

Review Article

The Gut Hormones in Appetite Regulation

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Obesity has received much attention worldwide in association with an increased risk of cardiovascular diseases, diabetes, and cancer. At present, bariatric surgery is the only effective treatment for obesity in which long-term weight loss is achieved in patients. By contrast, pharmacological interventions for obesity are usually followed by weight regain. Although the exact mechanisms of long-term weight loss following bariatric surgery are yet to be fully elucidated, several gut hormones have been implicated. Gut hormones play a critical role in relaying signals of nutritional and energy status from the gut to the central nervous system, in order to regulate food intake. Cholecystokinin, peptide YY, pancreatic polypeptide, glucagon-like peptide-1, and oxyntomodulin act through distinct yet synergistic mechanisms to suppress appetite, whereas ghrelin stimulates food intake. Here, we discuss the role of gut hormones in the regulation of food intake and body weight.

1. Introduction

Obesity is one of the major health challenges throughout the world, due to its association with an array of vascular, metabolic, and psychosocial complications [1, 2]. Obesity is traditionally associated with populations in Europe and North America; however Asian countries such as Japan have recently reported increasing prevalences of obesity, which may reflect changes in dietary patterns and lifestyles [3, 4].

Obesity is a state in which energy intake chronically exceeds energy expenditure. Body weight is tightly regulated by complex homeostatic mechanisms involving the hypothalamus and brainstem which integrate inputs from higher cortical centres with peripherally derived signals of the body's nutritional and energy status. In the hypothalamic arcuate nucleus (ARC), there are two neuronal populations with opposing effects on food intake: neurons which coexpress neuropeptide Y (NPY) and agouti-related peptide (AgRP) which stimulate food intake, whereas neurons coexpressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) suppress food intake (see Figure 1). Within the brainstem, the dorsal vagal complex (DVC) consisting of the dorsal motor nucleus of vagus (DMN), area postrema (AP), and the nucleus of the tractus solitarius (NTS) plays a pivotal role in relaying of

peripheral signals such as vagal afferents from the gut to the hypothalamus [5]. In human, higher cortical centres are implicated in psychological and emotional factors which can drive food intake beyond homeostatic requirements. In addition, the corticolimbic pathways are responsible for reward-associated feeding behaviour.

This article summarises our current understanding of the role of gut hormones in appetite regulation and its potential as therapeutic targets for obesity.

2. Gastrointestinal Tract

More than 30 gut hormone genes are known to be expressed, and more than 100 bioactive peptides are distributed in the gastrointestinal tract, which is thus regarded as the largest endocrine organ in the body [6]. Meal anticipation and the presence of food in the upper gastrointestinal tract stimulate the release of gut hormones and neurotransmitters from the gut. These neurohumoral signals are involved in the initiation and maintenance of food intake as well as termination of meals. The satiating effect of stomach distension is revealed by observing that infusion of either saline or nutrients into the rat stomach results in same reduction in food intake [7]. In humans, the effects of intragastric balloon insertion on body weight and food

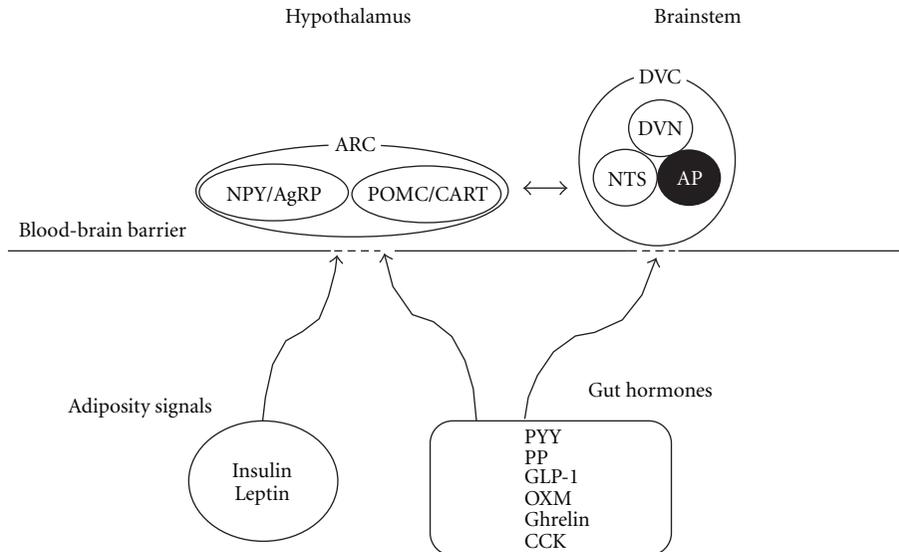


FIGURE 1: Humoral signals implicated in the physiological regulation of food intake. Diagram summarising the major signalling pathways which converge on the hypothalamus and brainstem in order to regulate food intake. ARC, arcuate nucleus; NPY/AgRP, neuropeptide Y and agouti-related peptide; POMC/CART, proopiomelanocortin and cocaine- and amphetamine-regulated transcript; DVC, dorsal vagal complex; DVN, the dorsal motor nucleus of vagus; NTS, the nucleus of the tractus solitarius; AP, area postrema; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; PP, pancreatic polypeptide; PYY, peptide YY; OXM, oxyntomodulin.

intake are conflicting [8, 9]; this may reflect differences in the types of balloon used during these studies.

Both meal duration and size are markedly increased during sham feeding, where ingested food is prevented from distending the stomach or small intestine by surgical intervention, whereas intraluminal gastrointestinal (GI) infusion of macronutrient before food access reduces subsequent meal size in a dose-dependent manner. These findings suggest that the upper GI tract has an important role in negative feedback regulation of food intake, and the upper intestine is critical for nutrient absorption [10]. The vagus nerve is closely implicated in the transmission of the food-induced negative feedback signals which are critical for determining meal size. Transection of all gut sensory vagal fibres results in increased meal size and meal duration but does not block gastric preload-induced feeding suppression; this implies that vagal afferent signals contribute to satiety during spontaneous meals [10, 11].

Perfusion of nutrients into the colon inhibits upper gastrointestinal secretion, motility, and transit; this negative feedback mechanism has been called the “ileal brake” [12]. Fat is the most potent trigger of the ileal brake, and glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) may be among the mediators of this phenomenon [13].

3. Bariatric Surgery and Weight Loss

Almost all pharmacological and behavioural treatments for obesity result in weight loss followed by weight regain [14]. In contrast, gastric bypass surgery is an established and effective treatment for obesity which provides sustained weight loss maintenance for at least 15 years [15, 16].

Bariatric surgery may be classified into malabsorptive surgery and restrictive surgery. Malabsorption-based techniques include the jejunio-ileal bypass, allowing nutrients to pass directly from the proximal jejunum to the terminal ileum, and roux-en-Y gastric bypass (RYGB), combining restrictive and malabsorptive procedures. In some cases, the former procedure may be associated with severe complications [17].

