baseline; yet left ventricular function had largely recovered. At no time did we observe segmental wall motion abnormalities of the left ventricle in either the circumflex or anterior descending vascular beds.

There are several interesting aspects to these data. First, global left ventricular function is dramatically reduced in conscious dogs given 4 mg/kg of cocaine despite abundant hemodynamic evidence of intense adrenergic stimulation. Second, the depression In global left ventricular function appears to be very transient, at least in this model. Third, even though there is indirect evidence of coronary vasoconstriction after cocaine administration, It seems unlikely that ischemia plays a major role in the depression of left ventricular function because the left ventricle recovers rapidly despite more prolonged hemodynamic effects of adrenergic stimulation. We believe that direct membrane depression is largely responsible for depressed myocardial function, an effect that occurs in conscious animals despite high levels of adrenergic tone.

HUMAN STUDIES

There are no studies on the myocardial depressant effect of cocaine in humans. Although sudden death has been temporally associated with cocaine use in many reported cases, a variety of other mechanisms have been proposed, including acute myocardial infarction (Isner et al. 1986), ventricular arrhythmias (Inoue and Zipes 1988), and respiratory depression (Catravas et al. 1978).

Germane to a discussion of myocardlal depression Is a single case report by Allred and Ewer (1981). A 36-year-old man developed severe dyspnea immediately after injecting freebase cocaine intravenously. Clinical and radiographic examinations were consistent with acute pulmonary edema. The patient died 3 hours later despite vigorous medical therapy. The time course of events in this case is consistent with the acute myocardial depressant effect of cocaine seen in animal studies. Whether this effect of cocaine plays a major role in cocaine-related sudden deaths remains to be proven.

CONCLUSIONS

Cocaine causes acute, severe, but transient depression of global left ventricular function in laboratory animals and probably in humans. This effect occurs despite intense adrenergic nervous system stimulation due to blockade of neuronal uptake of norepinephrine. The importance of this effect in those patients who die suddenly after cocaine ingestion remains unclear.

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Prevalence of Myocardial Ischemia in Cocaine Addicts

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INTRODUCTION

Americans have watched the number of cocaine users and cocaine-related cardiovascular diseases rise in the past 10 years (Isner et al. 1986; Cregler and Mark 1986). Around 1983, when the drug became readily available in stronger form, the trend toward prevalent cocaine abuse escalated sharply. Alerted by the increasing number of young cocaine users admitted to emergency rooms, the medical community began to examine the phenomenon of cocaine-related myocardial ischemic syndromes. In the past, coronary syndromes usually were limited to older patients who had coronary artery disease, but now some younger people who abuse cocaine are experiencing serious myocardial ischemic disorders.

Cocaine blocks the presynaptic reuptake of catecholamines, causing an increase in norepinephrine, epinephrine, and dopamine in the synapses and the circulation (Rathke and Green 1985). This stimulates sympathetic activity, which increases heart rate, blood pressure, and in turn myocardial oxygen demand (Resnick et al. 1977). Cocaine also enhances platelet and thrombus formation (Togna et al. 1985) and produces coronary vasoconstriction and vasospasm (Zimmerman et al. 1987). From these pharmacological effects, one can infer that addicts who chronically abuse cocaine face a great risk of developing myocardial ischemia or myocardial infarction and that those addicts who have a diseased substrate face an even greater risk. Since the incidence of ischemic syndromes among cocaine addicts had not yet been investigated, we initiated a prospective study to determine the nature and prevalence of myocardial ischemia in cocaine addicts. In this review we describe the preliminary results of our study.

PATIENT POPULATION

The study used 63 male cocaine addict patients (mean age, 34 years) who were enrolled in a 28-day inpatient substance abuse treatment program. Of the

63 patients, 62 smoked freebase: of those, 9 also used the drug intranasally, 1 intravenously, and 1 intravenously and intranasally (mean duration of cocaine use=5.17 years). After giving written informed consent, subjects underwent cardiac testing as soon as possible after admission and again just before discharge.

ECG ABNORMALITIES

We found that chronic cocaine users had a markedly high incidence of electrocardiogram (ECG) abnormalities (31 percent), usually manifesting as ST abnormalities (14 percent). Almost half the patients had chest pain, which markedly decreased after they were admitted to the hospital. This pain was not typical of angina, and its etiology was not known. However, because several patients had chest pain in the presence of ST changes, one cannot rule out myocarditis or the sequelae of myocardial ischemia as a cause of the pain or ST changes.

INCIDENCE OF MYOCARDIAL ISCHEMIA: HOLTER MONITORING VS. EXERCISE TREADMILL TESTING

Of these 63 patients, 21 consecutive male chronic cocaine addicts (mean age, 34±6 years) were analyzed to determine the prevalence of spontaneous and exercise-induced myocardial ischemia (Nademanee et al. 1989). A serial 24-hour electrocardiographic ambulatory (Holter) monitoring and exercise treadmill testing were used to detect the incidence of myocardial ischemia. Both tests were performed as soon as possible after admission and again just before discharge. All 21 patients had their first Holter monitoring during the first 2 weeks after admission to the program. The interval between the last dose of cocaine and the first Holter monitoring varied considerably among patients because there was no control over when the patients chose to enter the study after their last dose of cocaine. Of the 21 initial Holter tapes recorded, 4 were unanalyzable for various reasons (e.g., mechanical failure or early removal of electrodes by patients). Sixteen patients had a second Holter within 3 to 4 weeks after admission, and 5 of these patients had another Holter 6 to 12 weeks after admission.

All Holter tapes were coded, scanned blindly, and mixed with those of 42 normal volunteers and 119 patients with angina (70 chronic stable and 49 unstable angina patients). None of the volunteers (age 28.7±3.6 years) had a history of heart disease or coronary risk factors.

A significantly greater proportion of cocaine addict patients had episodes of ST elevation compared with normal volunteers. Eight of the 21 patients had a total

of 45 ST elevation episodes (range=1-13 episodes per 24-hour period; mean=5.6 episodes). The mean duration per episode was 57±77 minutes (range=1-362 minutes). These episodes occurred even though the patients had not used cocaine during Holter monitoring; abstinence was verified by negative urine drug assays. Forty-five percent of the patients had ST changes on Holter during the first week; 25 percent had ST changes during the second week; 28 percent had ST changes during the third week; and 11 percent had ST changes during the fourth week. However, there were no ischemic episodes after a longer withdrawal period (8 weeks) from the drug.

The ST changes of the cocaine addict patients were similar to episodes of ST elevation of Prinzmetal's angina patients. In contrast, none of the volunteers and chronic stable angina patients and only 4 percent of the unstable angina patients had ST elevation episodes on Holter (cocaine vs. volunteers; p=.0004). This observation suggests that cocaine users faced a significantly greater risk of developing ST changes than the healthy volunteers (relative risk=16). Thus, chronic cocaine users may be at risk of developing myocardial ischemia precipitated by coronary vasospasm even after they stop using the drug

Only 1 of the 20 cocaine addict patients had a positive exercise test for ischemia. Very few cocaine addict patients had exercise-induced ischemia, indicating that most did not have significant coronary artery obstruction. In line with this, only 3 of the 42 volunteers had ST changes characteristic of myocardial ischemia during exercise treadmill testing. There was a significant difference between the peak exercise blood pressure response to exercise in the exercise treadmill test of the first visit and that of the second visit. The peak exercise blood pressure was significantly higher at the first visit within the first week after admission and last dose of cocaine than at the second visit 3 weeks later--despite the fact that there was no difference in resting blood pressure between the two visits. The mean resting blood pressure during the first and second visits was 115±11 and 112±11 mmHg, respectively, whereas the peak exercise blood pressure of first and second visits was 177±22 and 185±20 mmHg, respectively (p<.01). This finding suggests that soon after cocaine withdrawal the patient's blood pressure may have risen (i.e., in response to exercise) and then reverted back toward baseline after a longer period of abstinence from the drug.

These observations suggest that chronic cocaine use may make the coronary arteries more vulnerable to vasospasm, an effect that lingers even during withdrawal. This may be because chronic cocaine use creates a dopamine-deficient state. Dopamine, a powerful coronary vasodilator, stimulates the dopamine receptors in the coronary arteries and inhibits the norepinephrine release at the presynaptic junction (Goldberg and Rajfer 1985). Thus, the

consequent lack of dopamine could lower the threshold for coronary spasm and enhance norepinephrine release. The finding that cocaine addicts had an exaggerated blood pressure response to exercise immediately after withdrawal suggests that chronic cocaine use may heighten sensitivity to adrenergic receptor stimulation. Several studies have shown that long-term use of stimulants causes the central dopaminergic, alpha-adrenergic, and beta-adrenergic receptors to become supersensitive (Gawin and Kleber 1986). These studies show that the primary neurophysiologic substrate of cocaine withdrawal is supersensitivity of the inhibitory receptors on the dopamine neuron (autoreceptors); this heightened sensitivity reduces dopaminergic neurotransmission. Chronic cocaine use, by causing dopamine depletion, could sensitize alpha-adrenergic receptor stimulation, thus lowering the threshold for vasospasm.

SUMMARY

The finding that most young cocaine addict patients had a negative exercise treadmill test suggests that they did not have preexisting obstructive coronary artery disease. Noninvasive testing did show, however, that these patients frequently had a high incidence of ST elevation episodes during the first 2 weeks of withdrawal. The pathophysiological mechanism of cocaine-induced cardiovascular disease is not yet clearly understood, but it is probably more complex than the drug's acute direct effects on the cardiovascular system. It may be complicated by fluctuations in catecholamine homeostasis and further temporally complicated by cycles of cocaine use and withdrawal. Research on how cocaine use alters catecholamine homeostasis will increase the understanding of the pathophysiology of cocaine and assist in developing effective pharmacologic and prophylactic treatment for its abuse.

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Cocaine-Induced Myocardial Infarction: Clinical Observations and Pathogenetic Considerations

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CLINICAL OBSERVATIONS

Among the alleged cardiac consequences of cocaine abuse, the one reported most frequently is acute myocardial infarction (Coleman et al. 1982; Schachne et al. 1984; Kossowsky and Lyon 1984; Pasternack et al. 1985; Howard et al. 1985; Cregler and Mark 1985; Gould et al. 1985; Wilkins et al. 1985; Weiss 1986; Simpson and Edwards 1986; Rollinger et al. 1986; Isner et al. 1985; Mittleman and Wetli 1987; Rod and Zucker 1987; Zimmerman et al. 1987; Smith et al. 1987; Ascher et al. 1988; Virmani et al. 1988; Isner and Chokshi 1989). At least 58 cases of acute myocardial infarction temporally related to cocaine abuse have been reported in the English-language literature. The 58 individuals had a mean age of 32.8 years, ranging from 19 to 44 years; 49 were male and 9 were female, perhaps a reflection of the demographics of cocaine abuse. Only 3 of these 58 individuals were first-time cocaine users; the remainder used cocaine on a chronic basis. Various routes of cocaine administration related to acute infarction were identified: intranasal in 38, intravenous in 17, freebase/mixed form in 2, and smoking in 1. A history of preexisting angina or prior myocardial infarction unrelated to cocaine abuse was positive in 18 of the 58 individuals; the 40 remaining persons had no antecedent cardiac history. Seven of the 58 (12 percent) individuals died as a complication of acute infarction.

The results of selective coronary angiography have been reported for 45 of these 58 patients. In 31 cases, filling defects involving the infarct-related major epicardial coronary arteries were observed, including occlusive lesions as well as focal stenoses. Intraluminal filling defects inferred to represent intracoronary thrombi were documented in 10 of 31 patients who received thrombolytic therapy (either streptokinase or tissue plasminogen activator) within 8 hours of onset of symptoms of acute infarction. Thrombolytic therapy was successful in lysing the clot and reestablishing patency of the "culprit" artery in all of these

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cases. In contrast, 14 of 45 patients (31 percent) were found to have angiographically normal epicardial coronary arteries; although 8 of these 14 patients underwent ergonovlne provocative testing, all 8 failed to develop angiographic evidence of focal coronary narrowing.

In one additional patient studied in our laboratory, cocaine was employed as the provocative agent. No focal angiographic narrowing was observed following standard provocation with intravenously administered ergonovlne. Following serial nasal inhalation of 1 g of cocaine, heart rate and blood pressure increased: coronary angiography disclosed focal coronary arterial spasm limited to the proximal-most portion of the right coronary artery, Immediately distal to the catheter tip. Although catheter-induced spasm could not be ruled out in this patient, it is intriguing to note that no such focal spasm was observed during rlght coronary angiography before cocaine provocation.

PATHOLOGIC OBSERVATIONS

The finding of Intracoronary thrombus in cases of myocardial Infarction related to cocaine abuse has been confirmed in multiple cases studied at necropsy. We previously described a 37-year-old man in whom cocaine-related acute infarction was associated with thrombotic occlusion of the left anterior descending coronary artery at the site of 90-percent cross-sectional area narrowing by atherosclerotic plaque (Isner et al. 1985). Simpson and Edwards (1996) observed platelet thrombi in one or more major coronary arteries of a 21-year-old cocaine user who died suddenly and at necropsy was found to have "microfocal areas of fibrosis or granulation tissue . . . interpreted to be ischemic in origin." Each of the major epicardial coronary arteries was severely narrowed by 50 to 95 percent in cross-sectional area. Mittleman and Wetli (1987) reported 24 cases of sudden death associated with cocaine abuse and attributed the etiology in 15 of these to ischemic heart disease. Two victims had evidence of acute infarction, and 10 others had gross or histologic findings of myocardial fibrosis. Complete thrombotic occlusion of one epicardial coronary artery was observed in three cases, while hemorrhage into an atherosclerotic plaque was observed in two. All cases were notable for the presence of severe focal arterial narrowing by atherosclerotic plaque in at least one major epicardial coronary artery.

Virmani and colleagues (1988) studied two individuals at necropsy in whom there was "severe coronary atherosclerosis" and another in whom an occlusive platelet thrombus in the left anterior descending coronary artery was superimposed on atherosclerotic plaque that had narrowed the native lumen by 40 percent in cross-sectional area. Likewise, Stenberg and coworkers (1989) observed underlying atherosclerotic plaque that narrowed the left anterior

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descending and right coronary arteries by 70 and 50 percent respectively in a 38-year-old man who died 13 hours after the onset of a clinically documented acute myocardial infarctlon.

Finally, Dressler and colleagues (1990) reported quantitative analysis of coronary arterial narrowing by atherosclerotic plaque among 22 chronic cocaine users studied at necropsy over a 10-year period, Of the 12 individuals in whom death was believed to be related to cocaine, at least one major epicardial coronary artery was narrowed by more than 98 percent. In six cases, at least one artery was narrowed by 78 to 95 percent; 51- to 75-percent cross-sectional area narrowing was observed in ail but four cases. In 1 of these 12 cases, intracoronary thrombus was superimposed on underlying atherosclerotic plaque; in this and 2 others of the 12 cases, examlnation of the myocardium disclosed microscopic foci of necrosis.

Although these necropsy studies of cocaine users whose death was attributed to a cardiovascular etiology typically have disclosed more extensive coronary narrowing by atherosclerotic plaque than has been suggested by premortem angiographic assessment of such individuals, certain methodologic differences among these various studies must be made explicit. The first difference concerns the diagnosis of acute infarction. The majority of individuals studied angiographically have had clinically documented acute myocardial infarction. In contrast, most individuals described at necropsy have had neither myocardial (confluent areas of coagulation necrosis) nor coronary (intracoronary thrombus) evidence of acute myocardial infarction. It is possible that the individuals studied at necropsy died from a nonischemic etiology; alternatively, these individuals may have died before there was sufficient time for myocardial necrosis to become evident and/or after spontaneous lysis of intracoronary clot. The second difference concerns documentation of coronary arterial narrowing. It is conceivable that premortem angiographic studies of patients with cocaine-related infarction have underestimated (Isner and Donaldson 1984) the degree of underlying atherosclerotic narrowing compared with that observed in necropsy studies; this is particularly feasible with regard to mild disease (less than 50-percent cross-sectional area narrowing). Necropsy studies, on the other hand, are complicated by the inherent bias involved in selecting out only those individuals in whom the cocaine-related infarction was fatal. This latter observation may be a contributing factor to the suggestion that chronic cocaine use may accelerate coronary arterial narrowing (Dressler et al. 1990).

Independent of the quantitative aspect of coronary arterial narrowing in these cocaine users, It is interesting to note that qualitative assessment of site of thrombotic occlusion in these individuals at necropsy has failed to disclose evidence of plaque rupture, plaque fissure, or plaque hemorrhage (Virmani et

al. 1988). These findings have been observed routinely in noncocaine-related thrombotic coronary arterial occlusion (Davies and Thomas 1984). The absence of these features in cocaine-related infarction suggests cocaine-induced spasm rather than plaque rupture as a contributing event in the pathogenesis of infarction in cocaine users.

A second pathologic finding that has been cited to support the role of spasm in cocaine-related infarction is increased foci of contraction band necrosis in cases of cocaine-related deaths studied at necropsy (Tazelaar et al. 1987). This finding also is consistent with the concept that myocardial damage resulting from cocaine abuse may represent the consequence of cocaine-induced catecholamine excess, since contraction bands previously have been observed in association with pheochromocytoma and exogenous catecholamine administration.

EXPERIMENTAL OBSERVATIONS

The results of experiments performed *in vitro* and *in vivo* in live animals and *in vivo* in human subjects lend support to the concept that cocaine may act independently to produce vasownstriction of vascular smooth muscle. *In vitro* experiments performed in our laboratory have shown that cocaine alone, in concentrations of 10^{-8} to 10^{-3} M, produces reproducible, reversible vasoconstriction of aortic rings freshly harvested from normal New Zealand white rabbits (Rongione and Isner 1989). In these experiments, the magnitude and direction of vasomotor response to cocaine for those specimens in which the endothelium had been purposely disrupted were similar to those in which the endotheiium had been shown pharmacologically to be preserved. Pretreatment with prazosin or phentolamine produced no consistent effect on cocaine-induced contraction, whereas pretreatment with diltiazem markedly inhibited cocaine-induced contraction. These preliminary results suggested that the vasoconstrictor effect of cocaine on vascular smooth muscle was calcium-dependent and endothelium-independent.

Similar findings have been reproduced in ring segments of human arteries, including coronary arteries, freshly harvested at the time of cardiac transplantation, and umbilical arteries obtained fresh at the time of cesarean delivery. In nonatherosclerotic and atherosclerotic human coronary arteries, vasoconstriction was observed in response to concentrations of cocaine ranging from 10^{-9} to 10^{-3} M (Chokshi et al. 1990). The onset of contraction appeared after a delay varying from 10 seconds to 6 minutes and increased until it reached a plateau within 30 minutes. The magnitude of vasownstriction induced in coronary arterial segments narrowed greater than 50 percent in cross-sectional area by atherosclerotic plaque was significantly less than that

observed in rings narrowed less than 50 percent at all concentrations of cocaine. In addition to quantitative differences, two qualitative features were typical of coronary arterial segments narrowed greater than 50 percent in cross-sectional area following exposure to cocaine: The rate of rise in tension was slower, and the time required to reach plateau was prolonged.

The response of human umbilical artery segments exposed to cocaine was similar to that observed for nonatherosclerotic human coronary arteries (Isner and Chokshi 1989). The finding that cocaine alone (i.e., without pharmacologic pretreatment) augments tension in human umbilical arterial segments is intriguing, since human umbilical artery segments are devoid of sympathetic innervation. Correspondingly, pretreatment with the alpha-blockers phentolamine and prazosin had no consistent effect on cocaine-induced vasoconstriction in these preparations, whereas pretreatment with the calcium channel blocker diltiazem markedly inhibited cocaine-induced vasoconstriction. These findings thus contradict the traditional concept that the effects of cocaine on vascular smooth muscle are the sole result of potentiating the response to endogenous catecholamines.

Although the above *in vitro* experiments confirmed the vasownstricting effect of cocaine alone on medium-size arteries, direct evidence for cocaine-induced vasoconstriction at the arteriolar level has been reported by Vitullo and colleagues (1989) using isolated rat hearts perfused with cocaine. Ultrastructural examination disclosed preserved endothelial integrity in the constricted arterioles. Morphologic evidence of constriction was supported by data obtained from Langendorff-heart preparations in which cocaine reduced myocardial flow rate under conditions of constant pressure. Consistent with the *in vitro* work cited above, spasm induced by cocaine was prevented by pretreatment with calcium channel blockers but not with alpha-adrenergic antagonists (Stenberg et al. 1989).

Preliminary reports of live animal experiments indicate that certain of these *in vitro* observations may be reproduced *in vivo.* Kuhn and coworkers (1989), for example, documented dose-dependent vasoconstriction of the left anterior descending coronary artery in anesthetized dogs given incremental doses of cocaine. Studies performed in our laboratory have demonstrated that intra-arterial administration of cocaine to microswine with experimentally induced nonocclusive atherosclerotic lesions (Shimokawa et al. 1983) produced intense vasoconstriction (Isner and Chokshi 1989). Such findings constitute further inferential evidence that the mechanism of cocaine-induced vasownstriction is alpha-adrenergic-independent, since provocation of spasm in this model is accomplished routinely with histamine but does not occur following administration of norepinephrine. Similar findings have been reported by

Egashira and colleagues (1990) in miniswine coronary arteries following administration of bolus intravenous cocaine (1-10 mg/kg). At 10 mg/kg, coronary arterial diameter decreased by nearly 40 percent, and coronary flow velocity decreased by 32 percent, despite a 60-percent increase in the rate-pressure product. In this model, pretreatment with prazosin (0.1 mg/kg) produced attenuation of the cocaine-induced coronary vasoconstriction.

Studies of human subjects performed noninvasively also support the hypothesis that cocaine may alter coronary reactivity. Nademanee and coworkers (1989) performed ambulatory electrocardiographic monitoring of 21 male cocaine users soon after admission to a 28-day substance abuse treatment program. Eight of the 21 patients with cocaine addiction had frequent episodes of ST elevation during Holter monitoring; these episodes occurred almost exclusively during the first 2 weeks of withdrawal. Of the 20 cocaine patients who underwent exercise treadmill testing, only 1 had a positive test for ischemia.

Perhaps the most intriguing evidence for cocaine-induced vasoconstriction consists of observations that have been made directly in human patients at the time of coronary arteriography. Angiographic evidence of spasm in the coronary artery subtending the site of cocaine-related acute myocardial infarction has been documented in at least two previous case reports (Zimmerman et al. 1987; Ascher et al. 1988). In at least eight other patients, an ergonovine provocative study was performed at the time of diagnostic arteriography and was interpreted to be negative in all eight cases, implying that an Inherent predisposition to spontaneous attacks of coronary artery spasm is neither a characteristic of nor a prerequisite for cocaine-related infarction.

More recently, Lange and colleagues have quantified the degree of vasoconstriction observed in human epicardial coronary arteries at the time of diagnostic cardiac catheterization (Lange et al. 1989). Among 45 subjects undergoing routine coronary arteriography, 2 mg/kg of 10 percent cocaine hydrochloride administered intranasally produced an 8- to 12-percent reduction in angiographic luminal diameter of the left coronary artery. Correspondingly, coronary sinus blood flow fell by 17 percent, while calculated coronary vascular resistance increased by nearly one-third. These alterations were observed despite an increase in myocardial oxygen demand, as evidenced by an increase in the rate-pressure product. Although the magnitude of epicardial vasoconstrlction observed was mild and diffuse, it is conceivable that larger doses of cocaine, particularly in individuals with a history of a cocaine-induced ischemic event, might have induced a more dramatic response. Because the observed reduction in extramural coronary artery diameter was modest, Lange and colleagues attributed the increased resistance to vasoconstriction of the intramural coronary vessels. Phentolamine, an alpha-adrenergic blocker, was

found to obviate the vasoactive effects of cocaine, in contrast to the *in vitro* and *in vivo* animal data cited above.

Although the data cited above are consistent with the hypothesis of cocaine-induced spasm, the possibility persists that cocaine-induced myocardial infarction is multifactorial. Cocaine has been shown *in vitro* to enhance the response of platelets to arachidonic acid, leading to increased thromboxane production and platelet aggregation (Togna et al. 1985). The possibility of cocaine-induced procoagulant effects recently was suggested Clinically by the finding of combined protein C and antithrombln III depletion in an individual with cocaine-related arterial thromboses (Chokshi et al., submitted for publication). Following discontinuation of cocaine use, the thromboses resolved and levels of anticoagulants returned to normal. Similarly, Lisse and colleagues (1989) have reported a high prevalence of upper-extremity, deep venous thrombosis (Paget-Schroetter syndrome) among cocaine users. While superficial thrombophlebitis is a recognized consequence of intravenous cocaine abuse, deep venous thrombosis is not; the apparent association suggests that the role of cocaine may be thrombotic in nature. Thus, *in situ* thrombosis resulting from cocaine-induced procoagulant effects might represent an alternative basis for acute infarction In patients with previously normal coronary arteries.

