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Centrally mediated hemodynamic effects of cocaine in rabbits: the role of local anesthetic actions and biogenic amine re-uptake blockade

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Abstract

This study sought to identify the central nervous system-mediated cardiovascular effects of cocaine and to determine if these effects result from local anesthetic actions or biogenic amine re-uptake blockade. New Zealand rabbits received multiple i.c.v. doses of cocaine, pseudococaine, lidocaine or desipramine while recording blood pressure and heart rate. Moderate dose cocaine produced a decrease in heart rate and mean arterial pressure while the highest dose produced increases in heart rate and blood pressure. Lidocaine and pseudococaine produced dose-dependent increases in blood pressure while desipramine produced decreases in heart rate and mean arterial pressure. In this model, the central nervous system-mediated cardiovascular effects of cocaine are dose-dependent; low doses produced cardiovascular depression while higher doses produced cardiovascular stimulation. The data also suggest that cocaine's local anesthetic effects are responsible for its central nervous system-mediated cardiovascular stimulation, while biogenic amine re-uptake blockade causes cardiovascular depression.

Keywords: Local anesthetic; Cocaine; Lidocaine; Pseudococaine; Hemodynamics; Blood pressure; Heart rate; Desipramine

1. Introduction

Cocaine ingestion by humans results in stimulation of both the central nervous system and the cardiovascular system (Fishman et al., 1985, 1976; Resnick et al., 1977). Cardiovascular stimulation is thought to play a role in the myriad cardiovascular complications associated with cocaine abuse including sudden death, myocardial ischemia/infarction, myocarditis, arrhythmias, etc. (Virmani, 1991). Given that cocaine is used regularly by tens of millions around the world, cardiovascular morbidity from recreational cocaine use is a major public health problem. Thus, understanding the mechanisms of cocaine's sympathomimetic effects has potentially important implications for preventing and treating the cardiovascular complications of cocaine abuse. However, the mechanisms and site(s) of action responsible for cocaine's cardiovascular effects are not clear.

Animal studies are conflicting with respect to the sites of action responsible for the cardiovascular stimulating effects of cocaine. Multiple studies in a variety of species suggest that the cardiovascular stimulating effects of cocaine are solely the result of catecholamine re-uptake blockade within the peripheral autonomic nervous system (Kuhn et al., 1988; Raczkowski et al., 1991; Tella et al., 1990). However, other studies suggest that the cardiovascular stimulating properties of cocaine result, to a significant degree, from stimulation of sympathetic centers within the central nervous system (Chiueh and Kopin, 1978; Kiritsy-Roy et al., 1990; Kneupfer and Branch, 1992; Schindler et al., 1992; Wilkerson, 1988). As if to underscore the degree of conflict within the literature, different studies from the same laboratory have reached opposite conclusions regarding the role of the central nervous system in cocaine's cardiovascular stimulating effects (Schindler et al., 1992; Tella et al., 1990).

Despite the conflicting literature, a number of well conducted studies clearly suggest that the cardiovascular stimulating effects of cocaine are, at least in part, mediated by the central nervous system. However, these studies do not indicate which of cocaine's pharmacologic actions – biogenic amine re-uptake blockade or sodium channel blockade – are responsible for the central nervous system-mediated cardiovascular stimulation observed in these studies. Local anesthetics have been shown to produce

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cardiovascular stimulation by actions within the central nervous system (Bernards and Artru, 1991; Heavner, 1986; Kao and Jalar, 1959), while biogenic amines affected by cocaine have been shown to produce both cardiovascular stimulation and depression, depending on the route and site of central nervous system administration (McCall, 1990). Thus, it is not possible to predict which of cocaine's many pharmacologic actions is responsible for the central nervous system-mediated cardiovascular stimulation documented in multiple animal studies.

The goals of this study were to identify the central nervous system-mediated cardiovascular effects of cocaine in the rabbit and to determine if these effects are the result of local anesthetic actions or biogenic amine re-uptake blockade. To address this question, equimolar doses of cocaine, pseudococaine, lidocaine and desipramine were administered to anesthetized rabbits by ventriculocisternal perfusion and the resulting changes in blood pressure and heart rate were followed over time. Multiple doses of each drug were studied in order to determine if the response was dose-related.

2. Materials and methods

Animal use was approved by the University of Washington Animal Care Committee. Guidelines of the American Association for Accreditation of Laboratory Animal Care were followed throughout the study.

