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Neuroendocrinological Control of Obesity

Bilgin Yüksel
Çukurova University School of Medicine, Department of Pediatric Endocrinology and Metabolism, Balcalı, Adana, Turkey

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Corresponding Author:
Bilgin Yüksel
Çukurova University School of Medicine, Department of Pediatric Endocrinology and Metabolism, Balcalı, Adana, Turkey
E-mail:
byuksel@cu.edu.tr

ABSTRACT

A complex physiological system of afferent and efferent pathways provides the balance between energy intake and expenditure. Hunger initiates eating. Satiety hormones assist digestion and also partake in the feeling of satiety upon food intake. The central circuit in the brain, by integrating the satiety signals and the long term signals of energy status, coordinates the responses to the changes in the nutritional status. The primary determinant of energy intake is appetite regulation, consisting of central regulation and peripheral regulation. The central nervous system receives hormonal and metabolic signals from the periphery, of long term or of short term regulatory nature, which are interpreted and redirected to centers in the brain and peripheral organs to plan the energy homeostasis. This integrating regulation mostly takes place at the arcuate and the paraventricular nuclei of the hypothalamus. The arcuate nucleus neurons secrete orexigenic substances, such as neuropeptide Y and agouti-related peptide, and anorexigenic peptides such as pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript.

Conflict of interest: None declared

SUPPLEMENT

Energy equilibrium and maintenance of body weight depend on the balance between energy intake and energy expenditure. Obesity is the expression of a net excess in energy intake.(1) A complex physiological system of afferent and efferent pathways provides the balance between energy intake and expenditure. Hunger initiates eating. Satiety hormones assist digestion and also partake in the feeling of satiety upon food intake. The central circuit in the brain, by integrating the satiety signals and the long term signals of energy status, coordinates the responses to the changes in the nutritional status.(2) The primary determinant of energy intake is appetite regulation, consisting of central regulation and peripheral regulation. The central nervous system (CNS) receives hormonal and metabolic signals from the periphery, of long term or of short term regulatory nature, which are interpreted and redirected to centers in the brain and peripheral organs to plan the energy homeostasis. This integrating regulation mostly takes place at the arcuate and the paraventricular nuclei of the hypothalamus. The arcuate nucleus (ARC), adjacent to the third ventricle, is the locus of the central control of food intake and contains two interrelated 'first order' neurons which stimulate appetite through the neuropeptide Y (NPY) and the Agouti-related peptide (AgRP), and inhibit appetite through the pro-opiomelanocortins (POMC) and the cocaine and amphetamine related transcript (CART). The axons of these neurons make projections into the 'second order' neurons localised in the paraventricular nuclei (PVN) which release thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH) and oxytocine

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which have appetite suppressing effects. Orexin and melanin-concentrating hormone (MCH) produced in the lateral hypothalamic areas (LHA) and in the perifornical area (PFA) of the hypothalamus are appetite promoting peptides. As the adiposity signals reach the ARC, the appetite suppressive peptides are released and the catabolic trend is activated. The activation of the anabolic pathways causes the release of appetite stimulating peptides.(3)

THE PERIPHERAL REGULATION OF FOOD INTAKE

The peripheral regulators of appetite are leptin, secreted from the adipose tissue, and insulin, secreted by the endocrine pancreas, along with intestinal hormones and neurological signals, also involved in this regulation. The intestinal hormones consist of endocrine signals communicated to the CNS over specific receptors and paracrine signals communicated by the intermediation of receptors on the vagal nerves. The neurological group of signals are carried to the pons and the hypothalamic centres via the afferent vagal nerves in response to the distention in the gastrointestinal sysem, the composition, volume and the pressure of the luminal content.

The hormonal and neural signals arriving at the CNS constitute the primary system preventing excess intake of food through the short-term control of appetite. The intestinal hormones secreted in response to ingested nutrients work locally or at the level of the CNS where the hormones and the peptides are responsible for the regulation of the appetite and energy equilibrium.(1) Intestinal hormones function also as stimulators of hunger and appetite.(2) The long-term control of appetite is associated with the storage of energy in the body in the form of fat where leptin and insulin play key roles.

