Interactions of Nimodipine and Cocaine on Endogenous Catecholamines in the Squirrel Monkey[1] (43020)

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Abstract. **The effects of nimodipine on the cocaine-induced alterations in blood pressure, heart rate, and plasma catecholamines were studied in the squirrel monkey. Cocaine in intravenously administered doses of 0.5, 1, and 2 mg/kg produced significant increases in blood pressure and significant decreases in heart rate. These cardiovascular changes were associated with transient episodes of arrhythmias and with significant increases in plasma concentrations of dopamine, epinephrine, and norepinephrine. Nimodipine, 1 μg/kg/min for 5 min administered intravenously 5 min after cocaine, corrects the cardiovascular and plasma catecholamine concentration changes induced by this alkaloid. The same dose of nimodipine administered 5 min before cocaine prevents elevations of blood pressure. Plasma catecholamine increments are also prevented except for the highest dose of cocaine. Cardiovascular changes induced by cocaine administration in the squirrel monkey are temporally associated with significant increments in plasma catecholamines. Administration of nimodipine prevents or minimizes these endocrine and physiologic changes.** [P.S.E.B.M. 1990, Vol 193]

Cocaine releases norepinephrine and epinephrine from the adrenal medulla (1, 2) and also inhibits norepinephrine reuptake in the isolated heart (3) and in sympathetically innervated tissues (4). These alterations in catecholamine release and disposition result in increased synaptic concentrations, and could account for the functional cardiovascular changes observed after cocaine administration which mimic those induced by norepinephrine (5, 6).

In man, cocaine self-administration produces elevated blood pressure and tachycardia (7). Myocardial infarction (8), subarachnoidal hemorrhage (9) as well as myocardial band necrosis (10) have been reported following cocaine intoxication. The causes of these toxic effects of cocaine have not yet been clearly ascertained. Previous studies on the rat have demonstrated that a dihydropyridine calcium antagonist (nitrendipine) prevents the cardiovascular changes and cardiac lesions induced by cocaine (11, 12). This protection was attributed to the properties of $Ca2^+$ antagonists of inhibiting catecholamine-induced vasoconstriction (13) and changes in catecholamine disposition (14).

The purpose of this study was 2-fold: (i) to investigate the relationship between the cardiovascular effects of cocaine administration and plasma catecholamine concentration in the nonhuman primate and (ii) to test the preventive and antidote effects of a dihydropyridine, nimodipine (15), on these cocaine-induced vascular and hormonal changes.

Materials and Methods

Five squirrel monkeys weighing 720–940 g were fitted with chronic polyvinyl chloride catheters in the internal iliac vein and artery under halothane anesthesia (16). During experimental sessions, the animals, previously trained to sit for 3 hr in restraining chairs, are placed in a soundproof chamber in order to protect them from any auditory stimuli. Computerized equipment is assembled for on-line recording of heart rate and mean, systolic, and diastolic blood pressures (17). Continuous recording of the electrocardiogram on

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Table I. Cardiovascular Changes in the Squirrel Monkey following Intravenous Cocaine Administration[a]

Time (min)	Heart rate	Diastolic pressure	Systolic pressure
0 Control	254 ± 34	118 ± 25	135 ± 21
5 Saline	276 ± 63	115 ± 28	132 ± 24
$Saline_a$	278 ± 43	116 ± 30	132 ± 24
35 Coc1	270 ± 48	116 ± 29	133 ± 23
Coc_a	242 ± 82	132 ± 22[b]	153 ± 20[c]
65 Coc2	251 ± 73	127 ± 31	140 ± 11
$Coc2_a$	205 ± 98[d]	134 ± 18	164 ± 23[b]
95 Coc3	241 ± 58	124 ± 24	144 ± 21
Coc3a	216 ± 92	136 ± 23[b]	163 ± 23[c]
135 Saline end	219 ± 73	118 ± 20	141 ± 17

[a] Computer-generated statistical analysis of cardiovascular markers in five squirrel monkeys treated with three successive doses of cocaine (coc1 = 0.5, coc2 = 1, coc3 = 2 mg/kg). Values correspond to mean ± SD. Numbers 1, 2, and 3 represent measurements recorded just before saline or cocaine administration. Measurement "a" is performed within 5 min following saline or cocaine administration and corresponds to the highest or lowest deviation from control measurements which is made just before drug administration.
[b] $0.01 < P \leq 0.025$.
[c] $0.025 < P \leq 0.05$.
[d] $P \leq 0.01$.

