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Review article

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BRAIN-GUT AXIS AND ITS ROLE IN THE CONTROL OF FOOD INTAKE.

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Gastrointestinal tract (GIT) and nervous system, both central (CNS) and enteric (ENS), are involved in two-way extrinsic communication by parasympathetic and sympathetic nerves, each comprising efferents fibers such as cholinergic and noradrenergic , respectively, and afferent sensory fibers required for gut-brain signaling. Afferent nerves are equipped with numerous sensors at their terminals in the gut related to visceral mechano- chemo- and noci-receptors, whose excitations may trigger a variety of visceral reflexes regulating GIT functions, including the appetitive behaviour. Food intake depends upon various influences from the CNS as well as from the body energy stores (adipocytes) that express and release the product of *Ob* gene, leptin, in proportion to fat stored and acting in long-term regulation of food intake. Leptin acts through receptors (Ob-R) present in afferent visceral nerves and hypothalamic arcuate nucleus (ARC), whose neurons are capable of expressing and releasing neuropeptide Y (NPY) and agouti related protein (AgRP) that activate the ingestive behaviour through paraventricular nucleus (PVN) ("feeding center"). In addition, to this long-term regulation, a short-term regulation, on meal-to-meal basis, is secured by several gut hormones, such as cholecystokinin (CCK), peptides YY (PYY) and oxyntomodulin (OXM), released from the endocrine intestinal cells and acting *via* G-protein coupled receptors (GPCR) either on afferent nerves or directly on ARC neurons, which in turn inhibit expression and release of food-intake stimulating NPY and AgRP, thereby inducing satiety through inhibition of PVN. In contrast, during fasting, the GIT, especially oxyntic mucosa, expresses and releases appetite stimulating (orexigenic) factors such as ghrelin and orexins (OX) -A and OX-B, and cannabinoid CB1 agonist. Ghrelin activates growth-hormone secretagogue receptor (GHS-R) in hypothalamic ARC and stimulates growth hormone (GH) release and in vagal afferents to promote the expression and release of hypothalamic NPY and AgRP stimulating PVN and driving ingestive behaviour. The balance and interaction between anorexigenic (CCK, PYY, OXM) and orexigenic (ghrelin and OX) factors originating from GIT appears to play an important role in short-term regulation of food intake and growth hormone (GH) release. An impairment of this balance may result in disorders of feeding behaviour and weight gain (obesity) or weight loss (cachexia).

Key words: *brain gut axis, appetite, CCK, leptin, ghrelin, orexin, PYY*

Brain-gut axis and its morphological basis

The gastrointestinal tract (GIT) receives a dual extrinsic innervation by the autonomic nervous system i.e. by its parasympathetic (cholinergic) division including vagal and pelvic nerves and sympathetic (noradrenergic) division comprising splanchnic nerves. The GIT receives both excitatory and inhibitory innervation, the former is provided mainly by the parasympathetic nerves and latter - by the sympathetic nerves. Langley (1) was first to postulate the existence of the third division of autonomic nervous system, consisting of network of intrinsic to the GIT neurons localized in the myeloectric (Auerbach) plexus between outer longitudinal and middle circular muscle layer and the submucous (Meissner) plexus - between middle circular layer and the mucosa. This Langley's enteric division has been named by Wingate enteric nervous system (ENS) (2). Unlike relatively small number of extrinsic (preganglionic) parasympathetic nerves (about 20000 vagal and pelvic afferents), the ENS contains about 100 million of neurons serving as local sensory neurons, interneurons and effector motor neurons. ENS can be considered as a part of CNS that has been displaced during development from the brain to the gut but retaining with brain two-way communication pathways (parasympathetic and sympathetic), each including efferent and afferent nerves (*Fig. 1*).

The efferent extrinsic parasympathetic (cholinergic) nerves are pre-ganglionic fibers ending on cholinergic ENS neurons either of the myenteric plexus to control motor activity of the gut or in the submucous plexus to regulate secretory activity of glandular cells or visceral circulation. The efferent extrinsic sympathetic (mainly noradrenergic) nerves are postganglionic and some of them

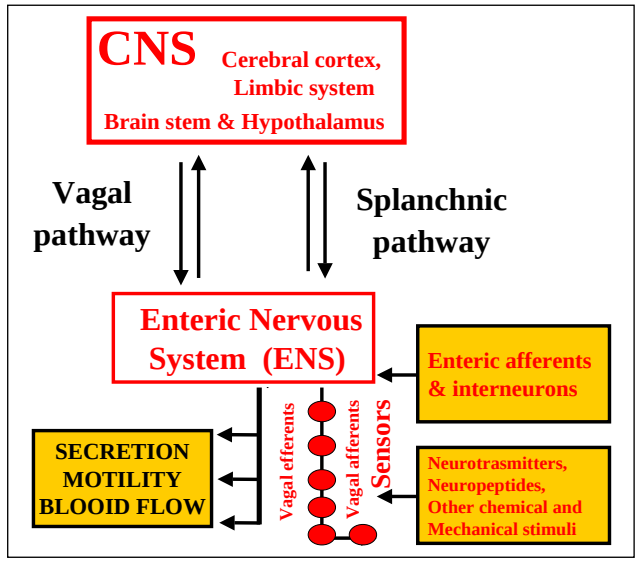

Fig. 1. Neuronal organization of the brain-gut axis showing two-way communication between CNS and ENS and the presence of sensors and their stimulants at the afferent neurons in ENS and efferents of ENS with their motor, secretory and circulatory effects.

terminate on postganglionic cholinergic neurons of ENS to inhibit acetylcholine release *via* activation of their α_2-presynaptic receptors or directly on intestinal smooth muscle cells to affect motility of the gut or of vasoactivity of visceral vessels to influence the visceral circulation (2, 3).

Characteristics and origin of enteric nervous system (ENS)

The unique feature of ENS differing it from extrinsic autonomic nerves is its complexity (various types of neurons) and plasticity (ability to encode and transmit sensory informations) but also autonomy with respect to CNS (2). GIT may function without extrinsic innervation such as after truncal vagotomy or in experimental studies with intestines bathed *in vitro* (Magnus experiment) using oxygen, nutrients and proper concentration of electrolytes required to maintain the viability of the tested gut. It responds to the changes in the gut lumen with the initiation of coordinated programs of functions that are appropriate to the altered conditions e.g. motor and secretory components of the migrating motor (myoelectric) complex (MMC) initiated in empty stomach probably by motilin and ghrelin generated in the gastric mucosa and passing along the entire bowel. Because of this autonomy, the ENS is considered as "gut brain" (3) that exerts its control activity over the GIT analogous to that of CNS exerting control over somatic part of the body.

As mentioned earlier, autonomic nervous system, including ENS, originates from the neural crest from which the cells migrate to the gut during development. The migrating cells colonize the gut wall to form its intrinsic innervation (ENS). The migration and maturation of neural crest cells require the expression of *c-ret* protooncogene that encodes a receptor tyrosine kinase. The ligand for this receptor is glial cell-derived neurotrophic factor (GDNF) (4). Another factor required for neural crest maturation and migration is endothelin-3 (ET-3) and its G protein-linked receptor, the endothelin-B (EB) (5) as well as Mash-1 transcription factor signaling through the ciliary-derived factor (CDNF) receptor (6).