Restrictive bariatric surgery involves the laparoscopic application of an adjustable gastric banding (LAGB). LAGB procedures result in slightly less weight loss compared with RYGB but have been reported to be safer [18]. Intriguingly, the mechanisms of long-term weight loss following bariatric surgery are yet to be determined; however several gut hormones have been implicated as contributory factors; a decrease in ghrelin and an increase in PYY and GLP-1 levels have been found following bypass surgery [19–21]. Recent evidence suggests that an increase in energy expenditure may play a role in part in weight loss after gastric bypass surgery as an additional factor [22]. Gastric bypass surgery also improves glycaemic control in patients with type 2 diabetes, and this often occurs prior to observable weight loss [23]. Thus emulating the altered gut hormone signals associated with bypass surgery may offer promising novel treatments for obesity.

4. Gut Microbiota

Recently, a potential link between gut microbiota and obesity has emerged [24]. The human gut harbours a large number of bacterial microorganisms collectively termed gut microbiota. Bäckhed et al. [25] have observed that adult

germ-free mice had 40% less total body fat than mice with normal microbiota; furthermore replacing the microbiota in adult germ-free mice produced a 60% increase in body fat content and insulin resistance within 14 days of replacement. In addition, germ-free mice may be protected against high fat diet-induced metabolic changes [26]. There has also been considerable interest in the potential benefits of prebiotic drinks containing bacterial cultures. The study by Cani et al. [27] evaluated the effect of prebiotics on plasma levels of gut hormones in healthy subjects. After two weeks of prebiotic treatment, they observed increased gut microbiota fermentation, decreased appetite, and improved postprandial glucose responses. Furthermore plasma levels of GLP-1 and PYY were increased in subjects following prebiotic treatment. Current data therefore suggest that gut microbiota may promote the development of obesity and that manipulation of gut microbiota using probiotics may alter gut endocrine function. Further studies are required in order to further investigate the pathophysiological basis of the association between gut microbiota and energy homeostasis.

5. Gut Hormones

5.1. PP-Fold Protein. The PP-fold family consists of neuropeptide Y (NPY), peptide YY (PYY), and pancreatic polypeptide (PP). PYY and PP are secreted from gastrointestinal tract, whereas NPY is predominantly distributed within central nervous system [28]. The members of PP-fold family act via G protein-coupled receptors: Y1, Y2, Y4, Y5, and Y6 [29].

5.2. Peptide Tyrosine Tyrosine (PYY). PYY was first isolated as a 36-amino acid peptide from porcine upper small intestine [28]. PYY is released by L cells of the distal gut. There are two circulating forms of PYY: PYY (1–36) and PYY (3–36). PYY (3–36), the major circulating form, is produced by cleavage of the N-terminal Tyrosine-Proline residues from PYY (1–36) by the enzyme dipeptidyl-peptidase IV (DPP-IV) [30]. PYY (1–36) has affinity to all Y receptors, while PYY (3–36) binds with highest affinity to the hypothalamic Y2 receptor, suppressing food intake. Circulating PYY concentrations are low in fasted state and rise rapidly following a meal with a peak at 1–2 hours and remain elevated for several hours [31]. Ingestion of fat results in greater release of PYY than observed with ingestion of carbohydrate or protein meals with a similar calorie content [31]. Peripheral PYY administration shows a decrease in food intake and body weight gain in rats [32]. In both lean and obese humans, intravenous injection of PYY reduces appetite and food intake [32, 33], suggesting that, unlike leptin, the sensitivity of PYY is preserved in obese subjects. PYY levels are found to be elevated in patients with gastrointestinal disorders including inflammatory bowel disease and steatorrhea [34, 35].

In addition to its effect on food intake, PYY may regulate energy expenditure [36, 37], delay gastric emptying, and reduce acid secretion [38, 39]. In obese subjects circulating PYY levels are low [33, 40], and PYY levels are reported to

be higher in patients with anorexia nervosa when compared with control subjects [41]. Studies of circulating levels of PYY in obese and lean people have yielded conflicting results [42, 43]. However a blunted postprandial rise in PYY is observed in obese people, which suggests its association with impaired satiety [39].

The anorectic effects of PYY (3–36) may be mediated centrally via a direct action in the ARC, through an indirect action involving the vagus and brainstem, or by a combination of both pathways. Peripheral administration of PYY (3–36) increases c-fos expression (a marker of neuronal activation) in the ARC, and direct injection of PYY (3–36) into the ARC inhibits food intake. This effect is most likely mediated through the Y2 receptor since the anorectic effect of peripheral PYY (3–36) administration is blocked in Y2 receptor-null mice and intra-arcuate injection of a Y2 receptor selective agonist also reduces food intake [32]. Although there have been conflicting results [44], the importance of vagal-brainstem signalling to the actions of PYY on food intake is suggested by observing that bilateral subdiaphragmatic vagotomy and brainstem-hypothalamic pathway transection abolish the anorectic effect of peripheral PYY (3–36) administration in rats [45, 46].

In contrast to peripheral and intra-arcuate PYY (3–36) administration, PYY (3–36) results in an increase in food intake when administered directly into the third ventricle of the brain [47] or directly into the paraventricular nucleus (PVN) [48]. This apparently confusing observation may be explained by considering that such effects might be endogenously mediated by the CNS-distributed peptide, NPY, through an action on Y1 receptor and Y5 receptors [49].

PYY may also act in areas of the brain other than the hypothalamus and brainstem. Batterham et al. [50] suggested that PYY (3–36) infusion modulates neural activity within corticolimbic and higher cortical brain using functional magnetic resonance imaging. Under conditions of high circulating PYY (3–36) designed to mimic the postprandial state, changes in neural activity within the caudolateral orbital frontal cortex predicted subsequent feeding behaviour. By contrast, hypothalamic activation correlated with food intake under conditions of low circulating PYY (3–36).

5.3. Pancreatic Polypeptide (PP). PP is secreted from PP cells in the pancreatic islets of Langerhans. PP appears to reduce food intake directly through the Y4 receptor in the brainstem and hypothalamus. The anorectic effects of PP are abolished by vagotomy in rodents, suggesting that PP may also act via the vagus nerve to reduce food intake [51]. Y4 receptor expression is found in the AP, NTS, DVN, ARC, and PVN [52]. An autoradiography study also identified saturable PP binding sites at the interpeduncular nucleus, AP, NTS, and DVN [53], thus suggesting the brainstem as the major site of action for PP. Like PYY, differential effects on food intake are observed following PP injection, depending on the route of administration. In contrast to the anorectic effects observed with peripheral PP administration, its central

administration stimulates food intake [54]. These differential effects may be explained by activation of distinct receptor populations, although the exact mechanism is not yet clear.

Circulating PP concentrations rise after a meal in proportion to the calorific load. Although reported differences in circulating levels of PP between lean and obese people have been conflicting [55, 56], some studies have demonstrated significantly reduced levels in obese subjects [57, 58]. Levels of PP are elevated after a test meal in anorexia [59]. Patients with Prader-Willi syndrome (PWS) have been reported to show reduced PP release both basally and postprandially when compared with age- and weight-matched control subjects [60].