Ghrelin

This peptide is primarily of gastric origin although its presence in lesser amounts was shown in the pancreas, intestine, kidney, placenta, lung, hypophysis, hypothalamus and the immune system. It is a major hormone with orexigenic effect and an endogenous ligand of the GH secretagogue receptor expressed in the hypothalamic ARC nuclei and in the brain stem.(4) It establishes an endocrine network between the stomach, the hypothalamus and the hypophysis which plays a dominant role in the regulation of the energy equilibrium by the stimulation of appetite both peripherally and centrally that leads to increased food intake in man and animals.(5, 6) The serum ghrelin levels peak before food ingestion, decreasing thereafter, which indicates that the hormone is an initiator of feeding. The levels are found to be consistently higher before feeding and decrease immediately after ingestion.(7) It may also have a role in the long-term control of energy equilibrium because chronic intake of ghrelin was shown to induce adiposity.(5, 8)

In the obese, serum ghrelin levels are lower compared to those estimated in individuals with normal body weight; and, characteristically increase with loss of body weight, showing a negative correlation with body mass index (BMI), while fasting insulin and leptin levels are increased.(2, 9, 10) These findings have been interpreted as pointing towards a co-regulatory role of ghrelin and the upper gastrointestinal tract on food intake.(11) Ghrelin increases gastric and intestinal motility. While stimulating the NPY and the AgRP in the ARC, it inhibits POMC and α-MSH.(12, 13) Exogenous ghrelin decreases the release and the activity of endogenous leptin and vice versa. Leptin and ghrelin appear to have a negative regulatory role on the release and activity of each other. This counter-regulatory relationship between ghrelin and leptin has been termed as "the Argentinian ghrelin-leptin tango".(14) The weight reducing effect of leptin is not exercised only on the hypothalamic centers but also by the peripheral inhibitory effects on secretion and activities of ghrelin.

Signals of satiety

The control of the amount of food intake is largely determined by the start of the satiety signals which develop in the gastrointestinal system during feeding. As nutrients enter the intestinal lumen the secretion of various peptides is stimulated and signals over the vagal and sympathetic pathways are directed to the NTS in the pons. This area may integrate the peripheral signals of satiety and adiposity with those in the hypothalamic centers.

Cholecystokinin: When nutrients enter the intestinal lumen, cholecystokinin (CCK), secreted by duodenal and ileal cells primarily in response to fats and proteins, bind specific receptors(15) and inhibition of food intake takes place.(16, 17) It also induces gall bladder contraction, gastric acid and pancreatic secretions, and slows down gastric emptying. Short-term infusion of CCK in humans suppresses appetite, though long-term effects are not known.(1, 2) CCK is also produced in the CNS and causes suppression of appetite through the hypothalamic centers.

Glucagon-like peptide-1: Following food intake, especially in response to ingestion of carbohydrates and lipids, glucagon-like peptide-1 (GLP-1) is released by the intestines in the form of pro-glucagon.(1, 18) This peptide slows down gastric emptying and intestinal motility, decreasing appetite, increasing insulin secretion and promoting the sensation of satiety. All of these effects can be made use of in the treatment of type-2 diabetes mellitus (DM).[1] In the obese, GLP-1 secretion is decreased and normalised by weight loss.(19, 20)

Peptide YY: Following food ingestion, peptide YY (PYY) is released from the L-cells in the distal segment of the small gut, resulting in the induction of satiety.(3, 11) It reduces the rate of intestinal motility and gall bladder and gastric emptying. It acts via the vagal paths and NTS, and the activation of hypothalamic POMC neurons and the anorexinergic cycle.(21) Peripheral infusion of PYY reduces appetite. Its circulatory level is lowered in obesity. PYY replacement is seen as a potential choice of treatment for reducing overweight.(2, 11, 22)

Oxyntomodulin: Like GLP-1, oxyntomodulin (OXM) is also released by the intestinal L-cells as a pro-glucagon following food ingestion. Intravenous infusion reduces food intake, appetite and promotes weight reduction.(1, 11)

