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PERIPHERAL MECHANISMS IN APPETITE REGULATION

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Abstract

Peripheral mechanisms in appetite regulation include the motor functions of the stomach, such as the rate of emptying and accommodation, which convey symptoms of satiation to the brain. The rich repertoire of peripherally released peptides and hormones provides feedback from the arrival of nutrients in different regions of the gut from where they are released to exert effects on satiation, or regulate metabolism through their incretin effects. Ultimately, these peripheral factors provide input to the highly organized hypothalamic circuitry and vagal complex of nuclei to determine cessation of energy intake during meal ingestion, and the return of appetite and hunger after fasting. Understanding these mechanisms is key to the physiological control of feeding and the derangements that occur in obesity and their restoration with treatment (as demonstrated by the effects of bariatric surgery).

Keywords

satiation; satiety; stomach; neurohormonal

INTRODUCTION

The objectives are to review the control of gastric motility and digestion; the gastrointestinal mechanisms controlling appetite including gut-brain communication, the effects of peripherally-released peptides and hormones on hypothalamic and brainstem control; and the effects of macronutrients on the functions associated with appetite and gastric functions.

Definitions of Satiation and Satiety

Satiation refers to the postprandial feeling of fullness that may be one of pleasure or distress and manifests other symptoms such as fullness, nausea or bloating. Operationally, satiation

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can be defined as the maximum tolerated volume of a liquid nutrient meal, and by intra- and postprandial symptoms experienced with the challenge.

Satiety reflects the appetite to ingest meals, and it may be operationally defined by the kilocalories ingested at a subsequent *ad libitum* buffet meal after a standard period of fasting or a specified time from a prior standard meal, typically ingested 4 hours previously (e.g., a 300kcal meal). It is relevant to distinguish these two terms, as satiation reflects the early postprandial experience, whereas satiety reflects the appetite to ingest food at a subsequent meal after a period of fasting.

Since obesity results from the imbalance between energy consumed and expended, postprandial satiation and satiety are critically relevant to the development of obesity.

Gastric Motility and Phases of Digestion

Gastric motility is critically involved in the cephalic, gastric and enteric phases of digestion; these functions are integrated.

Taste and other visceral sensations project into the nucleus of the solitary tract (NTS). The NTS is a sensory complex linked through the action of neurons secreting acetylcholine (Ach), neuropeptide Y (NPY) and thyrotrophin-releasing hormone (TRH) to the dorsal motor nucleus of the vagus (DMV) in the brainstem to activate the processes of digestion. The vagus nerve is the major mediator of the cephalic phase of gastric motility and digestion, and the main neurotransmitter is acetylcholine. Cholecystokinin (CCK) and gastrin are additional modulators that control a coordinated digestive response, including gastric acid and pepsin secretion, gastric motility and emptying, and integrated pancreatico-biliary secretion. Descending projections from higher senses, such as olfaction and vision, and from the forebrain also modulate these brainstem reflexes.

It is estimated that the cephalically-stimulated motor and secretory activities in the upper and mid-gut contribute >50% of the overall postprandial response.[1] Food ingestion releases gastrointestinal hormones and activates gastrointestinal motility, gastric and pancreatico-biliary secretion and absorption (Fig. 1). Gastrin, CCK, glucose-dependent insulinotropic peptide (GIP), ghrelin, gastric leptin and pancreatic polypeptide are secreted from the upper gut. Incretins such as GLP-1, peptide YY and oxyntomodulin, which are secreted from the proximal and distal small intestine, generally inhibit the cephalic phase mediated through the vagus nerve. Upper gut-derived hormones, such as CCK and GIP, also inhibit gastric motility by relaxing the fundus and antrum or stimulating pyloric contraction to inhibit gastric emptying. This results in slowing of meal digestion, and induction of satiation resulting in reduced ingestion of calories.

Role of Gastric Motor Functions in Postprandial Symptoms

There has been little attention to the role of gastric motor functions and development of postprandial symptoms in obesity.[2] However, a vast literature based on hundreds of patients with dyspepsia convincingly shows that gastric motor functions (such as emptying and accommodation) and gastric sensation are important determinants of intraprandial and postprandial symptoms.[3] Moreover, the proportion of fats with at least 12-carbon chain

length influences satiation in health and dyspepsia.[4] In obese individuals, apart from BMI, age and gender, the following factors contribute to postprandial symptoms: smaller fasting or postprandial gastric volume, accelerated gastric emptying at 1 hour and delayed gastric emptying at 4 hours.[5] The univariate association of postprandial gastric volume with symptoms is not independent of the fasting gastric volume. However, these data support the notion that gastric motor functions are important predictors of the sensation of fullness or satiation and may determine the individual's choice to stop ingesting food. The relevance of these factors is demonstrated by the effects of sleeve gastrectomy on appetite and weight loss (discussed below).

GUT-BRAIN COMMUNICATION

The *vagal nuclei and the vagus nerve* innervate most of the gastrointestinal tract involved in energy intake, satiation and digestion.[6] Vagal afferents are stimulated directly by change in viscus tension when food, or later chyme, passes through the gut gastrointestinal tract, and indirectly by chemical stimuli activating taste receptors (see below) releasing peptides from mucosal enteroendocrine cells. Some of these peptides act on vagal or other pathways to induce appetite (an orexigenic effect, e.g. ghrelin) whereas others (e.g. gastric leptin, CCK, GLP-1 or PYY) induce satiety – an anorexigenic effect.

Circulating nutrients, reflecting levels of nutrients in the periphery, influence brainstem nuclei after being sensed in the area postrema in the floor of the 4th ventricle, where there is a thin blood brain barrier.[7] In response, the brain stem controls the enteric nervous system,[8,9] modulating upper gut function or signalling to the hypothalamic circuits to reduce calorie intake. On the other hand, partial vagotomy or total sub-diaphragmatic vagotomy or intermittent vagal nerve electrical stimulation to inhibit vagal function in humans[10] decreases food intake and induces early satiety and weight loss, possibly by reducing gastric emptying and inducing satiation.