The anorectic effects of PP have been demonstrated in a number of experimental models. In mice, acute and chronic peripheral administration of PP reduces food intake [47, 57]. In leptin-deficient *ob/ob* mice, repeated intraperitoneal injection of PP decreases body weight gain and ameliorates insulin resistance and hyperlipidaemia [51]. Furthermore, transgenic mice overexpressing PP are lean and demonstrate reduced food intake compared with wild-type controls [61]. In normal-weight human subjects, intravenous infusion of PP results in a 25% reduction in 24-h food intake [62]. Furthermore twice-daily infusion of PP in volunteers with PWS caused a 12% reduction in food intake [63].

5.4. Proglucagon-Derived Peptides. GLP-1, GLP-2, oxyntomodulin (OXM), and glucagon are proglucagon-derived peptides. Proglucagon is expressed in the pancreas, L-cells of the small intestine, and in the NTS of the brainstem [64, 65]. Glucagon is produced in the pancreas, whereas OXM, GLP-1, and GLP-2 are the major products in the brain and intestine [66].

5.5. Glucagon-Like Peptide-1. GLP-1 is cosecreted with PYY from L cells in the intestine in response to nutrient intake. Enzymatic degradation by DPPIV and renal clearance rapidly inactivate and remove GLP-1 from plasma circulation, respectively [67, 68], thus accounting for its short plasma half-life of 1-2 minutes [69]. GLP-1 has two biologically active forms, GLP-1 (7–37) and GLP-1 (7–36) amide, the latter being the major circulating form in humans [70]. GLP-1 exerts its effect at the GLP-1R to stimulate adenylyl cyclase activity and thereby cAMP production [71]. GLP-1R is widely distributed particularly in the brain, GI tract, and pancreas [71, 72]. Circulating GLP-1 levels rise after a meal and fall in the fasted state. Recent evidence also suggests that levels rise in anticipation of a meal [73]. GLP-1 reduces food intake, suppresses glucagon secretion, and delays gastric emptying [74]. Intravenous infusion of GLP-1 results in a dose-dependent reduction of food intake in both normal weight and obese subjects [75]; however obese subjects have a blunted postprandial GLP-1 response compared to lean subjects [71].

GLP-1 possesses a potent incretin effect in addition to its anorectic action; it stimulates insulin secretion in a glucose-dependent manner following ingestion of carbohydrate.

Continuous subcutaneous infusion of GLP-1 to patients with type 2 diabetes for 6 weeks reduces appetite, body weight and improves glycaemic control [76]. Exendin-4, a naturally occurring peptide from the saliva of the Gila monster lizard, is a DPPIV-resistant GLP-1R agonist [77]. Exendin-4 (exenatide, Byetta) has been approved for type 2 diabetes in conjunction with either metformin, a sulphonylurea, or both drugs. Twice-daily subcutaneous injection of exendin-4 to type 2 diabetes patients failing to achieve glycaemic control with maximal doses of metformin improves glycaemic control and decreases body weight [78]. Once-weekly subcutaneous injection of a long-acting exenatide preparation and once-daily subcutaneous injection of the GLP-1 analogue called liraglutide demonstrate greater improvements in glycaemic control than twice-daily exenatide administration [79, 80].

GLP-1 possesses trophic effects on pancreatic beta cells in animal models [81]. Most recently, GLP-1 and exendin-4 have been shown to promote cellular growth and reduce apoptosis in nervous tissues [82]. GLP-1 receptor stimulation has been shown to have neuroprotective effect in models of Parkinson's disease [83–85], Alzheimer's disease [86, 87], cerebrovascular stroke [85], and peripheral neuropathy [88]. Further work is needed to determine if GLP-1 analogues could be potential novel therapies for patients with these neurological and neurodegenerative diseases.

5.6. Glucagon-Like Peptide-2. GLP-2 is released from enteroendocrine cells in a nutrient-dependent manner, like GLP-1. Acute or chronic administration with GLP-2 has no effect on food intake in either rodents or humans [89, 90]. However, GLP-2 has an intestinal trophic effect [91, 92], and chronic subcutaneous administration of GLP-2 stimulates crypt cell proliferation. As such, GLP-2 analogues have been developed for use in patients with inflammatory bowel disease [93]. In addition, some studies have demonstrated a reduction in gastric emptying in humans by GLP-2, although the effect is not as potent as GLP-1 [94].

5.7. Oxyntomodulin. OXM is another product of the proglucagon gene and is released from L-cells of the intestine in response to ingested food and in proportion to caloric intake [95]. Administration of OXM reduces food intake and increases energy expenditure in both rodents and humans [96–98]. The anorectic effect of OXM is blocked by the GLP-1R antagonist exendin 9–39 [99] and is abolished in GLP-1R null mice [100]; this suggests that OXM mediates its effects via the GLP-1R. However OXM has relatively low *in vitro* affinity for the GLP-1R which is 50 fold lower than the affinity of GLP-1 for GLP1R. This raises the possibility that a further receptor through which OXM mediates its anorectic effect has yet to be identified. Indeed, several actions of OXM appear to be independent of the GLP-1R [97, 101, 102]. For example, the cardiovascular effects of OXM are preserved in GLP-1R knockout mice [101]. Like GLP-1, OXM is inactivated by DPPIV; hence OXM analogues resistant to DPPIV degradation are being developed as potential obesity treatments [103].

5.8. Ghrelin. Ghrelin is the only known orexigenic gut hormone and was identified as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R) in rat stomach [104]. Lower levels of ghrelin are also localized to the hypothalamic ARC. Levels of circulating ghrelin increase preprandially and fall rapidly in the postprandial period [105]. Both central and peripheral administrations of ghrelin increase food intake and body weight with a reduction in fat utilisation in rodents [106, 107]. In human, negative correlations between circulating ghrelin levels and body mass index are found. Fasting plasma levels of ghrelin are high in patients with anorexia nervosa [108] and in subjects with diet-induced weight loss [19]. By contrast, obese subjects display a less marked drop in plasma ghrelin after meal injection [109]. Plasma ghrelin levels are elevated in cachectic patients with heart failure as compared with noncachectic patients with heart failure and control subjects [110]. Furthermore elevated circulating ghrelin levels are observed in patients with PWS compared with individuals with nonsyndromic forms of obesity [111]. Dysregulation of ghrelin secretion is also implicated in the mechanism through which sleep disturbance contributes to obesity. Subjects with short sleep duration have elevated ghrelin levels, reduced leptin, and high body mass index compared with subjects with normal sleep duration [112].