Brain-gut signaling

In general, the efferent fibers of the brain-gut signaling system, run in preganglionic vagal and pelvic nerves, representing major routes regulating the activity of ENS by CNS during interdigestive (e.g. MMC) and digestive phase (e.g. exogenous and endogenous secretion, motility patterns and circulation), whereas postganglionic splanchnic efferent pathways constitute the sympathetic outflow from the CNS to the gut occurring during stress, adaptation and nocireception (7).

The afferent fibers of the gut-brain signaling route run through afferent vagal and sympathetic (spinal) nerves transmitting to CNS the signals from a variety of sensors in the gut that respond to mechanical (distention, contraction) stimuli, various chemicals including nutrients in the gut lumen, neuro-hormonal stimuli

such as gut hormones, neurotransmitters and neuromodulators as well as cytokines and inflammatory mediators produced by microbes in the gut (3, 8). The excitation of gastrointestinal mechano-, chemo- or noci-receptors in the gut may be conveyed on short distance within ENS from sensory neurons to interneurons and then to effector neurons (for intramural motor, secretory or vascular reflexes) or may take longer pass, reaching either prevertebral ganglia (for longer reflexes) or the CNS through vagal and spinal afferents *via* the lumbar, colonic, hypogastric and pelvic nerves to enter brainstem (for vago-vagal reflexes) or spinal cord (for spinal reflexes) (2, 3, 6-8) (*Fig. 2*). Afferent extrinsic neurons responding to various stimuli arising from the gastrointestinal mucosa, muscle layer or serosa (nutrients, chemicals, motility, distention) are involved in gut-brain signaling but some of these visceral afferent neurons, particularly splanchnic ones, are capable of synthesizing in their cell bodies various neuropeptides such as calcitonin-gene related peptide (CGRP) or substance P (SP) and transport them along the peripheral afferent terminals to release them upon nerve stimulation to affect motor or vasomotor functions (for axonal reflexes) (7 - 9). Afferent neurons projecting to prevertebral ganglia trigger longer extramural visceral reflexes operating through these ganglia to affect various functions of the GIT. Most of afferent vagal fibers pass through nodose ganglia to terminate on *nucleus tracti solitari* (NTS) showing viscerotopic representation with fibers from esophagus and stomach ending at its rostral-lateral part, from stomach at caudal-medial part and from intestines at central and rostral parts of NTS. Splanchnic afferent nerves pass intervertebral ganglia and

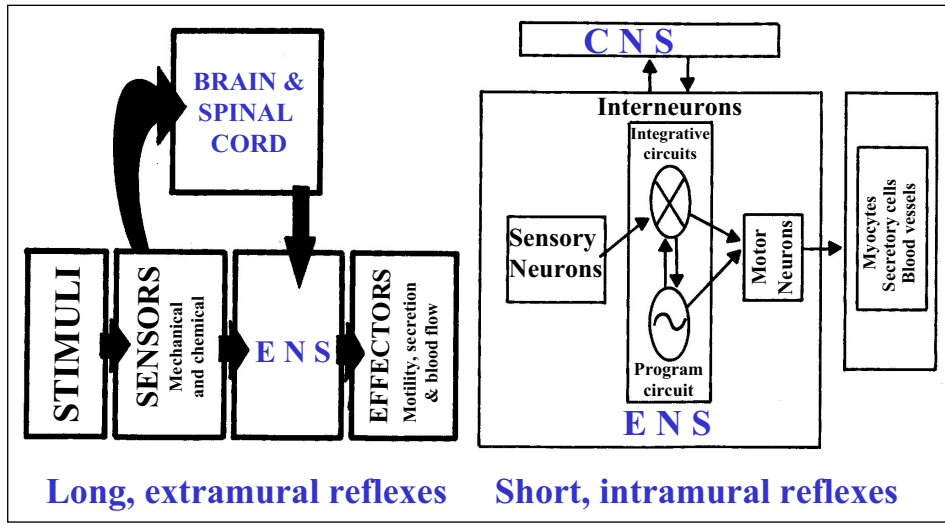

Fig. 2. Schematic presentation of the morphological basis of brain-gut-brain signaling systems involved in the long vago-vagal reflexes (A) and organization of ENS (B) communicating with CNS and with its own sensory neurons, interneurons, forming integrative centers for intrinsic reflexes.

dorsal roots to terminate on lamina I and V of the dorsal horn of spinal cord to tigger the spinal reflexes with intermedio-lateral horn interneurons as integrative centers controlling autonomic motor and circulatory function of the gut (9, 10).

The vagal afferent neurons with cell bodies in the nodose ganglia enter the brain stem, which is an important crossroads for information signaled from the gut to CNS and required to control gut functions *via* long vago-vagal reflexes. Information conveyed to the brainstem by afferent vagal nerves terminate in the NTS, which is adjacent to dorsal motor nucleus of the vagal nerve (DMN) within the dorsal vagal complex (DVC) area. Connection by interneurons to the bodies of DMN completes the vago-vagal reflex pathways controlling various functions of the digestive system. Some signals from the gut are transmitted onward toward higher neural centers *via* ascending tract from the NTS up to the hypothalamus and its paraventricular *nucleus* (PVN), *nucleus arcuatus* (ARC), central nucleus to amygdale (CAN) the bed *nucleus of the stria terminalis* (BNST) and the ventral thalamus (12) to influence higher autonomic centers such as involved in appetitive behaviour.

CNS projections initiated by gut-brain signaling run through vagal afferents. Expression of *c-Fos*, that serves as a marker for neurons stimulated by vagal signaling from gut to brain, confirmed an increase in this *cFos* gene expression in the area of vagal complex neurons in brain stem e.g. after gastric distention and activation of mechanoreceptors at the afferent vagal nerves. Similar *cFos* expression in the area of NTS was found after administration of CGRP or cholecystokinin (CCK) (11 - 13). The latter observation seems to be important considering e.g. the satiety stimulatory effect of CCK. CCK_1-receptors (CCK_1-R) have been found to be expressed in vagal afferent nerves (14) along with receptors for leptin , PYY and mechanoreceptors (GIT distention) (15) providing the basis for the potentiation between CCK and leptin, PYY and distention in the stimulation of vagal afferents and subsequently affecting feeding (satiety) centers in hypothalamus (16).

Satiety- and feeding-controlling mechanisms and brain-gut axis

Body weight depends on the balance between caloric intake and energy expenditure or caloric utilization. Obesity results when the former exceeds the latter. The mechanisms that serve to maintain body weight within relatively narrow limits over long period of time in phase of changing the caloric intake and changing metabolic demands can be divided into short-term (meal-to-meal) and those with long-term neuro-hormonal control. Older observations showed that force-fed animals for several weeks gain the weight but then when permitted free access to food they eat less and their body weight sharply falls to previous level. Conversely, if they are starved they loose weight but when permitted to eat freely, spontaneous food intake rises until the lost weight is regained. It is well known that during recovery after long or heavy illness, the food intake is increased to catch up fashion until lost weight is regained (17).

