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Hallmarks of appetite: a comprehensive review of hunger, appetite, satiation, and satiety

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Abstract

Purpose of review: The present review describes the available literature on the physiologic mechanisms that modulate hunger, appetite, satiation, and satiety with a particular focus on well-established and emerging factors involved in the classic satiety cascade model.
Recent finding: Obesity is a significant risk factor for numerous chronic conditions like cancer, cardiovascular diseases, and diabetes. As excess energy intake is considered by some to be the primary driver of weight gain, tremendous collective effort should be directed toward reducing excessive feeding at the individual and population levels. From this perspective, detailed understanding of physiologic mechanisms that control appetite, and in turn, the design of effective interventions to manage appetite, may represent key strategies in controlling the obesity epidemic.
Summary: With the obesity's prevalence on the rise worldwide, research on hunger, appetite, satiation and satiety is more relevant than ever. This research aims to provide practical insights for medical practitioners, nutrition professionals, and the broader scientific community in the fight against this global health challenge.

Keyword: Obesity · energy intake ·hunger· appetite ·satiety · review

1. Introduction

Obesity is a well-established risk factor for numerous chronic diseases, including cancer, cardiovascular diseases, and diabetes (**table 1**). Since 1980, the prevalence of overweight and obesity has doubled [1], and it is anticipated that the social [2], economic [3], and health [4] impacts of obesity-related conditions will continue to escalate. As excess energy intake is widely recognized as a primary driver of weight gain, tremendous efforts must be made toward mitigating excessive food intake at both individual and population levels. An in-depth understanding of the physiologic mechanisms that control appetite, and therefore, the design of effective interventions to manage appetite, may represent key strategies in controlling the obesity epidemic.

Historically, under ethological conditions, humans did not have continuos access to food until recent advancements [5]. Therefore, intermittent or patterned food consumption was

common [5]. In this context, appetite and the motivation to eat played pivotal roles in balancing food-seeking with periods of rest. However, nowadays in developed countries, food access is virtually limitless and constantly available. Nevertheless, it is interesting to note that humans do not eat continuously despite this abundance, and meal consumption is influenced by a very sophisticated system that finely tunes appetite through the integration of biological, psychological, and environmental inputs [6,7]. This multiorgan system orchestrates the delicate balance between hunger and satiety, influencing our food choices, feeding, body weight, adiposity, and indirectly, the incidence of obesity-related diseases.

The seminal work from the latter half of the 20th century identified satiation and satiety as the primary mechanisms regulating food intake. Satiation, or short-term inhibition of within-meal food intake, is the progressive decrease in the desire to eat that develops during a meal [8].

In particular, cognitive, sensory, hormonal, and social factors trigger the initiation of feeding. As the meal progresses, these stimuli are "satiated" by inhibitory signals, leading to a gradual decrease in the motivation to eat and, eventually, the cessation of food intake [6,7]. Satiation is a powerful regulator of meals size.

Conversely, satiety, or the inhibition of food intake during the inter-meal period, arises after a meal and inhibits the return of hunger for a variable period post-prandially [9].

Post-prandial satiety is orchestrated by neurohormonal inhibitory signals that serves as a crucial regulator of feeding frequency [6,7]. However, given that mealtimes in human societies are often dictated by cultural and social norms, satiety may be an inefficient modulator of feeding frequency but could act as an indirect regulators of meal size by decreasing hunger and, consequently, the amount of food consumed. Even though satiation and satiety have overlapping mechanisms and reflect a temporally continuous homeostatic process, this distinction is useful for interventional purposes. Indeed, it has been shown that satiation and satiety might be manipulated independently [6]. Acting on satiation could reduce the meal size or the caloric density of a meal (for example increasing the food volume without increment the caloric load), while acting on satiety could decrease feeding frequency or, indirectly, subsequent meal size (for example using foods with a slow digestion or absorption time). In addition, satiation and satiety should be differentiated from expected satiation (the immediate sense of fullness (post-meal) anticipated after consuming a particular food) and expected satiety (the anticipated relief from hunger provided by a specific food) [10].