Amylin: Amylin, the islet amyloid polypeptide (IAPP) is a 37-residue peptide hormone, produced and stored by the β-cells of the endocrine pancreas in the 'insulin granule' and secreted at the same time as insulin in response to meals. It is effective in the reduction of blood glucose concentration and promotes slowing of gastric emptying and the feeling of satiety by direct action on the CNS. It appears to act synergistically with insulin as an inhibitor of the appearance of nutrient, especially of glucose, in the plasma. In the obese, high amylin levels are seen to be sustained postprandially.(23)

Leptin: A 167-aminoacid protein encoded on *ob* gene, leptin was discovered in 1994. It is mainly produced by the *white adipose cells*, and in lesser quantities in the stomach, placenta, mammary gland tissue and skeletal muscle. Its levels in the plasma are closely correlated with the adipose tissue mass, volume and triglyceride content.

Adipose tissue mass and volume, visceral and sub-cutaneous distribution of fat, hormones like insulin, ghrelin, the glucocorticoids, sex hormones, cytokines like the tumour necrosis factor (TNF-α) and interleukin-1 (IL-1), and acute changes in the calory intake (like starvation or over ingestion) affect serum leptin levels.(24, 25, 26) The principal controlling factors are the energy stored in the fat cells and the acute changes in calory intake. Leptin biosynthesis is promoted by oestrogen in females resulting in higher circulating levels, whereas androgens, by inhibiting biosynthesis, lower these levels.(27) Leptin levels are also raised by chronic corticosteroid intake and by inflammatory cytokine levels, and lowered after exposure to cold and adrenergic stimulation, by thyroid hormones, fasting

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and increased levels of circulating free fatty acides (FFA).

Leptin levels rise in obesity, and regress in weight loss. The secretory pattern is pulsatile in character and shows diurnal variation.(28) It sustains a long-term control on the adipose tissue and regulates the adaptive metabolic changes in the cells.

Leptin levels rapidly fall during hunger, this reduction acts like a signal for transition from a state of satiety to that of hunger and results in suppression of energy expenditure, immune functions, release of thyroid and growth hormones. The net influence of leptin on these adaptive changes to lower the high energy demand of the reproductive system and of growth and have a positive effect on the build-up of immunity and energy reserves is, however, limited.

Leptin may be involved in the control of the short-term energy intake and the food intake comensurate with changes in the energy equilibrium. In overall negative energy balance, the lowered leptin signals result in the activation of the anabolic cycles by increasing the NPY/AgRP secretion, and inhibition of the catabolic cycles by blocking the POMC/CART neuron activities. Hence, food intake increases while energy expenditure decreases. Restriction of food intake lowers leptin levels. In the rodent, peripheral or central input of leptin results in reduced food intake and weight loss.(29) Leptin's influence on the ARC nucleus results in the stimulation of the anorexinergic neurons and the inhibition of the orexinergic neurons. It can be said that basically low leptin levels act as a signal for hunger and raised levels for storage of fat.(30)

Congenital lack or inadequacy of leptin results by way of negative feedback in hyperphagia and obesity. Leptin treatment in the mice with the *ob/ob* leptin insufficiency prevents the development of obesity; and similarly, in patients with leptin insufficiency the replacement suppresses appetite and reduces weight and especially the adipose mass. In patients heterozygous for leptin gene mutation, the resultant partial leptin insufficiency shows a strong correlation with body adipose mass. This condition reflects the presence of resistance to leptin. Leptin resistance in obesity either stems from a *transport defect* in the blood-brain barrier impeding the access of leptin to targets in the brain parenchyma or from *postreceptor defects* which induce inhibition of the leptin signals in the hypothalamic nuclei.