SUMMARY

Clinical and experimental data published to date suggest several possible mechanisms by which cocaine may result in acute myocardial infarction. In individuals with preexisting, high-grade coronary arterial narrowing, acute myocardial infarction may result from an increase in myocardial oxygen demand associated with cocaine-induced increase in rate-pressure product. In other individuals with no underlying atherosclerotic obstruction, coronary occlusion may be due to spasm, thrombus, or both. With regard to spasm, the clinical findings are largely circumstantial, and the locus of cocaine-induced vasoconstriction remains speculative. Although certain clinical and experimental findings support the hypothesis that spasm involves the epicardial, medium-size vessels, other data suggest intramural vasoconstriction. Diffuse intramural vasoconstriction is not consistent with reports of segmental, discrete infarction. Whereas certain *in vivo* data suggest that these effects are alpha-mediated, other *in vitro* data suggest the opposite. The finding of cocaine-induced vasoconstriction in segments of (noninnervated) human umbilical artery suggests that the presence or absence of intact innervation is not sufficient to explain the discrepant data involving the possibility of alpha-mediated effects. Finally, the contribution of a primary, thrombotic effect of cocaine has not been excluded.

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Cardiac Electrophysiological Effects of Cocaine in Animal Models

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INTRODUCTION

The pathophysiological mechanism for cocaine-related death is uncertain. A
few clinical case reports that associate specific cardiac arrhythmias with
cocaine abuse include asystole (Nanji and Filipenko 1984), accelerated
idioventricular rhythm (Benchimol et al. 1978; Jonsson et al. 1983), a wide
complex tachycardia at 136 beats per minute (Isner et al. 1986), nonsustained
ventricular tachycardia in the setting of acute myocardial infarction (Isner et al.
1986), supraventricular tachycardia (Boag and Havard 1985), and reciprocating
tachycardia in the setting of the Wolff-Parkinson-White syndrome (Chokshi et al.
1989). Of these, only the patient with asystole did not survive. Therefore,
although it is assumed that cardiac arrhythmia is often the immediate cause of
cocaine-related sudden death, both the type and the mechanism of possible
arrhythmias remain unknown.

The purpose of this chapter therefore is to examine the known cocaine-related
arrythmias and cardiac electrophysiological responses in animal models and to
review possible theoretical mechanisms for lethal arrythmias.

DIRECT ACTIONS OF COCAINE ON CELLULAR ELECTROPHYSIOLOGY

In vitro studies of the direct action of cocaine on cellular electrophysiology were
performed by Weidmann (1955), who examined the actions of cocaine on calf
and sheep Purkinje fibers. He observed a reduced resting membrane potential
and a decrease of amplitude and a decrease in the fast upstroke of the action
potential with cocaine. These results are associated with decreased
conduction. Weidmann also observed that spontaneous activity of the action
potential ceased. Recently, Przywara and Dambach (1989) extended these
observations in rabbit atrial and ventricular tissues. These investigators also
demonstrated that cocaine depressed the fast upstroke of action potentials, An
increase in action potential duration and in the effective refractory period of

atrial and ventricular tissues also was observed; however, the effect was more profound in atrial tissues, Przywara and Dambach also demonstrated a decrease in sinus rate. They concluded that direct cocaine effects are characteristic of the actions of Class I (local anesthetic) antiarrhythmic agents.

IN VIVO ELECTROPHYSIOLOGICAL EFFECTS OF COCAINE

Most of the current information regarding *in vivo* electrophysiological effects of cocaine to date comes from brief, preliminary reports, which are summarized in table 1. Although cocaine's effect on heart rate differs in various studies, these variations may be explained by the dose of cocaine used, the brief duration of action, and the presence or absence of anesthesia. Our results indicate that cocaine has a brief, dose-dependent increase of heart rate in the conscious animal (Temesy-Armos et al. 1989a). Slowing of conduction velocity in the ventricle and the atrium has been demonstrated by us and several other researchers (Schwartz et al. 1989a; Kanter et al. 1988; Temesy-Armos et al. 1989a). Kabas and colleagues (1989) demonstrated slowing of conduction velocity in the His-Purkinje system at 3 and 5 mg/kg while Tracy and coworkers (1989), using a lower dose of cocaine (2mg/kg), observed slowing of conduction velocity in the atrioventricular (AV) node and in the His-Purkinje system only after both limbs of the autonomic nervous system were pharmacologically blocked by propranolol and propantheline. We also have demonstrated cocaine-induced increase in the atrial effective refractory period (Temesy-Armos et al. 1989a). However, cocaine's effect on the ventricular effective refractory period differs in several studies as shown in table 1 (Schwartz et al. 1989b; Kanter et al. 1988; Tracy et al. 1989; Temesy-Armos et al. 1989a).

The above results suggest that cocaine has dose-dependent effects that can be explained either by cocaine's known action to augment sympathetic tone (Ritchie and Greene 1990) or by cocaine's Class I antiarrhythmic action, The effect on heart rate can be explained best by an augmentation in sympathetic tone, whereas the effects on conduction velocity and the atrial effective refractory period are most likely due to cocaine's local anesthetic effects. The variable effects on the ventricular effective refractory period may be due to the opposing actions of augmenting sympathetic tone and local anesthetic activity. Sympathetic input, which tends to shorten the effective refractory period, has a greater effect on the ventricle than on the atrium (Wit et al. 1975). Cocaine causes less lengthening of the effective refractory period in the ventricle than in the atrium (Przywara and Dambach 1989). Thus, the variable results of cocaine on the ventricular effective refractory period may be explained by the relative input of these opposing actions.

TABLE 1.   *Preliminary reports on in vivo electrophysiological effects of cocaine*

Author	Schwartz	Schwartz	Kanter	Tracy	Kabas	Temesy-Armos
Publication	J Cardiovasc Pharmacol 1989	J Electrocardiol 1989	J Am Coll Cardiol 1986 (Abstract)	J Am Coll Cardiol 1989 (Abstract)	J Am Coll Cardiol 1989 (Abstract)	Clin Res 1989 (Abstract)
Canine model	Conscious	Conscious or anesthetized	Anesthetized	Conscious	Conscious	Conscious
Cocaine dose (mg/kg)	Variable, bolus and maintenance; mean total 2.1	Variable, bolus, maintenance, and second bolus; mean total 19.5	Bolus of 10 or 15; maintenance of 0.096 or 0.144	As a bolus 2	As a bolus 3 5	As a bolus 1 4
Effects of Cocaine						
Heart rate	NC	NC			↑ NC	NC ↑
Conduction						
Intra-atrial						NC Slowed
Intraventricular	NC	Slowed	Slowed			NC Slowed
Atrioventricular		Slowed		NC[*]		NC Slowed
Atrial-His				NC[*]		
His-ventricular				NC[*]	Slowed Slowed	
Effective refractory period						
Atrium						↑ ↑
Ventricle	↓		↑	NC		NC NC

[*]Conduction slowed after treatment with propranolol and propantheline.

NC = No change

COCAINE-INDUCED ARRHYTHMIAS IN ANIMAL MODELS

Two studies suggest that an extremely large dose of cocaine can produce arrhythmias within a few minutes after cocaine infusion. In a preliminary report, Kanter and colleagues (1988), using a 10 or 15 mg/kg intravenous (IV) bolus of cocaine followed by an infusion of 0.096 or 0.114 mg/kg/min in anesthetized dogs, reported ventricular tachycardia in 5 of 19 dogs, AV block in 3 of 19 dogs, and sinoatrial block in 3 of 19 dogs within 2 minutes of the bolus. Schwartz and coworkers (1989a) reported a wide complex tachycardia in one anesthetized dog beginning 10 seconds after an IV cocaine bolus of 8.4 mg/kg was added to a previous infusion of 13.8 mg/kg. They also reported a slow idioventricular rhythm within minutes of a cocaine bolus of 37.7 mg/kg added to a previous infusion of 40 mg/kg in an anesthetized dog.

Lower doses have not been shown to produce such early arrhythmias unless a concurrent, second intervention is present. Ruben and Morris (1952) demonstrated that the combination of cocaine and epinephrine could produce ventricular fibrillation in conscious and unconscious dogs. Billman and Hoskins (1988) reported that cocaine could produce ventricular fibrillation in conscious dogs in the setting of acute coronary occlusion and exercise. Inoue and Zipes (1988) showed that cocaine produced ventricular tachycardia in dogs with acute myocardial infarction which also received IV norepinephrine.

Our recent study in dogs showed delayed cardiac arrhythmias following cocaine, recorded on long-term continuous (Holter) electrocardiograms (Temesy-Armos et al. 1989b). Twelve conscious dogs had 26 hour long continuous ambulatory electrocardiographic recordings performed prior to cocaine and after IV cocaine at 4 mg/kg. Of the 10 dogs that showed no ventricular tachycardia on the baseline recording, 5 developed ventricular tachycardia after cocaine, which appeared 5.7 ± 4.6 hours after cocaine administration. Two of these 5 dogs developed lethal arrhythmias: One of them was a ventricular tachycardia at 300 beats per minute progressing to ventricular fibrillation and the other was sinus bradycardia progressing to asystole.

POSSIBLE MECHANISMS OF COCAINE-INDUCED LETHAL ARRHYTHMIAS

Cocaine-associated sudden death may be due to multiple arrhythmias including asystole and ventricular fibrillation. Some preliminary reports suggest that there may be several phases after cocaine when lethal arrhythmias may appear: "early" arrhythmias related to large doses and, much later, arrhythmias that may occur with lesser doses. At present, the mechanism of cocaine-related arrhythmias is uncertain. Based on electrophysiological observations,

the following theoretical mechanisms seem plausible. Asystole may be due to cocaine's Class I antiarrhythmic effect, which results in decreased automaticity and a slowing of conduction velocity. This local anesthetic effect of cocaine also may result in a profound negative inotropic effect (Fraker et al. 1990), which could lead to cardiac arrest. Other theoretical mechanisms for decreased automaticity and conduction include an increase in parasympathetic tone mediated by ischemia to the inferoposterior left ventricle (Thames et al. 1978) and a cocaine-mediated hypertension response (Wilkerson 1988; Flschman et al. 1976; Javaid et al, 1978; Foltin et al. 1988).

Ventricular tachyarrhythmias may be due to reentry, abnormal Impulse initiation, or both. Reentry may be mediated by Increased sympathetic tone or Type I antiarrhythmic activity (Han and Moe 1964; Rosen and Wit 1987). Abnormal impulse initiation, including triggered automaticity, also may be mediated by increased sympathetic tone (Wit et al. 1975) or by agents with Type I antiarrhythmic activity (Rosen and Wit 1987). In addition, a change in myocardial substrate, such as ischemia (Han and Moe 1964; Wellens 1975) or myocarditis (Vignola et al. 1984), could predispose to reentry and ventricular tachyarrhythmias.

CONCLUSIONS

The electrophysiological responses to cocaine as observed in animal models can be explained by cocaine's opposing actions of increasing sympathetic tone and its Type I antiarrhythmlc activity. Preliminary reports of animal models suggest that cocaine-related sudden death may be due to multlple arrhythmias, including asystole and ventricular fibrillation. The mechanism for such lethal arrhythmias is uncertain; however, they may be due to a cocaine-mediated (1) increase in sympathetic tone, (2) Type I antiarrhythmic activity, (3) change In myocardial substrate, or (4) a combination of these cocaine actions.

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Effects of Cocaine on Intracellular Calcium Handling In Cardiac and Vascular Smooth Muscle

Cynthia L. Perreault, Kathleen G. Morgan, and James P. Morgan

INTRODUCTION

The purpose of these studies was to test the hypothesis that the major effect of the cardiovascular toxicity of cocaine is due to drug-Induced alterations in intracellular calcium ($[Ca^{2+}]_1$) handling. This hypothesis is reasonable because calcium is an important second messenger for excitation-contraction coupling of both the heart and blood vessels (Ruegg 1988; Morgan and Morgan 1984a). Excitation-contraction coupling in any muscle type can be outlined by the process shown in figure 1. Ca^{2+} can enter the cytoplasm from either the extracellular fluid or intracellular stores. Entry of Ca^{2+} from the extracellular fluid is thought to play a larger role with respect to individual contractions in smooth muscle than in cardiac muscle. In cardiac and smooth muscle, Ca^{2+} can enter the cell via a calcium-mediated action potential; in vascular smooth muscle, receptor-operated channels that are associated with little or no change in membrane potential also play a role. Ca^{2+} is thought to be extruded from the cell either by adenosine triphosphate (ATP)-dependent calcium pumps or by the Na+-Ca^{2+} exchanger. An increase in $[Ca^{2+}]$, acts on the regulatory proteins to cause contraction of the myofilaments. In cardiac muscle, the regulatory proteins (the troponin complex) serve to restrain the actin and myosin molecules from their natural tendencies to form cross-bridges and to split ATP; the function of Ca^{2+} is to remove this inhibition, When $[Ca^{2+}]$,declines to resting levels, inhibition is restored and the muscle relaxes. In smooth muscle, the situation appears to be quite different. When isolated and purified, smooth muscle actin and myosin have little tendency to form cross-bridges or to split ATP-they are in an inactive state. The function of the smooth muscle regulatory proteins appears to be to activate the myofilaments, and the function of Ca^{2+} is to turn on this activation process. This occurs via calcium-mediated activation of the enzyme, myosin light chain kinase, which in turn mediates the phosphorylation of the light chains of myosin (shown as pathway of force development in figure 2). The phosphorylated form of myosin is active and

can then combine with actin to split ATP and undergo cross-bridge cycling. Whether Ca^{2+} must be present during the cycling of cross-bridges of phosphorylated myosin remains controversial. However, it is clear that Ca^{2+} is essential for initiating the contraction of cardiac and vascular smooth muscle under most conditions.
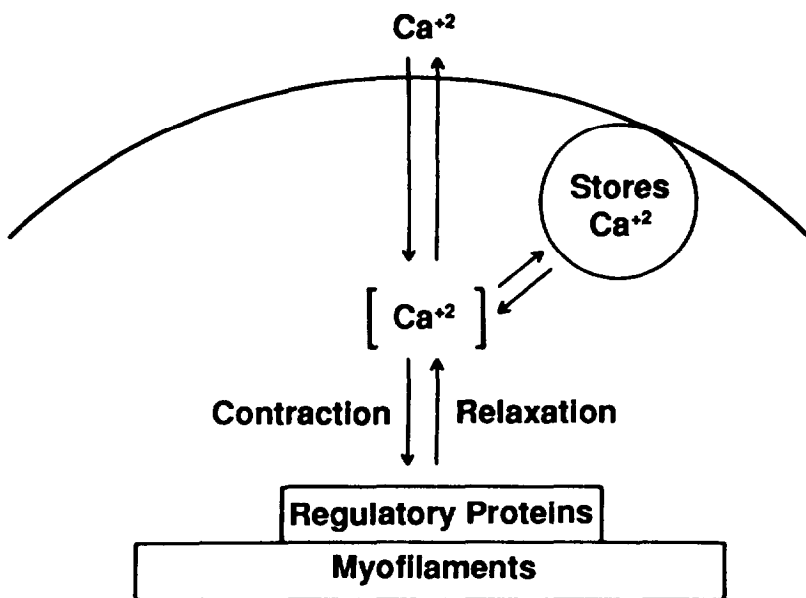
FIGURE 1. *Simplified scheme of excitation-contraction coupling in cardiac and vascular smooth muscle*

SOURCE: Morgan and Morgan 1984a, copyright 1984, American Journal of Medicine.

There also appears to be a second mechanism for altering the contractile state of cardiac and vascular smooth muscle that is independent of changes in $[Ca^{2+}]$, (Endoh and Blinks 1988; Morgan et al. 1988; Bradley and Morgan 1987). Under the influence of some drugs and during certain pathophysiologic states, the Ca^{2+}-force relationship can be altered so that a given level of $[Ca^{2+}]$, produces less or greater force per unit of cross-sectional area than would be expected under control conditions. This change reflects an alteration in the

Development

↑ $[Ca^{2+}]_i$

↓

↑ P-Myosin

↓

↑ Cross-Bridge Cycling Rate

↓

Rate of Contraction

Maintenance

↑ Ca   ↑ Diacylglycerol

↑ C-Kinase Activity

Amount of Force Maintained
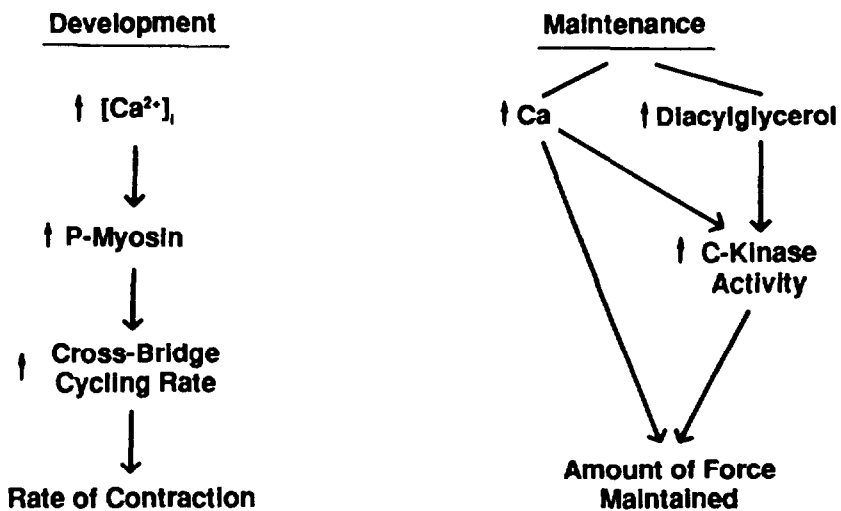
FIGURE 2. *Mechanisms of force development and maintenance in vascular smooth muscle*

SOURCE: Morgan et al. 1988, copyright 1988, New York Academy of Sciences,

myofilament Ca^{2+} responsiveness. Such a change can be produced in cardiac muscle by drugs such as caffeine or sulmazole which increase myofilament Ca^{2+} sensitivity, and by hypoxia, ischemia, and catecholamines, which decrease myofilament Ca^{2+} responsiveness, In vascular smooth muscle, dramatic increases in Ca^{2+} responsiveness can be produced by certain phorbol esters (Jiang and Morgan 1987, 1989) and by prostaglandin F_{2a}, which may activate the protein kinase-C pathway (shown as pathway of force maintenance in figure 2).

On the basis of the information presented above, the cellular mechanism of any drug which affects the inotropic state of cardiac muscle or the tone of vascular smooth muscle must be considered in terms of its actions on (1) intracellular Ca^{2+} levels and (2) myofilament Ca^{2+} responsiveness. The effects of cocaine on these two mechanisms were evaluated in mammalian cardiac and vascular tissues, as described below.

METHODS

Cardiac Muscle Experiments

Left and right atrial strips were excised from the hearts of adult male ferrets under chloroform anesthesia. The methods of preparation and instrumentation used in these studies have been described elsewhere in detail (Morgan et al. 1988; Bradley and Morgan 1987; Jiang and Morgan 1987, 1989; Blinks 1966; Kihara and Morgan 1989; MacKinnon et al. 1988). After removal from the hearts, muscles were maintained in a physiologic salt solution at 30°C and stimulated to contract at 3-second intervals with pulses of 5 msec duration. Unless otherwise specified, threshold voltage (i.e., $\leq$10 percent above threshold voltage, which typically is about 1 volt) was used to stimulate the muscles; under some circumstances, suprathreshold field stimulation was used to maximize catecholamine release from the adrenergic nerve endings (Blinks 1966). An initial P-hour equilibration period was allowed during which muscles were gradually stretched to the length where maximal isometric force developed. In one group of muscles, cumulative concentration-response relationships for norepinephrine and calcium were determined in the presence of 10^{-5} M cocaine. In a second group of muscles, the bioluminescent protein aequorin was loaded by a chemical approach described in detail elsewhere (Kihara and Morgan 1989; MacKinnon et al. 1988). Light signals were recorded with a photomultiplier by means of a light-collecting apparatus with the design described by Blinks (1982). A third group of muscles was subjected to increasing frequencies of field pulses before and after the addition of 10^{-5} M cocaine to the bathing medium.

Vascular Smooth Muscle Preparations

Left anterior descending coronary artery segments were removed from the hearts of swine that had been anesthetized with pentobarbitai before cardiac excision and placed in an organ bath containing physiologic salt solution at 37.5°C as described previously (Bradley and Morgan 1987; Morgan and Morgan 1984b, 1984c). In each smooth muscle experiment, the strip was stretched to the length at which maximal isometric tension developed as indicated by the contractile response to depolarization with 60 mM KCl. The luminal surface of each segment was rubbed with a rubber policeman to remove the endothelium. Lack of a functional endothelium in these preparations was indicated by a constrictor response to carbachol. Segments then were loaded with aequorin, the bioluminescent Ca^{2+} indicator, by a previously described method (Morgan et al. 1988; Bradley and Morgan 1987; Jiang and Morgan 1987, 1989).

Drugs and Chemicals

It is possible for drugs to interact directly with aequorin and modify the luminescent reaction or the sensitivity of aequorin to Ca^{2+}. Therefore, the potential for interaction of cocaine and aequorin was tested *in vitro* using the basic method and calibration device described by Endoh and Blinks (1988). After initiating the aequorin luminescence reaction with Ca^{2+}, *in vitro* cocaine was added to the reaction pipette; the drug had no effect on the luminescence reaction until concentrations in excess of 10^{-4} M were achieved. In these concentrations, the combination of cocaine plus aequorin appeared to decrease the light emission.

Peak tension, peak light, and relaxation times were compared by Student's *t*-test and multiple sample comparison tests; statistical significance was set at $p < 0.05$.

RESULTS

Cardiac Muscle Experiments

Figures 3, 4, and 5 show the actions of cocaine on ferret atrial strip preparations. Atropine, 2×10^{-6} M, was present in the bathing medium during all experiments to block the effects of acetylcholine released from the parasympathetic nerve endings. Figure 3 shows that 10^{-5} M cocaine produced a positive inotropic effect in $[Ca^{2+}]_o$ up to 4 mM; this effect was blunted at higher $[Ca^{2+}]$, where the muscles approached maximal activation. Figures 4 and 5 show that 10^{-5} M cocaine produced a leftward shift in the dose-response relationship of norepinephrine, whether applied exogenously into the bathing medium (figure 4) or released by suprathreshold field stimulation (figure 5).

