Drug Effects: A Search for Outcomes

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INTRODUCTION

The National Institute on Drug Abuse (NIDA) Technical Review that generated this monograph represents ongoing support to advance investi-gations regarding prenatal drug exposure. Previous research conferences that focused on defining the independent variable led to studies establishing the importance of the use of biological markers to more accurately identify prenatal drug use. Other issues, such as measuring and controlling appro-priate confounding variables and identifying nonbiased samples, continue to be refined in the present studies and further increase the validity of results. Identification of dose and timing remain underinvestigated in part because of the difficulty in conducting such studies in humans. The chap-ters presented in this monograph summarize the current status of findings, identify methodologic problems, and recommend fruitful avenues of future research while emphasizing the importance of selecting specific behavioral outcome measures so as not to miss adverse consequences of prenatal cocaine exposure.

SUMMARY OF PRESENT FINDINGS

Animal Studies

The chapters by Riley, Spear, and Vorhees provide important information and perspective on the present status of findings from animal studies on developmental, behavioral, and learning outcomes. Vorhees makes an important contribution by systematically reviewing the experimental animal literature on the effects of prenatal and/or early postnatal exposure to cocaine, covering studies published from 1982 to mid-1993 (Vorhees, this volume). Of the 24 behavioral teratologic studies, 15 reported finding cocainerelated effects. However, Vorhees cautions that this rate of 62percent positive studies may overstate the apparent strength of the finding, since for every report of positive findings, there were many (or in some cases, more) negative findings. Vorhees concludes that findings of an adverse

effect of prenatal cocaine exposure are inconsistent and prevent firm conclusions from being drawn at this time.

Vorhees (this volume) also provides an important critique of the study methodologies. Methodological problems that may have obscured more consistent adverse effects of prenatal cocaine exposure are as follows:

(1) Lack of consistent use of nutritionally matched pair-fed controls. This is especially important since cocaine induces anorexia and therefore suppresses food consumption and weight gain.

(2) Lack of control for the potential of maternal carryover effects since drug use may affect mothering.

(3) Limitation of studies to one species: rats.

(4) Exposure consisting only of a single daily dose of cocaine. This is theoretically important since cocaine has a short biological half-life, and preliminary data suggest it is an important consideration.

(5) Limitation to subcutaneous route of administration.

(6) Limitation of exposure to the whole pregnancy instead of discrete exposure intervals.

Riley (this volume) came to a similar conclusion on the research findings, stating that prenatal cocaine exposure does not appear to have "wide- ranging effects." However, this conclusion was qualified by Riley's citing the theoretical perspective and preliminary data by Spear that is described in more detail elsewhere (Spear, this volume). Spear hypothesizes that neural reorganization due to prenatal cocaine exposure may result in a decreased adaptability that may not be evident under basal, nondrug, minimal stress, low-distraction testing conditions. Spear's preliminary data support adverse effects in response to pharmacological and social stresses. Thus, studies that do not use a stress or challenge paradigm may miss important consequences of prenatal cocaine exposure. Interestingly, Hans' discussion of human studies offers a similar perspective in stating that the field of human behavioral teratology is moving beyond questions of inde-pendent effects of prenatal cocaine exposure to examining the conditions under which the adverse effects of prenatal cocaine exposure might be identified (Hans, this volume). Thus, two

important and prominent researchers, one in animal investigations and the other in human investigations, come to a similar perspective.

Human Studies

Although the earliest reports suggested the existence of dramatically disturbed newborn behavior associated with prenatal cocaine exposure, an overview of studies that used the Brazelton Neonatal Behavior Assessment Scale (BNBAS) fails to show any consistent pattern of effects (table 1). Where Chasnoff's studies showed deficits in orientation, motor and state control, and reflexes (Chasnoff et al. 1985, 1989), Eisen found only deficient habituation (Eisen et al. 1991), Neuspiel found abnormal motor develop-ment (Neuspiel et al. 1990), and Coles found differences in autonomic control and reflexes (Coles et al. 1992). Most recently, Mayes and colleagues (1993) have replicated Eisen's finding of decreased habituation as the sole correlate in the newborn period.

