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Review

Control of Food Intake by Gastrointestinal Peptides: Mechanisms of Action and Possible Modulation in the Treatment of Obesity

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This review focuses on the control of appetite by food intake-regulatory peptides secreted from the gastrointestinal tract, namely cholecystokinin, glucagon-like peptide 1, peptide YY, ghrelin, and the recently discovered nesfatin-1 via the gut-brain axis. Additionally, we describe the impact of external factors such as intake of different nutrients or stress on the secretion of gastrointestinal peptides. Finally, we highlight possible conservative—physical activity and pharmacotherapy—treatment strategies for obesity as well as surgical techniques such as deep brain stimulation and bariatric surgery also altering these peptidergic pathways.
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Key Words
Bariatric surgery; Brain-gut axis; Deep brain stimulation; Psychosomatic; Obesity

Introduction

The control of food intake is well balanced in healthy individuals with mostly peptidergic regulators stimulating the feeling of hunger to initiate food intake or satiety to terminate food intake when the necessary amount of externally delivered energy is reached. A dysregulation of this system can lead to obesity.[1] For a better understanding of the control of food intake it is necessary to understand the interaction of peripheral and central signals that regulate energy homeostasis. Briefly, several peptides are derived from the gastrointestinal tract, most of which inhibit food intake, namely cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), peptide tyrosine tyrosine (PYY),[2] and the recently discovered nesfatin-1,[3] while only one peripherally produced and centrally acting peptide is known to stimulate food intake, ghrelin.[2] These peptides affect brain centers involved in the central control of hunger and satiety via the gut-brain axis that involves crossing of the blood-brain barrier and targeting the arcuate nucleus (ARC) of the hypothalamus, or an action via the vagus nerve to reach the nucleus of the solitary tract (NTS) of the brainstem.[4] It is of note that these 2 pathways are not separated from each other but rather intertwined by neuronal networks; ie, the NTS and the paraventricular nucleus (PVN) of the hypothalamus are connected by nerve fibers.

When anorexigenic signals reach the ARC they activate proopiomelanocortin (POMC)- and cocaine- and amphetamine-related

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transcript- (CART) containing neurons, and deactivate neuropeptide Y (NPY)- and Agouti-related peptide (AgRP)- containing neurons.[4] POMC/CART leads to an activation of melanocortin receptors 3 and 4 in the PVN and the lateral hypothalamic area (LHA), which causes a reduction of food intake.[4] The melanocortin receptor 4 is expressed in the NTS as well, which also contains POMC neurons. In contrast, ghrelin as an orexigenic peptide activates NPY/AgRP-containing neurons and deactivates POMC/CART-containing neurons in the ARC.[5] NPY stimulates food intake by activating the Y_1 receptor in the PVN, whereas AgRP increases food intake as an antagonist of the melanocortin receptor 3 and 4.[5] Additionally, NPY can also act in the NTS to stimulate food intake. Taken together, peripheral and central signals are involved in the orchestration of food intake. While peripheral transmitters reach the brain via the blood-brain barrier or the vagus nerve and modulate brain neuronal activity, brain nuclei also release peptidergic transmitters such as oxytocin or corticotropin-releasing factor that affect peripheral binding sites eg, at the level of the enteric nervous system to modulate food intake.[4,5]

In the present review, we focus on gastrointestinal peptides mainly involved in the regulation of hunger and satiety. In comparison to other excellent reviews on gut peptides with a main focus on the reward system,[6,7] pharmacological treatment,[6,8] bariatric surgery[9] or the gut microbiota,[10] in the present review we comprehensively describe the main effects and routes of peptide signaling, the regulation by nutrients, and also external stressors increasingly recognized to affect gastrointestinal peptides. Lastly, we highlight strategies to modulate peptidergic signaling in the treatment of obesity: here, conservative (physical activity and pharmacological treatment) as well as surgical options will be highlighted (bariatric surgery and the rather novel method of deep brain stimulation).

Gastrointestinal Hormones Regulating Hunger and Satiety

Ghrelin

Ghrelin stimulates food intake after central and peripheral administration and subsequently also increases body weight.[11] These effects are blunted after vagotomy pointing towards this route of gut-brain signaling.[12] However, ghrelin can also pass the blood-brain barrier bidirectionally.[13] The main source of circulating ghrelin is the stomach, as indicated by a massive reduction of circulating ghrelin levels following gastrectomy.[14] Ghrelin is produced in gastric endocrine X/A-like cells (in humans termed P/D_1 cells)[15] and requires an acylation on its third serin residue necessary for the binding to and activation of the ghrelin receptor, the growth hormone secretagogue receptor 1a (GHSR1a, today often also called ghrelin receptor).[16] The enzyme that catalyzes this acylation is the ghrelin-*O* acyltransferase (GOAT),[17,18] also expressed in the X/A-like cells of rodents[19] and P/D_1 cells of humans.[20] It is important to note that GOAT was also detected in the circulation of rodents[19] and humans[21] giving rise to a possible extragastric acylation of ghrelin.

Besides the direct effect after central injection, ghrelin also increases food intake following intraperitoneal administration in rats[22] and intravenous infusion in humans[23] likely reaching the hindbrain via the vagus nerve (or directly, since it is known that the NTS expresses the GHSR1a in humans),[24] and the ARC also expressing the GHSR1a[25] via crossing the blood-brain barrier. In the ARC the GHSR1a is co-localized in neurons expressing NPY/AgRP[26] and ghrelin increases NPY/AgRP activity, while POMC is inhibited.[27] In NPY/AgRP knockout (KO) mice ghrelin failed to increase food intake pointing towards the important role of NPY/AgRP to mediate ghrelin's orexigenic effect.[28] In addition to ghrelin's food intake-stimulatory effects, peripherally injected ghrelin increases abdominal white adipose tissue in rodents.[29] Ghrelin is also involved in the regulation of thermogenesis in brown adipose tissue with GHSR1a KO mice showing an increased thermogenesis in brown adipose tissue giving rise to an energy expenditure-reducing effect of ghrelin.[30] Moreover, ghrelin stimulates gastric acid secretion as well as gastric motility in rats[31] and humans,[32] while often supraphysiological doses are needed in order to enhance motility.[31] Both effects are blunted by cervical vagotomy indicating a vagal mediation.[31] Lastly, ghrelin is also involved in glucose homeostasis with a decrease of insulin secretion following intravenous administration of ghrelin, while insulin sensitivity was not altered in humans.[33]