MECHANISMS REGULATING APPETITE

Several interacting control mechanisms (Fig. 2) that involve peripherally-released mediators are involved in the regulation of appetite.[6]

A. Hypothalamic and Brainstem Mechanisms

Hypothalamic circuits involve several peptide receptors that control appetite and food intake. These mechanisms include cannabinoid (CB1),[11] neuropeptide Y (NPY), pro-opiomelanocortin (POMC), melanin-concentrating hormone (MCH), α-melanocyte stimulating hormone (α-MSH), agouti-related peptide (AgRP), cocaine- and amphetamine-regulated transcript (CART), cholecystokinin (CCK), and glucagon-like peptide 1 (GLP-1) (Figs. 1 and 2).

Neural pathways link the hypothalamic nuclei to higher centers (that produce food reward or feeling of well-being) and to the brainstem nuclei. Through the brainstem nuclei, such as the NTS and DMV, the hypothalamus can slow gastric emptying by stimulating vagal fibers that

activate intramural gastric nitrergic neurons to decrease gastric motility,[12,13] retard gastric emptying, and, as a consequence, decrease calorie consumption.[14–16]

The precise pathways and centers involved in reward appear to involve NPY and dopaminergic receptors,[17] and eating for reward value is a primitive behavior observed in species such as *Drosophila*.[18]

Preliminary data in humans using MRI with pulsed arterial spin labeling (PASL) in response to a nutrient drink (Ensure ®) show that the sensation of satiation is associated with decreased cerebral blood flow (CBF) in the hypothalamus compared to a control brain region (posterior frontal cortex); using repeat measurements at 15-minute intervals, hypothalamic PASL MRI signal decreased significantly after ingesting the maximum tolerated volume (MTV) of the liquid meal, and this decreased signal persisted 30 minutes later.[19] The effect of nutrients in Ensure® may reflect the greater reduction in CBF in the hypothalamus to the monosaccharide glucose compared to fructose ingestion,[20] as well as increased functional connectivity between the hypothalamus and the thalamus and striatum with glucose, and increased connectivity between the hypothalamus and thalamus, but not the striatum, with fructose. In another study, blood oxygenation level dependent (BOLD) signal in the cortical control areas increased during glucose and decreased during fructose infusion.[21] The significance of these findings is unclear; however, fructose ingestion was associated with smaller increase in systemic glucose, insulin, and GLP-1 levels than glucose ingestion.[20] The time course of changes in hypothalamic and brainstem fluctuations in BOLD signal on functional MRI in response to sucrose (combination of glucose and fructose) is consistent with a rapid, vagally-mediated mechanism due to nutrient absorption, rather than sweet taste receptor activation.[22]

Gastrointestinal hormones including leptin, cholecystokinin, PYY, oxyntomodulin (OXM), and GLP-1 may affect nuclei in the hypothalamus and brainstem where the blood brain barrier allows direct interaction between these hormones with the nuclei, just as described above for nutrients. The circulating peptides inhibit the AgRP/NPY pathway in the arcuate nucleus of the hypothalamus thereby reducing appetite and stimulate the pro-opiomelanocortin / α-melanocyte stimulation hormone (POMC/αMSH) pathway thereby increasing satiety and indirectly reducing appetite (Figs. 2 and 3).[23]

B. Taste Receptors for Sweet or Amino Acids (umami)

Similarities between the chemosensory machinery in neuroepithelial taste receptor cells of the tongue and the molecular transducers localized in enteroendocrine cells in the gut that sense the chemical composition of the luminal contents of the gut[24] led to the concept of non-lingual taste receptors. Molecular sensing by gastrointestinal cells controls multiple fundamental functions in digestion and initiates hormonal and/or afferent neural (predominantly vagal) pathways leading to satiation, the regulation of caloric intake, pancreatic insulin secretion, and changes in metabolism. For example, glucose-sensing by gut enteroendocrine cells results in the release of incretin peptides, activation of vagal afferents and glucose homeostasis. Vagal afferent nerve terminals in the intestinal mucosa express receptors for a number of different regulatory peptides and neurotransmitters, including those released by glucose (GLP-1, GLP-2, 5-HT).

There are three distinct subunits of the G protein coupled taste receptors, T1Rs. These form heterodimers that mediate either sweet taste (T1R2 and T1R3) or sense amino acids or umami (T1R1 and T1R3). The subunits of T1R2 and T1R3, as well as other elements of the sweet taste transduction pathway found in the lingual epithelium including Gα-gustducin, are expressed in intestinal enteroendocrine cells. Gα-gustducin is co-localized in enteroendocrine cells that express PYY in the colon or GLP-1 and 5-HT in the small intestine. T1Rs upregulate the sodium-coupled transporters, SGLT-1 and GLUT2, in the intestinal epithelium in response to glucose, and T1Rs also regulate GLP-1 secretion. The T1R system has broad specificity for sweet sensing and can be activated by natural sugars, sweet proteins and artificial sweeteners.[25] There are also fat-sensing receptors, FFAR1 and GPR120, in enteroendocrine cells,[26] and the receptors sense both medium- and long-chain fatty acids.[27,28] Binding of basic tastants (sweet, bitter, umami, or fat) initiates second-messenger cascades that result in the release of peptides or neurotransmitters (e.g., ghrelin, CCK, GLP-1, PYY), resulting in physiological events. Each receptor is coupled to distinct gustatory G proteins; gustducin is the most common taste G protein.[27,28] Gut endocrine cells may also detect microbiota, as they also express toll-like receptor molecules that recognize bacterial breakdown products.[25]

C. Gut Peptidergic and Hormonal Control of the Response to Feeding and Satiation

Ingested nutrients and their digestion products initiate local actions in the upper gut, producing signals that initiate digestion and absorption. Other signals lead to the feeling of satiation, either directly or indirectly through effects on gastric function, and lead to meal termination. Even during ingestion of the meal, gastric emptying of liquids results in the rapid delivery of nutrients into the intestine. Gastric and duodenal vagal afferents are stimulated by the mechanical, chemical and osmotic effects of ingested nutrients, stimulating the release of a variety of peptides and hormones,[29] which mediate or modulate digestion, sensation after feeding and appetite.[30]

Following is a brief summary of the main effects of the predominant hormones or peptides on food intake or appetite. Ghrelin is an orexigen that is important in short-term food intake; in contrast, leptin (gastric) is a minor orexigen, and obestatin is a peptide encoded by the ghrelin gene that opposes ghrelin's effects on food intake, delays gastric emptying and inhibits jejunal motility.[31] CCK is a major mediator of satiation, providing negative feedback to the stomach (delaying emptying, at least in part by fundic relaxation and antral inhibition). GLP-1 is an incretin that modulates glucose control and provides similar negative feedback to the stomach. Peptide YY is involved in appetite control, the ileal brake, and negative feedback to the stomach. Table 1 expands on this summary, reviewing the role of gastrointestinal peptides and hormones released in response to feeding and their potential physiological effects of relevance to satiation or satiety in humans.[32–112]

