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Elevated Plasma Norepinephrine After In Utero Exposure to Cocaine and Marijuana

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Abstract

Objective—To compare plasma catecholamine concentrations between cocaine-exposed and unexposed term newborns and to determine the relationship between plasma catecholamines and newborn behavior.

Methods—Forty-six newborn infants participating in a prospective study of the neonatal and long-term effects of prenatal cocaine exposure were studied. Based on maternal self-report, maternal urine screening, and infant meconium analysis, 24 infants were classified as cocaine-exposed and 22 as unexposed. Between 24 and 72 hours postpartum, plasma samples for norepinephrine (NE), epinephrine, dopamine, and dihydroxyphenylalanine analysis were obtained. The Neonatal Behavioral Assessment Scale was administered at 1 to 3 days of age and at 2 weeks of age by examiners masked to the drug exposure status of the newborns.

Results—The cocaine-exposed newborns had increased plasma NE concentrations when compared to the unexposed infants (geometric mean, 923 pg/mL vs 667 pg/mL). There were no significant differences in plasma epinephrine, dopamine, or dihydroxyphenylalanine concentrations. Analysis for the effect of potential confounding variables revealed that maternal marijuana use was also associated with increased plasma NE, although birth weight, gender, and maternal use of alcohol or cigarettes were not. Geometric mean plasma NE was 1164 pg/mL in those infants with in utero exposure to both cocaine and marijuana compared to 812 pg/mL in those exposed to only cocaine and 667 pg/mL in those exposed to neither. Among the cocaine-exposed infants, plasma NE concentration correlated with an increased score for the depressed cluster ($r = .53$) and a decreased score for the orientation cluster ($r = -.43$) of the Neonatal Behavioral Assessment Scale administered at 1 to 3 days of age. Adjusting for marijuana exposure had no effect on these relationships between plasma NE and the depressed and orientation clusters.

Conclusion—Plasma NE is increased in newborns exposed to cocaine and marijuana. Increased plasma NE is associated with selected neurobehavioral disturbances among cocaine exposed infants at 1 to 3 days of life but not at 2 weeks.

Recent reports have investigated the effect of prenatal cocaine exposure on fetal growth and newborn behavioral and cardiovascular function.^{1–5} However, there are limited data describing the impact of cocaine on fetal catecholamine systems. Cocaine's pharmacological

action involves blockade of catecholamine reuptake at presynaptic nerve endings, resulting in acute increases in synaptic catecholamine concentrations and stimulation of both the peripheral and central nervous systems.⁶ The physiological response to cocaine is characterized by activation of peripheral adrenergic systems, leading to hypertension, tachycardia, and vasoconstriction, and during pregnancy, decreased uterine and placental blood flow, and fetal hypoxemia, hypertension, and tachypnea.⁷ Central response to cocaine, including its euphoric and self-reinforcing effects, is believed to result from accumulation of central nervous system dopamine (DA), especially in mesolimbic and mesocortical pathways.⁸ Long-term use of cocaine may lead to depletion of central dopamine stores, explaining dysphoria and drug craving during withdrawal.^{9,10}

The effect of cocaine exposure on developing fetal catecholamine systems remains unknown. Animal and human studies suggest that prenatal cocaine exposure may induce long-term alterations in central catecholaminergic pathways.^{11,12} The results of our previous pilot study show a trend toward increased circulating concentrations of norepinephrine (NE) and the catecholamine precursor dihydroxyphenylalanine (DOPA) in cocaine-exposed newborns. In addition, we observed an inverse relationship between the concentration of circulating NE and orientation behavior.¹³ The study was conducted to confirm these findings in a larger sample of infants.

METHODS

The study population consisted of infants participating in a large prospective study of the neonatal and long-term effects of prenatal cocaine exposure whose mothers consented to a venipuncture in place of heel puncture to obtain blood for routine newborn metabolic screening. Heel puncture is normally used in our nursery to obtain blood for newborn screening; infants participating in this study had a single venipuncture to provide samples for both the newborn screen and for plasma catecholamine assays. The study protocol was approved by the Boston City Hospital Human Studies Committee.

