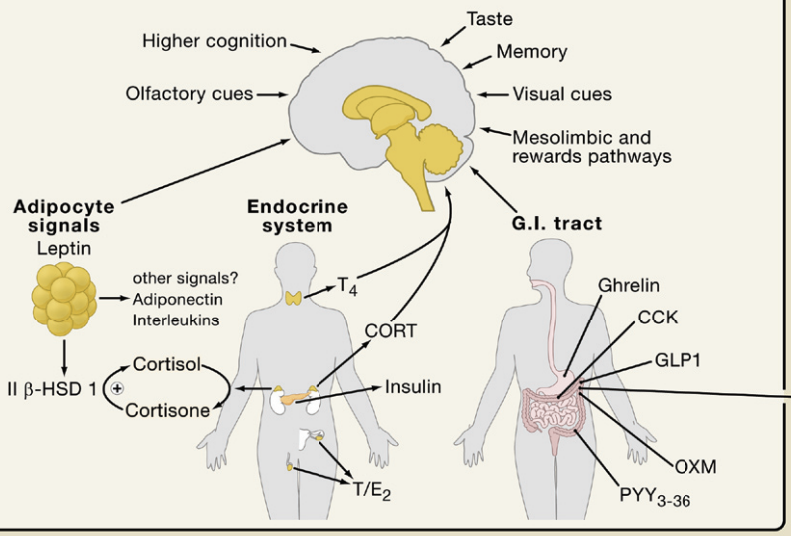
SnapShot: The Hormonal Control of Food Intake

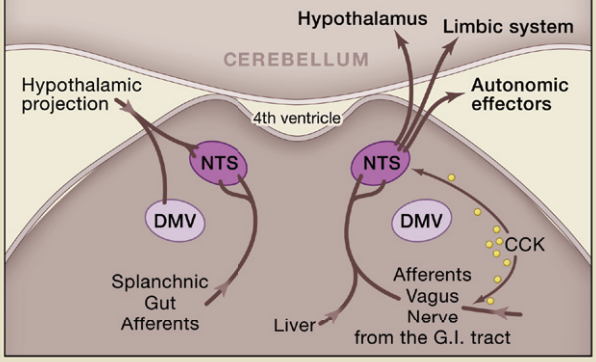
Anthony P. Coll, Giles S.H. Yeo, I. Sadaf Farooqi, Stephen O'Rahilly
Institute of Metabolic Science, University of Cambridge, Cambridge, CB2 0QQ, UK

Cell

Brain - The focal point of control



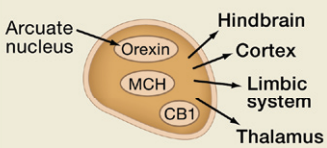
Brainstem



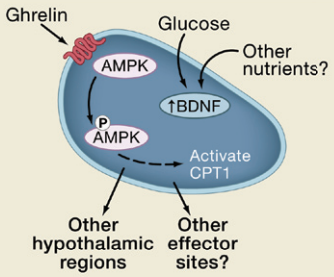
Endocannabinoids

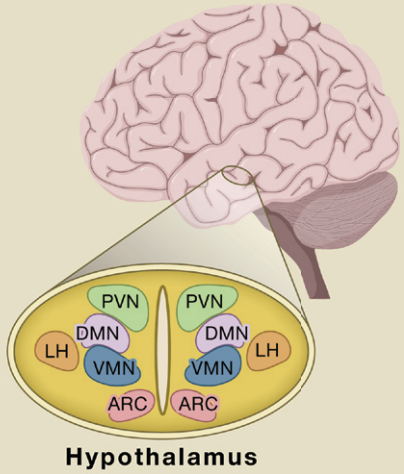
The endocannabinoid system controls food intake via central and peripheral mechanisms. CB1 receptors are present in multiple sites within the mesolimbic regions. This system may be involved in the motivation to find and eat rewarding foods. Within the hypothalamus, endocannabinoids may influence food intake by regulating expression and/or action of anorectic and orexigenic mediators in the PVN, LH, and VMN. Levels of endogenous cannabinoids, such as anandamide, are increased within the duodenum with fasting and may act via the vagus and brainstem to reduce feelings of satiety.

Lateral hypothalamus (LH)

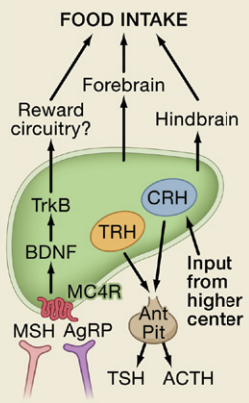


Ventromedial nucleus (VMN)