Over the last years, there has been increasing knowledge on desacyl ghrelin, the major circulating form of ghrelin[34] that for long was thought to be an inactive deactivation product of ghrelin without any endogenous activity due to the lack of binding to the GHSR1a.[16] However, desacyl ghrelin might also play a role in the modulation of hunger and satiety based on the finding that co-injection of desacyl ghrelin and ghrelin greatly blunts the orexigenic effect of ghrelin in rats.[35] In line with this finding, a recent study showed that desacyl ghrelin antagonizes the orexigenic effect of peripherally administered ghrelin in mice.[36] This points towards a counteracting function of desacyl ghrelin to modulate/balance ghrelin's food intake-stimulating effect. This antagonism was also observed on colorectal motility: desacyl ghrelin reduced the motility-

stimulating effect of ghrelin after intrathecal co-injection in rats.[37] This interesting interplay of ghrelin and desacyl ghrelin warrants further investigation; moreover, the receptor mediating desacyl ghrelin's effects is yet to be identified.

Nesfatin-1

Nesfatin-1 is a recently discovered peptide derived from the precursor protein nucleobindin2 (NUCB2) and was initially described to be expressed in the rat hypothalamus.[38] Early on it was shown that nesfatin-1 reduces food intake following central injection in rats,[38,39] mice[40] or goldfish.[41] Subsequent research showed a more widespread distribution of NUCB2/nesfatin-1 in the rat brain[42] and a prominent expression in the rat stomach with 10-fold higher expression levels in the gastric oxyntic mucosa compared to the brain.[43] It is important to note that nesfatin-1 was co-localized with ghrelin in gastric X/A-like cells in rats[43] and P/D_1 cells in humans[20] leading to the hypothesis that the peptide products of the X/A-like cell can stimulate food intake in both directions: either stimulate via ghrelin or inhibit via nesfatin-1.

Peripherally injected nesfatin-1 activates the NTS as indicated by increased Fos expression which might be involved in the satiety signaling.[44] Moreover, nesfatin-1 can cross the blood-brain barrier bidirectionally in a non-saturable manner[45,46] possibly leading to an activation of food intake-regulatory nuclei such as the PVN of the hypothalamus, a nucleus recently suggested to express the yet unknown nesfatin-1 receptor in a study using autoradiography.[47] However, it is of note that although one study reported a reduction of food intake following intraperitoneal injection of nesfatin-1 at high doses in mice,[44] other studies in rats[39] or mice[40] were unable to show this anorexigenic action of peripheral nesfatin-1. Also chronic peripheral administration of the peptide provided inconsistent results: while a reduction of food intake was observed in rats,[48] no effects were described in mice.[49] Whether species differences play a role remains to be further investigated. In summary, current data clearly point towards a role of central nesfatin-1 in the regulation of food intake, whereas peripheral nesfatin-1 seems to be rather involved in the reduction of gastric motility in dogs,[50] increase of hepatic β-oxidation[49] and glucose homeostasis with an increase of glucose-stimulated insulin release from the pancreas in rats[51] and humans.[52]

Cholecystokinin

Cholecystokinin (CCK) is mainly secreted from I cells of the upper small intestine;[53] however, expression has also been detected in the enteric nervous system encompassing the myenteric and submucosal plexus.[54] Various forms of CCK were detected since its discovery (CCK-5, -7, -8, -18, -22, -25, -33, -39, -58, or post-translationally sulphated forms), while only CCK-8 and CCK-58 have been observed in the central nervous system.[53] The anorexigenic effect of CCK was discovered in 1973 in rats[55] and confirmed in different species including rabbits, monkeys, pigs, sheep and humans.[53] CCK-8 is the most studied form; however, when blood processing was optimized and degradation inhibited using the RAPID method, only CCK-58 was detectable suggesting that the shorter CCK forms represent fragments derived from enzymatic degradation.[56] Although both forms reduce dark phase food intake following intraperitoneal injection in rats, CCK-58 exerts a different effect on the underlying food intake microstructure with a reduction of meal size, while the inter-meal interval following this meal was not shortened, a finding observed after injection of CCK-8.[57]

Originally, CCK was described as a stimulator of gallbladder contraction, pancreatic secretion, and synthesis of pancreatic enzymes as well as a modulator of gastric motility.[53] Part of these actions are different between species with CCK being an inhibitor of gastric motility in humans[58] and rats[59] and a stimulator in guinea pigs.[60] CCK's actions are mediated by binding to 2 G protein-coupled receptors, the CCK_A and CCK_B receptors. CCK_A (alimentary) is expressed in several tissues including the gastrointestinal tract, liver, pancreas and on vagal afferents,[53] whereas the CCK_B (brain) is the predominant form in the central nervous system.[61]

In addition to the functions described above CCK reduces food intake.[57,62] The peptide is released from intestinal I cells after food intake with the most potent stimulation by lipids and proteins,[63,64] binds to the CCK_A on vagal afferents and leads to an activation of cells in the NTS that ultimately induce a reduction of food intake.[65,66] In humans, stimulation of the CCK_A with the orally-active CCK_A agonist, GI181771X did not induce a reduction of body weight, while gastrointestinal side effects and effects on gallbladder and bile duct were observed.[67] Therefore, CCK_A monotherapy does not seem to be a promising anti-obesity strategy. While other feeding-regulatory peptides affect food intake by crossing the blood-brain barrier, for CCK vagal mediation is the predominant pathway.[68] This is further underlined by the finding that CCK's anorexigenic actions are attenuated by capsaicin treatment[68,69] or blocked by abdominal vagotomy.[66]

