GHRELIN, LEPTIN AND OBESTATIN

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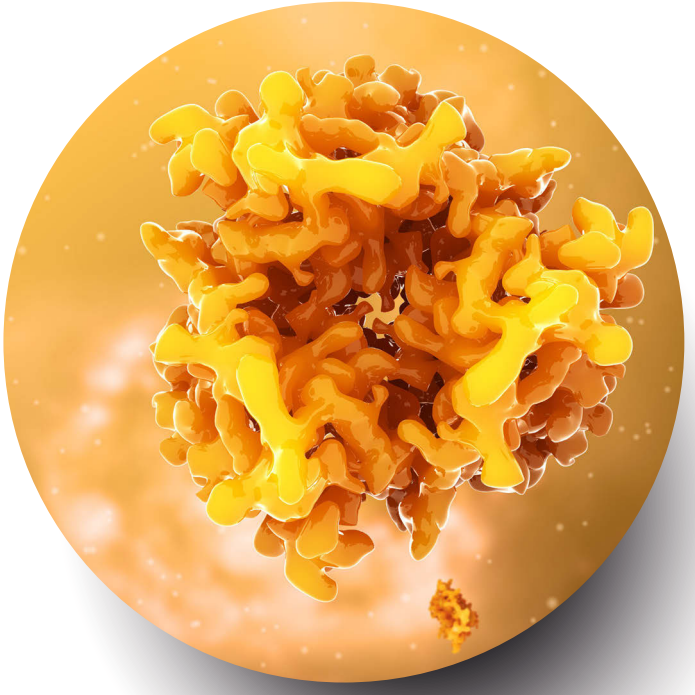


GHRELIN, LEPTIN AND OBESTATIN PEPTIDES OFFERED BY BACHEM

Ghrelin is an endogenous peptide discovered by Kojima et al. in 1999 during the search for an unknown endogenous ligand of a receptor of known structure and function. It is a 28 amino acid peptide with an essential n-octanoyl modification on the hydroxy group of Ser^3. It displays strong growth hormone-releasing activity mediated by the growth hormone secretagogue receptor 1a (GHS-R1a). Ghrelin participates in the regulation of energy homeostasis, increases food intake, and decreases energy expenditure by lowering the catabolism of fat. Several years after the isolation of ghrelin a second peptide derived from preproghrelin was isolated from rat stomach. This 23 amino acid peptide named obestatin was initially considered to oppose the orexigenic (appetite-stimulating) effects of ghrelin. It was also reported to be the cognate ligand for the G-protein-coupled receptor GPR39. Later studies, however, cast doubt on the initial findings as subsequent studies failed to confirm the anorexigenic effects of obestatin. Leptin, a satiety hormone produced by white adipose tissue, was discovered in 1994 and represents another appetite regulator. Leptin and ghrelin are supposed to share hypothalamic pathways regulating food intake and energy homeostasis.