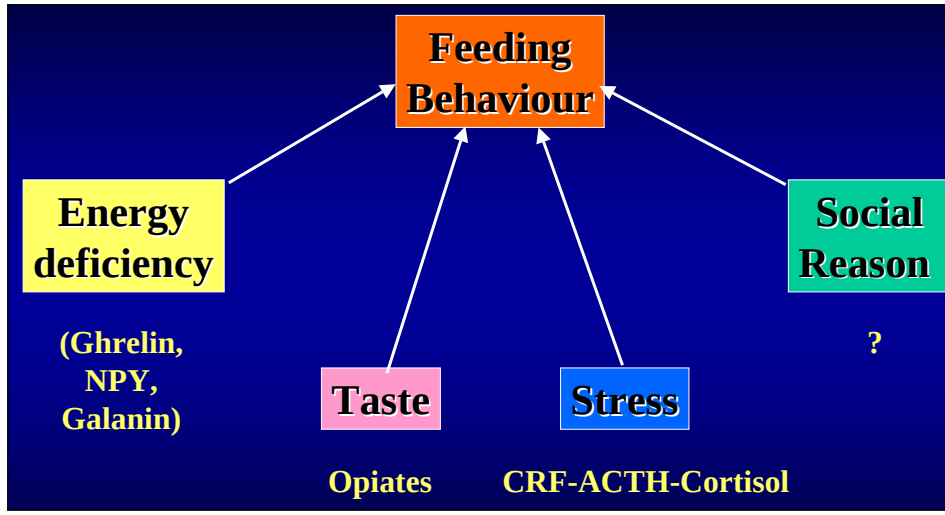

Fig. 3. Major reasons for feeding behaviour and hormonal mechanisms underlying these reasons.

In general, feeding occurs for various reasons, including energy deficiency following fasting or physical exercise, when the palatable food is presented, stress following isolation of pain and social reasons (*Fig. 3*). Each of these reasons is probably mediated by different signals and normonal mechanisms regulating food intake (18).

Role of brain-gut axis in the control of food intake

The question that arises is whether these signals and mechanisms originating in the gut affect the feeding behaviour by the use of gut-brain axis. According to classic concept, this behaviour remains under the control of two hypothalamic "centers" with opposite functions, a lateral hypothalamic area named "feeding or appetite center" and ventromedial hypothalamic area known as "satiety center" (18, 19). This simplified hypothesis was supported mainly by animal experiments with hypothalamic lesions performed bilaterally in the ventro-medial portion of hypothalamus (in satiety centers) causing loss of appetite, anorexia and caxechia, suggesting that satiety center functions by inhibiting the feeding center. It has been proposed that feeding center is chronically active and that its stimulation can be transiently inhibited after ingestion of food. It was confirmed that simple gastric distention with balloon reducing temporarily the desire for food due to neural stimulation of satiety centers and inhibition of feeding centers of hypothalamus (PVN), but ingestion of various nutrients, especially carbohydrates and fat, reduced hunger more effectively and induced satiety even before these food products were digested and absorbed from the gut. Therefore, signals from the upper gastrointestinal tract should be responsible for

prandial satiety that could explain the short-term control of food intake limiting the size of individual meals, thereby serving to match meal size with the capacity of gut for digestion.

Gut peptides in control of appetitive behaviour

Cholecystokinin (CCK). This hormone is produced by I-cells and exists in the mucosa and circulation in several molecular forms, the major forms in the plasma are CCK-8, CCK-33 and CCK-39. It is the most likely candidate for the mediation of this short-term inhibition of food intake (together with distention of upper GIT). As already mentioned CCK may signal to satiety center of CNS (20 - 22) and this effect can be reduced by vagotomy, lesions of the NTS, vagal transection or by deactivation of vagal afferents with the neurotoxic dose of capsaicin (22 - 25). Such evidences support the notion that the prandial satiety might be attributed predominantly to CCK released in the gut by protein and fat digests and acting via vago-vagal reflexes rather than directly on the target organs such as pancreas, gallbladder, liver or satiety center in CNS (*Fig. 4*). As mentioned before (13, 14), the presence of CCK1-receptors detected at the terminal and along of the afferent vagal nerves supports the involvement of CCK.

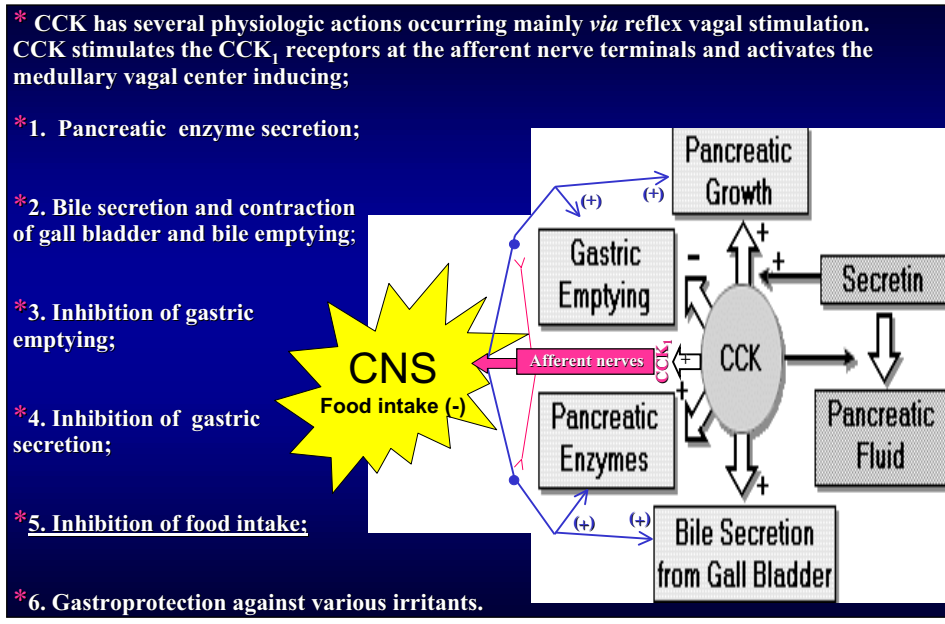

Fig. 4. The effects of cholecystokinin (CCK) on food intake and on various GIT functions mediated by the long vago-vagal reflexes triggered by activation of CCK_1-receptors on vagal afferents and controlling reflexly major GIT functions such as gastric emptying, pancreatic and biliary secretion and pancreatic growth.