2.1. Experimental preparation

New Zealand white rabbits of both sexes, weighing 3.0–5.0 kg, were anesthetized with isoflurane (1–2%) and N_2O (66%) in O_2. The animals were intubated via a tracheotomy and mechanically ventilated with a Harvard pump to maintain normal pH and P_aCO_2. The right femoral artery was cannulated for blood pressure monitoring and blood sampling. The right femoral vein was cannulated for venous access. Needle electrodes were inserted at both shoulders and both thighs to monitor the electrocardiogram. Temperature was maintained at 38 ± 0.5°C by a servo-controlled heat lamp and rectal temperature probe. Arterial blood gases were measured using a Corning model 170 pH/Blood Gas Analyzer. End-tidal CO_2 and end-tidal anesthetic concentrations were continuously measured with a Datex model 254 airway gas analyzer.

The head was secured in a stereotactic frame and a 20 gauge needle was inserted into the left lateral ventricle by means of a 2 mm Burr hole in the parietal bone. The posterior neck muscles were dissected and a 20 gauge cannula was inserted between the first cervical vertebra and the base of the cranium and into the cisterna magna. A T-piece connected to the ventricular cannula allowed simultaneous perfusion of the ventricular-cisternal system and measurement of cerebrospinal fluid pressure.

Ventriculocisternal perfusion was established by perfusing mock cerebrospinal fluid through the ventricular cannula at 100 μl/min using a syringe pump. The perfusion was considered successful if cerebrospinal fluid pressure did not increase above pre-perfusion values and mock cerebrospinal fluid flowed from the cisternal cannula. If ventriculocisternal perfusion failed during an experiment (i.e., cerebrospinal fluid pressure increased above pre-perfusion values or cerebrospinal fluid did not flow from the outflow cannula) the data were excluded from analysis.

After completing the surgical preparation, isoflurane was decreased to 1.0% inspired concentration, N_2O was discontinued and the animals were paralyzed by intermittent i.v. injection of vecuronium (0.1–0.5 mg/kg). Following the change in anesthetic, at least 20 min elapsed before beginning the experiments.

2.2. Drug administration

Prior to administering any study drugs, each animal received plain mock cerebrospinal fluid by ventriculocisternal perfusion for 10 min while recording mean arterial pressure and heart rate. The ventriculocisternal perfusion solution was then changed to the lowest concentration of the study drug which was then administered at 100 μl/min for 10 min. The drugs and concentrations studied were: cocaine = 0.08 mM ($n = 5$), 0.8 mM ($n = 6$), 8 mM ($n = 5$), and 16 mM ($n = 6$) pseudococaine: 0.8 mM ($n = 5$), 8 mM ($n = 5$) and 16 mM ($n = 5$); lidocaine = 0.8 mM ($n = 6$), 4 mM ($n = 6$), 8 mM ($n = 5$), and 16 mM ($n = 5$); and desipramine = 0.08 mM ($n = 5$), 0.8 mM ($n = 5$), 8 mM ($n = 5$), and 16 mM ($n = 5$). All drugs were mixed in mock cerebrospinal fluid.

At the end of 10 min, the ventriculocisternal perfusion solution was changed back to plain mock cerebrospinal fluid at 100 μl/min. Ventriculocisternal perfusion with plain mock cerebrospinal fluid continued until at least 20 min elapsed and a stable baseline blood pressure had returned. The animal then received the next higher dose of the study drug at the same rate for 10 min. This second dose of study drug was again followed by ventriculocisternal perfusion with plain mock cerebrospinal fluid for at least 20 min and until a stable baseline blood pressure had returned. This sequence of ventriculocisternal perfusion with increasing concentrations of the study drug followed by plain mock cerebrospinal fluid was continued until the animal had received at most four drug doses. Because of occasional technical problems with the ventriculocisternal perfusion, not all animals received each dose of study drug. During ventriculocisternal perfusion, mean arterial pressure, heart rate and cerebrospinal fluid pressure were continuously recorded on a strip chart recorder.

Blood samples (4 ml) were withdrawn following the 10 min infusion of the highest dose of study drug in order to determine the plasma concentrations of cocaine, lidocaine and desipramine. Cocaine samples were collected in tubes

containing sodium fluoride to prevent further metabolism by plasma cholinesterase.

2.3. Drug assays

2.3.1. Lidocaine

Plasma was alkalinized by addition of sodium hydroxide and lidocaine was extracted into heptane/ethyl acetate. Lidocaine was separated by gas chromatography and detected by a nitrogen-phosphorous detector. The limit of quantification was 2.5 ng/ml and the coefficient of variation at 1 μg/ml was 12.6%.

