

Endocrine and Hypothalamic Control of Appetite

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This lecture covers endocrine control of appetite. We will discuss the neural circuitry that regulates appetite and how peripheral signals from the gut, pancreas and adipose tissue can modify feeding behavior. This lecture covers the following pages in the textbook: 571-4¹.

¹ E Widmaier, H. Raff, and K. Strang. *Vander's Human Physiology: The Mechanisms of Body Function*. McGraw-Hill Science/Engineering/Math, 13th edition, 2013. ISBN 0073378305

Contents

| | |
|---|---|
| <i>Learning Objectives</i> | 2 |
| <i>Hypothalamic Control of Appetite</i> | 2 |
| <i>Neural Circuitry that Regulates Appetite</i> | 2 |
| <i>Glucose and Fatty Acid Sensing</i> | 3 |
| <i>Hormonal Regulation of Appetite</i> | 4 |
| <i>Pancreatic Regulation of Appetite</i> | 4 |
| <i>Ghrelin, PYY and the Gut Hormones</i> | 4 |
| <i>Leptin and the Adipokines</i> | 5 |
| <i>Obesity, Negative Feedback and the Role of the Blood Brain Barrier</i> | 5 |
| <i>Treatment of Neuroendocrine Obesity</i> | 6 |

Learning Objectives

For this lecture, the learning objectives are:

- Describe the appetite-regulating hormones secreted from the gut, how they are regulated and under what conditions they are released.
- Describe the AgRP/POMC circuit and its relationship to both circulating factors and neuropeptides.
- Understand the relationship between adipose mass and appetite regulation, including how adipokines are regulated and what role they play.
- List the effects of insulin on appetite and what the neurological targets of insulin are.
- Describe the role of the blood-brain barrier in the regulation of appetite and how it is altered in obesity.
- Describe how hypothalamic feeding circuits integrate with other pleasure and reward circuits in the brain.
- Explain how neuroendocrine obesity differs from idiopathic obesity and how they might be treated in different ways.

Hypothalamic Control of Appetite

Appetite regulation is a complex behavior, requiring both peripheral and cognitive inputs. The most important site for appetite regulation is within the hypothalamus, which as we discussed, is the most important location by which the central nervous system and the endocrine system intersect.

Neural Circuitry that Regulates Appetite

The primary neural circuit that regulates appetite is the POMC/AgRP system within the arcuate nucleus of the hypothalamus. Typically POMC² neurons signal to other parts of the brain to reduce food-seeking behavior. This signaling can be repressed by a second set of neurons, called AgRP³ neurons, other synaptic inputs or blood-borne signals. This circuit is shown below in Figure 1, modified from 4.

When they fire, POMC neurons release several neurotransmitters which regulate feeding and mood. One of the most important of these is α -MSH, a POMC derived peptide hormone which binds to receptors in the PVN⁵ of the hypothalamus. Downstream of the α -MSH receptor⁶, food intake is suppressed and energy expending

² Occasionally called CART neurons

³ These are sometimes called NPY neurons. These induce food seeking behavior when active.

⁴ Christopher G Bell, Andrew J Walley, and Philippe Froguel. The genetics of human obesity. *Nature reviews. Genetics*, 6(3):221–234, 2005. ISSN 1471-0056. DOI: 10.1038/nrg1556

⁵ paraventricular nucleus

⁶ known as the melanocortin 4 receptor or MC4R

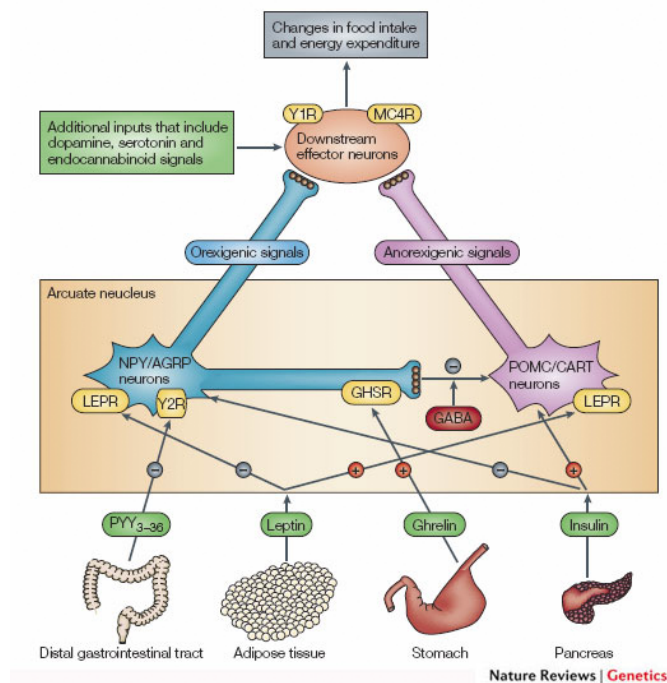


Figure 1: Neural circuitry of appetite regulation

processes are activated.

IN ADDITION TO α -MSH, another POMC-derived peptide, named β -endorphin is also released in response to feeding. Endorphins⁷ function on the reward centers of the brain and mediate the hedonistic response to food.

