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European Journal of Pharmacology 397 (2000) 139–150

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Post-junctional mechanisms involved in the potentiation of cardiac adrenergic responses by cocaine

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Received 16 August 1999; received in revised form 25 February 2000; accepted 3 March 2000

Abstract

Cocaine cardiotoxicity is partly due to sympathetic activation of the heart resulting from inhibition of catecholamine uptake at the sympathetic nerve terminal and possible central sympathetic stimulation and/or inhibition. This study evaluated the role of postsynaptic mechanisms in potentiation by cocaine of cardiac adrenergic responses. Cardiovascular responses (arterial and left ventricular pressure, contractility and heart rate) to increasing doses of noradrenaline and to isoproterenol were obtained in anesthetized cats during a control period, after irreversible α-adrenoceptor blockade with phenoxybenzamine (5 mg/kg i.v.), and after cocaine (5 mg/kg, i.v.). Responses to noradrenaline were significantly reduced by phenoxybenzamine with lowering of the maximal rise of all parameters. Cocaine shifted the dose–response curve of noradrenaline to the left and enhanced its maximal effects. Some responses to isoproterenol, which is not taken up by nerve terminals, were also enhanced by cocaine. Pretreatment with chlorisondamine or verapamil prevented the cocaine-induced enhancement of the maximal response to noradrenaline and the response to isoproterenol, but it did not inhibit potentiation of submaximal doses. Lidocaine did not potentiate the response to noradrenaline or isoproterenol. Use of chlorisondamine instead of cocaine potentiated responses to all noradrenaline doses and enhanced the responses to isoproterenol. These results suggest that the potentiation by cocaine of cardiac responses to adrenergic stimuli involves presynaptic mechanisms to block noradrenaline re-uptake, and postsynaptic mechanisms to raise the maximal responses. The latter may result from inhibition of central sympathetic outflow or from activation of cardiac Ca^{+} channels, leading to increased cardiac sensitivity to noradrenaline. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Cocaine; Potentiation; Noradrenaline; Blood pressure; Contractility; Chlorisondamine

1. Introduction

The major toxic effects associated with cocaine abuse are those related to the cardiovascular system. These manifest as increased arterial pressure, myocardial ischemia, infarction, and arrhythmias that are potentially fatal (Nanji and Filipenko, 1984; Pasternak et al., 1985; Isner et al., 1986; Majid et al., 1990), as well as numerous other manifestations such as myocarditis (Virmani et al., 1988) cardiomyopathy (Weiner et al., 1986; Hogya and Wolfson, 1990) and subarachnoid hemorrhage (Lichtenfeld et al., 1984). Numerous studies have tried to explain the mechanisms responsible for these effects. There appears to be agreement that one of the major factors involved in the cardiotoxic effects of cocaine is its sympathomimetic action, which leads to cardiac stimulation and increased oxygen demand, and predisposes to arrhythmias. Cocaine's local anesthetic effect, when superimposed, may further the arrhythmogenic potential (Billman, 1990).

The mechanisms of the sympathomimetic action of cocaine have also been studied. While the classically accepted mechanism of action involving inhibition of peripheral neuronal amine re-uptake is accepted by most investigators, its quantitative contribution to the magnitude of the effects of cocaine is controversial. A number of studies have shown increases in heart rate, blood pressure and contractility following cocaine administration (Fischman and Schuster, 1982; Wilkerson, 1988). These effects have been ascribed to both peripheral inhibition of re-uptake and central stimulation of sympathetic output (Tella et al.,

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PII: S0014-2999(00)00192-8

1989; Knuepfer and Branch, 1992) although in most cases no direct measurement of sympathetic nerve activity was undertaken and these conclusions were based on changes in cardiovascular parameters or in plasma catecholamine levels. Other studies in dogs and other animals have failed to demonstrate changes in these parameters after administration of cocaine (Roszkowski and Koelle, 1960; Seifen et al., 1989). Furthermore, a cocaine-induced decrease in central sympathetic output has been demonstrated in several studies, and has been linked to inhibition of neuronal amine re-uptake in the central nervous system (Gantenberg and Hageman, 1991; Raczkowski et al., 1991; Hernandez et al., 1996). There is thus a discrepancy among studies as to the effects of cocaine on adrenergic activation of the heart. Results of these studies suggest that low doses of cocaine (0.1–2 mg/kg) are usually associated with findings suggestive of increased sympathetic outflow from the central nervous system, while higher doses (3–5 mg/kg) result in decreased sympathetic nerve activity.

In the present study, a third possible explanation for the cardiac effects of cocaine is explored, based on preliminary observations in our laboratory suggesting a post-junctional site of action in the heart to potentiate adrenergic responses. These preliminary results were further explored to characterize the mechanism of this postsynaptic potentiation. The findings suggest that cocaine enhances the sensitivity of the heart to adrenergic stimuli by an indirect mechanism related to its inhibition of central sympathetic outflow.

2. Materials and methods

Cats of either sex weighing between 2 and 4.5 kg were used for these experiments. The investigation conformed with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996), and was approved by the Animal Care Committee of the Faculty of Medicine, American University of Beirut. Anesthesia was induced by an intraperitoneal injection of pentobarbital (30 mg/kg), following which the cats were intubated and artificial respiration was instituted using a Harvard respirator. Glass cannulae were introduced into the jugular vein for drug and fluid administration, and into the carotid artery for monitoring of systolic, diastolic and mean arterial pressures, using a Gould transducer connected to a pressure processor and TA11 recorder (Gould Instruments, Valley View, OH, USA). The chest was opened through a midline incision, the pericardium was cut and a needle puncture made at the apex of the left ventricle through which a polyethylene catheter was introduced. This catheter was connected to another pressure transducer and served to record left ventricular pressure. The maximal rate of rise in left ventricular pressure (dp/dt) was derived from this pressure signal using an electronic differentiator linked to the same recorder. An electrocardiograph was obtained using the four limb leads and a Burdick Elite II electrocardiogram machine (Milton, WI, USA). This was used to monitor heart rate and any disturbances in rhythm.

2.1. Preliminary studies

In preliminary studies, only mean arterial pressure was measured. In these animals, five groups were studied. The general protocol consisted of three experimental periods per animal and was as follows: responses to increasing intravenous doses of noradrenaline (0.5, 1, 2, 4 μg) were obtained during the first (control) experimental period. Phenoxybenzamine (5 mg/kg i.v.) was then administered over 20 min and was followed by a stabilization period of 1 h allowing for establishment of irreversible α-adrenoceptor blockade. The injections of noradrenaline were then repeated, but with the addition of a large dose of noradrenaline (20 μg) to obtain the maximal effect. Cocaine was then administered (5 mg/kg, i.v., $n = 9$), a period of 10 min was allowed for stabilization, and then the same injections of noradrenaline were repeated. The same protocol was followed in 4 other groups but with the following differences: in one group, an infusion of 0.9% saline was administered instead of cocaine ($n = 6$); in the second group infusions of noradrenaline at 2 μg/min and then 4 μg/min were administered instead of cocaine ($n = 4$); the injections of noradrenaline were repeated during each infusion. In the third group, the cats were pretreated with propranolol (1 mg/kg) prior to the control experimental period, and the experiment was repeated as in the first group ($n = 5$). In the fourth group, the cats were vagotomized prior to the start of the experiment to examine the role of baroreflexes in the effects of cocaine ($n = 8$).

2.2. Mechanisms of potentiation of cardiac adrenergic responses by cocaine

Further experiments were conducted with five other groups of cats. The protocol followed in these experiments was similar to that described above with a control, phenoxybenzamine and cocaine period, but with measurement of systolic pressure, diastolic pressure, mean arterial pressure, left ventricular pressure, dp/dt and heart rate responses, and with the modification described below. In the control group ($n = 10$), responses to increasing intravenous doses of noradrenaline (0.5, 1, 2, 4 μg) and one dose of isoproterenol (1 μg) were obtained during the first experimental period. Phenoxybenzamine (5 mg/kg i.v.) was then administered as described above. The injections of noradrenaline and isoproterenol were then repeated, but with the addition of a large dose of noradrenaline (20 μg) to obtain the maximal effect. Cocaine was then administered (5 mg/kg, i.v.), a period of 10 min was allowed for

stabilization, and then the same injections were repeated, including the 20-μg dose of noradrenaline.

