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Review Article

APPETITE REGULATION AND OBESITY: EMPHASIS ON GHRELIN AND GHRELIN RECEPTOR

Valentina Kubale

Institute of Anatomy, Histology and Embryology, Veterinary Faculty, University in Ljubljana, Gerbičeva 60, SI-1115 Ljubljana, Slovenia

E-mail: valentina.kubale@vf.uni-lj.si

Summary: Obesity is one of the leading preventable causes of death worldwide. In its epidemic it is of increasing interest for the pharmaceutical industry to develop drugs that reduce appetite. By reducing appetite overall energy consumption is also reduced. The idea is simple; however, the hormonal system and mechanisms regulating energy intake are extremely complex and therefore drug development is not straightforward. Throughout the central nervous system (CNS), central and peripheral hormones are involved in food intake and body weight balance. They are tightly regulated by the hypothalamus, brainstem and reward circuits, on the basis of both cognitive inputs and diverse humoral and neuronal signals of nutritional status. Several peptides and hormones such as: neuropeptide Y (NPY), melanocortins, cocaine and amphetamine-regulated transcript (CART), peptide YY (PYY), pancreatic polypeptide (PP), cholecystokinin (CCK), oxyntomodulin (OXM), glucagon-like peptide 1 (GLP-1), glucose-dependant insulinotropic hormone (GIP), bombesin, leptin and one of the latest discovered and not yet well known - ghrelin, have all revealed an important role in short- and long-term regulation of food intake. This review summarizes the complexity of factors involved in the regulation of appetite and food intake in different areas of the brain, especially in the hypothalamus, and the relationships between the central and peripheral peptides and hormones involved, with emphasis on ghrelin and its receptor together with their potential role as targets for treatment of obesity. The ghrelin receptor originally received considerable attention from pharmaceutical companies because of its prominent role in the release of growth hormone. However, the discovery of the orexigenic properties of ghrelin turned the ghrelin receptor (ghrR) into a target for anti-obesity drugs.

Key words: appetite regulation; obesity; ghrelin; ghrelin receptor

Introduction

Obesity is one of the most prevalent nutritional problems worldwide; therefore it is important to understand the role of the brain, the peptides and hormones secreted by brain, as well as the periphery organs that regulate appetite and food intake. Two-thirds of North Americans are overweight or obese (1), indicated by a body mass index (BMI) exceeding 30 kg/m^2. Similar trends are observed in Slovenia and other parts of Europe. Being overweight, especially if the body fat is concentrated around the abdomen, is associated with higher risk of various diseases: type 2 diabetes, hypertension, ischaemic heart disease, stroke, endometrial carcinoma, osteoarthritis, gall stones and cancers (colon, kidney, endometrial and postmenopausal breast cancer) (2). Even obesity in pets, especially dogs and cats, is becoming more frequent. Proportions of overweight and obese dogs in the USA range from 23% to 41%, with about 5.1 % classed as obese. In Australia the proportion of obesity in dogs and cats is even higher (7.6 % and 6.4 %, respectively) (3). Furthermore it has been shown that the risk of obesity in dogs is related to obesity of their owners; however, no correlation between cats and their owners was observed (4).

With the expanding knowledge about the areas of the CNS and the central and peripheral hor-

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mones involved in food intake and body weight balance, we are increasing our ability to influence the processes. Hormones, and more so their receptors, represent potential targets in the development of novel anti-obesity drugs. The neuroscience of obesity and the connecting knowledge about all factors influencing obesity is a target of intense interest. The emphasis of research is focused on transferring the knowledge into new treatments for obesity and its related diseases (5). Recent areas of interest are the orexigenic (appetite stimulant) properties of ghrelin and its receptor - ghrelin receptor (ghrR) (6). Discovery of both turned ghrR into a target for pharmaceutical industry to develop anti-obesity drugs.

