

Brain Proton Magnetic Resonance Spectroscopy and Imaging in Children Exposed to Cocaine in Utero

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ABSTRACT. *Objective.* The effects of prenatal cocaine exposure have been examined using neurobehavioral and brain structural evaluations; however, no study has examined the effects of prenatal cocaine on brain metabolism. Proton magnetic resonance spectroscopy (¹H-MRS) is a noninvasive method to examine the biochemistry of various brain regions. The purpose of this study was to examine the possible neurotoxic effects of prenatal cocaine exposure on the developing brain using ¹H-MRS.

Methods. Cocaine-exposed children ($n = 14$) and age-matched unexposed control participants ($n = 12$) were evaluated with MRI and localized ¹H-MRS. Metabolite concentrations of *N*-acetyl-containing compounds (NA), total creatine (Cr), choline-containing compounds, myoinositol, and glutamate + glutamine were measured in the frontal white matter and striatum.

Results. Despite an absence of structural abnormalities in either group, children exposed to cocaine in utero had significantly higher Cr (+13%) in the frontal white matter. NA, primarily a measure of *N*-acetyl aspartate and neuronal content, was normal in both regions examined by ¹H-MRS. Normal NA suggests no significant neuronal loss or damage in the 2 brain regions examined in children exposed to cocaine prenatally.

Conclusions. Consistent with findings in abstinent adult cocaine users, we found increased Cr in the frontal white matter, with normal NA in children exposed to cocaine. These findings suggest the need to investigate further possible abnormalities of energy metabolism in the brain of children exposed to cocaine in utero. In addition, this study demonstrates the feasibility of using ¹H-MRS to investigate the effects of prenatal drug exposure on the developing brain. *Pediatrics* 2001;107:227–231; cocaine, prenatal, brain, spectroscopy.

ABBREVIATIONS. MRI, magnetic resonance imaging; ¹H-MRS, proton magnetic resonance spectroscopy; NA, *N*-acetyl-containing compounds; MI, myoinositol; Cr, creatine; CHO, choline-containing compounds; GLX, glutamate + glutamine.

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Received for publication May 15, 2000; accepted Sep 26, 2000.

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Neuroimaging studies in children have yielded conflicting information regarding the effects of prenatal cocaine exposure on the developing central nervous system. Retrospective reports in children exposed to cocaine have suggested an increased incidence of periventricular hemorrhage^{1–3} and subependymal and periventricular cysts.⁴ However, prospective controlled trials have failed to find an association between in utero cocaine exposure and abnormalities on cranial ultrasound.^{5,6} More recently, a study demonstrated a positive correlation between the dosage of cocaine exposure and the incidence of subependymal hemorrhage.⁷ In addition to the conflicting neurosonographic data regarding brain structural abnormalities with cocaine exposure, the requirement for an acoustic window such as a fontanelle precludes the use of neurosonography past infancy. Computed tomography and magnetic resonance imaging (MRI) reports have found occasional structural abnormalities including cortical infarction,⁸ pachygyria,⁹ and schizencephaly.¹⁰ To date, no neuroimaging study has addressed the potential microscopic/biochemical damage to the normal appearing central nervous system when the developing human brain is exposed to cocaine.

Proton magnetic resonance spectroscopy (¹H-MRS) is a magnetic resonance-based technique that offers the opportunity to evaluate several markers of neuronal and glial integrity in targeted brain regions. ¹H-MRS is well-suited for studying children because it does not require ionizing radiation and has been used to study both normal brain development^{11,12} and a variety of brain injuries and diseases in children, including lead intoxication.^{13–16} To our knowledge, ¹H-MRS has not been used to study children exposed to cocaine antenatally. ¹H-MRS studies in adult cocaine users suggest that cocaine may result in metabolic abnormalities in the setting of relatively normal structural MRI. To determine whether neuronal loss, cell membrane injury, or ischemic changes are detectable in children exposed to cocaine prenatally, we evaluated a small group of children exposed to cocaine in utero and a control participant population using quantitative measures of MRI and in vivo ¹H-MRS.