Isolation of Ghrelin

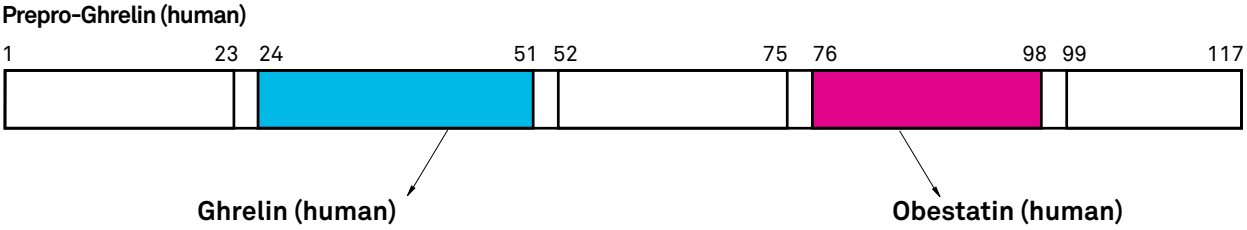
Studies on peptidyl growth hormone (GH) secretagogues (GHS), initially discovered by Bowers and Momany in 1976, led to the identification of the GHS receptor in 1996.
The GHS receptor belongs to the family of G-protein-coupled receptors containing seven transmembrane (TM) domains and three intracellular and extracellular loops.
Despite intensive search by various groups, the endogenous ligand of the GHS receptor could not be isolated for a long time. Only synthetic ligands, such as growth hormone-releasing peptide-6 (GHRP-6), or hexarelin were known for this receptor.
The cloning of the GHS receptor in 1996 was an important step towards the identification of the endogenous ligand. In 1999, a Japanese group of scientists (Kojima et al.) succeeded in the purification and identification of a peptide in rat stomach that could stimulate the GHS receptor stably transfected into Chinese hamster ovary (CHO) cells.
The purified ligand was found to be a peptide of 28 amino acids, called ghrelin (‚ghre' is a word root in Proto-Indo-European languages, meaning ‚growth', the suffix ‚relin' indicates that a peptide is a releasing hormone). The side chain of serine in position 3 of ghrelin was demonstrated to be modified by an octanoyl group. This unusual esterification has not been described before.
By using the rat cDNA sequence for screening a human stomach cDNA library under low stringency conditions, the human ghrelin sequence was subsequently identified.
The human ghrelin gene is localized on chromosome 3 at position p25-26 and comprises five exons. Human ghrelin is derived from a 117 amino acid precursor (Fig. 1). Like its rat analog, the human peptide consists of 28 amino acids and is post-translationally modified with an octanoyl group on serine at position 3. It differs from the rat sequence in two amino acids.
In 2008, the enzyme catalyzing the O-acylation of ghrelin was discovered by Yang et al. Ghrelin O-acyltransferase (GOAT) belongs to the superfamily of membrane-bound O-acyltransferases (MBOATs). Human GOAT is expressed in various tissues including stomach and pancreas and can also modify ghrelin with other fatty acids such as decanoate.
Octanoylation of ghrelin is required for receptor binding and activation. Non-octanoylated ghrelin does not stimulate GH secretion nor inhibit the activity of native ghrelin. Studies with synthetic ghrelin derivatives indicated that the amino-terminal sequence Gly-Ser-Ser(octanoyl)-Phe-Leu appears to be the ‚core' structure necessary for ghrelin function.
Interestingly, there is no structural homology between ghrelin and other growth hormone secretagogues (GHRP-6 or hexarelin).
Non-acylated ghrelin is far more abundant than acylated ghrelin and exists at significant levels in both stomach and blood.
Both acylated ghrelin and non-acylated ghrelin share some GHSR1a-independent effects such as stimulation of lipid accumulation in human visceral adipocytes, inhibition of isoproterenol-induced lipolysis in rat adipocytes, and inhibition of apoptosis in cardiomyocytes and endothelial cells.
Recent studies indicate a role of ghrelin, desacyl ghrelin, and GOAT in glucose homeostasis.

Physiological Functions of Ghrelin

Regulation of growth hormone secretion

GH secretion from the pituitary gland is controlled primarily by two hypothalamic peptides, growth hormone-releasing hormone (GHRH) (Bachem product H-3695) and somatostatin. With the isolation of ghrelin, a third regulator of GH secretion has been discovered.
Ghrelin acts as an antagonist of somatosta-

Fig. 1.
Prepro-Ghrelin can be processed to ghrelin and obestatin



tin that inhibits the secretion but not the synthesis of GH. Together with GHRH, ghrelin acts synergistically to stimulate the release of GH from the somatotrophic cells of the hypophysis.
Amongst a range of tested neuropeptides only GHSs bound specifically to the GHS receptor.
GHRH, somatostatin, and ghrelin mediate their effects through G-protein-coupled receptors. GHRH activates adenylyl cyclase, cyclic AMP, and protein kinase A pathways, whereas ghrelin stimulates phospholipase C activity leading to production of inositol-1,4,5-triphosphate and diacylglycerol, increase in cytosolic calcium levels, and GH release. Somatostatin acts through an inhibitory G-protein-coupled receptor thus blocking GH secretion.