Glucagon-like Peptide 1

Glucagon-like peptide 1 (GLP-1) is best known for its incretin effect with analogs used in the treatment of type 2 diabetes mellitus.[70] The most famous analogs of GLP-1 are exendin-4 and

liraglutide that also reduce food intake in animals[71] and humans.[72,73] Therefore, besides its incretin effects, GLP-1 mimetics are promising targets in the treatment of obesity.[70] GLP-1 is produced in endocrine L cells of the intestine and posttranslationally cleaved from the gene encoding *proglucagon* in its 2 biologically active forms, GLP-$1_{7\text{-}36}$ amide and GLP-$1_{7\text{-}37}$.[74] In humans, the major circulating form is the GLP-$1_{7\text{-}36}$ amide.[75] GLP-1 is released postprandially and directly after stimulation by nutrients or indirectly via other gastrointestinal hormones, such as gastric-inhibitory peptide[76] or gastrin-releasing peptide[77] or via the vagus nerve.[78] The early peak of GLP-1 secretion occurs shortly after meal ingestion (approximately after 15 minutes) and involves an indirect hormonal/neuronal loop,[78] whereas the second and larger peak appears later and is thought to be derived from direct contact of nutrients with L cells.[70] This results in a reduction of food intake in animals[79,80] and humans,[81] which can be exerted at a peripheral[81] as well as at a central level.[79] Moreover, GLP-1 has also been implicated in the modulation of gastrointestinal motility with a decrease in gastric emptying and intestinal motility observed in humans[82,83] and rats.[84,85]

Besides its expression in the gastrointestinal tract, GLP-1 is also expressed in neurons of the NTS which project to the PVN[86] and are activated by several factors that decrease food intake (bacterial components like lipopolysaccharide or hormones such as CCK, leptin or oxytocin).[70] Furthermore, the GLP-1 receptor (GLP-1R) is expressed on vagal afferents[87] and the peripheral satiety effect of GLP-1 is blocked by vagotomy.[88] Taken together, these data point towards a mediation of GLP-1's food intake-reducing effect by the vagus nerve and hindbrain circuits rather than crossing the blood-brain barrier. This is further supported by lesion experiments showing that disruption of the projections from the brainstem to the hypothalamus reduce the appetite-suppressing effect of peripherally injected GLP-1 in rats.[88] Moreover, peripheral as well as central injection of GLP-1 induces Fos, a marker for neuronal activity, in the PVN, while only central injection of GLP-1 induces Fos in the ARC.[89] Furthermore, knockdown of the proglucagon gene in the NTS results in an increase of food intake and body weight gain.[90] Lastly, microinjection of GLP-1 into the ARC affected glucose metabolism and insulin release, whereas food intake was only affected by injection of GLP-1 into the PVN.[91] This points towards a mediation of the peripheral anorexigenic GLP-1 effect by activation of vagal afferents and a subsequent hindbrain (NTS) to forebrain (PVN) signaling.

However, GLP-1 has also been shown to cross the blood-brain barrier by simple diffusion[92] and the GLP-1R is expressed in the hypothalamus as well.[93] In line with this expression, peripheral injection of liraglutide was shown to directly stimulate POMC/CART-containing neurons and to inhibit NPY/AgRP-containing neurons in the ARC resulting in a decrease of body weight.[94] However, it is of note that after reaching the circulation endogenous GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase IV.[95] Therefore, the vagal signaling pathway following paracrine receptor activation is likely to predominate.

A recent study in Sprague Dawley rats showed that knockdown of the GLP-1R in vagal afferents affects food intake by increasing meal size and meal duration, whereas the number of meals was reduced and overall food intake not altered compared to controls.[96] Whether all these changes encompass GLP-1's effects or reflect compensatory mechanisms will have to be further investigated.

Peptide YY

Two native forms of human PYY are known, $PYY_{1\text{-}36}$ and $PYY_{3\text{-}36}$, with $PYY_{3\text{-}36}$ (hereafter termed as PYY) being the major circulating form resulting from cleavage of $PYY_{1\text{-}36}$ by DPP IV.[97,98] PYY is primarily produced in L cells of the small intestine but also the colon.[97] It is important to note that it took 20 years following its discovery in the porcine intestine[99] to identify PYY as a peripheral inhibitory regulator of food intake postprandially acting via the Y_2 receptor in the central nervous system,[100] an effect blunted by central injection of the Y_2 antagonist, BIIE0246.[101] Microinjection of PYY into the ARC inhibited electrical activation of NPY-containing nerve terminals and activated adjacent POMC-containing neurons.[100] Taken together, these results give rise to PYY as a peripheral and central regulator of food intake in animals[100,102] and humans.[102]

Interestingly, Y_2 are localized on NPY-containing neurons in the ARC suggesting a direct action of PYY on hypothalamic neurons.[103] This hypothesis is supported by the finding that peripheral PYY can cross the blood-brain barrier by a non-saturable mechanism.[104] However, current data also point towards a vagal route of PYY signaling since the food intake-reducing effect of PYY following intraperitoneal injection was blocked by vagotomy in rats.[105] Moreover, vagotomy also greatly decreased the PYY-induced expression of Fos in the ARC.[105] Therefore, peripheral PYY is likely to signal to the brain both via the vagus nerve and via direct interaction with hypothalamic nuclei after crossing the blood-brain barrier. The peptidergic regulation of hunger and satiety is summarized in Figure 1.

