Third Pathophysiology of Prenatal Cocaine Exposure

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Abstract
The pathophysiology of the effects of cocaine on fetal development has been described along 2 major pathways: neurochemical effects and vasoconstrictive effects. Following a summary of these effects, we suggest a ‘third pathophysiology’ in which altered fetal programming affects the acute and long-term adverse effects of in utero cocaine exposure. We describe how cocaine as a stressor alters the expression of key candidate genes, increasing exposure to catecholamines and fetal cortisol-altering neuroendocrine (hypothalamic-pituitary-adrenal axis) activity, leading to infant behavioral dysregulation, poor behavioral control and emotion regulation during childhood and phenotypes that confer vulnerability to substance use in adolescence. This model is discussed in relation to follow-up studies of the effects of in utero cocaine exposure and maturational changes in brain development.

The First Pathophysiology: Neurochemical Mechanisms

The pathophysiology of the effects of cocaine on fetal development is most often attributed to neurochemical mechanisms. Cocaine acts primarily at the presynaptic level to block reuptake of the monoaminergic neurotransmitters dopamine, norepinephrine and serotonin [3, 4] by specific presynaptic plasma membrane transporters [5]. These transporters are expressed in discrete pathways of the central nervous system on postganglionic sympathetic neurons and in the adrenal medulla. These phar-
macologic actions lead to elevated circulating catecholamine levels and exaggerated sympathetic responses including hypertension, tachycardia, vasoconstriction, agitation, euphoria and excitation. These effects are particularly profound in the fetus, in which elevated sympathetic tone has been demonstrated [6–9]. Part of the high abuse potential of cocaine is due to increased dopaminergic activity in pathways involved in mood, pleasure and reward [10]. Tolerance is associated with escalating doses of the ingested drug. However, sensitization to the effects of repeated cocaine administration may also be seen, resulting in increased responses to equivalent doses. This is particularly true for the behavioral effects of cocaine [11, 12]. The mechanism for behavioral sensitization is due to an increase in extracellular neurotransmitter concentrations [12, 13], alteration in G protein-coupled neurotransmitter receptors [14] and alteration in the plasma membrane transporter expression [15, 16]. Although cocaine also interacts with other neurotransmitters (neuropeptides, GABA and glutamate receptors), less is known about these effects [17–20]. Cocaine affects neuronal formation, proliferation and early connectivity [21–23], and disrupts neuronal migration and resulting cortical architecture [24–27]. Cocaine also affects the expression of transcription factors (immediate early genes) along dopaminergic [28, 29] and serotonergic pathways [30].

It is important to note that in contrast to the effects of cocaine on the adult brain, which result in deformation of the developed brain, fetal effects are more likely to produce malformation of the developing brain, in which the brain is prevented from forming normally [31]. The effects of exposure during the first half of gestation will impact upon processes related to cytogenesis and histogenesis, whereas effects during the second half of gestation are related to brain growth and differentiation. In vitro studies of human fetal brain-derived neural precursor cells treated with cocaine showed marked inhibition of proliferation, migratory response and cell differentiation. These results point towards the existence of several molecular and cellular mechanisms triggered by exposure to cocaine that could adversely affect the fetal brain, with long-term implications.

**The Second Pathophysiology: Vasocostrictive Mechanisms**

The effects of cocaine on fetal development have also been attributed to indirect vasoconstrictive mechanisms. Physiological derangements in utero result in increased plasma catecholamine concentrations and marked secondary effects [6]. Redistribution of blood flow during fetal stress is secondary to increased sympathoadrenal system activity and results in exaggerated elevations in plasma catecholamine levels [32, 33]. This cascade of events is important in the pathophysiology of pregnancy disorders associated with placental dysfunction [34, 35], impaired placental blood flow and is a cause of intrauterine growth restriction [36–38]. This also explains the adverse effects on the fetus of uptake inhibitors, such as cocaine and amphetamines, which block catecholamine transport [6, 39]. Their effect on placental vascular function is to decrease placental blood flow, reducing the supply of oxygen and nutrients to the fetus. Fetal hypoxemia and possibly ischemic injury can compromise brain development. Blood flow to the developing brain can also be reduced by cocaine-related noradrenergic effects on the developing fetal vasculature [40, 41]. Norepinephrine, and particularly the monoamine serotonin (5-HT), exert vasoconstrictive effects on the umbilical vein; thereby, reducing blood flow from the placenta to the fetus [42, 43]. Furthermore, the vascular response to 5-HT is potentiated by uptake inhibition [44, 45]. As the umbilical cord is not innervated, the placental mechanisms for catecholamine uptake described below are protecting the umbilical-placental circulation from deleterious effects of these neurotransmitters [46, 47].