Adiposity- and Glycemia-related Hormones—Insulin from the pancreatic β cells and leptin from white adipocytes (as well as the stomach and other tissues) are each secreted in direct proportion to body fat. Both hormones are transported through the blood-brain barrier[113,114] and access neurons in the hypothalamus and other regions of the brain to influence energy homeostasis. In contrast to satiation signals, which primarily influence

calories eaten during individual meals, adiposity signals are more directly related to how much fat the body carries and maintains. Insulin systemically elicits hypoglycemia, which increases food intake. In obesity, there is insulin and leptin resistance; thus, more of each hormone is required to achieve the same physiological effect when compared to lean individuals.

EFFECTS OF MEAL PROPERTIES ON FOOD INTAKE, SATIETY, AND SATIATION

The nutrient content of a meal influences the rate of emptying from the stomach. For example, the maximum emptying rate of liquid food from the stomach is ~200 kcal/hour.[115] Compared to calorie density, the volume, carbohydrate and protein content of the meal have minor effects on the rate of gastric emptying, whereas fat has a major effect. CCK-mediated reflexes are activated by chylomicrons or by fatty acids with at least 12-carbon chain lengths in the upper small intestine and result in inhibition of antral motility,[116] thereby retarding gastric emptying. The energy density, meal volume and physical properties of a meal influence food intake, satiety and satiation, predominantly through effects on gastric emptying. The next section addresses the role of macronutrient content of food in food intake.

Does Macronutrient Class Influence Gastric or Pancreatic Function, or Food Intake?

Several studies have addressed whether intake of nutrients results in adaptation of gastric functions and satiation mechanisms. The adaptation of these mechanisms to different nutrients has been tested by means of nutrient “preloads”, typically for a two-week period. In these studies, calories in a macronutrient class were given in excess of caloric needs, and the effects on gastric or pancreatic function were assessed. Whereas, such studies can be done in animals with 90% or 100% of the calories designated in a certain class,[117] there are limitations to the degree of enrichment with a specific macronutrient class in diets ingested by humans. Hence, animal data are less relevant to the human situation.

Carbohydrate tends to reduce pancreatic enzyme output, and *fat* has the greatest potential to perturb digestive functions including interdigestive and postprandial outputs of pancreatic enzymes[118] and gastric emptying.

Nutrient preloads of *four different classes of macronutrients* (protein, carbohydrate, fat or mixed/balanced) did not significantly affect satiation, appetite (food ingested at an *ad libitum* meal) and gastric emptying.[119,120] These studies were conducted in 10 male, normal weight healthy volunteers[119] and in 52 healthy normal-weight, overweight, or obese participants (14 males, 38 females with BMI 19.4–47.0 kg/m^2).[119,120] However, nutrient pre-load with a *high-fat* diet (4800kcal) increased hunger ratings during duodenal lipid infusion compared with the same infusion after a lower fat (2670kcal) diet.[121] In contrast, a more physiological, *balanced nutrient*, orally administered meal (Ensure®) was associated with very similar postprandial gastric volumes after the four diets enriched with a specific macronutrient class.[120]

Carbohydrate influence on appetite was elucidated in classical studies.[122] Compared with soup that was not supplemented with carbohydrate, Blundell et al. found that carbohydrate supplemented soup significantly reduced subjective hunger and subsequent food intake by an amount that compensated for the higher carbohydrate content of the supplemented soup. Such studies provided evidence for the physiological regulation of short-term appetite by carbohydrates.

The effects of different fat molecules (i.e., MCFA, LCFA, saturated and unsaturated FA, as well as omega-3 FAs) are summarized in Table 2.[123–130]

The influence of *protein and amino acid* on the control of food intake remains incompletely understood. In studies performed in normal weight and obese people, food intake enriched with 500kcal protein for two weeks, had no demonstrable effect on gastric motor function, satiation or satiety.[120] The potential for oral protein and duodenal fat to influence satiety was evaluated in healthy volunteers[131] who were studied in a randomized, double-blind, four-period, cross-over design. An oral protein preload significantly reduced caloric intake (mean 19%). Simultaneous administration of an oral protein preload and intraduodenal fat did not result in a synergistic effect with respect to reduced caloric consumption.

However, after oral protein ingestion, only small quantities of intact proteins enter the duodenum because of the extensive intragastric digestion and, therefore, the total impact of protein intake on appetite may not be fully appreciated with oral protein supplement. Indeed, intraduodenal administration of protein results in higher CCK and GLP-1 levels, and reduced kcal intake at an ad libitum meal compared to oral protein administration, with greater effects observed in obese than in lean male volunteers.[132]

Potential Role of Functional Foods in Dietary Intake and Appetite

Functional foods are foods that, in addition to providing essential nutrients including proteins, carbohydrates, fats and vitamins, also improve the general well-being or health status; examples are fermented milk and orange juices.[133] Polyphenols are example of natural products that may provide health benefits and are widely present in plants and are ingested daily with food. Not all polyphenols and related compounds are absorbed in the small intestine; some of them reach the large intestine where they undergo metabolic transformation by the colonic microbiota.[134] Among the different functional foods and extracts, polyphenols seem to be yielding the most promising results on dietary intake or metabolic effects associated with obesity. Polyphenols reduce metabolic disturbances such as hyperglycemia, insulin resistance, and hyperleptinemia,[135,136] and they directly modulate neuropeptides involved in appetite regulation (reviewed by Panickar[137]). Polyphenols can cross the blood-brain barrier, and they reduced body weight and fat mass in rodent models of obesity, along with suppressing hypothalamic neuropeptide Y levels.[138,139] Clinical trials in humans point to beneficial effects of some polyphenol-rich foods (such as tea containing catechins, apple juice, cocoa, red berries, other fruits, and resveratrol in red wine) in the management of body fat.[140] Polyphenols may influence the composition of the gut microbiota, for example consumption of blueberry[141] and grape[142] juices, and red wine or gin[143] generally increased *Bifidobacterium spp*. in fecal samples from human volunteers.

