Development of The Hypothalamic Circuitry

The Absentees

http://bit.ly/2q54Lxn
Overview

1) Welcome to the Hypothalamus
2) Intro to Leptin
3) Mechanisms Controlling Feeding Behavior
4) Prenatal Influences
5) Postnatal Influences
6) Discussion
Hypothalamus 101

Anatomy and Circuitry
Hypothalamus Anatomy
5 Nuclei

- Nuclei of the Hypothalamus

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVN</td>
<td>Neuroendocrine regulation, regulation of ANS</td>
</tr>
<tr>
<td>Arcuate nucleus</td>
<td>Neuroendocrine regulation</td>
</tr>
<tr>
<td>Supraoptic nucleus</td>
<td>Neuroendocrine regulation</td>
</tr>
<tr>
<td>Suprachiasmatic nucleus</td>
<td>Circadian timing</td>
</tr>
<tr>
<td>Anterior nucleus</td>
<td>Control of ANS</td>
</tr>
<tr>
<td>Preoptic nucleus</td>
<td>Control of ANS</td>
</tr>
<tr>
<td>Dorsomedial nucleus</td>
<td>Control of behavior</td>
</tr>
<tr>
<td>Ventromedial nucleus</td>
<td>Control of appetite, body weight, insulin secretion</td>
</tr>
<tr>
<td>Posterior nucleus</td>
<td>Control of ANS</td>
</tr>
<tr>
<td>Mammillary nuclei</td>
<td>Control of emotional expression and memory</td>
</tr>
<tr>
<td>Lateral tuberal complex</td>
<td>Control of appetite</td>
</tr>
</tbody>
</table>
Hypothalamic Feeding Regions

- POMC (pro-opiomelanocortin)
- NPY (neuropeptide Y)
- AgRP (Agouti-related peptide)
- Sf1 (steroidogenic factor 1)
- Sim1 (single-minded homolog 1 gene)

Figure 1: Expression timeline of transcription factors directly implicated in the generation of the hypothalamic feeding nuclei.

### Knocking Out Certain Genes


#### Table 1 — Effect of global and conditional transcription factor knockout models on ARC neurons.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Type</th>
<th>Model</th>
<th>Effect on POMC neurons</th>
<th>Effect on NPY/AgRP neurons</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rax</td>
<td>Homeobox transcription factor</td>
<td>Six3::Cre;Rax^{flox/null}</td>
<td>x</td>
<td></td>
<td>[10]</td>
</tr>
<tr>
<td>Bmpr1a</td>
<td>Receptor</td>
<td>Olig1^{cre/+};BMPR1a_{-/-}</td>
<td>—</td>
<td>+</td>
<td>[14]</td>
</tr>
<tr>
<td>Ngn3</td>
<td>bHLH transcription factor</td>
<td>Ngn^{-/-}</td>
<td>—</td>
<td>+</td>
<td>[18,17]</td>
</tr>
<tr>
<td>Ngn3</td>
<td>bHLH transcription factor</td>
<td>Nkx2.1Icre/+;Ngn3^{flox/flox}</td>
<td>—</td>
<td>=</td>
<td>[19]</td>
</tr>
<tr>
<td>Nhhl2</td>
<td>bHLH transcription factor</td>
<td>Nhhl2^{-/-}</td>
<td>=</td>
<td>-</td>
<td>[22,24,25]</td>
</tr>
<tr>
<td>Nhhl2</td>
<td>bHLH transcription factor</td>
<td>POMC EGFP/GnRH Cre/NSCL-2^{loxP/loxP}</td>
<td>—</td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>Mash1</td>
<td>bHLH transcription factor</td>
<td>Mash1^{-/-}</td>
<td>—</td>
<td>-</td>
<td>[28]</td>
</tr>
<tr>
<td>Mash1</td>
<td>bHLH transcription factor</td>
<td>Mash1^{+/-}</td>
<td>=</td>
<td>+</td>
<td>[28]</td>
</tr>
<tr>
<td>Rbpjk</td>
<td>Notch cofactor</td>
<td>Rbpjk^{+/fl/fl};Nkx2.1^{cre/+;cre}</td>
<td>+</td>
<td>+</td>
<td>[29]</td>
</tr>
<tr>
<td>Notch1</td>
<td>Receptor</td>
<td>Rosa^{NotchICD/+}</td>
<td>x</td>
<td>x</td>
<td>[29]</td>
</tr>
</tbody>
</table>

x — Absent/ablated; + Increased; — Decreased; = No change.
Circuitry

- Limbic circuits
- Sensory and autonomic circuits
  - Control of feeding, insulin release, reproduction, and motivation
  - Bidirectional pathways (medial forebrain bundle and dorsal longitudinal fasciculus): bring visceral and somatic input to the hypothalamus
  - Afferent pathways:
    - Direct inputs (via receptors): thermoreceptors, osmoreceptors, energy balance
    - Indirect inputs (from bloodstream): temperature, osmotic pressure, hormone concentrations
  - Efferent pathways: biological clock, secretory neurons, hypothalamic hormones
- Neuro-humoral connections: pituitary and circumventricular organs
Audience Participation

What does the hypothalamus send signals to?
A. thalamus
B. hypophysis
C. brain stem
D. spinal cord
E. all of the above

Hint: The hypothalamus is very, very important and influential.