The inconsistency of these data makes conclusions regarding cocaine's behavioral teratogenicity difficult. If there is any agreement in these data, it might be in the early impairment of habituation. Decreased habituation in cocaine-exposed newborns most likely reflects an inability to dampen sensory input and control arousal. A related phenomenon might be the finding of augmented reactivity in cocaine-exposed infants to a controlled eye-blink stimulus (a glabellar tap), with or without a 90 decibel (dB) tone (Anday et al. 1989).

Mayes' preliminary data show infants beyond the newborn period may continue to have difficulty regulating arousal (Mayes, this volume). Cocaine-exposed infants became fussy and irritable early in the habituation procedure when presented with the first novel stimuli. When the infants were focused or able to attend, there were no differences in measures of habituation. Habituation in newborns is qualitatively different from habituation in later infancy, which, as Mayes points out, is thought to be associated with information processing. Thus, if the infant is able to maintain an alert, oriented state, there do not appear to be any differences in early information processing between drug-exposed and nondrug-exposed groups. However, difficulty in regulating arousal prevents cocaine-exposed infants' opportunities to take in and process information or function adaptively in selected situations. The author's clinical experience supports this observation. Cocaine-exposed infants appear to function normally in low-stress situations but show increased arousal and disorganization related

TABLE 1. Cocaine effects on Brazelton Neonatal Behavioral Assessment Scale (BNBAS) scores in term infants not exposed to opiates.

	Habituation	Orientation	Motor	State Range	State Regulation	Autonomic Regulation	Abnormal Reflexes
Chasnoff 1989 N = 79	0	+	+	0	+	0	+
Eisen 1991 N = 52	+	0	0	0	0	0	0
Neuspiel 1990 N = 111	0	0	+*	0	0	0	0
Coles 1992 N = 107	0	0	0	0	+**	+**	0
Mayes 1993 N = 86	+	0	0	0	0	0	0

KEY: + = less optimal scores in cocaine exposed; 0 = no difference between exposed and unexposed; * = only at 2 weeks of age; ** = only at 14 and 28 days.

to transitions or other stimuli. In addition, when they get upset, they appear to have difficulty self-regulating and continue to spiral out of con-trol. This observation is consistent with Spears and Hans' perspective that adverse behaviors due to prenatal cocaine exposure are contextually related.

Little is known about the development of cocaine-exposed infants beyond the neonatal period. A single study performed by nonblind examiners found that cocaine/polydrug-exposed infants scored more poorly on an assessment of motor functioning at 4 months of age than unexposed infants (Schneider and Chasnoff 1992). Subsequently, this same research group reported that cocaine-exposed infants were similar to unexposed infants on the Bayley Scales of Infant Mental Development at 24 months of age (Chasnoff et al. 1992) and on the Stanford-Binet intelligence quotient (IQ) test at 36 months of age (Azuma and Chasnoff 1993).

However, using path analysis with the data collected at 36 months, drug exposure (defined as cigarettes, alcohol, marijuana, with or without cocaine) was directly and indirectly associated with measurements on the Stanford-Binet IQ test. The indirect effects were mediated through head circumference at 3 years of age, the home environment, and perseverance at tasks. The only other longitudinal investigation of cocaine-exposed infants also included exposure to phencyclidine (PCP). Infants in this study showed deficits in unstructured play at 18 months and high rates of insecure, disorganized attachment (Rodning et al. 1991, 1993).

BIOLOGIC BASIS FOR CHOOSING OUTCOME MEASURES

Clinical impressions and preliminary data such as those by Mayes (this volume) suggest that cocaine-exposed infants and children are different. The findings from studies of prenatal exposure to methadone and mari-juana are summarized by Hans (this volume) and Fried (this volume), who emphasize that assessments limited to global developmental functioning potentially underestimate the effects of prenatal drug exposure on specific neurodevelopmental or neurobehavioral functions. Traditional clinical developmental outcome measures—the Bayley Scales and even the BNBAS—have not shown robust effects of prenatal exposure. The neuro-physiologic correlates of prenatal cocaine exposure provide a theoretical basis for choosing more selective outcome measures. Autonomic nervous system (ANS) dysfunction is thought to be associated with regulatory dis-orders of attention, arousal, and the ability to deal with complex environ-mental inputs necessary for learning and adaptive social interactions. Neurophysiological concepts can contribute to clinical research by selecting specific outcomes to measure. For example, deficient control of autonomic regulation and arousal may underlie observed hyper- or hyposensitivity to stimuli and the resulting learning and behavior problems.