Influence of food intake and energy balance

Ghrelin not only stimulates GH secretion, it also increases food intake and weight gain in experimental animals and induces hunger in humans.
Ghrelin is part of a complex neuroendocrine network involved in the regulation of appetite and energy homeostasis.
Peripheral ghrelin may exert its effects on the CNS by crossing the blood brain barrier (BBB) although the rate at which it passes the BBB is very low. Several studies suggested that the orexigenic signal of ghrelin secreted from the stomach is transmitted to the brain via the vagal afferent nerve. This was supported by the finding that vagotomy inhibits the ability of ghrelin to stimulate food intake. However, other studies concluded that abdominal vagal afferents are not required for the acute eating-stimulatory effect of ghrelin.
Ghrelin receptors are synthesized by a subset of vagal afferent neurons of the nodose ganglion and then transmitted to axon terminals where they bind to ghrelin. Ghrelin can influence gastric satiety signaling by altering the mechanosensitivity of gastric vagal afferents to distension.
The ghrelin receptor is expressed in several hypothalamic nuclei. Many of them are known to be involved in the regulation of food intake and body weight.
Ghrelin is also synthesized locally in neurons of hypothalamic areas such as the paraventricular and the arcuate nucleus but also in the sensorimotor area of the cerebral cortex and in the cingulate gyrus.
In the arcuate nucleus, ghrelin-containing neurons send efferent fibers onto neurons expressing neuropeptide Y (NPY) and agouti-related protein (AgRP) to stimulate the release of these orexigenic peptides.
This is complemented by a suppressive ef-

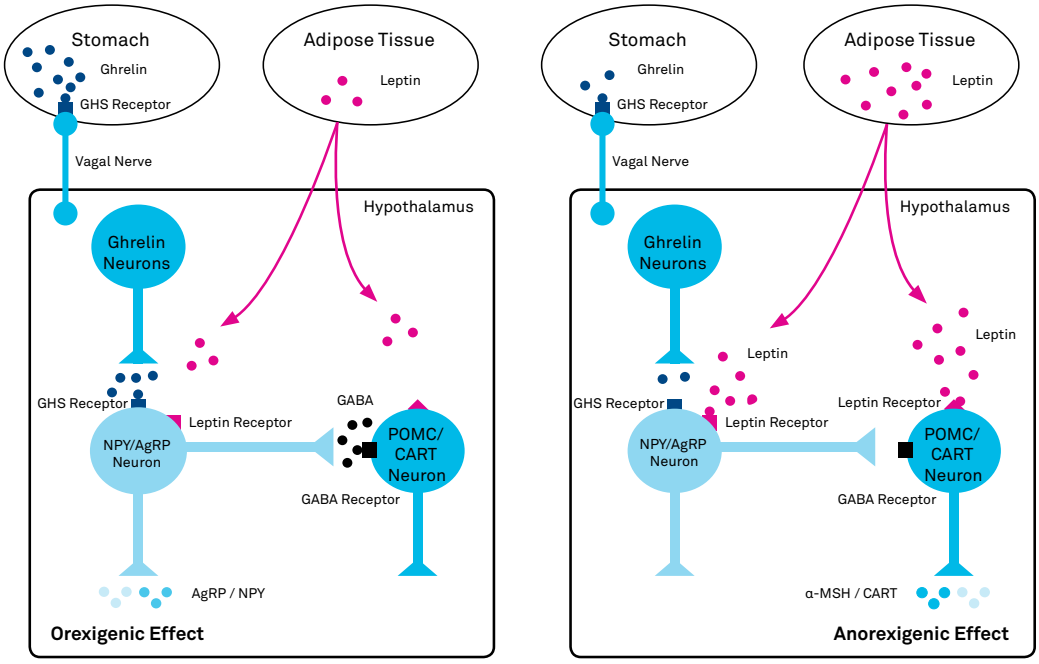


Fig. 2. Interrelationship of Ghrelin and Leptin. Activation of ghrelin receptors causes release of neuropeptide Y (NPY) and agouti-related protein (AgRP) thus stimulating hunger and food intake (orexigenic effect). Activation of leptin receptors increases expression of proopiomelanocortin (POMC), α-melanocyte-stimulating hormone (α-MSH) and cocaine and amphetamine-regulated transcript (CART) in the arcuate nucleus (anorexigenic effect). Leptin also inhibits the release of NPY and AgRP and prevents the suppressive effect of these neurons on POMC/CART neurons.

fect on proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART)-expressing neurons via inhibitory γ-aminobutyric acid (GABA) inputs from NPY/AgRP neurons. The hypothalamic NPY/Y1 receptor pathway is shared by leptin. Ghrelin antagonizes the anorectic effect of leptin through the activation of this pathway (Fig. 2).

