

46. Cerebral Oxygenation and Cerebral Blood Flow during Aminophylline Treatment in Premature Newborns: Quantitative Measurement by Near Infrared Spectroscopy

Manikum Moodley, Elke H. Roland, Brian A. Lupton, Andrew MacNab, and Alan Hill, Vancouver, BC, Canada

Aminophylline is a respiratory stimulant used for treatment of apnea and to permit weaning from ventilation in premature newborns. Previous reports have indicated that it may cause cerebral vasoconstriction and reduction in cerebral blood flow (CBF). The effect of possible reduction in pCO₂ and increase in minute ventilation is not clear. It is not known whether such reduction in CBF results in significant reduction in cerebral oxygenation. The purpose of this study is to evaluate the effect of aminophylline treatment on CBF, cerebral blood volume (CBV), and cerebral oxygenation using near infrared spectroscopy (NIRS—Hamamatsu 500). The study population comprised 19 stable premature newborns (mean conceptual age 32 wk) with hyaline membrane disease. Aminophylline (6.5 mg/kg) was given intravenously prior to weaning from the ventilator. Cerebral oxyhemoglobin (HbO₂), deoxyhemoglobin (deoxyHb), and cytochrome oxidase (CtO₂) were measured using NIRS before and after aminophylline infusion. Continuous recordings of mean arterial blood pressure (MAP), tcpCO₂, and tcpO₂ were correlated with NIRS data.

after stress. Plasma CORT increased with cold stress in all age groups studied. The magnitude and time-course of plasma CORT elevation did not differ in naive or prenatally stressed rats. CRH-mRNA abundance, however, increased in 9- but not in 6-day-old rats by 4 hours after stress. These results suggest the presence of vigorous pituitary and adrenal responses to cold-separation stress in the neonatal rat. The contribution of central nervous system stimulatory input to the hormonal stress response, specifically the role of CRH, differs in neonatal and older animals.

48. Effects of Psychosocial, Acculturative, and Medical Risk Factors on Academic Achievement and Social Competence in Children and Adolescents with Epilepsy

Wendy G. Mitchell, Lawrence M. Scheier, and Sherryl A. Baker, Los Angeles, CA, and Philadelphia, PA

Children and adolescents with epilepsy frequently do poorly academically and socially. Studies of psychosocial functioning in epilepsy often draw subjects from teaching hospitals, neglecting the importance of poverty, acculturation, and parental education on academic and social functioning. We studied psychosocial functioning and school-related outcomes longitudinally in children and adolescents with epilepsy. Baseline

Time	HbD* (HbO ₂ -deoxyHb) Median (μmol*cm)	CtO ₂ (Median) (μmol*cm)	CBF (Mean) (ml/100 g/min)	CBV (Mean) (ml/100 g)
Before aminophylline	-1.26	-14.77	15.5 (11-25)	2.1 (1.6-2.8)
After aminophylline	-5.78	+14.76	11.4 (6.7-18)	1.5 (1.1-1.9)

(*p* < 0.05) (Wilcoxon signed rank sum test).

In 15 newborns there was a marked reduction in both CBV and CBF following aminophylline infusion (Table). Changes in tcpCO₂ did not account for reduction in CBF. Despite reduction in CBF and CBV, cerebral oxygenation remained unchanged (HbD) or even improved (CtO₂) in stable premature newborns.

47. Molecular Stress Mechanisms in the Neonatal Brain Are Significantly Different than Those of the Mature Central Nervous System

Sujin Yi and Tallie Z. Baram, Los Angeles, CA

The neonatal hypothalamic-pituitary-adrenal axis response to stress has been considered immature ("stress hyporesponsive period"). More recently, the relative contributions of corticotropin-releasing hormone (CRH) and vasopressin to stress-induced surges of plasma adrenocorticotrophic hormone (ACTH) and corticosterone (CORT) have been debated. Further, such neonatal stress response may depend on previous pre- or postnatal stress. We studied the effect of cold-separation stress on CRH-mRNA abundance in the hypothalamic paraventricular nucleus, and on plasma CORT and ACTH levels. Two- to 13-day-old rats, born in our facility or exposed prenatally to transportation stress, were subjected to cold-separation for 20 to 60 minutes. Plasma CORT and ACTH were measured before and at several time-points after the exposure, in comparison to "stress-free" littermates. CRH-mRNA abundance was determined 4 and 28 hours