Peripheral and central appetite regulation

1. Central nervous system (CNS)

The most important part of the brain that processes signals from periphery regarding nutritional status is the hypothalamus, especially the morphologically defined areas such as the lateral hypothalamic area (LHA), ventromedial hypothalamus (VMH), arcuate nucleus (ARC), paraventricular hypothalamus (PVH), perifornical area (PFA) and dorsomedial hypothalamus (DMH). Besides hypothalamus, nucleus tractus solitarii (NTS) also plays an important role in appetite regulation.

LHA was defined as the hunger promoting feeding centre that includes neurons that produce orexigenic peptides. VMH was defined as the satiety centre, which when stimulated suppresses the desire for food. Lesions in this area have been shown to elicit rapid excessive food ingestion (hyperphagia) and abnormal body weight (7). It secretes specific anorexigenic and orexigenic neuropeptides and expresses high levels of VMH brain-derived neurotrophic factor (BDNF). VMH lesion-type hyperphagia and obesity could also be accomplished by other defects (8).

The ARC is one of the highly important areas for receiving signals from the periphery regarding appetite control in the CNS. It is closely connected to the median eminence (ME), which is not entirely protected by the blood-brain barrier (9), therefore enabling ARC to be accessible for satiety or starvation circulating signals of energy balance, such as insulin and leptin. The main neurotrasmitters in the ARC are pro-opiomelanocortin (POMC), yielding the melanocortin MSH as a cleavage product and cocaine and amphetamine-regulated transcript (CART), which both inhibit food intake (10). Furthermore, it was shown that PVH is very important for feeding behavior. Lesions in PVH cause hyperphagia in rats (7) and if an orexigenic signaling molecule (NPY, GAL, orexins, GABA, opioids, norepinephrine and epinephrine) is microinjected into PVH, it stimulates food intake (8). In feeding, it is involved in the opposite manner to LHA. PFA is one of the most sensitive areas for NPY stimulation of feeding. DMH has a role in the modulation of food intake. Lesion studies of this region resulted in hyperphagia and obesity, although not to the same degree as lesions in the VMN (8). Reward pathways that involve complex interaction between several signaling systems such as the dopaminergic and endocannabinoid system are also important. Food intake stimulated by central and peripheral administration of endocannabinoids is believed to be mediated through the cannabinoid receptor type 1 (CB1), which co-localizes with CART, MCH and orexin peptides in the hypothalamus. Opioids are important in the reward circuitry, as mice lacking either β-endorphin or enkephalin do not respond to the reinforcing property of food regardless of palatability (10).

On the other hand, the NTS as the visceral sensory part of the brainstem receives sensory inputs from the larynx, intestinal and respiratory tracts, heart, large blood vessels and taste buds. The NTS and the reward pathways mainly in nucleus accumbens (NAc) are involved in the control of energy intake. The NTS is in close contact with the area postrema (AP) which has an incomplete blood brain barrier. Therefore NTS is like the ARC, able to respond to peripheral circulating signals as well as receiving vagal afferents signals from the gastrointestinal (GI) tract and afferent signals from the glossopharyngeal nerves. Several connections between the hypothalamus and the NTS exist, including the glucagon-like peptide 1 (GLP-1) neuronal circuit, which is believed to be of major importance in the signaling circuit of the brainstem (11).

2. Neuropeptides in CNS

Various neuropeptides are involved in mediating signals regarding energy balance, such as neuropeptide Y (NPY), melanocortins, as well as cocaine and amphetamine-regulated transcript (CART). A review of examples is presented in Table 1.

Table 1: Overview of neuropeptides in the CNS involved in mediating signals regarding the energy balance