METHODS

Participants

Study participants included children (14 cocaine-exposed and 12 unexposed) with a history of cocaine exposure in utero and a

healthy control group of children without a history of drug exposure. Participants were recruited from the same population of predominately lower and middle socioeconomic urban residents. An informed consent, approved by our institutional review board, was obtained from the parent or the legal guardian for each of the 26 children. Exclusion criteria for the cocaine-exposed children included: 1) infantile gestation age ≤ 36 weeks; 2) diagnosis of developmental delay or seizure disorders; 3) the presence of implanted metallic objects; 4) significant maternal illnesses (eg, human immunodeficiency virus-positive, sickle cell disease, mental retardation); and 5) maternal history of illicit drug use except cocaine. Exclusion criteria for the unexposed children included 1 to 5 and any exposure to illicit drugs during gestation.

Children were included in the exposed group only if the mother was cocaine-dependent by *Diagnostic and Statistical Manual, IV* criteria for at least two thirds of the pregnancy including the first trimester. The majority of children were recruited from the greater Los Angeles area from a state-funded drug treatment program on the Harbor-University of California, Los Angeles Medical Center campus. Drug-using women are referred from many local area hospitals and community clinics to this drug treatment program.

Each child received an MRI scan and localized ^1H -MRS. Chloral hydrate and benadryl was required for sedation during the magnetic resonance studies in one cocaine-exposed child and none of the unexposed children.

MRI

The MRI studies were performed on a clinical 1.5 Tesla General Electric scanner. The MRI began with a sagittal T_1 -weighted localizer (echo time/relaxation time = 11/500 ms, 4-mm slice thickness, 1-mm gap, 24-cm field of view), followed by a coronal fast double spin echo (echo time₁/Echo time₂/relaxation time = 17/102/4000 ms, 5-mm slice thickness, no gap, 24-cm field of view). Next, an axial fast inversion recovery scan was performed (echo time/inversion time/relaxation time = 32/120/4000 ms, 3.5-mm slice thickness, no gap, 24-cm field of view). This inversion recovery sequence yields excellent contrast between the signal intensities from white matter, gray matter, and cerebrospinal fluid and was used for morphometric analysis.

Localized ^1H -MRS

After the structural MRI, spectroscopy locations were prescribed from the coronal images. Based on our preliminary ^1H -MRS findings in adult cocaine¹⁷ and methamphetamine¹⁸ abusers, right prefrontal white matter and right striatal voxels were chosen (see Fig 1). Voxel sizes ranged between 3 and 5 mL. After optimizing the magnetic field homogeneity (shimming) and water suppression, data were acquired using a double spin echo sequence, point resolved spectroscopy, with an echo time of 30 ms, a relaxation time of 3 s, 128 averages, 2-K acquisition size and 2.5-kHz bandwidth. For absolute quantitation, we measured the T_2 decay of the fully relaxed unsuppressed water signal at 10 different echo times using point resolved spectroscopy.¹⁹ This

allows determination of absolute metabolite concentrations corrected for the partial volume of cerebrospinal fluid.

The spectra and water measurements were transferred to a SPARC 2 workstation, where a semiautomatic program (written in SA/GE from General Electric) was used to determine metabolite concentrations. The spectra were corrected for residual eddy-currents, zero-filled to 8 K, apodized with a 1-Hz exponential, Fourier transformed, and manually phase-corrected. Next, spectra were zero-order baseline corrected using a narrow range at 2.75 ppm and, independently, a wider range below 0 ppm as baseline. Peak areas of *N*-acetyl-containing compounds (NA), myoinositol (MI), creatine (Cr), choline-compounds (CHO), and glutamate + glutamine (GLX; possibly γ -amino butyric acid) were determined using both automatic integration and fitting a Lorentzian. The resulting peak areas were referenced to the result of the compartmentation measurements (T_2 decay of the water signal at 10 different echo times) to determine the absolute concentrations. This quantitation protocol yields interindividual variations of $\sim 10\%$ for the major peaks.¹⁹ Although our primary aim is the measurement of metabolite concentrations, we also determined metabolite ratios using CR as an internal standard.