Effects of ghrelin on the cardiovascular system

A study of the peripheral distribution of GHS receptors has shown that ghrelin is also present in cardiovascular tissue, which has led to the exploration of the cardiovascular functions of ghrelin and synthetic growth hormone-releasing peptides. These ligands have several cardiovascular activities, including a cardioprotective effect against myocardial ischemia, and vasoactive and cardioprotective effects in both experimental models and humans. There is evidence that certain cardioprotective effects are mediated via a novel, yet to be identified cardiac receptor distinct from the GHS receptor. This is supported by the finding that both octanoylated and non-acylated ghrelin exhibited antiapoptotic effects on cardiomyocytes which do not express the GHS receptor. Both ghrelin and non-acyl ghrelin, recognize a common high affinity binding site, although only the fatty acid modified form of ghrelin binds to the GHS receptor.

The role of the ghrelin in reproduction

Ghrelin is also supposed to be involved in the regulation of reproductive function by acting at central and peripheral levels. Ghrelin has been described to predominantly negatively modulate the hypothalamic-pituitary-gonadal (HPG) axis. Recently, kisspeptin (KiSS-1) and its G-protein-coupled receptor GPR54 (KiSS-1R) have been identified as an essential component of the HPG axis controlling gonadotrophin secretion. Ghrelin has been demonstrated to decrease KiSS-1 mRNA expression in the medial preoptic area without affecting GPR54 levels.
At peripheral levels, ghrelin may also function in the direct control of follicular development, ovarian cell functions, and embryonal development. In addition, ghrelin has been suggested to influence the male reproductive axis in situations of energy deficit.

Identification of Leptin

Leptin has been discovered in 1994 by positional cloning of the mouse obese gene originally described in 1950. Mice which are homozygous for the recessive obese mutation exhibit hyperphagia and increase rapidly in weight. The ob/ob phenotype is also characterized by infertility and a form of diabetes similar to human type-II diabetes. The mouse obese gene was mapped to chromosome 6. It encodes a 167 amino acid protein containing a 21 amino acid signal sequence. The gene product was called leptin, after the Greek word leptos meaning thin. Human leptin also consist of 167 amino acids and is 83% similar to the mouse protein. The human gene resides on chromosome 7.
In 1995 the leptin receptor (Ob-R) was identified. It is a single membrane-spanning receptor and belongs to the class I cytokine receptor superfamily. The receptor is encoded by the diabetes (db) gene. Mice deficient for the leptin receptor (db/db mice) serve as a model for obesity, diabetes, and dyslipidemia. Both human and mouse leptin receptors exist in several isoforms generated by alternative splicing and can be divided into three classes: secreted, short, and long.

Physiological Functions of Leptin

Regulation of food intake and body weight

Leptin acts as a satiety hormone. It is mainly secreted by white adipose tissue and its serum levels positively correlate with the percentage of body fat. Leptin signaling is part of a feedback mechanism controlling food intake and energy homeostasis. Interestingly, elevated leptin serum levels are associated with leptin resistance in obese subjects.
Leptin exerts its effects by binding to its receptor expressed in the brain and in peripheral tissues. The long form of the leptin receptor (Ob-Rb), highly expressed in the hypothalamus, is supposed to mediate most of leptins effects. Leptin signals via the Janus Kinase / Signal Transducer and Activator of Transcription (JAK/STAT) pathway but also modulates a number of other signaling pathways in the brain, such as the PI 3-kinase,

MAPK, and mTOR pathway.
In the hypothalamus leptin inhibits neuronal pathways that stimulate food intake by counteracting the orexigenic effects of NPY/AgRP neurons and by activating anorexigenic POMC/CART neurons.

The role of the leptin in reproduction
Leptin is also involved in the regulation of reproductive development and function by indirectly influencing GnRH neuron activity. Leptin signaling is part of a complex neuronal network which involves NPY/AgRP, POMC/CART, and kisspeptin-1 neurons. As the kisspeptin-1 neurons express leptin receptors, they may participate in transmitting metabolic information to the GnRH neurons. Loss of KiSS-1 peptide or its receptor, GPR54, results in hypothalamic hypogonadism and infertility.

Identification of Obestatin

Obestatin was identified by Zhang et al. in 2005 on the basis of bioinformatic searches of putative hormones derived from the prepropeptides of known peptide hormones. Obestatin was predicted to be derived from a conserved region of preproghrelin that was flanked by potential convertase cleavage sites. Based on this information the peptide was subsequently isolated from rat stomach. Obestatin consists of 23 amino acid and is C-terminally amidated.

