

## GUT - AS ENDOCRINE ORGAN

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### Abstract

*The gastrointestinal tract is the largest endocrine organ in the body and it is connected through the vagal neurons with brainstem, which acts as a site of integration between endocrine and neuronal signals. Gut hormones function to optimize the process of digestion and absorption of nutrients by the gut. The most well studied in this regard are: cholecystokinin, pancreatic polypeptide, peptide YY, glucagon-like peptide-1, oxyntomodulin and ghrelin. Recent research suggests that gut hormones can be manipulated to regulate energy balance in humans. Gut hormone-based therapies may thus provide an effective and well-tolerated treatment for diabetes mellitus and obesity.*

**Keywords:** pancreatic polypeptide, peptide YY, ghrelin, glucagon-like peptide 1, oxyntomodulin, cholecystokinin.

## INTESTINUL - ORGAN ENDOCRIN

### Rezumat

*Tractul gastrointestinal este organul endocrin cu suprafața cea mai mare, fiind legat prin intermediul conexiunilor vagale cu sistemul nervos, care reprezintă locul de integrare al semnalelor neuronale și endocrine. Hormonii gastrointestinali acționează pentru a optimiza digestia și absorbția nutrienților din intestin. Cei mai studiați din acest punct de vedere sunt: colecistochinina, polipeptidul pancreatic, peptidul YY, glucagon-like peptide-1, oxintomodulina și ghrelină. Cercetări recente sugerează că hormonii gastrointestinali pot fi manipulați la oameni pentru reglarea bilanțului energetic. Terapiile bazate pe hormonii gastrointestinali pot fi folosite eficiente în tratamentul diabetului zaharat și al obezității.*

**Cuvinte cheie:** polipeptid pancreatic, peptid Y, ghrelină, peptid glucagon-like 1, oxintomodulină, colecistokinină.

### Introduction

Gut endocrine cells, classified as APUD cells, are derived from the endoderm. Observations that enteroendocrine cells share features with neurons have assumed new significance with recent discoveries showing that gut endocrine differentiation is regulated similarly to differentiation in the nervous system [1].

Both gut endocrine and neural differentiation appear to be controlled by similar, in some cases identical genes encoding basic helix-loop-helix (bHLH) transcription factors under control of the Notch signaling pathway [2,3]. Signaling by the cell surface protein, Notch, plays a critical role in endocrine cell determination in the intestine.

Transgenic mice with mutation that disrupt Notch regulate enteroendocrine differentiation by inhibiting expression of proendocrine bHLH transcription factors in the gastrointestinal tract. Gene inactivation studies in mice have identified three atonal-related bHLH factors implied in intestinal endocrine differentiation: Math1, neurogenin 3 (NGN3), BETA2/NeuroD (BETA2) [4].

The brain-gut axis, comprising both endocrine and neurological system, functions to optimize the digestion and absorption of nutrients. Gut hormones regulate energy intake by altering food intake directly and indirectly, the majority acting to reduce food intake and limit meal size. The importance of the brain-gut axis in the control of energy balance is reflected in the dual role presented by many gut peptides as both hormones and neurotransmitters [5].

Articol intrat la redacție în data de: 16.12.2009

Acceptat în data de: 19.04.2010

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### Energy Balance Signals

These peptides act as reliable endocrine hormones and exert effects at distant target organs. Signals from the gut converge on the hypothalamus where they are integrated, and in turn regulate energy intake and energy expenditure. In hypothalamus, arcuate nucleus acts as the site of integration of neurological and blood-borne signals. Two types of neuronal populations were identified within the arcuate nucleus: a type of neurons in the medial arcuate nucleus express neuropeptide Y and agouti-related peptide and act to stimulate food intake and weight gain. In the lateral arcuate nucleus, pro-opiomelanocortin, cocaine- and amphetamine - regulated transcript expressing neurons act to inhibit food intake and promote weight loss [5,6].

Satiety is also controlled by the hindbrain. Through the nucleus of the solitary tract and the area postrema, components of the dorsal vagal complex, receive information from vagal afferents and circulating factors, and are reciprocally connected with the hypothalamus controlling energy balance. Many circulating signals, as gut hormones, act to the arcuate nucleus. Leptin is the prototypical peripheral signal acting directly on the arcuate nucleus [7, 6]. Cholecystokinin binds to receptors on the vagus nerve, activating the solitary tract which relays information to the hypothalamus. Glucagon-like peptide 1, expressing neurons of the solitary tract project to hypothalamic regions controlling food intake, including the arcuate, dorsomedial and paraventricular nuclei. Ghrelin and peptide YY have a direct action on the arcuate nucleus and an action via the vagus nerve and brainstem [6].