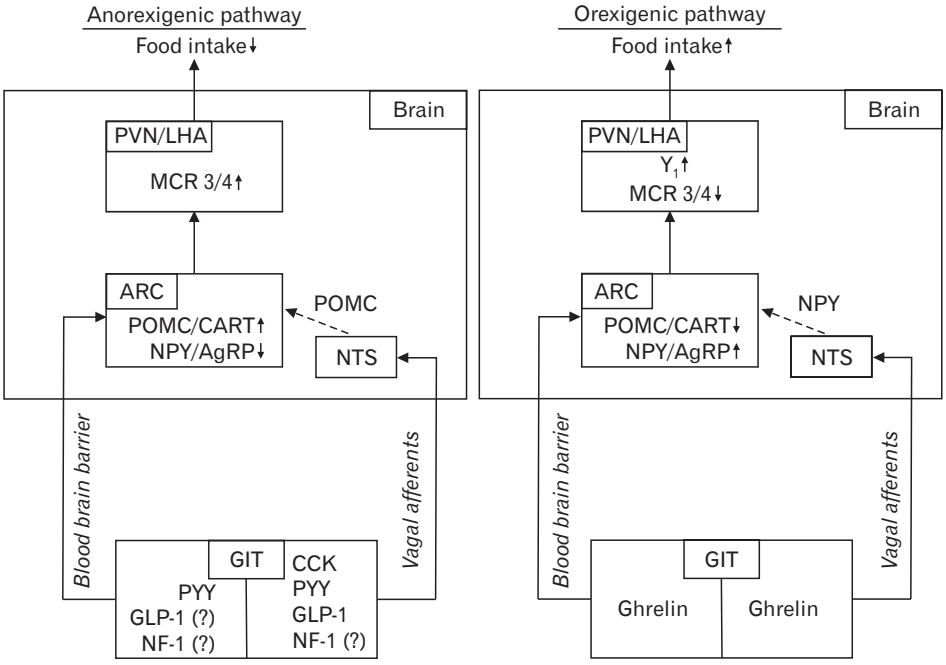

Figure 1. Effects of gastrointestinal peptides on food intake via the gut-brain axis. The left side shows the anorexigenic signaling pathway, whereas orexigenic signaling is shown on the right panel. PVN, paraventricular nucleus; LHA, lateral hypothalamic area; MCR 3/4, melanocortin receptors 3 and 4; ARC, arcuate nucleus; POMC, pro-opiomelanocortin; CART, cocaine-and amphetamine-regulatory transcript; NPY, neuropeptide Y; AgRP, agouti-related peptide; NTS, nucleus of the solitary tract; Y_1, NPY receptor 1; GIT, gastrointestinal tract; PYY, peptide tyrosine tyrosine; GLP-1, glucagon-like peptide 1; NF-1, nesfatin-1; CCK, cholecystokinin; ↓, decrease; ↑, increase; ?, controversial data (NF-1) or data that resulted from mimetics (GLP-1).

Influence of Nutrients and Stress on Peptidergic Regulators of Food Intake

Effects of Nutrients on Food Intake-modulating Hormones

The release of gastrointestinal food intake-regulating peptides is greatly affected by ingested nutrients. The early release of CCK has been well described when nutrients reach the duodenum, while GLP-1 and PYY are released later when nutrients further proceed through the intestine.[106] This points towards a direct contact of nutrients with enteroendocrine cells to trigger the release of anorexigenic peptides.[106] CCK is mainly stimulated by digested lipids and proteins,[107,108] while intraduodenal glucose load exerted only a small increase of circulating CCK in healthy subjects.[109] Further investigation of lipids and proteins showed that especially fatty acids with more than 12 carbons (oleate) or non-hydrolyzed and partially hydrolyzed proteins (casein or soybean trypsin inhibitors) stimulate CCK release.[110] A number of G protein-coupled receptors has been described that can sense oral lipids in the gastrointestinal tract including FFAR1, PPR120 or GPR119 or a G protein-coupled receptor for bile acids, GPBAR1. A recent study showed that lipid superfusion on human duodenal biopsies increased GPR119 expression but not FFAR1 or FFAR4 and stimulated the secretion of CCK and GLP-1.[111] Therefore, these receptors might be localized on the surface of I and L cells to trigger CCK and GLP-1 release following lipid sensing.

In contrast to CCK, GLP-1 is mainly triggered by glucose,[109,112] which is sensed by the same sweet taste receptors on GLP-1-expressing L cells that are also expressed on the tongue, namely T1R2 and T1R3.[113] Apart from the nutrients, the amount of energy also seems to play a role in gastrointestinal peptide release. PYY levels were shown to increase in response to nutrients proportionally to the amount of calories ingested[114] and to decrease during fasting.[115]

Moreover, oral administration of glucose, lipids, and proteins in male and female healthy subjects showed that levels of the orexigenic peptide ghrelin decreased after glucose and lipid meals, whereas proteins did not affect circulating ghrelin.[116] Interestingly, desacyl ghrelin can be directly acylated by GOAT using medium chain fatty acids or medium chain triacylglycerols of ingested foods.[117] In vitro studies of cultured stomach ghrelinoma cells (MGN3-1) showed that oleic acids increase the expression of orexigenic ghrelin and simultaneously decrease the expression of NUCB2 (the precursor protein of the anorexigenic peptide nesfatin-1)[118] also expressed in gastric X/A-like cells. Interestingly, L-tryptophan increased both NUCB2 expression and nesfatin-1 release as well as ghrelin expression, while glucose only stimulated NUCB2 expression.[118] Since both peptides are derived from the same cell, different downstream signaling is likely to mediate this differential regulation. This has to be further investigated in future studies.

Effects of Stress on Food Intake-regulating Hormones

The impact of psychological diseases and stress on food intake-regulatory peptides is well investigated for ghrelin and also for nesfatin-1, whereas studies for CCK, GLP-1, and PYY mostly focused on the impact of these peptides on the development of psychological disorders or stress.

Besides its orexigenic effect, ghrelin (subcutaneously injected or endogenously increased under conditions of caloric restriction) was shown to induce anxiolytic and antidepressant behavior in mice.[119] These effects are ghrelin-specific and mediated by the GHSR1a as GHSR1a KO mice do not display these behaviors following ghrelin injection.[119] In line with these acute findings, Wistar Kyoto rats which show more anxious behavior than Sprague Dawley rats have 2-fold lower fasting ghrelin levels.[120] Taken together, these data give rise to the assumption that ghrelin might have beneficial effects in disorders involving anxiety or depression.