Physiological Functions of Obestatin

Influence on food intake
The newly discovered gastric peptide was initially shown to oppose the effects of ghrelin by decreasing appetite and weight gain. For this reason it was named obestatin (from the Latin word ‚obedere', meaning ‚to devour', and ‚statin', denoting suppression). Similar to ghrelin, which requires posttranslational modification by acylation, the biological activity of obestatin depended on modification by C-terminal amidation.
Zhang et al. (1994) showed that obestatin binds to and activates the orphan receptor GPR39. This G-protein-coupled receptor has been mapped to human chromosome 2 and is expressed in multiple tissues, including stomach, intestine, and hypothalamus. Subsequent studies, however, failed to confirm the anorexigenic effect of obestatin and activation of GPR39 and thereby questioned the role of obestatin as cognate ligand for GPR39. The controversy about this peptide as a regulator of appetite still exists as the differences in the experimental findings could not be explained by methodological variations.
Obestatin has been reported to have additional roles such as the inhibition of thirst and the regulation of memory, anxiety, and sleep. It has also been shown to stimulate the proliferation of human retinal cells and to promote the survival of pancreatic β-cells and human islets (and to induce the expression of genes involved in the regulation of β-cell mass and function). Additionally, it may have functions in the regulation of adipocyte metabolism and adipogenesis.

Prospects

The increasing prevalence of obesity is a global problem. Body weight is regulated by complex mechanisms involving peptide hormones produced in the brain and gut.
The discovery of ghrelin and its receptor represents a milestone in understanding the complex mechanisms involved in appetite regulation and energy homeostasis, gastrointestinal function, and growth. Ghrelin represents a major component of a neuroendocrine network. It acts at several levels and regulates food intake and energy balance.
The function of obestatin is less clearly defined. Further studies are required to reconcile the controversial results concerning the physiological role of obestatin in opposing the effects of ghrelin.
As ghrelin is both orexigenic and adipogenic, the ghrelin system is an ideal therapeutic target for the treatment of anorexia, cachexia, and obesity. Ghrelin's cardioactive effects will possibly allow the development of new treatment options for chronic heart failure.
Leptin acts as a satiety hormone; but it is also involved in regulation of reproductive functions like ghrelin. Detailed knowledge of the molecular processes underlying these mechanisms will help to better understand the relationship between metabolism and reproduction.

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GHRELIN, LEPTIN, OBESTÁTIN AND RELATED PRODUCTS

Bachem also offers a range of products related to obesity research such as apelin peptides, CART fragments, growth hormone releasing factors, neuropeptide Y and analogs, and orexins.
For more information, please see our online shop at shop.bachem.com

GHRELINS

Ghrelin (human)
H-4864
GSS(octanoyl)FLSPE
HQRVQQRKESKKPPAKLQPR

Ghrelin-Cys(BMCC-biotinyl) (human)
H-6334
GSS(octanoyl)FLSPEHQRVQQRK
ESKKPPAKLQPRC(BMCC-biotinyl)

(Des-octanoyl)-Ghrelin (human)
H-7746
GSSFLSPEHQRVQQRKESKKPPAKLQPR

(Des-octanoyl)-Ghrelin (human)
H-5946
GSSFLSPEHQRVQQRKESKKPPAK
LQPR

([$^{13}C_6$]Leu^5)-Ghrelin (human)
H-7252
GSS(octanoyl)F[$^{13}C_6$]LSPE
HQRVQQRKESKKPPAKLQPR