⁷ these are endogenous opioids

Glucose and Fatty Acid Sensing

Since the blood-brain barrier of the hypothalamus is partially exposed to systemic blood factors, the hypothalamus can directly sense both glucose and fatty acids levels in the blood. In the case of glucose, a glucose/ K^+ co-transporter can cause depolarization of POMC neurons⁸. There are also glucose-responsive and fatty-acid responsive neurons in the subfornical organ⁹ and area postrema¹⁰, which can synapse to POMC neurons and inhibit them indirectly.

ASIDE FROM DIRECT SENSING OF METABOLITES, there are several hormones which can modify the POMC/AgRP circuit in order to suppress or promote appetite. These include adipose, gut and pancreatic derived hormones, which we will discuss below.

⁸ Laura E Parton, Chian Ping Ye, Roberto Coppari, Pablo J Enriori, Brian Choi, Chen-Yu Zhang, Chun Xu, Claudia R Vianna, Nina Balthasar, Charlotte E Lee, Joel K Elmquist, Michael A Cowley, and Bradford B Lowell. Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. *Nature*, 449 (7159):228–232, 2007. ISSN 0028-0836. DOI: 10.1038/nature06098

⁹ This area of the brain came up with a different hormone, do you remember which one?

¹⁰ These are two other brain regions which can sense blood factors directly, due to absent or weakened blood-brain barrier

Hormonal Regulation of Appetite

Conceptually, there are several reasons for why it would be beneficial for the periphery to stimulate or suppress appetite. One example is that in times of acute stress, adrenaline can cause anorexia^{11,12} as a way to focus on escaping from the immediate stressor. The major endocrine factors which modulate appetite are summarized below in Table 1:

| Hormone | Source | Signal | Response |
|---------------------|--------------------------|-----------------|------------|
| Adrenaline | Adrenal medulla | Acute stress | Anorexic |
| Insulin | Pancreatic β cells | Hyperglycemia | Anorexic |
| PYY ₃₋₃₆ | L-Cells of GI Tract | Food Intake | Anorexic |
| Ghrelin | Ghrelin Cells in Stomach | Stomach Stretch | Orexigenic |
| Leptin | Adipocytes | Adipocyte Size | Anorexic |

¹¹ reduced appetite

¹² M Russek and S Pina. Conditioning of adrenalin anorexia. *Nature*, 193: 1296–1297, 1962. ISSN 0028-0836. DOI: 10.1038/1931296a0

Table 1: Summary of the major appetite regulating endocrine hormones.

Pancreatic Regulation of Appetite

In the previous lecture, we discussed how the pancreas releases insulin in response to elevated blood glucose levels. If able to pass the blood-brain barrier¹³, insulin can also act on the brain as an appetite suppressing signal. There are insulin receptors both on POMC and AgRP neurons, which through mechanisms that are currently unclear, co-ordinately reduce food intake. If brain insulin receptors are genetically deleted, mice over-eat and become obese¹⁴

¹³ This process requires a transporter.

Ghrelin, PYY and the Gut Hormones

There are at least two major hormones released from the gastrointestinal tract that regulate food intake, ghrelin and PYY¹⁵.

Normally, ghrelin is released from specialized cells in the stomach. Ghrelin activates GPCR signaling¹⁶ on the AgRP neurons of the arcuate nucleus, resulting in decreased activation of POMC¹⁷ and MC4R cells and increased food intake. When the stomach is stretched¹⁸ ghrelin release is inhibited¹⁹. In this way, the stomach can signal to the brain to prevent further food intake.

¹⁴ J C Brüning, D Gautam, D J Burks, J Gillette, M Schubert, P C Orban, R Klein, W Krone, D Müller-Wieland, and C Ronald Kahn. Role of brain insulin receptor in control of body weight and reproduction. *Science (New York, N.Y.)*, 289(5487):2122–2125, 2000. ISSN 0036-8075. DOI: 10.1126/science.289.5487.2122

¹⁵ Peptide YY

¹⁶ Gq, but the mechanisms by which ghrelin regulates neuronal firing are not clear.

¹⁷ Due the release of AgRP inhibition.

¹⁸ As in after a meal

¹⁹ Just like renin release is blocked by reduced stretch of JG cells.

PYY IS A PEPTIDE HORMONE RELEASED FROM ENTEROENDOCRINE CELLS of the colon called L-cells. The release of this peptide is stimulated by elevated nutrients in the colon, but also can be stimulated by release of upper-GI tract hormones such as CCK²⁰. PYY has several roles in digestion, including stimulating exocrine release of pancreatic enzymes and modulating GI tract motility. In addition to these

²⁰ see Dr. Cordero-Morales' lectures for more information on this

effects, PYY also has potent appetite suppression effects. PYY signals via AgRP neurons, inhibiting their normal pro-feeding function. The mechanisms by which this GPCR-dependent signaling alters AgRP firing is still unclear.

