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Neural regulation of food intake and energy balance

Marcelo O. Dietrich and Tamas L. Horvath

Obesity has reached epidemic proportions worldwide, and the economic cost of treating its health consequences has been estimated at more than US$100 billion in the United States alone. Research efforts are aimed at increasing our understanding of how the brain regulates food intake to identify potential targets for anti-obesity drugs. Information about the body's metabolic state is conveyed to the brain by hormones, peptides and nutrients from the periphery. During a state of hunger, the brain triggers an orexigenic response; conversely, during satiety, the brain prompts an anorexigenic response. In the past few decades, numerous molecules have been identified as playing a part in the regulation of energy balance. Their discovery has helped to unravel a complex network involving peripheral tissues and the brain to coordinate food intake. This poster provides an overview of some of the molecules and circuits involved in the regulation of feeding behaviour.

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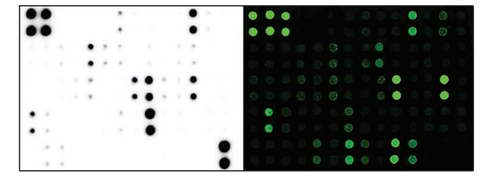
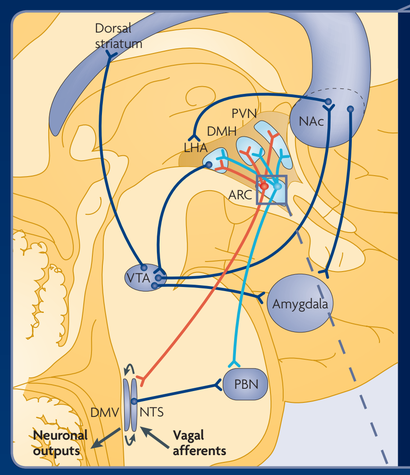


To adapt to daily variations in energy intake and expenditure, our bodies sense and integrate information about energy availability that is conveyed to the brain by hormones and nutrients from the periphery. These molecules regulate feeding behaviour by acting on neurons in the hypothalamus and the brainstem.

During periods of satiety, the body works towards storage of the acquired nutrients. Satiety is associated with increased sympathetic activity, which promotes both insulin release by the pancreas (and thus stimulates glucose storage in the liver and muscle) and fat deposition (which leads to a rise in leptin levels). Food ingestion results in a release of incretins by the gut. These include GLP1, which stimulates the pancreas to secrete insulin; both GLP1 and insulin are thought to reduce food intake by acting directly in the brain. In pancreatic β-cells, the hormone amylin is co-released with insulin in response to a meal. It is a potent satiety signal, inhibits digestive secretion and slows gastric emptying. The precise brain targets of amylin are not known, but include the area postrema (AP) in the brainstem and the lateral hypothalamus. Two further examples of gut peptides released in response to food intake are PP and OX, which act in the stomach to slow gastric emptying and putatively act in the brain to decrease food intake.

Conversely, during periods of hunger, the hypothalamus regulates the activity of the autonomic nervous system to promote fat release from white adipose tissue and trigger gluconeogenesis in the liver. These changes in peripheral nutrient levels lead to a decrease in the levels of thyroid hormones, insulin and leptin, and to an increase in the level of ghrelin and corticosteroids, which increase food-seeking behaviour through their effect on the brain.

The hormones and peptides mentioned above are only a few among a myriad of molecules thought to be involved in the regulation of energy balance. Research into this complex system continues to identify new candidates that could be pharmacologically targeted to regulate energy balance.

