Rewiew articles

S.J. KONTUREK¹, P.C. KONTUREK², J.W. KONTUREK³,
M. CZEŚNIKIEWICZ-GUZIK⁴, T. BRZOZOWSKI⁵, E. SITO⁶

NEURO-HORMONAL CONTROL OF FOOD INTAKE; BASIC
MECHANISMS AND CLINICAL IMPLICATIONS

¹Department of Physiology, Jagiellonian University Medical College, Cracow, Poland,
²Department of Medicine, Erlangen-Nuremberg University, Erlangen, Germany;
³Gastroenterologie, Elbe Klinikum Stade, Stade, Germany;
⁴Institute of Stomatology, Jagiellonian University Medical College, Cracow, Poland;
⁵Military Hospital, Cracow, Poland

Obesity is one of the most common metabolic diseases and the greatest threats of the health because of possibility of numerous complications. In order to design effective drugs or apply the helpful surgical procedure it is essential to understand physiology of appetite control and pathophysiology of obesity. According to the first law of thermodynamics, the energy input in the form of food, equals energy expenditure through exercise, basal metabolism, thermogenesis and fat biosynthesis. The control of body weight actually concerns the control of adipose tissue with the key role of hypothalamus, possessing several neuronal centers such as that in lateral hypothalamic nuclei considered to be "hunger" center and in ventromedial nuclei serving as the "satiety" center. In addition, paraventricular and arcuate hypothalamic nuclei (ARC) are the sites where multiple hormones, released from the gut and adipose tissue, converge to regulate food intake and energy expenditure. There are two distinct types of neurons in ARC that are important in control of food intake; (1) preopiomelanocortin (POMC) neurons activated by anorexigenic hormones and releasing α-melanocyte-stimulating hormone (α-MSH) in satiety center and (2) neurons activated by orexigenic peptides such as ghrelin that release the substances including neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) in hunger center. ARC integrates neural (mostly vagal) and humoral inputs such as enteropeptides including orexigenic (ghrelin and orexins) and anorexigenic peptides (cholecystokinin, polypeptide YY, glucagon-like peptide-1, oxyntomodulin, leptin and others) that exert a physiological role in regulating appetite and satiety. The peripherally (gut, adipose tissue) and centrally expressed modulators of appetitive behavior act through specific receptors in the afferent (mostly vagal) nerves and hypothalamic neurons implicated in adiposity signaling and regulation of food intake.

Key words: obesity, ghrelin, leptin, hypothalamus, H. pylori, food intake
INTRODUCTION

According to the first law of thermodynamics, energy can neither be created nor destroyed, but may be converted from one to another form (Fig. 1). When that energy or caloric intake equals the energy output, an energy balance is maintained and the proportion of carbohydrates (glycogen), protein and fat, averaging 0.75%, 20% and 15% of total body mass, is preserved.

Obesity is one of the greatest threats to health because of the elevated risk of type 2 diabetes mellitus, hypertension, cardiovascular diseases and cancer. It can develop as overweight, when the body mass index (BMI) is between 25 and 29.9 kg/m² or as clinically defined form of obesity, when BMI exceeds 30 kg/m². It is increasing world-wide at an alarming rate in United States and in other industrialized countries, raising by more than 30% over last decade to afflict on average 33% of adults in United States, and 17% in UK and elsewhere including Poland (1). In 1998 the World Health Organization (2) declared obesity as a chronic medical disease because of the risk of serious complications, which prompted extensive studies on its pathogenesis in order to apply appropriate treatment before the dangerous disorders develop (3).

When energy (in the form of food) enters the body in greater quantities than are expended, the body weight increases, and most of the excess of energy is stored as fat. Therefore, excessive adiposity (obesity) is caused by energy intake in excess of

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![Fig. 1. Schematic representation of energy homeostasis and body weight regulation in accordance with 1st law of thermodynamics.](image-url)

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energy output. Fat is stored mainly in adipocytes in subcutaneous tissue and in the intraperitoneal cavity, although the liver and other organs of the body may accumulate significant amounts of lipids in obese persons. It was believed previously that the number of adipocytes could increase substantially only during the infancy and childhood and that an excess of energy in children leads to "hyperplastic" obesity associated with increased number of adipocytes. In contrast, obesity in adults was thought to result from increased size of adipocytes leading to "hypertrophic" obesity. Recent studies have shown, however, that new adipocytes may differentiate from fibroblast-like preadipocytes at any period of life and the development of obesity in adults is accompanied by increased numbers, as well as increased size of adipocytes. Extremely obese persons may have as many as four times of adipocytes, than healthy controls, each obese subject containing twice as much lipids, as a lean person.