Chronic social defeat stress, representing a model of depression, increased circulating ghrelin levels.[119] In this model the upregulation of ghrelin seems to play an adaptive/counter-regulatory role as mice lacking the GHSR1a showed even greater social avoidance.[119] In line with these results, previous studies showed that acute stress resulted in increased circulating levels of ghrelin in mice[121] and rats.[122] In humans the results are divergent. A cold pressor test (a physiological laboratory stressor) increased circulating ghrelin levels in overweight women with and without night eating[123] and obese women with binge eating disorder,[124] while another study did not detect a correlation of plasma ghrelin with perceived stress in overweight and obese women[125] or showed that acute stress did not affect ghrelin levels in obese women.[126] Whether confounding factors such as comorbidities contribute to these inconsistent results remains to be further investigated. However, since intravenous administration of ghrelin reduced blood pressure and sympathetic nerve activity in response to mental stress,[127] ghrelin might still hold therapeutic potential under these conditions.

NUCB2/nesfatin-1 is involved in the stress response as initially described by Goebel and colleagues in 2009.[128] Abdominal surgery as a model for physical stress[129] and restraint stress as a psychological stressor[128] activated NUCB2/nesfatin-1-containing neurons in the forebrain (including the hypothalamus) as well as the hindbrain (including the NTS) in rats which was confirmed in a subsequent study.[130] Human studies showed increased circulating NUCB2/nesfatin-1 levels in depressed patients compared to healthy individuals.[131] Additionally, NUCB2/nesfatin-1 levels correlate positively with anxiety, depression and perceived stress in female obese patients.[132,133] Interestingly, in obese men an inverse correlation of NUCB2/nesfatin-1 and anxiety scores has been described[133] giving rise to a sex-specific regulation of the peptide.

CCK seems to be involved in the mediation of anxiety-like behaviors. CCK-8S and CCK-8N increase anxiety-like behavior, an effect likely mediated by the CCK_B as shown by decreased freezing behavior following injection of a CCK_B receptor antagonist, LY225910, and increased freezing behavior by injection of the CCK_B receptor agonist, CCK-4.[134] Moreover, CCK_B antagonism using LY288513 blunts conditioned fear stress induced by electric footshock in rats.[135] In line with these findings, CCK_B KO mice showed an anxiolytic phenotype.[136] Since mice lacking the CCK_B display an increased body weight,[137] brain CCK signaling seems to be involved in both, the modulation of anxiety as well as food intake. In humans, CCK has the most prominent role in panic disorder with exogenous CCK being able to provoke panic attacks and genetic variants of the CCK ligand and CCK_B being potentially involved in the pathogenesis of panic disorder.[138] Whether these alterations are also directly linked to alterations of food intake and body weight remains to be further addressed.

Similar to CCK, studies are lacking that investigate changes of peripheral GLP-1 expression due to stress, anxiety or depression. However, central GLP-1R stimulation acutely induces anxiety-like behavior in rats, while chronic administration of exendin-4 reduces depression-like behavior.[139] These interesting differential effects of acute *versus* chronic GLP-1 signaling warrant further investigation.

Lastly, mice lacking the Y_2 showed a suppression of anxiety and stress-related behavior[140] suggesting that the PYY-mediated reduction in food intake might also be associated with or be secondary due to a modulation of anxiety and stress. These data show that food-intake regulatory peptides often exert multiple, if not pleiotropic, actions and especially effects related to anxiety and stress may be associated with an acute or chronic modulation of food intake.

Modulation of Peptidergic Signaling in the Treatment of Obesity

Conservative Treatment: Physical Activity

Since it is known that long-term physical activity is able to reduce body weight,[141,142] an impact on gastrointestinal peptide hormones has been assumed as well. Exercise leads to a reduction of hunger, an effect observable shortly after performing sports.[143] In line with this finding, the concentration of ghrelin is reduced

following aerobic sports,[144,145] as well as resistance exercise,[145] likely contributing to the exercise-induced reduction of food intake. However, the exact role of ghrelin under these conditions needs to be further investigated as a correlation of hunger and circulating ghrelin was not detected,[144,145] likely suggesting an indirect effect of ghrelin and/or additional (peptidergic) mechanisms.

This hypothesis is underlined by the fact that the decrease of ghrelin levels during exercise is accompanied by reciprocal changes of anorexigenic hormones. Various studies reported that PYY concentrations rise during exercise in lean[144,146,147] as well as obese[148] individuals. Interestingly, one study showed that plasma concentrations of PYY increased at 5 hours after aerobic exercise, whereas anaerobic exercise did not affect PYY levels.[144] Similar results were found for the impact of aerobic exercise on GLP-1 levels, which where elevated during and up to 1 hour after exercise.[146-148] CCK concentrations were elevated in men performing 30-minute cycling but did not change after chronic training over a period of 4 weeks.[149] These results were confirmed by a 12-week individually designed and supervised exercise program in overweight and obese individuals without changes in CCK concentrations at the end of the treatment period.[150] Additionally, cumulative food intake was not altered after 12 weeks,[150] which might point towards a rather acute effect of exercise on CCK. Taken together, these results show that acute exercise might affect food intake regulation by changes of the secretion of food intake-regulatory peptides from the gastrointestinal tract, whereas long-term exercise might lead to adaptive changes also blunting the effects on food intake.

Interestingly, different from other anorexigenic peptides, circulating NUCB2/nesfatin-1 decreased after acute exercise at the individual anaerobic threshold.[151] In contrast to this acute regulation, aerobic exercise for a period of 8 weeks in overweight and obese females as well as a 6-week high-intensity interval training in overweight men increased circulating NUCB2/nesfatin-1 levels.[152,153] These results were confirmed in women with type 2 diabetes mellitus who performed a 10-week resistance training.[154] Since current data rather point to a central effect of nesfatin-1 on food intake, the observed peripheral changes of NUCB2/nesfatin-1 after acute and chronic exercise might impact on other regulatory processes such as glucose homeostasis.

