Fetal/ Neonatal Effects of Psychotropic Drugs

Pediatrics Department
Maria Teresa Ambat, MD
Botagoz A Hyams, MD PGY-2
December 2009
Introduction

• Drug abuse in pregnancy and neonatal psychomotor behavior consistent with withdrawal from opiate and polydrug withdrawal is currently a significant clinical and social problem.

• Approximately 3% of the 4.1 million women of child-bearing age who abuse drugs are believed to continue drug use during pregnancy.

• Behavioral teratology expanded the field of teratology to examine behavioral effects in the neonate caused by acute exposure to substances in utero, including environmental, nutritional, and drug exposures.

• True understanding of a developing system can occur with the study of its organization of form, structure and includes examination of the mutual influences of genes, physiology, and behavior.
Objectives

• Describe the effects of three drugs with similar molecular targets that involve monoaminergic transmitter systems
  – Cocaine and methamphetamine (MA)
  – Selective serotonin reuptake inhibitors (SSRIs)

• Discuss the mechanisms of action of each drug, including a possible common epigenetic mechanism for their effects on the developing child
Development of Human Embryo

- Central nervous system (CNS) insult related to the period during gestation of the exposure often result in prevention of normal formation of various brain areas

- First half of gestation impact processes related to cytogenesis and histogenesis
- Second half of gestation relate to brain growth and differentiation
Fetal Programming

- Progressive events (neuroblast proliferation and migration, axonal projection, and synaptogenesis) and regressive events (programmed cell death and selective elimination of processes) affect the maturation of brain circuitry.

  - Toxic influences during this period may dramatically alter brain development.

  - May also alter the regressive events that underlie the capacity of the developing brain to compensate for injury.
Programmed Organization
In the 1980s, cocaine became one of the most frequently abused illicit drugs during Pregnancy.

Cocaine affects neuronal formation, proliferation, and early connectivity, and disrupts neuronal migration and resulting cortical architecture.

Concern remains about more subtle effects that may affect development, particularly in childhood and adolescence.
Cocaine acts primarily at the presynaptic level to block reuptake of the monoaminergic neurotransmitters dopamine, norepinephrine, and serotonin.
Neurochemical Effects

- Monoamine neurotransmitter receptors (NA, 5-HT, and dopamine) are present early in corticogenesis and plays a key role in brain development
  
  - Areas highly expressing these neurotransmitter systems may be especially susceptible to elevated synaptic monoamine neurotransmitter levels secondary to cocaine’s main effect of blocking catecholamine reuptake at the presynaptic level
  
  - Prenatal cocaine increase monoamine neurotransmitters may alter normal mechanisms that modulate neuronal growth results in an altered set-point for physiologic, metabolic, and behavioral outcomes
Vasoconstriction at the uteroplacental complex coupled with anorexic effects of cocaine could explain the intrauterine growth retardation.
Vasoconstrictive Effects

- Vasoconstrictive effects lead to neurologic complications (infarct, IVH, cystic lesions)
- Higher incidence of prematurity, LBW, abruptio placenta
- Higher incidence of genitourinary tract and gastrointestinal anomalies (gastrochisis, ilial atresia)
- Increased rate of limb reduction defects
- Dysgenesis of corpus callosum
- Short and/or long term neurobehavioral abnormality
Epigenetic changes in phenotype (appearance) or gene expression without changes in the underlying DNA sequence
Epigenetic Effects

• Non-genetic factors cause the organism's genes to behave (or "express themselves") differently. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations.

• Decreased placental NET expression was associated with orthostatic intolerance later
Epigenetic Effects

- Cocaine affects the expression of transcription factors (immediate early genes) along dopaminergic and serotonergic pathway

- Two key genes important to placental function that maintain physiologic homeostasis and promote preparation for postnatal life

- NET and a steroid metabolic enzyme 11b-HSD-2 protect the fetus from excess catecholamines and glucocorticoids, which have harmful effects on the fetus

- 11b-HSD-2 converts maternal cortisol to inert cortisone, protecting the developing fetus from exposure to maternal cortisol
Epigenetic Effects

• Downregulation of norepinephrine transporter (NET) leads to increased circulating catecholamines → cause downregulation of 11b-hydroxysteroid dehydrogenase-2 (11b-HSD-2), and chronic fetal hypercortisolism

• Increase of norepinephrine levels in the placental microenvironment → alters the hypothalamic-pituitary-adrenal axis