*hypophysis: think hypophyseal portal system between the hypothalamus and the pituitary
<table>
<thead>
<tr>
<th>Nucleus of Hypothalamus</th>
<th>Hypothalamic-Related Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular Nucleus</td>
<td>Chronic pain; Gastroparesis; Orthostatic Hypertension; Arrhythmia/Bradycardia; Heart Failure; Hypo/Hyperthyroidism; Hypertension; Pulmonary Edema; No or Hyper-Lactation; Prolactinoma; SIADH; Diabetes Insipidus; Lethargy; Coma; Acromegaly; Dwarfism</td>
</tr>
<tr>
<td>Supraoptic Nucleus</td>
<td>Addictions; No or Hyper- Lactation; SIADH; Diabetes Insipidus; Gastroparesis; Hypertension; Angina; Arrhythmia/Bradycardia; Raynaud's Syndrome; Impotence</td>
</tr>
<tr>
<td>Preoptic Nucleus</td>
<td>Rage; Depression, Anxiety, Epilepsy; Addiction; Chronic pain; Infertility; Ovulation; Irregular/Painful menses; Hypogonadism; Low Sperm Count; Precocious Puberty; Gastroparesis; Hypertension; Angina; Arrhythmia/Bradycardia; Raynaud's Syndrome; Impotence; Baldness</td>
</tr>
<tr>
<td>Lateral Nucleus including the Tuberal Nucleus</td>
<td>Rage Disorder; Epilepsy; Anxiety; Addictions; Obsessive/Compulsive Disorders; Heart Failure; Hypothermia; Insomnia; Narcolepsy; Gastroparesis; Hypertension; Angina; Arrhythmia/Bradycardia; Raynaud's Syndrome; Hyperhidrosis; Hyperthermia; Psychogenic Polydipsia</td>
</tr>
<tr>
<td>Suprachiasmatic Nucleus</td>
<td>Circadian Rhythms; Insomnia; Narcolepsy</td>
</tr>
<tr>
<td>Mammillary Body</td>
<td>Epilepsy; Chronic pain; Gastroparesis; Hypertension; Angina</td>
</tr>
<tr>
<td>Ventromedial Nucleus</td>
<td>Chronic pain; Addictions; Rage Disorder; Movement Disorders; Psychiatric Disorders; Infertility; Ovulation; Irregular/Painful menses; Hypogonadism; Low Sperm Count; Precocious Puberty; Impotence; Baldness</td>
</tr>
<tr>
<td>Dorsomedial Nucleus</td>
<td>Epilepsy; Chronic pain; Depression; Rage; Hypo/Hyperthyroidism</td>
</tr>
<tr>
<td>Posterior Nucleus</td>
<td>Chronic pain; Taste Disorder; Rage Disorder; Hypertension; Anxiety; Heart Failure; Hypothermia; Insomnia; Narcolepsy; Precocious Puberty; Hypogonadism</td>
</tr>
<tr>
<td>Substantia Innominata</td>
<td>Taste Disorders; Chronic pain; Depression; Anxiety</td>
</tr>
<tr>
<td>Basal Nucleus of Meynart</td>
<td>Alzheimer's Disease; Dementias</td>
</tr>
</tbody>
</table>
JAK-STAT Pathway

JAK = Janus Kinase

STAT = Signal Transducer + Activator of Transcription

Helpful video: https://www.youtube.com/watch?v=G4K6IqZGHJc
Leptin
Lesions of the Hypothalamus

And anorexia

- Bilateral lesions of the lateral hypothalamus
- Loss of appetite
Lesions of the Hypothalamus

And obesity

- Bilateral lesions of the ventromedial hypothalamus
- Overeating
Hypothalamic Lesions

Lesions of lateral hypothalamus

Lesions of ventromedial hypothalamus

(a) Lateral hypothalamic syndrome

Normal

(b) Ventromedial hypothalamic syndrome

Bear, Mark F. Neuroscience: Exploring the Brain 4th Ed
Lipostatic Hypothesis

- By Gordon Kennedy in 1953
- Maintains homeostasis of energy storage
- Defends against immediate fluctuations

Bear, Mark F. Neuroscience: Exploring the Brain 4th Ed
Leptin is encoded by ob gene
- Released by adipocytes and more
- Stimulates neurons of the hypothalamus that controls feeding behavior
Too Much Leptin?

