Prenatal nicotine exposure induces sex-dependent changes in dopamine pathways in adolescent brain

Frances Leslie, Ph.D.
University of California, Irvine
Brain dopamine system

- Locomotion
- Motivated behavior
- Reward
- Drug abuse

**Hypothesis**

Nicotine exposure during sensitive developmental periods induces long-term dysfunction of dopamine transmission
Two sensitive periods for maturation of dopamine systems

Maternal smoking associated with increased incidence of:
- ADHD
- Conduct disorder
- Drug abuse
- Obesity

Possible involvement of DA dysfunction?
Early appearance of functional nicotinic receptors on fetal DA neurons

Chronic gestational nicotine (GN) exposure increases fetal nicotinic receptor binding

![Graph showing %[^3]HDA release above baseline vs. log [Nicotine]](chart)

- Nic | + Nic
Gestational drug treatment and rearing

- Dam arrives (G2)
- Minipump implanted (G4)
  - saline or nicotine (3 mg/kg/day)

Graph:
- Days of Gestation
- NICOTINE (mg/kg/day)
- Pups switched to surrogate dam (P0)
- Pups weighed daily and weaned at P21
The effects of GN treatment were studied during adolescence.

- Biochemical analyses
- Behavioral effects of cocaine
Gestational nicotine (GN) decreases DAT levels in female striatum
GN treatment alters prefrontal cortex DAT and DA in a sex-dependent manner.
GN treatment alters D1 binding only in the medial globus pallidus
GN treatment does not affect D2 binding

Dorsal Caudate D2 Binding

<table>
<thead>
<tr>
<th>Sex</th>
<th>GS</th>
<th>GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

fmol/mg
GN treatment increases D3 receptor binding in both males and females.
GN increases cocaine-induced neuronal activation in nucleus accumbens

GN increases cocaine-induced neuronal activation in nucleus accumbens.
GN treatment decreases sensitivity to the rewarding effects of low dose cocaine

Cocaine 200 µg/kg/injection

- GS, NR
- GS, Reinforced
- GN, NR
- GN, Reinforced

Day 1 Day 2 Day 3 Day 4 Day 5 Day 6

# of responses
GN increases self-administration of a higher dose of cocaine

Cocaine 500 µg/kg/injection
GN increases total cocaine intake

Cocaine (mg/kg)

Coc200  Coc500

P < 0.005 ***
GN decreases cocaine-induced stereotypy
Haloperidol blocks cocaine-induced stereotypy in GS but not GN rats

**Stereotypy score**

- **sal-sal**
- **halo-sal**
- **sal-coc15**
- **halo-coc15**
- **noinj-coc15**

*p < 0.0001*
Loss of a D2 receptor mediated stereotypy in GN rats

p < 0.001
Prior stress has different effects on cocaine-induced locomotor activity in GS and GN females.
Haloperidol reverses stress-induced decrease in cocaine locomotion in GS females
Both D1 and D2 receptors mediated cocaine-induced locomotion in GN rats.
Gestational nicotine treatment results in the following changes in adolescence:

- Sex-dependent alterations in biochemical markers of DA function
- Increased threshold for cocaine self-administration, with an increase in total intake
- Complex changes in locomotor behavior
Thanks

to the Leslie Lab

and the National Institute on Drug Abuse