DYSREGULATION OF GASTRIC FUNCTION, SATIETY, AND SATIATION MECHANISMS IN OBESITY

Comparisons of gastric emptying in normal weight and obese persons have shown inconsistent results with rapid, normal or slow gastric emptying (reviewed in ref. 144).

Autopsy studies in obese subjects showed that some intraabdominal organs such as the liver, small intestine and pancreas are heavier than in normal weight individuals.[145] Other studies showed wide variation of stomach size with no significant relationship to body weight.[146] Obese subjects have been shown to choose more food and to consume more food per minute than non-obese subjects.[147] Obese people with binge eating disorder also demonstrate greater motor impulsivity,[148] choosing small, immediately available rewards over larger, delayed rewards and/or the inclination to respond rapidly without forethought and/or attention to consequences.[149] Gastric capacity was larger in obese persons with binge eating disorder when tested with an intragastric latex balloon filled with water.[150,151] Other studies using the barostat or imaging (SPECT) techniques reported no differences in gastric volume or compliance between obese and lean subjects.[152,153]

However, all these reports are based on relatively small numbers of patients (<40). Recent studies in a prospective cohort of 328 participants across the spectrum of BMI from normal weight to class II or III obesity show that obesity is associated with higher fasting gastric volume, accelerated gastric emptying of solids and liquids, lower postprandial PYY, and higher postprandial GLP-1 levels (the latter being consistent with the accelerated gastric emptying of nutrients).[154] Obesity was also associated delayed satiation manifested as larger volume of liquid nutrient ingested at a steady state to induce fullness,[154] and larger maximum tolerated volume;[155] also, the total caloric intake at an *ad libitum meal* was greater in people with abnormal (high) waist circumference.[154]

Fasting gastric volume influences intraprandial satiation, and the rate of gastric emptying also influences postprandial fullness.[156,157] Principal components analysis identified latent dimensions accounting for ~81% of overweight-obesity variation, including satiety/satiation (21%), gastric motility (14%), psychological (13%), and gastric sensorimotor (11%). These observations suggest that quantitative traits of satiation, satiety and gastric functions are associated with higher BMI.[154]

LESSONS FROM EFFECTS OF BARIATRIC SURGERY ON GUT HORMONES, APPETITE, AND WEIGHT LOSS

The most commonly performed bariatric procedures for obesity are illustrated schematically in Figure 4. The impact of gastric volume on weight loss and dietary intake is illustrated by the success of vertical sleeve gastrectomy in inducing weight loss. In fact, in the absence of any direct effect on absorptive mechanisms [as would occur following Roux-en-Y gastric bypass (RYGB) or biliopancreatic diversion],[158] the restriction of gastric volume results in comparable 5-year outcomes of percent excess weight loss, daily energy intake, as well as the proportion of energy from carbohydrates, protein, and fat with vertical sleeve gastrectomy and RYGB.[159] The impact of restriction in gastric volume on dietary intake is

demonstrated by the observation in an adjusted multivariate regression model that energy intake and lipid intake independently predicted deficiency of vitamin D (based on plasma vitamin 25hydroxy-D levels) in the same study.[159] Clearly, other adaptive responses are also stimulated by the sleeve gastrectomy, and restoration of glycemic control is comparable to that of RYGB,[160] and recent data suggest an important activation of the farnesoid X receptor pathway in the small bowel.[161]

The main changes in gut hormones after bariatric surgery affect ghrelin, leptin, GLP-1 and PYY.[74] The lack of significant changes in these gut hormones and the modest restriction of overall gastric volume with banding gastroplasty are likely explanations for the lower weight loss documented in the long term with banding gastroplasty compared with the other restrictive or malabsorptive procedures.[162]

Initial studies suggested that **ghrelin** levels were much reduced after RYGB,[163] since the part of the stomach that secretes this hormone is removed; weight loss and appetite loss were partly attributed to the reduced plasma levels of ghrelin. Subsequent studies showed increased ghrelin after RYGB,[164] and that signaling of ghrelin which induces hunger may be attenuated in vagotomized patients.[164] Thus, the role of ghrelin in appetite control has not been clarified by experience in patients following bariatric surgery.

Leptin levels typically drop after RYGB and sleeve gastrectomy,[165,166] possibly reflecting reduced gastric production or reduced body fat mass. It is unclear whether this reduction in leptin levels affects energy intake in bariatric surgery patients.

Increased **GLP-1** (associated in some studies with a blunted GIP or ghrelin response) is one mechanism whereby RYGB induces weight loss and enhances glucose control.[167–169] Patients after RYGB had higher levels of GLP-1 than those losing a comparable amount of weight through diet.[169] GLP-1 levels were higher after RYGB than after gastric banding.[170,171] Increased GLP-1 levels and measurements of insulin sensitivity are comparable among patients who underwent sleeve gastrectomy and biliopancreatic diversion for obesity in the short term.[172] However, recent data question whether the increased GLP-1 levels are sufficient to maintain glycemic control in obese type 2 diabetics in the longer term.[173]

PYY levels increase after RYGB and sleeve gastrectomy.[174,175] However, it is unclear whether this contributes to weight loss, dietary intake or glycemic control relative to concomitant hormonal changes in GLP-1, GIP, and other hormones.

The type of gastric bypass surgery influences **nutrient preference**. For example, RYGB patients consumed less energy from fat (with no differences in carbohydrate or protein intake) compared with vertical-banded gastroplasty patients 1 and 6 years after surgery.[176] Attenuated appetite after RYGB is associated with elevated PYY and GLP-1 concentrations. Appetite increased when the release of gut hormones was inhibited by the somatostatin analog, octreotide.[177] Reduced preference for fat has been reported after sleeve gastrectomy in rats, but there are no reports to date in humans.[178]

In summary, different bariatric procedures impact a variety of the components involved in appetite, such as, total caloric tolerance, nutrient preference, as well as the hormonal and peptide responses that impact not only the intended effects on weight loss and glycemic control but also affect appetite, satiation and satiety. In addition to the relevance of these different mechanisms that result in weight loss after bariatric surgery, the lessons learned suggest novel opportunities to achieve the same physiological changes without bariatric surgery, as with endoscopic sleeve gastroplasty[179] or pharmacological agents such as GLP-1 agonists.[180]

