Dieting is really, really hard

Sean Algaier, *The Biggest Loser*, 2009

Start: 444 lbs

End: 289 lbs

Source: *New York Times*
Obesity rates have risen dramatically

Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥30, or about 30 lbs. overweight for 5’ 4” person)

Source: Behavioral Risk Factor Surveillance System, CDC.
Early postnatal diet can have life-long effects on metabolism

- Underfeeding
- Overfeeding
- High fat diet

Metabolic syndrome and adult obesity
Rewiring neural circuitry that regulates body weight

Altered neuronal activity
Selective neuronal death

Postnatal neurogenesis

Lee and Blackshaw. AJP 2014
Robust cell proliferation in hypothalamic median eminence

Lee, at al. *Nat Neurosci* 2012
Different classes of neurons are generated in postnatal ME

Lee, at al. Nat Neurosci 2012
Neurogenesis ends after weaning, but can be reactivated by high fat diet

HFD stimulates neurogenesis in young adult female, but not male, ME

Pak, at al.  *Front Neurosci* 2014
Hypothalamic tanycytes
Tanycytes can be selectively genetically labeled

18.09% of Sox2 β2 Tanycytes labeled with YFP

Lee, at al.  Nat Neurosci 2012
Tanycytes of the medial eminence (ME) generates neurons in postnatal hypothalamus

Lee, at al. Nat Neurosci 2012

(8.1%±0.4 of Hu+ neurons were YFP+; n=4)
Localized CT-guided irradiation to inhibit ME neurogenesis in young adults

Lee, at al. *Nat Neurosci* 2012
Lee, at al. *JoVE* 2014
Focal irradiation of ME decreases weight gain in females but not males

Pak, at al. Front Neurosci 2014
Focal irradiation of ME enhances activity levels and energy expenditure

Lee, at al. Nat Neurosci 2012
What we now know

1. New neurons are born in juvenile hypothalamic median eminence.

2. Neurogenesis can be triggered by high fat diet in young adult females, but not males.

3. These neurons are generated from tanycytes.

4. Inhibiting cell proliferation in ME in females reduces weight gain and increases activity.
What we don’t yet know

1. Do the effects of focal irradiation in ME result from blocking neurogenesis?
2. What molecular signals induce tanycyte-derived neurogenesis?
3. Do signals other than diet control hypothalamic neurogenesis?
4. Do dietary signals also induce neurogenesis in human hypothalamus?
Hong Wang
Ana Miranda
Lizhi Jiang
Joe Bedont
Daniel Lee
Thomas Pak
Juan Salvatierra
Sooyeon Yoo
Why should long-term weight gain be selectively adaptive for females?
Median Eminence (ME)

- Tanycyte
- Blood Vessel
- Neurons
- TRH Axon
- GnRH Axon
Tanycytes express stem and progenitor-specific markers

- Nestin
- GFAP
- Vimentin
- Sox2

**Markers:**
- Hes5
- Notch1
- Rax
- Gpr50
- Sox9
- CD63
- Notch2
- Neuronatin
- Ntrk2-T1
- Notch2
- Neurona
- Ntrk2-T1
- Gpr50
- Sox9

**Anatomical Regions:**
- VMH
- 3V
- ME
- ArcN
- HVZ