Figure 6 shows the effects of 10^{-5} M cocaine on an aequorin-loaded ferret atrial strip. The cocaine produced a marked positive inotropic effect that was associated with an increase in $[Ca^{2+}]_1$. This effect could be exacerbated by using field vs. punctate stimulation to enhance the release of norepinephrine from the adrenergic nerve endings; it could be ameliorated by the addition of propranolol. Higher concentrations of cocaine (i.e., $>10^{-5}$ M) produced a dose-related negative inotropic effect in this atrial preparation that was associated with a corresponding decline in $[Ca^{2+}]_1$.
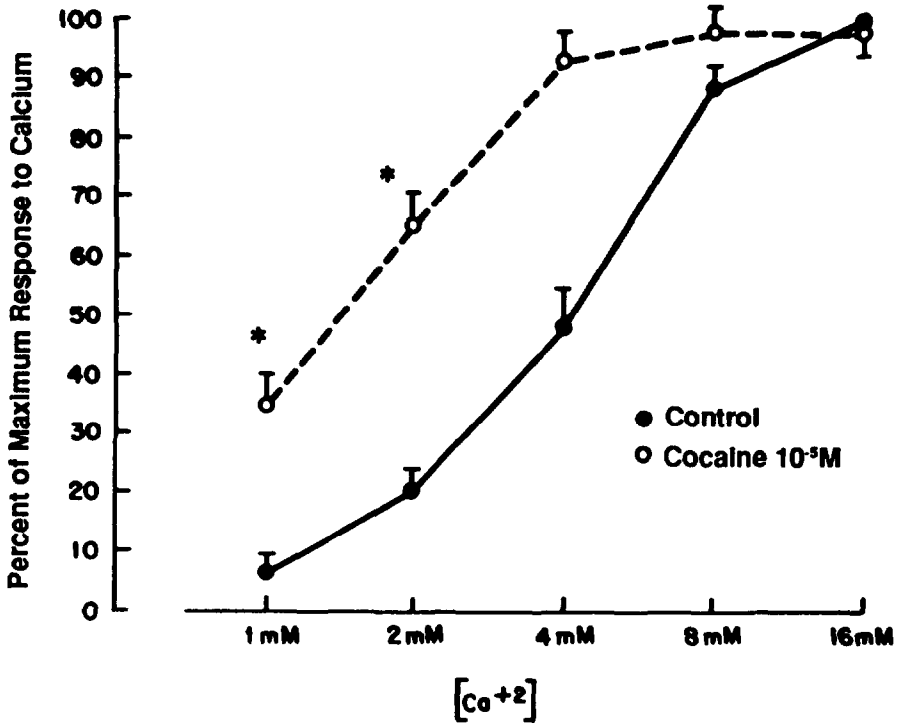
FIGURE 3. *Effects of cocaine, 10^{-5} M, on the calcium concentration response curve of ferret atrial muscle (30°C; 3 Hz; atropine, $2x10^{-5}$ M, in bath)*

NOTE: Values=mean±SEM
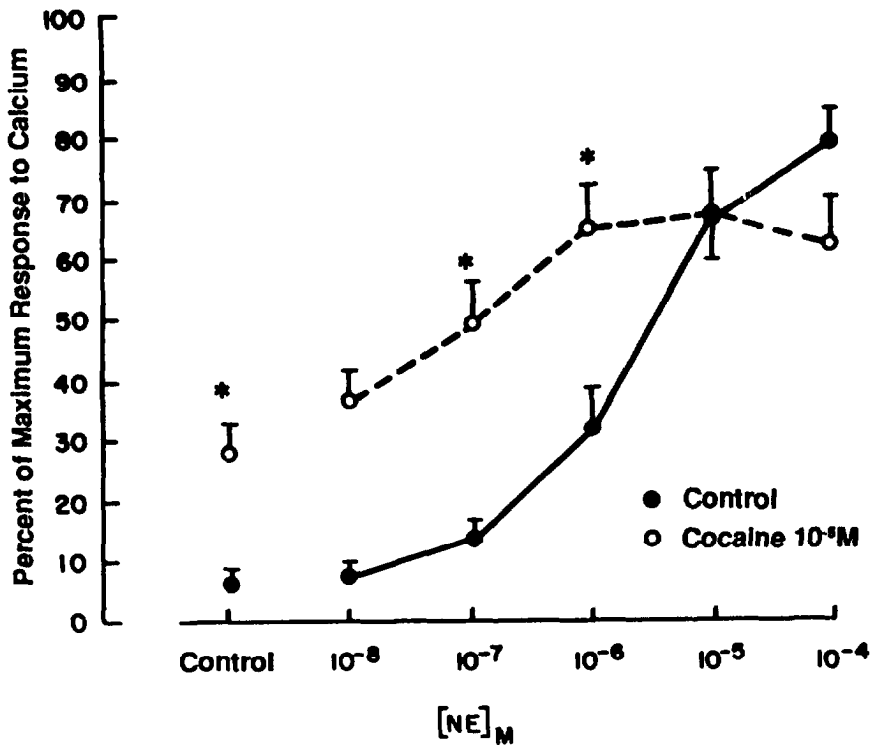
*p<0.05

FIGURE 4. *Effects of cocaine, 10^{-5} M, on the norepinephrine concentration response curve of ferret atria/ muscle (30°C; 3 Hz; atropine, $2x10^{-6}$ M, in bath). Responses have been normalized by maximum response to calcium.*

NOTE: Values=mean±SEM
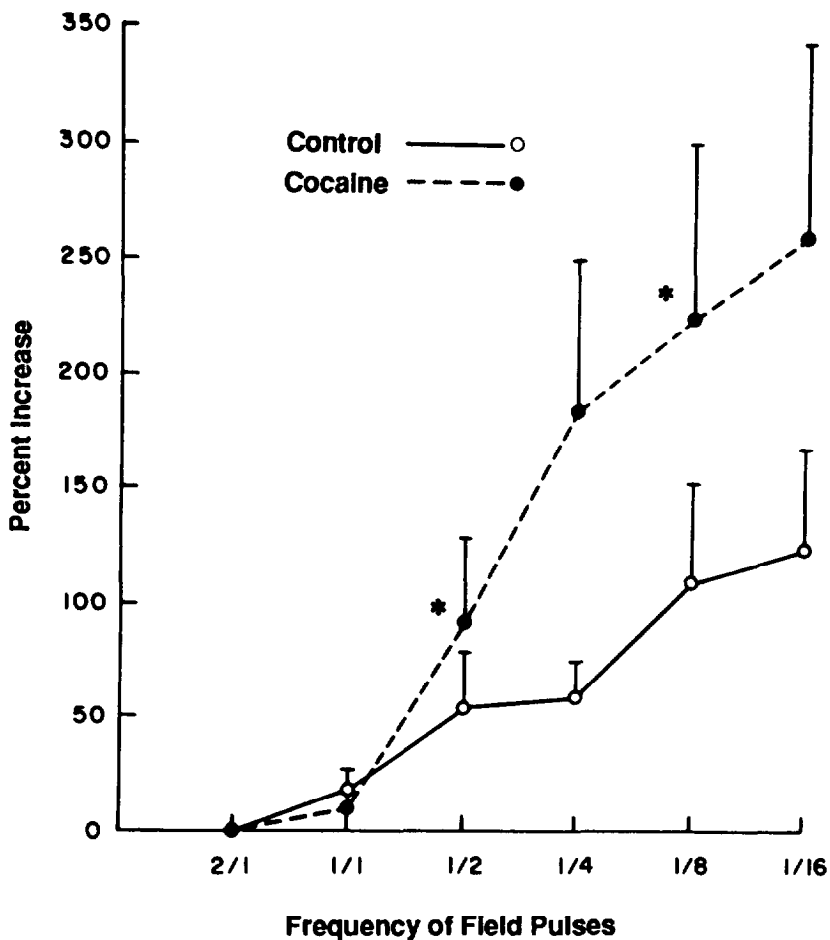
*p<0.05

FIGURE 5. *Effects of cocaine, 10^{-5} M, on the response to field stimulation (30°C; 3 Hz; atropine, $2X10^{-6}$ M, in bath)*

NOTE: Values=mean±SEM

*p<0.05

Solid line and open circles=control
Dashed line and solid circle=10^{-5} M cocaine
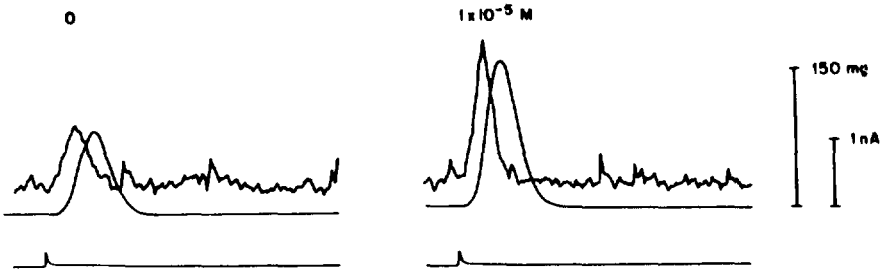
FIGURE 6. *Effects of cocaine, 10^{-5} M, on isometric tension and $[Ca^{2+}]_1$ in a ferret atrial strip. Upper trace, light (i.e., $[Ca^{2+}]_1$ recorded with aequorin in nanoAmperes (nA); middle trace, isometric tension in milligrams (mg); lower trace, stimulus artifact. Temperature=$3O°C$; 3 Hz punctate stimulation; atropine, $2x10^{-6}$ M, in bath.*

Vascular Smooth Muscle Studies

Figure 7 shows that cocaine and EGTA produced relaxation of a porcine coronary artery segment contracted with 60 mM KCl. The relaxation occurring in response to EGTA was associated with a marked decline in $[Ca^{2+}]_1$. In contrast, the relaxation in response to cocaine was accompanied by little change in the intracellular Ca^{2+} levels, suggesting that the drug was producing vasorelaxation through a Ca^{2+}-independent mechanism.

DISCUSSION

Cardiac Effects of Cocaine on Amplitude of Intracellular Calcium Transient and Isometric Contraction

As shown in figure 6 for a ferret atrial muscle, the aequorin light signal (i.e., $[Ca^{2+}]_1$ transient) from mammalian working myocardium consists of a single component that temporally precedes the corresponding tension response. These findings are consistent with current models of excitation-contraction coupling that predict that mechanical contractile events are preceded by changes in intracellular calcium concentrations (Ruegg 1988; Morgan and Morgan 1984a). Interpretation of the aequorin light signals has been detailed elsewhere (Morgan and Morgan 1984a, 1984b, 1984c; MacKinnon et al. 1988). Cocaine produces a positive inotropic effect in ferret atrial muscle under conditions in which catecholamine release from the adrenergic nerve endings is maximized (Perreault et al. 1988). This occurs due to cocaine-mediated blockade of adrenergic reuptake of norepinephrine
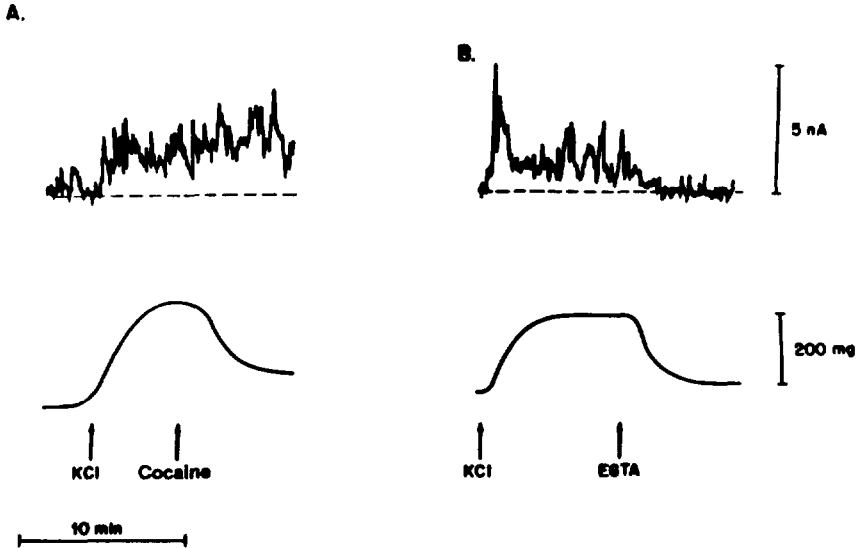
FIGURE 7. *Effects of cocaine, 10^{-3} M (panel A) and EGTA, 4 mM (panel B) on tone and $[Ca^{2+}]_1$ of a swine coronary artery segment stimulated to contract with 60 mM KCl. Upper panels show aequorin light signal (i.e., $[Ca^{2+}]_1$) in nA of anodal current from photomultiplier; lower panels show isometric force. Note that EGTA-induced relaxation is associated with a decline in $[Ca^{2+}]_1$, but cocaine-induced relaxation is not. Note that a wash artifact occurred at the beginning of the second trace, causing an uncharacteristic initial spike. Abbreviations are the same as those in figure 6.*

(Iverson 1971). In ferret papillary muscles (Hague et al. 1988) concentrations of cocaine in excess of 10^{-5} M produce the opposite effect, which probably is related to the local anesthetic actions of the drug. Local anesthetics characteristically block sodium influx via the voltage-dependent "fast" sodium channels in the sarcolemma. Under normal circumstances, intracellular sodium homeostasis is maintained, in part by a sodium-calcium exchange mechanism located in the sarcolemma, which transports intracellular sodium ions to the extracellular space in exchange for extracellular calcium ions. Decreased intracellular sodium concentrations impair the function of this exchanger so that intracellular calcium levels fall. It is important to note that the sarcolemmal actions of norepinephrine tend to antagonize this inhibitory effect of local anesthetics on the voltage-dependent sodium channels. In preparations in which the nerve endings are

depleted by the presence of disease or reserpine, positive inotropic responses to cocaine are not observed (Perreault et al. 1989a). Instead, a dose-related negative inotropic effect can be demonstrated from concentrations as low as 10^{-6}M.

As shown in figure 8, cocaine also abbreviates the light signal and twitch in concentrations of 10^{-5} M. This abbreviation may be due in part to catecholamine release by the adrenergic nerve endings (Morgan and Blinks 1982). However, in addition, cocaine and other local anesthetic agents may have direct effects on the cardiac sarcolemma (Josephson and Sperelakis 1976), sarcoplasmic reticulum (Blinks et al. 1972), and myofilaments (Perreault et al. 1990).

Vascular Effects of Cocaine on Isometric Tone

We have reported previously that cocaine produces relaxation of control and potassium-contracted coronary artery segments from pigs (Perreault et al. 1989a, 1989b). Moreover, cocaine produces similar vasodilatory responses in coronary artery segments from humans (Perreault et al. 1989a, 1989b). In contrast, cocaine produces an intense vasoconstrictor response in arterial segments from several animal species, including the ferret, that appear to be mediated by alpha-adrenergic stimulation (Ritchie and Greene 1985; Brown et al. 1984). Such an effect would not be expected in swine epicardial coronary artery segments because of their relative insensitivity to alpha-agonists due to a low density of alpha-adrenergic receptors (Bradley and Morgan 1987). A minimal response to alpha-adrenergic agonists also appears to be characteristic of epicardial coronary artery segments from humans (Ginsburg et al. 1980; Ginsburg 1983), although this responsiveness may be altered *in vivo* by the presence of ischemic heart disease (Mudge et al. 1976). Evidence is accumulating that suggests that the microvessels may contract in response to cocaine; this effect is ameliorated by alpha-adrenergic blockade (Lange et al. 1989).

Vascular Effects of Cocaine on Coronary Artery Calcium Sensitivity

We have reported previously that calcium-independent mechanisms play a major role in modulating contraction-relaxation cycles of vascular smooth muscle (Morgan and Morgan 1984a, 1984c; Morgan et al. 1988). The results shown in figure 7 suggest that cocaine-mediated vasorelaxation is produced by such mechanisms because intracellular Ca^{2+} levels appear to change little in the face of marked decreases in tonic tension. We have reported similar results in human coronary artery segments (Perreault et al. 1989a). Calcium-independent changes in vascular tone have been reported for prostaglandins and phorbol esters (Bradley and Morgan 1987; Jiang and Morgan 1987, 1989). The vasoconstriction produced by these agents has been interpreted in terms of

a change in a calcium-independent second messenger system involving protein kinase-C. Activation of protein kinase-C may result in phosphorylation of a site on the thick or thin filaments or the associated regulatory protein, which appears to alter the Ca^{2+} sensitivity of the contractile apparatus. This scheme is outlined in figure 2. Whether such a mechanism plays a role in mediating the Ca^{2+}-independent relaxation produced by cocaine remains to be established. However, relaxation appears to be primarily governed by a Ca^{2+}-independent mechanism rather than by decreased availability of intracellular calcium, as was seen in the heart.

SUMMARY AND CONCLUSION

The inotropic and lusitropic (i.e., relaxant) actions of cocaine on the heart appear to be caused primarily by changes in intracellular calcium handling. The positive inotropic and lusitropic effects of low and moderate concentrations (i.e., $<=10^{-5}$ M) are mediated by catecholamines; the negative inotropic effects of higher concentrations appear to be due to the direct local anesthetic effects of cocaine on excitation-contraction coupling mechanisms. The relevance of these findings to humans is suggested by the fact that blood levels of cocaine in excess of 10^{-5} M have been described in patients abusing this drug (Van Dyke et al. 1978; Paly et al. 1982). Blood vessels from certain vascular beds, including the epicardial coronary arteries of humans and swine, show little or no constrictor response to low concentrations of cocaine and relax at higher concentrations. In contrast to the effects on the heart, the relaxant effects of cocaine on vascular smooth muscle appear to be related to marked changes in myofilament calcium responsiveness, which may be mediated by the protein kinase-C system. These results at least indicate that the depressant effects of cocaine on cardiac vs. vascular smooth muscle occur by different mechanisms and suggest the need for specific therapeutic approaches to managing cardiac depression vs. vasodilatation when they occur in cocaine-intoxicated individuals. Moreover, these data provide evidence supporting the hypothesis that the net effects of cocaine in the intact organism are highly dependent on the underlying level of sympathetic adrenergic activity.

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Cocaine-Induced Changes in the Biochemistry and Morphology of Rabbit Aorta

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INTRODUCTION

The abuse of cocaine has been implicated in a number of cardiovascular toxicities, including coronary vasospasm and thrombosis, stroke, myocardial infarction, angina pectoris, arrhythmia, rupture of the aorta, and sudden death (Isner et al. 1986; Mittleman and Wetli 1987). These effects have been seen in all age groups with variable doses of cocaine and routes of administration, in individuals with cardiovascular disease, and in those with normal coronary artery angiography. The biochemical mechanisms involved in these responses to cocaine remain unknown.

Several current reports in the literature strongly suggest that cocaine can cause injury to blood vessels that may eventually precipitate an acute myocardial accident (Frischman et al. 1989; Simpson and Edwards 1986). Cocaine is known to interact with the sympathetic nervous system by potentiating the excitatory and inhibitory responses of sympathetically innervated organs to epinephrine and norepinephrine (Woods and Downs 1973). The sympathomimetic action of cocaine seems to be related primarily to its ability to block neuronal reuptake of norepinephrine.

Several investigators have demonstrated that the administration of catecholamines can result in both biochemical and histopathological changes which have many similarities to the early stages of human arteriosclerosis (Oester 1959; Lorenzen 1981). Langner and Fuller (1973) have demonstrated that, In the rabbit, one of the earliest catecholamine-induced biochemical changes in the arterial wall was an increase in the rate of aortic collagen synthesis, which was observed after only 4 days of treatment and before any gross alterations in aortic morphology were noted. These authors suggested that changes in aortic collagen synthetic rates represented a primary biochemical defect.

The catecholamine-induced aortic plaques were seen after 10 or 15 days of drug treatment and were primarily localized In the ascending and descending portions of the aortic arch and In the thoracic aorta. Histologically, changes were seen primarily in the medial layers of the aorta and were characterized by damage and/or disappearance of the elastic lamellae and an infiltration of the injured area with fluid, proteins, and glycosaminoglycans. Surrounding this necrotic area were layers of smooth muscle cells that appeared to be active both as fibroblasts and phagocytes. Calcification of the Injured area seemed to be a secondary event that followed the deposition of glycosaminoglycans. These catecholamine-induced lesions did not exhibit increased lipid accumulation: however, experimental studies by Constantinides and coworkers (1958) have shown that arteries injured by catecholamine administration incorporated lipids when rabbits were fed a high cholesterol diet.

The mechanisms whereby catecholamine caused these changes are unknown. Waters and de Suto-Nagy (1950) suggested that the hypertensive effect of the catecholamines caused an injury to the endothelial lining that was responsible for the observed changes. Based on current theories of atherogenesis (Ross 1986), this injury then could lead to the development of arteriosclerotic lesions.

Numerous theories have been proposed to explain the pathogenesis of arteriosclerosis. Currently, the most widely accepted theory is the response-to-injury hypothesis. Ross and Glomset (1976) proposed that all atherosclerotic risk factors, as well as mechanical, chemical, viral, and immunologic agents, injure the arterial endothelium and cause endothelial injury, which is followed by platelet adhesion and aggregation at the site of injury, with subsequent release of platelet-derived growth factor (PDGF). The release of PDGF stimulates migration and proliferation of smooth muscle cells in the intima and secretion of connective tissue components. In the presence of repeated damage or irritation to the endothelium, smooth muscle cells are thought to accumulate large amounts of cholesterol, resulting in cellular necrosis. This is complicated further by a buildup of fibrous tissue (mostly collagen) and calcium, leading to a clinically significant narrowing of the artery.

It has been hypothesized that cocaine-induced myocardial infarction results from an injury of the coronary artery that leads to increased platelet aggregation, thrombus, and arterial spasms (Frischman et al. 1989). Although this hypothesis is interesting, there is no direct evidence that the administration of cocaine has the potential to directly or indirectly injure blood vessels. Previous studies in our laboratory (Langner et al. 1988) have reported that cocaine can cause both histological and biochemical changes in aortic tissue, which suggests that cocaine has the potential to cause injury to the blood vessel wall. The purpose of the present studies was to determine the effects of

daily vs. alternate-day cocaine administration and to further define the biochemical and histological changes that occur following each pattern of cocaine administration.

METHODS

Adult male New Zealand rabbits weighing between 2.5 and 3.0 kg were used in this study. The animals were housed routinely in a room with a constant temperature (25°C) and a 12-hour light/dark cycle. Commercial rabbit chow and water were given *ad libitum.* For the daily cocaine treatment study, 25 rabbits were divided into two groups. Seven rabbits were placed in the saline control group; and 18 rabbits were placed in the cocaine treatment group. Each rabbit was weighed daily and injected via the marginal ear vein for 14 days using an infusion pump set to deliver fluid at a rate of 1 mL/min. The control animals were injected with sterile 0.9 percent saline for 1 minute. The cocaine-treated rabbits were injected with a 15 mg/mL solution of cocaine in 0.9 percent sterile saline at a concentration of 5 mg/kg. The dose of 5 mg/kg was selected because the authors' previous studies had demonstrated that this dose of cocaine would visibly stress the animals without causing excessive mortality.

For the alternate-day dosing study, 16 rabbits were divided into two groups. Six rabbits were placed in the saline control group, and 10 rabbits were placed in the cocaine treatment group and received cocaine injections at a dose of 5 mg/kg every other day for a total of 14 injections over 28 days. The animals in the alternate-day treatment group received the same total amount of cocaine as the daily cocaine-injected rabbits, but it was given over a longer period.

Twenty-four hours after the last injection, blood was drawn from the medial ear artery for determination of serum cholesterol, and the rabbits were killed. The thoracic cavity was opened, and the thoracic aorta from the beginning of the ascending aortic arch to the level of the celiac artery was quickly removed. The aorta was cleaned of loosely adhering tissue, opened longitudinally, and inspected for gross aortic plaques. A small section of the thoracic aorta located at the base of the aortic arch then was excised immediately, weighed, and frozen in liquid nitrogen. The sample was stored at -70°C until analysis for cyclic adenosine monophosphate (AMP) content. A second aortic section was taken from this region for histological evaluation. The tissue section was fixed in buffered formalin and stained with hematoxylin and eosin or Verhoeff's stain for elastin. The remaining tissue was minced into smaller pieces, placed in Krebs' bicarbonate buffer (pH 7.4) and preincubated for 20 minutes, The aortic minces were then placed in fresh Krebs' buffer containing 3 mCi of ^{14}C-proline and 0.2 mM L-proiine and incubated for 90 minutes following previously reported procedures (Langner and Bement 1985).

Following the incubation period, the tissue samples were rinsed with ice-cold 5 percent trichloroacetic acid (TCA) to prevent further incorporation of the labeled proline. The tissues were homogenized in nine volumes of normal saline using a glass, motor-driven, coaxial homogenizer. The synthetic rates of collagen and noncollagen proteins were estimated by the hot TCA-extraction procedure described by Newman and Langner (1975). Briefly, the procedure was as follows: An aliquot of homogenate was washed with ice-cold 5 percent TCA to remove any unincorporated ^{14}C-proiine and was centrifuged. The resulting pellets were extracted twice with 5 percent TCA at 90°C for 60 minutes. The TCA extracts were evaporated to dryness, resolubilized in distilled water, and counted in a liquid scintillation counter. These samples were used as an estimate of collagen synthetic activity. The pellet remaining after the extraction of collagen was digested overnight and then was counted in a liquid scintillation counter. These samples were used as an estimate of noncollagen protein synthetic activity.

The hydroxyproline content of the aortic homogenate was estimated by the method of Kivirikko and colleagues (1967) and was used as an index of tissue collagen content. Noncollagen protein concentrations were determined on the tissue homogenate using the method described by Lowry and colleagues (1951), with bovine serum albumin as the standard. The cholesterol content of each tissue was determined after lipid extraction following the procedures outlined by Omodeo and coworkers (1984) and Carlson and Goidfarb (1977). The calcium content of each aorta was estimated following the procedures described by Watts and coworkers (1987). The cyclic AMP content of the aorta was determined using a commercially available radioimmune assay kit. Serum cholesterol levels were determined on the ethanoiic extract of blood collected from the medial ear artery following the method described by Franey and Amador (1968). The data were compared for differences between means of groups by a one-way analysis of variance, When statistically significant differences were indicated, Duncan's multiple-range test was used for multiple comparisons between groups with unequal means at a level of significance of $p<0.05$ (Snedecor and Cochran 1976).

RESULTS AND DISCUSSION

The purpose of these studies was to test the hypothesis that the abuse of cocaine has the potential to cause serious injury to blood vessels. In these studies, rabbits were injected intravenously with cocaine at a dose of 5 mg/kg. This dose of cocaine, which is approximately one-third the reported LD50 for the intravenous (IV) administration of cocaine to rabbits (Rose et al. 1930), visibly stressed the rabbits but did not result in excessive deaths. The dose also is well within the dose range seen in humans since recent reports cite

doses of 0.5 to 1 g of cocaine as being administered before incidences of cardiac toxicity (Isner et al. 1986; Wang et al. 1988). Of the rabbits given daily injections of cocaine, one rabbit died after its 13th injection, and a second rabbit died after its 14th injection. Of the rabbits injected with cocaine on alternate days, one rabbit died immediately after its 6th injection, and a second rabbit died following its 10th injection. The exact cause of death in these rabbits was not determined, but it was presumably due to cardiac and/or respiratory depression, A third rabbit in this group broke its back as a result of a strong contraction that occurred after its flrst cocaine injection and had to be killed.