Mother-infant pairs were enrolled within 2 days of delivery if they met enrollment criteria that included gestational age of more than 36 weeks by obstetric history and newborn exam, absence of serious illness or congenital malformations, no evidence of fetal alcohol syndrome, no history of human immunodeficiency virus seropositivity noted in the mother's or infant's medical record, and no known maternal use of opiates, benzodiazepines, amphetamines, phencyclidine, barbiturates, or hallucinogens. Mother-infant pairs with clinically documented prenatal cocaine use at the time of entry were recruited as "exposed." Those without such use were recruited provisionally into the "unexposed" comparison group, and were reassigned to the "exposed" group if subsequent biological testing (maternal postpartum urine or infant meconium) indicated prenatal cocaine use.

Between 24 and 72 hours postpartum, study infants had a single venous blood sample (2 to 3 mL) obtained from the antecubital vein while the infant was supine. Samples were immediately placed in blood collection tubes with EGTA and reduced glutathione, then kept on ice until centrifugation at 4°C. The plasma was separated and stored at -70°C until analysis. Concentrations of NE, DA, and epinephrine were determined using a commercial radio-enzymatic method (CAT-A-KIT Assay Kit, Amersham Corp, Arlington Heights, IL). DOPA concentrations were determined by high-performance liquid chromatography with electrochemical detection after extraction with alumina.^{14,15}

Other study procedures in the nursery included collection of a meconium sample from the infant and a urine sample from the mother for drug testing, maternal interview documenting prenatal drug, alcohol and cigarette use, and administration of the Neonatal Behavioral

Assessment Scale (NBAS) between 24 and 72 hours after birth and again at 2 weeks. Meconium samples were analyzed by a modification of the method of Ostrea using methanol extraction.^{16,17} Meconium extracts and maternal urine samples were analyzed quantitatively for the concentration of benzoylecgonine (cocaine metabolite), opiates, amphetamines, benzodiazepines and cannabinoids by radioimmunoassay (Abuscreen RIA, Roche Diagnostics Systems, Inc., Montclair, NJ). NBAS exams were performed in a quiet room by examiners masked to the infant's drug exposure status. The NBAS behavioral items were reduced to cluster scores in two ways. Using Lester's method, seven neurobehavioral clusters were calculated: habituation, orientation, state regulation, range of state, autonomic stability, motor organization, and reflexes.¹⁸ Two additional clusters, excitable and depressed, were also calculated, as developed by Lester and Tronick.⁵

Maternal and neonatal characteristics, including catecholamine concentrations, of the cocaine-exposed and unexposed infants were compared using χ^2 analysis, Fisher's exact test, or two-tailed Student's *t* test. The effects of potential confounding variables (birth weight, gender, and maternal use of cigarettes, alcohol, and marijuana) on the relationship of prenatal cocaine exposure to catecholamine concentrations were assessed one at a time using multiple linear regression analysis. Analysis of variance was used to compare plasma catecholamine concentrations among multiple groups. Values for plasma catecholamines, daily maternal cigarette use, and daily maternal alcohol use were log transformed to normalize the variance and meet the assumptions of least squares regression. Geometric means are presented for log transformed variables; for nontransformed variables, arithmetic means are presented. The relationships between catecholamine concentrations and NBAS cluster scores were evaluated using Spearman's rank correlation, and partial correlation analysis was used to adjust for marijuana exposure.

RESULTS

Plasma samples were obtained from 46 infants whose mothers consented to the venipuncture instead of heel puncture. Based on maternal self-report, maternal urine screening, and infant meconium analysis, 24 were classified as cocaine-exposed and 22 as unexposed. The study infants reflect the characteristics of the inner city population cared for at Boston City Hospital; 87% were black and 89% did not have private health insurance.

The mothers using cocaine were comparable to the nonusers in age, ethnicity, education, and parity (see Table 1). There were no differences in mode of delivery. No infant in either group had an Apgar score less than 7 at 1 or 5 minutes. The gender distribution and mean gestational ages for the two groups were not different but the cocaine-exposed infants were significantly smaller in weight and head circumference than the control infants. The mothers using cocaine were more likely to smoke cigarettes, use alcohol, and smoke marijuana. All maternal postpartum urine samples and infant meconium samples were negative for illicit opiates and benzodiazepines. Two mothers (one cocaine-exposed and one cocaine-unexposed) had postpartum urines positive for amphetamines and one infant (cocaine-unexposed) had a meconium positive for amphetamines.