In another group the same protocol was followed except that the cats were treated with the ganglionic blocker chlorisondamine (1.5 mg i.v., $n = 6$), prior to the control period. In addition, cats in this group received two lower doses of noradrenaline (0.1 and 0.25 μg) and no isoproterenol doses. A third group was pretreated with verapamil (2 mg/kg i.v., $n = 5$) and the same protocol as in the control group was repeated. In a fourth group, the same protocol was followed except that chlorisondamine (1.5 mg i.v., $n = 5$) was used instead of cocaine prior to the third experimental period, while, in a fifth group, lidocaine (5 mg/kg i.v., $n = 8$) was infused instead of cocaine prior to the third experimental period. The dose of chlorisondamine used in this study was shown, in pilot experiments in our laboratory, to completely inhibit the rise in mean arterial pressure (51 ± 8 mm Hg, $n = 4$) induced by acetylcholine (100 μg/kg) in atropinized cats, an effect secondary to stimulation of ganglionic and adrenal nicotinic receptors, since it was also eliminated by combined treatment with phenoxybenzamine and propranolol.

In all experiments, the peak change in systolic pressure, diastolic pressure, mean arterial pressure, left ventricular pressure, dp/dt and heart rate was obtained in response to noradrenaline and isoproterenol. With the isoproterenol and noradrenaline (20 μg) injections, the peak changes were obtained at the peak increase in systolic pressure, which occurred prior to the peak reduction in diastolic pressure.

2.3. Drugs

The following drugs were used: lidocaine hydrochloride, noradrenaline bitartrate and verapamil hydrochloride (Sigma, St. Louis, MO, USA), isoproterenol hydrochloride and propranolol (ICN Biochemicals, Aurora, OH, USA), phenoxybenzamine hydrochloride (Sterling Winthrop Research Institute, Rewselaer, NY, USA), chlorisondamine hydrochloride (Ciba-Geigy, Basle, Switzerland), cocaine hydrochloride (May and Baker, UK).

2.4. Statistical analysis

Values are reported as means ± S.E.M. Comparison of two or more values from different periods in the same group of cats was conducted using the paired Student's *t*-test or repeated measures analysis of variance (ANOVA); multiple comparison post-hoc tests after ANOVA were done with the Student–Newman–Keuls test. Values from different groups of cats during the same experimental period were compared by ANOVA followed by Student–Newman–Keuls test. A P value < 0.05 was considered significant.

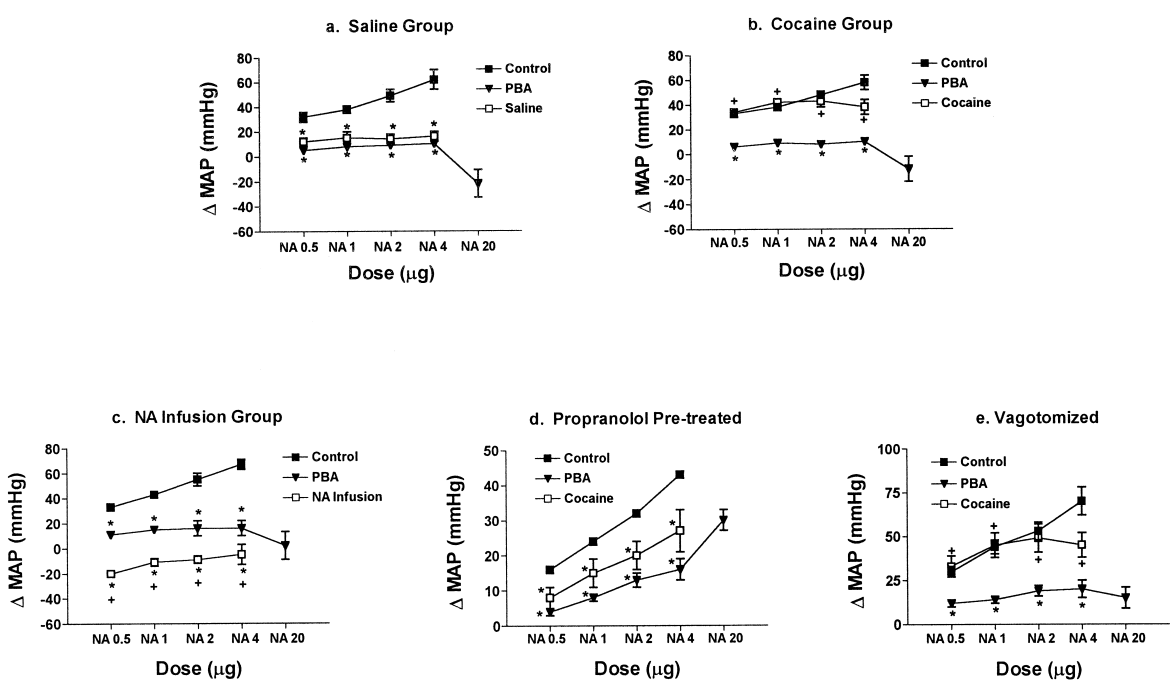

Fig. 1. Noradrenaline (NA)-induced change in mean arterial pressure (MAP) during the control, phenoxybenzamine (PBA) and last experimental period in five groups of cats where the last experimental period was a 0.9% saline infusion (a, $n = 6$), cocaine 5 mg/kg (b, $n = 9$), noradrenaline infusion at 4 μg/kg (c, $n = 4$), cocaine in cats pretreated with propranolol 1 mg/kg (d, $n = 5$), or cocaine in vagotomized cats (e, $n = 8$). Values are means ± S.E.M. $^{*}P < 0.05$ compared with control period. $+P < 0.05$ compared with phenoxybenzamine period.

3. Results

The design of this study allowed us to: (1) compare the dose–response relationship for noradrenaline during a control period, after phenoxybenzamine and after cocaine (or other interventions) in different groups under different conditions and (2) to compare the maximal responses to noradrenaline but only in the phenoxybenzamine and cocaine (or other intervention) periods, since we did not attempt to achieve a maximal effect during the control period. Hence, any referral to ''maximal effects'' hereafter necessarily involves comparisons between these two periods only.

3.1. Preliminary results

3.1.1. Baseline parameters (data not shown)

In all groups studied, phenoxybenzamine induced a significant reduction in baseline mean arterial pressure. No further change was observed after cocaine. However, although the mean arterial pressure values were different in the same group among periods, they were similar among groups during corresponding periods.

3.1.2. Effects of noradrenaline on mean arterial pressure in the five groups

In all groups studied, increasing doses of noradrenaline produced progressive increases in mean arterial pressure as expected (Fig. 1). After phenoxybenzamine, the responses to noradrenaline were markedly inhibited, such that the dose–response curve became horizontal except in the propranolol pretreated group. At this time, a very high dose of noradrenaline (20 μg) failed to increase mean arterial pressure further, but actually reduced it. The responses to noradrenaline during the last experimental period differed among groups, however. Following 0.9% saline infusion, the responses to noradrenaline were the same as those observed after phenoxybenzamine, and remained significantly depressed compared with those observed during the control period (Fig. 1a). Cocaine, in contrast, potentiated the noradrenaline-induced rise in mean arterial pressure (Fig. 1b). The maximal effect of noradrenaline was significantly greater after cocaine than that seen during the phenoxybenzamine period. Infusion of noradrenaline at either dose (only the higher dose is shown) failed to reproduce the effects of cocaine. Paradoxically, noradrenaline caused decreases in mean arterial pressure, responses significantly different from those obtained during both control and phenoxybenzamine periods (Fig. 1c). Pretreatment with propranolol successfully abolished the depressor effect of isoproterenol (not shown). Subsequent administration of cocaine did not potentiate the mean arterial pressure responses to any dose of noradrenaline, so that responses after phenoxybenzamine and after cocaine were not significantly different and remained significantly depressed compared to those obtained during the control period (Fig. 1d), in contrast to what was observed in the cocaine-treated group (Fig. 1b). In cats vagotomized prior to the start of the experiment, the effects of cocaine on adrenergic responses were identical to those described above for cocaine: there was potentiation of the effects of noradrenaline at all doses including enhancement of the maximal responses (Fig. 1e).