2.3.2. Cocaine

Plasma was alkalinized by addition of sodium hydroxide and cocaine was extracted into heptane/ethyl acetate. Cocaine was separated by gas chromatography and detected by a nitrogen-phosphorous detector. The limit of quantification was 100 ng/ml and the coefficient of variation at 1 μg/ml was 3%.

2.3.3. Desipramine

Plasma was extracted into butyl alcohol and back extracted in acid. Desipramine was separated by high pressure liquid chromatography and detected spectrophotometrically (242 nm). The limit of quantification was 25 ng/ml and the coefficient of variation at 70 ng/ml was 9.2%

2.4. Drug preparation

The study drugs were: cocaine HCl (Sigma Chemical Company, St Louis, MO, USA), desipramine HCl (Sigma Chemical Company, St Louis, MO, USA), lidocaine HCl (Sigma Chemical Company, St Louis, MO, USA) and pseudococaine HCl (National Institute on Drug Abuse, Division of Preclinical Research, Bethesda, MD, USA).

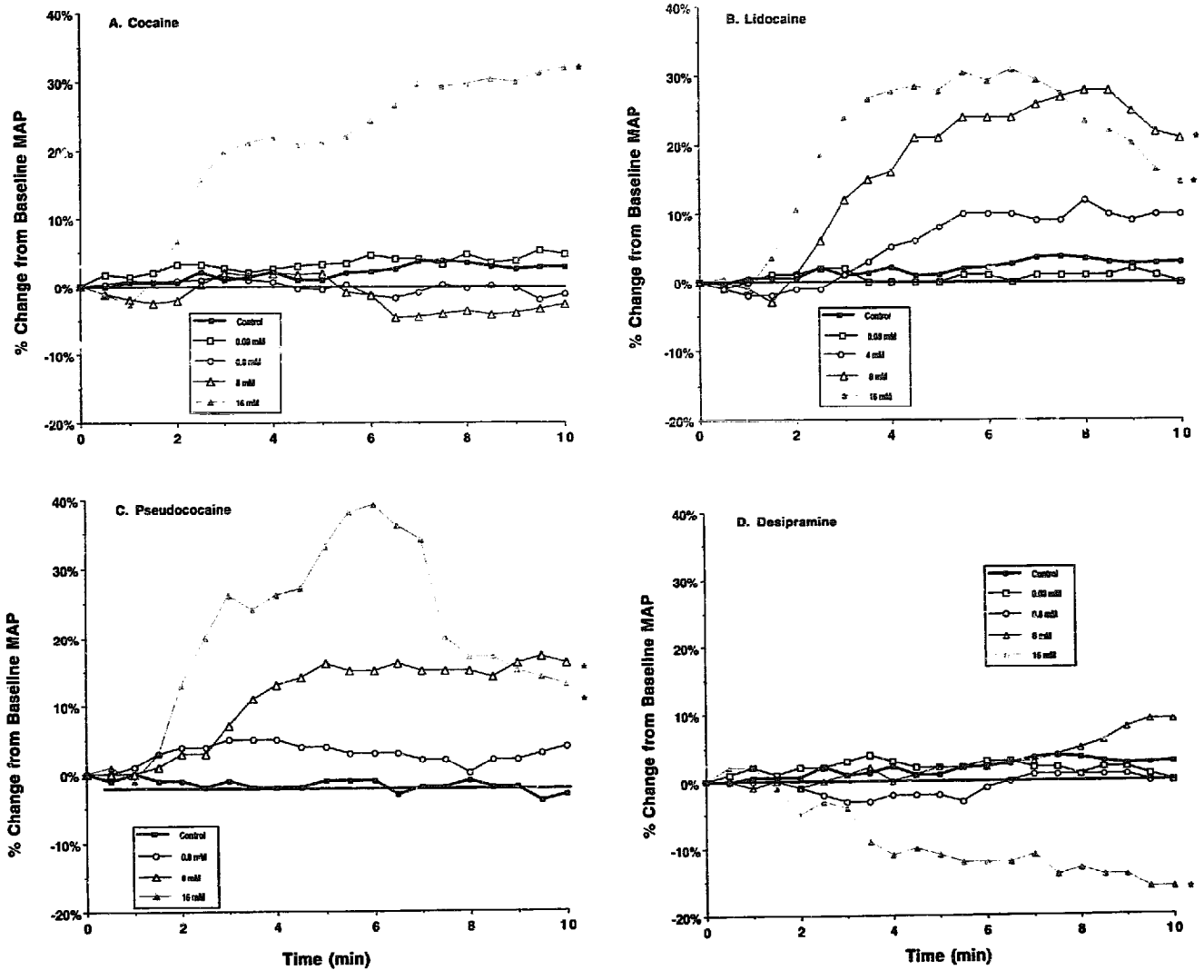

Fig. 1. Percentage change from baseline mean arterial pressure following ventriculocisternal perfusion with cocaine (A), lidocaine (B), pseudococaine (C) and desipramine (D). * The change in mean arterial pressure over time is significantly different from the change in mean arterial pressure during the control period. Error bars have been omitted for clarity.