Several studies have demonstrated that elevation of aortic protein synthetic rates is an early and reliable indicator of aortic injury. The data in table 1 clearly demonstrate that the administration of cocaine on either a daily or an alternate-day basis resulted in elevated rates of total protein synthetic rates in some of the rabbits, which were defined as responder rabbits. To be classified as a responder, a rabbit had to have a total aortic protein synthetic activity that was at least two standard deviations above the mean aortic protein synthetic rate of the control group. As shown in table 1, 8 of the 14 daily-injected rabbits were classified as responder rabbits, and 4 of the 7 alternate-day injected rabbits were classified as responders. The remaining rabbits in each group were classified as nonresponders. This classification of responders and nonresponders was maintained in all subsequent tables. The mechanism by

TABLE 1.   *Aortic protein synthesis in rabbits given either daily or alternate-day IV injections of cocaine*

Group	N	Total (DPM/TH)	Collagen (DPM/TH)	Noncollagen (DPM/TH)
		Dally Injections		
Control	7	21,356±2,962	7,622±1,197	13,7331±1,808
Cocaine				
Responder	6	49,002±4,565[a]	17,356±2,193	31,645±2,666
Nonresponder	6	18,557±1,276	6,604±5,488	12,463±8,064
		Alternate-Day Injections		
Control	6	18,308±1,226	5,464±458	12,842±830
Cocaine				
Responder	4	27,696±516	8,583±661	19,113±670
Nonresponder	3	17,810±337	4,771±344	13,038±295

NOTE: All results are presented as mean±SE; TH=thoracic aorta.

[a]p<0.05 when compared with control group

which cocaine-induced aortic collagen and noncollagen protein synthetic rates in the responder group of rabbits, but not in the nonresponder group, is unknown. Because the New Zealand rabbit is not a genetically homogenous breed, it is possible that inherent genetic differences are responsible for the observed results. Additional studies are needed to clarify this issue.

As shown in table 2, there are no significant differences in the amount of aortic collagen or noncollagen protein content in either the responder or the nonresponder rabbits. Total aortic collagen content was estimated by measuring the amount of aortic hydroxyproline. This amino acid is found primarily in collagen, with lesser amounts present in elastin and the C1q component of complement. The absence of change in the total amount of aortic collagen and noncollagen proteins suggests that the lesions may be in an early stage of development. Sufficient time may not have elapsed to allow for a detectable accumulation of these proteins, even though the aortas exhibit increased rates of protein synthesis. Another possibility is that cocaine treatment has induced both synthesis and degradation of proteins, resulting in no net accumulation of either collagen or total proteins.

TABLE 2. *Protein and collagen content in the aorta of rabbits given either daily or alternate-day injections of cocaine*

Groups	N	Protein (mg/TH)	Hydroxyprollne (mg/TH)
		Daily Injections	
Control	7	68.0±0.6	4,296±1,624
Cocaine			
Responder	8	68.6±9.9	4,863±423
Nonresponder	6	70.1±8.3	4,908±317
		Alternate-Day Injections	
Control	6	73.0 ± 2.9	4,649±131
Cocaine			
Responder	4	92.3±7.9	6,250±887
Nonresponder	3	72.0±5.7	4,866±136

NOTE: All results are presented as mean±SE; TH=thoracic aorta.

Catecholamines are known to stimulate tissue adenyl cyclase activity that results in increased levels of cyclic AMP. Since cocaine may produce many of its effects by potentiating the effects of endogenous catechoiamines, aortic levels of cyclic AMP were measured. Several studies have suggested that

cyclic AMP is a mediator of cellular proliferation and lipid metabolism and that increased levels of cyclic AMP may be used as a biochemical measure of aortic injury (Augustyn and Ziegler 1975; Chateiain 1983). Data in table 3 show a significant increase in aortic cyclic AMP in the daily cocaine-injected rabbits in both responders and nonresponders. Because an increase in arterial cyclic AMP has been shown to precede the initiation of aortic protein synthesis and collagen accumulation (Chatelain 1983) it is possible that, if we had continued the daily injections of cocaine, all the rabbits would have shown elevated protein synthetic rates.

TABLE 3. *Aortic cyclic AMP and calcium content in rabbits given either daily or alternate-day injections of cocaine*

Group	N	Cyclic AMP (pmoles/mg Protein)	Caldum (μg/mg Protein)
		Daily Injections	
Control	7	6.03 ± 1.04	0.49 I 0.06
Cocaine			
Responder	8	13.00 ±3.46[a]	0.84±0.15[a]
Nonresponder	6	13.14 ±3.36[a]	0.57± 0.10
		Alternate-Day Injections	
Control	6	5.17±1.06	0.71±0.13
Cocaine			
Responder		4.36±0.54	0.72±0.16
Nonresponder		5.24 ±0.91	0.49 ± 0.01

NOTE: All results are presented as mean±SE.

[a]$p<0.05$ when compared with control group

Of the rabbits given alternate-day injections of cocaine, neither the responder nor the nonresponder rabbits demonstrated any increase in aortic cyclic AMP levels. It is difficult to explain why the alternate-day cocaine-treated responders had increased rates of protein synthesis but did not have elevated levels of cyclic AMP. One explanation may be that cyclic AMP levels are influenced by the frequency of cocaine administration and that daily administration of cocaine is necessary to sustain elevated tissue levels. Another possibility may be that cyclic AMP is an early, transient cellular mediator in aortic tissues that can still be detected at 14 days but returns to control levels by 28 days in the alternate-day cocaine-treated rabbits. Additional studies are needed to clarify this issue.

Alteration of cellular calcium levels in vascular tissues is recognized as an important regulatory signal involved with many cellular processes. The accumulation of calcium has been implicated in several cellular functions such as platelet aggregation, smooth muscle cell proliferation, and lipoprotein binding to smooth muscle cell receptors. Elevated levels of aortic calcium have been demonstrated repeatedly in atherosclerotic aortas and are considered to be an indicator of cellular necrosis and cell death (Kramsch et al. 1981; Sugano et al. 1986). As shown in table 3, tissue calcium levels were significantly elevated in the aortas of the daily cocaine treated-responder rabbits, but not in the nonresponder animals. In the alternate-day cocaine-treated rabbits, aortic calcium levels were not altered in either the responder or the nonresponder rabbits. Calcium levels were determined by atomic absorption spectrophotometry; therefore, it is not possible to discriminate between intracellular and extracellular calcium. The presence of the increased calcium in only the daily treated cocaine responder rabbits is significant because it suggests that frequency of cocaine administration plays an important role in the expression of cocaine's toxicity. The data are also consistent with the hypothesis that cocaine has the potential to induce alteration of aortic function, which may possibly result in cellular necrosis and death.

The feeding of cholesterol to rabbits will cause increases in both serum and aortic cholesterol levels. These changes then are followed by increased rates

TABLE 4. *Serum cholesterol, aortic cholesterol, and visible lesions in rabbits given daily or alternate-day injections of cocaine*

Group	N	Serum Cholesterol (mg/100mL)	Aortic Cholesterol (mg/TH)	Number of Animals With Viable Lesions
		Dally Injections		
Control	7	36.6+ 4.4	0.88±0.11	1 of 8
Cocaine				
Responder	8	38.1±9.6	1.05±0.10	4 of 6
Nonresponder	6	46.5±11.1	1.03±0.16	1 of 6
		Alternate-Day Injections		
Control	6	53.7± 5.6	0.89±0.05	1 of 6
Cocaine				
Responder	4	67.2± 14.0	1.05±0.11	2 of 4
Nonresponder	3	64.0± 2.5	0.88±0.07	1 of 3

NOTE: All results are presented as mean±SE; TH=thoracic aorta.

of aortic protein synthesis, increased levels of aortic cyclic AMP, and increased aortic calcium levels. As shown in table 4, the daily or alternate-day injection of cocaine did not cause any alteration in the final serum cholesterol levels or in the aortic cholesterol content in either the responder or the nonresponder rabbits. These findings suggest that cocaine has a direct effect on the aortic wall and does not produce the observed changes by altering tissue cholesterol levels.

As shown in table 4, of the rabbits given daily injections of cocaine, four of eight responder rabbits and only one of the six nonresponder rabbits had grossly visible plaques on the surface of their aortas. Of the rabbits given cocaine on alternate days, two of four responder and one of three nonresponder rabbits had visible plaques. in ail cases the plaques were raised patches located primarily in the aortic arch and upper portion of the thoracic aorta. There was no apparent difference between the visible lesions in the daily-treated and the alternate-day-treated rabbits. Histological evaluation of the aortic tissue sections demonstrated that cocaine-induced lesions were focal and could be quite different. Medial lesions were the most frequent and had a spectrum of intensity. An example of histological damage induced by cocaine administration is shown in figure 1, which shows changes in both the intima and the media of

FIGURE 1. *Photomicrograph of aorta from a rabbit injected on alternate days with cocaine (14 injections). The lesion exhibits a necrotic area in the media that is characterized by infiltration of inflammatory cells and foam cells.*

the aortic wail. in the media, there is a necrotic center that has lost its normal morphology. The elastic fibers have lost their normal undulation and have become either broken or replaced with inflammatory cells and foam cells. The area above the necrotic core appears to be a thickened intima that protrudes into the lumen of the blood vessel. Attempts to correlate changes in aortic protein synthetic activity with histological changes were not possible. In these studies, only limited samples were taken for histological analysis; the remainder of the aortic tissues were used for biochemical analysis. Because of this limited histological evaluation and because of the focal nature of the lesions, it is not possible to determine whether the biochemically defined responder rabbits had more medial damage than the nonresponders. It is also not possible to determine whether a cause-and-effect relationship exists between histopathological and biochemical changes,

The mechanism by which cocaine produced the biochemical changes in the responder rabbits, but not in the nonresponder rabbits, is unknown. The biochemical and histological changes produced by cocaine administration are very similar to changes observed following epinephrine administration. It has been suggested that epinephrine causes an increase in heart rate and blood pressure that in some manner may cause an injury to the intimal lining of the blood vessel (Waters and de Suto-Nagy 1950). Because cocaine has the ability to potentiate endogenous catecholamine activity, the vessel-damaging effects of cocaine may be the result of increased heart rate and/or blood pressure. The exact mechanism by which increases in blood pressure and heart rate damage the arterial wail is unknown and needs to be investigated.

The significance of our observations in rabbits to the development of aortic damage in humans remains to be elucidated. In several cases evaluating cocaine-induced myocardial infarctions in humans, coronary arteriography has revealed significant vessel obstruction. In a study of patients with cocaine-induced heart disease, 9 of 13 patients who underwent cardiac catheterization had significant stenosis of one or more coronary arteries (Pasternack et al. 1985),

Atherosclerotic cardiovascular disease is now recognized as multifactorial in etiology (Kannel and Sytkowski 1987). Hopkins and Williams (1981) listed 246 risk factors that have been implicated in the development of atherosclerosis. it is generally believed that the propensity to develop cardiovascular disease is dependent on the type and number of risk factors present, duration of exposure to each factor, and an individual's genetically determined response to each factor. Many epidemiological, clinical, and experimental studies have suggested that the elimination or reduction of risk factors is necessary for the

prevention of atherosclerotic disease and that each risk factor makes its own contribution and may act synergistically with other risk factors.

Our data clearly demonstrate that, in rabbits, cocaine has the ability to cause an injury to the blood vessel wall, resulting in biochemical and morphological changes in the arterial wall. The significance of these changes and their relationship to cocaine-induced cardiotoxicity in humans cannot be determined from these studies. These data, however, are consistent with the hypothesis that the abuse of cocaine may be a risk factor in the premature onset of atherosclerotic disease and its complications in humans who chronically use cocaine in large amounts.

CONCLUSIONS

The results of these studies clearly demonstrate that, in sensitive animals, the administration of cocaine has the potential to injure the vascular wall of blood vessels, resulting in histopathological and biochemical changes. These data are consistent with the hypothesis that cocaine abuse may directly alter the blood vessel wall in such a manner as to induce the early onset of cardiovascular diseases.

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Effects of Cocaine on the Physiology of Exercise

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INTRODUCTION

It is well known that cocaine is a powerful sympathomimetlc drug (Fischman 1984). Many chapters In this monograph link the cardiotoxic effect of cocaine to this property, which has other physiological ramifications, such as exercise conditions, that have not been well explored. Exercise is also a powerful sympathetic enhancer (Marker et al. 1986) and the logical questions to ask are (1) What are the combined physiological effects of cocaine and exercise? and (2) Could these combined effects be deleterious? Since the pioneering work of Freud (1885) and Hanna (1970) it generally has been accepted that cocaine may be an ergogenlc aid due to its euphoric effects (Flschman 1984). The studies reviewed in this chapter refute that notion and provide considerable insight into the combined physiological and metabolic responses to cocaine and exercise.

METHODS

The following studies were performed using male Sprague-Dawiey rats that initially weighed between 200 and 250 g. The animals were trained to run on the motor-driven treadmill (Quinton, Seattle, WA) for 7 to 14 days before the experiment. This pretraining involved daily sessions of running at speeds of 22 to 26 meters per minute (m/min) up a 10-percent grade for 10 to 15 minutes duration. Three to four days before the experimental run In studies 2 and 3, jugular catheters were implanted for delivery of cocaine and/or for administration of the anesthetic. At the time of sacrifice, the animals were anesthetized wlth pentobarbital sodium (60 mg/kg), and samples of blood, skeletal muscle, or heart muscle were rapidly excised and stored frozen for subsequent biochemical analysis. Skeletal muscle samples were obtained from the white and red vastus lateralis muscles and the soleus muscle. These muscles in the rat are representative of fast-twitch glycolytic, fast-twitch oxidative, and slow-twitch oxldative fiber types, respectively (Baldwin et al. 1972).

Study 1. Effects of Cocaine on Endurance

Design. The purpose of the study by Bracken and colleagues (1988) was to determine if cocaine had an enhancing effect on endurance. Animals were injected intraperitoneally (IP) with cocaine (20 mg/kg) or isotonic saline and, beginning 20 minutes after injection, were run to exhaustion (22 m/min, 15-percent grade). This dose of cocaine was selected because Kershner and coworkers (1983) reported that it improved performance in their study.

Results. The cocaine-treated rats ran only 29±12 minutes compared to 75±17 (x±D) minutes for the saline-injected controls. Clearly, cocaine had a detrimental effect on performance. To understand the cause of the poor performance in the cocaine group, the glycogen content of the three different skeletal muscle fiber types common to the rat was analyzed. Glycogen is an important energy substrate in skeletal muscle, and any change in its concentration during exercise usually reflects muscle involvement (Conlee 1987). These results are shown in figure 1. It was clear that in the two fast-twitch muscles (red and white vastus) of the hind limb, glycogen appeared to be used at a much greater rate in the cocaine group than in the saline group. Since glycogen depletion is known to cause fatigue (Conlee 1987), the rapid use of glycogen in the cocaine-treated animals could have led to premature fatigue. On the other hand, when blood lactic acid levels were measured in these animals (figure 2) the values in the cocaine-treated animals were more than twice as high as those in the saline-treated group. This observation alone could explain the early fatigue in the drug-treated group. By some unknown mechanisms cocaine caused rapid glycogenolysis and concomitant lactacidemia, both of which could have contributed to early cessation of exercise. Some possible mechanisms are proposed in the discussion of studies 1 and 2.

Study 2. Effects of Various Doses of Cocaine on Exercise Endurance and Physlology

Design. The second study by Bracken and coworkers (1989) tested the effects of a wide range of doses on exercise endurance and gathered more physiological information that might help to clarify the observations of the first study. Animals were injected IP with saline or 0.1, 0.5, 2.5, 12.5, or 20 mg/kg cocaine and then, beginning 20 minutes after the injection, were run to exhaustion (26 m/min, 10-percent grade).

Results. Figure 3 shows the endurance results. Cocaine had no beneficial effect on endurance at any dose. At the two highest doses, cocaine severely limited endurance. The muscle-glycogen results from the dose-response study
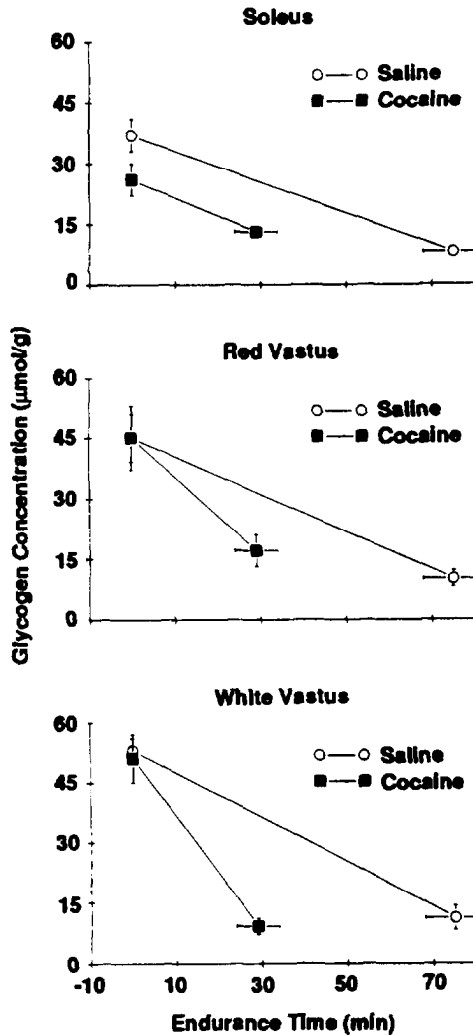
FIGURE 1. *Effect of cocaine and exercise on glycogen concentration in soleus, red vastus lateralis, and white vastus lateralis muscles of the rat*

NOTE: Each point=mean±SE for five to seven animals. Exhausted values are significantly different from preexercise values, p<0.05.

SOURCE: Bracken et al. 1988, copyright 1988, American Physiological Society.
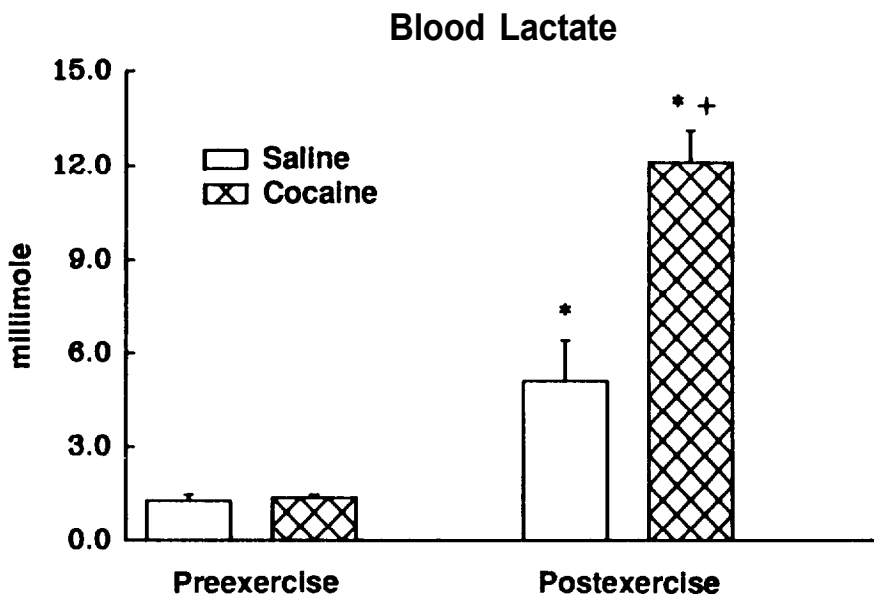
Blood Lactate

FIGURE 2.   *Effect of cocaine and exercise on blood lactate levels*

NOTE: Each bar=mean±SE for five to seven animals.

*Significantly different from at rest
+Significantly different from saline, p<0.05

SOURCE: Bracken et al. 1988, copyright 1988, American Physiological
            Society.

are shown in figure 4. Across all doses, cocaine treatment had no effect on resting glycogen content of the two predominantly fast-twitch muscles (white and red vastus lateralis). However, the two highest doses caused a reduction in the glycogen concentration in the slow-twitch soleus muscle at rest. This effect on soleus muscle at rest may reflect an Increased locomotor activity often observed in cocaine-treated animals (Post and Weiss 1988). At exhaustion, the glycogen levels in all muscles for all treatments were reduced to the same levels (figure 4), but because the cocaine animals (12.5 and 20.0 mg/kg) ran for a considerably shorter time (figure 3), it was concluded that the rate of glycogen depletion in those animals was greater.
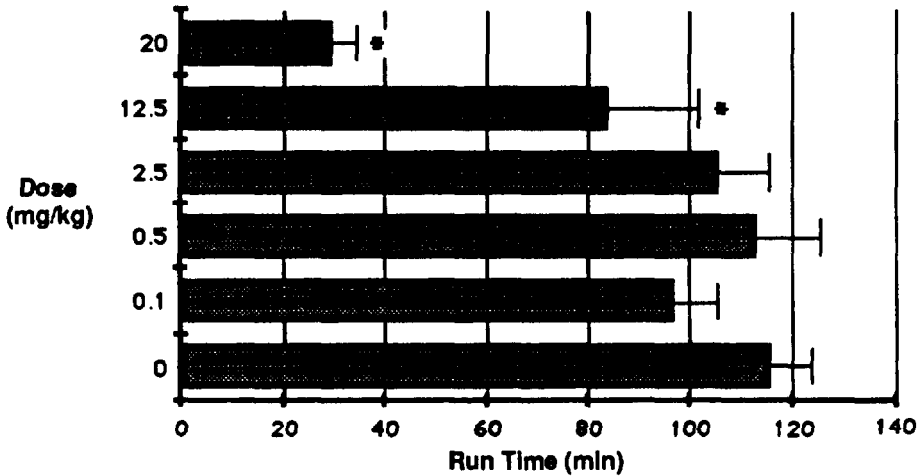
FIGURE 3. *Run times to exhaustion of rats Injected with five different doses of cocaine and run at 26 m/min up a 10-percent grade*

NOTE: Each bar=mean±SE; n=7 to 11 animals for each group.

*Significantly different from 0 dose (saline-treated controls), p<0.05

SOURCE: Bracken et al. 1989, copyright 1989, American Physiological Society.

Blood levels of epinephrine (E) and norepinephrine (NE) also were measured, and those results are shown in figure 5. Both amines showed a tendency to rise with increasing dose at rest. However, the increase was more dramatic for NE than E. During exercise, cocaine (20 mg/kg) clearly exaggerated the NE response, but the effect on E was less discernible. This latter result with E was more attributable to the design of the study than to a lack of effect of cocaine. in the last phases of an exhausting run, all animals tended to fall more often on the electric grid attached to the treadmill, which created an additional stress in the animal. Such additional stress in the saline animals could have exaggerated the catecholamine response and masked the real physiological effect of exercise alone (Marker et al. 1986). This opinion is supported by the

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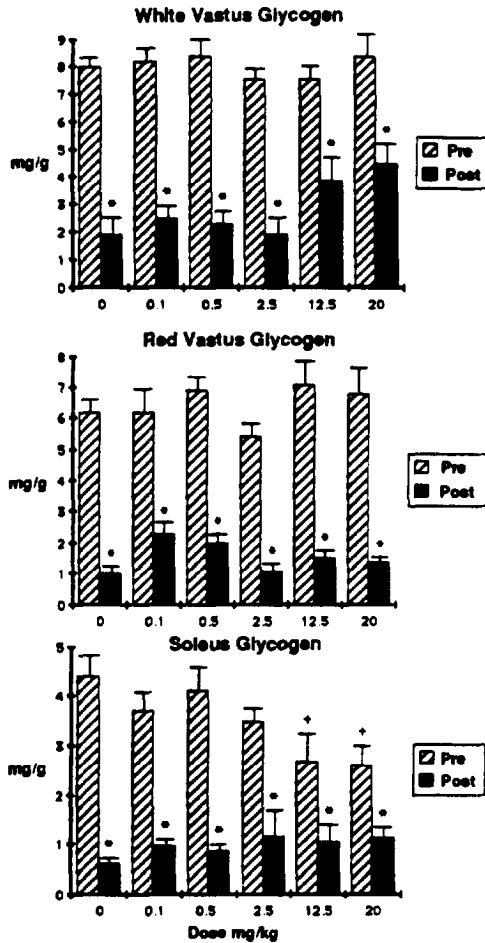
FIGURE 4. *Effect of various doses of cocaine on hind limb muscle glycogen content before (pre) and after (post) treadmill exercise (26 m/min, 10-percent grade) to exhaustion*

NOTE: Each bar=mean±SE; n=7 to 11 animals for each group.