Regulation of the placental mechanisms for catecholamine uptake should not be viewed solely in the context of protecting the fetus from exaggerated elevations in catecholamines and/or serotonin. Endogenous catecholamines are critical to embryological development, fetal and neonatal growth, and survival. This conclusion is supported by studies in mice in which the gene for either tyrosine hydroxylase [48, 49] or dopamine β-hydroxylase [50, 51] has been disrupted. The majority of fetuses homozygous for the disruption of either gene die during embryonic development. 5-HT is also important at critical stages of development [52]; it is present in early embryos and has been suggested to be maternal in origin [53]. However, embryos grown in the presence of high concentrations of 5-HT or 5-HT-uptake inhibitors develop cranio-facial and cardiac abnormalities of the 3rd–5th branchial arches [54]. Similar abnormalities have been seen in mouse, rat and chick embryos [55]. Thus, there are highly regulated mechanisms controlling the concentration of intrauterine biogenic amines that are central to fetal growth and development. Maternal administration of uptake inhibitors in early to mid-gestation during placentation and embryogenesis leads to a high incidence of
fetal/placental resorption [56, 57]. In survivors, there is a significant reduction in birth weight and delay in maturational milestones (ear opening) [56]. In addition, vasoconstriction at the uteroplacental complex coupled with anorexic effects of cocaine could also explain the increase in intrauterine growth retardation in cocaine-exposed infants that we [58], as well as others, have reported. Thus, the capacity for placental biogenic amine uptake and/or transport has a significant impact on intrauterine growth and development.

The Third Pathophysiology of Cocaine: Fetal Programming

In addition to the neurochemical and vasoconstrictive effects of cocaine on fetal development described above, cocaine may also act as an intrauterine stressor that alters fetal programming. By stressor, we mean a challenge that alters the internal milieu (homeostasis) of the organism. As a result of cocaine as a stressor, the fetal-placental neuroendocrine microenvironment and the genetic programming of fetal-placental development are disrupted. Increasing evidence from preclinical, prospective clinical and epidemiological studies suggest that, at least in the case of disease, early development does have echoes throughout life [59–61]. The literature on the influence of prenatal stress on the offspring suggests that many biological factors acting during prenatal life are associated not only with the development of common adult cardiovascular and metabolic disorders, but also with neurobehavioral abnormalities [62–72] and behavioral disorders [73–76]. Originally known as the 'Barker hypothesis', these findings have given rise to the concept of 'fetal origins of adult disease' or the 'developmental origins of health and disease'. There are few settings in which gene-environment interactions are more profound, critical windows are of a narrower duration, and the latency to onset of effect is shorter than the influence of an adverse intrauterine environment on neuroendocrine and neurobehavioral functioning in the newborn. The so-called Barker hypothesis has undergone several modifications to include adaptation to the postnatal environment [60] but has not, to our knowledge, been applied to the study of the effects of in utero exposure to drugs such as cocaine. We also show the application of 'fetal origins' beyond cardiovascular and metabolic consequences to neurobehavior in the developing child.

Although original studies related low birth weight to adult disease, it is generally accepted that low birth weight per se is not at the heart of these disorders, but that there are common factors that influence intrauterine growth as well as adult physiological systems [61]. The 'fetal origins' observations are due, in part, to environmental factors acting early in life that affect developing systems, altering structure, function and probably behavioral expression. It has been suggested that the biological purpose of this 'programming' is to alter the set points or 'hard-wire' physiological systems to prepare the fetus for optimal adaptation to the postnatal environment. Responses of the fetus to an adverse intrauterine environment, such as cocaine, may be developmentally disruptive with no long-term adaptive value, although the fetus may make homeostatic adjustments that confer immediate survival advantage.