Table 1
Group characteristics at baseline

Group	Weight	pH	PCO_2	PO_2	Mean arterial pressure	Heart rate
Cocaine	3.68 ± 0.12	7.41 ± 0.01	30 ± 1.0	475 ± 12	68.5 ± 2.7	228 ± 7
Pseudococaine	3.39 ± 0.09	7.41 ± 0.02	35 ± 1.1	463 ± 75	67.4 ± 1.8	273 ± 14 [a]
Lidocaine	3.53 ± 0.15	7.39 ± 0.01	30.4 ± 1.0	453 ± 12	67.9 ± 2.8	226 ± 9
Desipramine	4.41 ± 0.17 [a]	7.44 ± 0.02	36 ± 2.6	500 ± 12	75.8 ± 4.2	221 ± 12

Values are means ± S.E. [a] $P < 0.05$ compared to all other groups.

Mock cerebrospinal fluid consisted of NaCl 140 meq, $NaHCO_3$ 25 meq, KCl 2.9 meq, $MgCl_2$ 0.4 meq, urea 3.5 meq, glucose 4.0 meq, and $CaCl_2$ 2.0 meq. The osmolality of mock cerebrospinal fluid was 295–300, pH was adjusted to 7.38–7.42 by bubbling with 5% CO_2. All drugs were mixed in mock cerebrospinal fluid and then placed in gas-tight syringes.

2.5. Statistical analysis

The heart rate and mean arterial pressure just prior to beginning each drug administration were used as the baseline to calculate the change in mean arterial pressure and heart rate caused by the drug. Analysis of variance (ANOVA) for repeated measures was used to determine if ventriculocisternal perfusion with the study drugs produced changes in the animal's mean arterial pressure or heart rate which were significantly greater than those which occurred during perfusion with plain mock cerebrospinal fluid at baseline. Bonferroni corrected t-tests were used to compare baseline characteristics between the groups (weight, mean arterial pressure, heart rate, pH, P_aO_2, P_aCO_2). Differences were considered statistically significant at $P < 0.05$.

3. Results

Table 1 shows group characteristics at baseline. There was no difference between the groups in baseline mean arterial pressure, P_aO_2, P_aCO_2 or pH. The desipramine group weighed more than the other groups and the pseudococaine group had a higher baseline heart rate than the other groups.

Fig. 1 shows the effect of ventriculocisternal perfusion with cocaine, pseudococaine, lidocaine and desipramine on mean arterial pressure during the 10 min drug infusion period. The two lowest cocaine doses (0.08 mM, and 0.8 mM) had no significant effect on mean arterial pressure. The 8 mM cocaine dose produced a decrease in mean arterial pressure which did not reach statistical significance while the highest dose (16 mM) produced a significant mean arterial pressure increase. Both pseudococaine and lidocaine produced dose-dependent increases in mean arterial pressure which reached statistical significance at the two highest doses (8 mM and 16 mM). The three lowest doses of desipramine had no significant effect on mean arterial pressure while the highest dose (16 mM) produced a significant decrease in mean arterial pressure. The dose-dependent effects of each study drug on mean arterial pressure are shown more clearly in Fig. 2 which plots the maximum change in mean arterial pressure produced by each drug dose.