3.2. Mechanisms of potentiation of cardiac adrenergic responses by cocaine

3.2.1. Baseline values (data not shown)

Administration of phenoxybenzamine reduced the mean arterial pressure in all groups of cats except in those pretreated with chlorisondamine and verapamil. These two groups already had a reduced mean arterial pressure during the control experimental period relative to the control

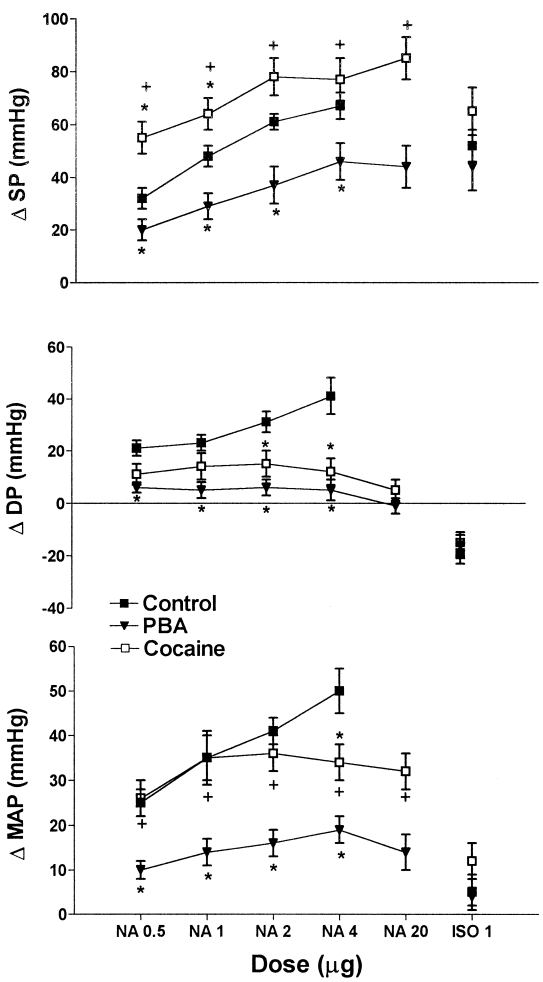

Fig. 2. Change in systolic, diastolic and mean arterial pressure (SP, DP, MAP) in response to noradrenaline (NA) and isoproterenol (ISO) during the control, phenoxybenzamine (PBA) and cocaine experimental periods ($n = 10$). Values are means ± S.E.M. $^{*}P < 0.05$ compared with control. $+ P < 0.05$ compared with phenoxybenzamine period.

group. Thus, after phenoxybenzamine, the mean arterial pressure was similar among all groups. Similarly, during the last experimental periods, the baseline mean arterial pressure was also similar in all groups of cats. There were no differences in baseline systolic pressure, diastolic pressure, left ventricular pressure or heart rate among groups during the phenoxybenzamine or the last experimental period either. As for dp/dt, baseline values during the control period were higher in the control group than in the groups pretreated with chlorisondamine or verapamil, as well as in the group treated with lidocaine. These differences persisted during the ensuing two periods.

3.2.2. Cardiovascular responses to noradrenaline and isoproterenol

3.2.2.1. Control group. Noradrenaline induced a dose-dependent increase in systolic pressure during the control period, which was significantly inhibited by phenoxybenzamine at all noradrenaline doses (Fig. 2). Even a dose of 20 μg of noradrenaline failed to raise systolic pressure more than did the lower doses of 2 and 4 μg, indicating that a maximal effect had been obtained. After cocaine, the rise in systolic pressure in response to noradrenaline was potentiated at all doses thus restoring, and at lower doses exceeding, the responses observed during the control period. The maximal rise in systolic pressure induced by noradrenaline during the phenoxybenzamine period was significantly enhanced by cocaine. Diastolic pressure responses to noradrenaline were significantly reduced and almost flattened by phenoxybenzamine, but were not potentiated by cocaine, the responses remaining significantly lower than those observed during the control period. Mean arterial pressure responses to noradrenaline were similar to those reported for systolic pressure, with inhibition by phenoxybenzamine and potentiation after cocaine, including enhancement of the maximal response.

Isoproterenol induced a rise in systolic pressure that was not significantly altered by phenoxybenzamine (Fig. 2). However, cocaine tended to potentiate the rise in systolic pressure though this was not quite significant ($P = 0.09$). Neither the isoproterenol-induced decrease in diastolic pressure nor the slight rise in mean arterial pressure was significantly influenced by phenoxybenzamine or cocaine.

The noradrenaline-induced dose-dependent increase in dp/dt was significantly less after phenoxybenzamine (Fig. 3a). Even a dose of 20 μg noradrenaline could not restore the rise in dp/dt to control levels. Cocaine potentiated the

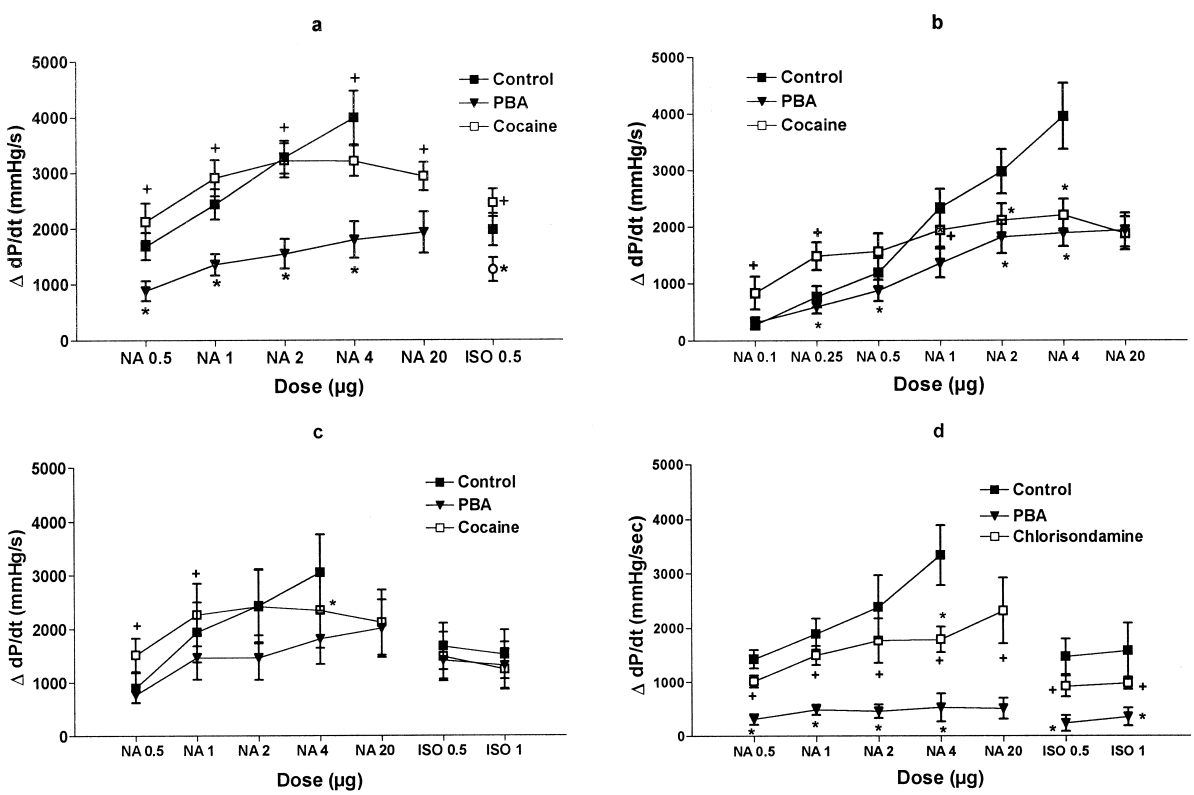

Fig. 3. Change in dp/dt induced by noradrenaline (NA) and isoproterenol (ISO) during the control, phenoxybenzamine (PBA) and last experimental period in cats in which the last experimental period consisted of treatment with cocaine 5 mg/kg (a, $n = 10$), cocaine in cats pretreated with chlorisondamine 1.5 mg (b, $n = 6$), cocaine in cats pretreated with verapamil 2 mg/kg (c, $n = 5$), and chlorisondamine 1.5 mg (d, $n = 5$). Values are means ± S.E.M. $^{*}P < 0.05$ compared with control. $+P < 0.05$ compared with phenoxybenzamine period.

response to all doses of noradrenaline and enhanced the maximal effect. Interestingly, the isoproterenol-induced rise in dp/dt, lowered after phenoxybenzamine, was also significantly potentiated by cocaine.

