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Differential Routes of Cocaine Administration Indicate a Peripheral Cardiotoxic Action

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JONES, L. F. AND R. L. TACKETT. *Differential routes of cocaine administration indicate a peripheral cardiotoxic action.* PHARMACOL BIOCHEM BEHAV **38**(3) 601–603, 1991.—The present study utilized different routes of administration in unanesthetized Wistar Kyoto (WKY) rats to determine whether *cocaine-induced death* was mediated through a *peripheral* or *central* site of action. Administration of cocaine via a route that resulted in high concentrations of cocaine reaching the heart produced arrhythmias, convulsions, a decrease in heart rate and mean arterial pressure, and death. However, administration of the same dose via a route that resulted in passage of cocaine through the liver before reaching the heart produced only a pressor response. Additionally, administration of the same dose via a route that resulted in high levels of cocaine reaching the brain did produce a pressor response that was followed by a decrease in blood pressure and heart rate, arrhythmias, convulsions and death. However, these effects were delayed in comparison to the response when high concentrations of cocaine reached the heart immediately. These results support a peripheral site of action for cocaine-induced death.

Cocaine Cardiotoxicity Arrhythmias Blood pressure Route of administration Sudden death

COCAINE-INDUCED death has been attributed to the cardiotoxic actions of cocaine, which include ventricular arrhythmias and myocardial infarction (11,12). Cocaine affects the sympathetic nervous system by blocking the reuptake of catecholamines (17). The subsequent increased availability of catecholamines at central or peripheral adrenoceptors could account for the enhanced sympathetic activity and cardiovascular effects observed. However, the site responsible for sudden death as a result of acute cocaine toxicity has not been elucidated.

A central site of action for the cardiovascular effects of cocaine has been postulated. Evidence that supports this includes the finding that hexamethonium, a ganglionic blocker, significantly reduced the pressor response produced by cocaine (22). Although sudden death caused by acute cocaine toxicity may be centrally mediated, this hypothesis has not been tested. A direct local anesthetic activity of cocaine may be responsible for sudden cardiac death. Cocaine has been shown to have depressant effects on the isolated guinea pig atria (4) and the isolated rat heart (8) and to have a local anesthetic action on cardiac Purkinje fibers (21). Kabas et al. (10) have recently shown that intravenous administration of cocaine in dogs produces significant conduction impairment at cocaine concentrations that did not produce seizures. The cardiotoxic actions of cocaine have also been attributed to the direct vasoactive properties of this drug. Clinical studies have indicated that coronary vasospasm may be the cause of sudden myocardial infarction associated with cocaine use (8,19).

Studies have shown that the regimen of drug administration can influence drug action, and this effect has been seen with cocaine in a study in which intravenous administration of cocaine produced significant changes in rates of glucose utilization in brain areas which were not seen following intraperitoneal injection (3,16). Therefore, the present study utilized different routes of administration in unanesthetized Wistar Kyoto (WKY) rats to determine whether the effects of cocaine, including cardiovascular parameters and convulsions, were mediated through central or peripheral sites.

METHOD

Experiments were performed in age-matched male WKY rats. Animals were anesthetized with a mixture of ketamine (1 mg/kg, IP) and acepromazine (4 mg/kg, IP). The femoral vein, femoral artery, and carotid artery were cannulated with polyethylene tubing (PE-10 connected to PE-50), which was exteriorized at the back of the neck. In all cases, the vessel distal to the cannula was ligated. The femoral venous cannula was advanced to the inferior vena cava for drug administration directly toward the heart, while the femoral arterial cannula was advanced into the abdominal