Geometric mean plasma NE concentration was significantly greater in the cocaine-exposed infants than the unexposed (923 pg/mL vs 667 pg/mL, $P = .03$). There were no significant differences in mean plasma epinephrine, DA, or DOPA concentrations (see Table 2). There was no relationship between plasma NE concentration and markers for heavier maternal cocaine use (maternal peripartum urine positive for cocaine or meconium benzoylecgonine concentration). The impact of the potential confounding variables of birth weight, gender, and maternal use of cigarettes, alcohol, and marijuana, on the relationship between cocaine use and plasma NE were examined individually, due to the limited sample size. The results of these

analyses showed that the only potential confounding variable to decrease the magnitude of the association between cocaine exposure and plasma NE was maternal use of marijuana. Geometric mean plasma NE was 1164 pg/mL in the seven infants with in utero exposure to both cocaine and marijuana compared to 812 pg/mL in the 17 infants exposed only to cocaine and 667 pg/mL in the 21 infants exposed to neither cocaine or marijuana ($P = .04$). Plasma NE was 657 pg/mL in the one infant exposed to marijuana but not cocaine. We found no relationship between markers for heavier maternal cocaine use (maternal peripartum urine positive for cocaine or meconium benzoylecgonine concentration) and marijuana exposure, suggesting that marijuana exposure was not serving as a marker for heavier maternal cocaine use in our population.

Among the cocaine-exposed infants, there was a statistically significant correlation between plasma NE and a higher score for the depressed cluster ($r = .53$, $P = .01$) and a trend toward a correlation between plasma NE and lower orientation cluster score during the newborn NBAS exam ($r = -.43$, $P = .06$). There were no significant correlations between plasma NE and any NBAS clusters from the 2-week exams of the cocaine-exposed infants or from the newborn or 2-week exams of the unexposed infants. Adjustment for marijuana exposure within the cocaine-exposed group using partial correlation analysis did not substantively alter the relationship between plasma NE and the depressed and orientation clusters.

DISCUSSION

Our study demonstrates that, in newborns 24 to 72 hours old, plasma NE is increased after in utero cocaine and marijuana exposure. These data expand the results of our original pilot study, which demonstrated a trend to increased circulating NE in cocaine-exposed newborns, and support the observations of Ward et al,¹⁹ of increased plasma NE in 1- to 3-month-old infants prenatally exposed to cocaine and other drugs.¹³ No increase in mean plasma DOPA, the NE precursor, was seen in our study, in contrast to our finding of a trend toward increased DOPA in the cocaine-exposed infants in our pilot study.

The mechanism for increased plasma NE after prenatal cocaine exposure remains unknown. Fetal effects of maternal cocaine use may be mediated by indirect or direct mechanisms.²⁰ The indirect effects of cocaine on the fetus may arise from cocaine-induced maternal uterine vasoconstriction, decreased uterine blood flow, impaired placental oxygen and nutrient transfer, and intrauterine growth retardation. The stress of chronic in utero hypoxemia may lead to a persistent increase in catecholamine release by the fetal sympathetic nervous system. In an animal model, intrauterine growth retardation produced by restriction of uterine blood flow increased newborn basal adrenal catecholamine synthesis and release, although basal plasma NE levels were not affected.²¹

Direct effects of cocaine on the sympathetic and/or central nervous systems may also be responsible for the elevation in plasma NE. Levels of plasma cholinesterase, which inactivates cocaine, are relatively deficient in pregnant women and the fetus.²² Elevated plasma NE in the infant may represent a prolonged peripheral noradrenergic response to residual cocaine remaining in the infant. Alternatively, chronic exposure of central catecholamine systems to cocaine may lead to down-regulation of these systems, including those that regulate peripheral sympathetic tone and NE release. In adult animal studies, chronic cocaine exposure has been shown to lead to depletion of presynaptic DA stores and reduced neurotransmitter release in the central nervous system.²³⁻²⁵ In studies of newborn animals exposed to cocaine in utero, some reports have demonstrated down-regulation of central dopaminergic systems^{10,26} although others have not.²⁷ Cocaine-exposed human neonates have been shown to have decreased cerebrospinal fluid concentrations of homovanillic acid, the principal metabolite of DA, suggesting reduced central dopaminergic activity.¹² If central dopaminergic systems that