Noradrenaline induced a dose-dependent increase in left ventricular pressure which was not markedly altered by phenoxybenzamine (Table 1). Administration of cocaine led to non-significant potentiation at 1, 2, and 4 μg doses of noradrenaline. The isoproterenol-induced rise in left ventricular pressure was not influenced by either phenoxybenzamine or cocaine. Phenoxybenzamine did not influence the dose-dependent increase in heart rate induced by noradrenaline (Table 2). However, cocaine significantly raised the maximal increase in heart rate induced by noradrenaline (20 μg). The isoproterenol-induced increase in heart rate was not altered by either phenoxybenzamine or cocaine.

3.2.2.2. Group pretreated with chlorisondamine. The dose-dependent increase in systolic pressure, diastolic pressure and mean arterial pressure in response to noradrenaline was significantly attenuated by phenoxybenzamine such that the maximal response was lower than responses observed in the control period (Fig. 4). Cocaine potentiated responses to the lower doses of noradrenaline. In contrast to the previous group, however, the maximal responses of systolic pressure and mean arterial pressure (at 4 and 20 μg noradrenaline) were not potentiated and remained significantly lower than those observed in the control period.

Similarly, cocaine potentiated the dp/dt responses to the lower doses of noradrenaline but did not enhance the maximal response observed after phenoxybenzamine, which remained significantly less than the responses obtained during the control period (Fig. 3b). Cocaine also potentiated the increase in left ventricular pressure induced by the lower doses of noradrenaline (0.1–1 μg) but not by the higher doses, and did not enhance the maximal effect of noradrenaline (Table 1).

There were no significant effects of phenoxybenzamine or cocaine on the noradrenaline-induced rise in heart rate except at the highest dose of noradrenaline (20 μg), where the response was less after cocaine.

3.2.2.3. Group pretreated with verapamil. The noradrenaline-induced increase in systolic pressure, diastolic pressure and mean arterial pressure was significantly attenuated by phenoxybenzamine (Fig. 5). Cocaine potentiated the rise in both systolic pressure and mean arterial pressure, but not in diastolic pressure, at all noradrenaline doses except for the two highest doses (4 and 20 μg), in contrast to what was observed in the control group, but similarly to the group pretreated with chlorisondamine.

Table 1
Change in left ventricular pressure (mm Hg) induced by noradrenaline (NA) and isoproterenol during the control, phenoxybenzamine (PBA) and last experimental periods
Values are means ± S.E.M.

	Dose (μg)						
	NA 0.5	NA 1	NA 2	NA 4	NA 20	ISO 0.5	ISO 1
Cocaine group							
Control	40 ± 4	60 ± 7	78 ± 6	100 ± 8			80 ± 14
PBA	32 ± 7	47 ± 7	60 ± 10	76 ± 12	88 ± 14		59 ± 11
Cocaine	46 ± 7	70 ± 8	87 ± 10[a]	99 ± 9	107 ± 12		68 ± 13
Verapamil pretreated group							
Control	28 ± 4	43 ± 5	47 ± 6	59 ± 9		12 ± 8	6 ± 7
PBA	19 ± 4	32 ± 11	37 ± 16	41 ± 15	48 ± 16	28 ± 14	29 ± 13
Cocaine	27 ± 4	37 ± 9	47 ± 15	48 ± 17	42 ± 16	28 ± 11	19 ± 9
Chlorisondamine instead of cocaine group							
Control	29 ± 4	50 ± 7	55 ± 13	85 ± 16		31 ± 13	39 ± 12
PBA	8 ± 5[b]	18 ± 10[b]	24 ± 15	29 ± 23[b]	14 ± 2	13 ± 8	13 ± 8[b]
Chlorison.	20 ± 3	26 ± 4[b]	33 ± 5	42 ± 12[b]	40 ± 10[a]	16 ± 7	20 ± 12[b]

Chlorisondamine pretreated group

	NA 0.1	NA 0.25	NA 0.5	NA 1	NA 2	NA 4	NA 20
Control	18 ± 3	32 ± 4	34 ± 8	72 ± 4	79 ± 4	114 ± 12	
PBA	9 ± 2	19 ± 4[b]	17 ± 5[b]	36 ± 7[b]	36 ± 8[b]	40 ± 5	50 ± 16
Cocaine	31 ± 9[a]	39 ± 7[a]	32 ± 10[a]	52 ± 8[a,b]	54 ± 11	52 ± 13	49 ± 5

[a] $P < 0.05$ compared with phenoxybenzamine period.
[b] $P < 0.05$ compared with control.

Table 2
Change in heart rate (beats/min) induced by noradrenaline (NA) or isoproterenol (ISO) during the control, phenoxybenzamine (PBA) and last experimental periods.
Values are means ± S.E.M.

	Dose (μg)						
	NA 0.5	NA 1	NA 2	NA 4	NA 20	ISO 0.5	ISO 1
Cocaine group							
Control	5 ± 3	14 ± 2	18 ± 3	20 ± 4			35 ± 3
PBA	3 ± 4	11 ± 5	13 ± 5	10 ± 9	17 ± 6		19 ± 6
Cocaine	11 ± 4	22 ± 4	26 ± 3[a]	25 ± 3	38 ± 6[a]		32 ± 5
Verapamil pretreated group							
Control	4 ± 1	11 ± 2	19 ± 5	45 ± 12		37 ± 6	35 ± 4
PBA	17 ± 6	23 ± 9	31 ± 9	36 ± 9	44 ± 9	33 ± 10	33 ± 8
Cocaine	34 ± 10[b]	32 ± 6	40 ± 9	37 ± 7	39 ± 5	22 ± 3	26 ± 4
Chlorisondamine instead of cocaine group							
Control	3 ± 1	2 ± 1	12 ± 4	18 ± 5		22 ± 9	23 ± 8
PBA	0 ± 1	6 ± 2	9 ± 3	11 ± 5	11 ± 4	9 ± 4	7 ± 3
Chlorison.	10 ± 3[a]	12 ± 6	25 ± 3[a,b]	28 ± 6	37 ± 6[a]	22 ± 3[a]	24 ± 4[a]

Chlorisondamine pretreated group

	NA 0.1	NA 0.25	NA 0.5	NA 1	NA 2	NA 4	NA 20
Control	5 ± 2	19 ± 6	30 ± 7	43 ± 8	64 ± 7	70 ± 5	
PBA	11 ± 9	22 ± 5	40 ± 7	58 ± 8	68 ± 9	89 ± 9	96 ± 8
Cocaine	29 ± 17	39 ± 8	40 ± 4	55 ± 6	64 ± 8	73 ± 9	67 ± 10[a]

[a] $P < 0.05$ compared with phenoxybenzamine period.
[b] $P < 0.05$ compared with control.

