Fetal (Prenatal) Alcohol Impairs Blood Flow and Stroke Recovery in Adult Mice

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Objectives

• Identify prenatal alcohol exposure (PAE) as a risk factor for adult cardiovascular diseases

• Recognize PAE can amplify/ aggravate the effect of a second adverse life experience in adulthood

• Understand that PAE causes greater disability after brain trauma in adults.
Fetal Origin of Adult Disease
(Barker Hypothesis)

In Utero Environment (Adverse Events/Undernutrition)

Birth/Infancy (Low Birth weight)

Childhood to Adult (Metabolic to Cardiovascular diseases)
Relative Risk For Coronary Heart Disease, Stroke And Low Birth Weight

121,700 American Nurses, self report study  BMJ 315:396,1997
Face and Brain in FASD

Courtesy of Kathy Sulik, University of North Carolina
Prevalance of PAE in the State of Texas as Assessed by Phosphatidylethanol in Newborn Dried Blood Spot Specimens

Bakhireva et al., Alcohol Clin Exp Res. 2017
Long term effects of low dose prenatal alcohol

Modest fetal growth restriction
(Probyn et al, Repro Fertil Dev, 2012)

Growth deficits in later life (males)
(Probyn et al, Repro Fertil Dev, 2012)

Changes in mammary–lactation
(Probyn et al, Am J Physiol; 2013)

Increased anxiety but no impairments in learning & memory

Increased fibrosis in the lung
(Probyn et al, J DOHaD, 2014)

Altered metabolic function
(Probyn et al, PLoS One, 2013)

Impaired cardiac function and altered heart structure
(Nguyen et al, Physiol Rep. 2014)
Alcohol around conception causes insulin resistance in male and female offspring at 8 months.

Gardebjer et al., FASEB 2015
Early Cardiovascular Effects of Prenatal Alcohol Exposure (PAE)
Acute Alcohol Exposure Model

Ultrasound imaging - pre

Alcohol treatment (intragastric gavage)

Ultrasound imaging - post

GD 12.5 40 min
Ultrasound Imaging- Fetal Blood Flow Analysis
Ultrasound imaging - Fetal Blood flow analysis

- Umbilical Artery
- Fetal Middle Cerebral Artery
- Fetal Internal Carotid Artery
- Fetal Heart/Aorta
- Umbilical Artery

- Velocity (mm/s)
- Acceleration (mm/sec²)
- VTI (mm³/Sec)

- ACA
- MCA
- PCA
- ICA
- CCA
- AA

- Middle Cerebral
- Internal Carotid
- Aorta
- Umbilical
Early Effects of PAE

Fetal Internal Carotid Artery

fAcc normalized to control

Control  |  IP  |  Gavage

VTI normalized to control

Control  |  IP  |  Gavage

Bake S et al., 2011 ACER.
PAE Is Associated with Flow Reversal

Control

Ethanol exposed

Ethanol Exposed
Summary

A single dose of ethanol significantly reduced blood flow in the developing fetus

- Middle cerebral artery
- Internal Carotid Artery
- Aorta
- Umbilical artery
Short-term effect of single dose of ethanol

Bake et al., ACER, 2012
Effects of Prenatal Alcohol Exposure Persist Across A Lifetime
Multiple Binge Exposure Model

Intragastric gavage of ethanol

Gestational day 21

Offspring born

Weaned

Post-natal 21 day

Adults (3, 6 & 12 mo.)

12.5  13.5  14.5  15.5

Ultrasound imaging
Effects of 1st trimester-equivalent exposure on late cardiovascular effects on the offspring

Bake et al., 2017  ACER
Summary

Fetal alcohol exposed adults showed region specific blood flow acceleration in
1. Carotid artery ✓
2. Intra-renal (lobar) artery ✓
3. Renal artery X
4. Femoral Artery X
Do early developmental life events affect outcomes from cardiovascular/cerebrovascular disease?
Stroke Epidemiology

- Stroke is the 5th leading cause of death and the leading cause of long term disability

- Yearly cost of $74 billion for stroke care

- 795,000 people will experience a new or recurrent stroke

- Sharp increase in stroke in young adults of both sexes (Ramirez et al., 2016; Tibaek et al., 2016.)
Experimental Plan

Prenatal Alcohol Exposure → Second Hit

MCA occlusion at 3 mo. → 24h post stroke

- Infarct analysis
- Behavioral tests
Impact of PAE on Brain infarction

Bake et al, 2017
Neurological Status

**Neurological Severity Score**: A tool used by investigators to assess multiple deficits induced by stroke in animals.

Components of Neurological Score

- Grip
- Forepaw placement
- Mobility
- Circling
Post-stroke Neurological Scores in Young Adult PAE mice

a) Females

b) Males

Item Scale Score

Grip  Fore paw placement  Mobility  Circling

Control  PAE

Bake et al, 2017  ACER
Sensorimotor Function: Adhesive Removal Test

**Females**

- Control
- PAE

Time to removal (secs)

**Males**

- Control
- PAE

Time to removal (secs)

Bake et al, 2017  ACER
Conclusions

◆ Doppler ultrasound analysis: Prenatal ethanol exposure resulted in significant arterial resistance in carotid arteries of young mice but hypoperfusion in middle-aged mice.

◆ MCAo in fetal alcohol exposed adults caused severe neurological deficits at 24 h post-stroke as evidenced by high neurological scores.

◆ Prenatal ethanol exposure persistently alters vascular function and impairs post stroke recovery.

◆ We need to be better prepared to anticipate the outcomes of adult onset diseases in the FASD population and to strategically plan prevention and rehabilitation strategies.
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