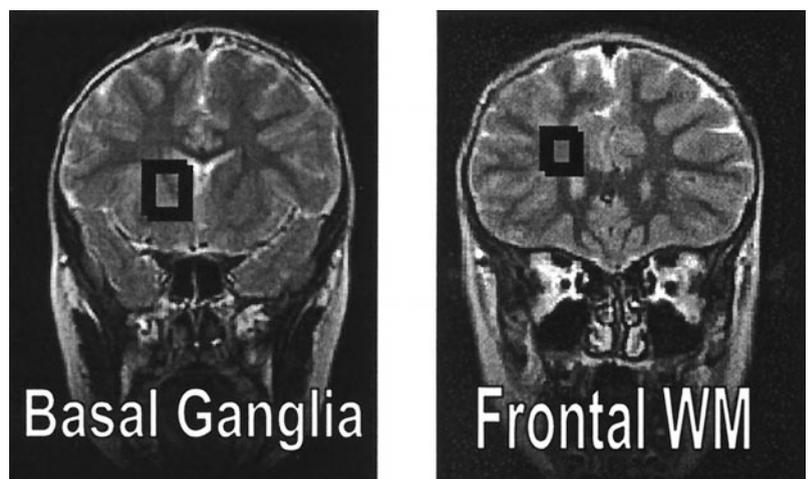
MRI Morphometry

MRIs were transferred to a DEC-ALPHA (Digital Equipment Corporation, Maynard, MA) workstation. Using an MRI segmentation program developed at our laboratory, the inversion recovery scans were processed automatically to segment the brain from the surrounding brain structures (skull, muscle, skin, etc).²⁰ From the extracted brain, the global brain volume and global cerebrospinal fluid volume were determined automatically. Right- and left-brain regions of interest including the midbrain, thalamus, globus pallidus, caudate, putamen, cerebellar hemispheres, and hippocampus were manually outlined on each slice. Because of the potential for bias, volumetrics were performed by an examiner blinded to the drug exposure status of the participants. For each brain region, the area was multiplied by section thickness to determine the volume. The volumes from all slices containing the same region were summed to yield the total volume of each region. The intrasubject region of interest measurements, drawn by the same observer 2 weeks apart, show high reproducibility ($r = .98$).²¹

Statistics

Statistical analyses were performed using StatView (Abacus Concepts, Inc, Berkeley, CA). Analysis of covariance was performed to evaluate the effect of cocaine exposure status, covaried for age and gender, on brain metabolite concentrations and metabolite ratios in both the frontal white matter and the basal ganglia of these children. All values are reported as means and standard error of the mean. In all analyses, *P* values below .05 were considered statistically significant.

Fig 1. Coronal MRI showing the typical locations of the MRS voxels: right basal ganglia and right frontal white matter.



RESULTS

All children completed the MRI and $^1\text{H-MRS}$ studies. The ethnicity of the groups (cocaine-exposed vs unexposed, respectively) were as follows: white (43% vs 30%), Hispanic (14% vs 47%), and black (43% vs 33%). Of the 14 drug-exposed children ($8.1 \pm .8$ years; 57% male), all were exposed to cocaine throughout pregnancy. An exact quantitation of the daily cocaine use was not available for the children. In addition, 11 were also exposed to nicotine and alcohol daily during all 3 trimesters. None of the children studied were previously diagnosed with or exhibited physical characteristics of fetal alcohol syndrome. Because some of the children studied were adopted through the foster care system, a quantitative nicotine and alcohol exposure history was unavailable for every study participant. Of the 8 children in whom quantitative information was available, the mean daily maternal cigarette usage was $16 \pm 8/\text{day}$ and the mean ounces of absolute alcohol consumed was $.5 \pm .8/\text{day}$.