Conservative Treatment: Pharmacotherapy

Despite the fact that our knowledge on the peptidergic regulation of food intake greatly increased during the past years, only few drugs targeting these hormones are on the market or are tested for the market. Nonetheless, several candidates are in the preclinical pipeline.

While several GHSR1a agonists such as ipamorelin[155] or BIM-2831[156] are known and able to stimulate food intake, body weight gain, and gastrointestinal motility,[155] there is a paucity on ghrelin antagonists. Intraperitoneal and intracerebroventricular administration of [D-Lys-3]-GHRP-6, a GHSR1a antagonist decreased food intake.[157] However, GSK1614343, another GHSR1a antagonist, was not able to reduce ghrelin-stimulated food intake and unexpectedly itself stimulated food intake and body weight in rats and dogs[158] likely due to GHSR1a-stimulating activity. It is also important to note that the ghrelin receptor GHSR1a displays considerable constitutive signaling activity,[159] therefore blockade by classical agonists cannot fully abolish ghrelin signaling. In line with this assumption, central administration of a substance P derivate, an inverse agonist of the ghrelin receptor, was able to reduce food intake and body weight by decreasing the expression of NPY in the hypothalamus.[160] Another possibility to reduce food intake is to inhibit the acylation of ghrelin. The most established GOAT inhibitor is GO-CoA-Tat, a peptide-based bisubstrate analogue that was shown to acutely reduce food intake in Siberian hamsters[161] and rats[162] as well as body weight following repetitive intraperitoneal injections in mice.[163] Whether these data can be translated to humans will have to be further investigated.

The food intake-reducing effect of nesfatin-1 is more readily observed after central injection[164] hampering the potential therapeutic use as a target in the treatment of obesity. However, one study described the use of an intranasal application of nesfatin-1 in rats inducing an acute reduction of food intake.[165] Whether this holds true over a longer period of time and also in humans warrants further investigation.

As described above, a soybean trypsin inhibitor stimulates CCK release from duodenal I cells, an effect mimicked by the non-nutrient trypsin inhibitor, Camostat following oral administration in rats.[166] It is known that CCK-8 reduces food intake in healthy volunteers.[167] However, no data exist so far on the food intake-modulating effect of the endogenous form, CCK-58 in humans which has a longer half-life in the circulation and might be more effective in the reduction of food intake.[53] While several CCK antagonists such as devazepide have been established to increase the amount of food intake or attenuate the anorexigenic effect of CCK in rats,[168] there is a paucity on CCK analogs. The use of native CCK is difficult and hampered by the rapid endogenous degradation resulting in a short half-life.[169] Amino terminal glycation of CCK-8 prolongs its half-life[169] and might therefore be a potential target for short-time therapeutic reduction of food intake. However, longer application

may be limited by the development of tolerance as observed after a 2-week intraperitoneal infusion of CCK in rats.[170] A recently developed CCK-8 analogue showed more promising results: (pGlu-Gln)-CCK-8 did not result in the development of an adaptation over a period of 28 days as reflected in a sustained decrease in food intake and body weight.[171] Moreover, this compound is not subject to rapid degradation and was shown to be stable for 180 minutes post injection.[171] Therefore, (pGlu-Gln)-CCK-8 as well as its polyethylene glycol-conjugated (PEGylated) form are promising targets in the treatment of obesity and deserve further testing.

Most of the studies investigating the effect of GLP-1 use the synthetic analogs exendin-4 and liraglutide, which are not degraded by dipeptidyl peptidase IV and able to cross the blood-brain barrier as active compounds to bind to the GLP-1R.[70] Exendin-4 injected intraperitoneally reduced cumulative food intake in mice by activating sensory afferent pathways due to binding to the GLP-1R, an effect attenuated by co-injection of capsaicin.[172] These results were confirmed in rats, where intraperitoneal as well as subcutaneous injection of exendin-4 and liraglutide reduced cumulative food intake after acute injection.[71] The same study investigated the effect of subacute intraperitoneal and subcutaneous administration of exendin-4 and liraglutide in diet-induced obese (DIO) rats over a period of 7 days. Both GLP-1 analogs reduced intake of a high fat/sucrose diet and led to a decrease of body weight.[71] Taken together, these results show that exendin-4 and liraglutide might be potential targets in the treatment of obesity. A recent meta-analysis comparing 21 studies investigating the effects of GLP-1 analogs on body weight changes in humans confirmed the results observed in rodents, and concluded that exenatide and liraglutide reduce body weight compared to controls.[173] These compounds are therefore already used—liraglutide was recently approved for the drug treatment of obesity—in the clinic.

Although PYY levels are reduced in obese patients, its anorexic effect is still visible after exogenous administration.[174] Therefore, PYY analogs and Y_2 agonists were suggested as possible targets in the treatment of obesity. The injection of PYY reduces food intake, an effect absent in mice lacking the Y_2.[100] Also, the use of a selective neuropeptide Y_2 PEGylated peptide agonist consisting of a peptide core corresponding to residues 13 to 36 of human PYY and a non-peptidic moiety (2-mercaptonicotinic acid) at the peptide N-terminus reduced food intake and body weight in lean rodents as well as in DIO rats.[175] This anorexigenic effect was blocked by co-administration of the Y_2 agonist, BIIE0246,[175] giving rise to direct competition at the Y_2. Recently, a group developed a strategy to create dual target peptides intended to inhibit the GHSR1a while stimulating the Y_2.[176] While the first results are promising in vitro,[176] more research is needed in vivo under acute and chronic conditions in experimental animals and ultimately in humans.