data included sociodemographic characteristics and measures of medical and social psychosocial risk, life events, and family environment. Previously we reported cross-sectional association between home environment, parental education, and academic underachievement, while epilepsy-related factors were not significantly related to achievement (Mitchell et al, *J Child Neurol* 1991;6:65-72). Currently, at 2-year follow-up, we reevaluated academic achievement and social functioning, using the Peabody Individual Achievement Tests, the Achenbach Child Behavior Checklist, and a teacher questionnaire assessing the child's relationships with peers. Using multivariate path analysis, we hypothesized that even after controlling for the influence of intelligence quotient (IQ), psychosocial and medical risk factors would decrease academic and social performance. Using confirmatory factor analysis, baseline measures were conceptually organized into 3 latent factors (sociocultural risk, seizure risk, and behavior problems) and outcome data into 2 (academic achievement and social skills). Single indicators of IQ and life events were included at baseline, and a measure of teacher-rated peer relationships at outcome. We used structural equation modeling to examine longitudinal effects of baseline factors on outcomes. After controlling for baseline associations, sociocultural risk and seizure risk decreased academic achievement (*b* = -0.58, *p* < 0.001 and *b* = -0.32, *p* < 0.05, respectively). As expected, IQ had a strong influence on academic achievement (*b* = 0.48, *p* < 0.001) and social skills (*b* = 0.41, *p* < 0.05). Baseline behavior problems

adversely influenced social skills ($b = -0.74, p < 0.01$). Seizure risk decreased teacher-rated peer relationships ($b = -0.32, p < 0.05$), but not parent-rated social skills. Life events had no effect on any outcome. While sociocultural risk decreased academic achievement, it had no influence on social skills or teacher-rated peer relationships. The overall model had excellent fit, with CFI = 0.92. Overall, the study reinforces the importance of including sociocultural factors in addition to medical risk factors in understanding the psychosocial effects of epilepsy in children and adolescents. Epilepsy interacts with factors in the child's family and social environment in affecting social functioning and academic achievement.

49. Neurological Outcome in Children Exposed in Utero to Cocaine: Children Who Outgrow Cerebral Palsy

Claudia A. Chiriboga, Martha Vibbert, Renée Malouf, Marisol Suarez, Elaine Abrams, Margaret Heagarty, John C. M. Brust, and W. Allen Hauser, New York, NY

To determine whether prenatal cocaine exposure has a long-term adverse effect on neurological function and development, we prospectively evaluated 62 children up to 24 months of age. The sample was drawn from a cohort at risk for perinatal human immunodeficiency virus (HIV) infection, mostly because of maternal drug abuse, in whom results of urine toxicology at birth were known. Infants were evaluated at 6-month intervals by examiners blinded to drug exposure and HIV status. A positive urine toxicology at birth defined cocaine-exposure in 25 infants. Sixty-two children were assessed at 6 months, 57 at 12 months, 46 at 18 months, and 28 at 24 months. Cocaine exposure was not associated with withdrawal syndrome at birth. At the 6-month evaluation, 14 of 25 (56%) cocaine-exposed children exhibited hypertonia compared to 10 of 37 (27%) cocaine-unexposed infants ($\chi^2, p = 0.02$). HIV infection at 6 months was not associated with hypertonia. Cocaine exposure remained significantly associated with hypertonia after adjusting for gestational age and methadone exposure with logistic regression (β odds ratio = 1.9, $p = 0.04$). Hypertonia in both groups was consistent with cerebral palsy; among cocaine-exposed 6-month-old infants, spastic tetraparesis was diagnosed in 10 children, spastic diparesis in 2, and spastic hemiparesis in 2. In 36% (5/14) of affected infants, hypertonia resolved by 12 months of age and in 92% (12/13) by 24 months. Upper-extremity hypertonia abated first; lower-extremity hypertonia remained in some children up to age 18 months. Findings failed to resolve by 12 months of age in 1 child with spastic hemiparesis and by 24 months in 1 child with spastic diparesis. Rates of hypertonia diminished over time in both groups (exposed and unexposed): 40% (10/25) versus 10% (4/32) at 12 months, 18% (4/22) versus 4% (1/24) at 18 months, and 7% (1/15) versus 0% (0/13) at 24 months. Underestimation of cocaine-exposure by urine toxicology among our control group may have contributed to their high rates of hypertonia. There were no differences in mental or motor development scores between cocaine-exposed and unexposed infants at any age interval. Prenatal cocaine exposure is associated with hypertonia during infancy independently of opiate exposure. Such cocaine-induced effects are symmetrical and transient; the majority of exposed children outgrow hypertonia by 24 months of life. There is no evidence of a cocaine-related withdrawal syndrome.