Hypothalamus centers and brain-gut axis in the pathomechanism of obesity

Generally, there are two systems that operate in the regulation of the quantity of food intake; short-term regulation, that is concerned primarily with preventing overeating at each meal, and long term regulation, which is primarily related with the maintenance of normal quantities of energy stores in the form of fat in the body (Fig. 2). The regulation of body weight is based on homeostatic system, however, this system is tuned toward weight gain and storage of fat, whereas only

![Fig. 2. Schematic presentation of the short- and long-term regulation in appetite and food intake.](image-url)
few mechanisms exist that encourage weight loss (4). This regulatory system evolved during thousands of years to cope with insufficient energy supply rather than with a need to burn off an excess of calories. On an individual long-term basis, energy balance is remarkable precise despite day-to-day variation of food intake and energy expenditure.

The possible mechanisms of eating disorders and obesity have been attributed since the mid of 20 century to hypothalamus, the key region in central nervous system (CNS) involved in feedback control of appetite and food intake though other brain regions have also been implicated (Fig. 3). Nucleus tractus solitarius (NTS) in the brain stem serves as gateway for neural signals from the gastrointestinal tract to the hypothalamic feeding centers. Also the amygdala, the cortex prefrontalis, as well as the area postrema have been held responsible for feeding disorders and inadequate conservation or storage of energy. In addition, both the nucleus arcuatus (ARC) and the nucleus paraventricularis (PVN) are important centers in the control of food intake (Fig. 4). Early animal experiments with hypothalamic lesions and post-mortem examinations in humans with morbid obesity led to a proposal of the „dual center hypothesis“, postulating that ventromedial nuclei (VMN) serve as the satiety center and the lateral hypothalamic area (LHA) - as the feeding or hunger center (4) that when stimulated results in hyperphagia and subsequently hypothalamic obesity (5, 6).

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**Fig. 3.** Feedback control of food intake including afferent vagal nerves activated by distention of the gastrointestinal tract and various gut hormones either stimulating (ghrelin) or inhibiting food intake (CCK, leptin, insulin etc.)
It appears that the feeding center is chronically (tonically) active and that its activity may be transiently inhibited by activity of the satiety center occurring just after the ingestion of food. The destruction of the feeding center in the lateral hypothalamus in animals leads to anorexia with subsequent cachexia. Thus, through the neuronal network systems in the lateral hypothalamus, the food intake is initiated as a basic behavioral drive, while the ventro-medial hypothalamus is involved in the limitation of food intake or satiety. In the short-term regulation of energy intake, the structures in the brain control the intake of single meal regarding its volume, energy content and duration. Following the food ingestion, the signals from the receptors in oro-pharyngeal and gastric area are conveyed to NTS in brain stem through afferent nerves. In addition to mechanical distention, the chemical stimulation of receptors in gastro-intestinal mucosa and various

![Diagram](https://example.com/fig4.png)

**Fig. 4.** Model of central regulation of food intake in the hypothalamus. Ghrelin, released from empty stomach activates NPY and AgRP containing neurons in the ARC to stimulate food intake in LHA, while inhibiting POMC and CART system responsible for the satiety. In contrast, leptin positively regulates POMC and CART neurons in ARC to activate satiety and to inhibit ghrelin-NPY/AgRP pathway. Peripheral neural (vagal) signals and various gut hormones act on hypothalamic centers through the *nucleus tractus solitarius* to affect food intake.
hormones released from the gastrointestinal mucosa by nutrients, contribute to the peripheral signaling from gastrointestinal tract and pancreas with orexigenic as well as anorexigenic properties (Fig. 5).

With the discoveries of various enteropeptides and the recognition of the enteric nervous system (ENS) and its two-way connections with CNS mainly via vagal nerves (7-9), the peripheral neurohormonal components have been implicated in the short-term regulation of food (energy) intake (Fig. 6). This reflects an active regulatory process termed energy homeostasis promoting the stability of the amount of body energy stored in the form of fat. It is of interest that mice or rats are quite suitable models for studying the patho-mechanisms of human obesity because substantial homology that exists across mammalian species in the neurohormonal organization of the body weight-regulatory system (11).