Surgical Treatment: Bariatric Surgery

For patients suffering from severe obesity, bariatric surgery is the most effective treatment to reduce body weight.[177] The most common procedures are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), whereas gastric banding (GB) is not frequently performed anymore, and biliopancreatic diversion/duodenal switch (BPD/DS) often reserved as a second option.[178] While our knowledge on the effectiveness of these techniques mentioned above (with the exception of gastric banding which does not result in a long-lasting reduction of body weight[179]) greatly increased over the past years, our knowledge on the underlying mechanisms is still incomplete. Besides the proposed restrictive and malabsorptive components of these techniques,[180] an altered gastrointestinal peptide signaling very likely plays a role as well.

While GB had no effect on circulating ghrelin levels,[181,182] SG[183] and BPD/DS[184] led to a pronounced and long-lasting decrease of circulating ghrelin. This regulation seems different under conditions of RYGB with an early decrease of ghrelin[184] followed by a later increase to reach preoperative levels,[183,185] which may be associated with retained vagal signaling in these patients.[185]

In type 2 diabetic rats, NUCB2/nesfatin-1 levels initially decreased after RYGB, but increased again at 2 months after the procedure, whereas SG did not affect nesfatin-1 levels.[186] In patients with type 2 diabetes mellitus, both RYGB and SG reduced nesfatin-1 levels after surgery with a positive correlation with decreasing BMI,[187] an adaptation possibly involved in the postoperative improvement of glucose control. A recent study showed that NUCB2/nesfatin-1 levels were decreased at 12 months following BPD/DS,[188] which positively correlated with weight loss. This might be an adaptation process as well, since it is known that peripheral nesfatin-1 is rather involved in hepatic lipolysis[49] or glucose homeostasis[51] than in body weight control.

The postprandial release of CCK, GLP-1, and PYY was increased following both RYGB[189] and SG,[183,190] a finding not observed after GB for GLP-1 and pancreatic polypeptide,[181] while the regulation of CCK after GB is unknown so far. This increased postprandial release of CCK, GLP-1, and PYY might be due to faster delivery of nutrients to the distal intestinal tract following surgery and contribute to the improvement of glucose control as well as the reduction of food intake and subsequently body weight. Additionally, combined blockade of GLP-1 and PYY in type 2 dia-

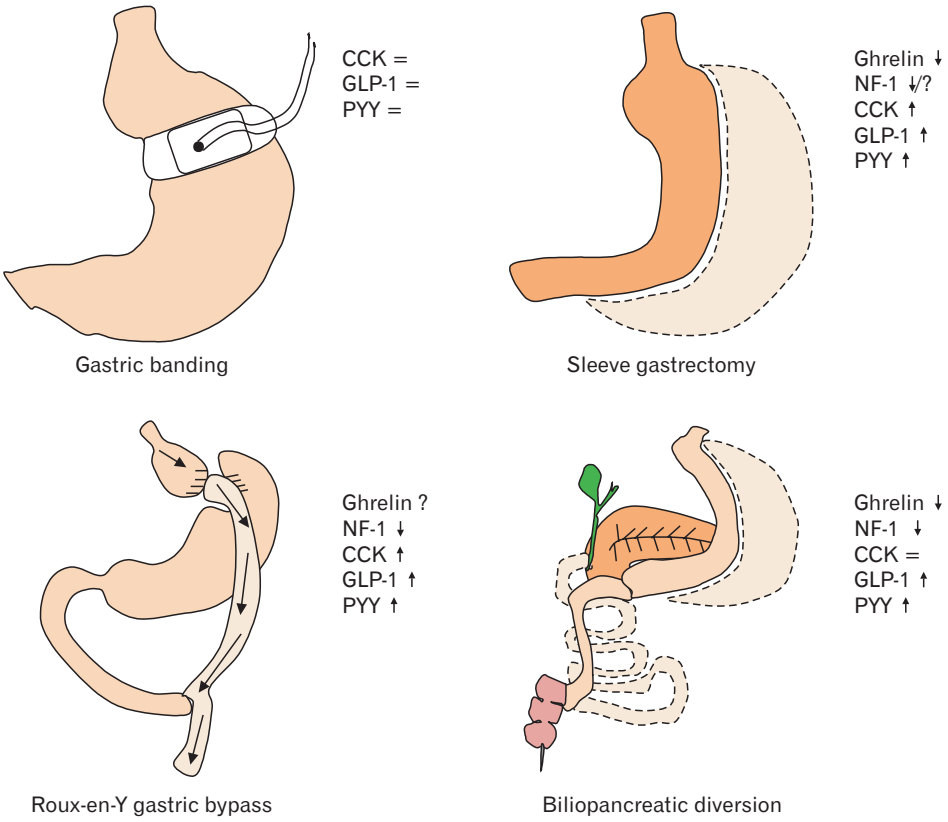

Figure 2. Effects of bariatric surgery on circulating levels of food intake-regulatory peptides. CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide tyrosine tyrosine; NF-1, nesfatin-1; ↓, decrease; ↑, increase; =, no change; ?, controversial data.

betic patients following RYGB increased food intake, supporting the hypothesis that these 2 peptides play a role in the postoperative attenuation of food intake.[191]

Taken together, these results show that bariatric surgery greatly affects signaling of food intake-regulatory gastrointestinal peptides that likely contributes to the body weight-reducing effect of these procedures. The impact of bariatric surgery on gastrointestinal peptides is summarized in Figure 2.