CONCLUSION

This review illustrates the important role of peripheral "taste" of nutrients and the rich and diverse mechanisms involved in communicating between the gut and the centers in the hypothalamus and brainstem that mediate food intake and digestion. Importantly, the hedonic (pleasures and desires related to food) and higher center responses to food are superimposed on these peripheral mechanisms and are the subject of the accompanying article.[181]

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Abbreviations used

5-HT	serotonin
α-MSH	α-melanocyte-stimulating hormone
AA	amino acid
Ach	acetylcholine
AgRP	agouti-related protein
Apo A-IV	apolipoprotein A-IV
BMI	body mass index
BOLD	blood oxygenation level dependent
CART	cocaine- and amphetamine-regulated transcript
CB1	cannabinoid 1 receptor
CBF	cerebral blood flow
CCK	cholecystokinin
CNS	central nervous system
DMV	dorsal motor nucleus of the vagus nerve
EC	enterochromaffin cells
GE	gastric emptying

GIP	glucose-dependent insulinotropic peptide
GH	growth hormone
GHS-R	growth hormone secretagogue receptor
GLP	glucagon like peptide (1 or 2)
GLUT	glucose transporter
MCH	melanin-concentrating hormone
NPY	neuropeptide Y
NTS	nucleus of the tractus solitarius
OXM	oxyntomodulin
POMC	pro-opiomelanocortin
PP	pancreatic polypeptide
PVN	paraventricular nucleus of the hypothalamus
PVN-ARC	paraventricular and arcuate nuclei of the hypothalamus
PYY	peptide tyrosine-tyrosine
RYGB	Roux-en-Y gastric bypass
SGLT	sodium-coupled glucose transporter
T1R, T1R2, T1R3	G protein coupled taste receptors
TRH	thyrotrophin-releasing hormone

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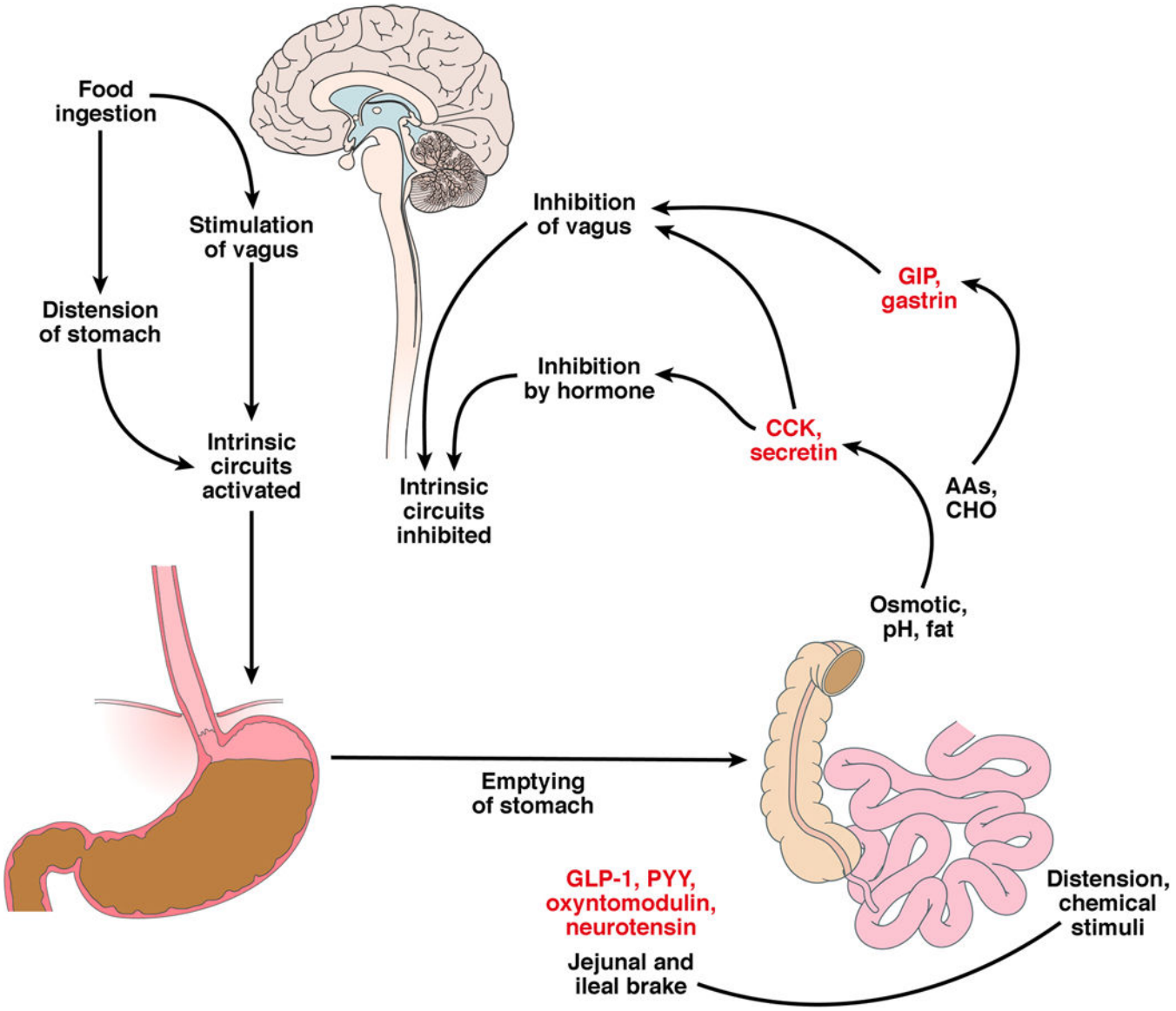

Figure 1.

Integrated neurohormonal response to the ingestion of food. Sensing of different nutrients by enteroendocrine cells results in the release of diverse hormones and peptides that result in gastric accommodation to the meal, stimulation of gastric contractions that lead to emptying and, when the nutrients reach different levels of the small intestine, the release of substances that provide generally negative feedback that delays gastric emptying (e.g. CCK in the duodenum, GLP-1 and PYY in the more distal small intestine and colon).

