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: 571-4 [1].

[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

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 POMC[2] signal to other parts of the brain to reduce food-seeking behavior. This signaling can be repressed by a second set of neurons, called AgRP[3] 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 and mood. One of the most important of these is α-MSH, a *POMC* derived peptide hormone which binds to receptors in the PVN[5] of the hypothalamus. Downstream of the α-MSH receptor[6], food intake is suppressed and energy expenditure

[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*

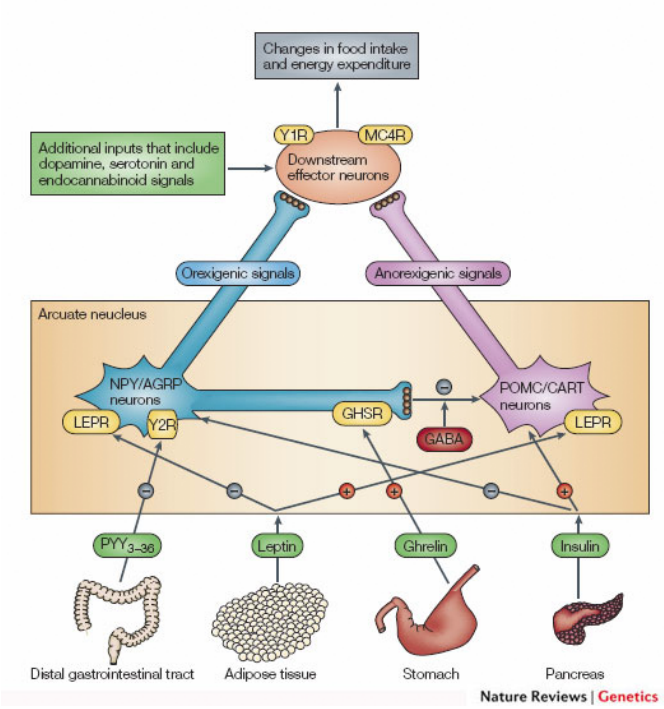

Figure 1: Neural circuitry of appetite regulation

processes are activated.

In addition to α-MSH, another *POMC*-derived peptide, named β-endorphin is also released in response to feeding. Endorphins[7] function on the reward centers of the brain and mediate the hedonistic response to food.

[7] these are endogenous opiods

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 neurons[8]. There are also glucose-responsive and fatty-acid responsive neurons in the subfornicular organ and area postrema[9], 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] 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 the periphery to stimulate or suppress appetite. One example is that in times of acute stress, adrenaline can cause anorexia[10,11] as a way to focus on escaping from the immediate stressor. The major endocrine factors which modulate appetite are summarized below in Table 1:

[10] reduced appetite

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

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

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 barrier[12], 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 obese[13]

[12] This process requires a transporter.

[13] 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

Ghrelin, PYY and the Gut Hormones

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

Normally, ghrelin is released from specialized cells in the stomach. Ghrelin activates GPCR signaling[14] on the AgRP neurons of the arcuate nucleus, resulting in decreased activation of POMC[15] and MC_4R cells and increased food intake. When the stomach is stretched[16] ghrelin release is inhibited[17]. In this way, the stomach can signal to the brain to prevent further food intake.

[14] Gq, but the mechanisms by which ghrelin regulates neuronal firing are not clear.

[15] Due the release of AgRP inhibition.

[16] As in after a meal

[17] Just like renin release is blocked by reduced stretch of JG cells.

PYY[18] 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 CCK[19]. PYY has several roles in digestion, including stimulating exocrine release of pancreatic enzymes and modulating GI tract motility. In addition to these

[18] Peptide YY

[19] see Dr. Johnson's 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 occuring mutant mouse was found that had extreme susceptibility to obesity due to unrestrained over-eating[20]. It took almost 50 years, but eventually the location of this mutation was identified to be a novel secreted polypeptide, exclusively expressed in adipose tissue[21]. Since that time, several other hormones have been identified as secreted from adipose tissue[22].

[20] 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

[21] 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

[22] Collectively these are known as adipokines.

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 efficient, for the same reason that providing insulin is minimally effective in type II diabetes. 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.

AMONG THESE NEGATIVE FEEDBACK MECHANISMS are receptor desensitization, 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.

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 leptin[23].

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.

Gene	Role	Incidence
LEP	Leptin	rare
LEPR	Leptin Receptor	2-5%
POMC	Several hormones	rare
MC4R	α-MSH Receptor	2-5%

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

[23] 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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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.