Does PAE Cause Metabolic Syndrome? (Non-)Evidence from a Mouse Model

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Mouse Model of PAE

C57Bl/6J
Teklad 8626

Exposed Litter
17 weeks old
(P_{119}, 3M/3F)

Dissection and Tissue Collection

Metabolic Cage Assessment & Body Composition
Ten Days

High Fat Diet Challenge & Body Composition
Thirty Days

Oral Glucose Tolerance

Intraperitoneal Glucose Tolerance
Seven Days

Blood Pressure Assessment

- H₂O
- 3 g/kg ETOH
- Isocaloric MD
- Isocaloric MCT
Our Controls

- Water gavage – to control for stress
- Maltodextrose – isocaloric with Alcohol
  - But elicits an insulin response
- Medium-Chain Triglycerides – isocaloric with Alcohol
  - C8-C10 (60:40)
  - Metabolized rapidly by liver, does not elicit insulin
Offspring Growth
Alcohol vs. Water Gavage
PAE reduces early growth, then catch-up
Offspring Growth
Alcohol vs. Maltodextrose
PAE reduces early growth, then catch-up
Offspring Growth
Alcohol vs. All Controls
Calories incr juvenile growth & decr later growth

<table>
<thead>
<tr>
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<th>Male</th>
<th>Female</th>
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<tr>
<td>Weight Gain During Lactation (g)</td>
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<td>H2O</td>
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| Weight Gain from P21 to P35 (g) |      |        |
| H2O                          |      |        |
| MCT                          |      |        |
| MD                           |      |        |
| ETOH                         |      |        |

| Weight Gain from P35 to P105 (g) |      |        |
| H2O                           |      |        |
| MCT                          |      |        |
| MD                           |      |        |
| ETOH                         |      |        |

* treat p=0.54 treat p=0.13
** treat p<0.02
*** treat p<0.0001
PAE doesn’t increase adiposity vs. MD

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>% Lean Mass</th>
<th>% Fat Mass</th>
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**Males**

- H2O
- MCT
- MD
- ETOH

**Females**

- H2O
- MCT
- MD
- ETOH

* treat p=0.27
* treat p=0.23
* treat p=0.21
* treat p=0.21
* treat p=0.23
* treat p=0.27
PAE doesn’t increase adiposity as compared with all controls

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* treat p=0.27
* treat p=0.21
* treat p=0.23
* treat p=0.27
* treat p=0.23
Metabolic Phenotyping of Mice using Environmental Chambers

- 3 days chow
- 3 days low-fat diet (10% kcals)
- 3 days high-fat diet (60% kcals)
- Measure body temp, food & water intake
- Measure CO2 exhaled & O2 consumed
- Calculate energy expenditure
PAE does not affect metabolic rate
PAE reduces adiposity vs. water controls in response to high-fat diet
PAE does not worsen adiposity in response to high-fat diet
PAE worsens Glucose Tolerance vs. Water-gavage
PAE does not affect Glucose Tolerance when compared with caloric controls.
High-Fat Diet worsens Glucose Intolerance: More in Maltodextrin Males; More in PAE Females
High-Fat Diet doesn’t Unmask Glucose Intolerance in PAE

**Males**

- **Blood Glucose (mg/dL)**
  - Graph showing blood glucose levels over time for H2O, MCT, MD, and ETOH treatments.
  - Key points:
    - Treat p=0.20
    - Timepoint p=0.0001
    - Treat*timepoint p=0.05

- **AUC (Biomass)**
  - Bar graph showing AUC for each treatment group.
  - Key points:
    - p=0.20

**Females**

- **Blood Glucose (mg/dL)**
  - Graph showing blood glucose levels over time for H2O, MCT, MD, and ETOH treatments.
  - Key points:
    - Treat p=0.11
    - Timepoint p=0.0001
    - Treat*timepoint p=0.08

- **AUC (Biomass)**
  - Bar graph showing AUC for each treatment group.
  - Key points:
    - p=0.21

**Males**

- **Blood Insulin (ng/mL)**
  - Graph showing blood insulin levels at 0 and 15 minutes for H2O, MCT, MD, and ETOH treatments.
  - Key points:
    - Treat p=0.69
    - Timepoint p=0.14
    - Treat*timepoint p=0.30

**Females**

- **Blood Insulin (ng/mL)**
  - Graph showing blood insulin levels at 0 and 15 minutes for H2O, MCT, MD, and ETOH treatments.
  - Key points:
    - Treat p=0.69
    - Timepoint p=0.14
    - Treat*timepoint p=0.30
High-Dose PAE doesn’t Cause Adiposity in PAE

- 4.5 g/kg
- GD 12.5 - GD 17.5
- PAE vs. Maltodextrin
CAVEATS

- Did we study the wrong exposure window? GD12.5 – GD17.5

- Was the dose too low? ~110 mg/dl
  - 30 mg/dl cause metabolic change in offspring (Probyn et al. 2013)

- Did we study the wrong mouse strain?
  - C57Bl/6J is commonly used to study obesity and diabetes & PAE

- Were the mice too young?
  - No hint of a problem in RER studies, nor in diet challenge study (Chen et al. 2004)

- Is fetal growth restriction necessary?
  - No, moderate doses alter glucose homeostasis (Gardebjer et al. 2017; Probyn et al. 2013; Yao et al. 2007 & 2013)
SUMMARY

- If we compare PAE & Water, we see some differences
- If we compare PAE and MD, we see some differences

**But..**

- Neither 3g/kg or 4.5 g/kg caused a unique adiposity
- 3g/kg did not cause glucose intolerance
- High-fat diet didn’t unmask a phenotype
- PAE didn’t affect metabolic rate
- *Extra Calories* caused glucose intolerance & adiposity (versus water)
- PAE resembles Caloric Intervention
- Alcohol is metabolized more like MCT, than carbohydrate or water
So…Does PAE Increase Obesity Risk in Later Life?

Yes…But the cause is not metabolic dysregulation or imprinting

- Influence of medications?
- Challenges in purchasing & preparing healthy food
- Challenges in sensing appetite signals?
- Influence of executive function?

Recommendations

- Assessment by Registered Dietitian to guide food choices
- Assessment by Physician to review medications & BMI concerns
Acknowledgements

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  - Robyn M. Amos-Kroohs, Ph.D.
- University of Wisconsin-Madison
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  - David W. Nelson, Ph.D.
  - Timothy A. Hacker, Ph.D.
- Vilas Professorship (SS), F32 AA0024364 (RMAK), R01 AA22999 (SS)
Pregnancy Parameters
PAE did not affect newborn weight

<table>
<thead>
<tr>
<th>Pregnancy Weight Gain (g)</th>
<th>Litter Size</th>
<th>Per Pup Weight Gain (g)</th>
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<tbody>
<tr>
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- treat p=0.34
- treat p=0.04
- treat p=0.19