Effects of Antidotes to Cocaine on the Deregulation of the Baroreflex by the Alkaloid (44011)

RENAUD TROUVÉ,* GABRIEL G. NAHAS,*·†·[1] PETKO I. ARNAOUDOV,† AND COLETTE LATOUR*
Hopital Fernand Widal, Paris 75010, France; and New York University Medical Center,† New York, New York 10016*

Abstract. **Cocaine exerts in the rat an inhibitory effect on the baroreflex induced by bilateral clamping of the carotid arteries. The present series of experiments were designed to test the effectiveness of cocaine antidotes on this deregulation of the baroreflex.**

Sprague-Dawley rats were fitted under pentobarbital anesthesia with a catheter in the caudal artery, and their carotid arteries were exposed. The pressure signal from the caudal artery was treated on line by a microcomputer for continuous display of blood pressure and heart rate measurements. The animals were administered intraperitoneally either 50 mg cocaine or an equal volume of saline. Five minutes later, they were administered either saline or proven antidotes to cocaine (diltiazem, nicardipine, enzyme converting inhibitor [ECI], enalaprilat associated with diazepam). After 2 min, stimulation of the baroreceptor was performed by bilateral clamping of the two carotids for a period of 2 min. The measures of the maximal variation in systolic pressure before and after clamping indicated a significant difference between saline and cocaine treated animals ($P < 0.05$), with the former displaying a much greater increment in blood pressure after clamping.

The cocaine-treated animals, administered diltiazem, nicardipine, and ECI associated with diazepam, presented after clamping of the carotid arteries a normal baroreflex with increments in blood pressure no significantly different from those occurring in the animals receiving saline, but significantly different from those administered cocaine only ($P < 0.05$). Baroreflex deregulation by cocaine may also be restored by an angiotensin II receptor antagonist. The possible role of this peptide in mediating in part baroreflex activity is discussed. [P.S.E.B.M. 1996, Vol 212]

Under normal physiological conditions, increase in arterial pressure evoke a compensatory reflex decrease, in heart rate and sympathetic outflow to blood vessels, which tend to restore normal arterial blood pressure. However, cocaine acute intoxication induces concomitant increases in heart rate and blood pressure, indicative of a deregulation of the baroreflex. This deregulation was reported by Andresen *et al.* (1), who observed that 0.1–100 μm cocaine will inhibit *in vitro* baro receptor afferents in the rat aortic arch. They also reported that cocaine perfused *in vivo* through the vascularly isolated carotid sinus of the rabbit reduced the slope of the baroreflex relationship between carotid sinus pressure and systemic mean arterial pressure. These observations were confirmed by Trouvé *et al.* (2), who reported that stimulation of the baroreflex in the rat induced by bilateral clamping of the two carotid arteries was inhibited by the systemic administration of cocaine.

The same authors also reported that the hypertensive effect of cocaine acute administration and its concurrent induced sympatho-adrenal stimulation and increased plasma catecholamines may be controlled by two markedly different classes of compounds used either as antagonists or as antidotes (3–6): selected calcium antagonists and inhibitors of kininase II (7, 8),

[1] To whom requests for reprints should be addressed at Department of Anesthesiology, New York University Medical Center, 550 First Avenue, New York, NY 10016.

Received October 4, 1995. [P.S.E.B.M. 1996, Vol 212]
Accepted February 27, 1996.

0037-9727/96/2123-0239$10.50/0

the latter associated with diazepam. This experiment suggested that cocaine affected cardiovascular regulation peripherally through direct stimulation of the sympatho-adrenal systems and centrally through a mechanism that was influenced by gabaergic neurones sensitive to benzodiaze pines, compounds also known to be inhibit cocaine (9).

The present series of experiments were designed to test the effectiveness of cocaine antidotes on the deregulation of the baroreflex by the alkaloid and explore the possible participation of angiotensin II in this deregulation.

Materials and Methods

Ten series of experiments were performed on Sprague-Dawley rats weighing 260 ± 35 g. There were 7–11 animals in each series. The rats were anesthetized with sodium pentobarbital and fitted with a catheter in the caudal artery. The two carotid arteries were exposed, and the animals tracheotomized. The caudal artery catheter was connected *via* a three-way stopcock to a strain gauge (Gould P.10 EZ). The blood pressure signal was recorded continuously and processed on line by a microcomputer for continuous digital display and printout according to a technique described earlier (10).

Systolic blood pressure recording were analyzed and the baroreflex pressor response measured by the difference between minimal systolic pressure before clamping and the maximum systolic pressure after clamping. The experimental protocol is presented in Figure 1.