*Significantly different from corresponding preexercise value, p<0.05
+Significantly different from preexercise 0 dose (saline-treated controls)

SOURCE: Bracken et al. 1989, copyright 1989, American Physiological Society.
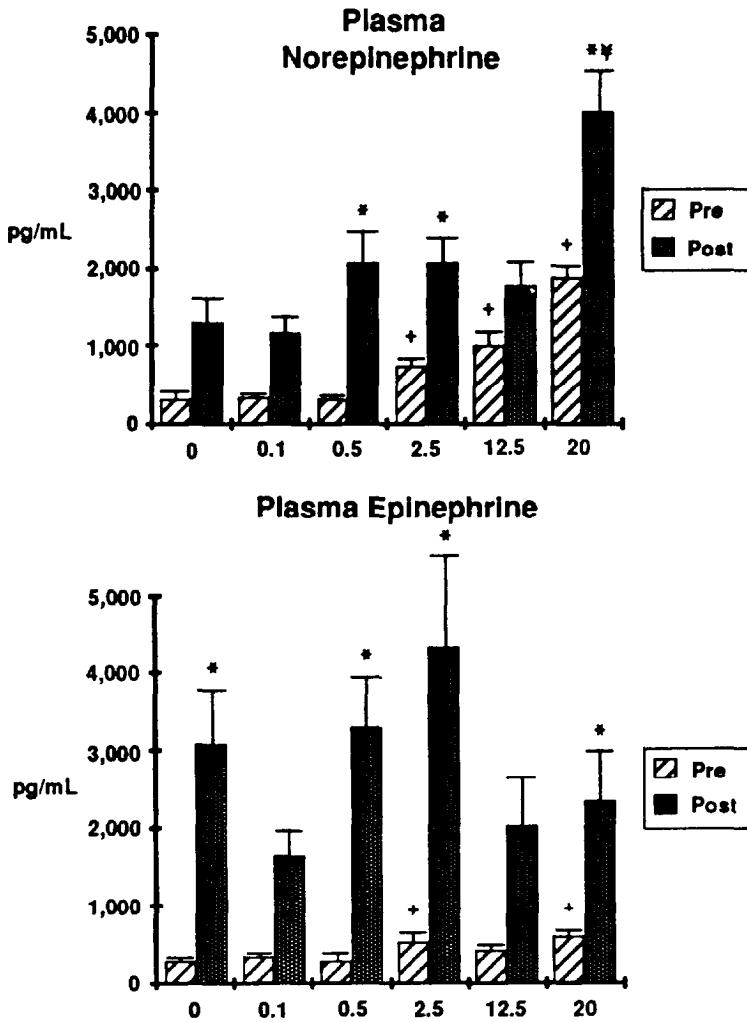
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FIGURE 5. *Effect of various doses of cocaine on plasma concentration of norepinephrine and epinephrine before (pre) and after (post) treadmill exercise (26 rn/min, 10-percent grade) to exhaustion (see figure 4 legend for details)*

¥Significantly different from postexercise 0 dose, p< 0.05

SOURCE: Bracken et al. 1989, copyright 1989, American Physiological Society.

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results in table 1, which were obtained from exhausted cocaine animals and paired-saline runners. It is clear that running for the same period results in higher NE and E values in the cocaine-treated animals compared to paired saline-treated rats. A marked contrast in lactate values also was observed between groups, similar to that shown in figure 2.

TABLE 1. *Comparison of plasma catecholamine and blood lactate levels from cocaine-treated fatigued rats and saline-treated, time-paired control runners*

	Norepinephrine (pg/mL)	Epinephrine (pg/mL)	Lactate (mM)
Cocaine	2,992* ±563	1,445 ±444	10.5* ±2.4
Saline	648 ±237	616 ±230	2.4 ±0.1

NOTE: Values=means±SE; n=five to six animals for each group.

*Significantly different from paired saline runners

SOURCE: Bracken et al. 1989, copyright 1989, American Physiological Society.

These results imply that cocaine dramatically exaggerates the normal sympathetic response to exercise, but the data in table 1 still can be criticized because they were obtained from cocaine animals being forced to run to fatigue, which, as alluded to earlier, may have additional physiological consequences above those derived from cocaine or exercise alone. With that in mind, another experiment was designed in which animals were injected with cocaine (12.5 mg/kg) or saline and then run for only 30 minutes. The animals were in a more steady-state regimen, thus eliminating the confounding factors associated with running to exhaustion. The preliminary results (unpublished observations) verify that the normal rise in plasma concentrations of E and NE during exercise is accentuated dramatically by cocaine. These are exciting observations of the peripheral physiological responses to cocaine. Because of these additive responses, it appears that the exercise model eventually could serve as an important research tool for studying the mechanisms by which cocaine exerts its effects.

Discussion of Studies 1 and 2

It is clear from studies 1 and 2 that cocaine has an adverse effect on prolonged exercise endurance. The physiological and biochemical observations made concomitantly with the endurance results suggest some possible mechanisms by which cocaine exerts its influence.

1. Cocaine is known to induce vasoconstriction in a variety of tissues (Ritchie and Greene 1980). This can occur indirectly because cocaine inhibits the reuptake of NE at sympathetic presynaptic terminals (Herting et al. 1961). An accumulation of NE in the synaptic space could induce vasoconstriction of arterioles through alpha receptors (Belfrage and Rosell 1976). If this happened in muscle during exercise, there would be reduction of blood flow, decreased delivery of oxygen, increased rate of glycogenolysis for energy, and eventual increase in lactic acid production, On the other hand, vasoconstriction also can occur as a seemingly direct effect of cocaine on the vasculature without any intervening hormonal or neurotransmitter response (Shuster et al. 1988). Whether direct or indirect, the vasoconstrictlon could lead to fatigue through the cascade of responses outlined above, with fatigue being the result of glycogen depletion or lactic acid accumulation (Conlee 1987).

2. The increased muscle glycogenolysis observed during exercise performed under the influence of cocaine could result from the effect of higher levels of E induced by the cocaine. Epinephrine during exercise is known to stimulate muscle glycogenolysis (Richter et al. 1981). A wasting of glycogen could lead to early fatigue (Conlee 1987).

3. It is possible that cocaine may stimulate glycogenolysis directly, although there is no evidence to support this contention,

Study 3. Effects of Cocaine on Cardiac Metabolism

Design. The study by Conlee and colleagues (1989) was designed to evaluate the combined effects of exercise and cocaine on myocardial carbohydrate metabolism as a logical extension of the authors' results from skeletal muscle. Animals were injected intravenously with either saline or one of three doses of cocaine (1.25, 5.0, or 10.0 mg/kg). It is important to point out some methodological considerations. In the preliminary work for this study, the authors found that single, rapid, bolus intravenous injections of cocaine caused seizures and, sometimes, death; 20 mg/kg was almost always fatal, and that dose was abandoned. After trial and error, a satisfactory injection scheme was established. The proper dose was delivered in a volume of 0.2 mL/100 g BW

(body weight) administered in six to eight small bolus injections over a 3-minute period while the animal was restrained by hand. Saline-treated animals were injected in exactly the same manner. Using this protocol, only two cocaine-injected animals were unable to begin running immediately after injection, and they were eliminated from the study. The treadmill protocol consisted of a 20-minute run at 22 m/min and 15-percent grade. Upon cessation of the run, the animals were anesthetized immediately (20 seconds), and the hearts were removed and frozen within 10 seconds of opening the thorax.

Results. Unlike the results with skeletal muscle (figures 1 and 4), there was no effect of cocaine on myocardial glycogen concentration at rest or exercise (figure 6). Nor was there any effect of the drug on the concentration of glucose-6-phosphate in the myocardium (figure 6). These results contrast to the dramatic dose-response increases seen In plasma-free fatty acids (figure 7).

Discussion of Study 3

Recent reports have temporally linked incidents of myocardial infarcts to the use of cocaine (Altieri et al. 1987; Zimmerman et al. 1987). One mechanism proposed to explain the seizures was the cocaine-induced vasoconstriction of the coronary vasculature. Support for this theory derives from two sources. First, Wilkerson (1989) showed that in dogs under the influence of cocaine, myocardial blood flow did not keep up with myocardial oxygen demand. Second, Lange and coworkers (1989) recently observed in humans that cocaine reduced the size of coronary arteries and caused vasoconstriction of the intramural resistance vessels. It could be reasoned that, because the use of stored glycogen for energy by the myocardium is closely linked to oxygen availability (Hewitt et al. 1973), any decrease in oxygen delivery due to cocaine-induced vasoconstrlctlon could Increase glycogen degradation, especially during exercise when oxygen demand is high. Unfortunately, no alteration of carbohydrate metabolism due to cocaine was observed. This would argue indirectly against the notion that cocaine interferes with blood flow to the myocardium. This does not mean, however, that cocaine may not have an effect under different experimental conditions (e.g., longer or more intense exercise). On the other hand, it may be that cocaine acts only on hearts that are uniquely susceptible to the drug. Evidence presented elsewhere in this monograph (Langner and Bement; Knuepfer et al.) supports the theory that not all organisms are responders. This is empirically true when one considers that only a small fraction of cocaine users ever experience a cocaine-induced heart seizure (Choy-Kwong and Lipton 1989). Nevertheless, preliminary results show an exaggerated sympathetic response to cocaine and exercise, which suggests that the two conditions combined may create a set of physiological conditions that could be detrimental to individuals predisposed to cardiovascular disorders. Whereas this point is speculative, it deserves further study.
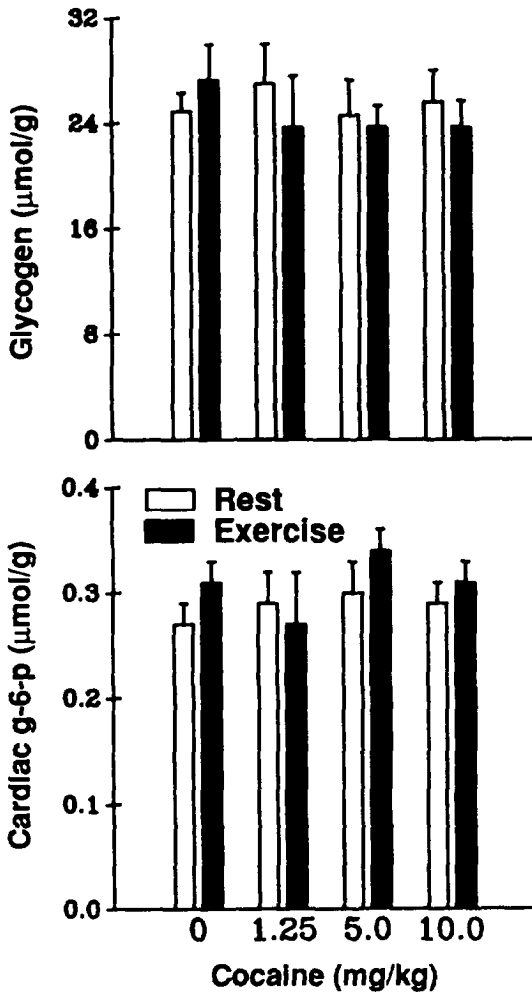
FIGURE 6. *Effects of various doses of cocaine after 20 minutes of exercise (22 m/min, 15-percent grade) on myocardial glycogen and glucose-6-phosphate   concentrations*

NOTE: Each bar=mean±SE; n=4 to 13 animals for each group.

No significant differences were observed among any treatments, p>0.05.

SOURCE: Conlee et al. 1989, copyright 1989, W.B. Saunders Company.

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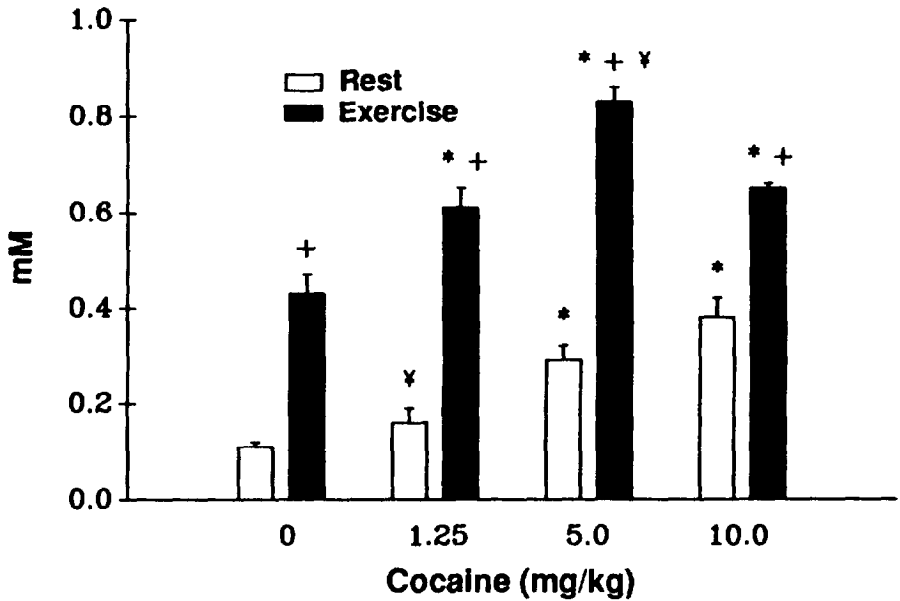
FIGURE 7. *Effects of various doses of cocaine after 20 minutes of exercise (22 m/min, 15-percent grade) on plasma-free fatty acid levels*

NOTE: Each bar=mean±SE; n=7 to 13 animals for each group.

* Significantly different from 0 dose (saline controls), $p < 0.05$
+Significantly different from at rest
¥Significantly different from other two cocaine doses, $p < 0.05$

SOURCE: Conlee et al. 1989, copyright 1989, W.B. Saunders Company.

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Effect of Acute Cocaine Administration on Cardiac and Respiratory Patterning in the Freely Moving Cat

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INTRODUCTION

Mechanisms underlying cardiovascular and respiratory changes following acute cocaine administration are extremely complex, since cardiovascular responses associated with cocaine administration are most likely dependent on drug action on both the peripheral and central nervous system (CNS). Moreover, respiratory and cardiovascular control systems are highly interactive, with changes in one system being associated with alterations in the other. Exaggerated inspiratory efforts, for example, are accompanied by enhanced venous return, which in turn triggers a set of cardiac reflexes, whereas rapid transient increases in arterial pressure can diminish somatic muscle tone and lead to short-term abolition of inspiratory efforts.

It is essential to understand both cardiovascular and respiratory control mechanism responses to cocaine, since high-dose acute cocaine administration is lethal. Death may result from apnea or apneusis, from some failure of cardiovascular function, or from some interaction of the two systems such as respiratory compromise leading to hypoxia, which then leads to an agonal cardiac rhythm. It is also essential to consider potential effects of cocaine on the CNS and how these effects may modify the interactions between respiratory patterning and the cardiovascular system. Cocaine has been shown to have a particular affinity for action on limbic forebrain structures (Jones 1984), which have major direct influences on cardiovascular action in intact systems.

The role of neural mechanisms in controlling respiration outside of central and peripheral chemoreceptors frequently is ignored, yet brain structures—in particular, rostral brain structures—can have profound effects on respiratory patterning. Although cyclic respiratory patterns and adequate blood pressure

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can be maintained in a preparation with suprapontine transection (Hoff and Breckenridge 1952), descending forebrain influences can greatly influence both cardiac and respiratory control structures (Frysinger et al. 1984; Marks et al. 1987).

Obvious instances of such higher brain influences include voluntary breathing, vocalization, temperature drive to respiration, and sleep states. In particular, sleep states, when combined with certain pathological conditions, can suppress normal respiratory patterning in some or all of the ventilatory musculature, for example, in central and obstructive sleep apnea (Severinghaus and Mitchell 1962; Harper and Sauerland 1978; Remmers et al. 1978). This suppression is thought to be initiated in pontine structures, which provoke atonia of respiratory muscles mediated through medial reticular structures in the caudal medulla (Schenkel and Siegel 1989). Cocaine may exert deleterious effects on the functions of particular brain structures that project to cardiac and respiratory control mechanisms in the brainstem, thus disturbing normal respiratory and cardiovascular control.

The available evidence on respiratory patterning after cocaine intoxication is sparse. Rapid shallow breathing (Wilson et al. 1976; Matsuzaki et al. 1978) and apnea have been reported: the latter frequently is observed following generalized convulsions (Catravas and Waters 1981; Jonsson et al. 1983). Clinical reports of acute cocaine intoxication suggest that respiratory "failure" is a frequent finding.

It is important to determine whether cocaine-related "failure" of respiration results from diminished activation of the diaphragm or whether "failure" results from (1) obstruction of the upper airway caused by extreme excitation of laryngeal adductors ("active obstruction"), (2) extreme sustained inspiratory effort by the diaphragm (apneusis) so prolonged as to cause a loss of O_2 stores, (3) collapse of the upper airway brought about by drug-induced loss of upper airway muscle tone and the consequential airway narrowing from the Venturi effect of negative diaphragmatic pressure (Harper and Sauerland 1978), or (4) a tachypnea of such enhanced rate as to make airflow ineffective. The reports that rapid, shallow respiration accompanies cocaine intoxication suggest that cocaine exerts a major effect on central respiratory timing mechanisms. However, the potential for active upper airway occlusion or sustained inspiration of the diaphragm exists, particularly as a consequence of localized limbic system seizure discharge.

Determining the mechanisms of cocaine action on different respiratory muscles is important because different mechanisms of action have an impact on toxic

management. Our first studies examined the action of high-acute doses of cocaine on upper airway and diaphragmatic patterning and potential interactivity with the cardiovascular system.

METHODS

These studies have been carried out on two female and three male adult cats. Under sodium pentobarbital anesthesia, a pair of insulated, flexible, multistranded stainless steel wires were placed into the posterior cricoatytenoid (PCA) muscles of the larynx, an upper airway dilator muscle, and four sets of wires were placed into the lateral costal diaphragm (figure 1). Bipolar stainless
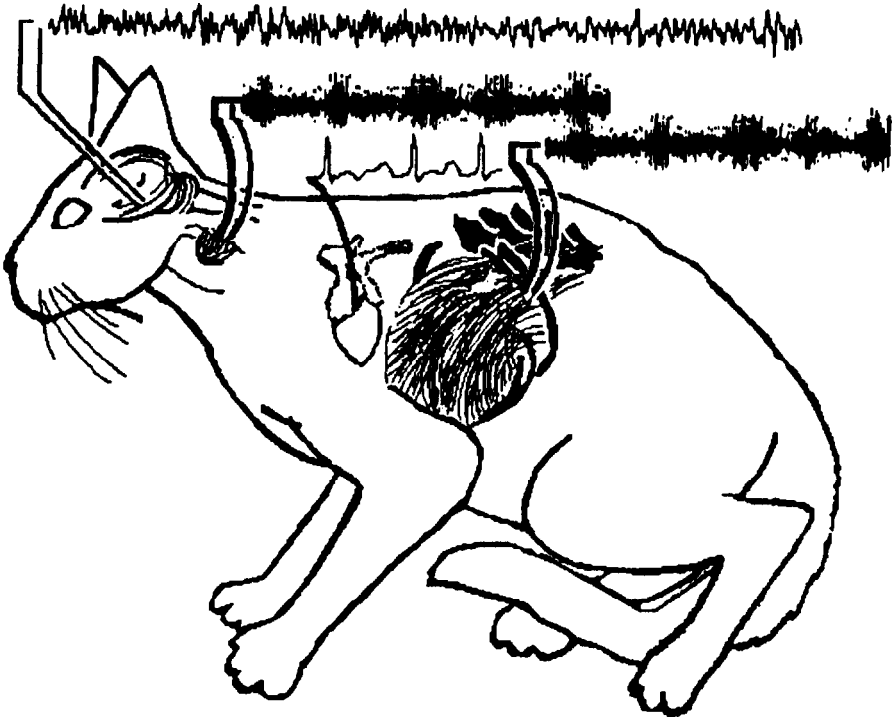

FIGURE 1. *Schematic outline of the principal measures taken from the subjects. Electromyographic activity of a laryngeal dilator, the PCA, and the costal diaphragm are recorded. ECG activity and hippocampal and cortical slow wave electrical activity also are measured.*

steel electrodes also were stereotaxically placed bilaterally into the dorsal hippocampus (Snider and Neimer 1961), and stainless steel screws were placed into the bone overlying the sensorimotor cortex. These hippocampal and surface electroencephalogram (EEG) electrodes were placed to record limbic system and cortical electrical activity, respectively, particularly during cocaine-related seizure discharge. A thermistor was placed on the cortex over the parietal cortex, and another thermistor was placed in muscle between the clavicles to record brain and core body temperature, respectively. Stainless steel cannulae, covered at one end, were placed within the lateral ventricle. Electrocardiogram (ECG) activity could be recorded from the same respiratory leads placed in the diaphragm (figure 1); however, this diaphragm-lead configuration does not readily provide indications of atrial pulses. For this reason, we also placed a 4-5 French five-pole recording catheter through the right jugular vein into the right ventricle so that atrial and ventricular activity could be recorded. Moreover, these recordings were supplemented by surface recordings with an electrode placed high on the right thoracic cage and low on the left abdominal wall to assist in P-wave differentiation on the ECG trace.

After 2 weeks of surgical recovery, the animals were placed in a sound-attenuated 1 m^3 recording chamber kept at room temperature. Electrodes were attached to a polygraph, and signals were simultaneously written on polygraph paper, digitized at appropriate rates as dictated by the Nyquist frequency (Harper et al. 1974), and stored on digital media as well as on analog tape. After a control recording of one sleep and waking cycle, the subjects were administered one of three doses of cocaine intravenously (5.0, 7.5, or 10.0 mg/kg or an equivalent volume of saline) or, in the case of ventricular administration, 0.625, 1.25, or 2.5 mg or an equivalent volume of artificial cerebrospinal fluid for control studies. Cortical EEG, hippocampal slow activity, ECG, PCA and diaphragmatic patterning, and brain temperature were all recorded and stored on digital and analog media. Diazepam (10 mg administered intravenously) was used to intervene in those cases in which cardiac arrhythmias appeared to be proceeding to sustained ventricular tachycardia or agonal rhythm.

RESULTS

Motor Characteristics

High-dose cocaine administration resulted in an extreme extension of the limbs and neck and arching of the back reminiscent of decerebrate rigidity (figure 2). This extreme extension was accompanied by clonic jerks associated with seizure discharge. A similar state (without seizures) can be produced in animals with lesions In the Interstitial nucleus of Cajal (Fukushima et al. 1987)

or with decerebration involving loss of cortical and basal ganglion structures, the classic preparation for decerebrate rigidity (Sherrington 1898). The pronounced motor extension produced by cocaine is of great theoretical and practical interest, since these findings raise the possibility of generalized involvement of much of the skeletal musculature, including the respiratory musculature. Moreover, the findings suggest action of cocaine on specific neural mechanisms controlling motor systems, and these actions can be experimentally partitioned. The extreme motor signs diminished 1 to 2 hours after cocaine administration, although animals had difficulty with motor behavior for an additional several hours. The motor expression is similar to that described in sheep following cocaine administration (Woods et al. 1989) and has been anecdotally reported in humans. Other autonomic motor behavior accompanies the somatic motor

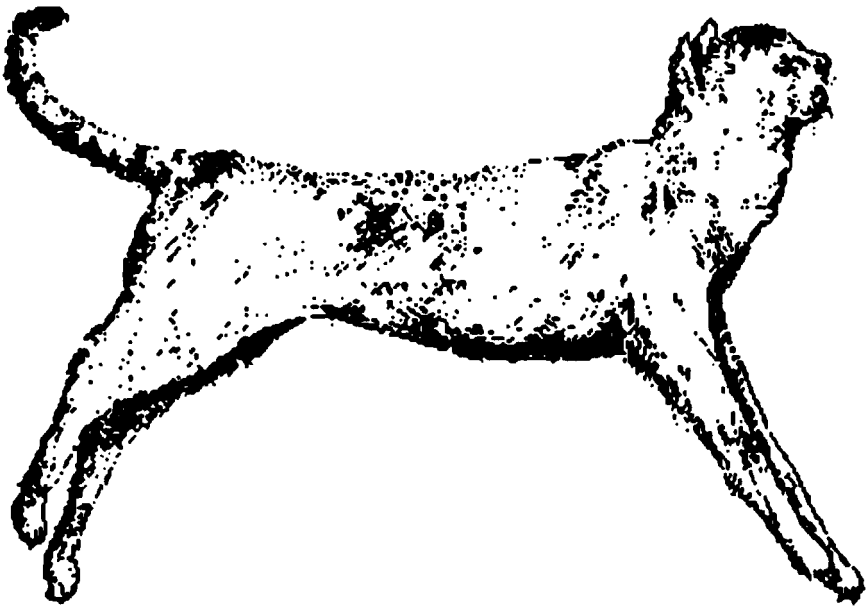**FIGURE 2.** *Typical posture following high-dose administration of cocaine (although the animal is lying on one side). This is a modification of an original drawing of decerebrate rigidity by Pollock and Davis (1930). The neck, back muscles, and limbs are in extreme extension; this motor behavior also is accompanied by periodic (12 per minute decreasing to approximately 9 per minute and then ceasing) myoclonic jerks.*

changes. The animals salivate profusely 5 to 30 minutes following drug administration, typically vomit 20 to 30 minutes after intravenous (IV) administration, and have a bowel movement 30 minutes to 1 hour after initial onset of drug action.