(Trp^3,Arg^5)-Ghrelin (1-5)
H-6456
GSWFR

Ghrelin (mouse, rat)
H-4862
GSS(octanoyl)FLSPE
HQKAQQRKESKKPPAKLQPR

(Des-octanoyl)-Ghrelin (mouse, rat)
H-6264
GSSFLSPEHQKAQQRKESKKPPAK
LQPR

(Ser(Ac)^3)-Ghrelin (mouse, rat)
H-7638
GSS(acetyl)FLSPEHQKAQQRKESKKP-
PAKLQPR

(D-Arg^1,D-Phe^5,D-Trp$^{7-9}$,Leu^{11})-Substance P
H-6935
rPKPfQwFwLL-NH_2

OBESTATINS

Obestatin (human)
H-6356
FNAPFDVGIKLSGVQYQQHSQAL-NH_2

Biotinyl-Obestatin (human)
H-6358
Biotinyl-FNAPFDVGIKLSGVQYQQHSQAL-
NH_2

Obestatin (rat)
H-6338
FNAPFDVGIKLSGAQYQQHGRAL-NH_2

Biotinyl-Obestatin (rat)
H-6362
Biotinyl-FNAPFDVGIKLSGAQYQQHGRAL-
NH_2

LEPTIN

Leptin (22-56) (human)
H-3424
VPIQKVQDDTKTLIKTIVTRINDISHTQS-VSSKQK

Tyr-Leptin (26-39) (human)
H-3494
YKVQDDTKTLIKTIV

Leptin (93-105) (human)
H-3426
NVIQISNDLENLR

Leptin (116-130) amide (mouse)
H-3966
SCSLPQTSGLQKPES-NH_2

Leptin (126-140) (human)
H-3492
ETLDSLGGVLEASGY

Leptin (138-167) (human)
H-3428
SGYSTEVVALSRLQGSLQDMLWQLDL-SPGC

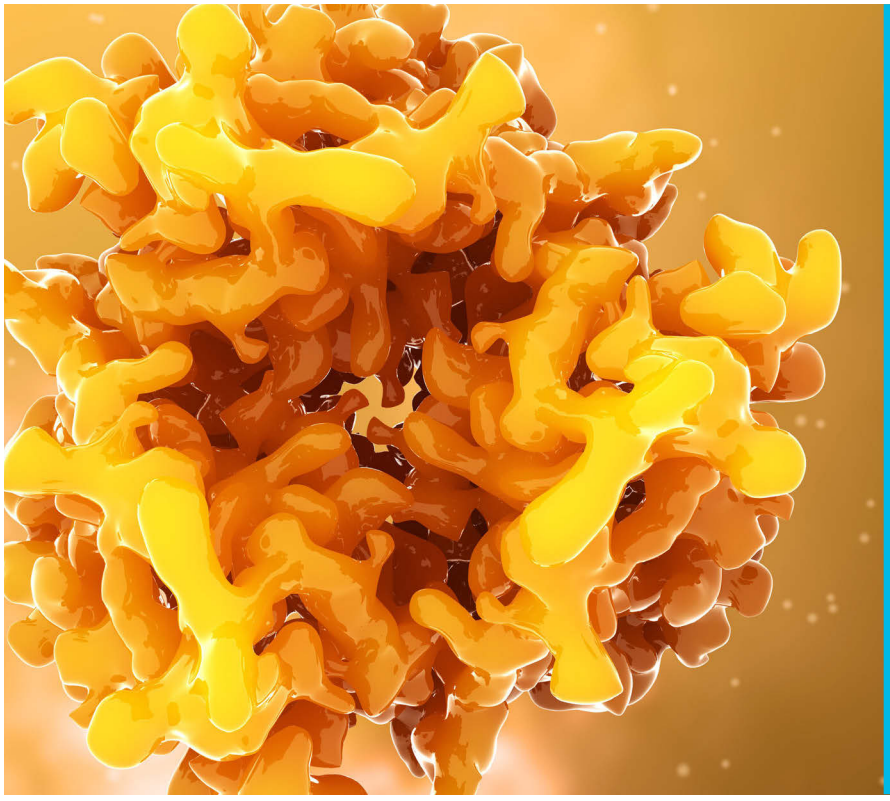
Leptin (150-167) (human)
H-3432
LQGSLQDMLWQLDLSPGC

rec Leptin (human)
H-5578

rec Leptin (mouse)
H-5582

GHRP-6

(D-Trp^{7},Ala^{8},D-Phe^{10})-α-MSH (6-11) amide
H-9990
HwAWfK-NH_2



LEPTIN MOLECULE

Computer model showing the structure of a molecule of the hormone leptin. Leptin is produced by adipose (fat) tissue. It interacts with receptors in the brain's hypothalamus to signal when a person is full. It also circulates in the blood at levels proportionate to body fat, which allows the brain to regulate appetite and metabolism. Mutations in the ob gene that codes for leptin are thought to be responsible for some forms of obesity.

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