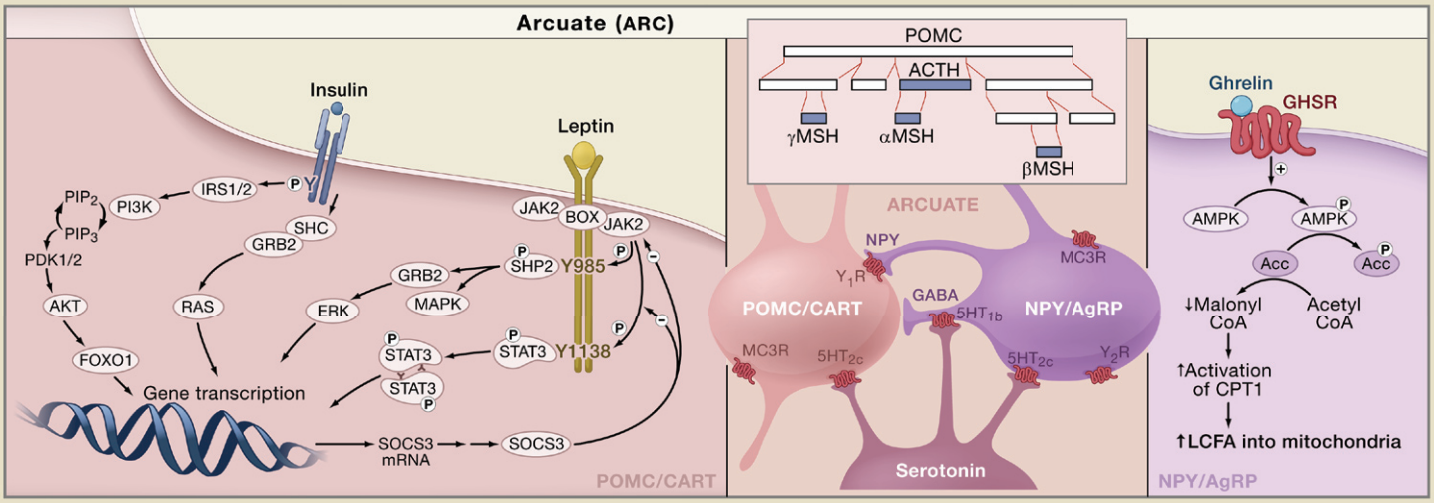


Paraventricular nucleus (PVN)



Pro-opiomelanocortin (POMC) is an inactive precursor that is posttranslationally modified to generate a range of smaller, biologically active peptides. These include ACTH and α-, β-, and γ-melanocyte-stimulating hormone (MSH), collectively known as the melanocortins. Abnormalities in POMC synthesis and processing and defects in the action of POMC-derived peptides lead to hyperphagia and obesity. Melanocortins act via a family of G protein-coupled receptors (MC1R to MC5R). MC3R and MC4R are both highly expressed in brain regions involved in the control of food intake and energy balance. Mutations within MC4R are the most common monogenic cause of obesity.

Arcuate (ARC)



See online version for legend and references.

SnapShot: The Hormonal Control of Food Intake

Anthony P. Coll, Giles S.H. Yeo, I. Sadaf Farooqi, Stephen O'Rahilly
Institute of Metabolic Science, University of Cambridge, Cambridge, CB2 0QQ, UK

Food intake is normally matched with great precision to changing energy requirements. A number of circulating peptides and endogenously produced steroids orchestrate appetitive behavior through their actions on the hypothalamus, the brain stem, or afferent autonomic nerves. These hormones come from at least three sites: fat cells, classic endocrine organs, and the gastrointestinal tract.

Hypothalamic Architecture

Within the brain, the hypothalamus is a critical region that receives and integrates these signals from the periphery. Contained within the arcuate nucleus of the hypothalamus are two populations of neurons highly responsive to leptin (Cone, 2005). One expresses POMC and CART, the other expresses both NPY and AgRP. The POMC-derived melanocortins α and βMSH are anorexigenic (appetite suppressing) whereas AgRP and NPY are potent orexigens (appetite stimulating). From the arcuate nucleus, these neurons project to other brain areas that are involved in energy homeostasis, including other regions of the hypothalamus such as the PVN, LH, and DMN. In the fed state an increase in leptin stimulates POMC neurons, increasing melanocortin levels while inhibiting AgRP neurons. This in turn increases signaling at MC4R, decreasing food intake and increasing energy expenditure. During fasting, a decrease in leptin inactivates POMC neurons (reducing melanocortin levels) and stimulates AgRP expression. The resultant decrease in MC4R signaling stimulates feeding and reduces energy expenditure. The arcuate melanocortin system is also a key site of action of 5HT (Heisler et al., 2006). Not only does 5HT inhibit NPY/AgRP neurons, but it also activates POMC neurons. The PVN receives projections from both POMC and AgRP arcuate neurons. Activation of MC4R in this region is particularly important in controlling food intake. Downstream of MC4R, the neutrophin BDNF can also act as a catabolic factor (Unger et al., 2007).

Circulating Factors

Leptin

Leptin and its downstream anorexigenic pathways have a critical role in the control of food intake (Flier, 2004). Leptin acts in the CNS through a class 1 cytokine receptor via the JAK-STAT pathway (Bates and Myers, 2003). Although its action within the hypothalamus is critical to its anorexigenic effects, there are other sites important for leptin action, including the caudal brainstem and the ventral tegmental area. Acting upon dopaminergic neurons in this latter region, leptin also influences the reward and motivational aspects of ingestive behavior (Fulton et al., 2006).