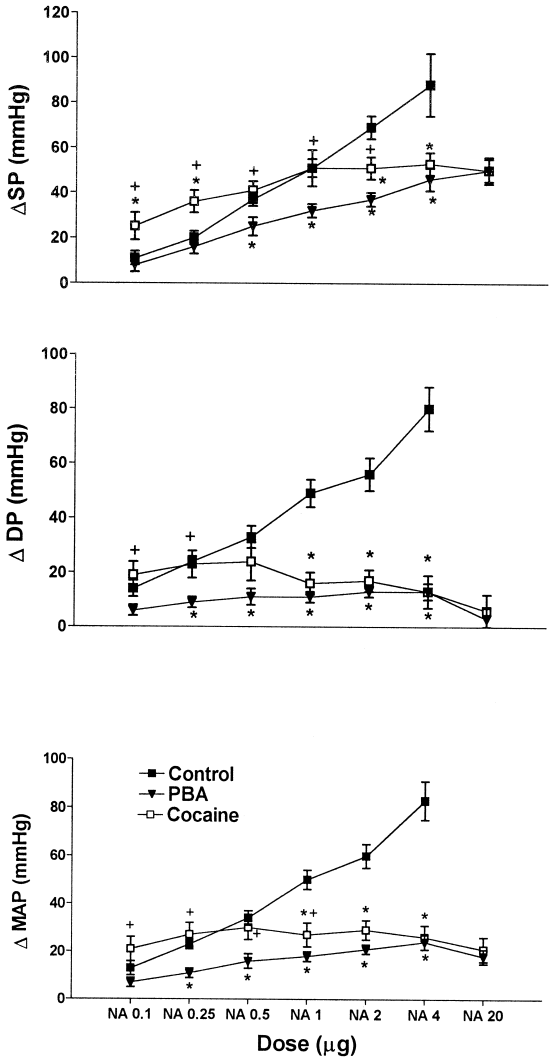

Fig. 4. Change in systolic, diastolic and mean arterial pressure (SP, DP, MAP) in response to noradrenaline (NA) during the control, phenoxybenzamine (PBA) and cocaine experimental periods in cats pretreated with chlorisondamine 1.5 mg ($n = 6$). Values are means ± S.E.M. $^{*}P < 0.05$ compared with control. $+P < 0.05$ compared with phenoxybenzamine period.

Isoproterenol responses (increase in systolic pressure and mean arterial pressure, and decrease in diastolic pressure) were not affected by phenoxybenzamine nor were they enhanced by cocaine.

The dose-dependent increase in dp/dt in response to noradrenaline was not significantly reduced by phenoxybenzamine except with noradrenaline 4 μg (Fig. 3c). Cocaine potentiated the responses to lower doses of noradrenaline (0.5–1 μg) but did not enhance the maximal effect. The isoproterenol-induced rise in dp/dt, also not affected by phenoxybenzamine, was not potentiated by cocaine, in contrast to the control group.

Phenoxybenzamine and cocaine did not affect any of the left ventricular pressure or heart rate responses to any noradrenaline or isoproterenol dose (Tables 1 and 2) despite a tendency for cocaine to potentiate the responses to the lower but not the higher doses of noradrenaline.

3.2.2.4. Group treated with chlorisondamine instead of cocaine. As in previous groups, the noradrenaline-induced increases in systolic pressure, diastolic pressure and mean arterial pressure were significantly inhibited by phenoxybenzamine (Fig. 6). Chlorisondamine potentiated responses to almost all doses for all three parameters. In contrast to the potentiation by cocaine observed in the control group (Fig. 2), however, the systolic pressure responses after chlorisondamine did not exceed those observed during the control period. However, and as in the control group, chlorisondamine potentiated the maximal responses to noradrenaline. Moreover, isoproterenol induced increases in systolic pressure, which were inhibited by phenoxybenzamine, but were significantly potentiated by chlorisondamine.

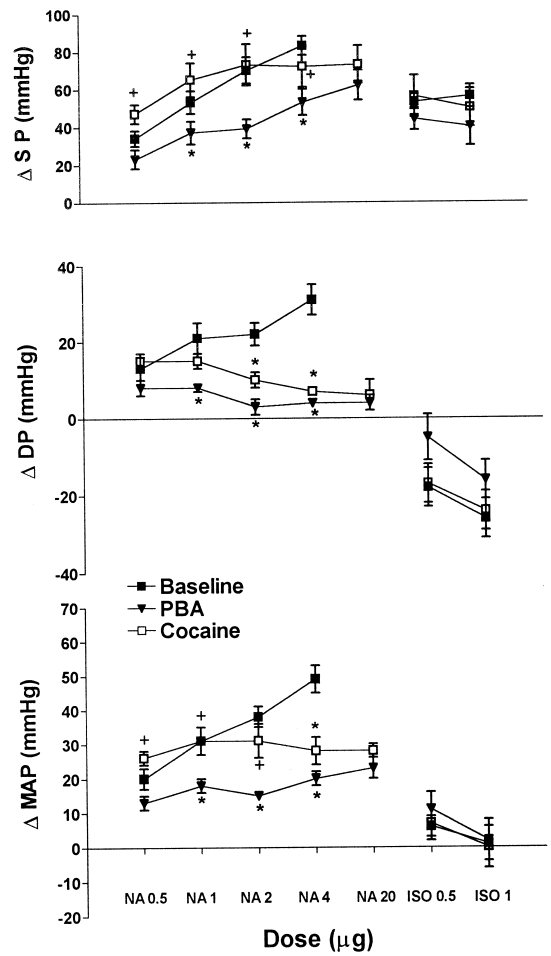

Fig. 5. Change in systolic, diastolic and mean arterial pressure (SP, DP, MAP) in response to noradrenaline (NA) and isoproterenol (ISO) during the control, phenoxybenzamine (PBA), and cocaine experimental periods in cats pretreated with verapamil 2 mg/kg ($n = 5$). Values are means ± S.E.M. $^{*}P < 0.05$ compared with control. $+P < 0.05$ compared with phenoxybenzamine period.

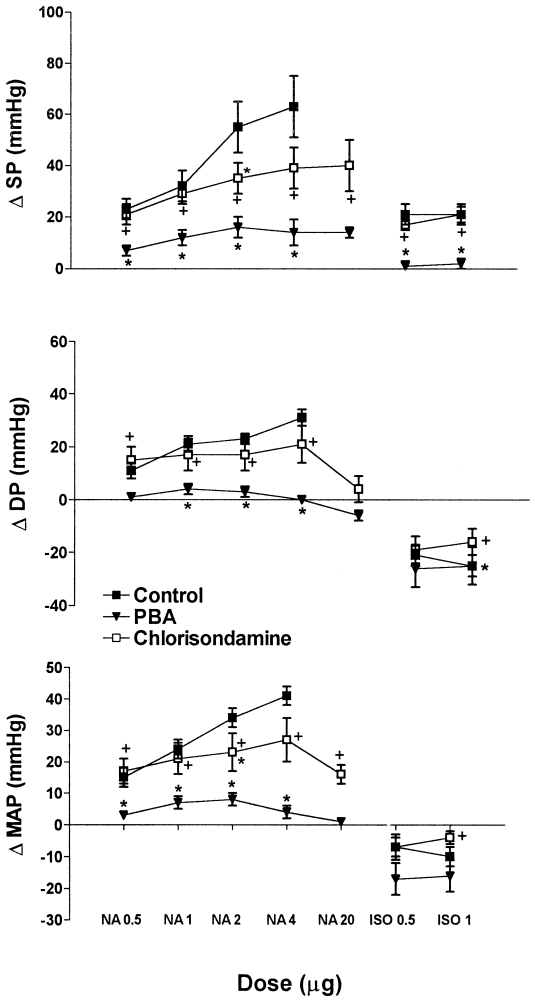

Fig. 6. Change in systolic, diastolic and mean arterial pressure (SP, DP, MAP) in response to noradrenaline (NA) and isoproterenol (ISO) during the control, phenoxybenzamine (PBA) and chlorisondamine experimental periods ($n = 5$). Values are means ± S.E.M. $^{*}P < 0.05$ compared with control. $+ P < 0.05$ compared with phenoxybenzamine period.