Stress hormones, such as catecholamines and glucocorticoids, can alter regulation of the neuroendocrine environment by acting on the hypothalamic-pituitary-adrenal (HPA) axis which results in an altered set point for physiologic, metabolic and behavioral outcomes [77]. Because they are an important feature of the stress response, glucocorticoids have become prominent candidates as mediators of the effects of 'programming'.

The brain is particularly sensitive to prenatal programming, including effects on the HPA axis. Pregnant dams exposed to stress show increased adrenocorticotropic hormone and CORT [61, 78, 79]. Prenatal stress also increases CORT and adrenocorticotropic hormone levels in adult offspring [60, 61, 75, 77]. The effect of prenatal stress on adult hippocampal corticosteroid receptor density [76, 80–83] may have implications for emotional reactivity. Prenatally stressed rats have a high degree of 'emotionality' [84], indicated by decreased locomotion and increased defecation [84–87]. They also show less play [88], more defensive freezing [89], less movement in an activity wheel [90] and increased vocalizations [79]. Prenatal stress affects cognitive abilities including operant discrimination [91], reversal task in a water maze [92, 93] and memory [94]. In other animal studies, maternal stress during pregnancy results in offspring that are more irritable, anxious and difficult to control [61, 95–98].

Brain neurotransmitter systems and glucocorticoids interact to modulate both behavior and HPA activity [99]. Disturbances in HPA regulation and brain monoamine levels have been associated with affective and anxiety disorders in humans [100–103]. Also, in human studies, poor health outcomes have been related to prenatal stress, including low birth weight, preterm birth and intrauterine growth retardation [104, 105]. Moderate to severe stressful life during mid-gestation was related to birth
weight and small head circumference, suggesting a specific effect on the brain [106]. Maternal first-trimester exposure to the stress of war has also been associated with an increased risk of the offspring developing schizophrenia in adult life [107]. Similar to the ‘emotionality’ reported in animal studies, human infants exposed to stress in utero show high reactivity, activity and irritability [108–110]. Psychological and behavioral abnormalities have also been reported in children exposed to prenatal stress [111–113], including learning and behavior problems [114]. The effect of prolonged exposure to chronic stress, or allostatic load [115], is the cost of wear and tear on the body produced by the repeated activation of biological stress response systems. This prolonged activation of the neuroendocrine stress axes has also been related to physical disease and behavioral disorder [116].

We suggest that stress, specifically stress-induced changes in the intrauterine environment, could lead to enduring developmental and behavioral alterations in children with prenatal drug exposure. The model that we propose (fig. 1) shows effects of an adverse intrauterine environment (cocaine) on catecholamines and glucocorticoids. As a stressor, cocaine programs the HPA axis as well as behavior due, in part, to plasticity of brain monoamine systems. Specifically, cocaine as a stressor alters the expression of key candidate genes and gene networks important to placental function in late gestation. We focus on the norepinephrine transporter (NET) [117], a steroid metabolic enzyme (11β-HSD-2) and placental gene networks.

Placental NET and 11β-HSD-2 are pivotal placental genes that program the intrauterine neuroendocrine environment during development. They protect the fetus from excess catecholamines and glucocorticoids, which have harmful effects on the fetus [118]. 11β-HSD-2 in particular converts maternal cortisol to inert cortisone protecting the developing fetus from exposure to maternal cortisol [119]. Lower placental 11β-HSD-2 activity is associated with smaller fetuses in rats [120] and humans [121–124]. Mutations of 11β-HSD-2 are also associated with low birth weight in human infants [125] and increased fetal cortisol levels are associated with intrauterine growth retardation [126]. 11β-HSD-2 modulates the programming effects of prenatal glucocorticoid exposure [127, 128]. The HPA axis is highly sensitive to the effects of glucocorticoids on perinatal programming [61, 129–131]. High levels of maternal glucocorticoids have been shown to disrupt intrauterine growth, postnatal HPA axis function and neurobehavioral outcome. Placental expression of this key enzyme is potently downregulated at the RNA, protein and functional levels by norepinephrine, which is in turn regulated by NET [132]. Downregulation of NET has been noted by ourselves and others in association with an adverse intrauterine environment,