### Gut Peptides and Appetitive Behaviour

Gastrointestinal tract is connected through the vagal neurons with brainstem, which acts as a site of integration between endocrine and neuronal signals.

CHOLECYSTOKININ, the archetypic satiety hormone, derived from a 115-amino acid precursor, pro-CCK, is produced by I-cells of the small intestine and exists in the mucosa and circulation in several forms, the major forms in the plasma are CCK-58, CCK-33, CCK-22, CCK-8 [5,6]. CCK-8 is the predominant form in nervous tissue and longer species are preferentially synthesized in the endocrine cells of the gut [8].

The basal plasma concentration is approximately 1 pM, and levels rise to 5-8 pM postprandially and remain elevated for up to 5 hours after a meal [5,6,9].

This hormone may signal to satiety center and the effect can be reduced by lesions of the nucleus of the solitary tract, by vagotomy or vagal transection [10,9].

CCK is rapidly released in response to nutrients in the gut, in particular, fat and protein rich meals. Its main actions include delaying gastric emptying, stimulating pancreatic enzyme secretion and gall bladder contraction [11,12] via the CCK receptor. There are 2 distinct G-protein-

coupled CCK receptor subtypes. CCK-A (also called CCK-1) receptors are found in the pancreas, on vagal afferent and enteric neurons. CCK-A receptors are also found throughout the brain, including the nucleus of the solitary tract, area postrema and dorsomedial hypothalamus. CCK-B receptors are present in the afferent vagus nerve and are found within the stomach [6]. CCK-B receptor has been implicated in schizophrenic and anxiety states [13,14].

CCK alters appetite, inhibits food intake by reducing meal size and duration [15]. CCK alone may be a very short-term modulator of appetite, its half-life is only 1-2 minutes, and it is not effective at reducing meal size if the peptide is administered more than 15 minutes before a meal [6]. Weight loss is reported with combination of peripheral CCK and central leptin administration [16]. Chronic administration of CCK antibodies or CCK-A receptor antagonists results in weight gain in rodent models but with no significant increase in food intake [17]. In addition, the CCK-A receptor knockout rat is hyperphagic and obese [18].

The therapeutic potential of CCK is in some doubt, physiological or pharmacological nature of the actions of CCK on food intake awaits further clarification because continuous CCK administration is ineffective after the first 24 hours [5,6].

### PYY and PP

Peptide YY, pancreatic polypeptide (PP) and neuropeptide Y (NPY) are members of the PP-fold peptide family and are 36 amino acids in length and undergo C-terminal amidation as a necessary requirement for biological activity. The PP family exert their effects via the Y family of G protein-coupled receptors (Gi), and mediate an inhibition of intracellular cyclic-adenosine monophosphate (cAMP) synthesis [6,5]. Y1, Y2, Y4, Y5 are receptor subtypes which are expressed in the hypothalamus [19]. NPY exerts its orexigenic action through Y1 and Y5 receptor. Y2 receptor is thought to function like an autoinhibitory presynaptic receptor, expressed on NPY neurons, and to mediate the anorectic actions of PYY, while the Y4 receptor appears to mediate the anorectic actions of PP [6].

PYY is secreted by the L-cells of the gastrointestinal tract and is widely expressed throughout the gut, but particularly in the distal portion. It occurs in 2 forms: PYY<sub>1-36</sub> and PYY<sub>3-36</sub>. PYY<sub>3-36</sub> is the major circulating form and is a truncated 34-aminoacid created by cleavage of the N-terminal Tyr-Pro residues by dipeptidyl peptidase 4 (DPP4) [20]. PYY<sub>3-36</sub> shows selectivity for Y2 receptor, for which it has high affinity, and some affinity for Y1 and Y5 receptors [6].

PYY is released into circulation following meals and suppressed by fasting. PYY levels rise to a plateau at 1-2 hours postprandially, with these peak levels influenced by both the number of calories and the composition of the food consumed [6,21]. The release of PYY in response to fat in

the proximal small intestine is atropine-sensitive, raising the possibility that a neural reflex may also mediate PYY release [22,23]. Other stimulants of PYY release include intraluminal bile acids, gastric acid and CCK [24].