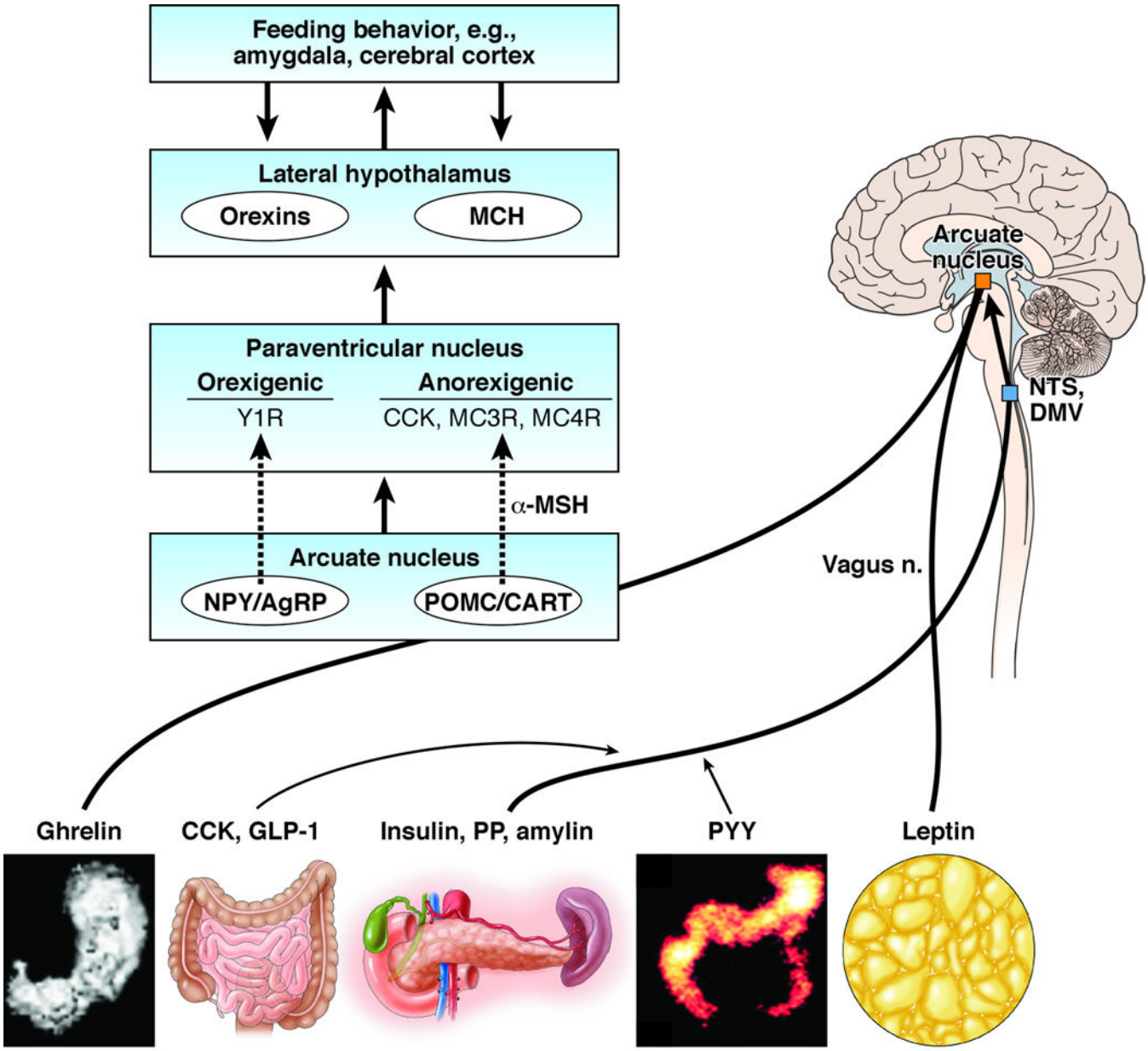

Figure 2.

Peripheral and central factors modulating appetite centers in the brain. Gastrointestinal and fat-derived hormones stimulate specific areas of the hypothalamus and brainstem that sense nutrients, and coordinate the response to hunger and the intake of food. The arcuate nucleus in the hypothalamus receives input from brainstem (e.g., vagal) nuclei as well as direct stimulation by circulating hormones through an incomplete blood brain barrier. Neurons in the arcuate nucleus are either orexigenic [e.g., contain neuropeptide Y via Y_1 receptors or agouti-related peptide (AgRP)] or anorexigenic [e.g., contain pro-opiomelanocortin (POMC)], cocaine- and amphetamine-related transcript (CART)]. POMC is a precursor of α-melanocyte stimulating hormone (α-MSH). Ultimately, other regions of the hypothalamus (the paraventricular nucleus and lateral hypothalamus) and higher centers (such as

amygdala, limbic system and cerebral cortex) are stimulated to change feeding behavior by influencing the functions of the same hypothalamic nuclei. *Redrawn from Camilleri M, Grudell AB. Appetite and obesity: a gastroenterologist's perspective. Neurogastroenterol Motil 2007;19:333–341*.