	Location	Neuropeptide	Effect (neuropeptide)	Receptor	Effect (receptor)	Reference
NPY	- ARC - autonomic nervous system	- 36 amino acids with many tyrosine residues - structurally related to PP and PYY	- regulation of energy balance - increases food intake and proportion of energy stored as fat - decreases physical activity - role in memory and learning - epilepsy - anorexia nervosa	- 7TM receptors: NPY_{1-5} (brain), NPY_6 (orexigenic) - $G\alpha_i$ coupled - combined signaling through these receptors and other unknown receptors	- role in eating disorders (obesity)	(10, 12-17)
Melanocortins	- ARC - NTS	- peptide hormones - cleavage products of proopiomelanocortin (POMC) in the pituitary gland - different forms of melanocyte-stimulating hormone (MSH) - adrenocorticotropic hormone (ACTH)	- suppresses food intake - POMC gene or gene product mutation or abnormally processing - early-onset obesity	- melanocortin receptors MC1R - MC5R in hypothalamus - very important MC3R and MC4R - $G\alpha_s$ coupled	- MC4R role in regulation of food intake and body weight - 3-5 % of the cases of high obesity in the humans are caused by MC4R mutations - early-onset obesity in humans with deletion or blockade of MC4R	(10, 18, 19)
CART	- hypothalamus - pituitary endocrine cells - adrenomedullary cells - somatostatin cells - rat antral gastrin cells	- anorexigenic peptide - neurotransmitter	- roles in reward, feeding, stress - endogenous psychostimulant - regulates energy homeostasis and interacts with several central appetite circuits	- not yet identified - *in vitro* studies show that CART binds to a specific 7TM receptor coupled to $G\alpha_i/G_o$	/	(8, 11, 20-23)

3. Peripheral Signals

Signals from the periphery importantly influence the energy status of the body, as well as the amount of fat and glucose in the blood. These signals are hormones secreted from various organs in connection with meal initiation satiety and long-term energy changes. The most important are peptide YY (PYY), pancreatic polypeptide (PP), cholecystokinin (CCK), oxyntomodulin (OXM), GLP-1, gastric inhibitory polypeptide (GIP), bombesin, leptin, adiponectin, resistin, visfatin and ghrelin. Review of examples is presented in Table 2. Ghrelin and its receptor are described in more detail below Table 2.

Table 2: Overview of neuropeptides in PNS that influence the energy status of the body, amount of fat and amount of blood glucose

	Location and secretion	Neuropeptide	Effect (neuropeptide)	Receptor	Effect (receptor)	Reference
PYY	- esophagus - stomach - duodenum - jejunum - L cells in ileum and colon (with GLP-1) - neurons - brainstem - concentration in the circulation increases after food ingestion and decreases on fasting - obese people secrete less PYY than non-obese people - released in response to feeding (presence of carbohydrates, lipids and proteins in the GI tract)	- 36 amino acids two forms: - $PYY_{1-3}6$, PYY_{3-36} structurally related to NPY and PP - it crosses blood brain barrier	- slows gastric emptying - increases efficiency of digestion and nutrient absorption after meal - reduces appetite - weight loss was observed after chronic peripheral administration of the peptide to mice - iv administration of PYY3-36 strongly decreased food intake and weight loss in humans	- 7TM receptors: NPY (especially for PYY_{3-36}) - PYY_{3-36} preferentially binds to NPY_2 and NPY_5 - $G\alpha_i$ coupled	- role in the food intake and immnune response	(24-29)
PP	- PP cells in endocrine pancreas secretion in humans is increased after a protein meal, fasting, exercise, acute hypoglycemia - secretion is decreased by somatostatin and iv application of glucose - the amount of peptide released depends upon calorie intake and the composition of a meal	- 36 amino acids - structurally related to PYY and NPY - does not cross the blood brain barrier	- regulates the endocrine and exocrine pancreas secretion - effects hepatic glycogen levels and GI secretions - peripheral infusion of PP reduces food intake, while central administration increases food intake	- 7TM receptors: NPY1, NPY_2, NPY_4, NPY_5 - $G\alpha_i$ coupled	- could mediate the orexigenic effect	(9, 30, 31)
CCK	- GI tract - enterocrine I cells (jejunum, duodenum) - secreted in response to the presence of nutrients in the lumen of GI tract - peripheral CCK crosses the blood-brain barrier and acts directly in the CNS	- different post-translational modification of the *CCK* gene product, preprocholecystokinin - e.g. CCK8, CCK33 and CCK58	- satiety hormones - stimulate digestion of fat and protein and act as a hunger suppressant - able to detect the presence of fat in the chime and inhibit gastric emptying and gastric acid secretion, together with mediating digestion in the duodenum - stimulatory effects oppose those of ghrelin - effect is dependant on the vagus nerve	- cholecystokinin B receptor (CCK2) - widely distributed in brain areas such as the NTS, AP and DMH - adrenal cortex - sensory fibers of the vagus nerve in the pyloric sphincter - $G\alpha_s$ and $G\alpha_q$ coupled	- inhibit gastric emptying, which might be involved in the satiety effect of CCK	(10, 29, 32, 33)