In common with other hormones of the gastrointestinal tract, PYY presents mitogenic properties, which has led to interest in its effects in pathological states, such as acute pancreatitis [5].

A number of observations proved that PYY<sub>3-36</sub> performs a significant role in the control of appetite in human. In disease states characterized by weight loss, such as cardiac cachexia, inflammatory bowel disease, tropical sprue, PYY<sub>3-36</sub> levels are elevated [5,25,21]. In opposite, in obese humans, fasting plasma concentration of PYY<sub>3-36</sub> is reduced and overweight subjects have a relative deficiency of postprandial PYY<sub>3-36</sub> release associated with reduced satiety.

Despite lower fasting plasma concentration of PYY<sub>3-36</sub> in obese humans, obesity does not appear to be associated with resistance to the effects of PYY<sub>3-36</sub> [26]. Infusion of PYY<sub>3-36</sub> into a group of obese volunteers revealed a comparable reduction in calorie intake when compared with lean controls [27].

Interestingly, in contrast to peripheral administration, intracerebroventricular administration of PYY stimulates food intake. This is thought to be an action through Y1 and Y5 receptors in the paraventricular nucleus, the second neurons targeted by orexigenic arcuate nucleus NPY neurons. Several investigations suggest a direct anorectic action of circulating PYY<sub>3-36</sub> on the arcuate nucleus. This action is thought to be via autoinhibitory Y2 receptors on the orexigenic NPY neurons. There is now evidence for an action of PYY<sub>3-36</sub> at the level of the vagus and of the dorsal vagal complex. The vagal-brainstem-hypothalamic pathways have been implicated in mediating sensations of nausea [6]. PYY<sub>3-36</sub>, at high doses, has been reported to cause taste avoidance in rodents and nausea in humans [21,28,29].

Observation that PYY<sub>3-36</sub> is involved in the pathogenesis of obesity, suggests a role for PYY in appetite regulation independent of adverse effects. PYY is therefore an attractive therapeutic target.

PP is principally produced in the endocrine pancreas, but also in the exocrine pancreas, colon, and rectum. It is released in response to a meal, and inhibits appetite. Pancreatic and gastrointestinal hormones can also regulate circulating PP levels. Motilin, ghrelin, and secretin stimulate PP release, whereas somatostatin and its analogs reduce plasma PP concentrations. PP demonstrates an affinity for Y4 receptors (with greater affinity than PYY) and Y5 receptors [6].

Peripheral administration of PP has been shown to reduce food intake in normal mice, gastric expression of ghrelin, and increased vagal tone [30]. PP increased oxygen consumption and stimulated sympathetic activity, PP may

also increase energy expenditure.

Plasma PP is increased in patients with anorexia nervosa and is suppressed in obese subjects. However, the results are conflicting; others have found no difference between lean and obese subjects or between obese subjects before and after weight loss.

Central injection of PP has opposite effect to peripheral administration, injection of PP into third ventricle stimulates food intake in satiated rats. PP is unable to cross the blood-brain barrier, acts on the CNS via areas that have a deficient blood-brain barrier, such as area postrema. The anorectic effect seen after peripheral administration of PP is through PP binding via the Y4 receptor, which is highly expressed in this region. The receptor mediating the orexigenic effect of PP after central injection is unclear [6].

## PRODUCTS OF PREPROGLUCAGON CLEAVAGE

Preproglucagon is a 160-amino acid prohormone with a 20-amino acid signal sequence at the N-terminal end, expressed in the pancreas, L-cells of the intestine, and in the nucleus of the solitary tract. The L-cells are the second most abundant population of endocrine cells in the human intestine, exceeded only by the population of enterochromaffin cells [31]. Preproglucagon undergoes differential cleavage by prohormone convertase 1 and 2 depending on the site of synthesis. In the pancreas, classical preproglucagon processing produces glucagon and the apparently inactive N-terminal fragment glicentin-related pancreatic polypeptide. GLP sequences remain with major proglucagon fragment. In the gut and in the brain, the glucagons sequence remains in a larger peptide, glicentin, which is thought to be inactive, but glicentin is further cleaved to oxyntomodulin and glicentin-related pancreatic polypeptide.

In the intestine and central nervous system, the products oxyntomodulin (OXM) and glucagon-like peptides-1 and -2 (GLP-1 and -2) have been implicated in the regulation of appetite [5,6].

