Metabolic programming
Part I

COGS 163 Week 6
May 5, 2015

Janet Tung and Miguel Wang
You are what your mom eats…?

- Does maternal diet matter?
- What effects does it have?
- How? When?
- Are these effects reversible?
Adult Obesity Rate by State, 2013

Select years with the slider to see historical data. Hover over states for more information. Click a state to lock the selection. Click again to unlock.

Percent of obese adults (Body Mass Index of 30+)

- 0 - 9.9%
- 10 - 14.9%
- 15 - 19.9%
- 20 - 24.9%
- 25 - 29.9%
- 30 - 34.9%
- 35%+

1990:
- 10-15% obese

2013:
- 35% obese

Childhood obesity:
- 17%
  (tripled since 1980)

Diabetes:
- 9.3%
  (29 million people)
Pregnancy rates of obesity and diabetes

- Maternal obesity: 15-40%
- Maternal diabetes: 3-10%
- Gestational diabetes: 7-18%
- In humans: offspring of obese, diabetic, and hyperglycemic mothers
- Increased risk of metabolic disorders
Metabolic programming

What’s the mechanism?
Mechanism: Hypothalamic circuitry

Neonatal Insulin Action Impairs Hypothalamic Neurocircuit Formation in Response to Maternal High-Fat Feeding

Previous studies showed:

- Gross changes in hypothalamic neurocircuits
- Differential neuropeptide expression
- Altered hypothalamic neuronal cell numbers
- Impaired formation of hypothalamic axonal projections

Timing? Molecular mechanisms?

From Adena and Andrea’s presentation
Developing a mouse model

- Differential developmental course than humans

**Mouse:**

- In utero: neuronal cells numbers are determined
- Lactation: formation of functional neuronal networks, including ontogeny of axonal projections and synaptic connections
Experiment design: Timing of diet

Maternal
Pregestation, Prenatal

NC or HF

Maternal
Postnatal

NC
HF

Offspring
8-12 weeks

NC
HF
NC
HF
Results: timing

HFD during Lactation = Elevated serum insulin

Figure 1. Maternal HFD Feeding Induces Pregestational Metabolic Abnormalities and Hyperinsulinemia during Lactation in the Offspring (A-C) Maternal (A) pregestational body weight, (B) fasted blood glucose levels, and (C) homeostatic model assessment indices of insulin resistance (HCMA-IR) (n = 48 vs. 50).

(D) Maternal preweaning serum insulin levels in the fed state (n = 4 for all groups).

(E) Serum insulin levels in the offspring at 3 weeks of age (n = 9 for all groups).

NCD, normal chow diet; HFD, high-fat diet. Data are presented as mean ± SEM. **p < 0.01, ***p < 0.001 versus all other groups within the same diet after week 6 if not indicated otherwise. See also Figure S1 for an overview of all experimental groups.
Results: mechanisms

1. Markers of predisposition to metabolic disorders
2. Effects on hypothalamic circuitry
3. Axonal projections of ARC neurons to downstream sites
4. Role of insulin signaling in offspring predisposition to metabolic disorders
5. Can predisposition be ameliorated by eliminating POMC insulin receptors?
6. Effects on pancreatic βcells
1. Offspring risk of metabolic disorders

“Exposure of mothers to HFD exclusively during the lactation phase exerts the strongest effects on alterations in energy and glucose homeostasis in offspring.”
2. Offspring hypothalamic circuits

- ARC mRNA expression of POMC, AGRP, NPY: no difference
- PVN expression of thyrotropine-releasing hormone (TRH): lower
- Hypothalamic mRNA expression of inflammatory markers: no difference
- ARC neuron cell numbers: no difference
- POMC processing to αMSH: no difference
- POMC neuron spontaneous firing rate, resting membrane potential, and synaptic input: no difference
2. Offspring hypothalamic circuits

- ARC mRNA expression of POMC, AGRP, NPY: no difference
- PVN expression of thyrotropine-releasing hormone (TRH): lower
- Hypothalamic mRNA expression of inflammatory markers: no difference
- ARC neuron cell numbers: no difference
- POMC processing to αMSH: no difference
- POMC neuron spontaneous firing rate, resting membrane potential, and synaptic input: no difference
Thyrotropine releasing hormone (TRH)

α-MSH exerts anorexigenic functions in part by upregulating TRH.
TRH regulation
“Offspring of undernourished mothers share several metabolic impairments with offspring with obese mothers…and decreased pancreatic parasympathetic activity”

But – no detected differences in classical markers for inflammation
3. ARC neuron projections to downstream sites in hypothalamus

- Three main downstream sites for projections from ARC:
  - PVN – posterior (preautonomic)
  - PVN – anterior (neuroendocrine, including TRH)
  - DMH
  - LA

- Robust reductions in αMSH and AgRP neuronal fiber densities in NCD/HFD offspring in all areas
Axonal fiber densities
4. Role of POMC insulin signaling

- HFD during lactation
- Increased glucose and insulin in milk
- Hyperinsulinemia in offspring at 3 weeks

POMC neuron
Role of POMC insulin signaling on predisposition to metabolic disorders

**NCD/NCD vs. NCD/HFD**
- Body weight: no difference
- Adiposity: higher in NCD/HFD
- Leptin levels: higher in NCD/HFD
- Insulin sensitivity: impaired in NCD/HFD (insulin tolerance test and HOMA-IR)

**NCD/HFD vs. NCD/HFD/POMC IR ko**
- No differences
- Except IR knockout rescues glucose intolerance

**POMC insulin receptor knockout during lactation improves insulin signaling**

**What other players? Leptin – role in gestational diet**
Effects of POMC IR knockout
5. Effect of POMC IR on axonal projections to PVN

**αMSH axonal projections**
- PVN anterior: no difference
- PVN posterior: **rescue**
- DMH: no difference
- LA: no difference

**AgRP axonal projections**
- PVN anterior: no difference
- PVN posterior: no difference
- DMH: no difference
- LA: no difference

Hyperinsulinemia during lactation impairs POMC axonal growth to posterior (preautonomic) PVN
6. Effect of POMC IR knockout on pancreatic βcells

Vesicular ACh transporter (vAChT)

- vAChT buttons per islet area: greatly reduced by NCD/HFD offspring
- Rescued by POMC IR knockout
- Glucose stimulated insulin secretion decreased in NCD/HFD offspring
- Rescued by POMC IR knockout
- (But impairments not seen with L-arginine stimulation, GLP-1, or FFA)
- No difference in βcell mass or islet size
Summary

- Lactation is most sensitive dietary period for offspring predisposition to metabolic disorders
- HFD during lactation impairs ARC innervation of intrahypothalamic target areas (recall mouse cross fostering experiments)
- Critical period: not reversible by reverting to normal chow after 8 weeks
- POMC IR signaling not critical under normal development conditions
- POMC IR knockout rescue of second order axonal projections is site-specific to posterior PVN
- Other mechanisms must contribute to impaired axonal projections to other areas (leptin, FFAs, et al.)
- HFD-induced reduction of pancreatic vagus innervation rescued by POMC IR knockout