	Location and secretion	Neuropeptide	Effect (neuropeptide)	Receptor	Effect (receptor)	Reference
OXM	- intestinal L cells of ileum and other parts of intestines - co-secreted with GLP-1 and GLP-2	- 37-amino acids - group of numerous tissue-specific cleavage products of proglucagon	- satiety hormone - appetite reducing effects when administered centrally or peripherally - could be used as a weight loss treatment - reduces circulating ghrelin levels in humans and rodents by 44 % and 20 %	- family B 7TM GLP-1 receptor glucagon receptor - $G\alpha_s$ coupled - cAMP accumulation with almost the same potency as glucagons	- L cells in ileum and colon (with GLP-1) - very important in appetite regulation and energy homeostasis - one of the most interesting new targets in the management of type 2 diabetes and obesity	(34-38)
GLP-1	- intestinal L cells - ileum and other parts of intestine (together with PYY and OXM) - secretion is dependent on the presence of nutrients in the lumen of the small intestine by carbohydrates, proteins and lipids - an inhibition of NPY signaling by GLP-1 and an increase by exendin is observed, indicating that the GLP-1 signal is mediated via NPY neurons	- tissue-specific cleavage product of proglucagon - biologically active forms of GLP-1 are: GLP-1-(7-37) and GLP-1-(7-36)	- satiety hormone - antihyperglycemic hormone - inhibits pancreatic β-cell apoptosis - stimulates the proliferation and differentiation of insulin-secreting β-cells - inhibits gastric secretion and motility - decreases acute food intake when administered centrally or peripherally to rats	- family B 7TM - GLP-1, GLP-2, GLP-3 receptors - central administration of exendin, a GLP-1 receptor antagonist abolishes anorectic effect of GLP-1 in OXM - OXM and glucagon are biased ligands on the GLP-1 receptor - $G_{\alpha}s$ coupled	- very important in appetite regulation and energy homeostasis - one of the most interesting new targets in the management of type 2 diabetes and obesity	(34, 39-42)
GIP	- synthesized and secreted after ingestion of fat from the K cells in the intestines - mucosa of duodenum and jejunum of the GI tract - transported by blood	- secretin family of hormones	- glucose-dependant insulinotropic hormone - increases secretion of insulin before rise in blood glucose is observed - effect on adipocytes, enhancing fatty acid synthesis and their incorporation into triglycerides - in ruminants role in nutrient partitioning in milk production (lipid metabolism)	- 7TM receptors - GIP receptors - on β-cells in the pancreas - $G\alpha_s$ coupled	- effect on glucocorticoid metabolism	(43, 44)
bombesin	- most likely secreted from the intestines	- 14-amino acids - closest homologs: neuromedin B (NMB) and gastrin releasing peptide (GRP)	- stimulates gastrin release from G cells - causes satiety with markedly increased plasma levels after feeding - together with CCK, is the source of negative feedback signals that stops eating behavior - peripheral and central administration of bombesin reduces food intake	- 7TM receptors - bombesin receptors: BB1, BB2 and BB3 - BB3 is of great interest for pharmacological industry as a drug target - $G\alpha_q$ coupled	- regulation of endocrine processes and metabolism responsible for energy balance and adiposity	(12, 41, 45, 46)