The dose-dependent increase in dp/dt induced by noradrenaline was significantly attenuated by phenoxybenzamine, and became almost flat (Fig. 3d). These responses were significantly potentiated by chlorisondamine at all submaximal and maximal doses. The extent of potentiation at lower doses was also less than that with cocaine in the control group (Fig. 3a).

Phenoxybenzamine significantly reduced the increase in left ventricular pressure induced by both noradrenaline and isoproterenol (Table 1). After α-adrenoceptor blockade, chlorisondamine tended to potentiate the responses to the lower doses of noradrenaline, but only the response to the maximal dose (20 μg) was significantly enhanced. Chlorisondamine also potentiated the rise in heart rate induced by both noradrenaline and isoproterenol, and enhanced the maximal response to noradrenaline (Table 2).

3.2.2.5. Group treated with lidocaine instead of cocaine (data not shown). Lidocaine did not alter systolic pressure, diastolic pressure and mean arterial pressure responses to noradrenaline except for a slight increase in systolic pressure at two doses of noradrenaline (1 and 2 μg). The maximal responses observed during the phenoxybenzamine period were not enhanced by lidocaine. Similarly, the responses to isoproterenol were not altered by either phenoxybenzamine or lidocaine.

The noradrenaline-induced increase in dp/dt was also not potentiated by lidocaine, and remained significantly less than that observed during the control period. The dp/dt responses to isoproterenol were also not affected by phenoxybenzamine or lidocaine.

The increases in left ventricular pressure and heart rate in response to most noradrenaline or isoproterenol doses were not significantly affected by either phenoxybenzamine or lidocaine, although phenoxybenzamine tended to inhibit them.

4. Discussion

The results of this study suggest that cocaine potentiates the cardiac responses to adrenergic stimuli by at least two mechanisms: presynaptic inhibition of noradrenaline re-uptake leading to potentiation of sub-maximal responses, and a postsynaptic mechanism resulting in enhancement of maximal effects. To our knowledge, this is the first in vivo study providing results consistent with the latter mechanism which may contribute to the cardiotoxic manifestations of cocaine abuse. This mechanism likely results from a central site of action of cocaine to inhibit sympathetic outflow, or from interference with baroreceptor function, thus senstizing the heart to adrenergic effects. Its inhibition by verapamil indicates the involvement of calcium mobilization from the extracellular space in the mechanism of potentiation. The local anesthetic property of cocaine does not appear to contribute to this effect.

It is important to point out that the baseline values for most parameters (except for dp/dt), were similar among groups during corresponding experimental periods. This made it possible to compare the responses to noradrenaline and isoproterenol during the same experimental periods eventhough, within the same group, baseline values changed during different experimental periods. Thus, differences among groups in the responses to noradrenaline and isoproterenol observed during the last experimental period relative to the phenoxybenzamine period cannot be explained by differences in baselines.

The preliminary studies described here indicated that cocaine potentiated the maximal responses to the endogenous catecholamine, noradrenaline, compared to those observed after phenoxybenzamine. This effect could not be

explained by inhibition of noradrenaline uptake into nerve terminals, since such a mechanism, which inhibits a major route of dissipation of noradrenaline from its site of action, should only increase the potency of noradrenaline. Thus, for any dose of noradrenaline more drug would be available to interact with postsynaptic receptors, which leads to a shift of its dose–response curve to the left. Consequently, for any dose of noradrenaline, a greater effect would be achieved in the presence of cocaine than in its absence and the maximal effect would be obtained at a lower dose of noradrenaline. However, the maximal effect itself should not be altered, since it is determined by the ability of the tissue to respond to noradrenaline, which in such a case is not altered. The fact that in the present study the maximal effects were found to be enhanced by cocaine, therefore, suggests the existence of mechanisms of action additional to inhibition of uptake. As the groups treated with saline and noradrenaline infusions showed, this potentiation of the maximal effect was not due to repeated administration of noradrenaline nor to waning of the α-adrenoceptor blockade with time or with increasing concentrations of noradrenaline that would result from cocaine's action to block re-uptake. The potentiation involved the cardiac effects of noradrenaline since β-adrenoceptor blockade with propranolol prevented the potentiation.

Further evidence in support of the above was obtained by measurement of cardiac parameters. The effects of noradrenaline on systolic pressure, and not diastolic pressure, were found to be potentiated by cocaine, and the enhancement of the mean arterial pressure responses was explained. Importantly, the fact that, in most cases, the maximal effects of noradrenaline on systolic pressure, mean arterial pressure, left ventricular pressure, dp/dt and heart rate were potentiated further supports the hypothesis that cocaine acts by mechanisms additional to inhibition of peripheral amine re-uptake. These mechanisms result from enhanced cardiac responsiveness to sympathetic activation. In support of this conclusion is the finding that the dp/dt response to isoproterenol, which is not taken up by nerve terminals, was significantly potentiated as well, though less so than the response to an equi-effective dose of noradrenaline (1 μg).

The mechanisms responsible for this postsynaptic potentiation could involve direct effects on the heart, indirect effects relating to modification of reflexes or of central sympathetic output, or to effects on neuronal activity possibly due to cocaine's local anesthetic effect. Previous studies have shown that cocaine decreases sympathetic output to the heart (Gantenberg and Hageman, 1991; Raczkowski et al., 1991; Hernandez et al., 1996). This may sensitize it to the effects of agonists acting on adrenergic receptors, by inducing receptor or post-receptor modifications. This possibility was explored by pretreating animals with the non-competitive ganglionic blocker, chlorisondamine, at doses known to inhibit ganglionic transmission, thus interfering with sympathetic tone to the heart. In these cats, cocaine could still enhance the responses to submaximal but not maximal doses of noradrenaline, and failed to enhance the responses to isoproterenol. The enhancement of the submaximal effects was, furthermore, less than that observed in the control group. Thus, in this group, cocaine behaved as expected from an inhibitor of neuronal uptake, enhancing the potency but not the maximal effects of noradrenaline. It is conceivable, therefore, that cocaine, itself inhibiting central sympathetic outflow, could potentiate the effects of exogenous noradrenaline and isoproterenol on the heart. By interrupting the central sympathetic outflow to the heart using chlorisondamine, these effects of cocaine were eliminated. If this hypothesis is true, then replacing chlorisondamine by cocaine should induce potentiation of the responses to adrenergic stimuli. To test this possibility, chlorisondamine was administered instead of cocaine during the last period of the experiment. This resulted in potentiation of both submaximal and maximal responses to noradrenaline and isoproterenol at all doses used. Here again, however, the potentiation at lower doses of noradrenaline was distinctly less than that observed in the control group. These results support the suggestion that inhibition of central sympathetic tone to the heart, whether by cocaine or by chlorisondamine, causes supersensitivity of the heart to adrenergic stimuli. In the case of cocaine, the peripheral effect to inhibit re-uptake further contributes to the potentiation, and therefore, the enhancement at lower noradrenaline doses is greater than that caused by chlorisondamine, which does not block re-uptake.

An alternative explanation for the enhancement of the maximal responses is interruption of the baroreceptor reflex which, normally, counters the rise in mean arterial pressure by withdrawing sympathetic activity and raising parasympathetic activity. Upon interruption of this reflex, the direct effect of noradrenaline to raise arterial pressure is unopposed, and thus enhanced. Ganglionic blockade with chlorisondamine can readily achieve this, but it is less clear how cocaine can. Recent work suggests that cocaine inhibits the baroreceptor discharge induced by suprathreshold pressure by a mechanism that may relate to its local anesthetic effect (Andersen et al., 1990), and that it reduces the rise in arterial pressure induced by bilateral clamping of the carotid arteries in rats at a total dose of 50 mg (Trouve and Nahas, 1986). While these two effects suggest interference with baroreceptor function, their relevance to our study is unclear. A dose of 50 mg/rat is approximately 30 times that used in our experiments. Furthermore, an effective dose of lidocaine (as judged from the lower baseline dp/dt) failed to reproduce the effects of cocaine, suggesting no role for the local anesthetic activity of cocaine. Finally, the present experiments on vagotomized cats, where the baroreflex is partially interrupted, showed the same cocaine-induced potentiation of the maximal effects of noradrenaline on mean arterial

pressure. Irrespective of the mechanism, the important finding in this study was the cocaine-induced exaggeration in cardiac responses to adrenergic stimuli that was greater than expected from blockade of neuronal re-uptake alone.