Two additional key concepts are hunger and appetite [11]. Hunger is a physiological process, arising from biological shifts within the body that signal the need to consume food to sustain energy levels. Appetite, on the other hand, is the inclination to eat and can stem from hunger, though it frequently arises from other sources like emotional or environmental factors [11].

Collectively, satiation, satiety, expected satiation, expected satiety, hunger and appetite work in concert to mantain the delicate balance of energy expenditure and energy requirements. The interplay of these mechanisms was thoroughly depicted at the end of twentieth century by the Blundell's seminal paper theorizing the satiety cascade [7](**figure 1**). In brief, at the start of a meal, intake is driven by sensory factors including gustatory, olfactory, and textural properties of foods. As ingestion proceeds, a phenomenon known as sensory-specific satiation devolops with regard to the ingested items. Simultaneously, a series of gastrointestinal cues (such as gastric expansion, decreased ghrelin levels in the stomach, and the release of various hormones and peptides) coupled with increases in glycemic index progressively reduce the urge to eat, culminating in the end of meal. Upon reaching satiation specific to the sensory characteristics of a certain food, alternative foodstuffs possessing distinct sensory profiles retain their stimulatory impact, thus prolonging consumption until the satiation signals robustly counterbalance the sensory enticement presented by all available dietary options [7].

This review examines the available literature on the physiological mechanisms that modulate hunger, appetite, satiation, and satiety. We further discuss the consolidated factors involved in the original satiety cascade model as well as newly characterized ones to provide an updated and pragmatic reference for physicians, nutrition professionals, and researchers. We strongly believe that appetite is a key component of overweight-and-obesity epidemic, and that improved medical and social management of hunger-satiety equilibrium could have a pervasive positive effect on our contemporary societies. While pharmacological interventions, such as GLP-1 receptor agonists, offer viable options by targeting specific biological pathways to regulate appetite, it is essential to prioritize cost-effective and accessible non-pharmacological approaches for appetite management due to their broader applicability and minimal side effects.

2. The satiety cascade

A vast array of stimuli orchestrates appetite. They can be classified according to their timing with respect to a meal or the organ or mechanism involved. In the following sections we categorize appetite modulating factors into four distinct categories: gastrointestinal factors, food-intrinsic factors, sensorial and cognitive factors, and complex factors (**table 2**). When possible, each mechanism is accompanied by a pragmatic strategy that might be used in clinical practice or in social environment to counteract overweight/obesity (**table 2**). It is noteworthy that , each strategy might be used to achieve the opposite outcome, such as increasing body weight in specific cases (e.g., elderly or anorexic cancer patients).

3. Gastrointestinal factors

Gastrointestinal factors include inhibitory effects on hunger mediated by gastrointestinal organs, triggered by mechanical, chemical or hormonal stimuli.

3.1 Hormones & neurohormonal regulation

Food intake can modulate the secretion of many gastrointestinal hormones and can also trigger direct gut-brain neuronal feedback (**figure 2**) (**table 3**).

Gastrointestinal hormones can be secreted before food intake (ghrelin), after nutrients intake (GLP1, GIP, PYY, OXM, insulin, amylin, CCK), or due to nutrients deprivation (ghrelin, glucagon, FGF21) [12–15]. Among their numerous physiological roles, they can modulate appetite after reaching specific brain areas via the bloodstream [12–15]. Key areas involved in the coordination of feedback signals from the periphery include the arcuate nucleus of hypothalamus, which houses the homeostatic centers for food intake (i.e., hungerand satiety center), the area postrema which communicates with the arcuate nucleus and the limbic system (e.g., ventral tegmental area and nucleus accumbens) that regulates the hedonic eating behavior. Additionally, the gastrointestinal tract can communicate directly with brain (e.g. following gastrointestinal stretching) through the vagal nerve, which projects to the nucleus tractus solitarius in medulla oblongata which, in turn, project to the arcuate nucleus in the hypothalamus [12–15]. Ultimately, both hormones and vagal nerve stimulus can, directly or indirectly, reach and modulate the activity of arcuate nucleus in the hypothalamus, where both orexigenic neurons and anorexigenic neurons (homeostatic center) are located, or the limbic system (which influences the hedonic center). Orexigenic cells in the arcuate nucleus co-express NPY and AgRP, activating the hunger center in the lateral hypothalamic area while inhibiting the satiety center in the ventromedial nucleus. Conversely, anorexigenic cells in the arcuate nucleus co-express POMC and CART, inhibiting the hunger center while activating the satiety center[12–15]. Of note, POMC neurons communicate via a POMC-derived peptide called MSH-α which bind to MC3R or MC4R receptor on the second order

neurons. Nearly 4% of early-onset severe obesity is caused by mutations on MC3R or MC4R genes [15].