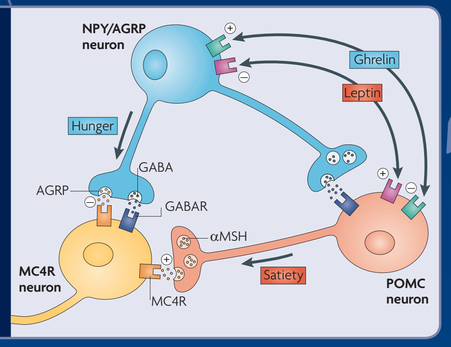


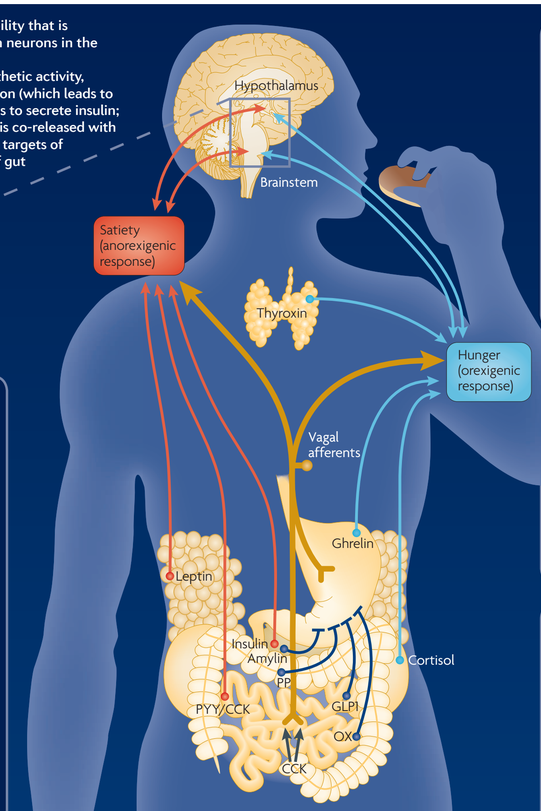
Brain nuclei involved in energy balance regulation

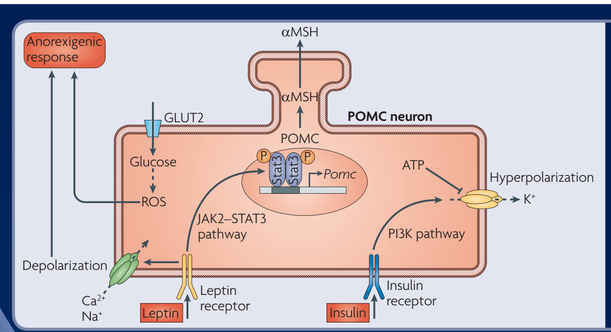
Neurons of the arcuate nucleus (ARC) in the hypothalamus project to the lateral hypothalamus (LHA), which sends projections to the nucleus accumbens (NAc) through the ventral tegmental area (VTA). The NAc is thought to mediate most of the rewarding effects of food intake. The dopaminergic neurons in the VTA also send projections to other brain regions that mediate the hedonic aspects of feeding, such as the amygdala and the dorsal striatum. ARC neurons also project to the parabrachial nucleus (PBN), which mediates food aversion. Furthermore, ARC projections regulate the activity of neurons in the paraventricular nucleus (PVN), the dorsomedial nucleus (DMH) and the ventromedial nucleus (VMN) (not shown) of the hypothalamus, which have a role in maintaining energy balance. In addition, the ARC projects to the nucleus tractus solitarius (NTS) in the brainstem. Local connections in the brainstem, such as that between the NTS and the dorsal motor nucleus of the vagal nerve (DMV), integrate hormonal and neuronal stimuli and so help to regulate feeding behaviour. Red lines indicate basic anorexigenic signals, light blue lines indicate basic orexigenic signals and dark blue lines indicate other, downstream signals.

Signalling in the arcuate nucleus

Two populations of neurons in the ARC have opposite effects on feeding. POMC-expressing neurons are activated by anorexigenic stimuli and release the POMC derivative αMSH, which is an agonist of MC4Rs. These receptors are expressed in neurons in various target nuclei that inhibit feeding behaviour. By contrast, NPY/AGRP-expressing neurons are activated by orexigenic stimuli. They inhibit both POMC-expressing neurons and MC4R-expressing neurons through the release of GABA and AGRP, resulting in the induction of food-seeking behaviour. AGRP acts as a potent endogenous antagonist of MC4Rs, in opposition to αMSH. Projections from NPY/AGRP-expressing neurons are mostly coupled to projections from POMC-expressing neurons, so that MC4R-expressing target neurons receive both negative and positive input.







Leptin and insulin signalling

By binding to its receptor in POMC-expressing neurons, leptin activates the JAK2–STAT3 pathway, which ultimately leads to an increase in POMC expression. Subsequently, convertases cleave POMC to generate αMSH. Once released, αMSH binds to and activates MC4R-expressing target neurons, inducing an anorexigenic response. Specific enzymes in the synapse (for example, PRCP) cleave and inactivate αMSH. Leptin can also rapidly depolarize POMC-expressing neurons by opening as yet unidentified, non-specific cation channels.