Respiration

The major cocaine effect on both upper airway and diaphragmatic activity after the initial extreme rise In blood pressure is tachypnea. The rise in discharge rate is extreme, and the resulting gas exchange may be ineffective for survival. We have not yet assessed tissue oxygen saturation following cocaine, but the animals show every sign of being hypoxic, including the mode of death (agonal rhythm). The rise in rate occurs in the PCA and diaphragmatic muscles. We also have not as yet determined whether the relative timing of activation of the PCA vs. the diaphragm is affected by cocaine; a derangement of phase between these two muscle systems might greatly affect air exchange, particularly if the airway were occluded when the diaphragm is in the inspiratory phase.

In addition to the initial increase in both upper airway (PCA) and dlaphragmatic muscle activity rate [in 3 some cases by a factor of four over normal baseline waking rates (figure 3)], cocaine administration was followed by a pronounced phasic increase in upper airway muscle activity, particularly of the genioglossal muscles of the tongue; moreover, panting occurred later (1 to 2 minutes post administration) in the recording session. These changes may be associated partially with temperature increases (see below) since there was a delay in the onset of the enhanced upper airway effect. Increased activation of airway dilators would assist in lowering core temperature by enhancing air movement.

Temperature

An increase in core and brain temperature occurred following administration of cocaine by any route (figure 4). Brain temperature increased markedly and rapidly following IV administration (average increase of 0.85°C in 30 minutes). A slight, gradual increase then followed, reaching a maximum temperature within 1 1/2 to 2 hours post intravenous injection (1.2°C mean increase over baseline, five cats); temperature then declined slowly, returning to baseline typically 2-1/2 to 3 hours following initial cocaine administration. Intracerebral ventricular administration resulted in a sharp rise in temperature, reaching a maximum 8 to 15 minutes post injection (0.7°C average), with a steady decline thereafter and return to normal baseline in 30 minutes.

Pre

Cocaine

Recov

1 sec
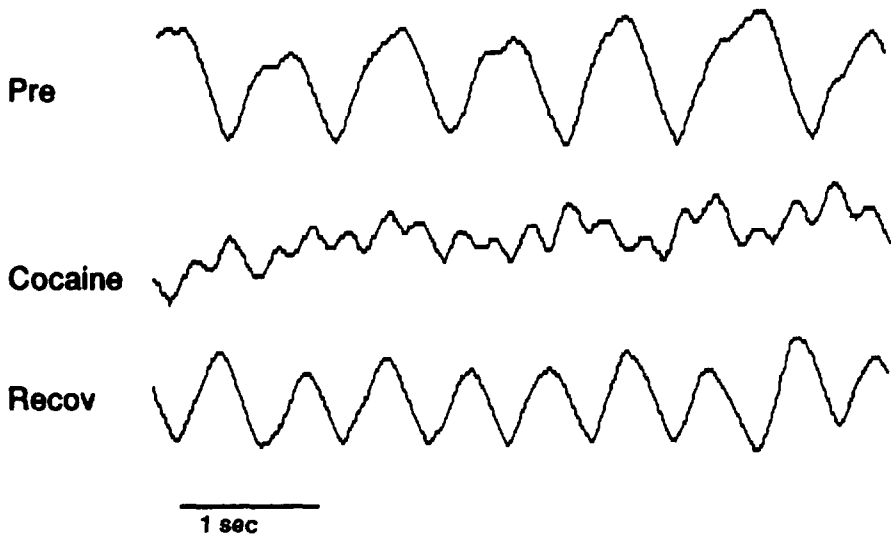
FIGURE 3.   *Root-mean-square (a close analog of integration) traces of PCA activity before cocaine administration, 15 minutes following 7.5 mg/kg administration, and 3 hours postadministration. Respiratory bursts increase by a factor of four over control periods; diaphragmatic bursts occur equally as often.*

A portion of the tachypnea observed following cocaine administration may result from the increased temperature noted here, since increased respiratory rates result from increases in core temperature and the extreme respiratory efforts in panting may serve to diminish core temperature. We still are partitioning the effect of temperature on respiratory patterning, relative to a direct effect of cocaine on brain structures that act directly on respiratory timing structures.

Cardiac

Examination of cardiac R-R intervals before cocaine administration revealed typical variation at the respiratory frequency as well as slower variation from movement, blood pressure variation, and temperature trends; the slower variation was particularly prominent during rapid eye movement (REM) sleep, and the respiratory variation was especially large during quiet sleep. Following cocaine administration, R-R intervals became fixed, with a total abolition of both respiratory and slower variation. Both types of variation gradually returned after
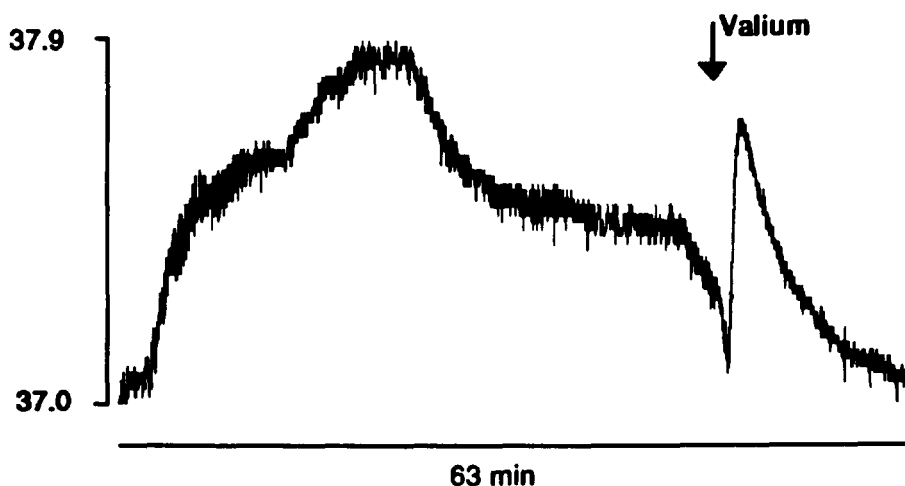
FIGURE 4. *Plot of trend in brain temperature (measured by an indwelling thermistor and continuously monitored by an analog voltmeter and then digitized) following administration of 10 mg/kg cocaine. Brain temperature reached a peak approximately 25 minutes post administration. A 10 mg IV administration of diazepam caused a second rise in temperature (possibly mediated by handling), followed by a more rapid decrease.*

several hours, with slower variation returning first (figure 5). The overall R-R interval duration decreased (i.e., heart rate increased) following cocaine administration; this heart rate increase gradually declined over time. In addition, R-R interval durations and variation increased immediately following diazepam administration (figure 8).

Large cocaine doses, administered intravenously, resulted in a variety of cardiac arrhythmias, including ventricular tachycardia. The largest IV cocaine doses typically resulted in generalized tonic seizure-like discharges that were characterized by extreme extension of the peripheral musculature typical of decerebrate rigidity described earlier. One seizure was accompanied by a widened QRS complex recurring at a very rapid rate with a period that matched the synchronized electrical activity recorded from the hippocampus (figure 7). Administration of the benzodiazepine diazepam (10 mg) caused an immediate (within 30 seconds) return of hippocampal activity to nonseizure state and a concomitant conversion of the arrhythmia to a sinus rhythm (figure 8). Two animals that received high-dose cocaine in which diazepam intervention was ineffective succumbed to an agonal rhythm, which classically results from

hypoxia. Death from hypoxia typically occurs in an agonal rhythm rather than ventricular fibrillation. Thus, cocaine may so constrict the vasculature as to cause hypoxia or may impair respiratory efforts, which in turn leads to hypoxia.

FIGURE 5. *Plot of cardiac R-R intervals before 7.5 mg/kg IV cocaine administration, 30 minutes post administration, and 3 hours post administration. R-R interval times in msec are on the y axis; successive intervals are on the x axis. Approximately 2 minutes of intervals are shown on each trace. Note the near flat line indicating virtually no variation 30 minutes after cocaine administration; the scale indicates 10 msec above and below 110.*

Cocaine administration initially was followed by an extreme rise in pressure and thus a pronounced baroreflex-initiated extreme vagal outflow. This enhanced vagal outflow was sufficient to alter conduction (figure 9).

DISCUSSION

The objectives of these studies were to examine the effect of acute administration of cocaine on upper airway and diaphragmatic respiratory musculature in the freely moving, conscious cat, to relate respiratory patterning in these muscles to electrical activity in limbic structures of the brain, and to examine cardiorespiratory interactions. Specific questions addressed by these
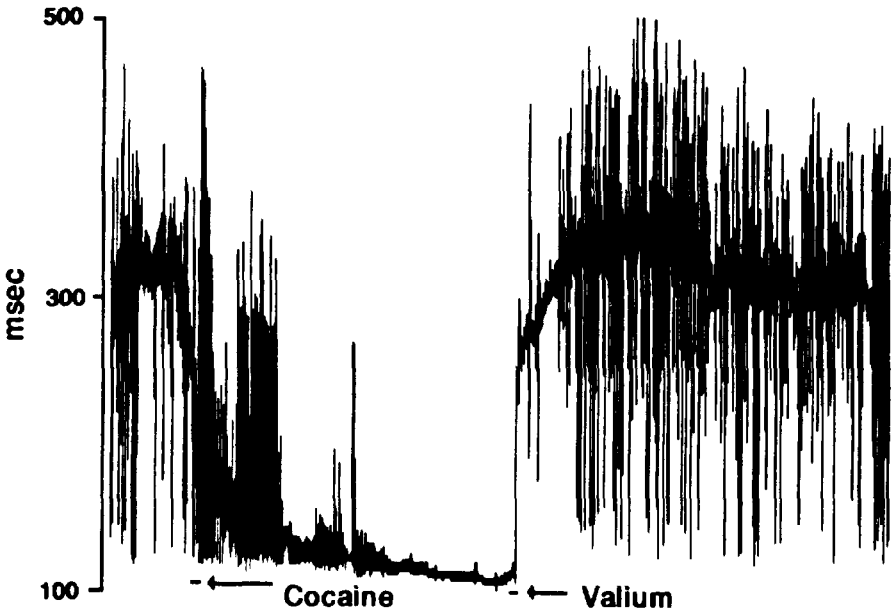
FIGURE 6. *Compressed record of R-R intervals plotted over an 80-minute period before administration, following cocaine delivery (bar), and following delivery of diazepam (second bar). Note the extreme shortening of R-R intervals (cardiac rate increase) and the virtual abolition of variation in these intervals following cocaine administration and the rapid return to longer intervals (slower rate) and increased variation following diazepam delivery.*

studies included examining the hypotheses that (1) cocaine exerts preferential enhancement of upper airway constrictors, thus potentially leading to upper airway obstruction and (2) cocaine causes extreme apneustic activity In the diaphragm, thus leading to a fall in O_2 stores. A second objective was to relate patterning of cardiovascular activity to electrical activity in brain structures and to partition the effect of cardiovascular changes secondary to respiratory changes induced by cocaine. Specifically, we wished to test the hypothesis that seizure discharge, particularly in limbic structures, provided such profound neural drive to cardiac innervation as to greatly modify cardiac conduction patterns. Moreover, we wished to examine the possibility that cocaine effects would greatly modify normal cardiorespiratory reflexes protective of cardiovascular function.
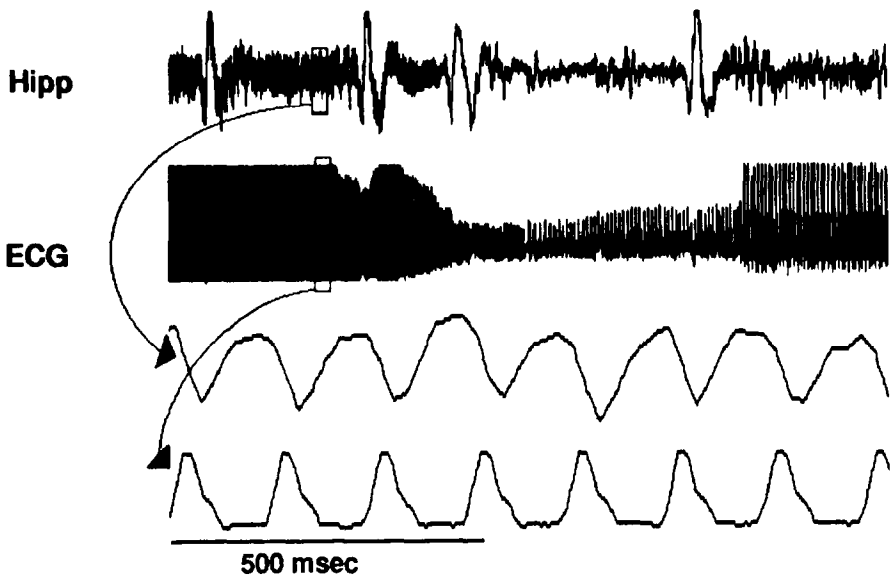
FIGURE 7. *ECG traces (recorded from two diaphragm leads) together with tracings from bipolar hippocampal leads during cocaine seizure discharge. The QRS complexes are extremely wide and recur at rapid rates. Note the close temporal relationship of discharge in the hippocampus with ECG activity.*

Acute administration of cocaine had a marked effect on patterning of upper airway and diaphragmatic respiratory musculature. Although apneic and apneustic episodes occurred, the most common respiratory effect was a tachypnea superimposed on increased tonic levels of activity In respiratory musculature. The cocaine effects extended not only to rate but also to greatly enhanced recruitment of at least upper airway dilators. The latter effect may be secondary to heat dissipation attempts to accommodate the pronounced rise in core temperature; however, the possibility of generallzed recruitment that might include airway constrictors as well as dilators cannot be overlooked.

Cocaine also had a marked effect on cardiac rate and variation. Rate was increased and variability virtually eliminated following cocaine administration, with a complete abolition of both respiratory-related and slow variation. A most unexpected and provocative finding was the entrainment of a ventricular arrhythmia with synchronous EEG discharge in the hippocampus accompanying a cocaine-induced seizure and the immediate conversion to a normal cardiac and EEG rhythm with diazepam. This finding suggests that cocaine-induced,

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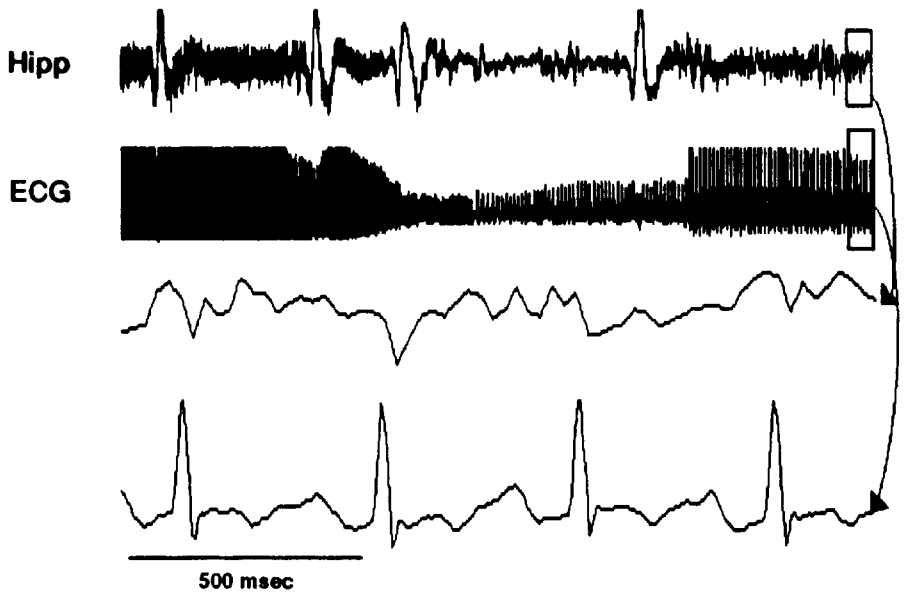
FIGURE 8. *ECG and hippocampal traces recorded during the recovery period. The coupling between hippocampal activity and ECG activity has diminished.*

seizure-like discharge may modify baroreflexes, output of the nucleus ambiguus to the vagus, or output to the intermediolateral sympathetic column, all modifications that would alter neural influences on the myocardium. The implication is that disruption of cardiac rhythm control may be accomplished in part by modification of CNS activity rather than by control of peripheral actions alone.

Our data on cocaine-induced elevations in heart rate confirm previous findings (Ritchie and Greene 1980; Resnick et al. 1977; Wilson et al. 1976; Fischman et al. 1976, 1983). Myocardial infarctions and symptomatic ischemia frequently have been associated with vasoconstriction (Coleman et al. 1982; Schachne et al. 1984; Kassowsky and Lyon 1984; Cregler and Mark 1986).

A portion of the cardiovascular changes may be determined indirectly by respiratory pattern changes. Cocaine may exert action on CNS structures that mediate respiratory patterning or may affect thermoregulatory structures that can modify respiration indirectly. This action of cocaine on respiratory patterning may indirectly modify the cardiovascular responses of classic

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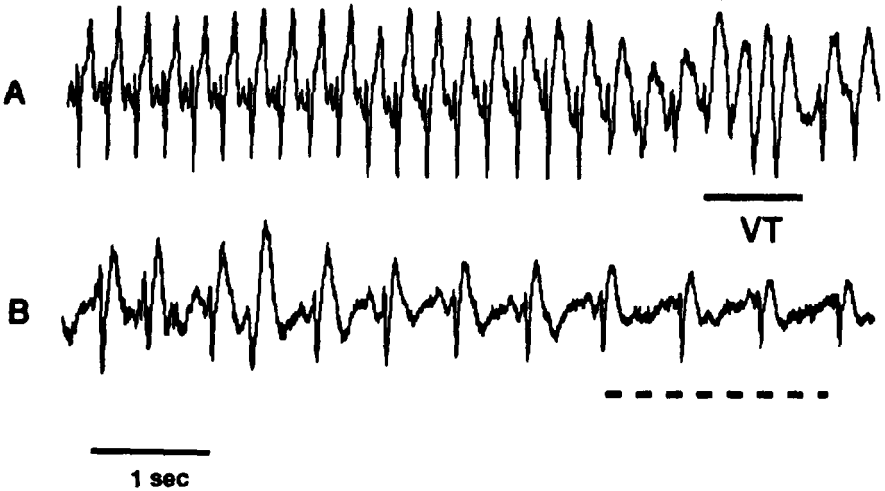
FIGURE 9. *ECG traces 1 minute post administration of 10 mg/kg cocaine administered intravenously. "A" and "B" are continuous, successive traces. The high sympathetic tone results in cardiac conduction changes together with high rate; a short burst of ventricular tachycardia (bar marked VT) is noted and is later followed by AV dissociation with junctional escape rhythm (dotted line), presumably as a consequence of concurrent high vagal lone.*

cardiopulmonary reflexes. Cocaine greatly increases diaphragmatic discharge rate, with potentially diminished effective tidal volume: the net effect is probably (although as yet unmeasured) reduced air exchange and the potential for hypoxia. The resulting hypoxia then can lead to a variety of cardiovascular sequelae. In addition, mechanical aspects of the resulting tachypnea will cause dramatic changes in simple cardiovascular dynamics such as venous return, which is partially dependent on respiratory efforts. Respiratory modulation of cardiac R-R intervals disappears under tachypnea, as is the case in these recordings (although the rapid heart rates also contribute to the disappearance of any respiratory modulation).

Changes in respiratory mechanics can alter cardiovascular action, but cardiovascular action also interacts with respiratory patterning. For example, a rapid rise in arterial pressure from basal levels of pressure is associated with a rapid and pronounced suppression of diaphragmatic activity (Trelease et al. 1983) and an even more pronounced suppression of upper airway dilator

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musculature activity (Marks and Harper 1987). Such reflexes serve as important protective mechanisms to prevent further rises in pressure from venous return assisted by respiratory movements but under certain conditions (e.g., those associated with obstructive sleep apnea) may prolong an existing suppression of respiratory movements. The implications for cocaine effects are that the rapid rise in arterial pressure may directly suppress respiratory activity.

Control of core temperature and sympathetic drive to the vasculature are interrelated. Cocaine-related hyperthermia (Wilson et al. 1976) may result partially from the lack of heat dissipation concomitant with extreme vasoconstriction and partially from cocaine actions on anterior hypothalamic and brainstem temperature-regulating areas. Elevated core temperature will profoundly affect respiratory rate: thus, a cocaine-related accelerated respiratory rate may result partially from hyperthermia-induced excitation of pontine phase-switching mechanisms.

A prominent characteristic of high-dose cocaine was the occurrence of seizures, which were prominent in limbic regions such as the hippocampus. Cocaine appears to have a special affinity for altering activity in limbic system structures, particularly in amygdaloid regions (Jones 1984). Although high levels of cocaine can elicit generalized convulsions (Catravas and Waters 1981; Myers and Earnest 1984), lower levels can elicit focal seizure discharge in the amygdala to the extent that cocaine-induced amygdaloid seizures have been proposed as a model for temporal lobe epilepsy (complex partial seizures) (Eidelberg et al. 1963). Cocaine lowers the current threshold necessary to Induce kindled afterdischarge activity In the amygdala and hippocampus (Lesse and Harper 1985). Cocaine increases the speed with which afterdischarge activity spreads to amygdaloid and hippocampal structures ipsilaterally and contralaterally from stimulation-elicited afterdischarge. Kindled seizure discharge within the central nucleus of the amygdala (ACE) results in profound cardiac and respiratory pattern changes, with prolonged apneusis and extreme tachycardia (Harper 1986). Partial seizures of focal temporal lobe origin are accompanied typically by tachycardia and are associated frequently with a variety of respiratory pattern disturbances, including obstructive apnea (Frysinger et al. 1987). Since cocaine intoxication results in localized amygdaloid seizures, the direct central limbic effects on respiratory and cardiovascular activity may be profound.

Particular structures within the limbic system, especially the ACE, can exert profound effects on cardiovascular and respiratory activity. Single-pulse electrical stimulation of the ACE at a rate slightly faster than the resting respiratory rate entrains respiration, an effect that is abolished in sleep (Harper et al. 1984). Train electrical stimulation of the ACE elicits a marked elevation in

arterial pressure, a relationship that is abolished in REM sleep, together with a pronounced apneusis (Frysinger et al. 1984). A proportion of ACE neurons discharge in phase with the respiratory cycle (Zhang et al. 1986a) and with a tonic discharge relationship with respiratory rate or arterial pressure (Frysinger et al. 1988), while bilateral cold-blockade of the ACE results in abolition of an aversively conditioned blood pressure and respiratory response (Zhang et al. 1986b).

It is particularly appropriate to address the role of the ACE in respiratory and cardiac regulation following cocaine intoxication, considering the anatomical relationships between the ACE and the nucleus accumbens (NA) in the ventral forebrain. The NA is considered to be part of the ventral (Heimer and Wilson 1975; Heimer et al. 1982) or "visceral" (Jayaraman 1985; Neafsey and Terreberry 1986) striatum and has a significant role in control of cocaine self-administration (Roberts et al. 1980; Zito et al. 1985) and amphetamine-induced locomotion (Vaccarino et al. 1986). The ACE, the lateral portion of the bed nucleus of the stria terminalis, and the medial portion of the NA contain a rostral-caudal continuum of neurons in the basal forebrain (Heimer et al. 1985; Zaborszky et al. 1985). The NA also receives a heavy midbrain dopaminergic input from A9 and A10 (Fallon and Moore 1978; Hokfelt et al. 1980). The ACE projects heavily to A8 and lateral A9 dopaminergic cells of the midbrain, rostral locus coeruleus (A6) noradrenerglc neurons, and the adrenergic (C2) and noradrenergic (A2) cells within the nucleus of the solitary tract (Wallace et al. 1989). These projections provide the functional substrate for cocaine to modify cardiovascular action by central mechanisms.