Ghrelin is a hormone produced by the stomach and duodenum that reaches and activates orexigenic neurons in the arcuate nucleus and stimulates the hedonic eating by activating the ventral tegmental area [12,13]. Ghrelin levels increase during fasting [12] and acute stress [16] but decrease after feeding [12]. In order to bind its receptor (GHS-R1a), ghrelin must be octanoylated by ghrelin O-acyltransferase (GOAT). Several GOAT inhibitors are under development aimed at reducing the orexigenic behavior induced by ghrelin [16].

GLP1 and GIP are two incretin hormones important to for reducing blood glucose levels. GLP1 is produced by L cells which are distributed in the gastrointestinal tract with an increasing frequency from duodenum to colon [16]. GLP1 blood concentration rise shortly after the ingestion of nutrients and acting on several organs causes a reduction of intestinal motility, acid secretion from stomach, and appetite with a concomitant increase of insulin secretion [16] facilitating weight loss [17]. While its suppressive activity on appetite could stem from several causes, GLP1 has shown to activate the anorexigenic neurons in arcuate nucleus. The weight-reducing effect of GLP1-agonists has been demonstrated in several clinical trials and meta-analyses [18].

GIP is the other incretin secreted by the enteroendocrine K cells which are distributed primarily in the duodenum and upper jejunum, with decreasing frequency along the distal intestine. In comparison to GLP1, GIP has a somehow less clear role on appetite and weight loss. Indeed, both the activation and inhibition of GIP receptor appear to induce weight loss [12,19]. Future studies are needed to clarify its roles.

Both PYY and OXM are hormones co-secreted after nutrient ingestion by L cells primarily located in distal intestine. While PYY can inhibit gastric motility and has a well-known anorexigenic role caused by the direct stimulation of anorexigenic neurons in arcuate nucleus [12] OXM exerts its appetite-reducing activity by binding to the receptors for GLP1 [12,20].

Insulin is a hormone involved in blood glucose homeostasis and have a crucial role in lowering blood glucose levels. Insulin is secreted by pancreatic beta-cells after the increase of glycemic levels. However, in addition to its hypoglycemic activity, it also reduces food intake through a central nervous system mechanism [12].

Amylin is a hormone co-secreted with insulin by pancreatic beta-cells that decreases food intake through a direct stimulation of anorectic neurons in area postrema [12]. Moreover, the food-reducing-effect of amylin is also caused by a modulation of hedonic eating behavior via a signaling on limbic system [21].

3.1.1 Adipose tissue

Given that obesity is associated with disruptions in homeostatic pathways that regulate caloric intake such dysregulation significantly contribute to an energy imbalance, which is a substantial factor in the escalation of chronic metabolic disorders and cardiovascular diseases.

Adipose tissue (AT), including both white (WAT) and brown (BAT) type), is a dynamic endocrine organ secreting hormones and metabolically active factors, called adipokines, involved in energy metabolism [22].

These molecules are classified pro- and anti-inflammatory adipokines [23].

Leptin is one of the proinflammatory hormones secreted by AT, reflecting body's energy stores. By acting on its hypothalamus cognate receptor, leptin provides a central weight control, reducing appetite and promoting energy expenditure thought the activation of POMC-expressing neurons, inhibition of NPY and the secretion of anorexigenic peptides [24,25].

Hyperleptinemia has been found in population with obesity, indicating that the obesity-induced chronic inflammatory state contributes to constant production of proinflammatory cytokines inducing leptin resistance with the consequent decreased satiety [152,153,155].

