Neurobiological effects of prenatal alcohol exposure and stress: a potential pathway to increased vulnerability to substance use problems

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Background and hypotheses

- Children with FASD exhibit cognitive, behavioral, physical abnormalities that can last a lifetime
- “Secondary disabilities”, including mental health problems, alcohol and drug use and trouble with the law, can add challenges
- Increased prevalence of substance use/addiction problems likely influenced by genetic, neurobiological, environmental and social factors
- **Our focus:** What are the neurobiological mechanisms by which prenatal alcohol exposure influences vulnerability to addiction
Overview: What is Known

Stress

Prenatal Alcohol Exposure

Reward

Vulnerability to Addiction

Prenatal Alcohol Exposure

Prenatal Alcohol Exposure
What is stress?

- A constant factor in modern life and a frequent topic of conversation
- Stressors can be physical or psychological
- Stress can be good or bad
  
  **Good stress** – mild and short-term, exciting or novel challenge
  
  **Bad stress** – severe or chronic challenges, negative events, inability to cope – “stressed out”

Slide from Dr. Bruce McEwen
The HPA Axis and Sympathetic Nervous System act together to mediate the stress response.

(Hiller-Sturmhofel & Bartke, 1998), Alcohol Res & Health
Location of the major endocrine (hormone-producing) glands in the body

The stress system involves the hypothalamus, the pituitary and the adrenal glands
The Hypothalamic-pituitary-adrenal (HPA) or Stress Axis

Stress, circadian changes → activate HPA axis

↓

Cascade of responses

↓

Increased levels of hormones (ACTH, glucocorticoids)

↓

Feedback to reduce activity to normal - Feedback to pituitary, hypothalamus, hippocampus, PFC and other brain areas

(Hiller-Sturmhofel & Bartke, 1998)
Both natural rewards and addictive drugs influence behaviour by increasing dopamine levels in the nucleus accumbens and PFC.
Drugs of abuse and dopamine

• The DA system responds to salient stimuli – something that is pleasurable, important, worth paying attention to
• All drugs of abuse increase DA activity
• DA generally stays within the synapse for a very short time, then is removed and recycled by the cell
• Addiction $\rightarrow$ ↓ in DA receptors $\rightarrow$ natural rewards less effective
• At the same time, transporter that removes DA from synapse is altered $\rightarrow$ DA stays around longer $\rightarrow$ greater and more lasting reward, despite fewer DA receptors
• PAE also $\rightarrow$ ↓ DA receptor activity
FASD, stress, dopamine and vulnerability to addiction

- The stress system (HPA axis) and dopamine reward system are key neurobiological pathways in addiction. They interact in numerous ways.

- The stress system has a role in initial vulnerability to drugs and in vulnerability to relapse.

- Brain area that mediate stress and reward overlap to a large extent.

- Both the stress system and the reward system are altered by prenatal exposure to alcohol.
FASD, stress, dopamine and vulnerability to addiction (cont’d)

- Intimate relationship between stress system (HPA axis) and substance use:
  - Distinct alterations in HPA function with different stages of substance use problems
  - Stress can sensitize healthy individuals to rewarding effects of drugs and can induce relapse after abstinence
    - ↑ stress responsiveness → ↑ propensity for drug self-administration
    - Repeated injections of stress hormones → drug self-administration occurs at a lower dose of drug
Alterations in stress response correspond with stage of substance use

<table>
<thead>
<tr>
<th>Stage of Use</th>
<th>HPA activity</th>
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<tbody>
<tr>
<td>Acute</td>
<td>↑</td>
</tr>
<tr>
<td>Dependence</td>
<td>↓</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>↑</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Returns to baseline</td>
</tr>
<tr>
<td>Abstinence</td>
<td>Failure of HPA recovery correlated with ↑ risk for relapse</td>
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Possible pathophysiological mechanisms mediating the effects of stress on drug intake

From: Piazza & Le Moal
TiPS, 1998
Current Research

Do prenatal alcohol and stress interact to increase vulnerability to addiction?

• **Objective 1:** Examine the effects of prenatal alcohol exposure and stress in adulthood on the HPA axis and the reward system in males and females
  – Neurobiological mechanisms underlying interactions between these systems and expression of related behaviours

• **Objective 2:** Examine behavioral and HPA cross-sensitization between amphetamine and stress, as a marker of vulnerability to addiction in males and females
Cross-sensitization: Stress and AMPH

- Bidirectional:
  - Previous exposure to a psychostimulant drug (AMPH) can sensitize the behavioral response to that drug and to another drug or to stress.
Sensitization:
A behavioural marker of neurobiological vulnerability or resilience to addiction

Some aspects of the sensitization phenomenon may represent a major component of addiction (Robinson and Berridge, 1993).