### • OXYNTOMODULIN

Oxyntomodulin is a 37-amino acid peptide comprising the 29 amino acids of pancreatic glucagon with an eight amino acid C-terminal extension, sometimes called spacer peptide 1. It is released into the blood following ingestion of food in the proportion to calories [6,5]. Physiologically, it acts to reduce gastric motility and secretion in rodents and man, and exert an incretin effect. Oxyntomodulin is also an effective anorectic peptide in human subjects, part of its anorectic effect may be via suppression of plasma ghrelin levels. Acute administration has been shown to increase voluntary activity in human subjects [32]. The circulating level of oxyntomodulin in obesity is not established.

Oxyntomodulin exert its effect via GLP-1 receptor. Exendin, the antagonists of GLP-1 receptor, antagonize the effect of both GLP-1 receptor knockout mouse [33]. The affinity of oxyntomodulin for GLP-1 receptor is approximately 2 orders of magnitude less than that of GLP-1, an oxyntomodulin receptor is not yet cloned. The GLP-1 receptor is present in the nucleus of the solitary tract and in the hypothalamic arcuate nucleus.

The duration of inhibition of appetite in response to peripheral oxyntomodulin administration is short, three times daily subcutaneous injection is necessary for weight loss in humans [34]. This may be due to rapid cleavage of the 2 N-terminal amino acid residues by DPP-4, as observed for GLP-1 and PYY [6].

Oxyntomodulin offers another promising target in the development of the therapy for obesity, its less incretin effect may make it an attractive option in the treatment of non-diabetic obese patients.

#### • GLUCAGON-LIKE PEPTIDE-1

GLP-1 is the most powerful known incretin in humans. GLP-1 exists in a number of forms in the circulation, it is cleaved from proglucagon as a 36- or 37- amino acid molecule, depending on whether the C-terminal glycine is present. Both peptide isoforms are equipotent in biological activities, although GLP-1<sub>7-36amide</sub> is present in the circulation in greater quantities and has attracted most attention.

GLP-1<sub>7-36amide</sub> inhibits gastric acid secretion and gastric emptying, suppresses glucagon release, stimulates insulin secretion, promotes an increase in pancreatic  $\beta$ -cell mass [35,36,5] and also exerts effects in the cardiovascular system. GLP-1<sub>7-36amide</sub> infusion may improve outcomes post-myocardial infarction in some circumstances [37].

Although the majority of L-cells are located in the distal gut, the presence of nutrients in the proximal small intestine stimulates GLP-1<sub>7-36amide</sub>, this effect is abolished by vagotomy, implying the influence of neural inputs on GLP-1<sub>7-36amide</sub> release [38]. The mechanism is similar with the release of PYY<sub>3-36</sub> and has led to the proposal of GLP-1<sub>7-36amide</sub> as another candidate mediator of the 'ileal brake' phenomenon.

Like other gut peptide, GLP-1<sub>7-36amide</sub> also functions within the CNS as a neurotransmitter. It is present within the dorsovaginal complex, the thalamus and the pituitary. The GLP-1 receptor is a G-protein-coupled, seven-transmembrane domain protein and binding of GLP-1<sub>7-36amide</sub> results in an increase in intracellular cyclic AMP. The peptide exendin-4 has proved a useful tool in determining the mechanism by which the actions of GLP-1<sub>7-36amide</sub> on appetite is mediated. This is a 39-amino acid peptide extracted from the saliva of the Gila monster, *Heloderma suspectum* and is a potent agonist at GLP-1 receptor acts as a competitive antagonist.

Both CNS-injected and peripherally administered

GLP-1<sub>7-36amide</sub> inhibit food intake in a number of species, the site action appears to be brainstem-hypothalamus axis [5].

Intracerebroventricular injections of GLP-1 in rats inhibit food and water intake and induce *c-fos* expression in the paraventricular nucleus of the hypothalamus. It is reported activation of *c-fos* by GLP-1<sub>7-36amide</sub> in other areas of the brain. These include the nucleus of the tractus solitarius and the area postrema in the brainstem, and the supraoptic nucleus in the hypothalamus. GLP-1<sub>7-36amide</sub> may induce the phenomenon of conditioned taste aversion and may induce anorexia [5].

In humans, GLP-1<sub>7-36amide</sub> levels are reduced in obesity and normalize with weight loss [39]. Manipulation of the GLP-1 system forms the basis of several major new treatments for type 2 diabetes [6] and in type 1 diabetes, treatment with GLP-1 shows promising effects [40].