Evidence suggests that ghrelin mediates its orexigenic action via stimulation of NPY/AgRP coexpressing neurons within the ARC of hypothalamus. Peripheral administration of ghrelin increases c-fos expression in ARC NPY/AgRP neurons [113], and ablation of both AgRP and NPY neurons completely abolishes the orexigenic effect of ghrelin [114]. Brainstem and vagus nerve may also contribute to the effects of ghrelin on food intake. Intracerebroventricular injection of ghrelin induces c-fos expression in NTS and AP [115]. GHS-R is expressed in the vagus nerve. Furthermore blockade of gastric vagal afferents in rats abolishes ghrelin-induced feeding and prevents the ghrelin-induced rise in c-fos expression within the ARC [116].

Ghrelin may promote food intake in part by enhancing the hedonic responses to food cues. The recent study by Malik et al. [117] using functional magnetic resonance imaging during exposure to food pictures revealed increased activation in the amygdala, orbitofrontal cortex, anterior insula, and striatum, during intravenous infusion of ghrelin. Furthermore the effects of ghrelin on the response of amygdala and orbitofrontal cortex were correlated with self-rated hunger ratings.

5.9. Cholecystokinin. CCK was the first gut hormone found to play a role in food intake [118]. CCK is secreted postprandially by the I cell of the small intestine into circulation [119], with a short plasma half-life of a few minutes. Plasma CCK levels rise within 15 minutes after meals [119]. CCK is reported to reduce food intake in human and rodents [119, 120]. There are two CCK receptor subtypes; CCK1 and CCK2 receptors, previously classified as CCK A and CCK B. The anorectic action of CCK appears to be mostly mediated via CCK1 receptors on the vagal nerve [121, 122]. CCK 1

and 2 receptors are widely distributed in brain including the brainstem and hypothalamus [123]. Intermittent prandial CCK infusion reduces meal size in rats but provokes a compensatory increase in meal frequency [124]. In addition, a 2-week continuous intraperitoneal infusion of CCK failed to suppress food intake at any time point [125].

5.10. Peripheral Adiposity Signals: Insulin and Leptin. Adiposity signals are involved in the long-term regulation of energy balance, while gut peptides modulate food intake on a meal-by-meal basis. Circulating levels of insulin and leptin are positively correlated with adipose tissue mass within the body and are implicated in the long-term regulation of energy balance. Insulin is synthesized in the β cells of the pancreas and secreted rapidly after a meal, with well-characterised hypoglycaemic effects [126]. However intracerebroventricular administration of insulin also results in a dose-dependent suppression of food intake and body weight gain in baboons and rodents [127, 128]. Insulin may therefore have an anorectic action in addition to its hypoglycaemic effects. Leptin is secreted by adipocytes with circulating levels proportional to fat mass [129] with a diurnal and pulsatile pattern, peaking at night [130]. Leptin administration alleviates the hyperphagia associated with congenital leptin deficiency. However obese subjects are resistant to leptin, which may account for its lack of effectiveness in such individuals [131, 132].

6. Conclusion

Obesity, the metabolic syndrome, and their associated risk factors of cardiovascular disease and diabetes mellitus are among the most important health issues facing modern economies regardless of geographical location. Recent work has revealed that energy homeostasis is maintained by an array of complex pathways. The presence of multiple, overlapping feeding mechanisms reflects the vital nature of feeding behaviour for survival. However these homeostatic feeding mechanisms may be viewed as maladaptive in obese individuals exposed to diets with a high calorific content. Several gut hormones are thought to play a role in the sustained weight loss observed following bypass surgery; hence mimicking bypass surgery by administration of gut hormone-derived therapies could offer a promising treatment for obesity. A further understanding of the pathogenesis of obesity and the role of gut hormones in appetite regulation is imperative.

Conflict of Interests

The authors declare that there is no conflict of interests.

References

- [1] A. E. Field, E. H. Coakley, A. Must et al., "Impact of overweight on the risk of developing common chronic diseases during a 10-year period," *Archives of Internal Medicine*, vol. 161, no. 13, pp. 1581–1586, 2001.