Fig. 3 shows the effect of ventriculocisternal perfusion

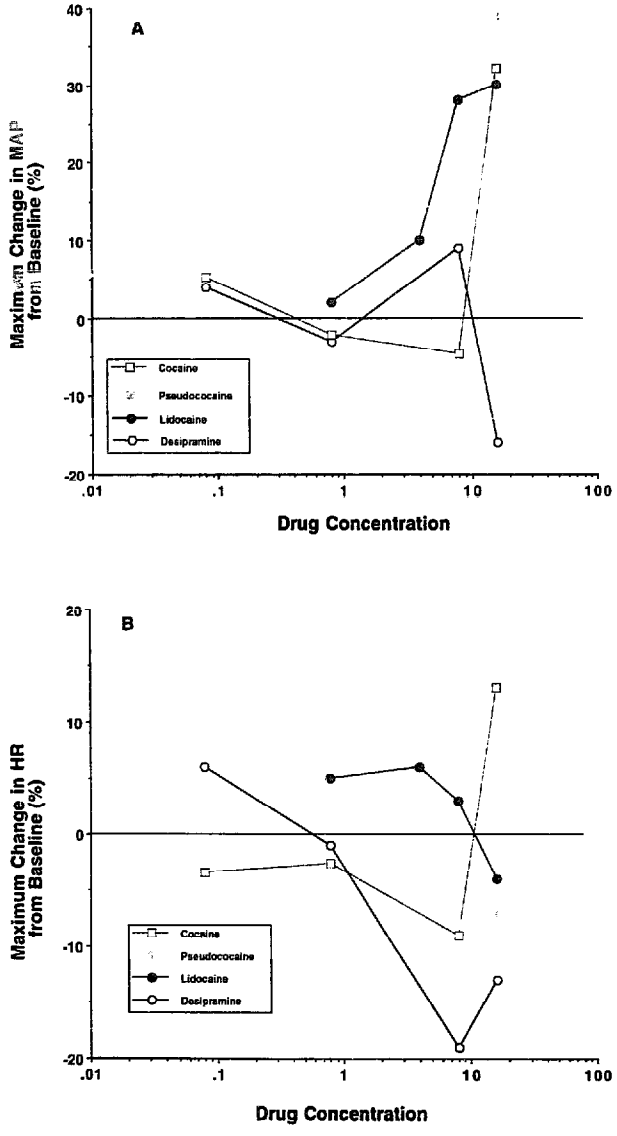

Fig. 2. Relationship between drug concentration (dose) and maximum change in mean arterial pressure (A) and heart rate (B).

