Inhibition by Cocaine of the Baroreflex in the Rat (43501)

RENAUD TROUVÉ,*,† GABRIEL NAHAS,†,‡,1 AND COLETTE LATOUR‡

C.N.T.S., Les Ulis, France; Department of Anesthesiology,† New York Medical Center, New York, New York 10016; and Laboratoire de Toxicologie Cellulaire INSERM U.26,‡ Hôpital Fernand Widal, 75010 Paris, France*

Abstract. **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/kg of cocaine or an equal volume of saline. Five minutes later, stimulation of the baroreflex was performed by bilateral clamping of the two carotids for a period of 2 min. The same maneuver was repeated at 12, 24, and 31 min. Analysis of variance for repeated measures indicated that before carotid artery clamping, there was no significant difference between blood pressure measurements of the saline- and cocaine-treated groups.

A two-factor analysis of variance of the repeated measures of the maximal variation in systolic pressure after each clamping showed a significant difference between control and cocaine-administered groups ($P < 0.001$), with the former displaying a much greater increment in blood pressure after carotid clamping.

Cocaine exerts an inhibitory effect on the baroreflex that may be mediated through the increased angiotension II caused by the alkaloid. [P.S.E.B.M. 1992, Vol 201]

The stimulation of the sympathoadrenal system by cocaine is well documented. In addition to its inhibitory effect on neuronal norepinephrine and dopamine reuptake (1), the alkaloid stimulates the release of catechols from peripheral stores (2, 3). As a result of central and peripheral catecholaminergic overflow, there is an overstimulation of the central nervous system that results in convulsions (4), and of the cardiovascular system that results in hypertension, tachycardia (5), and cardiac damage (6). This cocaine-induced sympathoadrenal stimulation and increased plasma catecholamines may be controlled by two markedly different classes of compounds used either as antagonists or as antidotes (7, 8): selected calcium antagonists and, to a lesser extent, inhibitors of kininase II, which, to be effective, have to be associated with diazepam. This observation implied that cocaine stimulates the renin-angiotensin system and the production of angiotensin II, a potent vasoconstrictor. By contrast, α- and β-antagonists and labetalol are ineffective in controlling central and peripheral sympathoadrenal stimulation induced by toxic doses of cocaine. In addition, this alkaloid deregulates cardiovascular function: hypertension is associated with tachycardia, instead of the normal bradycardic response mediated through an intact baroreceptor mechanism. Such an effect suggested that an inhibition of the baroreflex by cocaine could contribute to the tachycardia induced by this alkaloid in the presence of hypertension. The purpose of our experiments was to test this hypothesis.

Methods

Four series of experiments were performed on rats weighing 260 ± 35 g. There were six animals in each series. The rats were anesthetized with sodium pentobarbital and fitted with a catheter in the caudal artery, and the two carotid arteries were exposed. The caudal artery catheter was connected via a three-way stopcock to a strain gauge (Gould P.10 EZ). The pressure signal was recorded continuously and also treated on line by a microcomputer for continuous display of blood pressure and heart rate according to the technique described by Trouvé and Nahas (9).

[1] To whom requests for reprints should be addressed at Department of Anesthesiology, New York University Medical Center, New York, NY 10032.

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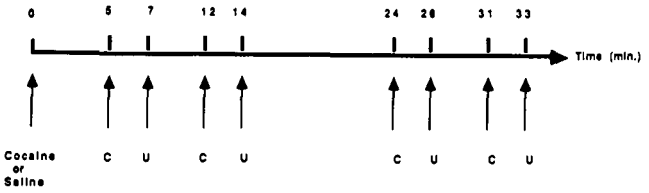

Figure 1. The following experimental protocol was used. At Time 0, saline or cocaine was administered intraperitoneally to the control or the test animals. The exposed carotid arteries were clamped (C) at the times indicated (5, 12, 24, and 31 min). After 2 min, the clamps were removed (U) at the times indicated (7, 14, 20, and 33 min) for 5 or 10 min.

In the first two series (Fig. 1), the animals were administered intraperitoneally either 50 mg/kg of cocaine or an equal volume of saline. Five minutes later, a stimulation of the baroreflex was performed by bilateral clamping of the two carotid arteries for 2 min. After that time, the clamp was released. This maneuver was repeated three times for 2 min at times of 12, 24, and 31 min. This maneuver, common in pharmacology, was performed repeatedly on the same preparation to test the reproducibility of its effects.

In the last two series, a second strain gauge was connected to the cephalic part of the left carotid artery. The animals were studied after the right carotid artery had been clamped for 2 min at 5 and 12 min following administration of saline or cocaine. These series were performed as control experiments. The residual pressure in the left carotid was measured after clamping of the right carotid in the cocaine- and saline-administered animals.