- [2] A. Must, J. Spadano, E. H. Coakley, A. E. Field, G. Colditz, and W. H. Dietz, "The disease burden associated with overweight and obesity," *Journal of the American Medical Association*, vol. 282, no. 16, pp. 1523–1529, 1999.
- [3] Y. Matsuzawa, T. Nakamura, M. Takahashi et al., "New criteria for 'obesity disease' in Japan," *Circulation Journal*, vol. 66, no. 11, pp. 987–992, 2002.
- [4] Y. Matsushita, Y. Takahashi, T. Mizoue, M. Inoue, M. Noda, and S. Tsugane, "Overweight and obesity trends among Japanese adults: a 10-year follow-up of the JPHC Study," *International Journal of Obesity*, vol. 32, no. 12, pp. 1861–1867, 2008.
- [5] E. F. Bailey, "A tasty morsel: the role of the dorsal vagal complex in the regulation of food intake and swallowing. Focus on "BDNF/TrkB signaling interacts with GABAergic system to inhibit rhythmic swallowing in the rat," by Bariohay et al," *American Journal of Physiology*, vol. 295, no. 4, pp. R1048–R1049, 2008.
- [6] J. F. Rehfeld, "The new biology of gastrointestinal hormones," *Physiological Reviews*, vol. 78, no. 4, pp. 1087–1108, 1998.
- [7] R. J. Phillips and T. L. Powley, "Gastric volume rather than nutrient content inhibits food intake," *American Journal of Physiology*, vol. 271, no. 3, pp. R766–R779, 1996.
- [8] C. K. Martin, D. E. Bellanger, K. K. Rau, S. Coulon, and F. L. Greenway, "Safety of the Ullorex oral intragastric balloon for the treatment of obesity," *Journal of Diabetes Science and Technology*, vol. 1, no. 40, pp. 574–581, 2007.
- [9] D. Rigaud, N. Trostler, R. Rozen, T. Vallot, and T. Apfelbaum, "Gastric distension, hunger and energy intake after balloon implantation in severe obesity," *International Journal of Obesity*, vol. 19, no. 7, pp. 489–495, 1995.
- [10] G. J. Schwartz, "The role of gastrointestinal vagal afferents in the control of food intake: current prospects," *Nutrition*, vol. 16, no. 10, pp. 866–873, 2000.
- [11] G. J. Schwartz, C. F. Salorio, C. Skoglund, and T. H. Moran, "Gut vagal afferent lesions increase meal size but do not block gastric preload-induced feeding suppression," *American Journal of Physiology*, vol. 276, no. 6, pp. R1623–R1629, 1999.
- [12] R. C. Spiller, I. F. Trotman, and B. E. Higgins, "The ileal brake—inhibition of jejunal motility after ileal fat perfusion in man," *Gut*, vol. 25, no. 4, pp. 365–374, 1984.
- [13] J. Wen, S. F. Phillips, M. G. Sarr, L. J. Kost, and J. J. Holst, "PYY and GLP-1 contribute to feedback inhibition from the canine ileum and colon," *American Journal of Physiology*, vol. 269, no. 6, pp. G945–G952, 1995.
- [14] S. Z. Yanovski and J. A. Yanovski, "Obesity," *New England Journal of Medicine*, vol. 346, no. 8, pp. 591–602, 2002.
- [15] R. E. Brolin, "Bariatric surgery and long-term control of morbid obesity," *Journal of the American Medical Association*, vol. 288, no. 22, pp. 2793–2796, 2002.
- [16] D. E. Cummings, J. Overduin, and K. E. Foster-Schubert, "Gastric bypass for obesity: mechanisms of weight loss and diabetes resolution," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 6, pp. 2608–2615, 2004.
- [17] J. A. Tadross and C. W. Le Roux, "The mechanisms of weight loss after bariatric surgery," *International Journal of Obesity*, vol. 33, no. 1, pp. S28–S32, 2009.
- [18] F. Favretti, D. Ashton, L. Busetto, G. Segato, and M. De Luca, "The gastric band: first-choice procedure for obesity surgery," *World Journal of Surgery*, vol. 33, no. 10, pp. 2039–2048, 2009.
- [19] D. E. Cummings, D. S. Weigle, R. Scott Frayo et al., "Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery," *New England Journal of Medicine*, vol. 346, no. 21, pp. 1623–1630, 2002.
- [20] J. Korner, W. Inabnet, G. Febres et al., "Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass," *International Journal of Obesity*, vol. 33, no. 7, pp. 786–795, 2009.
- [21] C. W. Le Roux, R. Welbourn, M. Werling et al., "Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass," *Annals of Surgery*, vol. 246, no. 5, pp. 780–785, 2007.
- [22] M. Bueter, C. Löwenstein, T. Olbers et al., "Gastric bypass increases energy expenditure in rats," *Gastroenterology*, vol. 138, no. 5, pp. 1845–1853.e1, 2010.
- [23] M. Laville and E. Disse, "Bariatric surgery for diabetes treatment: why should we go rapidly to surgery," *Diabetes and Metabolism*, vol. 35, no. 6, pp. 562–563, 2009.
- [24] G. Musso, R. Gambino, and M. Cassader, "Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded?" *Diabetes Care*, vol. 33, no. 10, pp. 2277–2284, 2010.
- [25] F. Bäckhed, H. Ding, T. Wang et al., "The gut microbiota as an environmental factor that regulates fat storage," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 44, pp. 15718–15723, 2004.
- [26] F. Bäckhed, J. K. Manchester, C. F. Semenkovich, and J. I. Gordon, "Mechanisms underlying the resistance to diet-induced obesity in germ-free mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 3, pp. 979–984, 2007.
- [27] P. D. Cani, E. Lecourt, E. M. Dewulf et al., "Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal," *American Journal of Clinical Nutrition*, vol. 90, no. 5, pp. 1236–1243, 2009.
- [28] K. Tatemoto and V. Mutt, "Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides," *Nature*, vol. 285, no. 5764, pp. 417–418, 1980.
- [29] S. Lin, D. Boey, and H. Herzog, "NPY and Y receptors: lessons from transgenic and knockout models," *Neuropeptides*, vol. 38, no. 4, pp. 189–200, 2004.
- [30] G. A. Eberlein, V. E. Eysselein, M. Schaeffer et al., "A new molecular form of PYY: structural characterization of human PYY(3-36) and PYY(1-36)," *Peptides*, vol. 10, no. 4, pp. 797–803, 1989.
- [31] T. E. Adrian, G. L. Ferri, and A. J. Bacarese-Hamilton, "Human distribution and release of a putative new gut hormone, peptide YY," *Gastroenterology*, vol. 89, no. 5, pp. 1070–1077, 1985.
- [32] R. L. Batterham, M. A. Cowley, C. J. Small et al., "Gut hormone PYY3-36 physiologically inhibits food intake," *Nature*, vol. 418, no. 6898, pp. 650–654, 2002.
- [33] R. L. Batterham, M. A. Cohen, S. M. Ellis et al., "Inhibition of food intake in obese subjects by peptide YY3-36," *New England Journal of Medicine*, vol. 349, no. 10, pp. 941–948, 2003.
- [34] T. E. Adrian, A. P. Savage, and A. J. Bacarese-Hamilton, "Peptide YY abnormalities in gastrointestinal diseases," *Gastroenterology*, vol. 90, no. 2, pp. 379–384, 1986.
- [35] P. J. Wahab, W. P. M. Hopman, and J. B. M. J. Jansen, "Basal and fat-stimulated plasma peptide YY levels in celiac disease," *Digestive Diseases and Sciences*, vol. 46, no. 11, pp. 2504–2509, 2001.