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**Fig. 1.** Effects of in utero cocaine exposure on placental genes affecting neuroendocrine function and behavioral development.
maternal/placental disorders such as preeclampsia, and exposure to drugs including cocaine and nicotine [133, 134]. Reduced placental NET expression from cocaine exposure may lead to increased circulating catecholamines, downregulation of 11β-HSD-2 and chronic fetal hypercortisolism, leading to altered neuroendocrine (HPA axis) activity and dysregulated neurobehavioral functioning. Because catecholamines are released during stress, this may be a mechanism linking prenatal stress with altered fetal development mediated by effects on 11β-HSD-2. Preliminary findings in figure 2 show decreased 11β-HSD-2 expression in mothers who used cocaine (n = 4), cigarettes (n = 4) or were depressed (n = 3) compared with 17 controls.

The altered expression of these 2 key candidate genes is likely associated with changes in networks of genes involved in critical placental functions which maintain physiological homeostasis in utero and otherwise promote intrauterine growth, development and preparation for postnatal life. Preliminary findings in figure 3 suggest that these changes in placental gene expression are associated with methylation of placental genomic DNA, particularly in promoter regions.

These findings are based on the same group of subjects with pregnancies complicated by cocaine, nicotine and depression and controls shown in figure 2. The relative incorporation of cytosine used to measure methylation was comparable in promoter and genomic DNA in the cocaine- and nicotine-exposed subjects, suggesting hypermethylation of the promoter regions of DNA that contain CpG islands. This hypermethylation of DNA suggests gene silencing related to in utero cocaine and/or nicotine exposure. Inheritance or persistence of these epigenetic modifications is referred to as epigenetic reprogramming. There is significant interest in modifications of DNA as one of the ways that ‘adaptation to the environment’ takes place mechanistically. Complex processes such as the development of memory are now being attributed to chromatin remodeling, epigenetic modifications of DNA and lasting alterations in gene expression [135]. Drugs of abuse induce ‘adaptations’ in brain regions. This may occur through alterations in gene expression, altered chromatin remodeling, as well as alterations in the number and projections of neurons in specific regions. Recently, cocaine was shown to induce neuroadaptations through altered gene expression [136]. Histone modifications of the c-fos promoter were seen in the striatum following short-term exposure to cocaine. This change was not permanent. In contrast, chronic cocaine administration was associated with alterations in the BDNF and Cdk5 promoters [136]. It is becoming widely accepted that chromatin remodeling is an important regulatory mechanism underlying gene-environment interactions, learning and drug-induced neural and behavioral plasticity. Increased methylation of the glucocorticoid receptor and altered salivary cortisol responses to a stress paradigm has been seen following prenatal exposure to increased third-trimester maternal depressed/anxious mood [137]. Similar alterations in DNA methylation and histone acetylation are seen following intrauterine growth.
Behavioral Dysregulation

In the model (fig. 1), the term behavioral dysregulation refers to the behavioral expression of deviations from normative biological processes in adverse environments. Behavioral dysregulation can begin in utero, and is proposed to be a dynamic developmental process as alterations in the quality of the environment (prenatal and postnatal) modify behavioral expression. Behavioral dysregulation is evidenced during infancy as neurobehavioral and neuroendocrine disorganization. During childhood, indicators of behavioral dysregulation reflect a deficient capacity to control behavior and regulate emotion commensurate with situational demands that have relevance for adaptation to environmental elements and substance use in adolescents. These phenotypes are important because they appear to be prognostic indicators for substance use [139]; the earlier a drug is used, the greater the likelihood of its abuse during adolescence and adulthood [140, 141]. These phenotypes reflect major domains of psychological function, cognition, affect and behavior, and include: impulsivity, reactive aggression, sensation seeking, excessive risk taking [142, 143], irritability, negative affect, difficult temperament [144–146], conduct disorder, attention-deficit hyperactivity disorder, oppositional defiant disorder, anxiety, depression [147] and impaired executive function [148–150]. This collection of disturbances in emotion regulation and behavior control is included in the construct of neurobehavioral disinhibition, and is thought to reflect disturbances in the prefrontal cortex [151] as well as other brain regions.