	Location and secretion	Neuropeptide	Effect (neuropeptide)	Receptor	Effect (receptor)	Reference
leptin	- fat tissue - secretion is proportional to the amount of white adipose tissue in the body	- 16 kDa - a product of the *ob* (obesity) gene, located on chromosome 7 in humans	- key role in regulating energy intake and its influence on appetite and metabolism - signal for status of energy stores - reduces appetite in response to feeding - obese people develop resistance to leptin - suppresses NPY expression in the brain - chronic administration - reduction in food intake and body weight - deficiency of the hormone has shown the opposite effect	- leptin receptor - LEP-R; CD295 (cluster of differentiation 295) - a protein in humans encoded by the *LEPR* gene	- the absence of a leptin or LEP-R - uncontrolled food intake - severe obese phenotype - variations in the leptin receptor have been associated with obesity	(47-52)
adiponectin	- fat tissue - releases into blood and abundant in plasma - levels are inversely correlated with body fat percentage in adults - plasma concentration of adiponectin is suppressed in obesity and when insulin levels rises	- 244-amino-acids	- modulates metabolic processes, including glucose regulation and fatty acid catabolism - role in the suppression of the metabolic disorders that may result in type 2 diabetes, obesity, atherosclerosis - non-alcoholic fatty liver disease (NAFLD) and is an independent risk factor for metabolic syndrome - contributes to increased energy expenditure by activating AMP-activated protein kinase in liver and muscle, leading to an increase in glucose utilization and fatty-acid oxidation in these tissues	- adiponectin receptors in the skeletal muscle (AdipoR1) and liver (AdipoR2)	- reductions in adiponectin receptors may play roles in the development of insulin resistance, type 2 diabetes, metabolic syndrome, and cardiovascular diseases that are linked to obesity	(53-57)
resistin	- adipose tissue of mice and rats, as well as macrophages of primates, pigs and dogs - activated by specific cytokines - a linkage to a certain type of inflammation connected with development of insulin resistance	- cysteine-rich protein - cytokine	- involvement with obesity and type 2 diabetes - may contribute to the mechanism of obesity-induced insulin resistance	- resistin receptor	- role in insulin resistance and type 2 diabetes	(58)
visfatin	- adipose tissue	- adipokine - cytokine	- promotes B cell maturation - inhibits neutrophil apoptosis - acts as an insulin mimetic by binding t insulin receptors and thereby stimulating glucose uptake	- might bind to insulin receptor	/	(59)

	Location and secretion	Neuropeptide	Effect (neuropeptide)	Receptor	Effect (receptor)	Reference
ghrelin	- X/A like cells in the oxyntic glands of the gastric fundus mucosa in the pre-meal situation (plasma levels decrease 80% after removal of stomach) - small intestine - kidney - immune system - placenta - gonads - pituitary - adrenal cortex - lung - hypothalamus - pancreas - collocalize with glucagons in X cells of pancreas or beta cells of pancreas or in E cells of pancreas	- 28 amino acids - chromoseome 3p - 3 introns - encodes 511 base pair cDNA	- only peripheral hormone that stimulates food intake - promotes adiposity if administered peripherally - effect on secretion of growth hormone	- 7TM receptor: ghrelin receptor (ghrR) - NPY/AGRP neuron in ARC - $G\alpha_q$ coupled	- mRNA found in hypothalamus, pituitary gland, pancreas, adrenal gland, spleen, myocardium, vagal nerve	(60-69)

Ghrelin and ghrelin receptor (ghrR)

The gastric hormone ghrelin was identified as the endogenous ligand for the former orphan receptor, the growth hormone secretagoue receptor (GHS-R_{1a}), later named ghrelin receptor (ghrR) (6). Pairing of the hormone to the receptor 20 years after its cloning made the discovery of ghrelin an example of reverse pharmacology. Both names for the receptor are still in use; however, in November 2005, the name "ghrelin receptor (ghrR)" was officially established by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) (70).

Different natural isoforms of ghrelin exist. One of them is isoform des-Gln 14-ghrelin, which has the same activity as ghrelin; however, it is present in much lower amounts in the serum (71). Interestingly, it was shown that the entire sequence of ghrelin is not necessary to exert its activity, therefore this isoform and other short peptides are very important. Short peptides encompassing the first four or five residues of ghrelin were capable of activating ghrR at about the same efficiency as the full length ghrelin in calcium mobilization assays *in vitro*. 80-90% of circulating ghrelin is in the non-acylated form which is not able to bind to and activate ghrR (6).