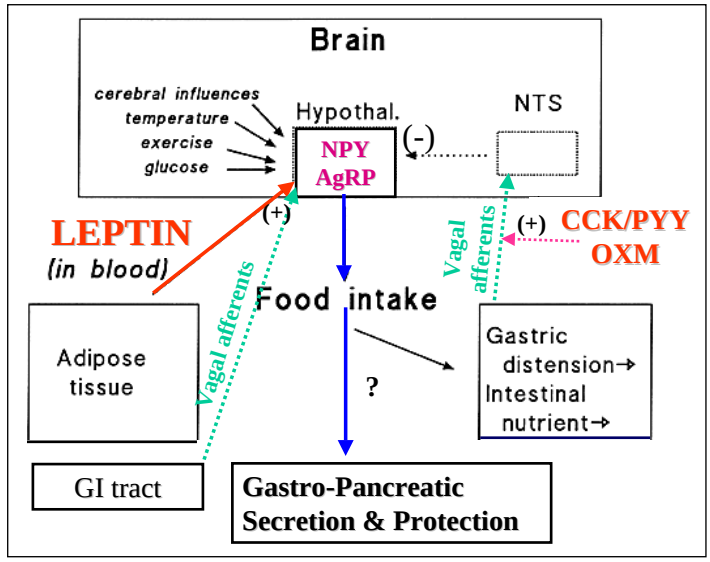

Fig. 5. Schematic presentation of neuro-humoral receptor stimulation and mechanoreceptor stimulation by gastric distention in control of food intake *via* mech-anism involving inhibi-tory afferent gut-brain signaling (for short-term regulation) and leptin release from adipose tissue (for long-term regulation).

CCK stimulates the discharge of afferent nerves (26, 27) and its action is potentiated by gastric distention indicating a synergism between CCK_1-receptors (and probably also PYY and OXM receptors) and mechanoreceptors in vagal afferents (*Fig. 5*). It is of interest that CCK exhibits also gastroprotective and pancreatoprotective activities by triggering shorter enterogastric or enteropancreatic reflexes or by long vago-vagal reflexes (28,29).

Our recent study on rats with large gastric fistula to drain the stomach to measure the amounts of eaten food and pancreatic fistulas to determine the pancreatic secretion, we found that liquid protein meal strongly stimulates pancreatic protein secretion probably due to marked increment in plasma immunoreactive CCK levels that was also accompanied by a marked rise in plasma levels of PYY. Blockade of CCK_1-receptors with devazepide (L-364), profoundly inhibited pancreatic secretion, while restoring the food intake and increasing plasma levels of PYY and CCK. Both capsaicin deactivation of sensory afferents and vagotomy reduced food intake and plasma levels of PYY and CCK. Addition of exogenous CCK to vagotomized animals restored in part the pancreatic secretion, while markedly reducing food intake. The experimental results performed on conscious fully conditioned rats could be interpreted to mean that there is an interaction between CCK and PYY in regulation of food intake and pancreatic secretion. Both CCK and PYY interact to inhibit food intake while their effect on pancreatic secretion appears to be opposite, CCK is involved in the stimulation of pancreatic enzyme secretion mediated by specific receptors located on vagal afferent, while PYY exerts the inhibitory on secretion by some unknown pathway (*Fig. 6*)

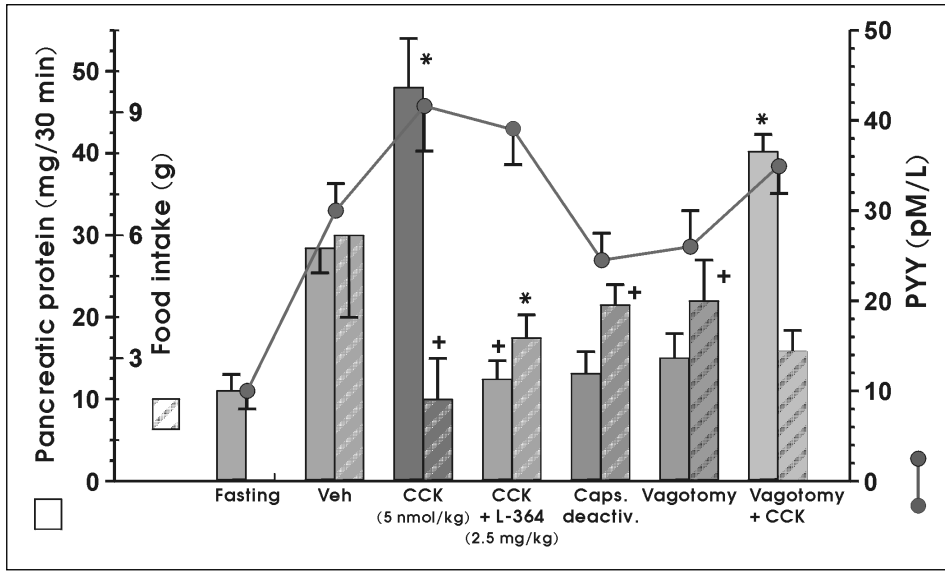

Fig. 6. Effect of peripheral administration of CCK (5 nmol/kg i.p.) alone or in combination with its receptor antagonist (L-364) (10 mg/kg, capsaicin (125 mg injected s.c. 2 weeks before experiments) induced deactivation of sensory afferent nerves, subdiaphragmatic vagotomy and the administration of CCK in vagotomized rats on pancreatic protein output from chronic pancreatic fistula, liquid (milk) food intake and plasma PYY levels measured by RIA in plasma of conscious fully conditioned rats (unpublished data).

PYY. Another candidate for short-term satiety induced by signals from the gut could be 36 amino acid peptide YY obtained initially from the colon mucosa (30) but then found to be expressed by L-cells in the mucosa of the small and large bowel including rectum (31) and released into circulation as PYY or PYY3-36 (31). Plasma levels of this peptide starts to increase almost immediately after feeding suggesting its neural regulation (32) but reaches its daily peaks after breakfast, lunch and dinner (33). It is of interest that obese people show increased PYY late after large evening meal and, in general, reduced increment in PYY in these subjects could explain deficient control of food intake and increased caloric intake. The involvement of PYY especially in its PYY 3-36 form is supported by the finding that exogenous administration of this peptides decreases appetite (34, 35). PYY 3-36 appears to act through Y2 receptors (*Fig. 7*), and as expected, this peptide fails to affect the food intake in the Y2 receptor knockout mouse but inhibits feeding in wide-type litter mates. PYY probably counterregulates ghrelin release, a potent orexigenic peptide present in oxyntic mucosa and in hypothalamus (36) acting *via* with specific receptors (growth hormone secretagogue receptor - GHS-R) expressed in vagus nerves (37) as well as in hypothalamus (ARC), this could be due to the fact that PYY-ghrelin negative interaction occurs both at the level of vagal afferents, nodose ganglion and

