Prenatal Alcohol Exposure: The Role of Chemosensory Fetal Programming in Adolescent Alcohol and Nicotine Acceptance

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Alcoholism Generator

Adapted from Miller & Spear (ACER, 2006)
Flavor Perception

- odor
- taste
- oral irritation
Fetal Programming

Mennella et al. (Pediatrics, 2004)
Fetal Programming

Dominguez et al. (Alcohol, 1998)
Fetal Alcohol Exposure

Koren et al. (CMAJ, 2003)
Overarching Hypotheses

* Fetal alcohol experience alters the developmental trajectory of one or more of the neural systems involved in the preference for alcohol odor and the perception and acceptability of alcohol’s flavor.

* These changes are important contributors to the initial risk of intake and continued abuse in adolescence because “alcohol smells and tastes better”.
Fetal Programming

Maternal Treatment
- Ethanol
- Pair-Fed
- Free Choice

Youngentob et al. (Behav Neurosci, 2007a,b)
Innate Odor-Mediated Response

Youngentob (Chem Senses 2005)
1: Respiratory Frequency
2: Average Expiratory Volume
3: Average Inspiratory Volume
4: Number of Expiratory Sniffs
5: Number of Inspiratory Sniffs
6: Average Expiratory Sniff Duration
7: Average Inspiratory Sniff Duration
8: Average Expiratory Flow Rate
9: Average Inspiratory Flow Rate
10: Total Expiratory Volume
11: Total Inspiratory Volume
12: Aver. Peak Expiratory Flow Rate
13: Aver. Peak Inspiratory Flow Rate
14: Total Apneic Period (ms)

Raw Data

Youngentob (Chem Senses 2005)
Effects of Fetal Ethanol Exposure on Olfactory Functioning

Neural Response

Ethanol Intake

Youngentob et al. (Behav Neurosci, 2007a,b)
Youngentob and Glendinning (PNAS, 2009)
Ontogeny of the Odor-Mediated Effect

Eade et al. (ACER, 2010)
The “At Risk” Period of Adolescence
The Social Interaction

Observe

Demonstrator
Ethanol Re-exposure Model

No Ethanol Exposure = PF/H2O, FC/H2O
Fetal Exposure Only = ET/H20
Adolescent Exposure Only = PF/ET, FC/ET
Fetal + Adolescent Exposure = ET/ET

Eade et al. (BBF, 2009)
Adolescent Ethanol Exposure Augments the Effect of Prior Fetal Experience

Eade and Youngentob (ACER, 2010)
A Cumulative Effect

Eade et al. (BBF, 2009)
Combined fetal ethanol exposure plus adolescent odor re-exposure leads to behavioral alterations in adulthood only in females.

ET/ET = fetal ethanol animals with ethanol odor re-exposure through social transmission in adolescence.

Control/ET = pair-fed and free choice animals with ethanol odor exposure through social transmission in adolescence.

While ethanol odor-specific exposure through social interaction is important, additional factors such as the pairing of retronasal and hematogenic olfaction with ethanol’s intoxicating properties appear necessary to achieve adult persistence in both sexes.
Prenatal Ethanol Exposed Animals are Attracted to an Intoxicated Peer
Prenatal Ethanol Exposed Animals are Attracted to an Intoxicated Peer
Eade et al. (ACER, In Press)
Specific Dysregulation Effects on Neurotransmission

A

$\Delta$ Ct (Cycles to threshold rel to 18S)

![Bar chart showing expression levels of various genes in EtOH treated vs Ctrl conditions.]

B

<table>
<thead>
<tr>
<th>Gene</th>
<th>Array</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA B1</td>
<td>-1.73</td>
<td>-1.59 **</td>
</tr>
<tr>
<td>mGluR2</td>
<td>-2.68</td>
<td>-1.45 *</td>
</tr>
<tr>
<td>DRD2</td>
<td>-2.22</td>
<td>1.24</td>
</tr>
<tr>
<td>CASKIN</td>
<td>-1.68</td>
<td>-1.90 **</td>
</tr>
<tr>
<td>Adra1d</td>
<td>-2.42</td>
<td>-1.30 **</td>
</tr>
</tbody>
</table>

*P < .05
**P < .005
We Measure Oro-sensory Responses with a Gustometer
Fetal exposure increases the acceptability of ethanol and QHCl, but not sucrose.
Fetal exposure increases the acceptability of (a) ethanol and (b) Capsaicin, but not (c) AITC.
Peripheral Oro-sensation

Yarmolinsky et al. (Cell, 2009)
Oro-sensory Gene Expression

Prestia et al. (In preparation)
Involved in Quinine sensitivity
* T2r106
* T2r105
* T2r104
* T2r130
* T2r120
* T2r107
* T2r116
* T2r113
* T2r136
* T2r140
* T2r114
* T2r121
* T2r129
* T2r124

T2r103
T2r125

Located on a quantitative trait locus for increased ethanol consumption (*mice*)

qRT-PCR
Adolescent CV
Log$_2$ Fold Change
BH-FDR
<table>
<thead>
<tr>
<th>Examples of Ligand</th>
<th>Trpa1-</th>
<th>AITC</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Trpv1-</td>
<td>Capsaicin</td>
<td></td>
</tr>
<tr>
<td>* Trpv3-</td>
<td>Camphor</td>
<td></td>
</tr>
<tr>
<td>* Trpm8-</td>
<td>Menthol</td>
<td></td>
</tr>
</tbody>
</table>

**Transient Receptor Channels (Trps) of the Adolescent CV**

**Taste Transduction**

* Trpm5 Calcium signaling for bitter, sweet and umami
Additional Taste Receptors of the Adolescent CV

Sweet and Umami
* \( T1r1 \)
* \( T1r2 \)
* \( T1r3 \)
Additional Taste Receptors of the Adolescent CV

Sweet and Umami
* $T1r1$
* $T1r2$
* $T1r3$
Epigenetic Basics
A Mechanism Underlying Alterations in Gene Expression?
Oro-Sensory Gene Expression Summary

* CV - Bitter, sweet and oral irritation transduction genes
  - Decreased during adolescence
  - Normalized by adulthood
  - Results consistent with previous behavior

* The fetal exposure effect was specific to the CV

* DNA Methylation is one mechanism for changes in expression
General Summary

* Our behavioral, genomic and neurophysiologic data provide evidence for the hypothesis there are epigenetic chemosensory mechanisms by which maternal patterns of alcohol use can be transferred to offspring, and via which, the adolescent system is primed to have the effects of fetal exposure augmented and/or preserved into adulthood
Lessons Learned from Animal Studies of Fetal Alcohol Exposure
Nicotine and Alcohol have Common Component Chemosensory Qualities

- Both are described as having an irritating and aversive odor
- Their orosensory qualities are described as irritating and having a bitter taste
Innate Odor-Mediated Response
Prenatal Alcohol Exposure Alters the Odor-Mediated Response to Nicotine

Mantella and Youngentob (PLoS one, 2014)
We Measure Oro-sensory Responses with a Gustometer
Oral Acceptability of Nicotine and Sucrose Solutions to Prenatal Alcohol- and Control-Exposed Adolescent Rats

Mantella and Youngentob (PLoS one, 2014)
Fetal exposure to alcohol also influences initial nicotine postnatal acceptability, at a minimum, by decreasing the aversive properties of both its smell and taste.

The present findings point to a broader mechanistic concern regarding the consequence of fetal exposure with one substance of abuse and its impact on the potential initial acceptability of others.
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