Obese subjects receiving GLP-1 for 5 days, reduced their calorie intake by 15% and lost 0.5kg in weight [41].

#### • GLUCAGON-LIKE PEPTIDE-2

GLP-2 is synthesized, like GLP-1<sub>7-36amide</sub>, by the action of prohormone convertase 1 on proglucagon in the central nervous system and intestinal L-cells. Fat and carbohydrates could stimulate GLP-2 release. From the perspective of energy balance, GLP-2 injected intracerebroventricularly into rats does inhibit food intake. Peripherally administered GLP-2 does not appear to affect energy intake in rodents, nor does affect appetite and feeding in humans [42,5].

As with GLP-1<sub>7-36amide</sub>, circulating GLP-2 is rapidly rendered inactive by the actions of DPP-4 (dipeptidyl peptidase-4). DPP-4 inhibitors developed for their actions on GLP-1<sub>7-36amide</sub> may also prolong the plasma half-life of GLP-2, resulting in unwanted GLP-2 mediated side effects on the bowel such as uncontrolled cell growth [5].

#### GHRELIN

Ghrelin, the hunger hormone, was discovered as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a). The GHS-R1a is widely expressed, in the central nervous system it is found in areas involved in regulation of appetite including hypothalamic nuclei, the dorsal vagal complex, and the mesolimbic dopaminergic system. Peripherally, it is expressed in the pituitary, and pharmacologically ghrelin acts at both pituitary and hypothalamic levels to powerfully stimulate growth hormone secretion. GHS-R1a receptor expression has also been described in myocardium, stomach, small intestine, pancreas, colon, adipose tissue, liver, kidney, placenta and T cells.

Ghrelin is a 28-amino acid peptide, cleaved from a precursor, preproghrelin. It is synthesized in endocrine cells of the stomach, termed X/A-like or ghrelin cells. About 2/3 to 3/4 of circulating ghrelin is of gastric origin, lesser concentration of circulating ghrelin are found throughout



the small intestine [6]. The first seven, or fewer, amino acids of ghrelin plus the octanoyl group on the third serine residue constitute the minimum fragment required for binding to and activation of the GHS-R1a [43,44].

Central nervous system-injected ghrelin stimulates food intake as potently as nucleus express neuropeptide Y (NPY), previously the most powerful known orexigen. Ghrelin also stimulates appetite and food intake when administered systemically in rodents [45,46] and humans [47], but duration of feeding stimulation in response to central or peripheral ghrelin administration is short.

Arcuate NPY/AgRP neurons are activated by ghrelin and although this neuronal population is the most well-characterized ghrelin target, there is also evidence for an indirect action on these neurons via vagus nerve [48]. Other ghrelin targets include other hypothalamic nuclei, the dorsal vagal complex of the brainstem and components of the mesolimbic dopaminergic system.

Ghrelin stimulates food intake across a broad range of species, including humans. Plasma ghrelin peaks preprandially in human subjects, who have been deprived of time cues, and initiates meals voluntarily. Postprandially, plasma ghrelin is suppressed in proportion to calories intake and interestingly, fat appears to suppress ghrelin less potently per calorie than carbohydrate or protein. This may, in part, explain the reduced satiety and enhanced weight gain associated with high-fat diets.

Infusion of antighrelin antibodies into the rat brain inhibits fasting-induced feeding, further supporting ghrelin's role as an endogenous regulator of food intake.

Chronic administration of ghrelin in rodents results in prolonged hyperphagia and weight gain. Actions of ghrelin that could combine to promote weight gain are: stimulation of adipogenesis, inhibition of apoptosis, transfer from fatty acid oxidation to glycolysis for energy expenditure, and inhibition of sympathetic nervous system activity.

In humans, ghrelin levels are inversely correlated with adiposity, being low in the obese, higher in lean subjects, decreased during pregnancy and markedly elevated in subjects that are cachectic (subjects with anorexia nervosa, cancer and chronic cardiac failure) [6,49,50].

There is in literature one case report of an individual with a malignant gastric ghrelinoma, who had extremely high circulating ghrelin concentrations and remained obese with preserved appetite, despite advanced disease [51].

The phenotype of ghrelin null mice might be further complicated by the observation that the gene that codes for ghrelin has been found to code for another peptide, named obestatin. Obestatin was originally reported to reduce food intake when administered peripherally or intracerebroventricularly, and to reduce body weight gain when administered peripherally. Much speculation followed as to why the same gene would produce an orexigenic and an anorectic signal [6].