Pretreatment with verapamil induced effects similar to those of pretreatment with chlorisondamine: potentiation by cocaine of the effects of smaller doses of noradrenaline but not of the maximal responses, nor of the responses to isoproterenol. Thus, verapamil, by not interfering with the inhibition of re-uptake, did not prevent cocaine from potentiating the submaximal effects of noradrenaline. Verapamil, however, inhibited the potentiation of the maximal effect of noradrenaline and of the responses to isoproterenol, i.e., the other component of potentiation due to postsynaptic mechanisms. This suggests that the postsynaptic mechanism of potentiation is dependent on mobilization of calcium ions from the extracellular space through voltage-dependent channels. Whether this is a consequence of cocaine's effect on the adrenergic receptors or on post-receptor events cannot be resolved from the present results, however.

Finally, with a dose of lidocaine equal to that of cocaine, and similar to doses used in other studies (Gantenberg and Hageman, 1991; Raczkowski et al., 1991; Hernandez et al., 1996), no consistent potentiation of the effects of noradrenaline or isoproterenol was observed. These results suggest that the effects of cocaine, whether exerted centrally or peripherally at the neural or cardiac level, cannot be explained by its local anesthetic activity.

To our knowledge, the results of this study are the first in vivo evidence supporting a post-synaptic site of potentiation of adrenergic responses by cocaine. Numerous earlier studies had suggested this, but all were in vitro (Bevan and Verity, 1967; Varma and McCullough, 1968; Kasuya and Goto, 1968; Greenberg and Innes, 1976; Summers and Tillman, 1979). Furthermore, numerous investigators demonstrated in vitro potentiation by cocaine of the effects of sympathomimetic agents which are not taken up by nerve terminals such as isoproterenol (Roszkowski and Koelle, 1960; Leszkovsky and Tardos, 1968; Davidson and Innes, 1970) and methoxamine (Kalsner and Nickerson, 1969). Some of the above studies suggested that cocaine may change the utilization of calcium by tissues, as calcium antagonists or chelating agents could prevent the observed potentiation (Kasuya and Goto, 1968; Greenberg and Long, 1971; Greenberg and Innes, 1976).

More recent studies also support our conclusions. A reduction in central sympathetic outflow was demonstrated in several recent studies (Gantenberg and Hageman, 1991; Raczkowski et al., 1991; Hageman and Simor, 1993; Hernandez et al., 1996; Abrahams et al., 1996). In those studies, the intravenous doses of cocaine were, in most cases, higher than 3 mg/kg. In other studies mostly with rats, however, a cocaine-induced increase in central sympathetic output was suggested, based mostly on indirect evidence such as the development of a pressor response and tachycardia, both of which were prevented by ganglionic blockers, and not on direct measurement of sympathetic nerve activity (Kiristy-Roy et al., 1990; Tella et al., 1992, 1993; Szabo et al., 1994). These effects were dose-dependent and occurred more consistently at doses lower than 1 mg/kg. In some cases, increasing the dose led to a greater effect, while in others the effect of cocaine shifted to a depressor effect at higher doses (5 mg/kg) (Szabo et al., 1994). A similar conclusion had been reached by Rhee et al. who reported that, in rats and rabbits, cocaine doses of 0.3–1 mg/kg raised the blood pressure, while doses of 3–5 mg/kg decreased blood pressure and other cardiac parameters (Rhee et al., 1990). Numerous factors have to be considered in interpreting these contradictory results, such as animal species, doses of cocaine used, whether the animals were conscious or anesthetized, conditions and routes of administration of cocaine, and the time after administration that the measurements were made. Nonetheless, it may be suggested that higher doses of cocaine similar to that used in the present study decrease sympathetic tone, while lower doses stimulate it. It is difficult to extrapolate from this model to the human situation. Most reports of cocaine-induced cardiac events which were able to document the dose of cocaine reported relatively high doses, ranging between 0.25 g and 2 g (Isner et al., 1986; Gillis et al., 1992). In most cases, these doses were taken by snorting or inhalation, not intravenously, and by addicts. In contrast, in the present study, acute i.v. doses were used in cocaine-naive cats. It should be noted, however, that the human doses were sometimes much higher than 5 mg/kg and that both routes of administration (intranasal, inhalation) provide for rapid absorption and by-passing of first-pass metabolism in the liver, thus leading to rapid elevations in plasma concentrations.

Further support for our results comes from studies which demonstrated that calcium channel blockers interfere with the effects of cocaine on the heart and other tissues, and suppress cocaine induced arrhythmias (Shibata et al., 1971; Trouve and Nahas, 1986; Billman and Hoskins, 1988; Billman, 1993). A very recent study showed that cocaine enhances, selectively and potently, L-type calcium channel currents in isolated rat myocytes (Premkumar, 1999). Such an effect may contribute to the enhancement of cardiac adrenergic responses by cocaine and may explain the inhibition by verapamil of this potentiation, which was observed in our study.

In conclusion, this study has provided in vivo evidence suggesting that the effects of cocaine on the heart may involve potentiation of adrenergic responses through mechanisms additional to inhibition of neuronal re-uptake, and sheds further light on the mechanisms involved in cocaine's cardiotoxicity. These mechanisms involve sensitization of the heart to the effects of sympathomimetic agents, indirectly through inhibition of central sympathetic outflow, or through interference with baroreceptor function, or may involve a direct effect on the heart through interaction with

cardiac L-type calcium channels. It is conceivable that such sensitization may, under conditions of sympatho-adrenal discharge such as stress or exercise, exaggerate the cardiac effects of cocaine mediated through peripheral inhibition of catecholamine re-uptake and contribute to the cardiotoxic manifestations of cocaine abuse. This is in agreement with the results of a study in humans where chronic cocaine abusers were found to have exaggerated pressor responses to exercise (Cigarroa et al., 1992). The results may also help explain the protective effect of calcium channel blockers against cocaine cardiotoxicity. The present results also emphasize the need to exercise care in interpreting the results of experiments conducted using cocaine as a selective inhibitor of neuronal re-uptake as it may have additional direct or indirect mechanisms of action in the cardiovascular system.

Acknowledgements

This study was supported by funds from the University Research Board, Diana Tamari Sabbagh Research Fund, and the Medical Practice Plan Research Fund, American University of Beirut, and from the Lebanese National Council for Scientific Research.

References

Abrahams, T.P., Faust, M.L., Varner, K.J., 1996. The depletion of monoamines blocks the sympathoinhibitory response to cocaine. J. Auton. Nerv. Syst. 58, 170–176.

Andersen, M.C., Yang, M., Nelson, S.H., Steinsland, O.S., 1990. Cocaine inhibits baroreflex control of blood pressure by actions at arterial baroreceptors. Am. J. Physiol. 258, H1244–H1249.

Bevan, J.A., Verity, M.A., 1967. Sympathetic nerve free vascular muscle. J. Pharmacol. Exp. Ther. 157, 117–124.

Billman, G.E., 1990. Mechanisms responsible for the cardiotoxic effects of cocaine. FASEB J. 4, 2469–2475.

Billman, G.E., 1993. Effect of Cab2-channel antagonist on Cab2-induced malignant arrhythmias: protection against ventricular fibrillation. J. Pharmacol. Exp. Ther. 266, 407–416.

Billman, G.E., Hoskins, R.S., 1988. Cocaine-induced ventricular fibrillation: protection afforded by the calcium antagonist verapamil. FASEB J. 2, 2990–2995.