Resistin is another proinflammatory polypeptide, mainly secreted by human macrophages. It exerts its action by activating hypothalamic neurons, modulating food intake and glucolipid metabolism and altering liver insulin sensitivity. Its inflammatory effect is mediated by the Toll Like Receptor (TLR) 4 signaling pathways activation that induces a decreased energy expenditure [26,27].

Similarly, visfatin is an additional adipocytokine influencing glucose metabolism by interacting with insulin receptors leading to an increased glucose uptake of muscle and liver cells.

Regarding anti-inflammatory adipokines, adiponectin stands out as an adipocyte-secreted hormone with anti-inflammatory, insulin-sensitizing and anti-atherosclerotic properties [26]. Binding the muscle AdipoR1 and liver AdipoR2 receptors, adiponectin enhances fatty acid oxidation, downregulate lipid and glucose hepatic production and increases peripherical glucose uptake [24–26]. Moreover, its levels seem to be affected by feeding status and nutrients. Indeed, an inverse correlation between serum adiponectin levels, body mass index and fat mass exists, with lower concentrations having been detected in individuals consuming high carbohydrate diet and in patients with obesity [23,26,28].

Bases on this evidence, these findings suggest that peripheral regulators of appetite are essential factors for ensuring appropriate energy and metabolic homeostasis [22,29–34].

CCK is a hormone secreted by the I cells of the upper small intestine after the ingestion of nutrients (especially fats but also proteins) CCK can slow the stomach emptying time and, through a direct vagal nerve stimulation, can stimulate meal termination and inter-meal satiety [12,35].

Glucagon is a well-known hyperglycemic hormone, and it can decrease body weight via lipolysis and reduction of food intake which appears to be mediated by a liver-vagal nerve-hypothalamus axis [12].

FGF21 is a hormone secreted by the liver during fasting and appears to induce weight loss through the increase of energy consumption [12] However, FGF21 has been linked to sugar and alcohol aversion [36].

Overall, a variety of hormones along with the afferent signals from the vagal nerve can modulate the balance between hunger and satiety. It is important to note that many, if not all, of these hormones play broader roles in digestion and gastrointestinal function, and there is ongoing debate as to whether their effects on appetitive are primary or secondary functions [15]. In addition, the statistical association between postprandial hormonal changes (and throughout an intervention) and alterations in subjective appetite or energy intake is not consistently observed [37]. While it is likely that additional hormonal regulators of appetite awit discovery, an in-depth understanding of their molecular pathways could lead to the development of drugs that leverage their appetite-suppressing effects. Agents that activate GLP1-receptors are a prominent success story in this regard.

3.2 Oral food processing

Oral food processing (OFP) has emerged as a relevant factor in modulating satiation and satiety. For example, the direct infusion of food into the stomach or in small intestine elicits a lower satiating effect in comparison to the oral ingestion Also, ultra-processed foods, which often need a low oral processing, may have and indirect role in favoring food consumption [38].

From the multiplicity of studies evaluating the link between OFP and appetite, five parameters have emerged as relevant: eating rate (the weight of food eaten per minute), oral food residence time, number of chews, size of bites, taste, and physical properties of food (see below) [39–43]. In a meta-analysis of 42 studies, short term satiety, measured as the subsequent food

intake or the desire to eat, increased with a longer eating time, longer food residency time and higher number of chews [44]. Another meta-analysis highlighted the association between eating rate and caloric intake [44]. Interestingly, subgroup analysis showed that slowing eating time appears to be sufficient to lower the caloric intake independently from the strategy adopted: instructions to eat slowly vs. manipulation of food form (soft vs. hard) vs. manipulation of eating rate by computerized feedback vs. food delivery (eating with a spoon vs. a straw or eating from a container that refilled quickly vs. slowly) [44]. Importantly, the reduction in short-term appetite seems not compensated in later meals [45].

In line with these findings, several case-control and longitudinal studies showed that overweight or people with obesity have a fasting eating speed or a greater bite size in comparison to people with normal weight [39]. In controlled experimental settings involving humans, the significance of bite size in modulating energy consumption has been evidenced. Some studies have highlighted a correlation between bites or sips size and spontaneous caloric intake [39].