The hypothalamus with its key regions, including ARC, LHA and closely related PVN, serving as the feeding or hunger center, VMN acting as the

![Image of schematic representation of neuro-humoral stimulation by cephalic, gastrointestinal and adiposity signals in control of food (energy) intake. Solid lines indicate stimulatory effects and dashes lines indicate inhibitory effects.]

*Fig. 5.* Schematic representation of neuro-humoral stimulation by cephalic, gastrointestinal and adiposity signals in control of food (energy) intake. Solid lines indicate stimulatory effects and dashes lines indicate inhibitory effects.
satiety center and NTS conveying the peripheral signals, particularly from the
gut to the feeding centers, are implicated in appetitive behavior. Thus, CNS
receives (through NTS) numerous neural impulses and hormones from
peripheral organs, especially from the gastrointestinal mucosa, and fat tissue
that are involved in short and long-term coordination of feeding and energy
expenditure in response to constantly altered energy balance (Fig. 6). The gut
peptides signaling to the hypothalamus act via the ARC to mediate the appetite
stimulation (+) effect through the activation of neurons containing
neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) or appetite-
inhibitory effects (-) via neurons containing the preopiomelanocortin (POMC)-
derived α-melanocyte stimulating hormone (α-MSH) and cocaine and
amphetamine regulated transcript (CART) peptide to hunger centers in the
LHA, the satiety center in PVN in the medial hypothalamus (16).

Peripheral orexigenic mechanisms

The major gastrointestinal hormone with potent orexigenic properties is ghrelin
(12) which has been identified in gastric ghrelin X/A cells characterized by large
eletrodense granules of P/D type in man and A-like type in rats (13). It is a 28-
amino acid peptide, primarily released by these endocrine cells in empty stomach

Fig. 6. Gut peptides signaling through NPY/AgRP neurons to stimulate food intake in LHA or PVN
or through POMC-α-MSH releasing neurons to induce satiety in medial hypothalamus.
Plasma concentration of ghrelin peaks under fasting conditions before the meal and then levels off after meal to a nadir to increase again after gastric emptying before next meal (14). The mechanisms of ghrelin action on appetite and food intake is suggested to be primarily mediated through peripheral input at the ARC and further spread to the NTS. Ghrelin exerts growth hormone (GH)-releasing properties (15) and is involved in the hypothalamic regulation of metabolic control and energy balance (12). Ghrelin serves as a ligand for growth hormone secretagogue receptors (GHS-R). The primary hypothalamic target for ghrelin are neurons in ARC that express and release NPY and AgRP in the lateral hypothalamus and LHA to mediate orexigenic effect in the brain (16, 17). It may also inhibit the neurons in the ARC that contain POMC-derivative α-MSH that mediate the anorexigenic effect in the PVN (9, 16, 18). An appetite stimulating action of ghrelin has been proven in humans (19). Clinical implications of this have been applied to patients with Prader-Willi syndrome that exhibit greatly increased circulating levels of ghrelin (20, 21). Furthermore, gastric bypass surgery for morbid obesity leads to the considerable weight loss (22, 23), pointing at a ghrelin as mediator of altered energy balance. Peripherally in the gut, ghrelin was shown by us to stimulate gastric acid secretion and gastrin release (24) and to exhibit the gastro- and pancreato-protective activities against various irritants (25). In addition, ghrelin was reported to exert a prokinetic effect on the small bowel,

*Fig. 7.* Schematic presentation of the release of ghrelin from the endocrine gastric cells and of the actions of this peptides on appetite and other functions including GH release, stimulation of cardiovascular system and metabolism.
where it stimulates activity front of the migrating motor complex (MMC) through cholinergeric mechanisms (26). It is of interest that food desire combined with an increased gastric acid secretion occurs after intake of ethanol at low concentration ("cocktail"), which appears to enhance the overexpression of ghrelin in the oxyntic mucosa and an increase in plasma levels of this peptide, gastric motility and gastric acid secretion (27). Thus, ghrelin seems to contribute to the initiation of food intake and to stimulation in motilin-like fashion of gastrointestinal motility.