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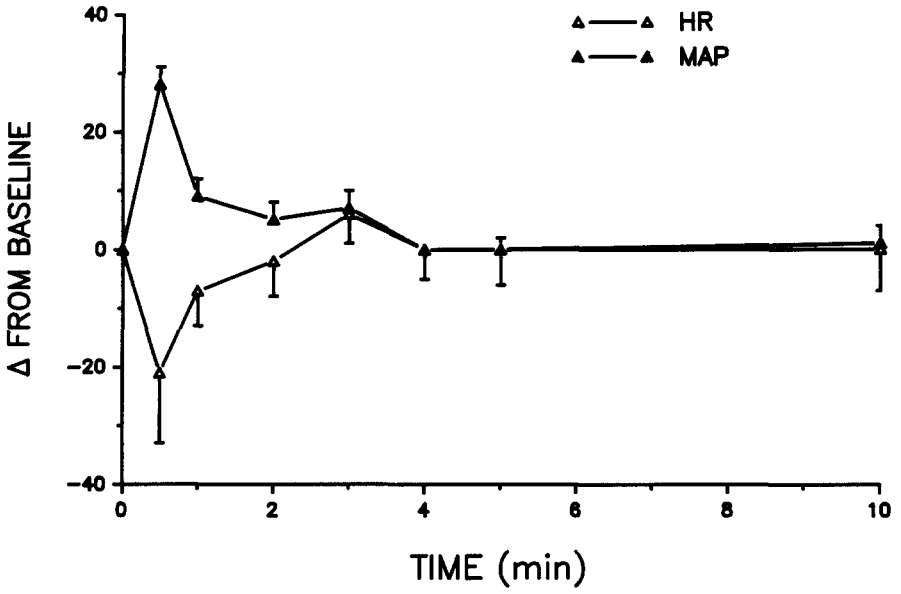

FIG. 1. The effect of cocaine (4 mg/kg, f.a.) on mean arterial pressure (MAP) and heart rate (HR) in WKY rats. Values represent the mean ± SEM.

aorta. The carotid arterial cannula was advanced 2 mm and placed for drug administration toward the brain. Each rat was instrumented with one cannula for drug administration and received one dose of cocaine in a volume of 0.15 ml administered as a bolus dose over 5 s. A cannula in the femoral artery was connected to a Statham pressure transducer for blood pressure recording, and heart rate was determined from the pulse rate of the blood pressure tracing. All experiments were performed at least 24 h after cannulation. Cocaine was dissolved in saline and administered via the femoral venous (f.v.) or femoral arterial (f.a.) cannulae at doses of 4 mg/kg or 16 mg/kg and by the carotid artery (c.a.) at a dose of 16 mg/kg.

All data are presented as the mean ± SEM and were analyzed using analysis of variance and the least squared difference test. The criteria for significance was $p<0.05$.

RESULTS

Baseline mean arterial pressure (MAP) and heart rate (HR) were 116 ± 4 mmHg and 356 ± 9 beats/min, respectively. Figure 1 illustrates the effect of cocaine (4 mg/kg, f.a., n = 7) on MAP and HR. Cocaine produced an increase in MAP of 28 ± 3 mmHg ($p>0.0001$) within 30 s. A reflex bradycardia occurred concurrently with the pressor response. The responses following f.v. (4 mg/kg, n = 6) administration did not differ significantly from f.a. administration.

Administration of a higher dose of cocaine (16 mg/kg) via the f.a. (n = 8) produced a similar response as the dose of 4 mg/kg, f.a. Cocaine significantly increased MAP by 27 ± 5 mmHg and also produced significant bradycardia (−50 ± 14 beats/min). However, administration of the higher dose via the f.v. (n = 5) did not produce an initial pressor response, rather arrhythmias and a decrease in MAP occurred until death. Bradycardia began within 30 s and arrhythmias, which occurred in all animals, began at 6 ± 2 s and continued until death. Mild tonic-clonic convulsions were observed in all animals, and death occurred at 89 ± 9 s.

Administration of cocaine (16 mg/kg) via the c.a. (n = 5) did produce a significant pressor response which occurred within 30 s, but this was also followed by a rapid decrease in blood pressure until death. Bradycardia occurred within 30 s, and arrhythmias, which occurred in all animals, began at 36 ± 7 s and continued until death. Tonic-clonic convulsions were observed in all animals. Death occurred at 177 ± 30 s. The effects of the high dose of cocaine following all 3 routes of administration are summarized in Table 1.