To explain these findings, several biological mechanisms have been proposed as relevant. Among them, the two most prominent appears the increase of anorexigenic hormones like GLP1, PYY, and CKK (see above) with a reduction levels of ghrelin in response to the increase in eating length or chews done [39] and a putative neural signaling stimulating satiety [41]. Another possible mechanism involved, is the increased energy expenditure associated with prolonged eating [39]. In particular, the activity of masticatory muscles and a greater sympathetic nervous activity could explain the increased thermal effect of food (the energy consumed in the food assumption and digestion) [39]. However, the overall increase in caloric consumption appears to be modest [39]. Finally, a longer food residency in mouth might evoke a stronger sensory-specific satiety (see below).

There is also evidence suggesting that OFP behavior may have a hereditary component [46], which could help explain familial tendencies toward overweight. However, more studies are needed this hypothesis.

In summary, OFP appears to be a promising regulatory point in the appetite balance, and its exploration shows potential in appetite regulation.

3.3 Oral receptors

Humans can sense at least five different tastes (sweet, salty, bitter, sour, and umami) and each of them is recognized by a different receptor array (**supplementary table 1A**) [41,43]. Tasty stimuli are transmitted to the brain by the facial nerve (from first third of the tongue), glossopharyngeal nerve (from the posterior two-thirds of the tongue), and vagal nerve (from the extreme posterior of the tongue). The mouth is also able to recognize a variety of non-tasting stimuli, like spicy, astringent, carbonation, temperatures that are signaled to brain via trigeminal nerve [41,43].

While little is known about the satiating effects of non-tasting stimuli, some preliminary data have shown a satiating effect from sweet and salt [41,43]. However, it is still debatable if this depend on the systemic increase of anorexigenic hormones (e.g., GLP1, GIP, PPY) or a direct nervous signaling or a sensory-specific satiety [41,43]. Moreover, an aversive-like behavior to sour and bitter has been reported and this might contribute to the regulation of food intake [46,47].

Interestingly, it appears that taste intensity may be one of the main features influencing satiety as it might represent a homeostatic process to avoid the excessive nutrients intake. For example, betweentwo tomato soups with the same palatability but a different salt intensity, the product with higher salt levels is consumed in smaller quantities [48]. However, the taste intensity is not solely determined by substance concentration; it also depends also on the food structure (i.e., the harder the texture the longer the oral exposure to the taste) [41].

Finally, besides the satiating effect of tastes, they might also induce a preference for foods with different tastes within the next 24 hours [41]. This might represent a homeostatic mechanism to increase chances to be exposed to a different number of nutrients.

In summary, oral receptors play a crucial role in the early regulation of appetite and contribute significantly to short term satiety and long-term food choice.

3.4 Gut taste receptors

Beyond the distribution on the tongue, taste receptors are also present throughout the gastrointestinal mucosa [42,49]. For instance, this observation helps explain the greater insulin release observed after oral glucose ingestion compared to the same amount administered intravenously (incretin effect) [42].

While the number of recognized gut taste receptors is increasing, their metabolic roles are still incompletely understood. However, at least two functions are evident. First, in response to nutrients they can directly or indirectly stimulate the release of many anorexigenic gastrointestinal hormones, like GLP1, CCK, and PYY [42].

Secondly, bitter receptors seem able to induce satiety through a direct inhibition of gastric emptying [50]. Despite the pharmacological challenges, some bitter-receptors agonist is currently tested for weight loss [45].

In summary, gut taste receptors represent a promising target for satiety induction, especially those specific for bitterness.

3.5 Gastrointestinal stretch

Mechanoreceptors located in the stomach and intestine are capable of detecting stretching resulting from food and fluid intake. It has been shown that such stimulation can activate signaling through the vagal nerve, leading to the inhibition of the hunger center in hypothalamus [51,52].

This mechanism has been utilized in treatments such as the intragastric balloon for obesity management [53]. It has been suggested that consuming foods with high volume yet low caloric before a meal may effectively reduce hunger and subsequent food intake in the short term [54,55].

4. Food-intrinsic factors

4.1 Physical features of foods & energy density

Physical features of food have been shown to significantly influence eating rate (ER, g/min) which, together with food energy density (FED, kcal/g), define the energy intake rate (EIR = ER * FED, kcal/min). Therefore, since EIR is a pivotal factor regulating the overall energy intake, food physical features could indirectly alter the caloric daily balance [48,56].