The binding of insulin to its receptor activates the classical PI3K pathway, which opens K_{ATP} channels and so hyperpolarizes the POMC-expressing neuron. Glucose uptake by neurons occurs through specialized glucose transporters, such as GLUT2. It has been proposed that the increase in glucose levels following feeding leads to an increase in glucose uptake in POMC-expressing cells, which raises levels of ATP and subsequently closes the the K_{ATP} channel. Glucose oxidation also produces ROS, which may be involved in the anorexigenic response.

Model of ghrelin signalling

Ghrelin binds to the GHSR in NPY/AGRP-expressing neurons, leading to an immediate depolarization of the cell membrane and an increase in neuron firing rate. Ghrelin signalling involves phosphorylation of AMPK, with consequent phosphorylation and inhibition of ACC. This decreases the levels of malonyl-CoA, leading to a disinhibition of CPT1, which enables the cell to β-oxidize LCFAs to generate ATP and ROS. ROS activate mitochondrial UCP2, which limits ROS production. This feedback loop between ROS and UCP2 provides a mechanism for cellular homeostasis. The sustained and regulated production of ROS also stimulates the transcription of genes involved in the production of mitochondria (for example, *Nrf1*) and in the orexigenic response (for example, *Npy* and *Agrp*), which helps to sustain the activity of these cells during periods of hunger.

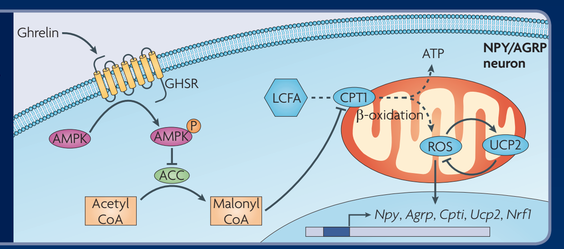


Table | Anti-obesity drugs in development

Drug (company)	Mechanism	Effect in humans	Development stage
Peptidase inhibitors	Inhibit peptidases, such as prolylcarboxypeptidase	• Decreased food intake • Decreased body weight (estimated)	Experimental
MCHR1 antagonists	Inhibits MCHR1	• Decreased food intake • Decreased body weight (estimated)	Experimental Awaiting clinical studies
Lorcaserin (Arena)	Stimulates the 5-hydroxytryptamine (serotonin) receptor 2C	• Decreased body weight (>5%) • No major side effects	Phase III
Qnexa: phentermine plus topiramate (Vivus)	Stimulates noradrenaline release Stimulates GABA receptors	• Decreased body weight (>5%) • No major side effects	Phase III
Contrave: bupropion plus naltrexone (Orexigen)	Inhibits dopamine reuptake Inhibits opioid receptors	• Decreased body weight (>5%) • Two cases of seizures reported	Phase III
Davalintide (Amylin Pharmaceuticals)	Mimics the effects of amylin	• Acutely decreased 24-hour food intake in obese subjects	Phase II
Pramlintide/ Metreleptin (Amylin Pharmaceuticals)	Mimics the effects of amylin and leptin	• Decreased body weight	Phase II
TM30339 (7TM Pharma A/S)	A PP analogue that binds to neuropeptide Y4 receptors	• Inhibited food intake • Reduced ghrelin levels	Phase II
Exenatide (Byetta) (Amylin Pharmaceuticals and Eli Lilly)	Mimics incretins such as GLP1	• Decreased body weight in some diabetic subjects	Phase III (obese non-diabetic subjects) Approved for glucose control in some diabetic patients

Obesity

Obesity can dramatically diminish both the quality and length of life. The causes of human obesity may lie in the circuitry of brain areas that regulate food-seeking behaviour in coordination with peripheral hormonal signalling. Pharmacological therapies for treating obesity are limited, mostly because of harmful side effects. Interestingly, an effective option is bariatric surgery, which has been shown to not only decrease body weight but also to improve diabetes, which is commonly associated with obesity. However, the effects of bariatric surgery on metabolism are still not completely understood.