The NA (Nauta et al. 1978) and the ACE (Hopkins and Holstege 1978) project to the nucleus parabrachialis medialis of the pons (NPBM), the latter projection being massive. The NPBM forms part of the so-called "pneumotaxic area" (Cohen 1971), which contains cells that discharge phasicaily with the respiratory cycle (Lydic and Orem 1979; Sieck and Harper 1980) on a state-related basis (Harper and Sieck 1980), and is heavily involved wlth respiratory phase switching. Stimulation of this area elicits premature transition from inspiration to expiration and can pace respiratory rate (Bassal and Bianchi 1982). The NPBM lesions in vagotomized preparations result in prolonged apneusis (Bertrand and Hugelin 1971; Cohen 1971; St. John et al. 1972; Gautier and Bertrand 1975; Euler et al. 1976) whereas NPBM lesions in the intact cat result in apneas during quiet sleep that are accentuated in REM sleep (Baker et al. 1981). This area also plays a role in regulation of blood pressure and bradycardia (Hamilton et al. 1981; Mraovitch et al. 1982). Thus, the potential exists for cocaine action on the ACE to greatly modify blood pressure and respiratory pattern. Seizure discharge within the ACE might potentiate effects on brainstem sites.

CONCLUSIONS

These studies suggest pronounced effects of cocaine on respiratory musculature and interaction between temperature, respiration, and cardiovascular control systems. Moreover, seizure discharge in rostral brain areas may elicit substantial cardiovascular effects. Cocaine has the potential to alter action in many homeostatic mechanisms, and many of these perturbations have lethal consequences.

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Direct and Indirect Morphological Markers of Cocaine Toxicity in the Human Heart

Margaret E. Billingham

INTRODUCTION

There is increasing evidence that cocaine can have serious adverse effects on the human heart. Angina, coronary artery spasm, arrhythmias, myocardial infarction, endocarditis, coronary atherosclerosis, myocarditis, and sudden death all have been reported in association with cocaine use. It is estimated that almost 25 million Americans use cocaine with regularity, and approximately 1 million are addicted to this drug (Chokshi et al. 1989). The use of different combinations of drugs and different routes of administration have further increased the frequency and complications of cocaine. Cocaine also has become a significant cause of heart disease and sudden death in athletes; however, the cardiovascular changes in this group remain unexplained, and the interaction between exercise and cocaine use is largely unstudied. This chapter summarizes and examines the pathologic changes already ascribed to cocaine abuse in the literature (table 1) under the following headings: (1) the pathologic lesion, (2) the evidence or rationale that the lesion is indeed induced by cocaine and the pitfalls of ascribing the lesions to cocaine, (3) the pathophysiological explanation for the lesions, and (4) the possible consequences of cocaine-induced lesions.

TABLE 1. *Pathologic lesions attributed to cocaine abuse in humans*

Myocardial ischemia
"Catecholamine" microinfarcts
Fibrosis
Myocardial infarction
Myocarditis
Coronary artery "spasm"
Coronary arteriosclerosis
Cardiomyopathy (dilated, acute, and chronic)
Endocarditis

MYOCARDIAL CONTRACTION BANDS

A. Lesion

Myocardial contraction bands associated with cocaine cardiotoxicity may have a patchy or very focal distribution and are not seen in a global distribution as one would expect with hypoxia. The lesions consist of dense hypereosinophilic bands within the myocytes as seen on light microscopy stained with hematoxylin and eosin (figure 1). In most cases, there is coagulative change in the cytoplasm of the affected cell, and the nucleus may show pyknosls. In the very focal lesions, actual myocyte necrosis also may be present (figure 2). On electron microscopy, not only is there hypercontraction of the actin and myosin but also swelling and redistribution of the intracellular mitochondria (figure 3). Early changes in the myocyte are often highlighted by special stains such as Masson's trichrome or periodic acid-Schiff.
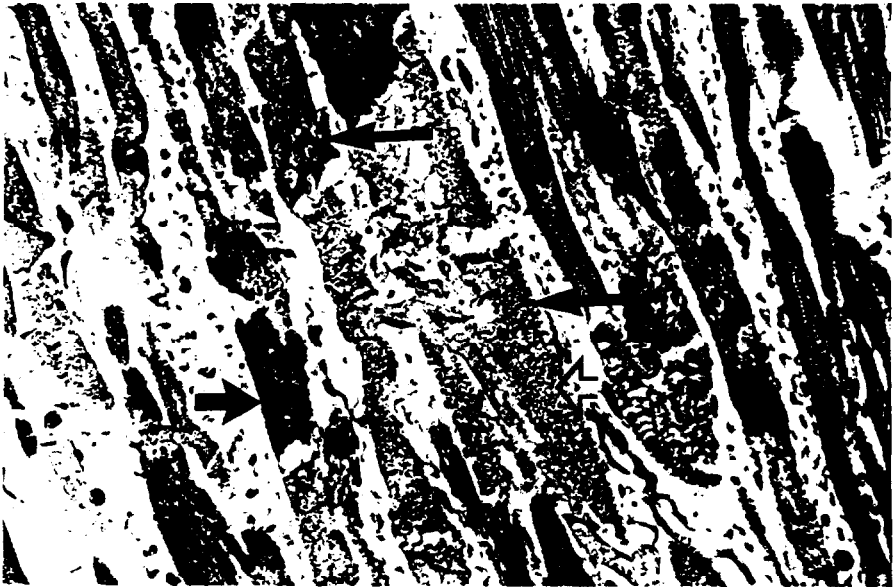
FIGURE 1. *Human myocardium showing a typical, focal "cocaine effect" of a hypereosinophilic myocyte (small arrow), contraction bands in myocytes (long arrows), and coagulative necrosis of myocyte cytoplasm (open arrow)*

NOTE: Hematoxylin and eosin, magnification x 450.

FIGURE 2. *Human myocardium showing a typical, focal "cocaine effect" or catecholamine effect of a single necrotic myocyte (arrow)*

NOTE: Hematoxylin and eosin, magnification x 500.

B. Evidence and Pitfalls

We studied 30 cases of sudden death in cocaine abusers with a mean age of 33.9 years and compared them with a control group of 20 patients with sudden death from sedative-hypnotic overdose who did not use cocaine (Tazelaar et al. 1987). A mean of 2.2 random sections was available from the myocardium of the cocaine abusers and 3.2 random sections from each control patient. The slides were examined and graded in a blinded fashion for the severity of contraction band changes. There was a strong correlation between the blood and urine levels of cocaine and the contraction bands in the myocardium compared with those of the controls (table 2). These data suggest that cocaine induces contraction bands in the myocardium.

FIGURE 3. *An electron micrograph of myocardium showing "contraction band effect" (arrows) in a catecholamine-affected myocyte (M)*

NOTE: Uranyl acetate, magnification x 4000.

TABLE 2. *Distribution of contraction band scores in cocaine addicts (sudden deaths) vs. hypnotic-sedative overdose used as control groups (sudden deaths)*

Control Group (N=20)	Cocaine Group (N=30)	Contraction Band Score (0-3+)
11	2	0
8	8	1+
1	7	2+
2	13	3+ (p<0.001)

SOURCE: Tazelaar et al. 1987.

On the other hand, contraction bands are not specific to cocaine. Many experimental and clinical conditions also are associated with contraction band changes in the myocardium. The nonspecificity of contraction bands has been previously described in detail elsewhere (Karch and Billingham 1986). The following list shows some other causes of myocardial contraction bands:

- Ischemia
- Catecholamines
- Hypopotassemia
- Intracranial hemorrhage
- Hypoxia, anoxia
- Defibrillation
- Steroids
- Endomyocardial biopsy artifact

C. Pathophysiology

In the heart, only 30 percent of norepinephrine is metabolized by catechol-O-methyl transferase. After transmission of a nerve impulse, the bulk of norepinephrine is transported back into the nerve terminal. Cocaine, however, prevents norepinephrine reuptake, resulting in high local concentrations of norepinephrine. The result of this is excessive beta receptor stimulation of myocytes and the pathologic elevation of intracytosolic calcium, which results in the formation of contraction bands or localized hypereosinophilia in a localized area of the myocardium (figure 4). A second explanation may be the suggested spasm of small vessels in the myocardium, causing "ischemia" or focal microinfarcts.
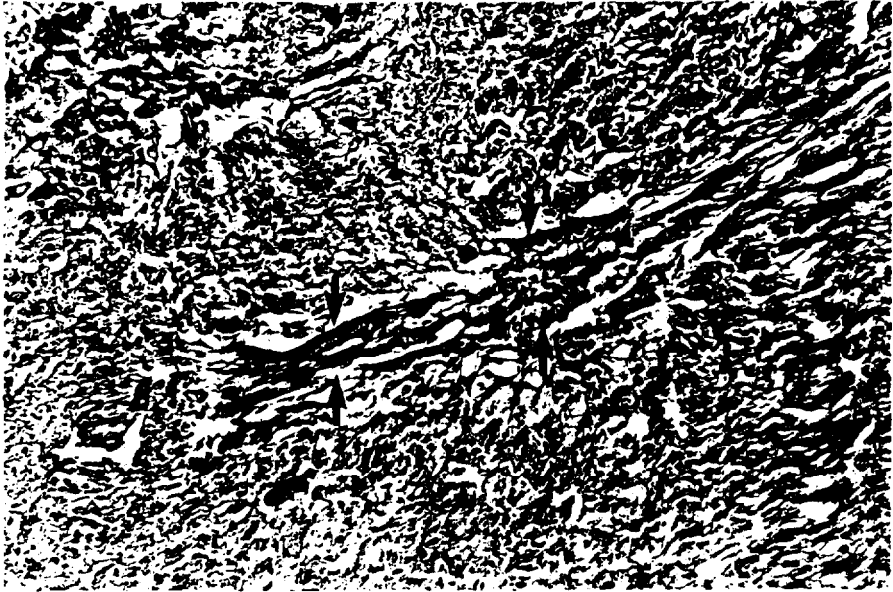
FIGURE 4.   *Human myocardium showing a focus of hypereosinophilic, contracted myocytes (darker areas, arrows) typical of catecholamine effect*

NOTE: Hematoxylin and eosin, magnification x 300.

D. Consequences

The consequences of these changes in humans, which are also supported by the high catecholamine blood levels in cocaine-intoxicated patients with chest pain (Karch 1987), may proceed to frank myocardial ischemia and even infarction. Later consequences are that ischemic areas may be a focus for the development of re-entrant arrhythmias.

MYOCARDIAL FIBROSIS

A. Lesion

The lesion consists of small focal scars with ongoing reparative changes and laying-down of early collagen. A later stage results in frank course fibrosis. In cocaine abusers, the lesions tend to be focal, and even the well-developed scars tend to be smaller than those observed in ischemic heart disease,

particularly where they result from small vessel spasm. If an infarct has taken place, then the resulting scar will be the same as in ischemic heart disease.

B. Evidence and Pitfalls

Several authors have noted fibrosis in the myocardium of autopsy tissue from habitual cocaine users. In some cases, continuing destruction and healing of the myocardium by fibrosis could explain a 'cardiomyopathic" appearance of the heart with ventricular dilatation and compensatory hypertrophy.

Fibrosis Is a nonspecific condition in the human myocardlum, with the possible exception of its presence in young people (normally with little coronary disease), which is more unusual. Fibrosis can be caused by several conditions in the heart and by itself cannot be attributed to cocaine use.

C. Pathophysiology

There are several explanations for the presence of fibrosis in the heart in cocaine abusers, and there is a possible relationship between them. Following focal ischemia (contraction band necrosis), actual myocardial death may occur which will result in replacement by fibrosis (figure 5). Lesions that develop from microfocal fibrosis in the myocardium as a result of catecholamine-induced lesions in pheochromocytoma are well known. They result eventually in the development of a cardiomyopathic state with larger lesions of fibrosis (figure 8). Myocardlal fibrosis also may result from coronary artery spasm or coronary atherosclerosis since there are published reports of both conditions in cocaine cardiotoxicity.

D. Consequences

Fibrosis, unless very focal, eventually can cause compensatory hypertrophy of the myocardium and a general reduction in contractile efficiency of the myocardium. Even focal scars can result in re-entrant arrhythmias such as is seen in right ventricular arrhythmogenic dysplasia.

MYOCARDITIS

A. Lesions

Cellular infiltrates have been reported in the myocardium of cocaine abusers by several researchers (Isner et al. 1980; Virmani et al. 1987; Isner et al. 1985). The significance of these infiltrates in cocaine toxicity is not clear, but initial studies suggest that they may result in focal myocardial necrosis and thus be
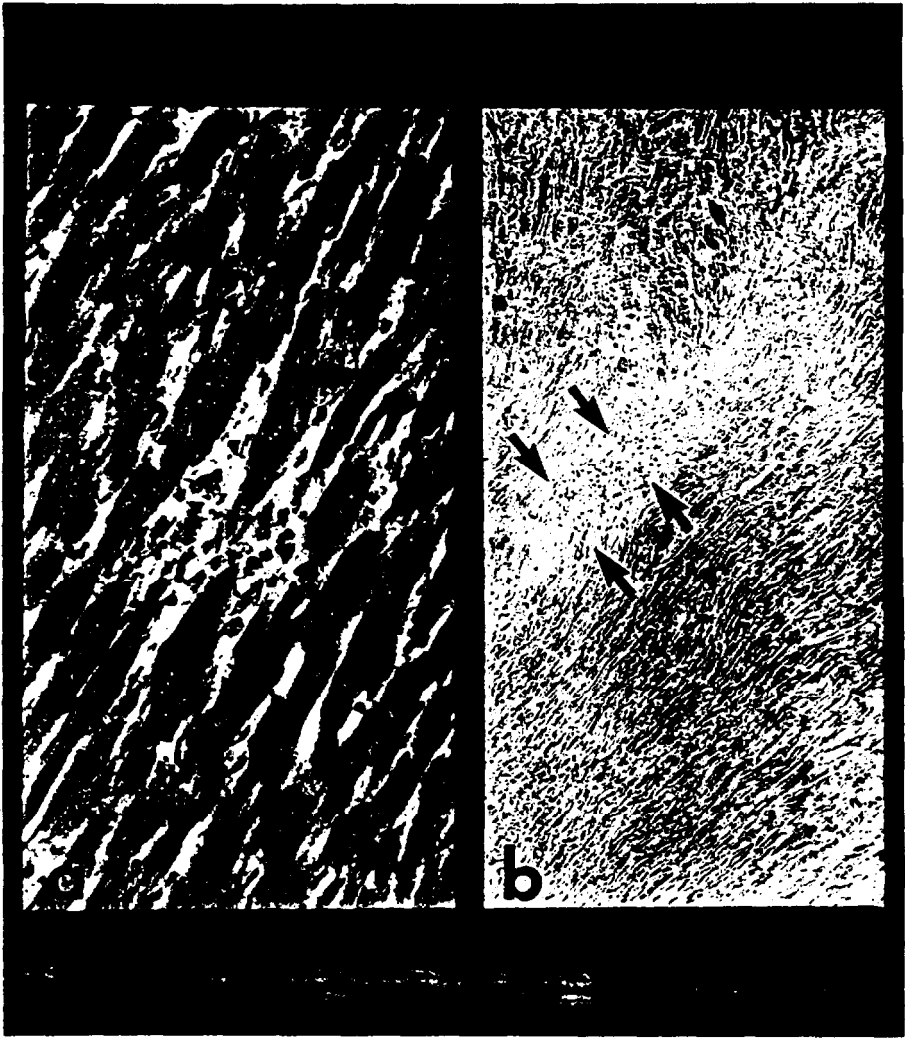
FIGURE 5. *Panel A: focal ischemia due to cocaine in human myocardium; panel B: focal scar or fibrosis resulting from lesion similar to panel A*

NOTE: Hematoxylin and eosin; magnification panel A=x 350, panel B=x 100.
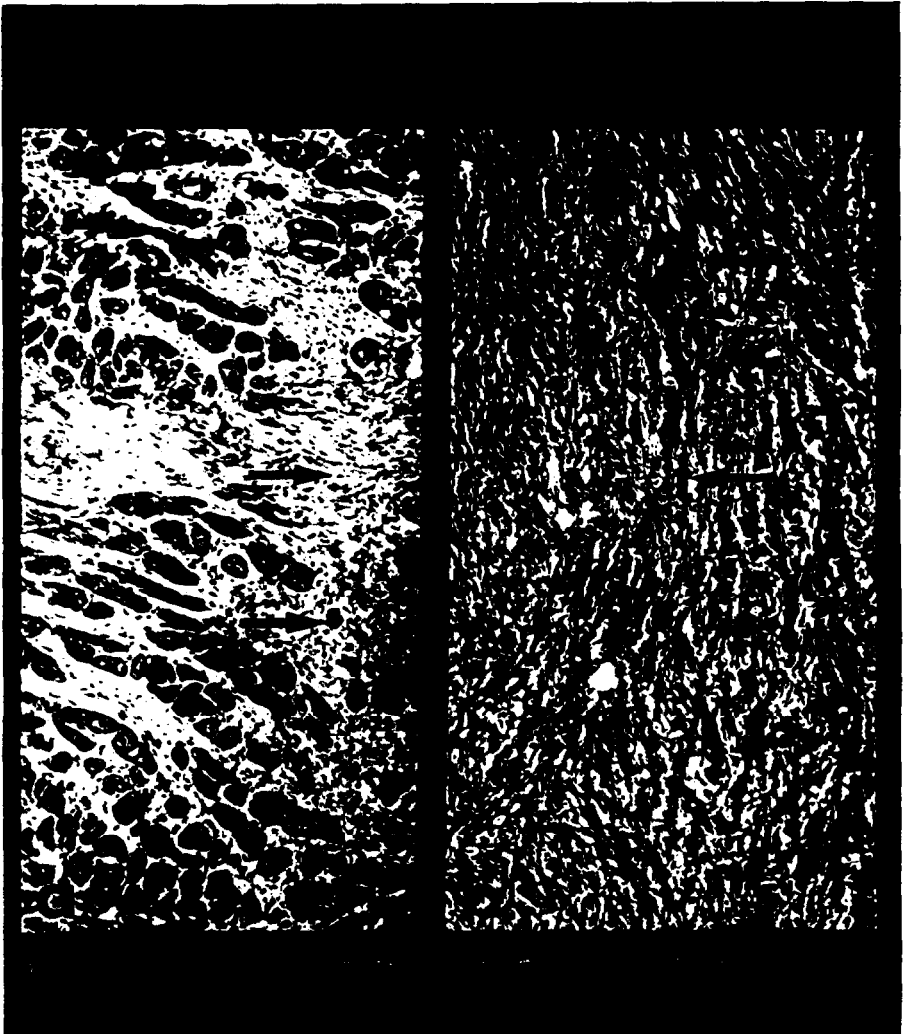
FIGURE 6. *Panel A: myocardium from a rat pheochromocytoma model with typical early fibrosis in which fibroblast nuclei still can be seen (arrows); panel B: resultant fibrous tissue (darker areas and arrows) in the same model as panel A*

NOTE: Masson's trichrome, magnification x 250.

classified as a true myocarditis conforming to the Dallas criteria (Aretz et al. 1986). Eosinophilic myocardial infiltrates also have been described in association with cocaine (Isner et al. 1980); however, these are more likely to be the result of a hypersensitivity reaction that can be caused by several unrelated agents. A hypersensitivity reaction to cocaine, or to drugs taken with It, is also a possibility. The inflammatory lesions described are usually those of a monomorphous infiltrate of lymphocytes; however, small focal lesions with mixed infiltrates also have been seen that are similar to those produced by catecholamine effect (figure 7).
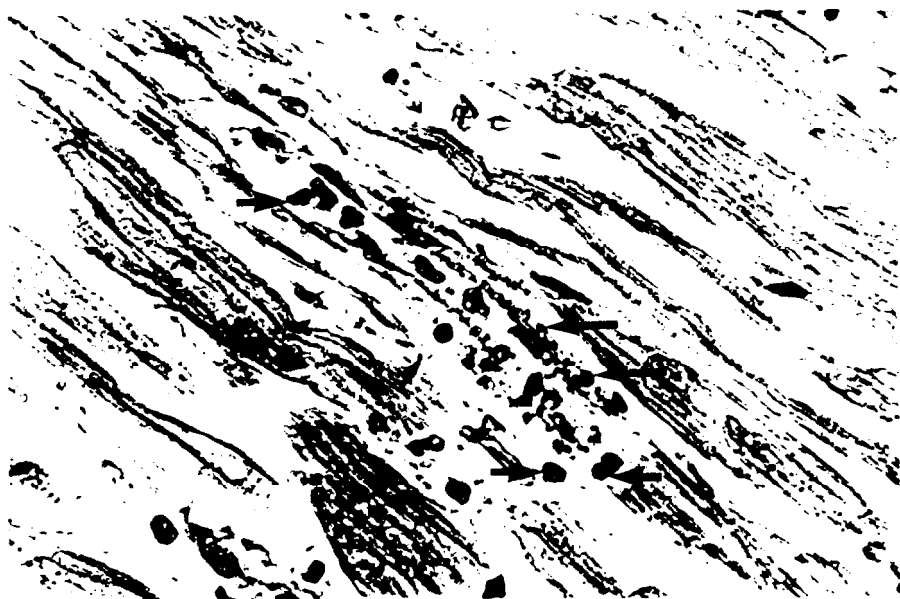
FIGURE 7. *Human myocardium showing focal myocarditis (short arrows point to inflammatory cells) with myocyte necrosis (long arrows)*

NOTE: Masson's trichrome, magnification x 500.

B. Evidence and Pitfalls

The evidence of myocarditis in cocaine abusers rests in the fact that many different researchers and observers have observed myocarditis in cocaine abusers. The descriptions, however, do not conform to a definite pattern, and both focal and diffuse patterns have been described as well as eosinophilic

rather than lymphocytic infiltrates. In some cases, the observers have not seen the association of the infiltrates with actual myocyte damage.

The pitfalls in ascribing myocarditis to cocaine abuse is that cocaine use can cause myocyte damage in a variety of ways and that the infiltrate may indeed be a result of myocyte damage rather than true myocarditis.

C. Pathophysiology

Many of the pathophysiologic mechanisms of cocaine (e.g., catecholamine effect) can cause focal lymphocytic infiltrates or focal myocarditis, which is in fact a secondary phenomenon rather than a primary one caused by cocaine. The myocarditis seen in cocaine abusers may be a true viral-related lymphocytic myocarditis acquired in the debilitated state of a drug abuser and not a primary effect of cocaine. Also, the eosinophilic infiltrate described may be a hypersensitivity reaction due to contaminants of the cocaine rather than to the drug itself. Until reliable experimental data with controls are available, it is probably unwise to ascribe myocarditis to be the effect of cocaine per se.

D. Consequences

The primary consequences of myocarditis in cocaine abusers is the enhanced probability of arrhythmias, particularly if the myocarditis involves the conducting system of the patient. True myocarditis may result in a large flabby myocardium with compromise of the ventricular function and may result in heart failure. The long-term effects of a healed myocarditis are thought to result in a dilated cardiomyopathy resulting in severe congestive heart failure.

CORONARY ARTERY CHANGES

A. Lesion

Vascular changes in cocaine abusers can be divided into reports of arterial spasm and reports of epicardial coronary artery narrowing.

There are reports that cocaine can cause myocardial infarction in patients without previous cardiovascular disease. It has been postulated that coronary artery spasm may occur as a result of the sympathomimetic effect of cocaine or even a direct effect on the smooth muscle of the coronary artery vessels (Factor and Cho 1985).

Other reports describe narrowing of epicardial coronary arteries by atherosclerotic plaque in cocaine abusers. Many of these patients die

suddenly, and some have had frank myocardial infarction. Patients with preexisting coronary artery disease are also more prone to myocardial ischemia from cocaine abuse. It appears that the incidence of coronary atherosclerosis with significant epicardial coronary narrowing is more common in cocaine users than in the normal population of the same age group (Bressler et al. 1990). In some cases, there is superimposed thrombus. Virmani and associates described two cocaine addicts with severe coronary atherosclerosis and a 23-year-old woman who had an occlusive platelet thrombus in the left anterior descending coronary artery (Virmani et al. 1988). Simpson and Edwards (1986) described a 23-year-old male cocaine addict who died suddenly and was found to have chronic coronary obstruction due to nonatherosclerotic concentric intimal proliferation of smooth muscle cells.

B. Evidence and Pitfalls

At present the evidence that there is coronary artery spasm with the use of cocaine is due to reports of fatal arrhythmia or myocardial infarction immediately following the taking of cocaine. Work by Karch has demonstrated a rise In catecholamine levels In patients with chest pain who have recently taken cocaine (Karch 1987). Whether cocaine acts on endothelial factors or acts directly on coronary vascular smooth muscle is not yet known (Van Houtte and Shimokawa 1989).