Humans cannot accurately discern food energy density. For example, when a pasta meal was mixed with an energy dense sauce or a less caloric alternative, the amount of pasta eaten was the same while the caloric intake was 60% higher in the energy dense version [48]. This phenomenon, which may lead to passive overconsumption of energy with energy dense foods, is consistent among many clinical variables (e.g., sex, age, single-meal vs. whole-diet) and is not compensated by a reduced caloric intake in the next meal of the day [48]. Supporting this observation, a shift from a high energy dense diet towards a low energy dense diet has been shown to decrease caloric intake and body weight [57]. However, the long-term efficacy of low energy dense diet seems less clear.

Beyond energy density, food physical structure could be modified to increase ER [58–61]. Although the exact mechanism by which ER increase satiety remains unclear, several hypotheses have already proposed (see the oral food processing section above). Briefly, ER can reduce hunger through the action of anorexigenic hormones, direct neural signaling, and the sensory-specific

satiety. All these effects could be caused by the oro-sensory exposure time (OET, i.e., the duration of chewing and/or the taste exposure from ingestion to swallowing) [61]. This is important because it explains why some strategies have deeper impact on increasing satiety than others. For example, OET could be increased with smaller bites and higher chewing cycles (number of chews per bite); however, chew frequency (number of chews per second) or longer pauses between bites seem less effective, probably because they do not augment oral residence time of foods or taste exposure [61]

Oral food breakdown is a complex phenomenon [61]. Briefly, it depends on three main components: food structure, lubrication, and time. Food structure is defined by several features: rheological properties (elasticity, hardness, viscosity, fracturability); surface-related properties (absorption capacity, initial lubrication); geometrical properties (i.e., food pieces size); particles in foods (number of particles, particle size). Each of these properties can impact on the ER (**supplementary table 1B**) [61]. In general, solid, semi-solid, and liquid foods require a decreasing oral processing effort. For instance, ER for solids is estimated between 10-120 g/min, while for liquids is up to 600 g/min. However, high elasticity and resistance to lubrication are also important features to predict higher ER (for a more detailed coverage of these aspects refer to **supplementary table 1B**).

In summary, the physical features of foods and their energy density are two important elements dictating ER and caloric intake. Since several technologies are widely available, acting on these points could be an easy strategy to reduce food intake (or increase it in underweight or malnourishing conditions).

4.2 Macronutrients composition (fats, proteins, fibers, carbohydrates)

Several lines of evidence show that the macronutrient composition of foods can influence the satiation/satiety process.

Triglycerides, phospholipids, and steroids are the primary categories of lipids, with triglycerides being the most encountered type in food sources. Despite providing the highest energy density per gram, lipids demonstrate lower satiety effects compared to other macronutrients such as proteins [62]. Lipids exert their inhibitory effect on short-term food intake by delaying gastric emptying and triggering the release of gastrointestinal (GI) hormones, including CCK, GLP-1, and PYY [63,64].

Long-chain triglycerides (LCTs) significantly increase the release of CCK and PYY, while medium-chain triglycerides (MCTs) have even more pronounced satiating effects [65].

Although lipids have the potential to trigger satiety mechanisms, their heightened palatability could paradoxically lead to increased food intake due to hedonic stimuli [66]. For example, excessive consumption of fats can impair the functioning of dopaminergic neurotransmitters involved in modulating the reward system, ultimately resulting in overeating [67]. Carbohydrates have emerged as significant regulators of appetite and satiety. Dietary fiber, starches and sugar are the three primary categories of carbohydrates and play a different role on appetite and satiety [68]. Firstly, several studies demonstrated that food high in dietary fiber, requiring more chewing, induces the suppression of appetite and increased satiety [69–71].

In addition, dietary fibers impact satiety through various mechanisms, including gastric distension, slowed gastric emptying, and stimulation of gastric juice secretion and hormone release, such as GLP-1 and CCK. Additionally, the fermentation process of fiber results in the production of short-chain fatty acids (SCFAs), which further stimulate the sympathetic nervous system (SNS) and reduce hunger by increasing the secretion of regulatory hormones like GLP-1 and PYY [72].