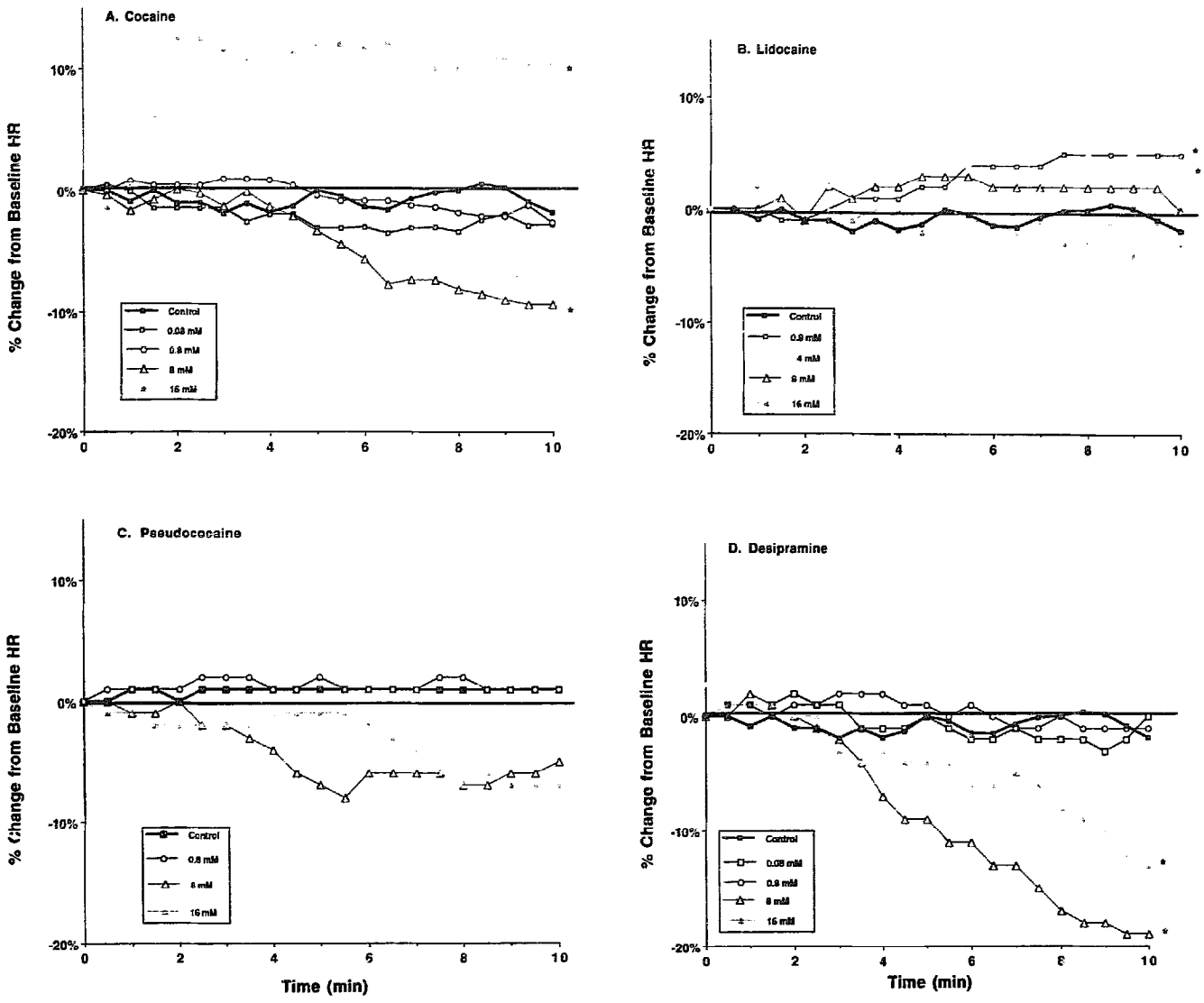

Fig. 3. Percentage change from baseline heart rate following ventriculocisternal perfusion with cocaine (A), lidocaine (B), pseudococaine (C) and desipramine (D). * The change in heart rate over time is significantly different from the change in heart rate during the control period. Error bars have been omitted for clarity.

with cocaine, pseudococaine, lidocaine and desipramine on heart rate during the 10 minute drug infusion period. The two lowest doses of cocaine (0.08 mM and 0.8 mM) had no effect on heart rate. The 8 mM cocaine dose produced a significant decrease in heart rate while the 16 mM dose produced a significant heart rate increase. The two lowest lidocaine doses (0.8 mM and 4 mM) produced significant heart rate increases while the two highest doses (8 and 16 mM) had no effect on heart rate. Pseudococaine had no significant effect on heart rate at any dose. The two lowest doses of desipramine (0.08 mM and 0.8 mM) had no effect on heart rate, while the two highest doses (8 and 16 mM) produced significant heart rate decreases. The dose-dependent effects of each study drug on heart rate are shown more clearly in Fig. 2 which plots the maximum change in heart rate produced by each drug dose.

Cocaine was not detected in any plasma samples. Lidocaine plasma concentration following the 10 min infusion of the highest dose (16 mM) was 0.31 ± 0.08 μg/ml. Desipramine plasma concentration following the 10 min infusion of the highest dose (16 mM) was 0.14 ± 0.015 μg/ml.

4. Discussion

The goals of this study were to identify the central nervous system-mediated cardiovascular effects of cocaine and to determine whether these effects are the result of local anesthetic actions or biogenic amine re-uptake blockade. To achieve these goals, the study drugs were delivered to the central nervous system by ventriculocisternal perfusion. Ventriculocisternal perfusion results in preferential distribution of the drugs through the ventricular

system and over the surface of the brainstem with little spread to more rostral structures lying above the tentorium. Thus, greatest drug exposure is to the thalamus, hypothalamus, and medulla. Since the neural structures responsible for control of the autonomic nervous system reside principally within these brain areas, we speculate that the autonomic control centers are the principal sites of action responsible for the cardiovascular effects observed in this study.

The data demonstrate that the central nervous system-mediated cardiovascular effects of cocaine are dose-dependent in this ventriculocisternal perfusion rabbit model. Cocaine doses less than 8 mM had no significant cardiovascular effects, while the 8 mM dose of cocaine produced a significant decrease in heart rate in the absence of a significant change in blood pressure. In contrast, the 16 mM cocaine dose significantly increased both heart rate and mean arterial pressure. These findings demonstrate that cocaine can both stimulate and depress the cardiovascular system by actions within the central nervous system. The absence of measurable concentrations of cocaine in plasma indicate that these effects were mediated by central nervous system actions of the drug and were not the result of peripheral actions following systemic uptake.