Results

Systolic blood pressure and heart rate in the first two series of saline- and cocaine-treated animals as measured 30 sec before the four successive bilateral clampings of the carotid arteries are tabulated in Table I. A two-way analysis of variance for repeated measures indicated no significant difference between the two groups in preclamping measurements of blood pressure. Successive clamping had no effect on control blood pressure measured just before clamping. The same analysis of variance applied to heart rate indicated no significant differences between the two groups. However, successive clamping was followed by a progressive fall in control heart rate measured before clamping ($P \leq 0.0127$).

Blood pressure records (Fig. 2) illustrate that in the saline-treated rat, there was a significant increase in blood pressure after bilateral clamping, followed by a rapid restoration of this variable to control value after clamp removal.

By contrast, there was a minimal change in blood pressure after carotid clamping in cocaine-administered animals. The extent of this response was gauged by measuring the difference between the maximal systolic pressure reached during carotid clamping and the systolic pressure measured just before clamping. A similar measurement was performed to assess changes in heart rate resulting from clamping (Table II). Analysis of variance of the differences between systolic pressures, measured successively before and after clamping, showed a significant difference between saline- and cocaine-treated rats ($P < 0.001$). Successive clamping had no significant, overall effect on the magnitude of blood pressure response to this stimulus ($P \leq 0.42$). Cocaine treatment impeded significantly the pressure increase caused by a stimulation of the baroreflex.

The same statistical analysis of heart rate change showed a significant difference between saline- and cocaine-treated rats, and no effect of successive clamping. The increase in heart rate that is associated with increased blood pressure after clamping is, therefore, inhibited by cocaine.

In the second series of experiments, an analysis of variance was performed on the minimal mean pressures measured in the cephalic portion of the carotid catheter before and after clamping (Table III). In either case, there were no significant differences in pressures recorded for saline- or cocaine-treated rats ($P < 0.23$ and $P < 0.40$, respectively). Furthermore, an analysis of variance of the magnitude of the pressure difference before and after clamping was not significantly different between groups.

Discussion

The first series of experiments demonstrates that cocaine significantly inhibits the increase in blood pres-

Table I. Systolic Blood Pressure and Heart Rate[a]

	No. of clampings							
	1		2		3		4	
	SBP (mm Hg)	HR (min)	SBP (mm Hg)	HR (min)	SBP (mm Hg)	HR (min)	SBP (mm Hg)	HR (min)
Saline-treated	132.8 ± 13.9	410 ± 32	131.8 ± 14.1	400 ± 35	123.5 ± 24.1	371 ± 38	134 ± 16	372 ± 39
Cocaine-treated	133.7 ± 22.9	399 ± 40	110.7 ± 13.9	370 ± 90	115.7 ± 13.5	349 ± 107	126.8 ± 21.4	361 ± 119

[a] Systolic blood pressure (SBP) and heart rate (HR) measured 30 sec before four successive carotic clampings (1, 2, 3, and 4) in rats treated with saline or cocaine according to the schedule described in Figure 1. For analysis of variance, see text.

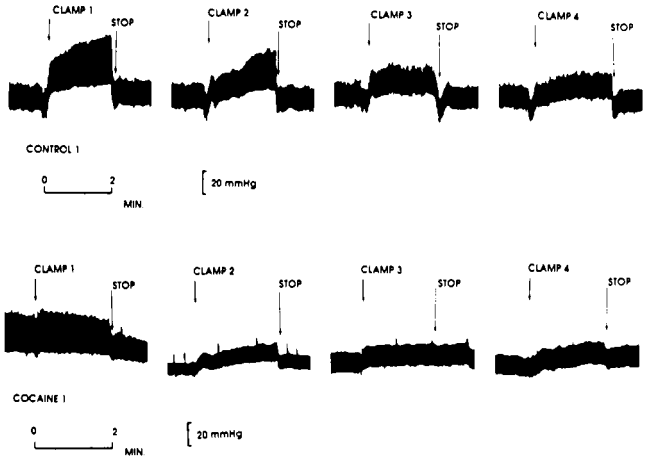

Figure 2. Changes in blood pressure recorded in the caudal artery of a rat after four successive bilateral clampings of the carotid arteries. Clamping and unclamping were performed at the times indicated in Figure 1. (Top) Saline-treated rat; (bottom) cocaine-treated rat.

sure caused by a stimulation of the baroreflex. The second series indicates that after clamping of the carotid artery, blood pressure in the cephalic part of this vessel is the same in the saline- and cocaine-treated animal. The difference in response to carotid artery clamping in both series is not caused by an altered stimulus resulting from a different residual pressure in the cephalic portion of the carotids of saline- or cocaine-treated rats. Pentobarbital, the anesthetic used in these experiments, also decreases the baroreflex. Results obtained will, therefore, underestimate the effects of cocaine, which appears to be the causal agent of the inhibition of the baroreceptor by a mechanism that remains to be clarified.