Anorectic Hormones from the Gastrointestinal Tract

CCK is a peptide released from the small intestine in response to fatty acids and acts as a post-prandial satiety signal. Acting via the afferent vagal terminals, CCK transmits signals to the caudal brainstem NTS, a region that receives a variety of gut-derived signals as well as hypothalamic projections. The NTS is reciprocally connected to a range of effector systems, both within the brain and in the autonomic nervous system. Other peptides released from the gut in response to a meal and thought to be involved in signaling satiety include PYY3-36, OXM, and GLP-1 (Chaudhri et al., 2006).

Ghrelin

Ghrelin is a hormone secreted by oxyntic glands of the stomach that stimulates appetite. Acting at several sites within the hypothalamus (Arc and VMN) the orexigenic action of ghrelin depends on the specific regulation of hypothalamic fatty acid metabolism mediated by AMPK, malonyl-coA, and CPT1 activity (Andrews et al., 2008; Lopez et al., 2008). GABA release from AgRP neurons also mediates ghrelin's stimulatory effect on food intake.

Insulin

Insulin derived from the endocrine pancreas has a major and nonredundant role in controlling the disposition of nutrients in the periphery. Insulin receptors are widely distributed within the brain (Schwartz et al., 1992) and are found within the Arc on POMC neurons. Insulin has a potent appetite-suppressive effect when given centrally, although it is unlikely that this is mediated via POMC neurons.

Endocrine System

Endocrine hormones such as cortisol, thyroxine, and estrogen all act centrally to bring about changes in food intake. However, interpretation of these effects must be tempered by the fact that each has actions across a range of other metabolically relevant tissues such as liver and muscle.

Abbreviations

AgRP, Agouti-related protein; AMPK, AMP kinase; Ant. Pit., anterior pituitary; Arc, arcuate nucleus; BDNF, brain-derived neurotrophic factor; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CNS, central nervous system; CPT1, carnitine palmitoyltransferase; DMN, dorsomedial nucleus; E_2, estrogen; GABA, gamma-aminobutyric acid; G.I., gastrointestinal; GLP-1, glucagon-like peptide 1; 5-HT, 5-hydroxytryptophan; JAK-STAT, janus kinase-signal transducer and activator of transcription; LCFA, long-chain fatty acid; LH, lateral hypothalamus; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NTS, nucleus of tractus solitarius; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; PYY 3-36, peptide YY 3-36; T, testosterone; T_4, thyroxine; VMN, ventromedial nucleus; 11 β-HSD 1, 11 β-hydroxysteroid dehydrogenase type 1.

REFERENCES

Andrews, Z.B., Liu, Z.W., Walllingford, N., Erion, D.M., Borok, E., Friedman, J.M., Tschop, M.H., Shanabrough, M., Cline, G., Shulman, G.I., et al. (2008). UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. Nature *454*, 846–851.

Bates, S.H., and Myers, M.G., Jr. (2003). The role of leptin receptor signaling in feeding and neuroendocrine function. Trends Endocrinol. Metab. *14*, 447–452.

Chaudhri, O., Small, C., and Bloom, S. (2006). Gastrointestinal hormones regulating appetite. Philos. Trans. R. Soc. Lond. B Biol. Sci. *361*, 1187–1209.

Cone, R.D. (2005). Anatomy and regulation of the central melanocortin system. Nat. Neurosci. *8*, 571–578.

Flier, J.S. (2004). Obesity wars: Molecular progress confronts an expanding epidemic. Cell *116*, 337–350.

Fulton, S., Pissios, P., Manchon, R.P., Stiles, L., Frank, L., Pothos, E.N., Maratos-Flier, E., and Flier, J.S. (2006). Leptin regulation of the mesoaccumbens dopamine pathway. Neuron *51*, 811–822.

Heisler, L.K., Jobst, E.E., Sutton, G.M., Zhou, L., Borok, E., Thornton-Jones, Z., Liu, H.Y., Zigman, J.M., Balthasar, N., Kishi, T., et al. (2006). Serotonin reciprocally regulates melanocortin neurons to modulate food intake. Neuron *51*, 239–249.

Lopez, M., Lage, R., Saha, A.K., Perez-Tilve, D., Vazquez, M.J., Varela, L., Sangiao-Alvarellos, S., Tovar, S., Raghay, K., Rodriguez-Cuenca, S., et al. (2008). Hypothalamic fatty acid metabolism mediates the orexigenic action of ghrelin. Cell Metab. *7*, 389–399.

Schwartz, M.W., Figlewicz, D.P., Baskin, D.G., Woods, S.C., and Porte, D., Jr. (1992). Insulin in the brain: A hormonal regulator of energy balance. Endocr. Rev. *13*, 387–414.

Unger, T.J., Calderon, G.A., Bradley, L.C., Sena-Esteves, M., and Rios, M. (2007). Selective deletion of Bdnf in the ventromedial and dorsomedial hypothalamus of adult mice results in hyperphagic behavior and obesity. J. Neurosci. *27*, 14265–14274.