Cocaine's effect on plasma oxytocin concentrations in the baboon during late pregnancy

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OBJECTIVE: The hypothesis for this investigation was that intravenous cocaine would result in an elevation of maternal plasma oxytocin levels in the baboon during late pregnancy.

STUDY DESIGN: Five gravid chronically instrumented baboons had timed arterial blood samples obtained before and after an intravenous bolus cocaine infusion at least 5 days after surgery. Plasma oxytocin concentrations were measured by specific radioimmunoassays, and baseline samples were compared with postcocaine samples.

RESULTS: The plasma oxytocin concentrations were significantly elevated at all sampling times after the 1.0 mg/kg cocaine dose ($p < 0.05$).

CONCLUSION: The increased oxytocin concentrations after cocaine use may be responsible for the increased incidence of preterm labor. (Am J Obstet Gynecol 1996;174:1026-7.)

Key words: Cocaine, oxytocin, baboon, pregnancy

Cocaine use during pregnancy has been associated with significant adverse perinatal outcomes, including preterm labor, premature rupture of membranes, intrauterine growth retardation, and congenital anomalies. Intravenous bolus infusions of cocaine have been observed to increase myometrial contractility in the gravid baboon.[1]

Oxytocin and oxytocin receptors are believed to contribute toward human parturition. Because cocaine increases catecholamine levels and α-adrenergic receptors have been observed to increase uterine sensitivity to oxytocin, we set out to determine cocaine's effect on oxytocin concentrations in the gravid baboon. We hypothesized that a cocaine infusion would elevate plasma oxytocin concentrations.

Material and methods

Five pregnant baboons, *Papio cynocephalus* or *Papio anubis,* at 86 to 150 days' gestation (term 180 days) were studied. All procedures were reviewed and approved by the Institutional Animal Care and Use Committee of Cornell University. A modified jacket was placed on each baboon while the animal was under light ketamine anesthesia 1 week before a tethering and swivel system was attached to the jacket.

Two weeks after acclimation to this system surgical instrumentation was performed as previously described.[1] Briefly, catheters were placed in the femoral artery and vein with the animal under general halothane anesthesia. This instrumentation was passed into a box attached to the tether, anchored to the jacket on the baboon's back, and through the flexible tether out the top of the cage allowing access to this instrumentation while at the same time permitting the baboon free mobility. The catheters were flushed daily with 3 to 5 ml of 10 IU/ml heparinized saline solution.

All studies were conducted at least 5 days after surgery. The five baboons received slightly different dosage regimens. Cocaine hydrochloride (Sigma, St. Louis) at 0.5, 0.75, and 1.0 mg/kg by maternal weight were dissolved in 5 ml of normal saline solution. The cocaine dosages used in this investigation are similar to those used in other investigations.[1] These one time acute bolus cocaine infusions were infused in a random order at least 24 hours apart and were determined time zero. All infusions were initiated between 9 and 10 AM hours. Because of abortion in two baboons, three baboons are in the 0.5 and 0.75 mg/kg dosage groups. Arterial blood samples (3 ml) were obtained at −30, −15, and −5 minutes before each cocaine infusion and at +5, +15, and +30 minutes after the infusion. The −30, −15, and −5 values were averaged to obtain the baseline concentration for each hormone assayed. Plasma oxytocin concentration was measured by radioimmunoassay after acetone extraction, as previously

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Supported in part by National Institutes of Health grant No. HD 21350.
Received for publication May 24, 1995; accepted June 5, 1995.

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0002-9378/96 $5.00 + 0 6/1/66852

Table I. Gravid baboon's oxytocin concentrations in response to cocaine administration

Hormone	*Cocaine (mg/kg)*	*No.*	*Baseline (ng/ml)*	*Time after cocaine infusion*		
				+5 min	*+15 min*	*+30 min*
Oxytocin	0.5	3	3.9 ± 0.1	3.5 ± 0.5	3.2 ± 0.3	4.0 ± 0.4
	0.75	3	3.0 ± 0.2	3.4 ± 0.4	3.9 ± 0.6	3.5 ± 0.6
	1.0	5	3.1 ± 0.2	3.9 ± 0.4*	3.8 ± 0.3*	4.0 ± 0.4*

*$p < 0.05$.

described.[2] The interassay and intraassay coefficients of variation were 12.1% and 9.4%, respectively. Assay sensitivity, calculated as the 90% confidence interval of B/BO, was 1 pg per tube. The oxytocin concentrations before and after each cocaine infusion were compared and reported as mean ± SEM. Statistical analysis was performed by analysis of variance for repeated measures and one-tailed paired *t* test. Statistical significance was set at $p < 0.05$.

Results

The mean gestational age of the baboons at the time of cocaine administration was 126 ± 6 days. The mean baseline plasma oxytocin concentrations of each baboon before the intravenous cocaine infusions and the oxytocin response to the intravenous cocaine infusion of 0.5, 0.75, and 1.0 mg/kg are given in Table I. The plasma oxytocin concentrations were significantly increased by 25%, 22%, and 30% over baseline at 5, 15, and 30 minutes after the 1.0 mg/kg cocaine infusion dose.

Comment

Cocaine hydrochloride administered intravenously to pregnant baboons was observed to result in elevation of plasma oxytocin concentrations (Table I). The observed changes did not fit a classic dose-response curve, suggesting that there is considerable biologic variability in cocaine's effects in nonhuman primates. Some of this variability is undoubtedly due to individual animal variability in response. In addition, it is likely that catecholamines and possibly cocaine have both stimulatory and inhibitory responses on some of the neuroendocrine systems studies.

Owiny et al.[3] recently reported that maternal plasma oxytocin concentrations remain unchanged after intravenous cocaine dosages of 0.5, 1.0, and 2.0 mg/kg administered to gravid ewes. This is in contrast to the significant elevation of plasma oxytocin concentrations after a 1.0 mg/kg dose of intravenous cocaine administered to gravid baboons (Table I). The increase in oxytocin concentrations in the nonhuman primate after cocaine administration could result in the increased myometrial contractility previously reported.[1] Increased plasma oxytocin could also explain the reported increased incidence of preterm labor in women using cocaine during pregnancy. Elevated oxytocin concentrations together with catecholamine stimulation of α-adrenergic receptors would increase myometrial sensitivity to oxytocin, leading to increased myometrial contractility.

In conclusion, we observed that intravenous cocaine elevated plasma oxytocin concentrations compared with baseline in the baboon during late pregnancy (Table I). This response to cocaine may explain how adverse perinatal outcomes occur in women using cocaine during pregnancy. Further investigation into possible interventions that may prevent some of these adverse outcomes, such as the use of oxytocin antagonists to inhibit cocaine-stimulated myometrial contractions, could be promising.

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