Leptin was discovered in 1994. Individuals with rare mutations in the leptin gene developed profound, early-onset obesity that could be reversed by leptin replacement, which suggested that leptin had potential as an anti-obesity drug. Normally, however, leptin levels increase during the development of obesity. Consequently, the ARC in the hypothalamus becomes less responsive to leptin, thus promoting continuous food intake and fat deposition.

Many pharmacological approaches now attempt to promote or enhance the downstream effects of leptin by stimulating melanocortin signalling, activating POMC-expressing neurons (using serotonin and noradrenaline mimetics) or by activating MC4Rs. In addition, synthetic peptide analogues that mimic the effects of endogenous gut peptides on feeding are being tested alone or in combination with other compounds to promote weight loss (TABLE). The main objective of these studies is to activate anorexigenic brain areas or to enhance the signalling of other anorexigenic molecules. In addition, molecules that bind to peptide receptors, such as MCHR1 antagonists, are being designed with the aim of inhibiting orexigenic signalling in the brain.

Our increasing understanding of the hormonal, molecular and cellular mechanisms involved in regulating energy balance is opening several new avenues for the pharmaceutical industry to develop and test molecules aimed at treating obesity. These efforts could provide individually tailored treatment options based on the complex genetic and environmental nature of this condition.

RayBiotech, the Protein Array Pioneer Company, is committed to developing innovative proteomics tools. Since introducing the first commercially available antibody array in 2001, RayBiotech's array products have been featured in hundreds of publications, including many top-tiered journals. By offering over 500 ELISA and EIA kits and more array choices than any of its competitors, RayBiotech continues to be a pioneer in protein array technology.

To meet the growing need for obesity research, RayBiotech has expanded its diverse product range to include the most comprehensive toolkit for detection of obesity-related proteins available in today's market. RayBiotech's repertoire of products includes a wide assortment of antibodies, peptides and protein reagents, ELISA kits, EIA kits, and an exclusive line of obesity-focused antibody arrays for screening and quantification of multiple adipokines.

Antibody arrays represent a mature technology that is exceptionally easy to use; a typical array experiment can be performed in a single day. Using this technology, the researcher can screen almost any liquid biological sample for expression of multiple obesity-related neuropeptides and adipokines, including neuropeptide Y, cholecystokinin, cocaine- and amphetamine-related transcript (CART), ghrelin, orexins A and B, adipocyte complement related protein of 30 kD (ACRP30), resistin, leptin, C-reactive protein (CRP), adipsin, Agouti-related protein (AGRP), insulin, and many others. Many of these factors may be also be detected individually using RayBiotech's sandwich-based ELISA and competitive EIA kits.

RayBiotech's arrays are available in a choice of membrane or glass-slide solid supports, as well as quantitative or semi-quantitative platforms. In addition, their expert team of technicians and scientists can test large batches of samples for researchers. For more information, visit us at www.raybiotech.com.

Abbreviations

ACC, acetyl-CoA carboxylase; AGRP, agouti-related protein; AMPK, 5′-AMP-activated protein kinase; CCK, cholecystokinin; CPT1, carnitine *O*-palmitoyltransferase 1; GABA, γ-aminobutyric acid; GABAR, γ-aminobutyric acid receptor; GLP1, glucagon-like peptide 1; GLUT2, glucose transporter 2; GHSR, growth hormone secretagogue (ghrelin) receptor; JAK2, Janus kinase 2; K_{ATP} channel, ATP-sensitive K^+ channel; LCFA, long-chain fatty acids; MCH, melanin-concentrating hormone; MCHR1, melanin-concentrating hormone receptor 1; MC4R, melanocortin 4 receptor; αMSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; NRF1, nuclear respiratory factor 1; OX, oxyntomodulin; PI3K, phosphoinositide 3-kinase; POMC, pro-opiomelanocortin; PP, pancreatic peptide; PRCP, prolylcarboxypeptidase; PYY, peptide YY; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; UCP2, uncoupling protein 2.

Contact information

Marcelo O. Dietrich and Tamas L. Horvath are affiliated with the Program on Integrative Cell Signaling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University, School of Medicine, New Haven, Connecticut 06510, USA.
e-mails: marcelo.dietrich@yale.edu; tamas.horvath@yale.edu

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