**FIGURE 16.8**
The response to elevated leptin levels. A rise in leptin levels in the blood is detected by neurons in the arcuate nucleus that contain the peptides αMSH and CART. These neurons project axons to the lower brain stem and spinal cord, the paraventricular nuclei of the hypothalamus, and the lateral hypothalamic area. Each of these connections contributes to the coordinated humoral, visceromotor, and somatic motor responses to increased leptin levels. (Source: Adapted from Sawchenko, 1998, p. 437.)
Not Enough Leptin?

Figure 16.9
The response to decreased leptin levels. A reduction in blood levels of leptin is detected by neurons in the arcuate nucleus that contain the peptides NPY and AgRP. These arcuate nucleus neurons inhibit the neurons in the paraventricular nuclei that control the release of TSH and ACTH from the pituitary. In addition, they activate the neurons in the lateral hypothalamus that stimulate feeding behavior. Some of the activated lateral hypothalamic neurons contain the peptide MCH (melanin-concentrating hormone).
Anorexigenic

Rise in leptin levels

Release of aMSH and CART from arcuate nucleus

Projects to lateral hypothalamus and other areas

Inhibit feeding and increase energy expenditure
Orexigenic

- Fall in leptin levels
- Release of NPY and AgRP from arcuate nucleus
- Inhibits neurons in PVN and stimulates neurons in lateral hypothalamus
- Activates feeding and decrease energy expenditure
More on responses to leptin levels

- Blood leptin level: 
  - Fat: +
  - Lean: -

- αMSH/CART neuron activity: 
  - Fat: +
  - Lean: -

- NPY/AgRP neuron activity: 
  - Fat: -
  - Lean: +

- TSH and ACTH release: 
  - Fat: +
  - Lean: -

- Sympathetic NS activity: 
  - Fat: +
  - Lean: -

- Parasympathetic NS activity: 
  - Fat: -
  - Lean: +

- Feeding behavior: 
  - Fat: -
  - Lean: +

- Arcuate nucleus response
- Humoral response
- Visceromotor response
- Somatic motor response

Bear, Mark F. Neuroscience: Exploring the Brain 4th Ed
How Feeding Works

http://neuroscience.uth.tmc.edu/s4/chapter04.html
Mechanisms for Feeding Behavior

Feeding mechanisms regulate caloric homeostasis after eating, post-absorption, and during fasting.

- 2 Hypotheses
  - Depletion - Repletion
  - Primed Response

Figure 4.2
Schematic of the depletion-repletion hypothesis of caloric homeostasis.

http://neuroscience.uth.tmc.edu/s4/chapter04.html
Mechanisms of Satiety

- **Neural signals**
  - Afferent
  - Efferent

- **Humoral signals**
  - Signal satiety
    - Main factors in CNS that limit feeding:
      - Insulin
      - Leptin
      - Glucose
      - CCK
    - Chief signaling site = ARCUATE NUCLEUS
    - Main transmitter substance = CCK

A hypothetical model for the short-term regulation of feeding behavior. This graph shows a possible means of regulating food consumption by satiety signals. Satiety signals rise in response to feeding. When satiety signals are high, food consumption is inhibited. When the satiety signals fall to zero, the inhibition is eliminated, and food consumption ensues.
Dual Center Hypothesis

- VMH = Obesity
- LH = Anorexogenic

Neurochemistry:

- Orexogenic - EAT
  - NPY, AGRP, MCH, Orexin and Galanin
- Anorexogenic - DON'T EAT
  - POMC, MSH, CART, GLP-1 and GLP-2, PrlRP
Figure 4.5
Schematic of the neurochemistry of the hypothalamic satiety network.
Prenatal Effects

Embryonic development of the hypothalamic feeding circuitry: Transcriptional, nutritional, and hormonal influences

Harry MacKay, Alfonso Abizaid
Prenatal Environment

- Critical period for the organization and development of the feeding circuitry
- Developmental Programming
  - Maternal Food Restriction
  - Maternal Obesity
  - Maternal Insulin Resistance
  - Maternal Protein Deprivation
Maternal Food Restriction

- Prenatal food restriction
- Offspring demonstrate relative *hyperphagia*
  - Hypothalamus reconfigured
  - ↓ POMC expression and ↑ NPY expression in the ARC
    - Upon postnatal exposure to high fat diet
  - Hypocellularity in the ARC
    - Revealed by hematoxylin/eosin staining
- Leads to *decreased neurogenesis* and *retarded migration* in the hypothalamus
Maternal Obesity