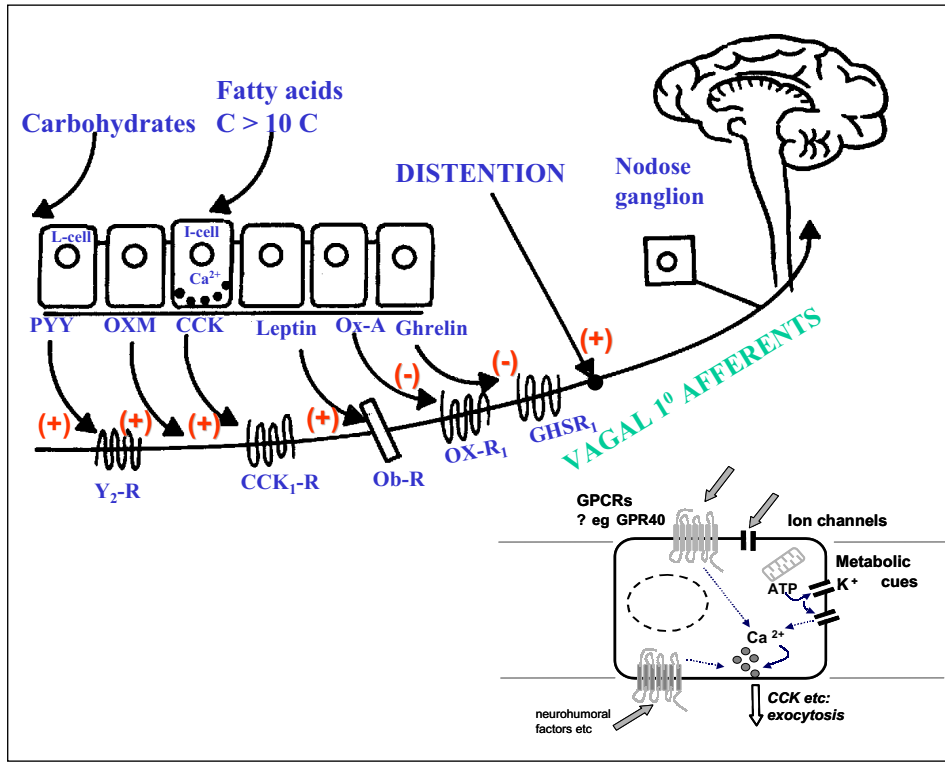

Fig. 7. The interaction between anorexigenic and orexigenic hormones acting on GPCR in afferent neurons signaling increase (+) or decrease (-) of food intake. Insert shows the action of GI hormons on Ca^{2+} release in receptor on vagal afferent fibers.

hypothalamus, particularly at its ARC. Indeed, circulating PYY penetrates to hypothalamus through semipermeable capillaries in the median eminence area of hypothalamus (37) and acts on vagal nerves mainly *via* Y2 receptors (38) that, like other GPCR of afferent nerves originate from the cell body and are transported retrogradualy along these nerves to periphery. Interestingly, obese people show lower PYY level compared to lean control, suggesting the impaired inhibition of hunger signals by PYY from the gut which may function in these obese people as a positive feedback loop promoting further weight gain (38 - 40). Further studies are needed to determine the mechanism of PYY and ghrelin interaction and possible implication in explaining increased food intake based on this hormonal interaction in obese people.

Oxyntomodulin (OXM). Another anorexigenic gut peptide that has been recently suggested to contribute to physiological short-term suppression of food intake is oxyntomodulin (OXM), a 37 amino acid peptide released after a meal from endocrine cells of distal portion of the small bowel (39) (*see Fig. 7*). In humans, i.v. administration of OXM was found to cause immediate decrease in

hunger score and food intake as well as the suppression of plasma levels of ghrelin (40, 41). The mechanism of anorexigenic action of OXM is not clear, but like PYY, it may act directly on hypothalamic centers as intracerebroventricular application of OXM in rodents inhibited food intake or on terminal of vagal afferents as has been shown for ghrelin (38, 39). It should be noticed that OXM does not affect PYY or leptin release because the plasma levels of these peptides were not affected by OXM administration. There is evidence that OXM may play some role under pathological conditions such as after jejuno-ileal bypass surgery for morbid obesity (41 - 43). OXM may contribute to the loss of appetite and weight loss observed under these conditions.

Ghrelin. As mentioned before, the deficiency of energy during fasting or starving is one of the reasons stimulating feeding behaviour (18) . Since the discovery of ghrelin, an endogenous ligand for GHS-R (44), and the observation that this peptide is expressed in oxyntic mucosal cells (A/X cells) of empty stomach and sharply rises before meal, while falling within one hour after a meal

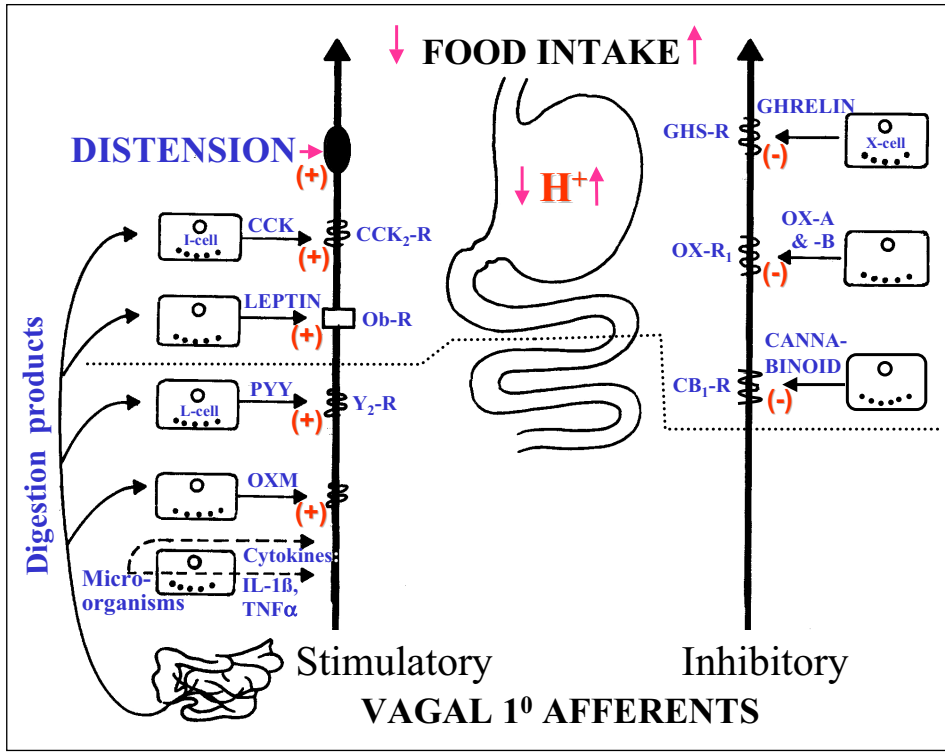

Fig. 8. Activation of stimulatory and inhibitory vagal afferent by anorexigenic peptides (CCK, leptin, PYY, OMX and microbes and their proinflammatory mediators) on left and orexigenic peptides such as ghrelin and orexins (on right). The origin of these hormones and receptors of their action on afferent stimulatory and afferent inhibitory afferents.