- [36] B. Sloth, J. J. Holst, A. Flint, N. T. Gregersen, and A. Astrup, "Effects of PYY₁₋₃₆ and PYY₃₋₃₆ on appetite, energy intake, energy expenditure, glucose and fat metabolism in obese and lean subjects," *American Journal of Physiology*, vol. 292, no. 4, pp. E1062–E1068, 2007.
- [37] D. Boey, S. Lin, R. F. Enriquez et al., "PYY transgenic mice are protected against diet-induced and genetic obesity," *Neuropeptides*, vol. 42, no. 1, pp. 19–30, 2008.
- [38] T. Talsania, Y. Anini, S. Siu, D. J. Drucker, and P. L. Brubaker, "Peripheral exendin-4 and peptide YY₃₋₃₆ synergistically reduce food intake through different mechanisms in mice," *Endocrinology*, vol. 146, no. 9, pp. 3748–3756, 2005.
- [39] D. Ashby and S. R. Bloom, "Recent progress in PYY research—an update report for 8th NPY meeting," *Peptides*, vol. 28, no. 2, pp. 198–202, 2007.
- [40] M. A. Bartolomé, M. Borque, J. Martinez-Sarmiento et al., "Peptide YY secretion in morbidly obese patients before and after vertical banded gastroplasty," *Obesity Surgery*, vol. 12, no. 3, pp. 324–327, 2002.
- [41] M. Misra, K. K. Miller, P. Tsai et al., "Elevated peptide YY levels in adolescent girls with anorexia nervosa," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 3, pp. 1027–1033, 2006.
- [42] B. J. Kim, O. D. Carlson, H. J. Jang, D. Elahi, C. Berry, and J. M. Egan, "Peptide YY is secreted after oral glucose administration in a gender-specific manner," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 12, pp. 6665–6671, 2005.
- [43] P. T. Pfluger, J. Kampe, T. R. Castaneda et al., "Effect of human body weight changes on circulating levels of peptide YY and peptide YY₃₋₃₆," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 2, pp. 583–588, 2007.
- [44] I. G. Halatchev and R. D. Cone, "Peripheral administration of PYY₃₋₃₆ produces conditioned taste aversion in mice," *Cell Metabolism*, vol. 1, no. 3, pp. 159–168, 2005.
- [45] C. R. Abbott, M. Monteiro, C. J. Small et al., "The inhibitory effects of peripheral administration of peptide YY 3-36 and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway," *Brain Research*, vol. 1044, no. 1, pp. 127–131, 2005.
- [46] S. Koda, Y. Date, N. Murakami et al., "The role of the vagal nerve in peripheral PYY₃₋₃₆-induced feeding reduction in rats," *Endocrinology*, vol. 146, no. 5, pp. 2369–2375, 2005.
- [47] J. E. Morley, A. S. Levine, M. Grace, and J. Kneip, "Peptide YY (PYY), a potent orexigenic agent," *Brain Research*, vol. 341, no. 1, pp. 200–203, 1985.
- [48] B. G. Stanley, D. R. Daniel, A. S. Chin, and S. F. Leibowitz, "Paraventricular nucleus injections of peptide YY and neuropeptide Y preferentially enhance carbohydrate ingestion," *Peptides*, vol. 6, no. 6, pp. 1205–1211, 1985.
- [49] A. Kanatani, S. Mashiko, N. Murai et al., "Role of the Y1 receptor in the regulation of neuropeptide Y-mediated feeding: comparison of wild-type, Y1 receptor-deficient, and Y5 receptor-deficient mice," *Endocrinology*, vol. 141, no. 3, pp. 1011–1016, 2000.
- [50] R. L. Batterham, D. H. Ffytche, J. M. Rosenthal et al., "PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans," *Nature*, vol. 450, no. 7166, pp. 106–109, 2007.
- [51] A. Asakawa, A. Inui, H. Yuzuriha et al., "Characterization of the effects of pancreatic polypeptide in the regulation of energy balance," *Gastroenterology*, vol. 124, no. 5, pp. 1325–1336, 2003.
- [52] R. M. C. Parker and H. Herzog, "Regional distribution of Y-receptor subtype mRNAs in rat brain," *European Journal of Neuroscience*, vol. 11, no. 4, pp. 1431–1448, 1999.
- [53] D. C. Whitcomb, I. L. Taylor, and S. R. Vigna, "Characterization of saturable binding sites for circulating pancreatic polypeptide in rat brain," *American Journal of Physiology*, vol. 259, no. 4, pp. G687–G691, 1990.
- [54] J. T. Clark, P. S. Kalra, W. R. Crowley, and S. P. Kalra, "Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats," *Endocrinology*, vol. 115, no. 1, pp. 427–429, 1984.
- [55] R. Jorde and P. G. Burhol, "Fasting and postprandial plasma pancreatic polypeptide (PP) levels in obesity," *International Journal of Obesity*, vol. 8, no. 5, pp. 393–397, 1984.
- [56] O. Wisen, H. Bjorvell, P. Cantor, C. Johansson, and E. Theodorsson, "Plasma concentrations of regulatory peptides in obesity following modified sham feeding (MSF) and a liquid test meal," *Regulatory Peptides*, vol. 39, no. 1, pp. 43–54, 1992.
- [57] B. Glaser, G. Zoghlin, K. Pienta, and A. I. Vinik, "Pancreatic polypeptide response to secretin in obesity: effects of glucose intolerance," *Hormone and Metabolic Research*, vol. 20, no. 5, pp. 288–292, 1988.
- [58] V. Lassmann, P. Vague, B. Vialettes, and M. C. Simon, "Low plasma levels of pancreatic polypeptide in obesity," *Diabetes*, vol. 29, no. 6, pp. 428–430, 1980.
- [59] A. M. Uhe, G. I. Szmukler, G. R. Collier, J. Hansky, K. O'Dea, and G. P. Young, "Potential regulators of feeding behavior in anorexia nervosa," *American Journal of Clinical Nutrition*, vol. 55, no. 1, pp. 28–32, 1992.
- [60] W. B. Zipf, T. M. O'Dorisio, S. Cataland, and K. Dixon, "Pancreatic polypeptide responses to protein meal challenges in obese but otherwise normal children and obese children with Prader-Willi syndrome," *Journal of Clinical Endocrinology and Metabolism*, vol. 57, no. 5, pp. 1074–1080, 1983.
- [61] N. Ueno, A. Inui, M. Iwamoto et al., "Decreased food intake and body weight in pancreatic polypeptide-overexpressing mice," *Gastroenterology*, vol. 117, no. 6, pp. 1427–1432, 1999.
- [62] R. L. Batterham, C. W. Le Roux, M. A. Cohen et al., "Pancreatic polypeptide reduces appetite and food intake in humans," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 8, pp. 3989–3992, 2003.
- [63] G. G. Berntson, W. B. Zipf, T. M. O'Dorisio, J. A. Hoffman, and R. E. Chance, "Pancreatic polypeptide infusions reduce food intake in Prader-Willi syndrome," *Peptides*, vol. 14, no. 3, pp. 497–503, 1993.
- [64] J. J. Holst, "On the physiology of GIP and GLP-1," *Hormone and Metabolic Research*, vol. 36, no. 11-12, pp. 747–754, 2004.
- [65] M. Tang-Christensen, N. Vrang, and P. J. Larsen, "Glucagon-like peptide containing pathways in the regulation of feeding behaviour," *International Journal of Obesity*, vol. 25, supplement 5, pp. S42–S47, 2001.
- [66] J. D. Tucker, S. Dhanvantari, and P. L. Brubaker, "Proglucagon processing in islet and intestinal cell lines," *Regulatory Peptides*, vol. 62, no. 1, pp. 29–35, 1996.
- [67] C. F. Deacon, "Circulation and degradation of GIP and GLP-1," *Hormone and Metabolic Research*, vol. 36, no. 11-12, pp. 761–765, 2004.
- [68] R. Mentlein, B. Gallwitz, and W. E. Schmidt, "Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum," *European Journal of Biochemistry*, vol. 214, no. 3, pp. 829–835, 1993.