• These changes in placental gene expression are associated with methylation of placental genomic DNA, particularly in promoter regions of DNA that contain CpG islands
Mean 11b-HSD-2 expression in risk groups
Hypermethylation of DNA in placentas from cocaine/nicotine exposed.
Neurobehavioral Dysregulation

• Brown University Study
• Behavioral antecedents of prenatal cocaine exposed infants starting in the neonatal period up to age 7

  – Problem with arousal, higher reactivity and stress: irritable, demanding infants at 1 month

  – Predicts difficult temperament at 4 month: poorly consoled, markedly increased appetite and decreased sleep requirements

  – Associated with more behavior problems (externalizing and internalizing) at ages 3 and 7 on CBCL
Cocaine Effects

• Structural and functional changes to circuitry subserving functions such as arousal, hypertonicity and excitability, acoustic cry characteristics, *regulation and reactivity changes* and auditory brain response

• Differences in the right inferior frontal cortex and caudate during response inhibition
  - Suggesting decrease in the regulation of attention and response inhibition: increased distractibility, and consequent impaired attention to novel, structured tasks
  - Affects executive function and long-term behavior problems
  - More likely referred for special education services
Executive Functions

• Organizational and planning abilities
• Working memory
• Inhibition and impulse control
• Self-reflection and self-monitoring
• Time management and prioritizing
• Understanding complex or abstract concepts
• Using new strategies
METHAMPHETAMINE

• MA is the dominant drug problem in the Western and Midwestern portions of the United States, second only to alcohol and marijuana

• The number of adults age 12 and over who have tried MA once in their lifetime has increased to 5.3% in 2007 from 4.3% in 1999 and 2.5% in 1997

• MA is the growing drug of choice for adults in the United States, including pregnant women

• Weight control may also help explain the popularity of MA with women
METHAMPHETAMINE
METHAMPHETAMINE

- Closely related chemically to amphetamine, but the CNS effects are greater. Additional methyl radical.
  - These structural characteristics account for the wide distribution and long duration of action of amphetamine

- Amphetamines are considered noncatecholamine sympathomimetics because they lack catecholamine structure yet have sympathomimetic actions
  - By releasing norepinephrine, dopamine and serotonin, blocking monoamine reuptake mechanisms, and inhibiting monoamine oxidase
The Mechanism of Action
METHAMPHETAMINE

• Neurotoxic to mature dopaminergic and serotonergic axons and axon terminal arbors, and potentially neurotoxic to mature glutaminergic axons

• Induces the production of reactive oxygen species and nitric oxide, p53 activation resulting in apoptosis, and mitochondrial dysfunction
Metamphetamine

Eroding the Mind
Researchers have mapped brain decay caused by methamphetamine use. The damage affected memory, emotion and reward systems.

Average difference in brain tissue volume of methamphetamine users, as compared with non-users:

Source: Dr. Paul Thompson, U.C.L.A.
METHAMPHETAMINE

• Early and widespread influence of serotonergic, dopaminergic, and glutaminergic systems on neuronal growth and connectivity \( \rightarrow \) may result in alterations in developing neural circuitry, monoaminergic system

• Decreases uteroplacental blood flow \( \rightarrow \) causes fetal hypoxia

• Has anorexic effects on the mother. Infants born at term, are more likely to be small for gestational age.
METHAMPHETAMINE

- MA $\rightarrow$ placental NET downregulation $\rightarrow$ could lead to increases in circulating catecholamines, downregulation of 11b-HSD-2, and chronic fetal hypercortisolism which could affect behavior
  - Through alteration of the hypothalamic-pituitary-adrenal axis, especially arousal regulation, physiologic stress and attention
Effects on Neonate

• Direct effect: such as cleft lip, heart defects, spina bifida, club foot

• Indirect pathway that results in neurobehavioral dysregulation:
  – Ear-piercing cry, inconsolable for long periods, increased motor activity, problem with coordinating the suck-swallow-breathe process

• Increase risk for SIDS
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

• Each year at least 600,000 infants born in the United States are exposed to maternal major depressive disorder during gestation

• Pharmacologic treatment of major depressive disorder during pregnancy remains the most common form of treatment

• Maternal major depressive disorder is associated with newborn medical and neurobehavioral deficits and long-term emotional, behavioral, and social problems in the child.
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- SSRIs block the presynaptic reuptake of serotonin (5-HT) by binding to the serotonin transporter (SERT).