Coronary artery disease, however, is a nonspecific finding and although the studies described above are in fairly young patients in whom it is unusual to have coronary artery disease, it is now known that there is an increasing incidence of coronary disease in younger subjects. In several cardiac transplantation cases, the hearts of young, apparently heart disease-free donors frequently have shown significant but unexpected coronary artery lesions. To be sure that cocaine indeed induces atherosclerotic coronary disease, a reliable control study is necessary (so far this has not been shown in animal studies either).

C. Pathophysiology

Coronary artery spasm may occur as a result of sympathomimetic effect of cocaine or even a direct effect on the smooth muscle of the vessels as is thought to occur in conditions such as pheochromocytoma. Whether cocaine is acting on the endothelial factors or by direct action on coronary vascular smooth muscle is not yet known.

D. Consequences

The consequences of coronary artery disease, whether by spasm or an increase in coronary artery atherosclerosis, may be thrombosis and occlusion of the vessels with consequent ischemia or infarct of the myocardium. This also may play a part in some of the sudden deaths attributed to cocaine use, particularly in athletes whose hypertrophied myocardium may be more susceptible.

CARDIOMYOPATHY

A. Lesion

There are a few reported cases of cocaine-induced cardiomyopathy. At Stanford, we have seen at least three cases of dilated cardiomyopathy diagnosed hemodynamically and clinically with a very strong history of cocaine abuse. All three patients came to cardiac transplantation. The lesions in two of these patients showed more focal lymphocytic infiltrates and less myocyte hypertrophy than is normally seen in end-stage cardiomyopathy. However, the size of the heart and the ventricular dilatation were the same as for idiopathic cardiomyopathy. The cocaine abusers had a different pattern of fibrosis from that normally seen in end-stage cardiomyopathy, in that the fibrous scars tended to be smaller and more focal. The number of cases is too small at this point to clearly define these lesions.

B. Evidence and Pitfalls

There is some evidence that cocaine use may result in acute cardiac dilatation; however, it seems to result in a characteristic dilated cardiomyopathy in the chronic abuser.

It is not clear whether these patients develop idiopathic cardiomyopathy as a result of cocaine abuse or whether they are patients with idiopathic cardiomyopathy who happen to be cocaine abusers. At this stage, there is little evidence that shows cocaine can cause a cardiomyopathy of the dilated type.

C. Pathophysiology

The pathophysiological explanations of cocaine-induced dilated cardiomyopathy is the same as that for the development of cardiomyopathy in pheochromocytoma (Rosenbaum et al. 1987). The mechanism of catecholamine effect is the same in both.

D. Consequences

The consequences of dilated cardiomyopathy with a low ejection fraction is a marked congestive heart failure and possibly even death due to poor ventricular contractility.

ENDOCARDITIS

A. Lesion

The lesion of endocarditis on the heart valves is similar to those in other conditions. Grossly, the lesions of infective endocarditis are vegetations, small flat adherent nodules to large friable masses, containing microorganisms occasionally extending to the chordae. Microscopically, vegetations consist of fibrin, platelets, and neutrophils at the bases. The underlying valve may be eroded depending on the organism involved. In the case of self-administered drugs, the lesions are usually on the right side of the heart, particularly the tricuspid valve (figures 8 and 9). A recent study suggests that there is an increased risk for endocarditis in intravenous (IV) cocaine drug abusers (Chambers et al. 1987). Although endocarditis is well known as a complication of IV drug use, this study suggests an increased risk involving cocaine abusers. The lesions manifest themselves as endocarditis either in the acute or the chronic stage on the tricuspid valve. Patients with bioprosthetic valves from previous endocarditls (a common situation in IV drug users) are even more at risk in the setting of cocaine addiction (figure 9). It has been suggested that because cocaine is not "cooked" to dissolve it before injection, infection from primary sites of bacteremia in the skin is more common in IV cocaine users.

B. Evidence and Pitfalls

One of the pitfalls of suggesting that endocarditis is due to cocaine use Is that cocaine abusers also use other IV drugs. Illicit IV drug use often will result in bacterial endocarditis. The evidence that endocarditis occurs more in cocaine abusers is slight at this time and based on only one study.

C. Pathophysiology

The use of contaminated IV needles or contaminated material injected intravenously by drug abusers may result in fungal, bacterial, or even foreign body contaminants, which may lodge on the endothelium of the tricuspid valves or other areas in the heart. It is known that foreign body and infectious granulomas can occur in the lungs of self-administering IV drug abusers.

FIGURE 8. *Panel A: human endocarditis valve v with a flat adherent vegetation containing gram-positive organisms (arrow panel B)*

NOTE: Panel A=hematoxylin and eosin, magnification x 50; panel B=gram stain, magnification x 400.
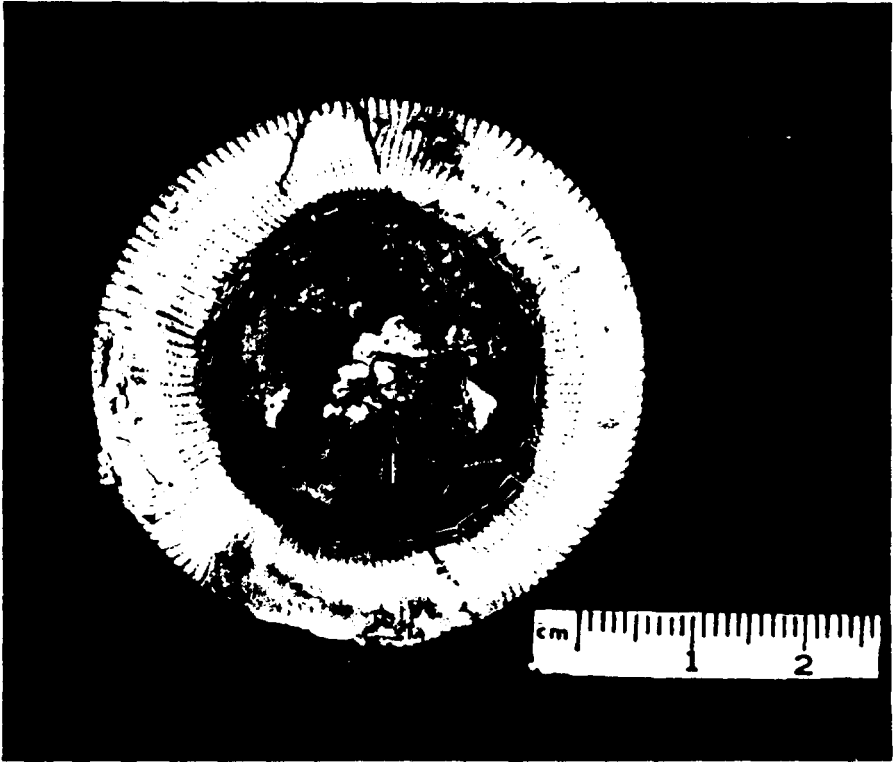
FIGURE 9. *Explanted bioprosthetic (porcine) heterograft valve only 6 months after implantation in a drug addict*

NOTE: Magnification x 2.5.

D. Consequences

The consequences of bacterial endocarditis are embolization from the lesions with resultant lung infarcts or lung abscesses and even myocardial septicemia. If the tricuspid valve is eroded sufficiently from endocarditis, it will become incompetent or even stenotic.

CONCLUSIONS

Both definite and equivocal pathologic lesions due to cocaine cardiotoxicity are now emerging as pathological entities in humans. None of the lesions are

specific, and in some cases the association is only circumstantial. It appears that not only are there diverse types of lesions associated with cocaine use such as those described above but also that the mechanisms for the production of these lesions are quite varied. In most cases, there exists a plausible clinicopathologic correlation to associate the various lesions with cocaine abuse. The magnitude of the problem is unknown, and the temporal and dose relationships to cocaine are still unclear and anecdotal; it is also unclear whether some of the lesions are reversible. Estimates are not feasible without a better understanding of how cocaine affects the cardiovascular system. It is first necessary to establish definitely the different mechanisms of cocaine cardiotoxicity; only then can a rational and effective therapy be applied to those who have symptoms from cocaine abuse. Further studies and observations by pathologists will assist in corroborating the presence of different lesions that have been attributed to cocaine.

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Cocaine-Associated Cardiovascular Disease: Clinical and Pathological Aspects

Renu Virmani

INTRODUCTION

Since pre-Columbian times, South American native peoples have ingested cocaine as a stimulant by chewing coca leaves (Karch 1989). Subsequent generations have discovered the "high" of cocaine's psychologic stimulation and have developed new ways to process and ingest cocaine to increase and augment the intensity of the drug's psychological effects. Initially, the use of cocaine was promoted as a safe *high" however, with the increasing morbidity and death associated with cocaine abuse, it is imperative to learn the mechanisms involved with the toxic effects of cocaine (Gawin and Ellinwood 1988).

EPIDEMIOLOGY

Contemporary cocaine abuse is epidemic. In September 1987 the National Institute on Drug Abuse reported that there were 5,000 new cocaine users daily (Kozel and Adams 1986). Twenty-two million Americans have used cocaine at least once: there are 6 million regular users and 0.2 to 1 million compulsive users (Kozel and Adams 1986). Among persons 25 to 30 years of age, almost 40 percent have tried cocaine at least once (Gawin and Ellinwood 1988). Although the annual prevalence of cocaine use among high school students peaked during 1985 and 1986 at 13.1 percent and 12.7 percent, respectively, it decreased to 10.3 percent in 1987, possibly as a result of adverse publicity about the dangers of cocaine abuse (Kozel and Adams 1986; Barnes 1988) and, in particular, the deaths of well-known athletes (Virmani et al. 1988). In the past 20 years, there has been a 300-percent increase in emergency room visits for cocaine-related conditions such as myocardial infarction, stroke, and seizures as well as for possible adverse effects to unborn fetuses (Kozel and Adams 1986). Cocaine deaths rose from 195 in 1981 to 580 in 1985. Many of these deaths are attributed to cocaine's adverse effects on the cardiovascular system.

Cocaine's Effects on the Heart

The effects of cocaine on the cardiovascular system are numerous. They
include the following:

- Functional effects
  —Hypertension and tachycardia
  —Increased coronary vascular resistance
  —Arrhythmias
    -Sudden death

- Pathologic effects
  —Myocardial infarction with/without coronary atherosclerosis
    -Coronary atherosclerosis and/or intimal smooth muscle cell proliferation
    -Platelet aggregation
  —Myocarditis
    Catecholamines
    -Small vessel spasm
  —Contraction band necrosis
    Catecholamines
  —Rupture of the ascending aorta

Cocaine may induce myocardial ischemia by increasing the work of the heart
and increasing the demand for oxygen by elevating the blood pressure and
heart rate. It also could be caused by decreasing the blood supply in the
epicardial coronary arteries in the presence of fixed obstruction by
atherosclerosis (figure 1) and/or by inducing vasoconstriction of intramyocardial
coronary arteries and/or increased platelet aggregation and thrombosis (Cregler
and Mark 1986).

Myocardial Ischemia

Since 1982 acute myocardial infarction, with or without thrombosis, has been
related temporally to cocaine use in at least 52 patients clinically or at autopsy
(Virmani et al. 1988; Cregler and Mark 1986; Isner et al. 1986). Of these, the
majority had little or no fixed underlying coronary atherosclerosis by
angiography. Coronary thrombosis was suspected or present in at least nine
patients studied angiographlcally or at autopsy (Virmani et al. 1988; Cregler and
Mark 1986; Isner et al. 1986; Zimmerman et al. 1987).

Mittleman and Wetli (1987) recently reported 24 cases (ages 20 to 71 years) of
sudden death associated with cocaine abuse; 15 of these individuals had
severe coronary atherosclerosis; 10 had coronary stenosis with 70- to 85-

FIGURE 1. *Pathologic findings from the autopsy examination of young adults dying with cocaine detected in body fluids. A platelet thrombus in the left anterior descending coronary artery overlying an eccentric atherosclerotic plaque that occupied 40 percent of cross-sectional luminal area in a 23-year-old woman with a history of chemical abuse of freebase cocaine (crack) and marijuana B. Eccentric atherosclerotic plaque with pultaceons debris and a fibrous cap (H&Ex40). C. High-power view of platelet thrombus (H&Ex 300).*

percent cross-sectional luminal narrowing; and 5 had 90-percent luminal narrowing. Complete thrombotic occlusion occurred in 3 patients; healed myocardial infarction was present in 10 patients; and 2 had acute myocardial infarction. Therefore, cocaine also may play a contributory role in natural death in the presence of severe underlying coronary atherosclerosis, either through increase in oxygen demand or through induction of coronary spasm.

Etiology. Myocardial ischemia is a well-recognized sequela of coronary atherosclerosis and accounts for the majority of patients with myocardiai infarction. However, myocardial infarction with normal coronary arteries is uncommon, with a reported prevalence of 1 to 3 percent (Zimmerman et al. 1987). The pathophysiology of myocardial ischemia may be coronary spasm and thrombosis. The majority of the coronary arteriograms of patients with cocaine abuse and myocardial infarction have demonstrated normal or minor irregularities (isner et al. 1986; Zimmerman et al. 1987). This raises the possibility that cocaine induces coronary spasm and thrombosis with subsequent lysis of the thrombus. Coronary artery spasm In humans has been shown angiographically to be localized at sites with insignificant coronary atherosclerosis (Maseri et al. 1978). We and others hypothesize that cocaine induces vasoconstriction through the sympathomimetic action of cocaine, which may result in compromised blood flow and endothelial disruption at sites of atherosclerosis. Endothelial disruption at these sites initiates a cycle of platelet aggregation (Simpson and Edwards 1986; Hueter 1987). Platelets release prostaglandins, which may further cause vasoconstriction. Coronary artery spasm and thrombosis have been demonstrated in a 29-year-old man with angiographically normal coronary arteries with cocaine abuse (Zimmerman et al. 1987).

Platelet Aggregation. The alpha-adrenergic properties of cocaine increase platelet aggregation, which may precipitate thrombi in the coronary artery in the presence or absence of fixed stenosis. *In vitro* studies of platelet function have shown that cocaine enhances both thromboxane production and the aggregating response of platelets, which may be mediated by calclum-membrane binding and calcium influx (Virmani et al. 1988; Hueter 1987). The vasoconstrictor properties of thromboxane A_2 on medium- and small-size arteries may contribute further to coronary vasoconstriction. In young adults who abuse cocaine, increased platelet aggregability may lead to fibromuscular intimal proliferation through the release of platelet-derived growth factor and nonatherosclerotic coronary luminal narrowing (Zimmerman et al. 1987; Hueter 1987).

Myocarditis

Several studies have reported the presence of lymphocytic and eosinophilic myocarditis in patients with detectable cocaine or cocaine metabolites in body fluids (Virmani et al. 1988; Isner et al. 1986; Simpson and Edwards 1986; Karch and Billingham 1988). Myocarditis was diagnosed histologically using the Dallas criteria, defined as a mononuclear infiltrate with or without eosinophilic leukocytes of five or more cells per focus and myocyte necrosis manifested either by hypereosinophilic myocytes, coagulation necrosis, or scalloped margins of myocytes. These criteria document a noxious effect on the myocardium but do not identify an etiologic agent or agents.

We reviewed the files of the medical examiner of the State of Maryland and identified 40 deaths associated with cocaine abuse (Virmani et al. 1988). Patients were divided into two groups: group 1—natural deaths, 31 patients (mean age 38±5 years, 22 males and 9 females) in whom death was attributed directly to cocaine toxicity (cocaine blood levels 5.3±8.1 mg/L)—and group 2—homicide deaths, 9 patients (mean age 33±8 years; 7 males and 2 females) in whom presence of cocaine was not the cause of death (0.3±0.3 mg/L). Four of the 31 natural death patients had lymphocytic myocarditis; of the 9 homicide deaths, 2 had lymphocytic myocarditis (figure 2, panel A), and 2 had lymphocytic and eosinophilic myocarditis (figure 2, panel B). The foci of myocarditis were focal and sparse with equal distribution in both the right and left ventricles.

Etiology. The cause of myocarditis in these patients is unknown but may be infectious agents such as bacteria, fungi, or viral inclusions, although none were found. The myocarditis may be due to indirect induction of myocyte necrosis with secondary inflammatory infiltrate elicited by cocaine-evoked inhibitions of norepinephrine reuptake. On the other hand, cocaine may cause vasoconstriction of small intramyocardial coronary arteries with a resultant increase in coronary vascular resistance, which has been documented in humans and animals (Lange et al. 1989; Hale et al. 1989; Bedotto et al. 1988). These factors may lead to isolated myocyte necrosis, secondary to ischemia. Also, the action of cocaine on endogenous catecholamines may affect lymphocytic activity. An increase in natural killer-cell activity has been reported with the use of intravenous cocaine (Dyke et al. 1986). Natural killer cells may cause myocyte death with inflammatory infiltrate. However, the precise mechanism of myocarditis remains unknown.

Eosinophilic myocarditis has been associated with hypersensitivity myocarditis secondary to an adverse reaction to various drugs. Hypersensitivity myocarditis usually is located in the natural tissue planes within the myocardium and consists of lymphocytes and eosinophils in the absence of myocyte necrosis.
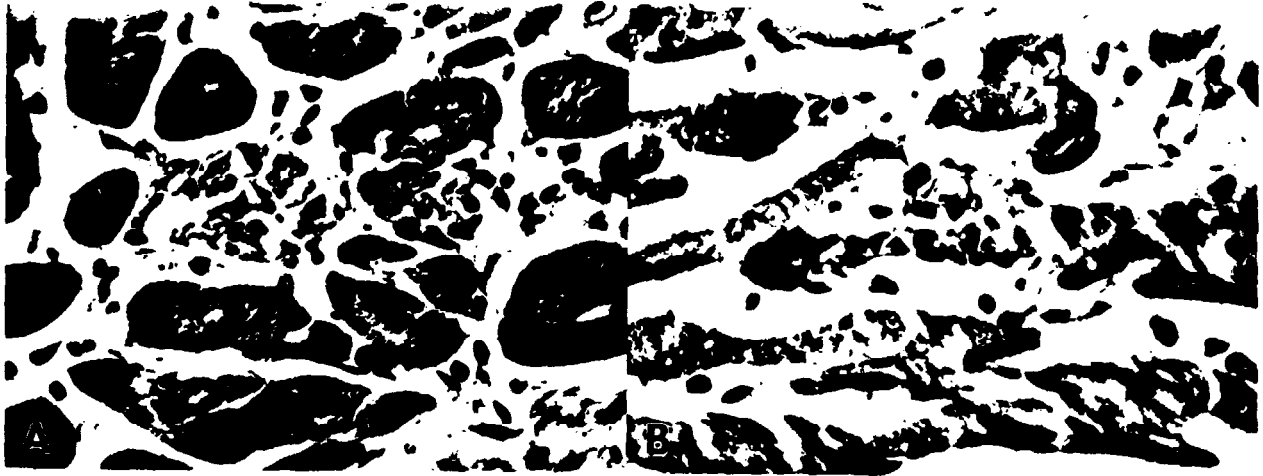
FIGURE 2.   *A Myocardium of a 37-year-old female chronic cocaine abuser and homicide victim. Note focus of lymphocytic myocarditis surrounding a necrotic myocyte (H&E x 630). B. Myocardium of a 27-year-old chronic cocaine abuser and drug-related homicide victim. Note focus of eosinophilic (arrowhead) and lymphocytic myocarditis with myocyte necrosis (H&E x 750).*

The two cases of eosinophilic myocarditis In Maryland may represent a hypersensitivity reaction to cocaine, its metabolites, or other unidentified chemicals that may be contaminants.

Contraction Band Necrosis

Contraction band necrosis is defined as the hypercontraction of some sarcomeres, interspersed with other sarcomeres that are torn apart within the myocytes. Under light microscopy, these appear as dense, amorphous areas of hypercontracted myofilaments alternating with lighter areas with decreased amounts of myofilaments (figure 3) incapable of further contraction (Karch and Billingham 1988). Contraction bands may be due to elevated levels of norepinephrine triggered by cocaine, which may Induce intramural coronary artery spasm or directly stimulate hypercontraction of myocardial cells via an influx of calcium ions (Karch and Billingham 1988).

Tazelaar and colleagues (1987) reported a 93-percent incidence of contraction band necrosis in the myocardium of cocaine-associated deaths in contrast to an incidence of 45 percent in deaths associated with sedative-hypnotic overdose. They attributed the presence of contraction band necrosis to cocaine-induced catecholamlne myocardial injury. Norepinephrine and epinephrine levels have been found to be elevated in cocaine users who present to the emergency room (Karch and Billingham 1988). Similar lesions of contraction band necrosis have been shown to occur in experimental animals with elevated serum catecholamlne levels (Gopinath et al. 1978). However, in our recent study (Virmani et al. 1988) of 40 patients In whom cocaine or Its metabolites were detected in body fluids, contraction band necrosis occurred in only 10 patients (25 percent). The incidence of contraction band necrosis was higher in the study's sudden traumatic death control group (41 percent) (Virmani et al. 1988). The lower incidence in this study is difficult to explain but may reflect differences in the population studied or in cocaine preparations, contaminants and adjuvants in the drugs of abuse, rate of drug delivery, and/or chronicity of drug abuse (Virmani et al. 1988).

Aortic Rupture

To our knowledge, only one patient, a 45-year-old man, has been reported to have died of aortic dissection and rupture after smoking freebase cocaine off and on for several hours before death (Barth et al. 1986). The dissection, which involved the ascending aorta 2 cm above the sinotubular junction, suggests that a marked elevation of blood pressure must have occurred after cocaine ingestion, which has been clinically documented to occur in humans and animals (Lange et al. 1989; Hale et al. 1989; Bedotto et al. 1988; Dyke et al. 1986; Barth et al. 1986).
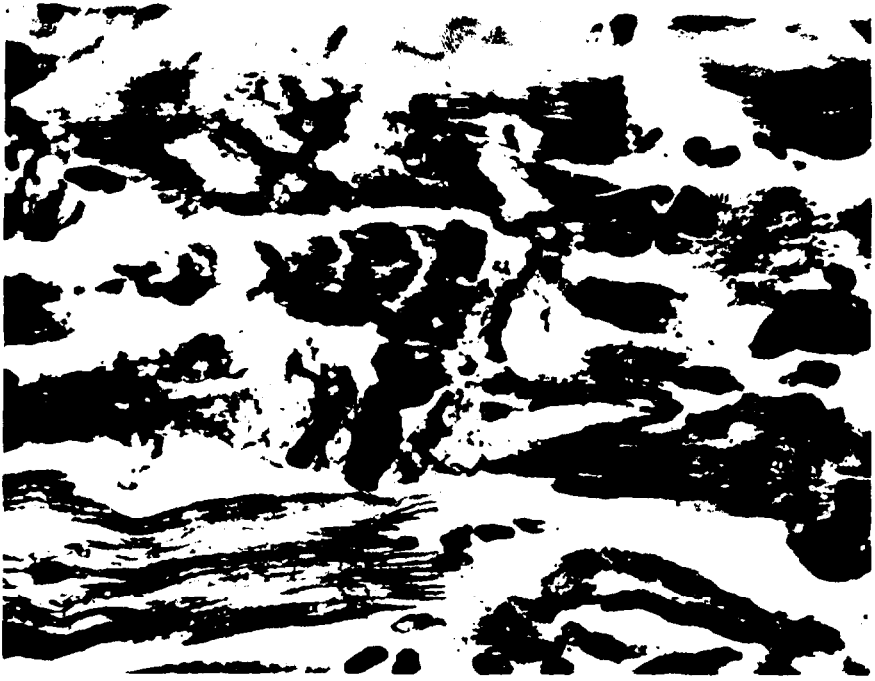
FIGURE 3. *A 22-year-old man with sudden onset of seizure who died while snorting cocaine. Note contraction band necrosis with hyperwntracted eosinophilic bands alternating with light areas within myocytes (H&E x 300).*

SUMMARY

With regard to cardiac findings in cocaine abuse, at autopsy the vast majority of patients dying with cocaine toxicity have either no pathologic change in the heart or only minimal changes that could not account for the patient's death. The second most frequent finding is underlying, mild-to-moderate coronary atherosclerosis, with or without coronary thrombosis. There may be acute or healed myocardial infarction or a sudden cardiac death without myocardial changes of ischemia. A high incidence of contraction band necrosis has been reported in the absence of coronary artery disease and may cause a sudden arrhythmic death. Myocarditis also has been described in a few cases as either lymphocytic or lymphocytic and eosinophilic infiltrate in the presence of myocyte necrosis. Usually, the foci are sparse and not always associated with contraction band necrosis. The underlying mechanisms are thought to be either

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direct effects of norepinephrlne on myocytes or through vasospasm of resistance vessels and secondary myocardial ischemia. Cocaine rarely has been associated with aortic dissection, which is probably a result of cocaine's hypertensive effects.

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