Ghrelin is able to reach the brain through the areas where the blood brain barrier is incomplete. A minor quantity of ghrelin is produced within the hypothalamus in neurons adjacent to the third ventricle and between the VMH, DMH, PVH and ARC, therefore ghrelin modulates the neurotransmission and interacts pre- and post-synaptically with NPY/AGRP, POMC and CRH circuits (72). Ghrelin transduces signals to hypothalamic regulatory nuclei that control energy homeostasis. NPY/AGRP neurons of the ARC are major targets for ghrelin. In the hypothalamus, ghrelin increases the firing rate and induces increased expression and release of NPY and AGRP. Ghrelin also seems to exert important actions on energy expenditure, both through ghrR on adipocytes and through modulation of thermogenesis. Therefore it has been suggested that the high constitutive signaling activity of the ghrR could serve as a signaling set-point in the control of appetite and energy expenditure, where it would counteract a large number of inhibitory hormones and neurotransmitters such as leptin and insulin (73, 74). Besides its actions through the hormonal route, ghrelin is also believed to exert its actions through the vagus nerve. Ghrelin produced in the stomach could conduct some of its orexigenic signals via the vagus nerve which signals to areas of the brain very much involved in appetite regulation. It is interesting to note that the stomach may play an important role not only in digestion, but also in pituitary growth hormone release and central feeding regulation (75).

The main effect of ghrelin is observed regarding food intake and metabolism. Ghrelin secretion is

regulated by many factors. In humans, ghrelin level changes during the day. High level is detected during fasting, with a peak before meal initiation, and then it drops after food intake (74). In humans the rise in ghrelin is also associated with feeling hungry (76). Ghrelin levels decline to basal within an hour after food intake (74), proportional to the load of ingested calories (77). In rats, ghrelin is released in a pulsatile manner with a regularity of about 2 episodes per hour. Ghrelin levels change in response to acute changes in nutritional status but chronic changes also have an influence on the plasma ghrelin level. Fasting plasma ghrelin levels are lower in obese research participants compared to normal weight participants, while those with low BMI (patients suffering from anorexia nervosa or carchexia) have an increased ghrelin secretion (76). Ghrelin level is decreased by oral glucose load, after secretion and/or expression of OXM, PYY^{3-36}, administration of somatostatin and its natural analogue cortistatin and agonist/antagonist binding of cholinergic muscarinic receptors (67). Levels of ghrelin are increased by energy restriction, thyroid hormones, testosterone, parasympathetic activity, leptin, and low BMI. The importance of ghrelin in the metabolism has not been entirely clarified. Despite all important actions, deletions of ghrelin or ghrR do not have any major effect on food intake and body weight (8).

As reported in several publications on ghrelin and ghrR, ghrelin plays an important role in appetite stimulation and increase of food intake. Chronic administration of ghrelin to lean rats is followed by an increase in food intake and bodyweight (78); however, the increase in fat mass following ghrelin administration is not caused only by increased food intake. When administering ghrelin twice a day to rodents in a period of four days, it was observed that body weight increases due to reduced fat utilization and fat deposition becomes independent of food intake, suggesting a role for ghrelin in lipid metabolism (79). Therefore, ghrelin may stimulate food intake and at the same time induce adiposity by reducing the use of fat as an energy source (79), which was also supported by calorimetric studies. In humans it was shown, that iv administration of ghrelin increases appetite and food intake in normal weight volunteers (80) and increases food intake in patients with cancer-related anorexia by more than 30% (81, 82).