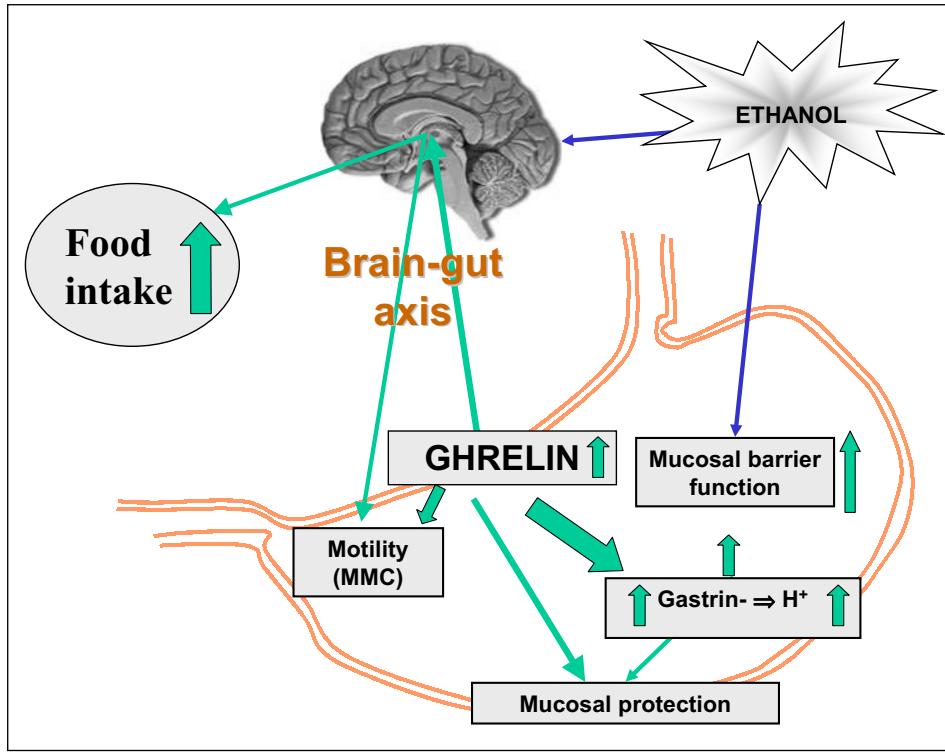

Fig. 9. Mechanism of the effect of alcohol on food intake as well as on gastric integrity, secretion and motility mediated by gut-brain axis and ghrelin release.

(44-46), a great attention has been paid regarding the possible role of this peptide in stimulating food intake (*Fig. 8*).

Ghrelin is 28 amino acid peptide, primarily secreted by X/A-like endocrine cells in oxyntic mucosa of the stomach. Its release into the circulation reaches the higher level in fasting state, peaking before the meal or when the subject is expecting or requesting a meal suggesting that the actions of ghrelin on initiation of food intake are under neural control. We found (47) that sham-feeding in dogs (without entering of food into the stomach) was also accompanied by increased plasma levels of this peptide but food ingestion in dogs as well as in rats (48, 49) caused almost immediate fall in plasma ghrelin level suggesting that central reflex vagal nerve activation as documented by the increase in gastric and pancreatic secretion and gastric or pancreatic protection against injury (50). A plausible exception appears to the food desire combined with an increase in gastric acid secretion after intake of small amounts of alcohol (“coctail”), which appears to enhance the overexpression of ghrelin in the oxyntic mucosa (50) and increase plasma levels of this peptide, gastric motility and gastric acid secretion (*Fig. 9*). Thus, ghrelin seems to play a major role in the initiation of food intake

and stimulation in motilin-like fashion of gastrointestinal motility (MMC) (*51*) and increased plasma levels of this hormone as confirmed by the finding that administration of a dose of exogenous ghrelin given either peripherally to raise plasma hormone level comparable to that observed in fasted animals or intracerebroventricularly strongly stimulates ingestive behaviour.

In humans, the appetite may also be stimulated by ghrelin and inhibited by leptin, PYY3-36 and OXM, all at physiological doses (44). Exogenous ghrelin infusion resulted in about 30% increase of intake of free buffet meal without the typical postprandial satiety so continuous ghrelin administration resulted in an increase of accumulative food intake for the infusion period. In contrast, exogenous PYY3-33 infusion during the same time period, decreased food intake by about 40% without a decrease of subjective hunger or accumulation of injected food during the infusion period. Thus, PYY seems to play a counterregulatory role to ghrelin in both short- and long-term control of food intake (44). From the practical point of view, ghrelin treatment could be useful in raising the weight loss and improving appetite in patients with severe weight loss (e.g. cancer cahexia).

In addition to important role in initiation of food intake and thus in control of energy homeostasis, exogenous ghrelin decreases the release and action of leptin and *vice-versa*, exogenous leptin at a dose causing about 5% of weight loss, reduces the plasma levels of ghrelin (44). It has been proposed that leptin exerts a negative regulatory influence on the release of ghrelin and that increments in ghrelin induced by weight loss arise because of the diminished inhibitory input from leptin and possibly from PYY (45). This might imply that the weight-reducing effects of leptin are mediated not only *via* direct central action the peptide but also through its peripheral inhibitory effect on the release and action of orexigenic hormone such as, ghrelin.

According to our experience in 24 h fasted rats (46), plasma ghrelin is highly elevated, while leptin barely detectable. After feeding, a marked (by about 70%) fall in plasma ghrelin can be observed and this is accompanied by significant rise (by about 18%) of plasma leptin. Exogenous ghrelin administered intraperitoneally at a dose (1μg/kg), that raised plasma ghrelin to the level comparable with that observed in fasted animals, significantly attenuated plasma leptin to the fasting level, while markedly increasing food intake. Pretreatment with IgG anti-leptin antibody that immunoneutralized plasma leptin caused marked increase in plasma ghrelin and increased food intake. As expected, exogenous ghrelin almost tripled food intake and suppressed (by about 30%) the postprandial increment in plasma leptin and both these effects were completely abolished by immunoneutralization of plasma ghrelin using specific IgG ghrelin specific antibodies. These results clearly confirm the hypothesis that ghrelin negatively controls the plasma release of leptin and *vice-versa*, leptin has counterregulatory influence on ghrelin, though the former effect is much stronger than the latter. It remains to establish whether the negative interaction between ghrelin and leptin ("ghrelin-leptin tango") (45, 46) (*Fig. 10*) not only initiates

