Estrogen Mediates the Pregnancy-Enhanced Cardiotoxicity of Cocaine in the Isolated Perfused Rat Heart

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Objective: **To determine whether pregnancy enhances cocaine toxicity in the isolated perfused whole rat heart model and whether this enhanced toxicity can be simulated by pre-treatment with either estrogen or progesterone.**

Methods: **Hearts excised from 65 female Sprague-Dawley rats were attached to a Langendorff apparatus for measurement of left ventricular systolic pressure, heart rate, and contractility. Before excision, the animals were assigned to one of five groups: 1) nonpregnant, 2) pregnant, 3) nonpregnant pretreated with progesterone, 4) nonpregnant pretreated with estrogen, and 5) nonpregnant pretreated with estrogen and progesterone. Each group was exposed serially to the following cocaine concentrations: 5×10^{-6}, 1×10^{-5}, and 6×10^{-5} mol/L.**

Results: **Heart rate declined at all doses of cocaine (9.2, 6.9, and 31.0%, respectively). The lowest dose of cocaine had positive inotropic effects, with a 23.2% increase in left ventricular pressure and a 15.3% increase in contractility. Exposure to the two higher doses resulted in negative inotropic effects (a 24.8% decrease in left ventricular pressure and a 39.7% decrease in contractility for the highest dose). Although pre-treatment with estrogen, alone or with progesterone, resulted in responses similar to those seen in pregnant animals, progesterone pre-treatment alone failed to do so.**

Conclusions: **Cocaine displayed cardiotoxicity in isolated rat hearts similar to that in other animal models. This toxicity was enhanced by pregnancy. We were able to simulate changes by pretreating the animals with estrogen. Perhaps the enhanced cardiotoxicity of cocaine in pregnancy is partially mediated by estrogen.** ***(Obstet Gynecol 1994;83: 613–5)***

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Cocaine use by gravid women has been associated with cardiovascular complications, including arrhythmias, hypertension, cardiac arrest, and death.[1] One recent study in gravid ewes[2] suggested that pregnancy enhances the cardiovascular toxicity of cocaine, perhaps through a progesterone-mediated delay in cocaine metabolism.[3] An experiment performed with isolated papillary muscle strips demonstrated that progesterone pre-treatment enhanced cocaine-induced myocardial depression (Sharma A, Plessinger M, Miller RK, Woods JR. Progesterone antagonist mifepristone [RU486] decreases cardiac toxicity of cocaine. Society for Gynecologic Investigation, abstract #224, 1991, San Antonio, Texas). These observations suggest that in pregnancy, cocaine has enhanced cardiotoxicity which is progesterone-related.

This study was designed to determine whether pregnancy enhances the cardiotoxicity of cocaine in the isolated perfused whole rat heart model and whether this enhanced toxicity is due to estrogen or progesterone.

Materials and Methods

This project was approved by the Committee on Animal Research at the University of North Carolina at Chapel Hill. All care and procedures were within committee guidelines. Sixty-five female Sprague-Dawley rats (15 pregnant, 50 nonpregnant) were anticoagulated and anesthetized with ether. Their hearts were excised rapidly (within 15 seconds), attached to a Langendorff apparatus, and perfused with aerated Kreb's solution at 37C. The left ventricle of each heart was catheterized with a microtip transducer. Left ven-

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Table 1. Baseline Cardiovascular Measurements

Group	*n*	Heart rate (bpm)	Left ventricular systolic pressure	Contractility
Nonpregnant	15	238.8 ± 17.2	93.8 ± 13.5	1736 ± 247.4
Pregnant	15	247.0 ± 22.0	89.5 ± 9.5	1810 ± 273.3
Nonpregnant with progesterone	10	245.2 ± 26.6	97.7 ± 19.6	1906 ± 407.1
Nonpregnant with estrogen	10	242.7 ± 20.4	92.5 ± 8.7	1835 ± 268.1
Nonpregnant with progesterone and estrogen	15	240.9 ± 30.8	93.9 ± 11.0	1808 ± 170.1
All	65	243.0 ± 22.3	93.1 ± 12.7	1811 ± 278.6
ANOVA*		$P = .89$	$P = .64$	$P = .69$

Bpm = beats per minute; ANOVA = analysis of variance.
Data are presented as mean ± SD.
* Differences between groups at baseline.

tricular systolic pressure, heart rate, and contractility were measured after 10 minutes of equilibration.

Before excision, the animals had been assigned to one of five groups and treated as the group assignment dictated. The groups were as follows: 1) nonpregnant ($n = 15$); 2) pregnant ($n = 15$); 3) nonpregnant pretreated with progesterone ($n = 10$), 10 mg/kg injected intramuscularly (IM) for 3 days; 4) nonpregnant pretreated with estrogen ($n = 10$), 100 μg/kg IM for 3 days; and 5) nonpregnant pretreated with progesterone and estrogen ($n = 15$) at similar doses and duration. No animal had undergone oophorectomy. Gestational ages ranged from 12–15 days in the pregnant animals. Steroid hormone doses were chosen based on previous work by Plessinger and Woods[3] in a sheep model. Hearts in each group were exposed to serial cocaine doses of 5×10^{-6}, 1×10^{-5}, and 6×10^{-5} mol/L. Doses were increased at 10-minute intervals.