- Differences in behavioral sensitization are predictive of subsequent drug self-administration and relapse
- Once established, the sensitization of dopamine systems can be observed for months and often up to one year later in the rat.
  - Clinical implications
- Sex difference (e.g., effects of estrogen)
Present Study: Cross-sensitization between AMPH and stress in PAE males and females

- How is the interaction between stress and drug use altered by alcohol exposure *in utero*?
- Are males and females differentially affected?
Study design

Prenatal treatments

Pregnant Dams

Control (C)  Lab chow

Pair-Fed (PF)  Liquid control diet

Alcohol (PAE)  Liquid ethanol diet (36% EDC)

Offspring

C  PF  PAE

Offspring Tested in Adulthood (60 days of age)
### Experimental Groups and Subjects:

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>AMPH</th>
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</thead>
<tbody>
<tr>
<td><strong>Basal</strong></td>
<td>C</td>
<td>C</td>
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<tr>
<td></td>
<td>PF</td>
<td>PF</td>
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<tr>
<td></td>
<td>PAE</td>
<td>PAE</td>
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<tr>
<td><strong>Stress</strong></td>
<td>C</td>
<td>C</td>
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<tr>
<td></td>
<td>PF</td>
<td>PF</td>
</tr>
<tr>
<td></td>
<td>PAE</td>
<td>PAE</td>
</tr>
</tbody>
</table>

n=10 per group, males and females
Experimental Timeline:

Every other day, 16 days

Inject (1mg/kg), TEST

Inject (1mg/kg)

Inject (1mg/kg)

Inject (1mg/kg)

Inject (2mg/kg)

Inject (2mg/kg)

Inject (2mg/kg)

Inject, TEST (2mg/kg)

Inject AMPH (1mg/kg), sensitization TEST

Basal/ Stress sample following stressor

Every other day, 16 days

2 wk

5 d
Results to be shown:

• Locomotor activity on the sensitization test day
  – Animals previously exposed to AMPH or to Saline
  – 20 min pre-injection exploration → AMPH injection
  – Measure: Distance travelled, speed

• Hormone response to restraint stress in animals previously exposed to AMPH or Saline
Experimental Timeline:

- Breed, Wean
- Every other day, 16 days
  - Inject (1mg/kg), TEST
  - Inject (1mg/kg)
  - Inject (1mg/kg)
  - Inject (2mg/kg)
  - Inject (2mg/kg)
  - Inject, TEST (2mg/kg)
- Inject AMPH (1mg/kg), sensitization TEST
- Basal/ Stress sample following stressor
- 2 wk
- 5 d
DISTANCE TRAVELLED - Males

Enhanced response to AMPH challenge in Control and PF males previously treated with AMPH.

In contrast, enhanced response to AMPH in PAE males previously treated with Saline.

%change pre-to-post injection: Distance Traveled

Minutes post-injection

(Control)  (Pair-fed)  (PAE)

(%change from pre- to post-injection)
SPEED – Males
Enhanced response to AMPH challenge in Control and PF males previously exposed to AMPH
Enhanced response to AMPH in PAE males previously treated with Saline

Control

Pair-fed

PAE

Minutes post-injection

Minutes post-injection

Minutes post-injection

(%change from pre- to post-injection)
DISTANCE TRAVELLED - Females

Enhanced response to AMPH challenge in Control females previously treated with AMPH

No significant differences between AMPH and Sal groups for PF and PAE females

(%change from pre- to post- injection)
**SPEED – Females**

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 Inject (2mg/kg)
 Inject (2mg/kg)
 Inject, TEST (2mg/kg)

Inject AMPH (1mg/kg), sensitization TEST
Basal/ Stress sample following stressor

Breed, Wean

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2 wk

5 d
Increased stress hormone levels (CORT, ACTH) in AMPH-treated PAE males following subsequent stressor challenge.
Enhanced stress hormone levels (ACTH) in AMPH-treated PAE females following subsequent stressor challenge
Conclusions:

• Differential effects of prior AMPH exposure on behavioral and hormonal responses to AMPH challenge in PAE compared to control animals

• Sex differences in both AMPH sensitization and PAE effects on sensitization observed

• HPA response to stress reflects cross-sensitization between AMPH and stress in PAE but not control animals

• Altered neurobiological and neurobehavioral responsiveness induced by PAE may increase vulnerability to addiction
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