Cigarroa, C.G., Boehrer, J.D., Brickner, M.E., Eichhorn, E.J., Grayburn, P.A., 1992. Exaggerated pressor responses to treadmill exercise in chronic cocaine abusers with left ventricular hypertrophy. Circulation 86, 226–231.

Davidson, W.J., Innes, I.R., 1970. Dissociation of potentiation of isoprenaline by cocaine from inhibition of uptake in cat spleen. Br. J. Pharmacol. 39, 175–181.

Fischman, M.W., Schuster, C.R., 1982. Cocaine self-administration in humans. Fed. Proc. 41, 241–246.

Gantenberg, N.S., Hageman, G.R., 1991. Cocaine depresses cardiac sympathetic efferent activity in anesthetized dogs. J. Cardiovasc. Pharmacol. 17, 434–439.

Gillis, R.A., Quest, J.A., Wilkerson, R.D., 1992. Mechanisms responsible for the cardiovascular disorders associated with cocaine abuse. In: Lakoski, J.M., Galloway, M.P., White, F.J. (Eds.), Cocaine: Pharmacology, Physiology and Clinical Strategies. CRC Press, Boca Raton, FL, pp. 371–390.

Greenberg, R., Innes, I.R., 1976. The role of bound calcium in supersensitivity induced by cocaine. Br. J. Pharmacol. 57, 329–334.

Greenberg, S., Long, J.P., 1971. The effects of cocaine, norepinephrine and ionic stimulants on the isolated superfused rat vas deferens: antagonism by ''adrenergic and neuron blockers'' and reserpine. J. Pharmacol. Exp. Ther. 177, 136–145.

Hageman, G.R., Simor, T., 1993. Attenuation of the cardiac effects of cocaine by dizocilpine. Am. J. Physiol. 264, H1890–H1895.

Hernandez, Y.M., Raczkowski, V.F.C., Dretchen, K.L., Gillis, R.A., 1996. Cocaine inhibits sympathetic neural activity by acting in the central nervous system and at the sympathetic ganglion. J. Pharmacol. Exp. Ther. 277, 1114–1121.

Hogya, P.T., Wolfson, A.B., 1990. Chronic cocaine abuse associated with dilated cardiomyopathy. Am. J. Emerg. Med. 8, 203–204.

Isner, J.M., Estes, N.A.M. III, Thompson, P.D., Costanzo-Nordin, M.R., Subramanian, R., Miller, J., Katsas, J., Sweeney, K., Sturner, W.Q., 1986. Acute cardiac events temporally related to cocaine abuse. N. Engl. J. Med. 315, 1438–1443.

Kalsner, S., Nickerson, M., 1969. Mechanism of cocaine potentiation of responses to amines. Br. J. Pharmacol. 35, 428–439.

Kasuya, Y., Goto, K., 1968. The mechanism of supersensitivity to norepinephrine induced by cocaine in rat isolated vas deferens. Eur. J. Pharmacol. 4, 355–362.

Kiritsy-Roy, J.A., Halter, J.B., Gordon, S.M., Smith, M.J., Terry, L.C., 1990. Role of the central nervous system in hemodynamic and sympathoadrenal responses to cocaine in rats. J. Pharmacol. Exp. Ther. 255, 154–160.

Knuepfer, M.N., Branch, C.A., 1992. Cardiovascular responses to cocaine are initially mediated by the central nervous system in rats. J. Pharmacol. Exp. Ther. 263, 734–740.

Leszkovsky, G.P., Tardos, L., 1968. Potentiation by cocaine and 3.3-di(*p*-aminophenyl)-propylamine (TK 174) of the effect of isoprenaline and noradrenaline on isolated strips of cat spleen. J. Pharm. Pharmacol. 20, 377–380.

Lichtenfeld, P.J., Rubin, D.B., Feldman, R.S., 1984. Subarachnoid hemorrhage precipitated by cocaine snorting. Arch. Neurol. 41, 223–224.

Majid, P.A., Patel, B., Kim, H.S., Zimmerman, J.L., Dellinger, R.P., 1990. An angiographic and histologic study of cocaine-induced chest pain. Am. J. Cardiol. 65, 812–814.

Nanji, A.A., Filipenko, J.D., 1984. Asystole and ventricular fibrillation associated with cocaine intoxication. Chest 85, 132–133.

Pasternak, P.F., Colvin, S.B., Baumann, F.G., 1985. Cocaine-induced angina pectoris and acute myocardial infarction in patients younger than 40 years. Am. J. Cardiol. 55, 847–848.

Premkumar, L.S., 1999. Selective potentiation of L-type calcium channel currents by cocaine in cardiac myocytes. Mol. Pharmacol. 56, 1138–1142.

Raczkowski, V.F.C., Hernandez, Y.M., Erzouki, H.K., Abrahams, T.P., Mandal, A.K., Hamosh, P., Friedman, E., Quest, J.A., Dretchen, K.L., Gillis, R.A., 1991. Cocaine acts in the central nervous system to inhibit sympathetic neural activity. J. Pharmacol. Exp. Ther. 257, 511–519.

Rhee, H.M., Valentine, J.L., Lee, S.Y., 1990. Toxic effects of cocaine to the cardiovascular system in conscious and anesthetized rats and rabbits: evidence for a direct effect on the myocardium. Neurotoxicology 11, 361–366.

Roszkowski, A.P., Koelle, G.B., 1960. Enhancement of inhibitory and excitatory effects of catecholamines. J. Pharmacol. Exp. Ther. 128, 227–232.

Seifen, E., Plunkett, L.M., Kennedy, R.H., 1989. Cardiovascular and lethal effects of cocaine in anesthetized dogs and guinnea-pigs. Arch. Int. Pharmacodyn. Ther. 300, 241–253.

Shibata, S., Hattori, K., Sakurai, I., Mori, J., Fujiwara, M., 1971. Adrenergic innervation and cocaine-induced potentiation of adrener-

gic responses of aortic strips from young and old rabbits. J. Pharmacol. Exp. Ther. 177, 621–632.

Summers, R.J., Tillman, J., 1979. Investigation of the role of calcium in the supersensitivity produced by cocaine in cat spleen strips. Br. J. Pharmacol. 65, 689–699.

Szabo, B., Obergfell, A., Starke, K., 1994. Involvement of monoamine uptake inhibition and local anesthesia in the cardiovascular response to cocaine in conscious rabbits. J. Pharmacol. Exp. Ther. 273, 128–137.

Tella, S.R., Schindler, C.W., Goldberg, S.R., 1989. The role of central and autonomic neural mechanisms in the cardiovascular effects of cocaine in conscious squirrel monkeys. J. Pharmacol. Exp. Ther. 252, 491–499.

Tella, S.R., Schindler, C.W., Goldberg, S.R., 1992. Cardiovascular effects of cocaine in conscious rats: relative significance of central sympathetic stimulation and peripheral neuronal monoamine uptake and release mechanisms. J. Pharmacol. Exp. Ther. 262, 602–610.

Tella, S.R., Schindler, C.W., Goldberg, S.R., 1993. Cocaine: cardiovascular effects in relation to inhibition of peripheral neuronal monoamine uptake and central stimulation of the sympathoadrenal system. J. Pharmacol. Exp. Ther. 267, 153–162.

Trouve, R., Nahas, G., 1986. Nitrendipine: an antidote to cardiac and lethal toxicity of cocaine. Proc. Soc. Exp. Biol. Med. 183, 392–397.

Varma, D.R., McCullough, H.N., 1968. Dissociation of the supersensitivity to norepinephrine caused by cocaine from inhibition of ^{3}H-norepinephrine uptake in cold-stored smooth muscle. J. Pharmacol. Exp. Ther. 66, 26–34.

Virmani, R., Robinowitz, M., Smialek, J.E., Smyth, D.F., 1988. Cardiovascular effects of cocaine: an autopsy study of 40 patients. Am. Heart J. 115, 1068–1075.

Weiner, R.S., Lockhart, J.T., Schwartz, R.G., 1986. Dilated cardiomyopathy and cocaine abuse: report of two cases. Am. J. Med. 81, 699–701.

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