We examined differences between groups at baseline using one-way analysis of variance. Two-way analysis of variance was used to assess the independent contributions of group and dose. Comparisons of individual means were corrected using the Tukey correction for multiple comparisons.[4]

Results

Baseline values of heart rate, left ventricular blood pressure, and contractility were similar among the five groups (Table 1).

Heart rates declined slightly after administration of the two lowest cocaine doses. A more substantial decrease occurred with the highest dose (Table 2). The mean percent decrease at the highest dose was 31.0%,

Table 2. Changes in Cardiovascular Indices With Administration of Cocaine

	Cocaine concentration		
	5×10^{-6} mol/L	1×10^{-5} mol/L	6×10^{-5} mol/L
Heart rate (bpm)			
Mean ± SD	220.6 ± 22.0	226.3 ± 22.9	167.7 ± 40.7
Change from baseline	−9.2%	−6.9%	−31.0%
Left ventricular systolic pressure (mmHg)			
Mean ± SD	114.8 ± 16.1	76.6 ± 14.7	70.0 ± 16.2
Change from baseline	+23.2%	−17.7%	−24.8%
Contractility (mmHg/s)			
Mean ± SD	2088 ± 320.6	1391 ± 237.7	1092 ± 308.1
Change from baseline	+15.3%	−23.2%	−39.7%

Bpm = beats per minute.

which was significantly different ($P < .05$) from baseline and from the lower doses. The five groups did not differ significantly with respect to this pattern.

A different pattern was observed for the blood pressure and contractility measures. A positive inotropic response was seen with the lowest cocaine concentration, whereas the two higher doses resulted in progressive and predictable negative inotropic effects (Table 2). The blood pressure values plateaued somewhat at the second cocaine dose, but contractility declined further upon administration of the highest dose. At the highest cocaine concentration, the decline from baseline was −24.8% and −39.7% for blood pressure and contractility, respectively; however, there were differences between groups in the magnitude of these decreases. The pregnant, nonpregnant pretreated with estrogen, and nonpregnant pretreated with estrogen and progesterone groups showed larger differences from baseline than the progesterone-only group ($P < .05$) (Table 3). Thus, treatment with estrogen or estrogen and progesterone appears to enhance the depressive effects of cocaine.

Table 3. Mean Changes From Baseline With Administration of Cocaine (6×10^{-5} mol/L)

Group	*n*	Left ventricular systolic pressure (mmHg)	Contractility (mmHg/s)
Nonpregnant	15	−13.1%	−27.9%
Pregnant	15	−32.9%	−49.7%
Nonpregnant with progesterone	10	−18.3%	−32.4%
Nonpregnant with estrogen	10	−32.2%	−45.4%
Nonpregnant with progesterone and estrogen	15	−31.4%	−44.6%

Discussion

Our experiment demonstrates that cocaine at low doses has mild inotropic effects and that cocaine at higher levels is a cardiotoxin in the isolated perfused rat heart model. This study suggests that estrogen may be the mediator of this enhanced cardiotoxicity. Animals pretreated with progesterone alone did not display potentiation of cardiac depression.

Cocaine exerts many of its effects by blocking extraneuronal catecholamine uptake.[5] Investigators have demonstrated in sheep models that pregnancy[2] and sex steroids[3] potentiate the cardiotoxicity of cocaine. These authors have speculated that sex steroids induce changes in alpha-adrenergic receptors and increase sensitivity to the cocaine blockade of synaptic uptake.[2,3] Evidence in support of this includes studies demonstrating the increases in sympathetic nervous activity in rat hearts during pregnancy[6] and the changes in the alpha-adrenergic contractile responses seen in other tissues exposed to cocaine in pregnancy.[7,8]

Contrary to work done in intact sheep[3] and in a papillary muscle-strip model (Sharma A et al. Society for Gynecologic Investigation, abstract #224, 1991), estrogen rather than progesterone pre-treatment was necessary to show a pregnancy-like effect. This could result from differences between models, the species of animals studied, or the steroid dosages. In neither experiment was estrogen pre-treatment studied. Like cocaine, hydrocortisone (a glucocorticoid) inhibits extraneural uptake of catecholamines in both rat hearts[9] and rabbit ear arteries.[10] Thus, further study of the interactions between cocaine and steroid hormones is needed.

The isolated perfused rat heart model measures central hemodynamic indices devoid of peripheral vasculature and the nervous system. Further experiments in intact animal models or hemodynamic testing of cocaine-intoxicated gravidas or women taking oral contraceptives will be necessary before these findings can be extrapolated to intact animals or humans.

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