Ghrelin may have therapeutic potential. Inhibition of ghrelin, particularly in enhancing further weight loss and preventing weight regain following diet induced weight loss, when ghrelin levels become elevated. The GHS-R1a exhibits constitutive activity, suggesting that an inverse agonist may be more therapeutically useful than an antagonist [52].

A novel group of molecules called RNA spiegelmers, oligonucleotides containing L-ribose, have been designed that are highly effective at blocking interaction of ghrelin with the GHS-R1a in vitro and in vivo. Indeed, there would be theoretical safety concerns about such agents in view of the possible role of ghrelin in regulation of growth axis, as well as reported beneficial cardiovascular [53] and anti-inflammatory [54,55] effects of ghrelin.

A more direct therapeutic application of ghrelin is in the treatment of anorexia and cachexia. Ghrelin administration by intravenous infusion over 3 weeks results in weight gain in patients with cardiac cachexia and chronic obstructive pulmonary disease [56,57].

## MOTILIN

Motilin is released by cells in the upper part of the duodenum, its main physiological role is thought to be as a regulator of interdigestive gut motility. It also stimulates gallbladder contraction and enzyme secretion in the stomach and pancreas.

Some authors have reported the presence of motilin in the central nervous system, as evidenced by the presence of motilin immunoreactivity in a number of brain areas in a variety of species.

Intracerebroventricular injection of motilin into rodents has an orexigenic effect.

It is possible that this effect on feeding may be secondary to the hormone's primary actions on gut motility [6].

## SOMATOSTATIN

It is synthesized in the D-cells of the gut and endocrine pancreas and its function is broadly antisecretory. Somatostatin inhibits release of other hormones such gastrin, CCK, secretin, motilin, vasoactive intestinal polypeptide and OXM, it inhibits gastric acid production, prolongs gastric emptying, reduces intestinal motility and decreases splanchnic blood flow, and it inhibits release of insulin, glucagons and release of exocrine pancreatic secretions.

The effects on feeding are inhibitory, although reduces food intake only in animals with a mild degree of hunger.

The mechanisms by which somatostatin reduces appetite is unclear. Vagotomy abolishes the effect. A mild effect on food intake is brought about indirectly, by reducing levels of ghrelin [58].

## OTHER GASTROENTEROPANCREATIC PEPTIDES

A number of other peptides affect food intake. Amylin is co-secreted with insulin by pancreatic  $\beta$ -cells and inhibits gastric secretion and emptying. Both intracerebroventricular and peripheral injection of amylin inhibits food intake [6,59].

Apolipoprotein A-IV (apoA-IV) is a 46kDa protein synthesized by enterocytes in response to intake of lipids and secreted together with chylomicrons and very low density lipoproteins. ApoA-IV is also present in the central nervous system, and in particular in the arcuate nucleus [5]. Fasting causes a marked reduction in hypothalamic expression of apoA-IV mRNA levels in the hypothalamus. Peripheral administration of apoA-IV reduces feeding in rats and intracerebroventricular injection of apoA-IV results in a decrease in food intake in rats.

Leptin is product of the *ob* gene, synthesized in white adipose tissue, but also synthesized by cells in the gastric mucosa. An energy balance role have been revised following recognition of the phenomenon of leptin resistance in the obese state, but the physiological importance of gastric leptin remains uncertain [5].

### Manipulation of Gut Hormones

A cause of the current obesity epidemic may be that modern processed foods bypass our natural satiety mechanisms. A low-fat diet does not produce the expected elevation in plasma ghrelin, this may be due to an increase in the proportion of calories consumed as carbohydrate, that more potently suppresses ghrelin per calorie consumed, than does fat. Diets high in protein have been reported to elevate PYY and enhance satiety more effectively than other macronutrients, but at a single meal, higher plasma concentrations of PYY were stimulated by high-fat isocaloric meals, compared with protein or carbohydrate.

Obesity is the most significant growing health concern worldwide. Current treatments, barring bariatric surgery are insufficiently effective [6]. Gut hormones regulate when and how much we eat for every meal and offer a safe, logical antiobesity treatment. GLP-1 is the most powerful known incretin in humans, and manipulation of the GLP-1 system forms the basis of several major new treatments for type 2 diabetes.

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