Cocaine blocks the reuptake of norepinephrine, epinephrine, and dopamine at the presynaptic membrane. This results in a magnification of activity of these agents at the postsynaptic membrane, leading to behaviors such as increased motor activity, increased vigilance, euphoria, and physiologic responses such as increased heart rate and increased blood pressure. Three studies in humans have been published so far that have directly measured neurochemical changes associated with prenatal cocaine exposure.

One study reported levels of venous norepinephrine 1.8-fold higher in 22 infants exposed to cocaine compared with 15 age-matched controls (Ward et al. 1991). The samples were obtained at approximately 2 months of age. Venous epinephrine and dopamine did not differ between groups, nor did measures of alpha and beta receptor binding on peripheral blood components. No attempt was made to separate out the effects of cocaine from that of other drugs of abuse. Birthweight was not controlled, although this differed significantly, with a high predominance (27percent) of low birthweight (< 2500 grams (g)) among exposed infants. Elevated plasma norepinephrine was interpreted as possibly reflecting increased sympathetic tone.

Circulating catecholamines were measured in a small pilot study by Mirochnick and colleagues (1991). In 12 infants known to be cocaine exposed, with negative histories and toxicology screens for opiates or other illicit drugs, the mean concentration of dihydroxyphenylalanine was increased nearly two-fold (10.3 versus 5.9, $p = 0.055$). Dopamine and norepinephrine were not different between groups. Norepinephrine, however, was negatively correlated with the orientation cluster on the BNBAS. Other chemicals measured were not significantly related to behavior. As with the previous study, the potential confounding effect of gestational age and intrauterine growth were not controlled, due to small sample size. Samples were obtained at 24 to 48 hours postpartum, when acute effects of recent cocaine exposure might still be operative in some children.

Studies of peripheral catecholamine levels provide data that are several steps removed from the area of greatest interest, the central nervous system (CNS). In order to obtain more proximal information about CNS function-ing, monoamine precursors and metabolites in the cerebrospinal fluid of infants exposed to cocaine were assessed (Needlman et al. 1993). The major finding was lower homovanillic acid (HVA) among cocaine-exposed infants. Other substances—tyrosine, tryptophan, 3-methoxy-4-hydroxy-phenyl-glycol (MHPG), and 5-hydroxyindole acetic acid (5-HIAA)—did not differ between groups. The association between cocaine and lower HVA remained significant after removing from the analysis mothers who used other substances including cigarettes and other potentially confounding factors. Interpretation of this finding is difficult because of the small sample size and because of the uncertain relationship between spinal fluid levels of neurotransmitters or metabolites and actual alterations in structure or function in the brain. For example, decreased levels of HVA could be due to decreased global production or decreased

production only in specific brain regions. Despite these limitations, these findings provide the most direct look at neurochemical changes associated with prenatal cocaine exposure in humans.

In the fetal brain, neurotransmitters contribute to brain development by influencing neuronal migration and differentiation, synaptic proliferation (Lauder 1988), and receptor number (Miller and Friedhoff 1988). Cocaine readily crosses the placenta as well as the blood-brain barrier. Brain concentrations of cocaine have been reported as high as four times that of plasma levels (Farrar and Kearns 1989). Thus, cocaine may affect the development of brain structure, especially in areas of the brain that have a higher concentration of dopamine. When cocaine was injected into pregnant rats or directly into rat fetuses on day 20 of gestation, the dopamine receptors in the suprachiasmatic nuclei (SCN) were most affected, with little effect elsewhere in the fetal brain and in the maternal SCN (Weaver et al. 1992). Since the SCN contributes to circadian functioning, prenatal cocaine exposure at a specific time might lead to selected behavioral and/or endocrine changes associated with perturba-tions of circadian rhythm. Cocaine has also been shown to deplete dopamine in the corpus striatum (Weese-Mayer et al. 1993). Since the corpus striatum is linked to the prefrontal lobe, executive functions such as behavioral flexibility, planning, and self-monitoring may be affected and therefore need to be assessed.