Disruption of neuroendocrine homeostasis in utero by cocaine can be observed at birth and lead to lasting behavioral dysregulation that increases vulnerability to substance use resulting in early-onset substance use in adolescents. The understanding that addiction is a developmental disease means that it is critical to consider the influence of specific developmental periods [152]. In addition to fetal development, we know that brain development continues well beyond childhood and adolescence [153, 154]. The ‘immaturity’ or abnormal development of the adolescent brain may be related to risk taking behavior including substance use.

Extensive maturational changes that occur in brain development in adolescence may confer vulnerability to substance use through disruption to the HPA system [155, 156]. Maturation of high-order association cortices, including changes in the prefrontal cortex, occurs later than low-order sensory cortices during late adolescence [157]. The frontal cortex has been shown to be disrupted in youths at high risk of substance use onset in neurophysiological [158, 159] and functional neuroimaging (fMRI) [160] studies. These high-risk youths show deficits in affect modulation, behavior control and executive function processes thought to reflect a neuromaturational disturbance subserved by neural systems in the anterior cerebral cortex [142, 161–163]. Stress reactivity is related to pubertal development and brain regions such as the hippocampus, prefrontal cortex and amygdala that are highly sensitive to stress hormones and regulate emotionality, and continue to mature during the peripubertal period [164]. Glucocorticoid receptors are present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus and parahippocampal gyrus) and cortical structures, and, within cortical regions, the prefrontal cortex demonstrates preferential expression of glucocorticoid receptors [99, 165–167]. The distribution of glucocorticoid receptors in the primate brain are more closely related to the human brain in terms of neocortical development [168, 169], and nonhuman primate studies suggest that the behavioral effects of prenatal cocaine exposure may not be manifested until later in development [170, 171]. Chronic exposure to stress or allostatic load leads to atrophy and impaired neuronal function in the hippocampus and medial prefrontal cortex [172–174], regions that are responsible for executive function and adaptation to stress. Cocaine-related ‘fetal programming’ could have long-term effects on HPA axis activity, resulting in a physiological endophenotype of cortisol reactivity that could be a harbinger of substance use.

Understanding Other Findings

This view of cocaine as affecting fetal programming is different from the teratological view of cocaine as a toxin. There is a substantial literature on the effects of cortisol on children [175], including a few findings on infants with prenatal cocaine exposure [176–178]. The view of cocaine-induced effects as ‘reprogramming’ that alters
the developmental plan may be useful for understanding the contemporary literature on the effects of prenatal cocaine exposure on behavioral development in children. Preclinical studies suggest effects of prenatal cocaine exposure on the developing monoaminergic system, resulting in both structural and functional changes to circuitry subserving functions such as arousal, regulation and reactivity [179, 180]. Human infant studies show similar, although more generalized cocaine effects. We have shown effects of prenatal cocaine exposure on arousal, hypertonicity and excitability, and acoustic cry characteristics [181], auditory brain response [182], motor development [183], parenting stress [184], mother-infant interaction [185] and attachment [182, 186]. Others have reported difficulties in arousal regulation, greater excitability, poor state regulation, more rapid changes in arousal with stimulation, and increased arousal from sleep and physiological lability [187–193]. Cocaine-exposed infants have shown altered salivary cortisol in response to noninvasive (neurobehavioral exam) and invasive (heel stick) challenges [176], as well as decreased salivary cortisol levels at baseline compared to controls [177]. An additional study showed higher urinary cortisol levels in premature cocaine-exposed infants [178]. Alterations in HPA stress responses may be a mechanism/marker underlying long-term behavioral and emotional disorders [194, 195].