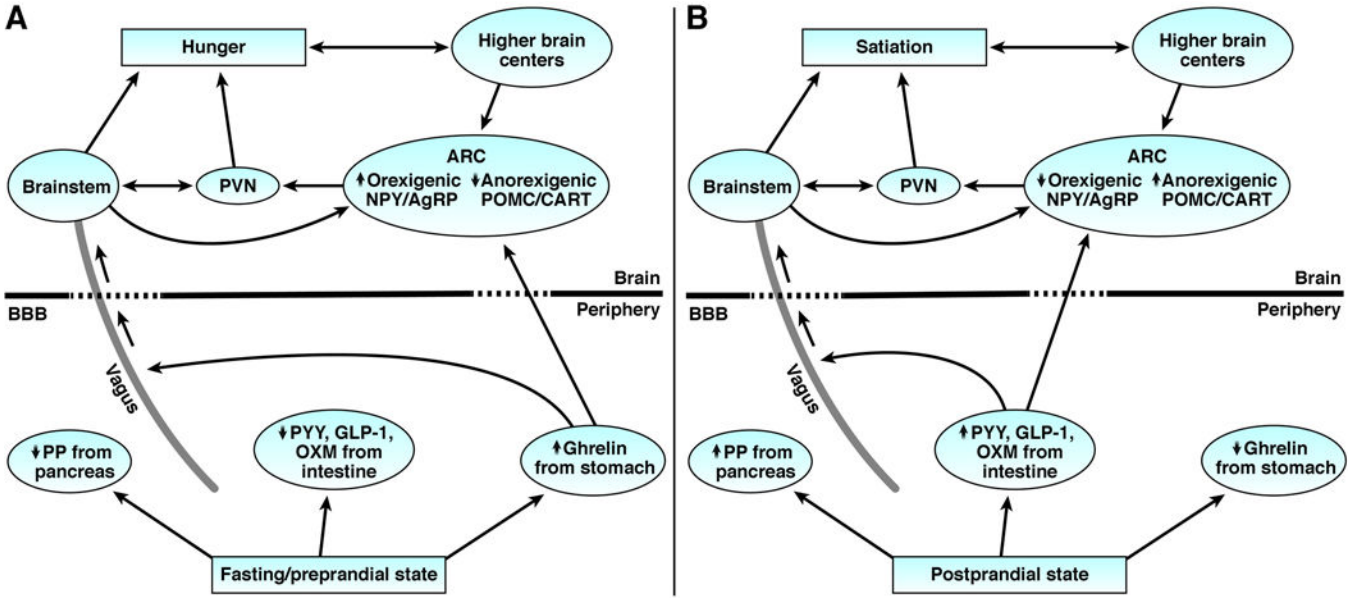

Figure 3.

The gut hormone signaling to the brain to mediate sensations of hunger and satiation. Left panel: During the fasting/preprandial state, ghrelin release from the stomach acts upon the arcuate nucleus of the hypothalamus and vagus nucleus in the brainstem to stimulate hunger. Right panel: In the postprandial state, release of anorectic hormones, PYY, GLP-1, OXM, and PP from the intestine act upon the ARC, brainstem, and vagus to cause satiation.

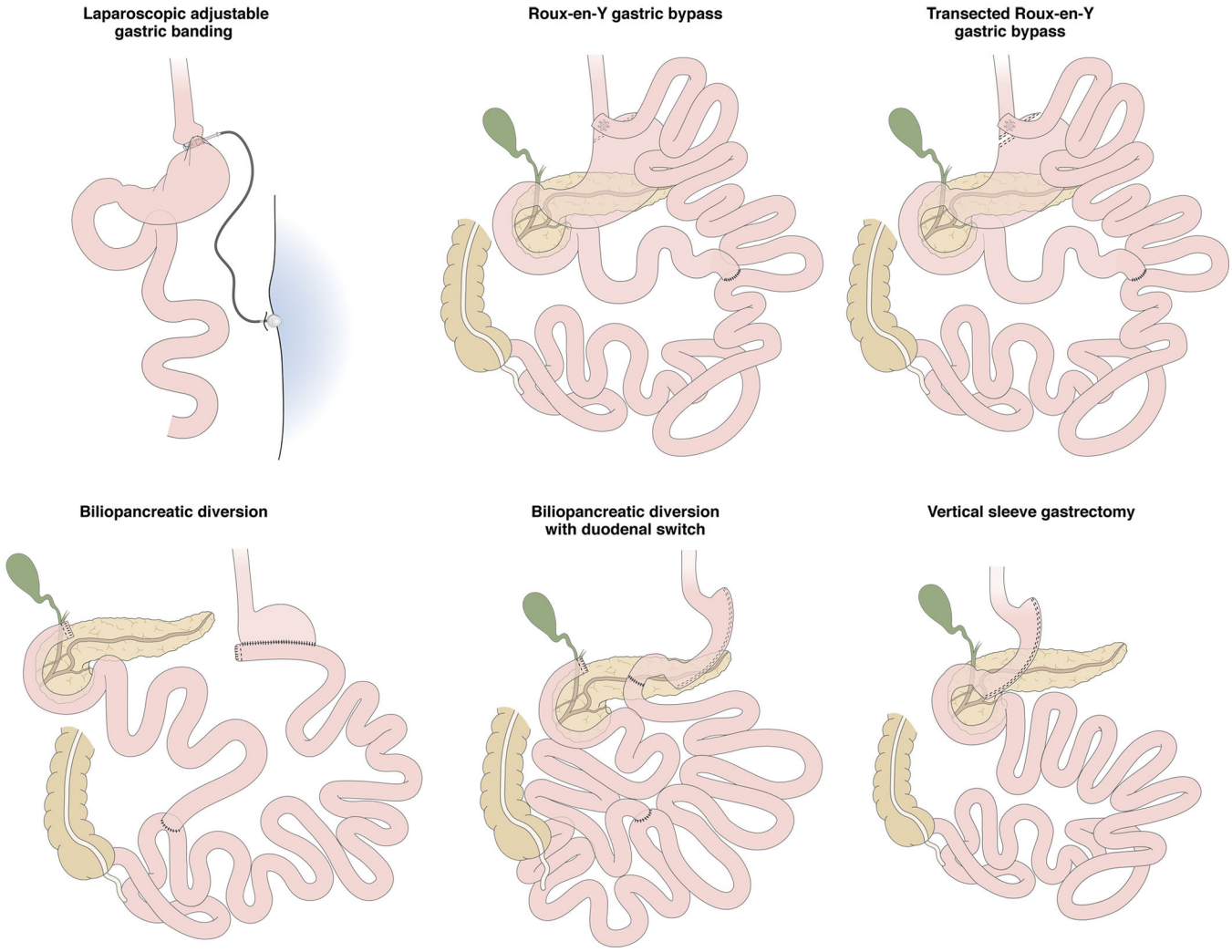

Figure 4.

Most frequently performed operations to treat obesity (*figure adapted from Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. BMJ. 2014 Aug 27;349:g3961. doi: 10.1136/bmj.g3961).*

Table 1

Peptides, hormones and receptors involved in the peripheral gastrointestinal control of upper gastrointestinal functions associated with satiation and appetite.