- Some of the SSRIs also bind to NET.
  - SERT and NET are responsible for the reuptake and transport of 5-HT and norepinephrine out of the synapse.
  - Inhibition of SERT and NET activity by SSRIs prolongs neurotransmitter signaling

- Serotonin causes vasoconstriction and a transient decrease in uterine artery blood flow

- Fluoxetine has also recently been found to antagonize 5-HT2c receptors
SSRI

Blockade of Serotonin Reuptake by Fluoxetine

Serotonin is deactivated in the synapse by reuptake into the presynaptic neuron.

Prozac blocks the uptake of serotonin, thus increasing the activation of serotonin receptors.
Dorsal raphe nucleus
Serotonergic system
Serotonin

- 5-HT is present in early embryos and has been suggested to be maternal in origin
- Serotonin acts as a growth factor during embryogenesis
- Mouse embryos grown in the presence of high concentrations of 5-HT or serotonin uptake inhibitors develop craniofacial and cardiac abnormalities of the 3rd to 5th brachial arches
- Highly regulated mechanisms control the concentration are central to fetal growth and development
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

• The serotonergic system
  – Develops early in gestation and is likely to be influenced by serotonin levels in all trimesters of pregnancy
  – The role of the serotonergic system in the neuroplastic events that create, repair, and degenerate the brain
  – Critical to the development of neurobehavioral systems involved in mood, anxiety, aggression, and substance abuse

• Alterations in the serotonergic system during development → changes in somatosensory processing, motor output, and emotional responses
SSRI Exposure

- Increased risk of spontaneous abortion, lower birth weight, younger gestational age at birth, and lower Apgar scores

- Neonate irritability, tremors, jitteriness, trouble feeding, agitation, respiratory distress, and poor sleep

- Infants exposed to SSRIs during the last trimester of pregnancy may exhibit neonatal adaptation syndrome.

- “Poor neonatal adaptation,” which included poor motor tone, hypothermia, hypoglycemia, weak or absent cry, convulsions, abnormal posturing, and shivering
SSRI Exposure

• Neonates who are exposed to SSRIs (eg, fluoxetine, paroxetine, sertraline, citalopram) medications during gestation → increased risk of neonatal abstinence syndrome.

  – Manifested as CNS (eg, irritability, seizures), motor (eg, agitation, tremors), respiratory (eg, increased respiratory rate, nasal congestion), and GI signs (eg, emesis, diarrhea)

  – These manifestations are self-limiting and usually disappear by age 2 weeks.
Neurobehavioral Observation

• Fetal actocardiography with ultrasound

• The fetal neurobehavior coding system is a method of fetal neurobehavioral observation and scoring that includes measurement of fetal heart rate, motor activity, behavioral state, and responsiveness to external or extrauterine stimuli
Fetal Neurobehavioral Observation
Fetal jerky movements

![Bar chart showing mean % of movements (SE) at gestational ages 26 GA and 36 GA for NonSRI and SRI groups.](image)

**p < .01**
Fetal breathing movements

F(SRI)=2.73, p=.033 *p<.05
Placental SERT levels.

MDD Diagnosis

- MDD-NO
- MDD-YES

Mean SERT (SE)

F_{int}(1,29)=3.52, p<.071
Conclusion

• Highly regulated mechanisms control the concentration of intrauterine biogenic amines, which are critical to fetal and neonatal growth, development, and survival.

• Cocaine, MA, SSRI affect fetal development at multiple levels of the system: disruptions in fetal placental monoamine transporter expression and altered neuroendocrine, neurotransmitter system development and gene expression through epigenetic mechanisms

• Need for follow-up assessments and early intervention

• Approaches to minimize or reverse the consequences of such early life events may have therapeutic importance
References

- Cheston M Berlin, Jr: Effects of drugs on the fetus
- Amy L. Salisbury, PhDa,c,d,*, Kathryn L. Ponder, BSb,c, James F. Padbury, MDb,c, BarryM. Lester, PhDa,c,d: Fetal Effects of Psychoactive Drugs
- Barry M. Lester, PhD, Daniel M. Bagner, PhD, Jing Liu, PhD, Ronald Seifer, PhD: Infant Neurobehavioral Disregulation: Behavior Problems in Children with Prenatal Substance Exposure
- McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming.
- Lester BM, LaGasse LL, Seifer R. Cocaine exposure and children: the meaning of subtle effects
- Quinton MS, Yamamoto BK. Causes and consequences of methamphetamine and MDMA toxicity
- Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine
Thank You!

Happy Holidays!!!