Follow-Up Studies
Follow-up studies of children with prenatal cocaine exposure include children through age 15 years. Cocaine-exposed children show deficits in intelligence [196–201], language [200, 202–206] and component academic skills, including poor sustained attention, visual-motor integration and visuospatial memory, more disorganization, impairment in procedural learning and less abstract thinking [196, 198, 207–213]. They are at risk of developing a learning disability [214], and more likely to be referred for special education services in school by age 7 years [215]. Problem behavior as well as externalizing and internalizing behaviors have been reported in cocaine-exposed children up to 7 years [211, 212, 216–219]. Effects on impulse control and attention were reported in 10-year-olds [220]. Although these effects are not consistent across studies [221–223], there is mounting evidence relating in utero cocaine exposure to phenotypes implicated in substance use. There are a few quantitative neuroimaging studies using diffusion tensor imaging [224], volumetric MRI [225–227], fMRI [228, 229], cerebral blood flow [230] and magnetic resonance spectroscopy [231] that are starting to show findings related to prenatal cocaine exposure that support long-term effects on brain structure and function.

It has been well documented that the effects of prenatal cocaine exposure need to be understood in the context of the interaction(s) between drug exposure, windows of vulnerability and the environment [200, 232, 233]. A number of reviews have described inconsistencies in these findings [200, 233] thought to be due to methodological confounding of cocaine exposure with exposure to other drugs, lack of biochemical verification for exposure status and levels and lack of adequate control for demographic variables (such as prenatal care, SES and out-of-home placement). Another possibility is that there may be inconsistencies in the findings because different pathophysologies could result in different behavioral outcomes. Findings of an altered cortisol response to stimulation in cocaine-exposed infants [176–178], although limited, are consistent with our model that glucocorticoid-mediated (HPA) activation may be altered by in utero cocaine exposure, and could suggest specific neurobehavioral endophenotypes associated with this particular pathway in infants that would help interpret findings in the literature.

No doubt our model oversimplifies the human situation and describes one of many pathways that may be involved. Women who use cocaine during pregnancy typically use other substances [234], and we have not addressed the issue of polydrug use. However, the view of cocaine as a stressor could suggest that polydrug exposure be studied as cumulative stress. The model could have wider applicability and generalize to other substances including illicit (methamphetamine, heroine, marijuana) and legal (tobacco, alcohol) drugs of abuse, abuse of prescription medication (e.g. OxyContin, Vicodin) and psychotropic medication such as SSRI taken during pregnancy for the treatment of depression. The model may also be relevant beyond just drug effects to other perinatal stressors. Poor nutrition in these women is an additional important factor that can cause fetal growth restriction, in addition to the placental vascular mechanisms described above. Factors such as poverty, domestic violence and comorbid psychopathology, all of which have been documented in these women, may also affect fetal development. Again these factors could suggest the applicability of cumulative stress models.

Finally, the model may also be relevant for other outcomes, including obesity. Compulsive disorders such as drug addiction, obesity and gambling have been described as part of a ‘reward deficiency syndrome’ [235].

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Obese individuals show reduced brain dopamine D₂ availability [236] raising the interesting possibility that drug addiction and pathological eating could represent 2 forms of compulsive behavior as a means to compensate for decreased activation of dopamine circuits. Prenatal cocaine exposure could also lead to compulsive behavior and obesity through this neurochemical pathway (our first pathophysiology of cocaine) by which prenatal cocaine exposure could lead to compulsive behavior which in turn leads to obesity. Our ‘cocaine stress’ model suggests that neuroendocrine changes in the intrauterine environment could also lead to compulsive behavior and obesity. In addition, the idea that neuroendocrine mechanisms are related to physiological and metabolic changes that lead to the fetal origins of adult disease [61] suggests a direct effect between prenatal cocaine exposure and obesity. Some support for this comes from our work showing that prenatal cocaine exposure was related to higher body mass index (BMI) at 9 years of age [237]. Higher BMI was also related to higher blood pressure in these children, suggesting that the effects of cocaine on blood pressure are mediated through BMI.

The cascade of events that initiates the repeated activation of biological stress-response systems or allostatic load [116] begins as fetal reprogramming of the neuroendocrine system due to drugs and other intrauterine stressors, leading to infant behavioral dysregulation and poor behavioral control and emotion regulation during childhood. The toll that allostatic load takes on the HPA system further affects the vulnerable adolescent brain and leads to phenotypes that confer vulnerability to substance use in adolescence.

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