inhibit sympathetic outflow are down-regulated, increased sympathetic tone and circulating NE could result. Studies in rats have identified a descending dopaminergic pathway from the caudal diencephalon to the spinal cord.²⁸ Some of the fibers from this pathway terminate in the intermediolateral cell columns, where sympathetic preganglionic neurons are located. Recent research indicates that DA can act spinally to inhibit sympathetic outflow, thereby producing bradycardia and hypotension.²⁹ Reduced central nervous system dopaminergic activity could therefore produce increased sympathetic outflow and increased circulating NE.

Our data suggest that sympathetic nervous system tone is increased in some cocaine-exposed newborns and infants. Van de Bor and colleagues^{4,30} have demonstrated decreases in cardiac output and stroke volume and increases in arterial blood pressure and cerebral blood flow velocity on day 1, but not day 2, of life in cocaine-exposed newborns. The hemodynamic differences observed on day 1 of life are consistent with increased circulating NE but were transient in nature, disappearing by day 2. Elevations in plasma NE appear to persist much longer. The infants in our study were sampled between 24 and 72 hours of life, and Ward et al¹⁹ documented increased circulating NE in infants between 1 and 3 months of age. One explanation for the discrepancy between the brief duration of the hemodynamic evidence of increased sympathetic tone and the persistence of elevated plasma NE may lie with the ability of the peripheral adrenoreceptors to down-regulate in the face of elevated plasma NE. Circulating catecholamines play a major role in the cardiovascular, pulmonary, and metabolic adaptations of the fetus to extrauterine life during and after birth.³¹ All newborns have a catecholamine surge in response to the stress of labor and delivery. After birth plasma catecholamines decline rapidly and fall to the levels of supine adult resting concentrations by 12 hours.³² Prenatal cocaine exposure may result in up-regulation of NE release, resulting in an excessive catecholamine surge in response to birth and a persistent increase in basal plasma NE. Excessive NE release in response to labor and delivery may be a significant factor in the increased incidence of ultrasonographic lesions consistent with intracranial hemorrhage in cocaine-exposed newborns.³³ Down-regulation by peripheral adrenoreceptors during the first days of life may result in a gradual return to normal physiological manifestations of sympathetic tone despite the persistent elevation of plasma NE.

In our study, prenatal marijuana exposure was also associated with increased circulating NE. We know of no previous data describing the impact of prenatal marijuana exposure on plasma catecholamines in the human newborn. However, definitive conclusions cannot be drawn from our data. Meconium assay for marijuana is not as reliable as for cocaine.¹⁷ Our study population included only eight infants known to be exposed to marijuana, and all but one were also exposed to cocaine. There are animal data that support our observation. Exposure of adult rats to δ -9-tetrahydrocannabinol, the active ingredient of marijuana, has been shown to affect plasma and adrenal medullary NE concentrations, although both were decreased as opposed to the increase in plasma NE seen in our infants.^{34,35} Marijuana may also have an impact on central nervous system catecholamines. One recent hypothesis for the mechanism of action of THC proposes that THC acts indirectly to block DA reuptake in those reward or pleasure areas of the brain where other drugs of abuse are thought to act.³⁶ Several studies of adult animals show changes in catecholamine concentration and activity in specific brain loci associated with cannabinoid exposure^{37–39} although at least one study shows no effect.⁴⁰ Prenatal exposure of mice to cannabinoids has been shown to alter brain catecholamine concentration and binding.^{41–43} Although these animal studies demonstrate that both prenatal and postnatal marijuana exposure can influence catecholamine functioning, further human studies are needed to confirm the present finding of a relationship between maternal marijuana use and increased plasma NE concentrations.