Peptide/ Hormone/ Receptor	Predominant Site of Synthesis/ Release	Main Functions	Refs.
Gastrins	17-AA peptide from gastric mucosa	- Blood-borne regulator of gastric acid secretion, interacting with somatostatin and EC cells - Regulates gastric epithelial organization, proliferation, and function	32–34
CCK	I cells in duodenal mucosa, particularly ≥12 carbon chain long fatty acids; multiple molecular forms	- Activates vagal afferents directly and modifies the response of vagal mechanosensitive fibers to gastric and duodenal nutrients - Relaxes the proximal stomach to increase its reservoir capacity, inhibits gastric emptying and acid secretion, gallbladder contraction, and exocrine pancreatic secretion - Limits amount of food consumed during an individual meal	35–38
CCK1R	Vagal afferents	- Induces fullness and nausea in response to duodenal lipid and gastric distention	39
CCK2R	CNS, hypothalamic (e.g. arcuate) nuclei	- Controls satiety and appetite	40–42
Ghrelin	28-AA peptide expressed mostly in stomach	- Growth hormone secretagogue that stimulates pituitary release of GH - Stimulates food intake - Induces metabolic changes, increases body weight, fat mass through NPY/AgRP system - Stimulates appetite via secretion of NPY and orexin - Inhibits appetite via POMC)/αMSH system - Effects mediated through vagus nerve - Stimulates gastric emptying and contracts gastric fundus - Other actions: stimulates gastric acid, vasodilatation, inhibition of insulin, and antiproliferative effects	43–45 46 47–49 50 51–63 64–66
GHS-R	G protein-coupled receptor	- Distributed in hypothalamus and pituitary, adrenal, thyroid, pancreas, myocardium, spleen, ovary, enteric neurons and stomach	43
Leptin	Circulating 16-kDa protein (167 AA) secreted by adipose tissue, placenta, skeletal muscle	- Central regulation (arcuate nucleus and other) of food intake and energy balance, storage of fat and insulin signalling - Secretion is proportionate to fat stores of the body - Decreased leptin induces hunger; starvation reduces leptin levels and increases appetite - Regulates feeding behavior and short-and long-term satiation by providing information to brain on availability of external (food) and internal (fat) energy resources	67–73 74 75–78

Peptide/ Hormone/ Receptor	Predominant Site of Synthesis/ Release	Main Functions	Refs.
Gastric leptin	Fundic glands, and chief cells	Reduced during fasting, rapidly released after food intake by vagal cholinergic stimulation, CCK and secretin, or in response to satiety factors (e.g., CCK and insulin)	79
GLP-1	Co-secreted with PYY from intestinal L cells: $GLP\text{-}1_{7–36\ amide}$ is located in the PVN, DMV, NTS, pituitary, and thalamus	- Two biologically active forms: $GLP\text{-}1_{7–37}$ and $GLP\text{-}1_{7–36\ amide}$ (the major circulating form) - Incretin hormone that enhances insulin secretion stimulated by oral nutrients - Control of appetite and energy intake in humans - Enhanced satiety and fullness after an energy-fixed breakfast, reduced energy intake at an *ad libitum* lunch, retarded gastric emptying, inhibited antral motility, reduced postprandial glycemia and increased gastric volume or reservoir capacity	80–82 83 84–87
NPY	36-AA peptide in hypo-thalamus, and intestinal neurons	- Appetite induction through NPY network in the PVN-ARC of hypothalamus; opposing hormonal signals, such as leptin and ghrelin, regulate secretion of NPY in PVN-ARC; - Antisecretory effects in small intestine and especially colon; motor inhibitory effects	88 89
NPY (Y) receptors	Multiple receptor subtypes Y_1 to Y_5	Y_1, Y_2, and Y_5 receptor subtypes mediate NPY-induced feeding; central NPY delays GE in rats (through Y_2 receptors); in humans, i.v. NPY had no effect on GE	90,91
PP	36-AA peptide from D cells in pancreas	Experimentally, anorectic effects with peripheral PP, central PP stimulates food intake; Circulating PP levels inversely proportional to adiposity; higher levels with anorexia nervosa, reductions in circulating PP in some studies in obese subjects; PP may delay GE	92–96
PYY	Co-secreted with GLP-1 from ileocolonic L cells; active form $PYY_{3–36}$	- Stimulates Y_2 receptors in hypothalamic ARC nucleus circuitry to regulate food intake; - Activates ileal brake and other feedback control of regional motor function - Inhibits gastric acid, pancreatic exocrine and bile acid secretion	97 98–103 104–107
OXM	37-AA peptide, from intestinal L cells	Acts via GLP-1 receptors to decrease food intake and inhibit gastric acid secretion and GE	108,109
Apo A-IV	46kDa protein from small bowel enterocytes	synthesized and secreted in response to lipid absorption; exogenous apo A-IV decreased food intake (mediated centrally) and inhibited gastric acid secretion and motility in rodents	110–112

AA: amino acid; Apo A-IV: apolipoprotein A-IV; CCK: cholecystokinin; CNS: central nervous system; DMV: dorsal motor nucleus of the vagus nerve; EC: enterochromaffin cells; GE: gastric emptying; GHS-R: growth hormone secretagogue receptor; GLP-1: glucagon like peptide-1; NPY: neuropeptide Y; NTS: nucleus of the tractus solitaries; OXM: oxyntomodulin; PP: pancreatic polypeptide; PVN: paraventricular nucleus of the hypothalamus; PVN-ARC: paraventricular and arcuate nuclei of the hypothalamus; PYY: peptide tyrosine-tyrosine;

italics refers to receptors of peptides/hormones

Table 2

Summary of effects of different fat molecules on appetite, food intake and weight

Fat variation	Effects on appetite/satiety, food intake or weight	Reference
LCFA	C18 fatty acids reduce food intake; effect not related to rate of absorption but partly by CCK release	123
MCFA	No significant effect of fatty acid chain length (LCFA vs. MCFA for 3 days) on ratings of hunger, fullness, satisfaction or current thoughts of food, nor did energy or macronutrient intake at next meal differ between diets	124 125
Triacylglycerol (olestra)	Olestra does not influence signals of satiation including cholecystokinin and stomach emptying; most studies of olestra on human satiation found no additional energy consumption when olestra was substituted for dietary fat	126
MUFAs, PUFAs, or SFAs	Short-term studies indicate that PUFA may exert a relatively stronger control over appetite than MUFA and SFA	127
	SFA-rich meal elicited greater subjective feelings of fullness compared to MUFA-and PUFA-rich meals; postprandial PYY response (area under the curve) was significantly lower for the MUFA-rich meal vs. the SFA-rich or PUFA-rich meals	128
Long-chain omega-3 PUFAs	Observational studies (Health Professional Follow-up Study and Nurses' Health Study) and RCTs provide conflicting evidence of weight gain or loss	129
	High amount (>1300 mg/day; n = 121) associated with lower hunger sensations immediately after test dinner (fullness) and after 120 min (fullness and hunger) compared to low amount (<260 mg/day; n = 112)	130

MUFA=Monounsaturated fatty acids; PUFAs=,polyunsaturated fatty acids; SFAs=saturated fatty