- [69] T. Vilsbøll, H. Agersø, T. Krarup, and J. J. Holst, "Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 1, pp. 220–224, 2003.
- [70] C. Orskov, L. Rabenhøj, A. Wettergren, H. Kofod, and J. J. Holst, "Tissue and plasma concentrations of amidated and glycine-extended glucagon-like peptide I in humans," *Diabetes*, vol. 43, no. 4, pp. 535–539, 1994.
- [71] J. J. Holst, "The physiology of glucagon-like peptide 1," *Physiological Reviews*, vol. 87, no. 4, pp. 1409–1439, 2007.
- [72] E. Yamato, H. Ikegami, K. Takekawa et al., "Tissue-specific and glucose-dependent expression of receptor genes for glucagon and glucagon-like peptide-1 (GLP-1)," *Hormone and Metabolic Research*, vol. 29, no. 2, pp. 56–59, 1997.
- [73] T. P. Vahl, D. L. Drazen, R. J. Seeley, D. A. D'Alessio, and S. C. Woods, "Meal-anticipatory glucagon-like peptide-1 secretion in rats," *Endocrinology*, vol. 151, no. 2, pp. 569–575, 2010.
- [74] D. E. Cummings and J. Overduin, "Gastrointestinal regulation of food intake," *Journal of Clinical Investigation*, vol. 117, no. 1, pp. 13–23, 2007.
- [75] C. Verdich, A. Flint, J. P. Gutzwiller et al., "A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on Ad Libitum energy intake in humans," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 9, pp. 4382–4389, 2001.
- [76] M. Zander, S. Madsbad, J. L. Madsen, and J. J. Holst, "Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β -cell function in type 2 diabetes: a parallel-group study," *Lancet*, vol. 359, no. 9309, pp. 824–830, 2002.
- [77] J. Eng, W. A. Kleinman, L. Singh, G. Singh, and J. P. Raufman, "Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas," *Journal of Biological Chemistry*, vol. 267, no. 11, pp. 7402–7405, 1992.
- [78] R. A. DeFronzo, R. E. Ratner, J. Han, D. D. Kim, M. S. Fineman, and A. D. Baron, "Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2," *Diabetes Care*, vol. 28, no. 5, pp. 1092–1100, 2005.
- [79] D. J. Drucker, J. B. Buse, K. Taylor et al., "Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study," *The Lancet*, vol. 372, no. 9645, pp. 1240–1250, 2008.
- [80] J. B. Buse, J. Rosenstock, G. Sesti et al., "Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)," *The Lancet*, vol. 374, no. 9683, pp. 39–47, 2009.
- [81] J. M. Egan, A. Bulotta, H. Hui, and R. Perfetti, "GLP-1 receptor agonists are growth and differentiation factors for pancreatic islet beta cells," *Diabetes/Metabolism Research and Reviews*, vol. 19, no. 2, pp. 115–123, 2003.
- [82] A. Harkavyi and P. S. Whitton, "Glucagon-like peptide 1 receptor stimulation as a means of neuroprotection," *British Journal of Pharmacology*, vol. 159, no. 3, pp. 495–501, 2010.
- [83] A. Harkavyi, A. Abuirmeleh, R. Lever, A. E. Kingsbury, C. S. Biggs, and P. S. Whitton, "Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease," *Journal of Neuroinflammation*, vol. 5, article no. 19, 2008.
- [84] S. Kim, M. Moon, and S. Park, "Exendin-4 protects dopaminergic neurons by inhibition of microglial activation and matrix metalloproteinase-3 expression in an animal model of Parkinson's disease," *Journal of Endocrinology*, vol. 202, no. 3, pp. 431–439, 2009.
- [85] Y. Li, T. Perry, M. S. Kindy et al., "GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 4, pp. 1285–1290, 2009.
- [86] T. Perry, D. K. Lahiri, K. Sambamurti et al., "Glucagon-like peptide-1 decreases endogenous amyloid- β peptide ($A\beta$) levels and protects hippocampal neurons from death induced by $A\beta$ and iron," *Journal of Neuroscience Research*, vol. 72, no. 5, pp. 603–612, 2003.
- [87] T. A. Perry and N. H. Greig, "A new Alzheimer's disease interventional strategy: GLP-1," *Current Drug Targets*, vol. 5, no. 6, pp. 565–571, 2004.
- [88] T. Perry, H. W. Holloway, A. Weerasuriya et al., "Evidence of GLP-1-mediated neuroprotection in an animal model of pyridoxine-induced peripheral sensory neuropathy," *Experimental Neurology*, vol. 203, no. 2, pp. 293–301, 2007.
- [89] D. J. Drucker, "Glucagon-like peptide 2," *Trends in Endocrinology and Metabolism*, vol. 10, no. 4, pp. 153–156, 1999.
- [90] P. T. Schmidt, E. Näslund, P. Grybäck et al., "Peripheral administration of GLP-2 to humans has no effect on gastric emptying or satiety," *Regulatory Peptides*, vol. 116, no. 1–3, pp. 21–25, 2003.
- [91] D. J. Drucker, P. Ehrlich, S. L. Asa, and P. L. Brubaker, "Induction of intestinal epithelial proliferation by glucagon-like peptide 2," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 15, pp. 7911–7916, 1996.
- [92] K. Wallis, J. R. F. Walters, and A. Forbes, "Review article: glucagon-like peptide 2—current applications and future directions," *Alimentary Pharmacology and Therapeutics*, vol. 25, no. 4, pp. 365–372, 2007.
- [93] A. L. Buchman, S. Katz, J. C. Fang, C. N. Bernstein, and S. G. Abou-Assi, "Teduglutide, a novel mucosally active analog of glucagon-like peptide-2 (GLP-2) for the treatment of moderate to severe Crohn's disease," *Inflammatory Bowel Diseases*, vol. 16, no. 6, pp. 962–973, 2010.
- [94] C. F. Nagell, A. Wettergren, J. F. Pedersen, D. Mortensen, and J. J. Holst, "Glucagon-like peptide-2 inhibits antral emptying in man, but is not as potent as glucagon-like peptide-1," *Scandinavian Journal of Gastroenterology*, vol. 39, no. 4, pp. 353–358, 2004.
- [95] M. A. Ghatei, L. O. Utenthal, and N. D. Christofides, "Molecular forms of human enteroglucagon in tissue and plasma: plasma responses to nutrient stimuli in health and in disorders of the upper gastrointestinal tract," *Journal of Clinical Endocrinology and Metabolism*, vol. 57, no. 3, pp. 488–495, 1983.
- [96] M. A. Cohen, S. M. Ellis, C. W. Le Roux et al., "Oxyntomodulin suppresses appetite and reduces food intake in humans," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 10, pp. 4696–4701, 2003.
- [97] C. L. Dakin, I. Gunn, C. J. Small et al., "Oxyntomodulin inhibits food intake in the rat," *Endocrinology*, vol. 142, no. 10, pp. 4244–4250, 2001.
- [98] K. Wynne, A. J. Park, C. J. Small et al., "Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised

- controlled trial," *International Journal of Obesity*, vol. 30, no. 12, pp. 1729–1736, 2006.
- [99] C. L. Dakin, C. J. Small, R. L. Batterham et al., "Peripheral oxyntomodulin reduces food intake and body weight gain in rats," *Endocrinology*, vol. 145, no. 6, pp. 2687–2695, 2004.
- [100] L. L. Baggio, Q. Huang, T. J. Brown, and D. J. Drucker, "Oxyntomodulin and glucagon-like peptide-1 differentially regulate murine food intake and energy expenditure," *Gastroenterology*, vol. 127, no. 2, pp. 546–558, 2004.
- [101] G. L. Sowden, D. J. Drucker, D. Weinschenker, and S. J. Swoap, "Oxyntomodulin increases intrinsic heart rate in mice independent of the glucagon-like peptide-1 receptor," *American Journal of Physiology*, vol. 292, no. 2, pp. R962–R970, 2007.
- [102] K. Ban, K. H. Kim, C. K. Cho et al., "Glucagon-Like Peptide (GLP)-1(9-36)amide-mediated cytoprotection is blocked by exendin(9-39) yet does not require the known GLP-1 receptor," *Endocrinology*, vol. 151, no. 4, pp. 1520–1531, 2010.
- [103] M. R. Druce, J. S. Minnion, B. C. T. Field et al., "Investigation of structure-activity relationships of oxyntomodulin (Oxm) using oxm analogs," *Endocrinology*, vol. 150, no. 4, pp. 1712–1721, 2009.
- [104] M. Kojima, H. Hosoda, Y. Date, M. Nakazato, H. Matsuo, and K. Kangawa, "Ghrelin is a growth-hormone-releasing acylated peptide from stomach," *Nature*, vol. 402, no. 6762, pp. 656–660, 1999.
- [105] D. E. Cummings, J. Q. Purnell, R. S. Frayo, K. Schmidova, B. E. Wisse, and D. S. Weigle, "A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans," *Diabetes*, vol. 50, no. 8, pp. 1714–1719, 2001.
- [106] M. Nakazato, N. Murakami, Y. Date et al., "A role for ghrelin in the central regulation of feeding," *Nature*, vol. 409, no. 6817, pp. 194–198, 2001.
- [107] M. Tschöp, D. L. Smiley, and M. L. Heiman, "Ghrelin induces adiposity in rodents," *Nature*, vol. 407, no. 6806, pp. 908–913, 2000.
- [108] B. Otto, U. Cuntz, E. Fruehauf et al., "Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa," *European Journal of Endocrinology*, vol. 145, no. 5, pp. 669–673, 2001.
- [109] C. W. Le Roux, M. Patterson, R. P. Vincent, C. Hunt, M. A. Ghatei, and S. R. Bloom, "Postprandial plasma ghrelin is suppressed proportional to meal calorie content in normal-weight but not obese subjects," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 2, pp. 1068–1071, 2005.
- [110] N. Nagaya, M. Uematsu, M. Kojima et al., "Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors," *Circulation*, vol. 104, no. 17, pp. 2034–2038, 2001.
- [111] D. E. Cummings, K. Clement, J. Q. Purnell et al., "Elevated plasma ghrelin levels in Prader-Willi syndrome," *Nature Medicine*, vol. 8, no. 7, pp. 643–644, 2002.
- [112] S. Taheri, L. Lin, D. Austin, T. Young, and E. Mignot, "Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index," *PLoS Medicine*, vol. 1, article e62, 2004.
- [113] L. Wang, D. H. Saint-Pierre, and Y. Taché, "Peripheral ghrelin selectively increases Fos expression in neuropeptide Y—synthesizing neurons in mouse hypothalamic arcuate nucleus," *Neuroscience Letters*, vol. 325, no. 1, pp. 47–51, 2002.
- [114] H. Y. Chen, M. E. Trumbauer, A. S. Chen et al., "Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein," *Endocrinology*, vol. 145, no. 9, pp. 2607–2612, 2004.
- [115] C. B. Lawrence, A. C. Snape, F. M. H. Baudoin, and S. M. Luckman, "Acute central ghrelin and GH secretagogues induce feeding and activate brain appetite centers," *Endocrinology*, vol. 143, no. 1, pp. 155–162, 2002.
- [116] Y. Date, N. Murakami, K. Toshinai et al., "The role of the gastric afferent vagal nerve in Ghrelin-induced feeding and growth hormone secretion in rats," *Gastroenterology*, vol. 123, no. 4, pp. 1120–1128, 2002.
- [117] S. Malik, F. McGlone, D. Bedrossian, and A. Dagher, "Ghrelin modulates brain activity in areas that control appetitive behavior," *Cell Metabolism*, vol. 7, no. 5, pp. 400–409, 2008.
- [118] J. Gibbs, R. C. Young, and G. P. Smith, "Cholecystokinin decreases food intake in rats," *Journal of Comparative and Physiological Psychology*, vol. 84, no. 3, pp. 488–495, 1973.
- [119] R. A. Liddle, I. D. Goldfine, and M. S. Rosen, "Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction," *Journal of Clinical Investigation*, vol. 75, no. 4, pp. 1144–1152, 1985.
- [120] H. R. Kissileff, F. X. Pi-Sunyer, J. Thornton, and G. P. Smith, "C-terminal octapeptide of cholecystokinin decreases food intake in man," *American Journal of Clinical Nutrition*, vol. 34, no. 2, pp. 154–160, 1981.
- [121] T. H. Moran, A. R. Baldessarini, C. F. Salorio, T. Lowery, and G. J. Schwartz, "Vagal afferent and efferent contributions to the inhibition of food intake by cholecystokinin," *American Journal of Physiology*, vol. 272, no. 4, pp. R1245–R1251, 1997.
- [122] T. H. Moran, L. F. Katz, C. R. Plata-Salaman, and G. J. Schwartz, "Disordered food intake and obesity in rats lacking cholecystokinin A receptors," *American Journal of Physiology*, vol. 274, no. 3, pp. R618–R625, 1998.
- [123] S. A. Wank, "Cholecystokinin receptors," *American Journal of Physiology*, vol. 269, no. 5, pp. G628–G646, 1995.
- [124] D. B. West, D. Fey, and S. C. Woods, "Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats," *The American journal of physiology*, vol. 246, no. 5, pp. R776–R787, 1984.
- [125] J. N. Crawley and M. C. Beinfeld, "Rapid development of tolerance to the behavioural actions of cholecystokinin," *Nature*, vol. 302, no. 5910, pp. 703–706, 1983.
- [126] K. S. Polonsky, B. D. Given, and E. Van Cauter, "Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects," *Journal of Clinical Investigation*, vol. 81, no. 2, pp. 442–448, 1988.
- [127] E. L. Air, S. C. Benoit, K. A. Blake Smith, D. J. Clegg, and S. C. Woods, "Acute third ventricular administration of insulin decreases food intake in two paradigms," *Pharmacology Biochemistry and Behavior*, vol. 72, no. 1-2, pp. 423–429, 2002.
- [128] D. Porte Jr. and S. C. Woods, "Regulation of food intake and body weight by insulin," *Diabetologia*, vol. 20, pp. 274–280, 1981.
- [129] R. V. Considine, M. K. Sinha, M. L. Heiman et al., "Serum immunoreactive-leptin concentrations in normal-weight and obese humans," *New England Journal of Medicine*, vol. 334, no. 5, pp. 292–295, 1996.
- [130] M. F. Saad, M. G. Riad-Gabriel, A. Khan et al., "Diurnal and ultradian rhythmicity of plasma leptin: effects of gender and adiposity," *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 2, pp. 453–459, 1998.
- [131] I. S. Farooqi, S. A. Jebb, G. Langmack et al., "Effects of recombinant leptin therapy in a child with congenital leptin

deficiency,” *New England Journal of Medicine*, vol. 341, no. 12, pp. 879–884, 1999.

- [132] P. M. J. Zelissen, K. Stenlof, M. E. J. Lean et al., “Effect of three treatment schedules of recombinant methionyl human leptin on body weight in obese adults: a randomized, placebo-controlled trial,” *Diabetes, Obesity and Metabolism*, vol. 7, no. 6, pp. 755–761, 2005.