- Prenatal high-fat diet exposure
- Offspring display *increased body weight* and *hyperleptinemia* in adulthood
  - ↓ NPY, ↓ POMC, ↓ ObRb expression in ARC
  - ↓ expression of intracellular leptin signalers STAT3 and SOC3
- Other rats have shown:
  - ↑ number of orexin and ↑ McH expression in the LH
  - ↑ galanin, ↑ enkephalin, and ↑ dynorphin in PVN
  - ↑ proliferation in PVN and LH
- Surplus neurons assume *orexigenic* identity in feeding areas

http://bit.ly/1g5VcGa
Maternal Insulin Resistance

- Maternal diabetes → studied independent of maternal obesity
- Predispose offspring to obesity & metabolic disorders
- Maternal Mice injected with STZ
- Offspring:
  - Obesity
  - Hyperphagia
  - Hyperglycemia
  - Leptin sensitivity & ↑ POMC expression

http://bit.ly/2q5tm50
Maternal Protein Deprivation

- Prenatal low-quality nutrition
  - Dams (rat) fed isocaloric, 8% protein diet
- Offspring:
  - Adult onset obesity
  - Glucose intolerance
  - Reduced brain volume in general
    - PVN: ↓ volume, ↑ density
    - VMH: ↑ volume, ↑ density
    - ARC: no change
  - ↓ NPY immunopositive cells

To Summarize-
Leptin: A neurotrophic factor

- Embryonic neurogenesis and differentiation in the hypothalamic feeding region is positively correlated with gestational nutrition
  - Maternal nutrition has been linked with fetal leptin exposure
  - ↑ nutrition = ↑ rates of proliferation and adult hypercellularity
    - Leptin is the genesis of these effects
- Leptin is neurotrophic in the embryonic brain
  - Rodent placenta produces little leptin, BUT is permeable to leptin derived from the maternal side of circulation
  - Circulating leptin rises during pregnancy period
    - Peaking at gestation

LEPTIN

Mediates effects through interactions with the mechanisms of the hypothalamic development

Levels vary in proportion to maternal energy balance
Postnatal Effects

POSTNATAL DEVELOPMENT OF HYPOTHALAMIC LEPTIN RECEPTORS

Elizabeth C. Cottrell,*†1 Julian G. Mercer,† and Susan E. Ozanne*
Postnatal Leptin Surge

- Increase in circulating leptin concentrations during first 2 postnatal weeks
- Saw a reduction of circulating leptin concentrations with:
  - Restricted maternal food intake
  - Feeding of a high-carb diet during first 2 postnatal weeks
- Independent of concentration of insulin or glucose
Leptin Concentrations Between Birth and Weaning

- Tested leptin concentrations from the serum of *ob/ob*, wild-type and *ob/+*
- Wild-type presented surge, heterozygote did not and *ob/ob* was undetectable

![Graph showing leptin concentrations over postnatal days](https://giphy.com/gifs/baby-bunny-feeding-xzc6AIk6qatZS)

Postnatal Development of Hypothalamic Leptin Receptors, Elizabeth C. Cottrell, Julian Merce, Susan Ozanne
## Leptin Insensitivity

<table>
<thead>
<tr>
<th>Time of administration</th>
<th>Food Intake</th>
<th>Energy Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks postnatal</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>P18</td>
<td>No effect</td>
<td>Increase</td>
</tr>
<tr>
<td>P28</td>
<td>Inhibit</td>
<td>Increase</td>
</tr>
</tbody>
</table>
Neurotrophic Actions

- Establishment of hypothalamic neuroendocrine system
- Bouret and colleagues
  - Absence of leptin led to a failure to form projections from the ARC to the downstream PVN
  - \( ob/ob \) mice had a reduced fiber density within the PVN at P12 and continued to adulthood
  - Leptin administration to \( ob/ob \) postnatally was able to increase projections
Hypothesized *ob/ob* and wild-type would have similar levels of ObR in the ARC until responsiveness of leptin occurred.
The changes in leptin with age may correlate with distinct roles for leptin at different stages of development.
Discussion
LET'S REVIEW SOME CONCEPTS

**JAK-STAT**
- Signaling pathway
- Affects gene transcription
- Feedback on the system

**Hypothalamus**
- Bilateral Lesions
- Leptin Pathway

**Feeding**
- Orexigenic v. Anorexigenic
- VMH v. LH

**Prenatal Leptin**
- Maternal Nutrition
- Leptin Exposure
- Embryonic Neurogenesis

**Postnatal Leptin**
- Postnatal Leptin surge
- Hypothalamic Circuitry Development
What are the implications of leptin in neonatal development? (2)
How can this information be used to promote healthy hypothalamic development?
Do you think that there are any realistic manipulations of postnatal nutrition or hormone profiles in order to improve adult metabolic health and reduce disease?
THANKS!

Any questions?

http://bit.ly/2qgEgBm