Besides the effect of ghrelin administered either orally or iv, growth hormone (GH) -releasing effect of iv administered ghrelin in pharmacological doses is also described in humans and animals. Co-administration of ghrelin and GHRH has a significant synergistic effect on GH secretion, indicating that they act via different mechanisms (83). The GH-releasing effect of ghrelin varies with age. It increases at puberty. The rise in estrogens at this time leads to an increase in the expression of the ghrR, which is probably responsible for the GH increment. When reaching adulthood, the level reaches a plateau and declines during further aging (67). In both humans and animals, ghrelin was reported to act as a functional antagonist to the GHRH hormone somatostatin (67). In families with naturally occurring ghrR mutation (Ala204Glu), it leads to selective loss of constitutive activity of the ghrR, but does not affect ghrelin affinity, potency, or efficacy to ghrR. Furthermore, a tendency for developing obesity around the time of puberty was observed (84).

Besides appetite stimulating effect, some other effects of ghrelin have also been observed. It was shown that ghrelin stimulates the release of ACTH and prolactin and consequently increases cortisol levels in humans (85). It has also been reported to cause anxiogenic behavior in humans, creating a possible link between the main place of ghrelin production- the stomach and the brain (stress/anxiety). Furthermore, sleeping patterns have been reported to be affected by ghrelin treatment. In rats it improved memory retention (76). Chronic administration of a ghrelin mimic to old mice restored IGF-I levels and stimulated growth and differentiation of the thymus with an increase in the production of T-cells (86). The GI functions of ghrelin in rats are reported to be a slight increase in acid secretion, ileal peristalsis and modulation of gastric motility (76). Ghrelin also has an influence on the cardiovascular system; improving cardiac contractility and performance in humans following ghrelin injection and counter inflammation in these tissues (67). Decreased ghrelin levels are independently associated with type 2 diabetes mellitus, insulin sensitivity and secretion in humans (87), except in lean humans with type 2 diabetes mellitus.

It is interesting to note that normally, a reciprocal relationship exists between leptin and ghrelin levels. It is suggested that leptin plays a regulatory role in the secretion of ghrelin (88), by having a role in the circadian and ultradian rhythmic fluctuation of ghrelin secretion. This makes it tempting to believe that there might be a feedback mechanism between ghrelin and leptin such that ghrelin also has an ef-

fect on leptin secretion. However, according to experiments performed by Sun et al., which included ghrelin knockout and ghrR knockout mice, this is not the case (89). No difference in the postprandial leptin levels was observed, indicating that ghrelin does not effect leptin secretion. Considerable evidence points to leptin being a regulator of ghrelin levels and an important part of the hypothalamic appetite regulating circuit. In March 2010, researchers reported that mice with type 1 diabetes treated with leptin alone or in conjunction with insulin, had better values of blood sugar and cholesterol than mice with type 1diabetes treated with insulin alone, raising the prospect of a new treatment for diabetes (52).

Ghrelin transmits its signal through the ghrelin receptor (ghrR) (40). GhrR has features characteristic of family A 7TM receptors, including conserved cysteine residues in the top of TM-III and in extracellular loop 2, conserved prolines, E/DRY motif, polar transmembrane residues and several potential sites for posttranslational modifications (N-linked glycosylation and phosphorylation) (90). GhrR signals through $G\alpha_{q/11}$, which results in accumulation of inositol (1,4,5)-triphosphate (IP) and Ca^{2+} release. Ghrelin has also been shown to activate the MAP kinase cascade and the PI3-K/AKT pathway (91). GhrR pharmacology started with the synthesis of analogs long before the discovery of its natural ligand (6, 92). It belongs to a subfamily of receptors for peptide hormones and neuropeptides. Besides ghrelin, the family includes receptors for motilin (previously orphan receptor GPR38), neurotensin, neuromedin U (NMU) and orphan receptor GPR39 (40). GhrR is encoded by a single gene found at chromosomal location 3q26.2. As a result of alternate processing of pre-mRNA, two different variants of the ghrR exist (93). The full length ghrR contains 366 amino acids (ghR R1a). The other splice variant, designated ghR R1b, consists of 289 amino acids and has 5 TM regions. Unlike ghR R1a, GhR R1b is not activated by ghrelin or a synthetic analogue such as the ghrR agonist hexarelin or non-peptidyl GHS such as MK-0677 (94).