50. Neurological and Ophthalmological Findings in Asymptomatic Infants with Gestational Cocaine Exposure

J. C. Partridge, C. Tsay, W. V. Goode, and D. M. Ferriero, San Francisco, CA

Infants exposed to cocaine during gestation are at higher risk for neurological sequelae and developmental delay. Whether asymptomatic neonates have similarly increased risks is unknown. To investigate the outcome of the asymptomatic cocaine-exposed infant, a prospective study of all cocaine-exposed, well infants born at the University of California-San Francisco was initiated. Proof of gestational exposure to cocaine was obtained from either maternal or neonatal urine and a neonatal plasma cocaine level was drawn. All infants had a detailed physical and neurological examination, Neurologic and Adaptive Capacity score (NACS), funduscopic examination by a pediatric ophthalmologist, and an electroencephalogram (EEG). Additionally, 5 infants have had magnetic resonance imaging (MRI) of the brain in the first 6 months of life. Of the 26 infants enrolled in the neonatal period, 9 were female, 17 male; 4 were white, 17 black, 2 Hispanic, 2 of mixed ethnicity, and 1 unknown. None of the infants had an Apgar score < 7 at 5 minutes. Mean gestational age was 39.3 weeks (± 2.4 wk). Mean birth weight was 2,957 grams (± 455 g), mean head circumference was 33.5 centimeters (± 1.7 cm). Mean NACS was 28.6 (± 4.6). Nine infants had normal neurological examinations; the remaining 17 had neurological abnormalities such as hypertonia, hypotonia, or tremulousness. Of the 24 EEGs done, 22 were normal, 1 was abnormal. Of 18 funduscopic examinations, 7 were normal, and 11 showed either retinal hemorrhages or palpebral edema. Of the 5 MRI scans, 2 demonstrated delayed myelination, 4 were normal. Congenital anomalies were not noted; however, the mean birth weight and mean head circumference were below norms for our nursery. Additionally, 2 infants were microcephalic, 1 had dysmorphic facies, and 1 had bilateral supernumerary nipples. Neurological findings were more subtle than in previous reports, and were limited to hypertonia, early hypotonia, and tremulousness. In contrast, ophthalmological examination demonstrated frequent but subtle signs of fetal cocaine exposure, including 1 infant with a significant refractive error. The asymptomatic, well infant exposed to cocaine during gestation appears to have subtle manifestation of toxic, or perhaps neuropathic, exposure. Subsequent follow-up studies in these infants will determine if these findings regress or are markers for subsequent neurodevelopmental delay or visual deficits.

51. Alternate Mechanisms for Cerebral Vasoconstriction due to Cocaine and Its Major Metabolite, Benzoyllecgonine

Richard J. Konkol, Peter A. Keller, and Jane A. Madden, Portland, OR, and Milwaukee, WI

Newborns and adults exposed to cocaine may experience ischemic events. In vitro studies suggest that vascular constriction induced by the major, long-lasting cocaine metabolite, benzoyllecgonine (BE) is greater than that due to cocaine (Life Sciences 1990;47:1109-1114). The present study was designed to investigate mechanisms underlying the vasoconstrictor activity of these 2 substances. Approximately 8-mm segments of cat middle cerebral artery with tied off side branches were mounted on glass cannulas in a chamber containing warmed, oxygenated physiological saline solution (PSS). The lumen of the vessels was filled with PSS at 100