In addition to the initiation of food intake, exogenous ghrelin decreases the release and action of leptin and vice-versa exogenous leptin reduces the plasma level of ghrelin (28). It has been proposed that leptin exerts a negative regulatory effect on the release and action of ghrelin and that an increase in ghrelin level induced by fasting or weight loss arises because of the diminished inhibitory effect from leptin and probably also from PYY. This may imply that weight-reducing effects of leptin are mediated not only by its direct central action on hypothalamus but also through its peripheral inhibitory effect on the release and action of ghrelin. According to our experience in rats, the parenteral administration of ghrelin at a dose that raised plasma hormone to the level observed under fasting conditions, significantly attenuates plasma levels of leptin, while markedly increasing food intake. Immunoneutralization of circulating plasma ghrelin with specific IgG anti-ghrelin antibodies, causes a marked increase in plasma leptin and decrease in food intake. In contrast, exogenous leptin, at the dose (10 µg/kg ip) that raised plasma leptin to the level occurring postprandially, reduced markedly plasma levels of ghrelin and attenuated food intake and these effects can be reversed by the administration of specific IgG anti-leptin antibodies (28). These results clearly support the hypothesis that ghrelin negatively controls plasma release of leptin and vice-versa that leptin has a counter-regulatory influence on ghrelin release and action, though the former effect appears to be much stronger than the later. This interaction between ghrelin and leptin in control of food intake is called "argentinian ghrelin-leptin tango" (Fig. 8).

In addition to ghrelin, orexin A (OXA) and B (OXB), the novel neuropeptides were found to play the role in the stimulation of food intake and energy homeostasis (29). OXA has been detected in the mucosa and neuronal plexuses of the gastrointestinal tract and in the CNS, especially in LHA that is involved in the stimulation of food intake (30, 31). Plasma levels of OXA are increased during fasting in humans (32) and are lower in obese subjects than normal-weight people (33), suggesting that peripheral OXA modulates food intake as an orexigenic peptide (34). However, intravenous infusion of OXA in humans does not appear to induce any hunger-stimulating drive but increases gastric emptying (35).

**Peripheral anorexigenic mechanisms**

The postprandial satiety has been ascribed to numerous signaling molecules, expressed and released in the gastrointestinal tract and also in hypothalamic
ARC, to inhibit food intake via activation of the receptors on afferent (mostly vagal) nerves stimulating the satiety center and inhibiting the feeding center (9) (Fig. 9). Among the anorexigenic peptides, the first recognized inhibitor of food intake in rodents (36) and then in humans (37-40) was cholecystokinin (CCK), the product of duodeno-jejunal endocrine I cells acting via CCK₁ receptors on vagal afferent nerves. This hormone exists in the mucosa and circulation in several molecular forms such as CCK-8, CCK-33, CCK-39 and CCK-58. All these molecular forms derive from a single CCK gene through posttranslational processing and have the same C-terminal five amino acid sequence. CCK was found not only in the intestinal mucosa but also in peripheral nerves and in neurons of the brain (41).

Fig. 8. Negative interactions of gut hormones, especially ghrelin and leptin, on food intake.
CCK is the likely candidate for the physiological mediation of short-term inhibition of food intake. It cooperates with signals originating from the mechanoreceptors of the gut that are generated by the distention of the gut and transmitted to the brain through vagal afferents. This is in keeping with earlier findings that sub-diaphragmatic vagotomy abolishes anorexigenic activity of exogenous CCK (42) and, as we found it for the first time (36), and the blockage of CCK₁ receptors with loxiglumide abolishes the anorexigenic effects of both exogenous and endogenous hormone. The clinical usefulness of CCK as an anti-obesity, appetite reducing agent was found, however, to be transient due to the development of tolerance to CCK and its analogs (43). Furthermore, even removal of gene for CCK_{1} receptors, (CCK_{1} receptor knockout mouse) failed to increase the food intake, but resulted in the lack of the sensitivity of these animals to anorexigenic action of exogenous CCK (44). Since CCK only intermittently preserves its anorexigenic activity between injections of exogenous CCK, compensatory overeating occurs, so it is unlikely that this peptide could be useful in anti-obesity therapy.