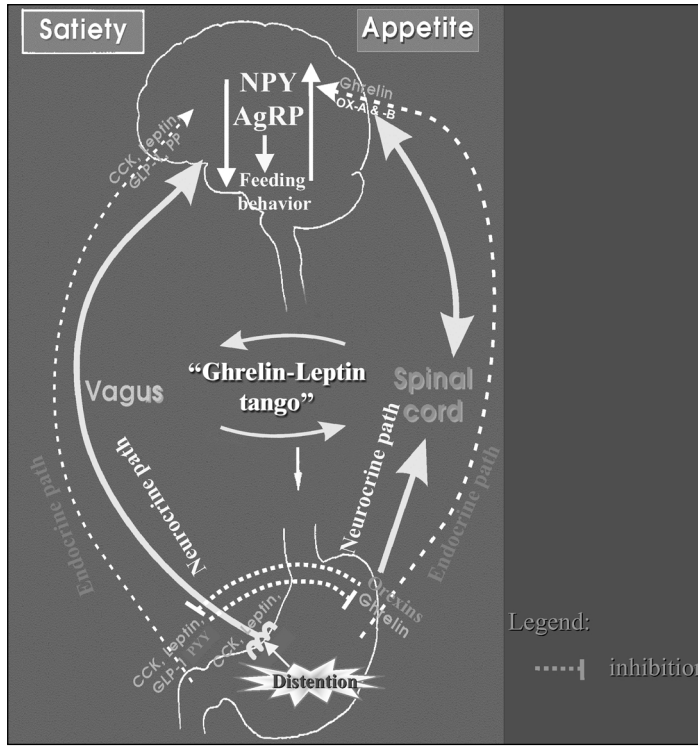

Fig. 10. Negative inter- action of gut peptides on satiety and appetite center in hypothalamus reminds the "ghrelin-leptin tango".

food intake, mainly by stimulating NPY and AgRP expression in arcuate nucleus of hypothalamus, but appears to exerts remarkably numerous effects, some in the stomach (mucosal protection and stimulation of gastrin release and HCl secretion (50, 51) in the pancreas (inhibition of pancreatic secretion and protection against caerulein pancreatitis) (52), control of gastrointestinal motility (motilin-like action) (53), cardiovascular action and most important - stimulation of release of growth hormone in synergism with GHRH (54).

In addition to ghrelin, an orexigenic effects are also displayed by two orexins (OX)-A and -B that originate from common precursor (54 - 56). Like ghrelin (57), they are expressed in the gut and increase in plasma after fasting period to act *via* receptors OX-R1 localized in vagal afferent nerves. OX inhibit food intake by stimulating OX-R1 on vagal afferents and reduced CCK-induced discharge of gut afferent fibers that otherwise inhibits food intake. Thus, both ghrelin and OX provide inhibitory action to restrain stimulation of vagal afferent discharge that would otherwise lead to inappropriate inhibition of food intake.

In summary, numerous neuropeptides affect the food intake by either stimulating (ghrelin, OX) or inhibiting (CCK, leptin, OXM) the expression and release in the arcuate nucleus of hypothalamus of NPY and AgRP, which are the central (hypothalamic centers) orexigenic substances responsible for ingestive

behaviour in animals and humans. Using ghrelin antagonists (60) it may be possible to control food intake in obese people without gastric or intestinal bypass surgery which were reported to attenuate circulating ghrelin and PYY release.

This issue of Journal of Physiology and Pharmacology contains several original papers presented at the Brain-Gut Axis symposium, Cracow November 15, 2003. The review papers appeared as supplement 3 of 2003 issue J Physiol Pharmacol. The control of food intake was not separately presented at this symposium, therefore, the present article was designed to emphasize the importance of brain-gut axis and gut hormones in feeding behaviour. We greatfully acknowledge the editorial help and English correction by Dr. med John Czarnecki from Harrisburg, Pt, USA.

REFERENCES

1. Langley JN. The autonomic nervous system. Part. I. W. Heffer (ed). Cambridge 1921.
2. Wingate DL, Ewart WR. The brain-gut axis. In: Textbook of Gastroenterology. T Yamada, DH Alpers, C Owyang, DW Powell, FE Silverstein (Eds.) B. Lippincott Co., Philadelphia, 1981, pp. 50-60.
3. Langley K. The neuroendocrine concept today. *Ann NY Acad Sci* 1994; 733: 1-17.
4. Trupp M, Arenas E, Fainzilber M, et al. Functional receptor for GDNF encoded by the c-ret proto-oncogene. *Nature* 1996; 381: 785-789.
5. Baynash AG, Hosoda K, Giaid A, et al. Interaction of endothelin-3 with endothelin-B receptor is essential for development of epidermal melanocytes and enteric neurons. *Cell* 1994; 79: 1277-1285.
6. Blaugrund E, Pham TD, Tennyson VM.et al. Distinct subpopulations of enteric neuronal progenitors defined by time of development, sympathoadrenal lineage markers and mash-1-dependence. *Development* 1996; 122: 309-32
7. Janig W, Morrison JFB. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs with special emphasis on visceral nocireception. Prog Brain Res 1986; 67: 85-95.
8. Holzer P. Peptidergic sensory neurons in the control of vascular functions: mechanisms and significance in the cutaneous and splanchic vascular beds. *Rev Physiol Biochem Pharmacol* 1992; 121: 49-146.
9. Maggi CA. The pharmacology of the efferent function of sensory nerves. *J Auton Pharmacol* 1991; 11: 173-208.
10. Green T, Dockray GJ. Characterization of the peptidergic afferent innervation of the stomach in the rat, mouse and guinea-pig. *Neuroscience* 1988; 25: 181-193.
11. Sternini C, Reeve JR, Brecha N. Distribution and characterization of calcitonin gene-related peptide immunoreactivity in the digestive system of normal and capsaicin-treated rats. *Gastroenterology* 1987; 93: 852-862.
12. Berthoud H-R, Jedrzejewska A, Powley TL. Simultaneous labeling of vagal innervation of the gut and afferent projections from the visceral forebrain with DiI injected into dorsal vagal complex in the rat. *J Comp Neurol* 1990; 301: 65-79.
13. Rinaman L, Hoffman GE, Stricker EM, Verbalis JG. Exogenous cholecystokinin activates cFos expression in medullary but not hypothalamic neurons in neonatal rats. *Dev Brain Res* 1994; 77: 140-145.