One of the 12 control children ($9.1 \pm .9$ years; 50% male) was exposed to nicotine during pregnancy. No prenatal alcohol exposure was reported in the control group. Except for one child in the control group and one child in the cocaine-exposed group, all children were right-handed.

Structural MRI and Volumetrics

All cocaine-exposed and comparison participants had normal MRI scans on visual inspection by a board-certified neuroradiologist (I.W.). Two of the cocaine-exposed participants had minimally dilated perivascular spaces but no structural abnormalities were noted in any participant. The results of the volumetric measurements, performed by an investigator blinded to the drug-exposed status, are shown in Table 1. There was a trend toward decreased right and left midbrain volumes in the cocaine-exposed children, but there were no significant differences in brain volume for any of the other regions evaluated.

$^1\text{H-MRS}$ representative spectra from the right frontal white matter of a cocaine-exposed child (right) and from an unexposed matched control participant are shown in Fig 2. In the cocaine-exposed children, the Cr was significantly increased in the white matter of the frontal lobe compared with the control participants (+13%; $P = .03$; Table 2). The MI, CHO, and

NA were not different from the control children in the frontal white matter. There were no differences in any of the metabolite concentrations or ratios in the striatum, except for a trend for decreased CHO/Cr in the frontal white matter (-16% ; $P = .07$). No differences in the biochemical spectra were noted in the one child sedated with chloral hydrate relative to the other cocaine-exposed children.

Linear regression of NA on age in all children demonstrated an increase with age in the frontal white matter ($P = .01$) but not in the striatum. In addition, no changes in MI, CHO, Cr, or GLX with age were noted in either brain region.

DISCUSSION

This preliminary study provides the first evidence for in vivo brain metabolite alterations in a small group of cocaine-exposed children. Consistent with findings in adult abstinent cocaine users, children exposed to cocaine in utero had increased creatine in the frontal white matter without differences in NA in the absence of any visible structural changes or atrophy on MRI. These findings suggest biochemical alterations may occur at the cellular level in response to prenatal cocaine exposure.

$^1\text{H-MRS}$ evaluates several markers of neuronal and glial integrity in targeted brain regions. NA contains primarily *N*-acetyl aspartate, which is a marker of neuronal integrity and is reduced in conditions of neuronal damage or loss.^{22,23} $^1\text{H-MRS}$ is also used to assess markers of energy metabolism Cr, neurotransmission (glutamate/glutamine and possibly γ -amino butyric acid), and glial function MI. $^1\text{H-MRS}$ studies of cocaine-dependent adults have found neurochemical abnormalities in the absence of visible or quantitative structural changes on MRI.^{17,24} Former male cocaine users had increased MI and Cr, suggestive of gliosis, in white matter compared with normal participants. A gender study of abstinent adult cocaine users also found elevated Cr and MI in both men and women but decreased NA in the frontal lobe only in the men. A more recent study also found decreased NA in the thalamus of active cocaine users.²⁵

The cause for the increased brain Cr concentration in children with cocaine exposure is unclear. The higher Cr may be secondary to glial proliferation because glial cells have higher creatine levels than neurons.²⁶ However, the concomitant increase in the

TABLE 1. Brain Region Volumes by Volumetric Assessment of Children Exposed to Prenatal Cocaine and Healthy Unexposed Controls

Brain Region	Control		Cocaine-Exposed		
	Right	Left	Right	Left	
Midbrain	$3.8 \pm .1$	$3.9 \pm .1$	$3.2 \pm .2^\dagger$	$3.4 \pm .2^*$	
Cerebellum	76.5 ± 1.9	75.4 ± 2.0	71.6 ± 1.9	72.3 ± 2.4	NS
Globus pallidus	$2.5 \pm .2$	$2.6 \pm .2$	$2.7 \pm .1$	$2.6 \pm .1$	NS
Caudate	$5.2 \pm .2$	$5.3 \pm .2$	$5.1 \pm .2$	$5.3 \pm .2$	NS
Thalamus	$8.1 \pm .4$	$7.8 \pm .4$	$8.7 \pm .3$	$8.4 \pm .5$	NS
Putamen	$6.5 \pm .3$	$6.6 \pm .3$	$6.6 \pm .2$	$6.2 \pm .3$	NS
Hippocampus	$.76 \pm .04$	$.72 \pm .06$	$.79 \pm .07$	$.80 \pm .06$	NS
Whole brain	1378 ± 47		1450 ± 43		NS

NS indicates not significant.