Importantly it was discovered (84) that the ghrR signals with ~ 50% of its maximal activity in the absence of its ligand. GhrR has constitutive activity by demonstrating a gene dose dependent but ligand independent increase in IP accumulation (85). It was suggested that the constitutive activity of the ghrR could function as an appetite set-point against the signals from the many anorexigenic hormones such as leptin and insulin. The level of the receptor could then be regulated by ghrelin and perhaps by an endogenous inverse agonist, which would act by decreasing the constitutive activity of the receptor. Biological effects different from those seen after ghrelin treatment have been observed following administration with non-acylated ghrelin and synthetic homologs, suggesting the existence of one or more receptors in the ghrelin receptor family that have not yet been identified (60).

Conclusions

The discovery that ghrelin is one of the most powerful orexigenic and adipogenic agents known in mammalian physiology, triggered the exploitation of ghrR antagonists and/or inverse agonists that can be used to treat obesity (60). GhrR antagonist could be used to block the stimulation generated by ghrelin and thereby reduce meal size. A specific inverse agonist of ghrR would lower constitutive activity of the ghrR and thereby lower the set point of signaling from the receptor between meals. This could increase the sensitivity to the multiple inhibitory signals, e.g. leptin, insulin and PYY_{3-36} and consequently eliminate between-meal food intake. The advantages of combining ghrR antagonist and a ghrR inverse agonist in an anti-obesity drug would be that the antagonist could block the effect of the increase in plasma ghrelin seen before meals (40).

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UREJANJE APETITA IN DEBELOST: POUDAREK NA GRELINU IN GRELINSKEM RECEPTORJU

V. Kubale

Povzetek: Debelost je eden od prevladujočih vzrokov smrtnosti po svetu, kljub temu da bi jo lahko preventivno zmanjšali. Epidemska razsežnost debelosti je postala podlaga za veliko zanimanje farmacevtske industrije za razvoj zdravila, ki bi vplivalo na zmanjšanje apetita. Z zmanjšanjem apetita bi se zmanjšal tudi skupen vnos energije. Ideja je enostavna, vendar so hormonski sistem in mehanizmi, ki urejajo vnos energij,e zelo kompleksni in ne omogočajo enostavnega razvoaj takšnega zdravila. V centralnem živčnem sistemu so peptidi in hormoni, ki se izločajo na periferiji in v centralnem živčnem sistemu, vključeni v vnos hrane in urejanje telesne teže. Vsi so tesno povezani. Uravnavajo jih hipotalamus, deli možganskega debla ter sistem nagrajevanja na osnovi kognitivnih zaznavanj in različnih sporočil telesnih tekočin ter živčevja glede prehrambenega položaja. Veliko nevropeptidov, kot so nevropeptid Y (NPY), melanokortini, prepis, uravnavan s kokainom in amfetaminom (CART), peptid YY (PYY), pankreasni polipeptid (PP), holecistokinin (CCK), oksintomodulin (OXM), glukagonu podobni peptid 1 (GLP-1), od glukoze odvisni inzulinotropni hormon (GIP), bombezin, leptin ter eden zadnjih odkritih in zato manj poznanih - grelin, imajo pomembno vlogo pri kratkoročnem in dolgoročnem urejanju vnosa hrane. Pregledni članek povzema zapletene dejavnike, vključene v urejanje apetita in prehranjevanja, od različnih področij možganov, še posebej hipotalamusa, do povezave med ključnimi centralnimi in perifernimi peptidi in hormoni, s poudarkom na grelinu in receptorju za grelin, skupaj z njihovimi potencialnimi pomeni kot tarče za zdravljenje debelosti. Receptor za grelin je sprva pritegnil pozornost farmacevtske industrije zaradi svoje pomembne vloge pri sproščanju rastnega hormona. Njegova apetit spodbujajoča funkcija je spremenila grelinski receptor (ghrR) v tarčo farmacevtske industrije za razvoj zdravila proti debelosti.

Ključne besede: urejanje apetita; debelost; grelin; receptor za grelin