Among the cocaine-exposed infants, plasma NE concentration correlated with increased score on the NBAS depressed cluster and decreased score on the NBAS orientation cluster in at 2 to

3 days of life but not at 2 weeks. Adult studies have demonstrated increased concentrations of NE and its metabolites in plasma and cerebrospinal fluid associated with depressive symptoms, including apathy and sleep disorders.⁴⁴ Stress-induced activation of noradrenergic systems in association with depressive behavior has been demonstrated in the rat.⁴⁵ The relationship between the newborn behaviors measured by the depressed cluster of the NBAS, including decreased activity, arousal and orientation, and circulating NE may be analogous to those seen in these adult and animal studies of depression. The lack of a similar relationship in the unexposed infants argues against this analogy, suggesting that NE may be serving as a marker for increased stress, increased cocaine exposure, and/or biological susceptibility.

There are several limitations of our study. Although larger than our pilot study, the sample size is too small to allow conclusive evaluation of potential confounding variables. The lack of a larger population of infants exposed to marijuana but not cocaine makes it impossible to determine if prenatal marijuana exposure has an independent effect on plasma NE. We did not measure physiological parameters of sympathetic tone, such as cardiac output or heart rate variability, preventing definitive conclusions concerning the physiological impact of our findings. Prenatal influences can produce modifications in postnatal neurotransmitter systems⁴⁶ and prenatal cocaine exposure, whether through direct or indirect effects, could have profound consequences on subsequent function of catecholamine systems. Without long-term follow-up, the implications of our findings regarding long-term behavioral and cognitive effects of cocaine use remain speculative.

In summary, we have demonstrated a relationship between prenatal cocaine and marijuana exposure and increased plasma NE, suggesting that maternal cocaine and marijuana use may result in elevated sympathetic tone in the newborn. Among cocaine-exposed newborns, there was a relationship between increased plasma NE and greater depression of behavior and poorer orientation at 1 to 3 days of life but not at 2 weeks. These behavioral characteristics of cocaine-exposed infants may make them difficult interactive partners and disrupt attentional processes associated with learning.⁴⁷ Larger, longitudinal studies are needed to delineate the long-term implications of these findings.

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ABBREVIATIONS

DA	dopamine
NE	norepinephrine
DOPA	dihydroxyphenylalanine
NBAS	Neonatal Behavioral Assessment Scale

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TABLE 1

Comparison of Characteristics of Cocaine-exposed and Cocaine-unexposed Mother-Infant Pairs*

	Cocaine-exposed (n = 24)	Cocaine-unexposed (n = 22)	P
Maternal age (yr)	27.6 ± 4.9	24.9 ± 4.1	0.058
Ethnicity			
African-American/Caribbean	20	20	
White/Hispanic/Other	4	2	0.667
Education (yr completed)	10.9 ± 1.5	11.9 ± 2.4	0.085
Parity (number primiparous)	6	10	0.146
Cesarean delivery	2	4	0.405
Sex (female/male)	11/13	11/11	0.777
Weight, g	2982 ± 335	3422 ± 497	0.001
Gestational age, wk	39.9 ± 1.4	40.3 ± 1.2	0.247
Length, cm	47.7 ± 2.1	49.1 ± 4.1	0.141
Head circumference, cm	33.5 ± 1.1	35.6 ± 3.6	0.011
Average daily number of cigarettes during pregnancy	6.6 (0–64.5)	0.26 (0–15)	0.001
Average daily number of ounces of alcohol (last 30 days of pregnancy)	0.4 (0–10)	0	0.023
Marijuana use during pregnancy (number of users)	7	1	0.049

* Results are given as arithmetic means ± SD except for ethnicity, parity, cesarean delivery, sex, and marijuana use, which are presented as counts, and cigarette and alcohol use, which are presented as geometric untransformed means followed by the range in parentheses.

TABLE 2

Comparison of Circulating Catecholamine Concentrations in Cocaine-exposed and Cocaine-unexposed (Control) Newborns*

Catecholamine	Cocaine-exposed (n = 24)	Cocaine-unexposed (n = 22)	<i>P</i>
Norepinephrine, pg/mL	923 (325–2523)	667 (276–4237)	0.03
Epinephrine, pg/mL	77 (13–413)	51 (6–179)	0.14
Dopamine, pg/mL	48 (17–118)	52 (8–194)	0.74
Dihydroxyphenylalanine, ng/mL	8.5 (3.4–18.2)	8.6 (3.8–13.7)	0.98

* Results are given as geometric untransformed means followed by the range in parentheses. *P* values from *t* tests on log-transformed data.