TABLE 1

COMPARISON OF THE RESPONSE TO COCAINE (16 mg/kg) FOLLOWING INTRAVENOUS AND INTRAARTERIAL ADMINISTRATION IN WKY RATS

Femoral Artery (n = 8)	Femoral Vein (n = 5)	Carotid Artery (n = 5)
A maximum pressor response occurred at approximately 30 s.	No initial pressor response was observed. MAP decreased until death.	A maximum pressor response occurred at approximately 30 s and was followed by a rapid decrease in blood pressure until death.
Bradycardia occurred within 30 s.	Bradycardia occurred within 30 s.	Bradycardia occurred within 30 seconds.
Blood pressure returned to baseline within 10 min.	Arrhythmias, which occurred in all animals, began at 6 ± 2 s. and continued until death.	Arrhythmias, which occurred in all animals, began at 36 ± 7 s and continued until death.
	Mild tonic-clonic convulsions were observed in all animals.	Tonic-clonic convulsions were observed in all animals.
	Death occurred at 89 ± 9 s.	Death occurred at 177 ± 30 s.

DISCUSSION

Several studies have demonstrated the ability of cocaine to produce a rapid increase in MAP in various species including the rat (9,15), dog (22), monkey (6), and human (5). In this study, cocaine produced a significant pressor response in unanesthetized WKY rats. A decrease in heart rate occurred concomitantly with the pressor response. Reflex bradycardia has also been reported in rats at doses of 5 mg/kg (15).

Cocaine has also been shown to produce cardiotoxic actions such as ventricular arrhythmias and myocardial infarction (7, 12, 18). However, the site of these actions is not known. Arrhythmias and myocardial necrosis were reported following continuous intraarterial infusion of cocaine at a dose of 2 mg/kg resulting in total doses of 146 to 618 mg (20). In the present study, arrhythmias and sudden death were observed at much lower total doses of 5 to 6 mg administered IV as a bolus dose. Cardiovascular responses to f.v. administration of cocaine (4 mg/kg) did not significantly differ from f.a. administration. However, a dose of 16 mg/kg via the femoral vein produced arrhythmias, convulsions, a decrease in heart rate and mean arterial pressure, and death, while 16 mg/kg via the femoral artery produced only a pressor response. These results could be attributed to a greater dilution of cocaine in the blood prior the reaching the heart following intraarterial administration. Cocaine has a very short half life of 18 min in rats (14). It is rapidly metabolized by oxidation followed by n-demethylation, and by hydrolysis by esterases in the plasma and liver (13,19). Therefore, another possibility is that plasma levels of cocaine would decline rapidly before reaching the heart following f.a. administration due to tissue distribution, metabolism, and excretion. A final possibility is that cocaine may cause intense vasoconstriction in the hindlimbs following f.a. administration, slowing the entrance of cocaine into the central circulation enough to allow dilution of the drug prior to reaching the heart. Any of these explanations would predict that a larger amount of the parent compound would reach the heart following f.v. administration. Evidence which further supports the lethality of the parent compound includes the finding that phenobarbital pretreatment decreased the acute lethality of cocaine by enhancing mixed function oxidase (2). The absence of a pressor response following the high dose of cocaine via the femoral vein may be due to a decrease in cardiac output secondary to arrhythmias that rapidly occur following f.v. administration.

Administration of cocaine (16 mg/kg) via the carotid artery produced a pressor response which was not observed following f.v. administration. However, the pressor response was followed by a decrease in mean arterial pressure and heart rate, arrhythmias, convulsions, and death. The onset of arrhythmias and the occurrence of death was delayed in comparison to f.v. administration. This could be due to the binding of cocaine to high affinity sites in the brain or to the increased time needed for cocaine to reach the heart (1).

It has been suggested that sudden death from cocaine is due to direct cardiac effects (10,11). The results of this study support a peripheral site of action for cocaine-induced death. This is due to the finding that a high dose of cocaine produced death more rapidly when administered via the femoral vein, which would result in a high concentration of cocaine reaching the heart faster than administration via the carotid artery, which would result in a high concentration of cocaine reaching the brain before the heart. Additionally, convulsions produced by cocaine were not of sufficient intensity or duration to produce death. The direct cardiotoxicity appears to be mediated through myocardial depression, which may be due to the local anesthetic effect of cocaine or to coronary vasoconstriction resulting in myocardial ischemia.

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