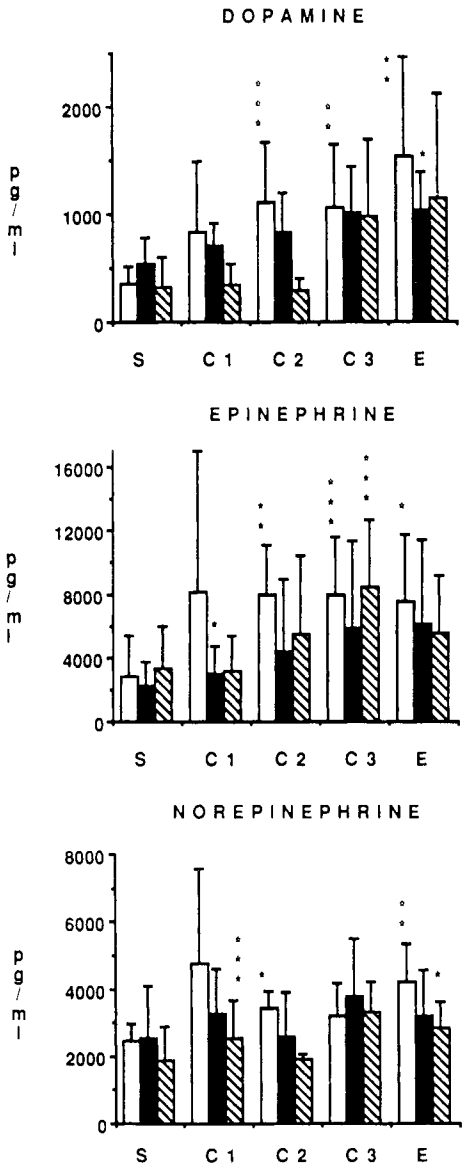

Figure 1. Bar graphs of dopamine, epinephrine, and norepinephrine plasma concentrations in the squirrel monkey after saline administration (S) and after intravenous administration of 0.5 (C1), 1 (C2), and 2 (C3) mg/kg cocaine intravenously. Epinephrine (E) samples taken 40 min after last administration of cocaine. The mean measurements of three experiments on five animals are illustrated. In the first bar graph (open) only cocaine was administered. In the second (dark) nimodipine was administered as an antidote 5 min after cocaine. In the third (diagonal) nimodipine was given preventively 5 min before cocaine. *$0.025 < P < 0.05$, **$0.01 < P < 0.25$, ***$P < 0.01$.

standard leads is also performed. The blood pressure signal, recorded on a Grass polygraph recorder, is also treated, on-line, by a computer which displays and prints out systolic, diastolic, and mean pressure as well as heart rate every 30 sec. The computer is programmed to average heart rate and blood pressure over a period of 4 sec (which corresponds to about 20 pulses).