Insulin: This hormone is the long-term regulator of the energy equilibrium and is essential for the formation of the adipose tissue. Weight increase results in hyperinsulinaemia and insulin resistance. Insulin enters the brain and promotes the reduction of energy intake through the activation of the catabolic pathways. Binding specific receptors in the brain cause reduction of appetite and increase energy expenditure. This effect takes place, similar to that of leptin, by inhibition of the NPY and AgRP in the ARC nuclei and the PVN, and the activation of the POMC and CART neuronal paths which stimulate the satiety center. However, serum insulin levels being very sensitive to the acute effects of food ingestion, the basic physiological function of insulin is to control glucose homeostasis rather than body weight.(31)

THE CENTRAL REGULATION OF FOOD INTAKE

Neuropeptide Y

NPY is the most effective appetite promoter, so far only studied in animal models, primarily through action on the ARC nuclei.(3) In the rat, central uptake of NPY results in hyperphagia and adipogenesis and inhibition of thermogenesis.(32, 33) NPY expression in the CNS increases with low circulating leptin levels, hypoglycaemia, hypoinsulinaemia and with negative energy balance.(3) To date 6 different NPY receptors have been recognised, the anabolic effects being exercised through the Y1 and Y5 receptors.

Agouti-related peptide

AgRP is a powerful orexinergic peptide, the release of which from the ARC neuclei can be inhibited by leptin infusion.(3) AgRP stimulates appetite by antagonising the Melanocortin Receptors MC-3 and MC-4. Its levels are raised in obesity. The human chromosomal polymorphism '199G→A' has been shown to be correlated with late onset obesity.(34)

Pro-opiomelanocortin

POMC is the precursor of the molecules known as the melanocortins, the most important member of which, the α-melanocyte stimulating hormone (α-MSH) is localised in the ARC nuclei and inhibits food intake.(2, 3) This anorexinergic effect is expressed through the MC3R and MC4R, a genetic mutation for the MC4R having been determined in more than 5% of the cases with nonsyndromic obesity. Heterozygous mutations are characterised with severe obesity, hyperphagia, hyperinsulinaemia, increased body fat mass and tall stature. Homozygotic mutations present with more severe phenotypic anomalies.(35) In humans a mutation on the POMC gene has been shown to progress with early onset of severe obesity, adrenal insufficiency and red pigmented hair.(36) Some MC4R analogues may be candidates for long acting anorexinergic therapeutic agents. Mutations on the human MC3R gene have also been demonstsrated to lead to obesity.(3, 37)

Cocaine and amphetamine regulated transcripts

Approximately 90% of the cocaine and amphetamine regulated transcript (CART), neurons are localised in the ARC neuclei. It is thought that the anorexinergic effect of CART is mediated by the central uptake of GLP-1, since the hypophagia induced by CART is inhibited by the blockage of the GLP-1 receptors.(38) In the animal model, intraventricular CART uptake reduces food intake. In the genetically obese *ob/ob* mice CART expression is diminished and returns to normal by leptin replacement which suggests that the anorexinergic effects of leptin are partially expressed by the CART intermediation.(1) A missense mutation on the human CART gene has been shown to result in severe obesity and reduction in resting energy expenditure.(39)

Endocannabinoids

These neuromodulator group of compounds function in the transfer of metabolic information on feeding habits from the CNS to the peripery.(3) They contribute through their central and peripheral effects to the regulation of the energy equilibrium, food intake and fat and glucose metabolism. The endocannobinoid system is highly active in the genetically obese animal models. The *anandamides* or AEA, derived from membrane phospholipids and 2-*arachidonoylglycerol* or 2-AG, derived from triglycerides are the two major cannabinoid receptor ligands in the brain, acting as retrograde messengers. In the *ob/ob* mice with leptin insufficiency the hypothalamic endocannabinoid levels increase, but decrease with leptin replacement. The levels of endogenous cannabinoids were found to be increased in obese women. The use of cannabinoid antagonists in the treatment of obesity is currently being investigated.(40)

The monoaminergic neurotransmitters

These amninated aromatic group of neurotransmitting and modulating agents interact with hormones in the control of the satiety mechanisms and feeding habits. Serotonin, norepinephrin and dopamine are examples of this group of compounds.

Serotonin: It plays a role in the reduction of appetite, food intake and weight loss by increasing energy utilisation.

Norepinephrin: Norepinephrin (NE) causes stimulation of food intake by the intermediation of α2 receptors. In the *ob/ob* mice with leptin insufficiency NE levels are increased.

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Dopamine: Dopamine (DA) supresses food intake by action on the ARC nuclei and the LHA, and stimulates the ventromedial hypothalamic (VMH) neurons. In the *ob/ob* mice with leptin insufficiency DA levels have been found to be decreased.

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