Two studies looking at physiological functions in human newborns that may be related to CNS dopaminergic or ANS functioning support this approach. Evaluation of cry data suggests the existence of two distinct types of infant behavioral response (Lester et al. 1991). Another study has found an elevated sensitivity to sugar: Cocaine-exposed infants sucked less on the pacifier and more on a sweetened pacifier than did controls, suggesting a possible difference in CNS reward circuitry (Maone et al. 1992)

Outcome Measures

Outcome measures need to include tasks that assess regulation of arousal and attention as well as frontal lobe executive functions such as planning, behavioral flexibility, and self-monitoring. Preliminary data support the need for such assessments. Performance on the continuous performance test (CPT) (a computer-administered measure of sustained attention) has been shown to be more sensitive than IQ scores or caretaker reports to the effects of prenatal exposure to cigarettes and polychlorinate biphenyl (PCB) on sustained

attention, speech processing, and impulsivity (Jacobson et al. 1992; Streissguth et al. 1984, 1986). In the face of finding no impact of prenatal marijuana exposure on cognitive and language scores, Fried (this volume) found that an increase in omission errors, especially at the end of a vigilance task, may reflect a deficit in sustained attention in early school-aged children. Children prenatally exposed to marijuana were also rated as more impulsive and hyperactive by their mothers. Hans (this volume) also identified attention deficits in children prenatally exposed to methadone.

Importance of Longitudinal Followup

Failure to find strong cocaine effects on infant developmental tests after the neonatal period does not obviate the need for evaluation of cocaine-exposed children at later ages (Hans, this volume). Findings from followup of other perinatal insults support this recommendation. Effects of prenatal marijuana exposure were noted at birth and again at age 48months, with no effects on interim developmental test scores at 12 and 24months (Fried and Watkinson 1990). Low birthweight children found to have learning disabilities at school-age frequently perform in the normal range during infancy (Hunt et al. 1982). Furthermore, the manner in which an early biological insult is expressed may change over time. Among low birthweight infants, delayed motor function at 1 year of age significantly predicted lower IQ, expressive language delay, and articulation deficits at age 3 years (Ross et al. 1985).

Some domains are difficult to assess during infancy due to limitations in an infant's response capacities, the lack of suitable assessment tools, or the immaturity (i.e., developmental unavailability) of higher order skills. Children's performance on tasks purported to assess prefrontal functions (e.g., selective attention, organization, sensory-motor integration) under-goes substantial changes with maturation. Potential developmental deficits in areas such as social competence with peers, complex language, and sustained attention may not be evident until the social/cognitive demands of school entry.

Hans (this volume) further emphasizes the potential importance to follow children through adolescence and even young adulthood because some CNS-related disorders usually do not appear until this time. Other problems such as drug use and abuse need a specific social context to occur. Whether children exposed to drugs prenatally have a greater susceptibility to later drug abuse or addiction has important clinical and public policy implications.

SUMMARY

In order to best understand the developmental and behavioral effects of prenatal cocaine exposure, two important activities must occur. The first is the continuing development and refinement of research methodologies. Information-sharing activities such as conferences support this goal. Second, agencies such as NIDA need to support longitudinal followup of prenatally drug-exposed child cohorts and controls to identify outcomes beyond infancy and toddler years. Without support for information exchange and longitudinal followup, researchers will still be in the dark regarding the effects of prenatal drug exposure on school functioning when the next drug epidemic occurs. This message was not heeded in the 1970s and early 1980s, leaving researchers in the 1990s in the uncomfort-able position of saying they do not know the longer term effects of prenatal drug exposure.

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