Three series of experiments were performed on each animal at 3-week intervals. In the first series, the animals were given, at 30-min intervals, three successive intravenous doses of cocaine (0.5, 1, and 2 mg/kg) in a single bolus administered over 30 sec. These doses were selected because they are well tolerated by the animal even when given daily over several months (18) according to a protocol approved by the Animal Research Committee of the Addiction Research Center. Similar doses have been administered to human volunteers (7). The 30-min interval between injections was selected to study dose-response effects and on the basis of a 24-min half-life for cocaine (19). Five 0.7-ml arterial blood samples were taken: one 20 min before cocaine administration; one 10 min after the end of administration of each of three successive doses of cocaine; and the fifth 40 min after the last injection. In the second series, 5 min after administration of each dose of cocaine, nimodipine (1 μg/kg/min iv) was infused for a period of 5 min. In the third series, nimodipine infusion (1 μg/kg/min iv) preceded the administration of cocaine. In two animals, nimodipine, 1 μg/kg for 5 min, was administered on three successive occasions at 30-min intervals. In the second series, 5 min after administration of each dose of cocaine, nimodipine (1 μg/kg/min iv) was infused for a period of 5 min. In the third series, nimodipine infusion (1 μg/kg/min iv) preceded the administration of cocaine. In two animals, nimodipine (1 μg/kg for 5 min) was administered on three successive occasions at 30-min intervals. Blood samples were immediately refrigerated and centrifuged and the plasma was separated and frozen. Each animal was studied three times at 3-week

Table II. Antagonistic Effects of Nimodipine on Cardiovascular Changes Induced by Cocaine Intravenous Administration in the Squirrel Monkey[a]

Time (min)	Heart rate	Diastolic pressure	Systolic pressure
0 Control	336 ± 37	136 ± 26	144 ± 26
5 Saline	310 ± 58	134 ± 25	143 ± 25
$Saline_a$	317 ± 50	136 ± 23	145 ± 23
35 Coc1	298 ± 22	127 ± 17	137 ± 16
$Coc1_a$	297 ± 52	136 ± 23	152 ± 20[b]
40 Nim1	289 ± 29	129 ± 22	140 ± 23
$Nim1_a$	315 ± 38	124 ± 22[c]	134 ± 21[c]
65 Coc2	338 ± 57	126 ± 19	135 ± 20
$Coc2_a$	275 ± 70[b]	132 ± 24	141 ± 24[d]
70 Nim2	266 ± 80	121 ± 24	135 ± 24
$Nim2_a$	313 ± 35	116 ± 20[d]	128 ± 22[d]
95 Coc3	310 ± 53	120 ± 23	132 ± 25
$Coc3_a$	247 ± 79[d]	126 ± 28	143 ± 32[b]
100 Nim3	238 ± 83	119 ± 30	138 ± 35
$Nim3_a$	256 ± 65	110 ± 26[b]	124 ± 26[d]
135 Saline end	304 ± 74	118 ± 29	128 ± 29

[a] Computer-generated statistical analysis of cardiovascular markers in five squirrel monkeys treated with three successive doses of cocaine (coc1 = 0.5, coc2 = 1, coc3 = 2 mg/kg) followed by nimodipine (Nim). Values correspond to mean ± SD. Numbers 1, 2, and 3 represent measurements recorded just before saline, cocaine, or nimodipine administration. Measurement "a" is performed within 5 min following saline, cocaine, or nimidopine administration and corresponds to the highest or lowest deviation from control measurements which is made just before drug administration (cocaine and nimodipine).
[b] $0.01 < P \leq 0.025$.
[c] $P \leq 0.01$.
[d] $0.025 < P \leq 0.05$.

Table III. Antidote Effects of Nimodipine on the Cardiovascular Changes Induced by Cocaine Intravenous Administration in the Squirrel Monkey[a]