The central nervous system-mediated cardiovascular stimulation observed following the highest dose of cocaine is consistent with earlier studies suggesting that the central nervous system contributes to cocaine's cardiovascular stimulation. For example, Kiritsy-Roy et al. (1990) demonstrated that i.c.v. cocaine administration in rats produced dose-dependent increases in blood pressure and that ganglionic blockade prevented cardiovascular stimulation following intra-arterial cocaine administration. Similar studies in conscious dogs (Wilkerson, 1988) and rats (Kneupfer and Branch, 1992) also demonstrated that ganglionic blockade attenuated the pressor response to systemically administered cocaine. These observations led the authors of these studies to conclude that cocaine produces cardiovascular stimulation by increasing central sympathetic outflow. Using a different experimental approach, Schindler et al. (1992) demonstrated that i.v. administration of cocaine methiodide, an ionized quaternary cocaine derivative which does not cross the blood-brain barrier, was much less effective than cocaine in stimulating the cardiovascular system of conscious squirrel monkeys (Schindler et al., 1992). These findings led the authors to reverse their conclusions from an earlier study (Tella et al., 1990) and to assert that central nervous system actions of cocaine are involved in the drug's cardiovascular stimulating effects. Thus, these earlier studies and the present investigation support the idea that cocaine's cardiovascular stimulating effects may be, at least in part, the result of a central nervous system-mediated increase in sympathetic outflow.

The heart rate effects of the study drugs are not as clearly related to drug dose and are more difficult to characterize than the mean arterial pressure effects. This may reflect a variable interaction between direct central nervous system-mediated chronotropic effects and reflexive baroreceptor-mediated responses to associated changes in mean arterial pressure.

An additional goal of this study was to determine whether cocaine's central nervous system-mediated cardiovascular effects were the result of biogenic amine re-uptake blockade or local anesthetic effects. Pseudococaine is an epimer of cocaine which is approximately 3 times more potent than cocaine as a local anesthetic (Matthews and Collins, 1983), but is several fold less potent as an epinephrine (Krell and Patil, 1972; Schmidt et al., 1961) and dopamine re-uptake blocker (Williams et al., 1977). Therefore, the dose-dependent increases in mean arterial pressure following pseudococaine administration were likely the result of this drug's local anesthetic effects and not its ability to block biogenic amine re-uptake. Consistent with this conclusion is the fact that lidocaine produced similar dose-dependent increases in mean arterial pressure while desipramine, a biogenic amine re-uptake blocker, produced significant decreases in both mean arterial pressure and heart rate. Based upon these observations, it seems reasonable to conclude that the marked increase in mean arterial pressure produced by the highest dose of cocaine was likely the result of the drug's local anesthetic effects and not the result of biogenic amine re-uptake blockade. This conclusion is consistent with earlier reports that local anesthetics produce cardiovascular stimulation by actions within the central nervous system (Bernards and Artru, 1991; Heavner, 1986; Kao and Jalar, 1959).

As noted earlier, not all studies support the existence of a central nervous system-mediated component of cocaine's cardiovascular effects. For example, Kuhn et al. (1988) found that i.v. cocaine methiodide was just as effective as i.v. cocaine in producing cardiovascular stimulation in sedated dogs. This contrasts with the findings of Schindler et al. (1992) who found i.v. cocaine methiodide to be much less potent than i.v. cocaine in stimulating the cardiovascular system of conscious squirrel monkeys. Whether species differences or the use of sufentanil sedation explains the conflicting findings is unclear. Raczkowski et al. (1991) have also presented evidence that the central nervous system is not involved in cocaine's cardiovascular stimulation. Using an anesthetized, decerebrate cat model, these investigators demonstrated that selective central nervous system administration of cocaine produces significant decreases in both mean arterial pressure and heart rate (Raczkowski et al., 1991). The fact that the 8 mM cocaine dose produced a significant decrease in heart rate in this study is consistent with the findings of Raczkowski et al. (1991) and suggests that the central nervous system-mediated cardiovascular effects of cocaine can be cardiodepressant if the appropriate dose is selectively administered into the central nervous system. Raczkowski et al. (1991) concluded that the cardiodepressant effects of cocaine were the result of catecholamine re-uptake blockade and not

local anesthetic effects. This conclusion is consistent with findings in this study that i.c.v. administration of desipramine, a catecholamine re-uptake blocker, also produced marked reductions in mean arterial pressure and heart rate. Presumably, the fall in mean arterial pressure and heart rate observed in this study and in the study by Raczkowski et al. (1991) is the result of decreased sympathetic outflow. The mechanism by which sympathetic outflow is decreased is not clear, but could result from α_2-receptor stimulation following accumulation of norepinephrine in the synaptic cleft.