**Anorexigenic effects of adiposity factors**

The control of body weight is actually limited to the control of adipose tissue that not only plays a role in copious energy storage but also serves as thermal

![Schematic presentation of the release and action of various gut and adipose tissue peptides on the ARC neurons affecting food intake.](image-url)
isolator, protector of inner organs as well as a site of hormone secretion (aromatase). With the discovery by Zhang et al. in 1984 of leptin (45), a peripheral active appetite inhibiting hormone produced by adipocytes and acting both via specific receptor (Ob-R) on afferent vagal nerves and directly on ARC neurons enhancing satiety, raised a hope in progress in obesity therapy (44). Although leptin inhibits expression of orexigenic NPY/AgPR hypothalamic neurons, while stimulating anorexigenic POMC neurons in ARC (45), its practical therapeutical application in fighting excessive appetite in obese people appears to be unjustified because the majority of obese humans already exhibit high plasma levels of leptin, proportional to the body fat storage, indicating their resistance to circulating leptin (46). The mechanism of this is unknown but poor penetration of peripheral leptin to hypothalamic regions due to reduced capillary transport system in hypothalamic microcirculation could be responsible for its limited efficacy as an anti-obesity drug (47). Leptin is produced not only in the adipose tissue but also in the gastrointestinal tract, particularly in the stomach, where it has been shown to protect the gastric mucosa against various topical irritants and ulcerogens, acting, at least in part, via enhancement of mucosal blood flow due to increased production of nitric oxide (NO) caused by upregulation of NO synthase as well as the activation of brain-gut axis pathways (48, 49). Since leptin is released by excitation of vagal nerves by sham-feeding, that operates entirely via brain-gut axis (49), it may be assumed that gastroprotective and hyperemic effects of leptin are centrally mediated, at least in part, by the activation of sensory vagal fibers (50). This is supported by our finding that the pretreatment of with neurotoxic dose of capsaicin abolished the gastroprotective activity of leptin (51). Unfortunately, the effects of such treatment on appetite reducing action of leptin have not been tested.

**Leptin - insulin lipostat**

Although there is rather low local expression of leptin in the stomach, probably responsible for local antagonism of gastric release of ghrelin and named "leptin/ghrelin tango" operating along the brain-gut axis (9, 52), leptin belongs together with insulin to a "lipostat" substances that play a role in adiposity signaling (Fig. 9). Insulin, like leptin, is thought to inhibit NPY/AgRP neurons in ARC region of the hypothalamus and reduce food intake (53, 54). This is supported by the observations that insulin applied intra-cerebro-ventricularly (icv) inhibits food intake. Accordingly icv administration of insulin antibodies increased food intake and body weight (53). Thus, leptin-like insulin, represents adiposity signal inhibiting food intake by interacting with hypothalamic receptors activated through POMC and CART neuronal pathways stimulating satiety center, and reducing the activity of NPY/AgRP neurons driving the appetitive behavior.

**Other anorexigenic peptides**

This list of anorexigenic substances is long and includes numerous gut peptides such as pancreatic polypeptide (PP), peptide-YY (PYY) and glucagon-like peptide-
1 (GLP-1) (Fig. 10). Two first peptides are 36 amino-acid long peptides that act via G-protein receptor subtypes-Y1, Y2, Y3, Y4, Y5 and Y6 mediating the overlapping physiological actions of PP-family peptides. PP is primarily expressed in the endocrine PP-cells of the pancreas. The amounts of PP released depend upon the digestive state; the release is low when fasted and increases during all phases of digestion (55, 56). The main stimulus of PP release is the ingestion of protein and fatty meal. It has been demonstrated that PP is released by other gut hormones such as ghrelin, motilin and secretin, but somatostatin was shown to inhibit its release. PP exerts its effects through the specific receptors (Y1-Y5) and exhibits inhibitory action on pancreatic secretion (55, 56) and gastrointestinal motility (57). As shown recently by Asakawa et al. (58) Katsumura et al. (59), peripheral administration of PP attenuates food intake and gastric emptying, while icv injection of PP increases food intake and delays gastric emptying, but it is not excluded that PP effects on food intake are secondary to changes of gastric emptying (59). Using transgenic technology it has been shown that mice overexpressing PP exhibit a significant decrease in total food intake (60). The reduction in appetite in those mice was
associated with a decreased rate of gastric emptying of solid meal. The anorexigenic activity of PP was demonstrated in humans and PP was found not to develop tolerance. Batterham et al. (61) showed that PP infusion in humans reduces both appetite and food intake. Such PP infusion had no significant influence on plasma concentrations of ghrelin, PYY, GLP-1, leptin and insulin, suggesting that anorexigenic action of PP is independent of changes in these hormones. PP is also released during strenuous exercise and may, therefore, account for a reduced appetite following the exercise (62). It is of interest that children with Prader-Willi syndrome, which exhibit hyperphagia and obesity have a low level of plasma PP and infusion of PP in those children leads to reduction in food intake (63).