* $P = .06$ versus corresponding control value.

† $P = .07$ versus corresponding control value.

Fig 2. Representative proton MRS spectra from the frontal white matter region of a prenatally cocaine-exposed participant and an unexposed control participant. The prenatally exposed participant shows an increased Cr concentration compared with the control participant.

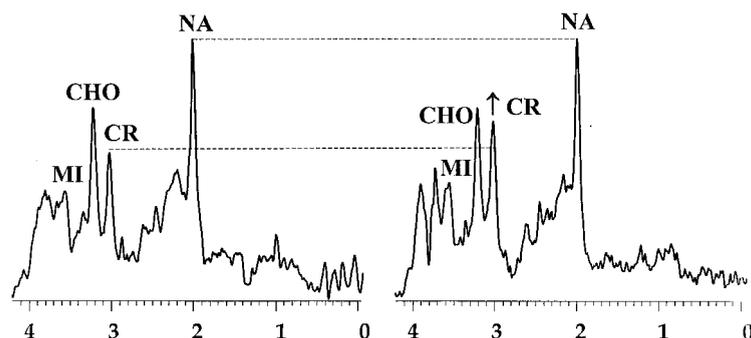


TABLE 2. Metabolite Concentrations (mmol/kg) From MRS (Mean \pm SEM)

Voxel Location	Cr	NAA	CHO	MI	GLX*	NA/Cr	CHO/Cr	MI/Cr	GLX/Cr
Frontal white matter									
Cocaine-exposed	5.65 \pm .22	6.75 \pm .24	1.51 \pm .06	5.51 \pm .25	11.9 \pm .6	1.20 \pm .04	.27 \pm .01	.97 \pm .05	7.9 \pm .9
Control	5.00 \pm .17	6.64 \pm .28	1.56 \pm .06	5.29 \pm .25	11.2 \pm .4	1.31 \pm .06	.32 \pm .02	1.07 \pm .06	8.2 \pm .8
	<i>P</i> = .03	NS	NS	NS	NS	NS	NS (<i>P</i> = .07)	NS	NS
Striatum									
Cocaine-exposed	8.27 \pm .12	7.74 \pm .19	1.91 \pm .07	5.58 \pm .21	18.6 \pm .6	.94 \pm .03	.23 \pm .01	.68 \pm .03	7.9 \pm .9
Control	8.07 \pm .20	7.50 \pm .17	1.98 \pm .08	5.40 \pm .23	18.1 \pm .3	.94 \pm .03	.25 \pm .01	.68 \pm .04	8.7 \pm .9
	NS	NS	NS	NS	NS	NS	NS	NS	NS

NS indicates not significant.

* GLX data were quantifiable in 12/14 cocaine-exposed and 12/12 of the unexposed participants. Normal GLX concentration is based on an estimated sum of glutamate and glutamine.

glial marker MI seen in the adult abstinent cocaine users is not found in these cocaine-exposed children.¹⁷ The different metabolite abnormalities in the adult cocaine users compared with the drug exposed children may reflect the different response to the drug in the adult brain compared with the immature developing brain. Alternatively, because creatine is a measure of high-energy phosphate stores, the increased Cr in the cocaine-exposed children may reflect an abnormality in energy metabolism. Consistent with our findings, phosphorus MRS studies in the brains of polydrug abusing adults have demonstrated alterations in high-energy metabolites.²⁷ In the animal model, cocaine results in decreased uterine blood flow and increased uterine vascular resistance causing fetal hypoxia.²⁸ It is possible that multiple episodes of decreased uterine blood flow to the fetus could result in an alteration in cell energy metabolism.