The reason for such contradictory findings with respect to the central nervous system-mediated cardiovascular effects of cocaine is not clear, although species and methodological differences are possible explanations. However, the finding in this study that cocaine is capable of producing both cardiovascular stimulation and depression suggests that differences in drug dose may also be important in determining the central nervous system-mediated cardiovascular effects of cocaine. At lower doses, the biogenic amine re-uptake blocking effects of cocaine may predominate resulting in cardiovascular depression as seen in this study and in the study by Raczkowski et al. (1991). At higher doses, local anesthetic effects may predominate resulting in cardiovascular stimulation as seen in this study and in other studies discussed above.

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References

Bernards, C. and A. Artru, 1991, Hexamethonium and midazolam terminate dysrhythmias and hypertension caused by intracerebroventricular bupivacaine in rabbits, Anesthesiology 74, 89-96.

Chiueh, C. and I. Kopin, 1978, Centrally mediated release by cocaine of endogenous epinephrine and norepinephrine from sympathoadrenal medullary system of unanesthetized rats, J. Pharmacol. Exp. Ther. 205.

Fishman, M., C. Schuster, J. Javaid, Y. Hatano and J. Davis, 1985, Acute tolerance development to the subjective and cardiovascular effects of cocaine, J. Pharmacol. Exp. Ther. 235, 677.

Fishman, M., C. Schuster, L. Resnekov, J. Shick, N. Krasnegor, W. Fennel and D. Freedman, 1976, Cardiovascular and subjective effects of intravenous cocaine administration in humans, Arch. Gen. Psychiatry 33, 983.

Heavner, J., 1986, Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle in cats, Anesth. Analg. 65, 133.

Kao, F. and U. Jalar, 1959, The central action of lignocaine and its effects on cardiac output, Br. J. Pharmacol. 14, 522.

Kiritsy-Roy, J., J. Halter, S. Gordon, M. Smith and L. Terry, 1990, Role of the central nervous system in hemodynamic and sympathoadrenal responses to cocaine in rats, J. Pharmacol. Exp. Ther. 255, 154.

Kneupfer, M. and C. Branch, 1992, Cardiovascular responses to cocaine are initially mediated by the central nervous system in rats, J. Pharmacol. Exp. Ther. 263, 734.

Krell, R.D. and P.N. Patil, 1972, Steric aspects of adrenergic drugs. XX. accumulation of (−) and (+) norepinephrine [14C] by peripheral tissues of rat, J. Pharmacol. Exp. Ther. 182, 273.

Kuhn, F., R. Gillis, S. Wahlstrom, R. Tessel, M. Visner and G. Schafer, 1988, Cocaine-induced cardiovascular effects: lack of evidence for a central nervous system site of action, Circulation 78, part II, 360.

Matthews, J.C. and A. Collins, 1983, Interactions of cocaine and cocaine congeners with sodium channels, Biochem. Pharmacol. 32, 455.

McCall, R.B., 1990, Role of neurotransmitters in the central regulation of the cardiovascular system, in: Progress in Drug Research, Vol. 35, ed. E. Jucker (Birkhauser Verlag, Basel) p. 25.

Raczkowski, V., Y. Hernandez, H. Erzouki, P. Abrahams, A. Mandal, P. Hamosh, E. Friedman, J. Quest, K. Dretchen and R. Gillis, 1991, Cocaine acts in the central nervous system to inhibit sympathetic neural activity, J Pharmacol. Exp. Ther. 257, 511.

Resnick, R., R. Kestenbaum and L. Schwartz, 1977, Acute systemic effects of cocaine in man: a controlled study by the intranasal route and intravenous routes, Science 195, 696.

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

Schmidt, G., B. Kalisher and B. Wockel, 1961, Vergleichende Untersuchungen über die Wirkungen von normal Cocain and Pseudococain, Naunyn-Schmied. Arch. Exp. Pathol. Pharmacol. 240, 523.

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

Virmani, R., 1991, Cocaine-associated cardiovascular disease: clinical and pathological aspects, in: Cardiovascular Toxicity of Cocaine: underlying Mechanisms, National Institute on Drug Abuse Research Monograph 108, ed. P. Thadani (Supt. of Docs., U.S. Govt Printing Office, Washington D.C.).

Wilkerson, R., 1988, Cardiovascular effects of cocaine in conscious dogs: importance of fully functional autonomic and central nervous systems, J. Pharmacol. Exp. Ther. 246, 466-471.

Williams, N., D.H. Clouet, A.L. Misra and S.J. Mule, 1977, Cocaine and metabolites: relationship between pharmacological activity and inhibitory action on dopamine uptake into striatal synaptosomes, Prog. Neuropsychopharmacol.