PYY is another candidate for the short-term control of food intake (64, 65) that originates from the L-cells in the ileal and colon mucosa following stimulation by feeding, particularly when ingested nutrients, namely fatty acids, reach the distal portion of the small bowel and colon (66). In addition to nutrients, PYY also released by gastric acid, CCK, and by bile salts. It is of interest that an intraduodenal meal increases plasma PYY even before nutrients reach the PYY-containing cells in the ileum or colon. This suggests the release of PYY through neural reflex, possibly mediated by the vagus. Plasma PYY levels are increased by insulin-like growth factor 1 (IGF-1), bombesin, and calcitonin-gene-related peptide and decreased by GLP-1. PYY is usually stored in endocrine cells of intestinal mucosa as 36-amino-acid peptide (67), but in the blood circulation it is converted into truncated form, PYY3-36, acting via Y1, Y2, Y3 and Y5 receptors.

Early studies on the action of peripherally administered PYY demonstrated numerous effects of this peptide on gastrointestinal tract. PYY delayed gastric emptying and inhibited gastric and pancreatic secretion and gall-bladder emptying while increasing ileal postprandial fluid and electrolyte absorption (67-69). Peripheral PYY3-36, like PP, was reported to decrease appetite and to inhibit food intake and weight loss in rodents and humans by inhibiting ARC expressions of NPY/AgPR (70-72). In contrast, injections of PYY3-36 into the third, lateral or fourth cerebral ventricle, the paraventricular nuclei or the hippocampus in rodents potently stimulated food intake and feeding behavior by enhancing expression of NPY/AgRP in neurons of ARC. The discrepancy between peripheral and central administration of PYY on food intake has not been explained, but Batterham et al (72) proposed that it may be due to the activation by this peptide of Y2 receptors in hypothalamic ARC neurons where the blood-brain barrier is relatively permeable.

It is of interest that obese people have similar sensitivity to the appetite inhibitory action of exogenous PYY3-36 as lean subjects indicating a lack of the resistance to the action of peptide. Since tolerance did not develop with applications of PYY3-36, it is reasonable to assume that this peptide (similar to PP, but opposite to leptin) has potential in long-term obesity therapy. The mechanisms of hunger reduction in subjects treated with PYY is not clear but the
finding of the reduction in plasma preprandial ghrelin concentration suggests that the interaction between these two gut peptides could contribute to the anorexigenic effect of PYY (Fig. 10).

Glucagon-like peptide-1 (GLP-1) is produced and secreted by endocrine L-cells found in the ileal and colonic mucosa in response to food intake (73, 74). GLP-1 has received attention as being the chief contributor to ileal brake mechanisms of the upper gastrointestinal tract regarding gastric and pancreatic secretion and gastric emptying (75, 76). By slowing gastric emptying of a liquid or solid meal, GLP-1 reduces the postprandial demand of insulin to maintain euglycemia after a meal (77, 78). Accumulating evidence supports the notion that the effects of GLP-1 on gastrointestinal functions are mediated through its distinct receptors on vagal nerves both in animals and man (79-81).

In humans, GLP-1 was found to increase satiety and decrease food intake in normal-weight subjects, diabetes patients and obese subjects (82-85). As obese humans show lower circulating glucagon-like peptide-1 (GLP-1), similar to that of PYY, it has been thought that the resistance to this gut hormone contributes to the obesity. However, GLP-1 is an effective anorexigenic peptide, inhibiting effectively food intake, even after prolong administration, indicating that this peptide could be a physiological regulator of food intake. As obese subjects appear to display a more rapid gastric emptying of solids compared to normal weight subjects (86) and the natural increase in plasma GLP-1 is attenuated in obese subjects (86, 87), the smaller release of GLP in the obese subjects could cause less pronounced satiety of food intake, leading to earlier onset of the next meal. After jejun-ileal bypass, the postprandial GLP-1 is enhanced concomitant with slower gastric emptying (87). This indicates that peripheral action of GLP-1 is important for the satiety and that it involves vagal nerves controlling gastric motor activity.