Leptin and the Adipokines

One of the most surprising sources of hormones, identified in the past 20 years or so is leptin. In the 1950s, a naturally occurring mutant mouse was found that had extreme susceptibility to obesity due to unrestrained over-eating²¹. It took almost 50 years, but eventually the location of this mutation was identified to be a novel secreted polypeptide, exclusively expressed in adipose tissue²². Since that time, several other hormones have been identified as secreted from adipose tissue²³.

LEPTIN'S PRIMARY ROLE IS TO INHIBIT FOOD INTAKE IN THE BRAIN. Leptin signals through JAK/STAT receptors in both POMC and AgRP neurons. When adipose tissue expands, and animals are fed, leptin release is elevated. This causes transcriptional and post-translational changes in both POMC and AgRP neurons, which result in reduced food intake.

Obesity, Negative Feedback and the Role of the Blood Brain Barrier

The identification of appetite suppressing hormones such as PYY and Leptin lead to a lot of excitement in the obesity field. It was hoped in the same way that exogenous insulin "cured" type I diabetes, obesity could be treated by administration of these hormones. Unfortunately this has not proven to be effective, for the same reason that providing insulin is minimally effective in type 2 diabetes²⁴. In both cases, the circulating hormone is already at elevated levels in the disease state and negative feedback mechanisms have been activated. This means, that further leptin is ineffective, because in obese states, people are normally already effectively leptin resistant.

ONE OF THESE NEGATIVE FEEDBACK MECHANISMS is receptor desensitization in the hypothalamus, but this problem is further exacerbated by the presence of the blood-brain barrier. Many of these hormones require transport mechanisms to cross into the hypothalamus, and in the case of at least insulin and leptin, this transport is reduced in obesity.

²¹ A M Ingalls, M M Dickie, and G D Snell. Obese, a new mutation in the house mouse. *The Journal of heredity*, 41(12):317-8, December 1950. ISSN 0022-1503. URL <http://www.ncbi.nlm.nih.gov/pubmed/14824537>

²² Y Zhang, R Proenca, M Maffei, M Barone, L Leopold, and J M Friedman. Positional cloning of the mouse obese gene and its human homologue. *Nature*, 372(6505):425-32, December 1994. ISSN 0028-0836. DOI: 10.1038/372425a0. URL <http://www.ncbi.nlm.nih.gov/pubmed/7984236>

²³ Collectively these are known as adipokines.

²⁴ Now would be a good time to remember why insulin is also not effective long-term for the control of type 2 diabetes!

Treatment of Neuroendocrine Obesity

The majority of obese individuals do not have a single-gene defect that results in their phenotype, but a small subset of patients do have a defined genetic lesion. Many of these mutations are in these described endocrine pathways (see Table 2).

These patients are suffering from an etiologically distinct disease, relative to the general population. They have a specific endocrine defect that is in principle able to be repaired. As an example, the patients with *LEP* mutations *can* be effectively treated with exogenous leptin²⁵.

This was the last informational lecture in this series, in our final lecture we will discuss a clinical case from the textbook, putting some of the principles and hormones we have learned to practice. We will also do a review session of quiz questions during that lecture time.

List of Figures

- 1 Neural circuitry of appetite regulation 3

List of Tables

- 1 Summary of the major appetite regulating endocrine hormones. 4
- 2 Selected monogenic disorders of obesity. Percentages are the percent of obese individuals 6

References

- Christopher G Bell, Andrew J Walley, and Philippe Froguel. The genetics of human obesity. *Nature reviews. Genetics*, 6(3):221–234, 2005. ISSN 1471-0056. DOI: 10.1038/nrg1556.
- J C Brüning, D Gautam, D J Burks, J Gillette, M Schubert, P C Orban, R Klein, W Krone, D Müller-Wieland, and C Ronald Kahn. Role of brain insulin receptor in control of body weight and reproduction. *Science (New York, N.Y.)*, 289(5487):2122–2125, 2000. ISSN 0036-8075. DOI: 10.1126/science.289.5487.2122.
- I Sadaf Farooqi, S A Jebb, G Langmack, E Lawrence, C H Cheetham, A M Prentice, I A Hughes, M A McCamish, and S O’Rahilly. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *The New England journal of medicine*, 341(12):879–84, September 1999. ISSN 0028-4793. DOI: 10.1056/NEJM199909163411204. URL <http://www.ncbi.nlm.nih.gov/pubmed/10486419>.

| Gene | Role | Incidence |
|-------------|------------------------|-----------|
| <i>LEP</i> | Leptin | rare |
| <i>LEPR</i> | Leptin Receptor | 2-5% |
| <i>POMC</i> | Several hormones | rare |
| <i>MC4R</i> | α -MSH Receptor | 2-5% |

Table 2: Selected monogenic disorders of obesity. Percentages are the percent of obese individuals

²⁵ I Sadaf Farooqi, S A Jebb, G Langmack, E Lawrence, C H Cheetham, A M Prentice, I A Hughes, M A McCamish, and S O’Rahilly. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *The New England journal of medicine*, 341(12):879–84, September 1999. ISSN 0028-4793. DOI: 10.1056/NEJM199909163411204. URL <http://www.ncbi.nlm.nih.gov/pubmed/10486419>

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