The increased blood pressure observed during cocaine intoxication results from peripheral and central stimuli. Peripheral stimulation is reflected by significant increases in all circulating catecholamines and general vasoconstriction, which account, at least in part, for the increase in blood pressure. Furthermore, cocaine exerts a direct arteriolar vasoconstriction effect that is inhibited by nitrendipine or, and only partially, by a converting enzyme inhibitor (7, 8).

Angiotensin II released peripherally by cocaine might circumvent the blood-brain barrier at some locations or even, because of the very high blood pressure, intermittently cross the blood-brain barrier; if this was the case, the peptide would interact with central mechanisms that control blood pressure (10). Angiotensin II, which potentiates peripherally the α-stimulating effects of catechols and mediates epinephrine release in the adrenal medulla, also modulates central mechanisms (11–12). Angiotensin II has been reported to be an important factor that modulates the baroreflex by its action on the tractus solitarius in the rat (13).

Garner *et al.* (11) have described the effects in the baboon of angiotensin II on the control of heart rate. The peptide decreases the sensitivity of the baroreflex, whereas captopril, a converting enzyme inhibitor, increases its sensitivity. Goldsmith and Hasking (14) have reported that in humans, angiotensin II inhibits the efferent response to an acute stimulation of the baroreflex (baroreflex loading). Angiotensin II is reported to inhibit acetylcholine release in the vagal cardiac outflow, thereby decreasing vagal tone (15). This mechanism could account for the tachycardia observed in humans following cocaine intoxication, which is associated with a decreased vagal tone (16).

Angiotensin II is readily accessible to the area postrema, which modulates the regulation of blood pressure and heart rate (17). Angiotensin III, a degradation product of angiotensin II, also decreases the baroreflex (18). Another neurotransmitter, γ-aminobutyric acid, is involved in baroreflex modulation (19–20), which could account for the effectiveness of diazepam to control cocaine toxicity, in association with enalaprilat. However, diazepam given separately does not alter the peripheral sympathoadrenal stimulation and resulting vasoconstriction induced by cocaine.

Although angiotensin II concentrations of plasma and brain have not been assayed in the course of cocaine intoxication, we surmised that the suggested inhibition of the baroreflex caused by this alkaloid might be mediated by the peptide and could account for the cardiovascular deregulation that occurs after severe intoxication (8). Consequently, a treatment limited to the

Table II. Differences in Maximal Systolic Blood Pressure and Heart Rate[a]

	No. of clampings							
	1		2		3		4	
	ΔSBP (mm Hg)	ΔHR (min)	ΔSBP (mm Hg)	ΔHR (min)	ΔSBP (mm Hg)	ΔHR (min)	ΔSBP (mm Hg)	ΔHR (min)
Saline-treated	48.8 ± 12.6	25.5 ± 8.3	39.5 ± 8.6	20.3 ± 5	46 ± 22.7	20.5 ± 15.9	32.2 ± 12.7	27.8 ± 20.9
Cocaine-treated	9.7 ± 12.1	0.33 ± 24	14.3 ± 8.5	−4.5 ± 16	13.3 ± 3.8	11.8 ± 6.4	12.2 ± 5.5	9.5 ± 15.6

[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 with saline or cocaine according to the schedule described in Figure 1. Differences in heart rate (ΔHR) were measured at the same time. For analysis of variance, see text.

Table III. Blood Pressure Measurements[a]

	A		B		C	
	1	2	1	2	1	2
Saline-treated	80.5 ± 8.5	73.0 ± 11.9	41.0 ± 7.8	32.5 ± 11.5	39.9 ± 9.9	40.0 ± 3.9
Cocaine-treated	78.5 ± 10.1	60.0 ± 18.4	41.0 ± 13.0	23.5 ± 8.5	37.5 ± 6.2	36.0 ± 13.1

[a] Blood pressure measurements in the cephalic portion of the carotid artery in rats treated with cocaine or saline after two successive clampings (1 and 2). A, Mean pressures before clamping of carotid; B, minimal mean pressure after clamping; C, pressure difference before and after clamping.

correction of coronary vasoconstriction with α- or β-blockers is only targeted to the local cardiac action of the alkaloid and would be inoperative to correct the destabilization of the baroreflex.

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