Oxyntomodulin (OXM) is produced by the same L-cells as GLP-1 in the distal portion of the gut and also in the brain (88, 89). It is a 37 amino acid peptide released after ingestion of meal and exerting various biological effects, including inhibition of gastric secretion and emptying, decrease in pancreatic secretion and stimulation of intestinal glucose uptake (89-91). Furthermore, it has been suggested to be involved in the short-term suppression of food intake in rats (90) and humans (91). The mechanism of anorexigenic action of OXM is not known but it may involve the suppression of plasma ghrelin levels (91). It is not clear whether OXM, acting through GLP-1 receptors will be effective in the decrease of appetite and food intake in obese subjects and this requires further studies.

_Helicobacter pylori (H. pylori) infection and feeding behavior_

Recently, gastric _H. pylori_ infection has been shown to affect expression and release of leptin and ghrelin (92). The prevalence of _H. pylori_ infection is about 60-
80% of asymptomatic humans, but in all infected humans, it causes active chronic gastritis, sometimes peptic ulcer (10-15%) or even cancer (2-5%). Such an infection was found to be accompanied by an increase in plasma leptin that normalized following eradication of *H. pylori* (Fig. II). The *H. pylori*-induced rise in plasma leptin (49) could contribute to the loss of appetite in infected patients. However, even more important than the rise of leptin may be the fall in gastric expression and release of ghrelin, as reported by Nwokolo et al (94), confirming that indeed, *H. pylori* infection could be responsible for the loss of appetite, the decrease of food intake and the growth retardation in children. The mechanism by which *H. pylori* infection leads to reduction in plasma ghrelin concentration is unknown, but since leptin was shown to inhibit ghrelin expression, it is not excluded, that the rise in plasma leptin that follows *H. pylori* infection might explain the decreased ghrelin release. Alternatively, the possibility exists that hypergastrinemia that usually accompanies *H. pylori* infection inhibits the release of ghrelin and this is supported by the recent finding that eradication of *H. pylori* that caused an immediate suppression of plasma gastrin was associated with a significant elevation in plasma ghrelin and restoration of good appetite (95) (Fig. II).

![Diagram](https://example.com/diagram.png)

**Fig. II.** Effects of *H. pylori* infection on gastric leptin and ghrelin release and action on hypothalamus and pituitary as well as food intake and body weight.
Current treatments

The recognition of obesity as chronic medical disease by World Health Organization in 1998 (2) and co-morbid pathologies including cardiac diseases, type 2 diabetes mellitus, hypertension and dyslipidemia or cancer, all should be considered, when selecting the most appropriate treatment of obesity. Although morbid obesity is a multi-genetic state in majority of patients, no gene therapy has so far been successfully applied. The dietary restriction and the long therapy such as the use of Orlistat, which interferes with gastric or pancreatic lipases to reduce intestinal fat absorption or Subitramine to enhances central noradrenaline or serotonine signalling to promote satiety and reduce appetite, result in rather small weight loss and has to be limited to application during only 1-2 years. The prolong use of certain gut peptides such as PYY$^{3-36}$ and GLP-1, seems to be rational, particularly, that the deficiency of these peptides in obesity has been documented (95). The wider use of those agents requires, however, the approval by reliable health protection authority.

The only therapy that provides transient or even permanent weight loss and prolong suppression of appetite are various procedures of bariatric surgery, because their relatively low cost, almost immediate improvement of co-morbid conditions and obesity-related side-effects. These bariatric procedures include more or less drastic restrictive operations, such as gastric bands of various types but also more effective operations such as restrictive gastric and intestinal procedures aiming at decreasing the amount of absorbed nutrients. It is of interest that these procedures reverse the abnormal profile of gut hormone expression/release, particularly of ghrelin, orexigenic peptide, while raising the deficient anorexigenic peptides such as PYY$^{3-36}$, GLP-1 and leptin.

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Author’s address: Prof. S.J. Konturek, M.D., Department of Physiology, Jagiellonian University Medical College, 31-531 Krakow, Grzegorzecka 16, Poland. Tel. +48-12-4211006.

E-mail: mpkontur@cyf-kr.edu.pl