14. Moriarty P, Dimaline R, Thompson DG, Dockray GJ. Characterization of cholecystokininA and cholecystokininB receptors expressed by vagal afferent neurons. *Neuroscience* 1997; 79: 905-913.
15. Burdyga G, Spiller D, Mirris R, et al. Expression of the leptin receptor in rat and human nodose ganglion neurons. *Neuroscience* 2002; 109: 339-347.
16. Barrachina MD, Martinez V, Wang L, Wei JY, Tache Y. Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. *Proc Natl Acad Sci USA* 1997; 94: 10455-10460.
17. Stricker EM. Hyperphagia. *N Engl J Med* 1978; 298: 1010-1016.
18. Erlanson I, Albertsson C. Appetite regulation and pancreas. In: Biology and the Pancreas in Growing Animals. Elseview Science BV, 1999, pp. 287-313.
19. Stevenson JAF. The Hypothalmus. Haymaker W, Anderson E, Nauta WJH (eds), Thomas 1969.
20. Gibbs J, Young RC, Smith GP. Cholecystokinin elicits satiety in rats with open gastric fistulas. *Nature* 1973; 245: 323-325.
21. Reidelberger RD, O'Rourke MF. Potent cholecystokinin antagonist L364718 stimulates food intake in rats. *Am J Physiol* 1989; 257: R1512-1518.
22. Garlicki J, Konturek PC, Majka J, Kwiecień N, Konturek SJ. Cholecystokinin receptors and vagal nerves in control of food intake in rats. *Am J Physiol* 1990; 258: E40-45.
23. Smith GP, Jerome C, Cushin BJ, Eterno R, Simansky KJ. Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. *Science* 1981; 213: 1036-1037.
24. Edwards GL, Ladenheim EE, Ritter RC. Dorsomedial hindbrain participation in cholecystokinin-induced satiety. *Am J Physiol* 1986; 251: R971-977.
25. Smith GP, Jerome C, Norgren R. Afferent axons in abdominal vagus mediate satiety effect of cholecystokinin in rats. *Am J Physiol* 1985; 249: R638-R641.
26. Schwartz GJ, McHugh PR, Moran TH. Gastric loads and cholecystokinin synergistically stimulate rat gastric vagal afferents. *Am J Physiol* 1993; 265: R872-876.
27. Blackshaw LA, Grundy D. Effects of cholecystokinin (CCK8) on two clases of gastroduodenal vagal afferent fibers. *J Auton Nerv Syst* 1990; 31: 191-201.
28. Brzozowski T. Experimentral production of peptic ulcer, gastric damage and cancer models and their use in pathophysiological studies and pharmacological treatment - Polish experience. *J Physiol Pharmacol*, 2003; 54(Suppl 3): 99-126.
29. Konturek PC, Konturek SJ. The history of gastrointestinal hormones and the Polsih contribution to the elucidation of their biology and relation to nervous system. *J Physiol Pharmacol* 2003; 54 (Suppl 3): 83-98.
30. Tatemoto K, Mutt V. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. *Nature* 1980; 285: 417-418.
31. Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology* 1985; 89: 1070-1077.
32. Anini Y, Fu-Cheng X, Cuber JC, Kervran A, Chariot J, Roz C. Comparison of the postprandial release of peptide YY and proglucagon-derived peptides in the rat. *Pflugers Arch* 1999; 438: 299-306.
33. Soffer EE, Adrian TE, Launspach J, Zimmermann B. Meal-induced secretion of gastrointestinal regulatory peptides is not affected by sleep. *Neurogastroenterol Motil* 1997; 9: 7-12.
34. Okada S, Ohshima K, Mori M. Peripheral not central administered PYY decreases high fat diet intake. *Endocrinology* 1993; Suppl. 180.
35. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature* 2002; 418: 650-654.

36 Cone RD, Cowley MA, Butler AA, Fan W, Marks DL, Low MJ. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int J Obes Relat Metab Disord* 2001; 25: (Suppl) 5, S63-67.
37. Neary NM, Small CJ, Bloom SR. Gut and mind. *Gut* 2003; 53: 918-921.
38. Keire DA, Mannon OP, Kobyashi M *et al.* Primary structure of PYY, [Pro(34)]PYY, and PYY3-36 confer different conformations and receptor selectivity. *Am J Physiol* 2000; 279: G126-131.
39 Bataille D, Tatemoto K, Gespach C, Jornaval H, Rosselin, Mutt V. Isolation of glucagon-37 (bioactive enteroglucagon/oxyntomodulin) from porcine jejuno-ileum. Characterization of the peptide. *FEBS Lett* 1000; 146: 79-86.
40 Dockray GJ. Luminal sensing in the gut; an overview. *J Physiol Pharmacol* 2003; 54 (Suppl 4): 9-18.
41. Dakin CL, Gunn I, Small CJ et al. Oxyntomodulin inhibits food intake in the rat. *Endocrnology* 2001; 142: 4244-4250.
42. Searson DL, Scapinaro N, Bloom SR. Gut hormone changes after jejuno-ileal (JIB) or biliopancreatic (BPB) bypass surgery for morbid obesity. *Int I J Obes* 1981; 5: 471-480.
43. Wren AM, Seal LJ, Cohen MA. Et al. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 2001; 86: 5992.
44. Berazzoni R, Zanetti M, Stebel M, Biolo G, Cattin L, Guarnieri G. Hyperleptimenia prevents increased plasma ghrelin concentration during short-term moderate caloric restriction in rats. *Gastroenterology* 2003; 124: 1188-1192.
45. Cummings DE, Foster KE. Ghrelin-leptin tango in body-weight regulation. *Gastroenterology* 2003; 124: 1532-1544.
46. Konturek SJ, Pepera J, Zabielski K *et al.* Brain-gut axis in pancreatic secretion and appetite control. *J. Physiol. Pharmacol* 2003; 54: 393-418.
47. Konturek SJ, Zabielski K, Konturek JW, Czarnecki J. Neurophamacology of exocrine pancreas. *Eur J Pharmacol* 2003; 481: 1-14.
48. Pico C, Oliver P, Sanchez J, Palou A. Gastric leptin: a putative role in the short-term regulation of food intake. *Br J Nutr* 2003; 90: 735-741.
49. Beck B, Richy S, Sticker-Kongrad A. Ghrelin and body weight regulation in obese Zucker rat in relation to feeding state and dark/light cycle. *Exp. Biol Med (Maywood)* 2003; 228: 1124-1131.
50. Konturek PC, Brzozowski T, Pajdo R *et al.* Ghrelin; a new gastroprotective factor. *J Physiol Pharmacol* (submitted)
51. Peeters TL. Central and peripheral mechanisms by which ghrelin regulates gut motility. *J Physiol Pharmacol* 2003; 54: Suppl 4, 95-103.
52. Dembinski A, Warzecha Z, Ceranowicz P, et al. Ghrelin attenuates the development of acute pancreatitis in rat. *J Physiol Pharmacol* 2003; 54: 561-573.
53 Brzozowski T, Konturek PC, Konturek SJ *et al.* Exogenous and endogenous ghrelin in gastroprotection against stress-induced gastric damage. *Reg Peptides* 2004 (in press)
54. De Ambrogi M, Volpe S, Tamanini C. Ghrelin: central and peripheral effects of a novel peptide hormone. *Med Sci Monit* 2003; 9: RA217-224.
55. Cohen MA, Ellis SM, Rachel CW et al. Oxyntomodulin suppresses appetitte and reduces food intake in humans. *J Clin Endocrin Met* 2003; 88: 4696-4701.
56. Asakawa A, Inui A, Kaga T, et al. Antagonism of ghrelin receptor reduces food intake and body weight gain in mice. *Gut* 2003; 52: 947-952.
57. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in human. *Diabetes* 2001; 50: 1714-1719.

58. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2001; 346: 1623-1630.
59. Naslund E, Gryback P, Hellstrom PM, et al. Gastrointestinal hormones and gastric emptying 20 years after jejunoileal bypass for massive obesity. *Int J Obes Relat Metab Disord* 1997; 21: 387-39.
60. Sakawa A, Anui A, Kaga T, *et al.* Anatagonism of ghrelin receptor reduces food intake and body weight gain in mice. *Gut* 2003; 53: 947-952.

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