A second important finding of our study is a lack of decreased NA in either the frontal lobe or striatum. Because *N*-acetyl aspartate accounts for ~75% of the NA peak²³ and is found only in mature neurons, normal NA suggests normal concentrations of *N*-acetyl aspartate and a lack of significant neuronal damage in these brain regions of the cocaine-exposed children. In contrast, abstinent male adult cocaine users were found to have decreased NA in the frontal white matter, which indicated neuronal injury resulting from heavy chronic exposure to cocaine.¹⁷ The brain damage in adult cocaine users is thought to be mediated, in part, by injury to brain dopaminergic systems. Positron emission tomography and single photon emission computerized tomography studies in adult cocaine users demonstrate perfusion

and metabolic abnormalities in the dopaminergic projections areas of the brain.²⁹⁻³¹ In addition, dopamine transporter density is decreased in the striatum and prefrontal cortex on postmortem examination of cocaine addicts, which is suggestive of neuronal damage or loss.^{32,33} These differences in neuronal integrity between children and adults exposed to cocaine may be caused by several factors including possible differences in the pharmacokinetics of cocaine in these 2 groups. Second, because only 2 brain regions were evaluated in this study, it is possible that other regions, such as the thalamus,²⁵ might demonstrate biochemical evidence of neuronal damage after prenatal cocaine exposure. Furthermore, studying children during the neonatal period may demonstrate evidence of neuronal injury not found later in childhood.

Our findings of increased Cr with cocaine exposure has important implications for ¹H-MRS. Total Cr is often used as an internal standard to which the resonance intensities of metabolites are normalized. This approach is based on the assumption that total cerebral Cr remains constant even in different metabolic conditions.³⁴ However, Cr is reduced in neoplasms and degenerative brain lesions^{35,36} and elevated in various conditions including chronic cocaine abuse²⁴ and myotonic dystrophies.³⁷ This finding of a trend toward decreased CHO/Cr is caused by a higher Cr with CHO being normal in these children exposed to cocaine prenatally. Of note, no differences were noted in the biochemical spectra of the one child sedated with chloral hydrate. These findings are consistent with studies in adults noting no changes in NAA/CHO, NAA/Cr, or CHO/Cr in healthy adults secondary to barbiturate sedation.³⁸

There are limitations to the current investigation; therefore, these preliminary results should be interpreted with caution. First, our sample size is rather small; a larger study will be needed to validate these initial observations. In addition, a meconium biochemical assay was not performed to determine the amount of cocaine exposure to the children. However, the meconium assay does not provide information regarding cocaine exposure in early pregnancy, a time critical for central nervous system development.

This study is the first to demonstrate neurochemical alterations in children exposed to cocaine in utero. Consistent with previous spectroscopy findings in adults, we found increased Cr levels, but relatively normal NA in the frontal lobe of a group of cocaine-exposed children. In addition, these findings on ¹H-MRS were found in the absence of structural abnormalities, with normal brain volume, suggesting structural imaging is less sensitive than ¹H-MRS. This study suggests a possible abnormality in energy metabolism in the frontal lobe of children exposed to cocaine in utero.

ACKNOWLEDGMENTS

This study was supported in part by Grant 3 M01 RR00425-2754 from the National Institutes of Health, General Clinical Research Center Branch (to L.M.S.) and Grant 5K20-DA00280 from the National Institute on Drug Abuse (to L.C.).

We thank Diane Osborn and Dr Oliver Speck for their valuable technical input to this study.

In addition, we thank Christine Mori, Sylvia Villanueva, Sarah Harrington, Kar Lee Young, and Lorrie Horst for their contributions to the completion of these studies.

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Pediatrics 2001;107:227

DOI: 10.1542/peds.107.2.227

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American Academy of Pediatrics

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