Time (min)	Heart rate	Diastolic pressure	Systolic pressure
0 Control	298 ± 30	125 ± 19	140 ± 24
5 Saline	281 ± 25	125 ± 14	140 ± 18
$Saline_a$	296 ± 25	126 ± 21	141 ± 23
30 Nim1	291 ± 38	126 ± 19	135 ± 21
$Nim1_a$	321 ± 33[b]	121 ± 14	137 ± 18
35 Coc1	327 ± 38	122 ± 16	137 ± 20
$Coc1_a$	243 ± 25[c]	126 ± 16	141 ± 23[b]
60 Nim2	353 ± 22	128 ± 11	143 ± 15
$Nim2_a$	345 ± 38	123 ± 12[c]	140 ± 17[c]
65 Coc2	348 ± 29	124 ± 12	139 ± 17
$Coc2_a$	267 ± 50[c]	121 ± 15	137 ± 20
100 Nim3	315 ± 58	122 ± 13	139 ± 17
$Nim3_a$	348 ± 35[b]	118 ± 13[c]	134 ± 18[b]
105 Coc3	348 ± 35	118 ± 14	134 ± 18
$Coc3_a$	211 ± 69[c]	115 ± 17	137 ± 26
135 Saline end	303 ± 50	120 ± 18	137 ± 21

[a] Computer-generated statistical analysis of cardiovascular markers in five squirrel monkeys treated with three successive doses of cocaine (coc1 = 0.5, coc2 = 1, coc3 = 2 mg/kg) preceded by nimodipine (Nim). Values correspond to mean ± SD. Numbers 1, 2, and 3 represent measurements recorded just before saline, cocaine, or nimodipine administration. Measurement "a" is performed within 5 min following saline, cocaine, or nimodipine administration and corresponds to the highest or lowest deviation from control measurements which is made just before drug administration (cocaine and nimodipine).
[b] $0.025 < P \leq 0.05$.
[c] $P \leq 0.01$.

intervals. The experimental data were processed by a computer which is programmed to analyze, on a three-point basis per minute, the lowest or highest measurements of heart rate and blood pressure. Measurements performed within 5 min following saline, cocaine, or nimodipine administration were compared (t test) to the highest or lowest deviation from control measurements which were made just before drug administration (cocaine or nimodipine). The radioenzyamtic method of Peuler and Johnson (20), as modified by the "Cat A Kit" instructions supplied by Amersham International (1986) was used for catecholamine measurements.

Results

Cocaine induced significant increases in blood pressure, while heart rate is unchanged or decreased (Table I). Within 1 min after administration of cocaine in a 1- or 2-mg/kg dose, premature ventricular contractions and arrythmias occur. They are spontaneously corrected within 2 min. Plasma catecholamines were increased significantly ($P < 0.05$) after the second and third administration of 1 and 2 mg/kg cocaine (except for norepinephrine after 1 mg) (Fig. 1). Significant increases in all three catecholamines were still present 40 min after the last administration of 2 mg/kg cocaine. Nimodipine administered as an antidote after cocaine normalizes cardiovascular values (Table II) and minimizes changes in plasma catecholamine concentration induced by this alkaloid. When nimodipine was administered preventively before cocaine, cardiovascular changes in pressures, but not in frequency, were minimized (Table III) and so were catecholamine increments after the first two doses. Administration of nimodipine alone was followed by decreases in blood pressure and increases in heart rate; catecholamine plasma concentration was increased.

Discussion

In the squirrel monkey cocaine administration significantly increased systolic and diastolic blood pressure and decreased heart rate. The observed cardiovascular "tolerance" to increasing doses of cocaine administered sequentially every 30 min was described by others in the human primate (7). However, when the increasing doses of cocaine were administered at 24-hr intervals to the same animals, dose-related cardiovascular effects were observed (21).

The cocaine-induced bradycardia recorded in the present experiments was similar to that observed in the

cocaine-intoxicated rat, another animal with a rapid resting heart rate (22, 23). By contrast, cocaine induced tachycardia in the rhesus monkey (24) and in man (7), indicating that in these primates cocaine alters the normal baropressure response.

The concentration of cocaine required to induce changes in cardiac markers in the isolated heart is much higher than those which are effective *in vivo* (25). Cardiac effects of cocaine *in vivo* could be attributed, at least in part, to the increases in circulatory catecholamines released from adrenal and ganglionic stores.

