Biological Interventions: Choline as a Treatment for Fetal Alcohol Spectrum Disorders

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Many studies simply could not be done on humans. Answers can be obtained more quickly.

Basic Science
Animal models and prenatal alcohol

Confounding factors can rarely be controlled in human studies (other drug use, nutritional status, prenatal care, maternal factors)
Many studies simply could not be done on humans
Answers can be obtained more quickly

Interventions during prenatal alcohol exposure:
Experimental Therapeutics

Block ethanol’s mechanisms of damage
Alcohol has many mechanisms of damage, so the task is not simple

Alcohol disrupts cell adhesion molecules that help developing cells stick together

Control 0 mM 5 mM 25 mM

L1-transfected

Blockade of ethanol’s effects on L1 cell adhesion molecules reduces ethanol’s teratogenic effects

Control Ethanol Ethanol + Functional L1 cell adhesion

Chen et al. 2001

Courtesy of Michael Charness from Ramanathan et al., 2001
Oxidative Stress

- Free radicals are formed and can be damaging
- Alcohol increases free radicals and reduces natural antioxidants, leading to oxidative stress and cell death

Antioxidants prevent limb malformations

Chen et al. 2004

Antioxidants prevent cell death

Control Ethanol Ethanol + Antioxidants

Blocking ethanol’s effects on neurotransmitter systems

Chen et al. 2004

Blockade of NMDA receptor during withdrawal can protect against brain damage and behavioral alterations

NMDA receptor is important for brain development
Too much stimulation!
I'm dying!

EtOH

EtOH + MK-801 (blocks NMDA receptor)

0
5
10
15

MEAN (± SEM) NUMBER OF ERRORS

ETOH Controls

Perseverative-type errors

Hippocampal CA1 Cell Number

**

EtOH

EtOH + MK-801

GROUP

CONTROL
Potential Therapeutics

- Agents that prevent ethanol’s blockade of cell adhesion molecules
- Agents that block cell death (Anti-apoptotic agents)
- Growth factors
- Drugs that activate serotonin
- Drugs that block NMDA receptor

How can we treat individuals who are already exposed to alcohol prenatally?

Identify ways to enhance neuronal plasticity

Phosphodiesterase type 1 inhibition improves learning in rodents exposed to alcohol

Are these treatments safe? Would they ever be used in a clinical population?

Experience alters alcohol’s teratogenic effects

Stress exacerbates ethanol’s teratogenic effects

Environmental enrichment, acrobatic training, exercise enhance neuronal plasticity
Enriched environments

Remediation of prenatal alcohol effects with acrobatic motor training

Female Rat Performance on Parallel Bars

Exercise reduces learning deficits

Exercise improves hippocampal functioning

Nutritional Supplementation

- Folate
- Zinc
- Choline

Folate supplementation during prenatal alcohol exposure reduces the severity of heart defects
Choline is important for brain development, particularly during pre/perinatal periods. Choline supplementation can lead to long-lasting enhancements in cognitive functioning. Can choline supplementation reduce the severity of FASD?

Choline supplementation during prenatal alcohol exposure:
- Prenatal alcohol exposure (6.0 g/kg/day; GD 5-20 via intubation), Pair-fed and lab chow controls
- Choline chloride (250 mg/kg/day) or saline vehicle during prenatal development

**Body Weight**

<table>
<thead>
<tr>
<th></th>
<th>Choline</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>EIOH</td>
<td>*</td>
<td></td>
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<tr>
<td>Pair-Fed Controls</td>
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<tr>
<td>Lab Chow Controls</td>
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**Thomas et al., 2010**

**Reflex Development**

**Palmar Grasp**

**Righting Reflex**

**Thomas et al., 2009**
Choline supplementation during prenatal alcohol exposure reduces deficits in spatial working memory.

Choline supplementation attenuates ethanol’s teratogenic effects even when administered postnatally, after developmental alcohol exposure.

Choline supplementation after prenatal alcohol mitigates learning deficits.

MORRIS MAZE
Spatial Learning PD 150

MORRIS WATER MAZE
PATH LENGTH

Thomas et al., 2004
Choline administration attenuates ethanol’s effects on trace, but not delay eyeblink conditioning. This suggests that choline affects the hippocampus, an area of the brain important for learning and memory.

Is choline still effective if administered during adolescence/young adulthood? Postnatal Days 40-60

Choline supplementation did not mitigate overactivity.

Choline did not influence ethanol’s effects on spatial learning.

Choline supplementation during adolescence mitigates working memory deficits.

Summary of Postnatal Choline Treatment Findings:
- Choline supplementation can mitigate ethanol’s effects on activity level and learning tasks.
- Choline is effective even when administered after ethanol exposure and during a period of development equivalent to early postnatal development in humans, to some extent even into adolescence.
- The beneficial effects are observed even months after choline treatment is complete.
Questions:
- What parameters control the effectiveness of choline?
- What is the relationship between the behavioral effects and neuronal changes?
- What are the mechanisms of choline’s actions?

Perinatal choline alters cholinergic receptors in the brain.

Choline supplementation mitigates ethanol's effects on M2 muscarinic cholinergic receptors.

Can drugs that operate on the cholinergic system also be effective?

Donepezil, a drug that increases action of the neurotransmitter acetylcholine, reduces the severity of alcohol-related behavioral deficits.
Can betaine reduce the severity of FASD?

Administration of betaine reduces the behavioral alterations associated with developmental alcohol exposure.

Summary

Choline supplementation may influence brain development by altering cholinergic activity, cell membrane structure and signaling, and as a methyl donor.

The mechanisms likely depend on the timing of choline supplementation.

Is choline compensating for a choline deficiency?

Even modest dietary choline inadequacies exacerbate ethanol's teratogenic effects.

Choline Deficiency and Prenatal Alcohol Exposure

The combination of a diet with 40% recommended levels of choline (levels that are commonly consumed among pregnant women) and prenatal alcohol exposure delays eye opening, a physical marker of development.
The combination of a diet with 40% recommended levels of choline (levels that are commonly consumed among pregnant women) and prenatal alcohol exposure impairs motor development. Does prenatal alcohol affect choline levels? Pregnant dams were exposed to 6.0 g/kg/day from GD 5-20. Choline and choline metabolites were measured in blood, brain and liver in dams and fetuses.

Prenatal alcohol exposure does not affect maternal plasma choline levels. Nutritional effects on fetal plasma choline:

- Prenatal alcohol does not affect fetal blood choline levels.

Prenatal alcohol reduces maternal plasma betaine.
Maternal plasma dimethylglycine levels

Prenatal alcohol transiently reduces dimethylglycine levels, suggesting that alcohol interferes with metabolism of choline.

Data to date suggest that prenatal alcohol does not induce choline deficiency, but may transiently interfere with choline-related pathways.

Still need to examine brain and liver levels of choline and choline metabolites.

CONCLUSIONS

Dietary supplementations may serve as safe and effective interventions for some fetal alcohol effects.

Thank you

Thanks to NIAAA who has funded this research.

CIFASD

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