Surgical Treatment: Deep Brain Stimulation

Since obesity still is an increasing threat to global health, new approaches have been tested to reduce body weight and food intake. One of the most promising and interesting approaches—besides the well-established use in Parkinson's disease[192,193] and depression[194]—is the application of deep brain stimulation (DBS), which is a minimally invasive and reversible method to modulate the central neuronal network.[195] Interesting regional targets of the brain encompass the LHA, ventromedial hypothalamus (VMH) and the core and shell of the nucleus accumbens (NAc).[196]

Recently, a study investigated the effects of bilateral DBS in the LHA in 3 morbidly obese patients. The authors did neither report any serious side effects nor effects on body weight gain with the DBS settings used for movement disorders.[197] However, when DBS stimulation was performed in the monopolar mode, the resting metabolic rate increased in 2 out of 3 patients and all 3 patients reported a decreased urge to eat.[197] The follow-up investigations under monopolar settings showed a weight loss ranging from 12.3-16.4% in 2 of the 3 patients (and 0.9% in the third patient).[197] Interestingly, food intake-regulatory peptides such as insulin, insulin-like growth factor, ghrelin, leptin, NPY, AgRP, and PYY were not altered under these conditions[197] giving rise to local mechanisms. These results on food intake and body weight are extended by animal studies investigating the effects of bilateral DBS of the LHA in obese Zucker rats, which decreased food intake after 15 days of stimulation associated with a slight reduction of body weight that did not reach statistical significance.[198] Taken together, monopolar stimulation seems to be necessary in order to induce weight loss. Although the LHA might be a promising target area, more research investigating larger patient populations over a longer follow-up period is needed to better characterize these effects.

Application of DBS to the VMH of a morbidly obese patient produced several unexpected side effects affecting memory or recol-

lection.[199] No weight changes were seen during the first 6 months using monopolar stimulation at 130 Hz.[199] However, after lowering the frequency to 50 Hz the patient lost 12 kg in 5 months and reported a reduced desire to eat.[199] Subsequent studies were performed in female Göttingen minipigs, which were fed a restricted diet for one month after surgery without stimulation, followed by a 2-months period with twice the amount of food and half of the animals receiving DBS 50 Hz within the VMH, while the other half was not stimulated.[200] No motoric or behavioral side effects were monitored and all animals consumed the increased amount of food; however, the DBS-treated animals showed a reduced cumulative weight gain compared to non-stimulated pigs.[200] This points towards a DBS-mediated increase in energy expenditure resulting in a reduction of body weight. In 2 vervet monkeys, bilateral DBS (monopolar, 185 Hz) of the VMH increased food consumption without serious side effects,[201] while a study in rats with unilateral, bipolar (150 and 500 Hz) DBS stimulation of the VMH did not show changes in body weight after 32 days of stimulation.[202] Whether these different results are due to species differences or differences in the strength and mode of stimulation remains to be further investigated. In order to possibly target the VMH to treat obesity further analyses are necessary, especially observations of psychological and behavioral side effects. Until then, other areas appear to be more promising targets.

Another interesting approach is to target the NAc as part of the reward circuitry. The NAc is divided into core and shell and was first targeted to treat neuropsychiatric disorders, like Tourette's syndrome[203] or alcoholism.[204] Based on these studies, it is known that electrical stimulation of the NAc is safe and feasible in humans.[196] Direct stimulation of the NAc shell results in a modulation (either stimulation or inhibition) of food intake,[205,206] an effect likely involving GLP-1 signaling.[207,208] Treatment of the NAc shell and core with exendin-4 reduced food intake, especially of highly palatable food.[207] However, only injection of exendin-4 into the NAc core reduced intake of 15% sucrose, whereas no effects on sucrose intake were observed after injection into the NAc shell.[207] On the other hand, antagonism of GLP-1 signaling using exendin-9 injected into the NAc core and shell increased food intake.[207] These data point towards a role of the endogenous GLP-1 signaling in the NAc to regulate food intake. Also, CCK is involved in the regulation of palatable food intake by affecting the NAc as shown in rats.[209] Moreover, ghrelin injected into the NAc also stimulates food intake[210] and increases extracellular dopamine levels following administration into the NAc shell.[211] This indicates that the NAc shell might be an interesting target to increase food intake, as shown by a Dutch group that reported an increase of food intake in rats after DBS stimulation of the NAc medial shell, whereas DBS stimulation of the NAc core did not alter food intake.[205] Interestingly, subsequent research in DIO rats showed that DBS stimulation of the NAc shell reduced food intake and body weight gain despite the fact that dopamine levels were increased in the NAc shell.[206] Whether these discrepancies are due to different settings of stimulation, species or nutritional status needs to be further elucidated. The main effects of DBS on body weight and food intake are summarized in the table.

Conclusion

Although the basic mechanisms regulating hunger and satiety

Table. Overview of Current Studies on the Effects of Deep Brain Stimulation on Body Weight and Food Intake

Target area	Mode	Species (n)	Results	References
Lateral hypothalamic area	Bilateral, monopolar, 185 Hz	Humans (3)	2 out of 3: body weight ↓	197
	Bilateral, bipolar, 130 Hz	Obese Zucker rats (10)	Body weight ↓, food intake ↓	198
Ventromedial hypothalamus	Bilateral, monopolar, 50 Hz	Human (1)	Body weight ↓	199
	Bilateral, monopolar, 50 Hz	Göttingen minipigs (8)	Body weight gain ↓	200
	Bilateral, monopolar, 185 Hz	Vervet monkeys (2)	Food intake ↑	201
	Unilateral, bipolar, 150 Hz	Sprague Dawley rats (4)	No effect on body weight	202
	Unilateral, bipolar, 500 Hz	Sprague Dawley rats (5)	No effect on body weight	202
Nucleus accumbens shell	Bilateral, bipolar, 130 Hz	Wistar rats (8)	Food intake ↑	205
	Unilateral, stimulation mode not specified, 130 Hz	Diet-induced obese rats (8)	Body weight ↓, food intake ↓	206
	Unilateral, stimulation mode not specified, 130 Hz	Sprague Dawley rats (8)	No effects on body weight and food intake	206
Nucleus accumbens core	Bilateral, bipolar, 130 Hz	Wistar rats (8)	No effect on food intake	205

↓, decrease; ↑, increase.

were extensively investigated, the complex and redundant system is still difficult to modulate. Besides (so far not very successful) conservative treatment options, surgical techniques can be applied. While bariatric surgery has become an effective treatment option for obesity associated with a long-term alteration of gastrointestinal peptidergic signaling, deep brain stimulation might be a promising and less invasive tool for the treatment of obesity.

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