In the first two series, the animals were administered intraperitoneally either 50 mg/kg of cocaine in 1 ml or an equal volume of saline. This dose of cocaine produces within 2 min significant and sustained increase in blood pressure. Five minutes later, a stimulation of the baroreflex was performed by bilateral clamping of the two carotids for 2 min. After that time, the clamp was released.

In the following series, 5 min after saline or cocaine administration the preparations were given a calcium antagonist (diltiazem or nicardipine) or enalaprilat with diazepam. All of these medications were used in dosage which, in other experiments, prevented or corrected the acute cardiovascular effects of sublethal dose of cocaine (4–7) (Table I), while producing minimal effect on blood pressure when administered separately to the same preparation (4).

One-way analysis of variance was used to determine whether the changes in blood pressure, after the clamping of the carotid arteries, were influenced by cocaine and antidotes applied independently of each other. The same one-way analysis of variance was used to study the blood pressure effects of cocaine alone and the mixture of cocaine and antidotes. The Levene test was used for testing the equality of the variances of the groups. The Bonferroni multiple comparison procedure was used to determine which means were significantly different from each other at level of significance $P < 0.05$. All analyses were performed using SPSS software (1992) (11).

Results

Changes in mean systolic blood pressure after bilateral clamping at the carotid arteries in rats administered cocaine, saline, and different antagonists of the alkaloid are presented in Table II.

The observed significance level of the Levene test showed that the assumptions needed for analysis of variance in this study were not violated ($P > 0.7$ for cocaine and antidotes applied independently of each other, and $P > 0.2$ for cocaine alone and the mixture of cocaine and antidotes).

There was significant difference between systolic pressures measured before and after clamping of the carotid arteries in saline- and cocaine-treated rats ($P < 0.05$).

There was a significant difference between systolic pressures measured before and after carotid clamping in the animals exposed to cocaine alone and those given cocaine followed by antidotes ($P < 0.05$) (except for the animal given diazepam, which alone does not restore the baroreflex deregulated by cocaine). Conversely, changes in blood pressure of the cocaine-treated animals administered antidotes were not different from those observed in animals only administered saline and which present a normal barore-

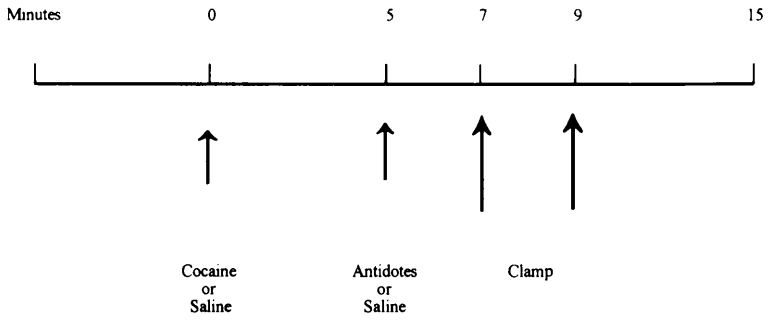

Figure 1. Experimental protocol. At Time 0, saline or cocaine was administered intraperitoneally to the animal. Five minutes later, the cocaine antagonists (Table I) were administered to the animal previously treated with cocaine or saline. At 7 min, carotid arteries were clamped for 2 min and then released.

Table I. Mode of Administration and Dose of Drugs Administered

Series	*n*	Treatment	Route	Dose
1	11	Saline	ip	1 ml
2	10	Cocaine	ip	50 mg/kg
3	11	Saline	ip	1 ml
		Nicardipine	ia	1.5 μg/ml/kg/ for 6 min
4	10	Cocaine	ip	50 mg/kg
		Nicardipine	ia	1.5 μg/ml/kg/ for 6 min
5	7	Saline	ip	1 ml
		Diltiazem	ia	40 μg/kg + 8 μg/kg/ min, 8 min
6	7	Cocaine	ip	1 ml
		Diltiazem	im	40 μg/kg + 8 μg/kg/min, 8 min
7	7	Saline	ip	1 ml
		Diazepam	im	0.7 mg/kg
8	7	Cocaine	ip	50 mg/kg
		Diazepam	im	0.7 mg/kg
9	7	Saline	ip	1 ml
		Diazepam	im	0.7 mg/kg
		Enalaprilat	ia	0.3 mg/kg
10	7	Cocaine	ip	50 mg/kg
		Diazepam	im	0.7 mg/kg
		Enalaprilat	ia	0.3 mg/kg

Note. Intraarterial administration was performed with an electrical syringe in minute amounts which did not alter blood pressure recording (4, 6, 7). ip, intraperitoneal; ia, intra-arterial; im, intramuscular.

ceptor response. Furthermore, similar doses of diltiazem, of nicardipine, or of diazepam and enalaprilat do not significantly alter baroreceptor function of the saline-treated animal.