The changes in heart rate and blood pressure induced by cocaine in the squirrel monkey were similar to those produced in the same animal by norepinephrine administration which induces increases in pressure associated with bradycardia (6). Cocaine also induced in the squirrel monkey increases in plasma catecholamine concentration. Increases in dopamine and epinephrine were larger than those observed for norepinephrine and could be accounted for by the sustained adrenal release of these catechols. Increments in plasma norepinephrine following cocaine administration have been mostly attributed to inhibition of reuptake mechanisms (4) as well as increased release of this monoamine by the presynaptic neuron. In agreement with the present study, Chiueh and Kopin (2) also found that cocaine elicited a 3- to 6-fold increase in release of epinephrine and norepinephrine from the adrenal medulla of the awakened rat administered cocaine intraperitoneally or intravenously. This increment in adrenal medullary discharge by cocaine was attributed by these authors to a centrally mediated mechanism. As catecholamine stores are depleted by cocaine they are promptly replenished, and an increase in turnover occurs in the adrenal medulla (1).

Nimodipine, if administered after cocaine, reverses the cardiovascular effects of cocaine including its arrhythmic properties. Nimodipine has minimal effect on cardiac muscle contraction but may affect cardiac conduction (26). It is a less potent vasodilator of coronary and peripheral vessels than nitrendipine and is specific for the cerebral vascular bed (15). In doses similar to those clinically administered, nimodipine, given as an antidote to cocaine, partially normalizes the elevated catecholamine plasma concentration produced by cocaine; administered preventively nimodipine limits the catecholamine increments produced by the drug. Little change in systolic pressure and a significant decrease in heart rate ($P < 0.01$) was observed with an animal that was pretreated with nimodipine prior to administration of cocaine. Nimodipine alone increased heart rate significantly while decreasing blood pressure, and catechols were increased as reported previously (15). The drop in rate following cocaine administration to a nimodipine-pretreated animal was of greater magnitude than when the initial baseline heart rate was lower.

Dihydropyridines are believed to act mainly on L-type calcium channels and therefore may not be effective in controlling neurotransmitter release (27). However, it has been reported (28) that calcium channel antagonists inhibit norepinephrine release in the ischemic heart. Changes in the clearance of norepinephrine as a result of blood flow redistribution in the peripheral vascular bed should also be considered (29). Nimodipine administered after cocaine limits or reverses the cardiovascular response to this alkaloid. In the latter case, norepinephrine and dopamine concentrations are higher than when nimodipine is administered before cocaine, but epinephrine is lower. The discrepancy in catechol concentration supports the hypothesis that following cocaine injection epinephrine release is delayed when compared with that of norepinephrine or dopamine. The reason for this lag is unclear but may be related to the ability of nimodipine to limit the sympathetic stimulation of the adrenal medulla.

These results indicate that elevated circulating catecholamines might play a role in the genesis of the cardiac alterations produced by cocaine and which were previously reported (5, 11, 12). The morphologic changes which occur after administration of a large dose of cocaine are similar to the myocardial lesions in the canine heart following norepinephrine administration (30). Manger and Gifford (31) also reported myocardial infarction and catecholamine cardiomyopathy in some patients dying of pheochromocytoma. The present experiments confirm other studies performed on rats administered a lethal dose of cocaine and treated successfully with another dihydropyridine, nitrendipine (11, 12, 22). Cocaine cardiovascular effects and toxicity may be related to increased catecholamine synaptic and tissue concentration. These conclusions are supported by subsequent studies performed on rats administered 50 mg/kg of cocaine, a dose associated with significant elevations of plasma catecholamines as well as cardiac morphologic and functional alterations. Administration of nitrendipine corrected these hormonal and cardiovascular changes (32).

If the cardiovascular effects of cocaine are mediated by catecholamine release and corrected by Ca^{2+} antagonists, one might suggest an hypothesis (33) to account for the tolerance to repeated dosages of cocaine: The catechols released by the alkaloid would induce a down-regulation of their postsynaptic receptors (34). As a result of their increased secretion one might expect an up-regulation of the calcium channel receptors.

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