Discussion

As reported (2), cocaine inhibits the baroreflex-mediated increase in blood pressure produced by bilateral clamping of the carotid arteries. Pentobarbital, the anesthetic used in these experiments, also decreases the baroreflex. The results obtained will therefore underestimate the effects of cocaine, which appears to be the causal agent of the inhibition of the baroreceptor.

Administration of nicardipine or diltiazem, or of enalaprilat associated with diazepam, restores the function of the baroreflex. These same pharmacological agents were effective in correcting the hypertension and elevated plasma catechol concentrations in rats (6) and squirrel monkeys (3) acutely intoxicated with cocaine. But while calcium channel antagonists were effective α- and β-blockers were not (4). Other authors also reported the lack of effectiveness of α-blockers in correcting the deregulation of the baroreflex by cocaine (1).

While enalaprilat controls the peripheral cardiovascular effects of cocaine intoxication, it does not alter the central effects of the alkaloid, especially convulsions which might be due to the slow penetration of the converting enzyme inhibitor through the blood-brain barrier. The effectiveness of enalaprilat (associated with diazepam) in offsetting the toxic effects of cocaine on cardiovascular function suggests that angiotensin II may still play a role in mediating these effects.

The blockade of angiotensin II receptors by their antagonists H.R. 720 (12) restores the baroreflex after its deregulation by the alkaloid, in the same model preparation as presently used. An iv dose of 0.3 mg/kg is administered 30 min before the start of the experiment. This latest study is an other indication of the possible role of the peptide in controlling the central mechanisms regulating blood pressure (13). Angiotensin II potentiates peripherally the α-stimulating effects of catechols and mediates epinephrine release in the adrenal medulla. Angiotensin II released peripherally by cocaine might circumvent the blood-brain barrier at some locations or even, because of the high blood pressure, intermittently cross the blood-brain barrier.

Table II. Differences in Maximal Systolic Blood Pressure (mm Hg)[a]

Series	*n*	ΔSBP	SD	S[b]	S[c]
Saline (S)	11	38.0	7.0	—	$P < 0.05$
Cocaine (C)	10	16.9	8.7	$P < 0.05$	—
S + Diazepam	7	37.0	7.7	NS	$P < 0.05$
S + Diltiazem	7	35.9	9.3	NS	$P < 0.05$
S + Nicardipine	11	28.7	6.8	NS	$P < 0.05$
S + Diazepam + Enalaprilat	7	29.1	7.4	NS	$P < 0.05$
C + Diazepam	7	16.4	3.2	$P < 0.05$	NS
C + Diltiazem	7	43.7	6.6	NS	$P < 0.05$
C + Nicardipine	10	28.5	10.4	NS	$P < 0.05$
C + Diazepam + Enalaprilat	7	33.3	9.2	NS	$P < 0.05$

[a] Differences between the maximal systolic blood pressure (ΔSBP) reached during bilateral carotid clamping and systolic blood pressure measured immediately before clamping in rats treated according to the schedule described in Table I.
[b] Significance between saline and the other series (Bonferroni tests; $P < 0.05$).
[c] Significance between cocaine and the other series (Bonferroni tests; $P < 0.05$).

The peptide might also be released by cocaine in the central nervous system and interact with central mechanisms (14, 15). Very low concentrations of angiotensin II have been reported to modulate the baroreflex by its action on the tractus solitarius in the rat (16).

Garner *et al.* (14) have described the effects of angiotensin II on the control of heart rate in the baboon. The peptide decreases the sensitivity of the baroreflex. Goldsmith and Hasking (17) have reported in humans that angiotensin II will inhibit the efferent response to an acute stimulation of the baroreflex (baroreflex loading). Angiotensin II is also reported to inhibit acetylcholine release in the vagal cardiac outflow, thereby decreasing vagal tone (18). This mechanism would contribute to the tachycardia observed in humans following cocaine intoxication, which is associated with a decreased vagal tone (19).

Angiotensin II is readily accessible to the area postrema which modulates the regulation of blood pressure and heart rate (20). Angiotensin III, a degradation product of angiotensin II also decreases the baroreflex (21). While angiotensin II concentrations of plasma or brain have not been assayed in the course of cocaine intoxication, it is suggested that this peptide may play a role in the inhibition of the baroreflex caused by this alkaloid.

Another neurotransmitter, GABA, appears to be involved in baroreflex modulation (22, 23), which could account for the effectiveness of diazepam to control central cocaine toxicity, in association with enalaprilat. However, diazepam given separately does not alter the peripheral sympathoadrenal stimulation and resulting vasoconstriction induced by cocaine.

These studies were supported by New York University, the City of Paris, and INSERM.

1. Andresen MC, Yang M, Nelson SH, Steinsland OS. Cocaine inhibits baroreflex control of blood pressure by actions at arterial baroreceptors. Am J Physiol **258;** Heart Circ Physiol **27:**H1244–H1249, 1990.
2. Trouvé R, Nahas G, Latour C. Inhibition of cocaine of the baroreflex in the rat. Proc Soc Exp Biol Med **201:**215–218, 1992.
3. Trouvé R, Nahas GG, Manger WM, Vinyard C, Goldberg S. Interactions of Nimodipine and cocaine on endogenous catecholamines in the Squirrel Monkey. Proc Soc Exp Biol Med **193:**171–175, 1990.
4. Trouvé R, Nahas GG. Antidotes to lethal toxicity in the rat. Arch Int Pharmacodyn **305:**197–207, 1990.
5. Trouvé R, Nahas GG, Manger WM. Catecholamines, cocaine toxicity, and their antidotes in the rat. Proc Soc Exp Biol Med **196:**194–187, 1991.
6. Nahas G, Trouvé R, Manger W, Latour C. Cocaine and sympatho adrenal system. Advances in biosciences, Pergamon Press 80:151–164, 1991.
7. Trouvé R, Latour G, Nahas G. Cocaine and the renin angiotensin system. Advances in Biosciences **80:**165–176, 1991.
8. Nahas GG, Trouvé R, Manger WW. Cocaine catecholamines and cardiac toxicity. Acta Anesth Scand **34**(Suppl 94):77–81, 1990.
9. Ikeda M, Dohi T, Tsujimoto A. Inhibition of GABA release from synaptoomes by local anesthetics. Anesthesiology **58:**495–499, 1985.
10. Trouvé R, Nahas G. Nitrendipine: an antidote to cardiac and lethal toxicity of cocaine. Proc Soc Exp Biol **183:**392–397, 1986.
11. SPSS for Windows: Advanced Statistics, Release 5. Copyright 1992 by SPSS Inc., 444 North Michigan Avenue, Chicago, IL 60611.
12. Trouvé R, Sitbon M, Bourdel V. Blockade of angiotensin II receptors with HR720 abolishes the cocaine induced baroreflex deregulation. FASEB J **9**(3):A400, 1995.
13. Lindpaintner K, Ganten D. The cardiac renin-angiotensin system. Circ Res **68:**906–921, 1990.
14. Garner MG, Phippard AF, Fletcher PJ, Maclean JM, Duggin GG, Horvath JS, Tiller DJ. Effect of angiotensin II on baroreceptor reflex control of heart rate in conscious baboons. Hypertension **10:**628–634, 1987.
15. Korner PI, Head GA, Badoer E, Bobik A, Angus JA. Role of brain amine transmitters and some neuromodulators in blood pressure, heart rate, and baroreflex control. J Cardiovasc Pharmacol **10:**S26–S32, 1987.
16. Casto R, Phillips I. Angiotensin II attenuates baroreflexes at nucleus tractus solitarius of rats. Am J Physiol **250:**R193–R198, 1986.
17. Goldsmith SR, Hasking G. Effect of pressor infusion of angiotensin II on sympathetic activity and heart rate in normal humans. Circ Res **68:**263–268, 1991.
18. Potter EK. Angiotensin inhibits action of vagus nerve at the heart. Br J Pharmacol **75:**9–11, 1982.
19. Newlin DB, Pretorius MB, Wong CJ, Stapleton JM, London ED. Acute intravenous cocaine reduces cardiac vagal tone in cocaine abusers. Committee on problems of drug dependence, Palm Beach, June 16–20, 1991.
20. Skoog KM, Mangiapane ML. Area postrema and cardiovascular regulation in rats. Am J Physiol **254:**H963–H969, 1988.
21. Lin KS, Chan JYH, Chan SHH. Reduction in baroreceptor reflex response by angiotensin III and its modification by Ileangiotensin III and bestatin in the rat. Neurosci Lett **90:**172–176, 1988.
22. Tubo T, Kihara M. Evidence for γ-aminobutyric acid receptor-mediated modulation of the aortic baroreceptor reflex in the nucleus tractus solitarii of the rat. Neurosci Lett **89:**156–160, 1989.
23. Bauer RM, Vela MB, Simon T, Waldrop TG. GABAergic mechanism in the posterior hypothalamus modulates baroreflex bradycardia. Brain Res Bull **20**(5):633–641, 1988.