Interestingly, the perception that a higher glycemic index (GlyI) correlates with greater short-term satiety (1-2 hours), although seen in some works [70,73,74] has been rejected by empirical

evidence, highlighting the inadequacy of GlyI alone in predicting satiety impacts in mixed meals [75,76]. Regarding starches, although some works have been shown that resistant starch may reduce appetite [77] a consensus is still lacking [78].

Moreover, according to Mellinkoff's aminostatic theory, proteins play a fundamental role in satiety regulation and food consumption control by elevating plasma amino acid concentrations [79]. The presence of amino acids in the GI system triggers the release of satiety hormones, including CCK, glucose-dependent insulinotropic polypeptide (GIP), GLP-1 and PYY, regulating satiation and promoting feelings of fullness and satisfaction [79–81]. Recent studies have also uncovered an intriguing link between proteins and brainstem sensitivity to anorexigenic hormones, as protein intake has been shown to enhance the brainstem's responsiveness to these hormones, further influencing the satiety response [82]. Nevertheless, beyond the aminostatic [79] and protein-static [83] theories of satiety, it is worth mentioning that outside periods of growth, there is few evidence showing the role for amino-or-protein-static feedback in the human control of FI [84].

5. Sensory & cognitive factors:

5.1 Food perceptions by senses

The sensory properties of food not only influence likes and dislikes but also play a functional role in guiding food choices and intake behaviors beyond mere “liking” [56]. These properties are essential for the development and optimization of products in the food industry. Sensory complexity appears to be a key factor in preference development. Although there is no consensus on its definition, sensory complexity can be categorized into three dimensions: sensory, cognitive, and emotional [85].

Sensory complexity is often described as a multidimensional attribute of a product, which is assessed through various sensory inputs [85]. It may involve factors such as the number of aromas, ingredients, flavors, or perceived sensations [86–88]. Conversely, some authors define complexity as the opposite of ‘simplicity,’ where a product with few sensations is considered simple, while one with multiple sensations is deemed complex [89–91].

In the cognitive dimension, complexity is defined by the ease or difficulty of identifying the aromas present and the cognitive effort required to form a complete sensory representation [86, 88, 92, 93]. The emotional aspects of complexity are related to the level of surprise a product elicits and the familiaritythe consumer has with it.

There are various methods to evaluate complexity, including scales and comparisons [88–90]. One straightforward method, supported by several authors, involves asking participants to rate how complex they perceive a product to be [79, 91, 94–98]. However, a limitation of this approach is the assumption that all participants interpret complexity in the same way, which may lead to inconsistencies in the data[95].

Sensory perception of food encompasses appearance, odor, flavor, taste, and texture attributes, all of which influence consumer preferences and intake [99]. Rolls and colleagues conducted experiments to explore these effects [100]. They found that after consuming chocolates of a single color, the pleasantness of the taste of the eaten color decreased more than that of the non-consumed colors, despite the chocolates differing only in appearance. Additionally, changes in food shape (affecting both appearance and mouthfeel) were shown to impact food intake. Offering subjects three different shapes of pasta led to a decrease in the pleasantness of the eaten shape and a significant increase (14%) in food intake when three shapes were provided compared to intake of the subject's favorite shape [101]. Similarly, variations in food taste (e.g., cream cheese sandwiches flavored with salt, lemon, saccharin, or curry) were associated with a 15% increase in

food intake when all three flavors were presented sequentially compared to intake of the favorite flavor [102].

Taste quality and intensity also affect intake. Foods with higher umami intensity have been shown to reduce subsequent food and energy intake [103, 104], while foods with balanced savory taste and protein content increase post-meal satiety [105, 106]. Taste quality and intensity reflect the concentration of taste substrates in the food, such as sweeter foods having more mono- and disaccharides, while salty foods contain more NaCl. An exception is fat (in the form of triacylglycerol), which, despite its low sensory impact, has a significant effect on the energy content of food. Fat influences mouthfeel, flavor release, and can substantially affect energy intake [Forde-influence of sensory properties].

Smell, mediated by specialized olfactory sensory neurons [84], also affects food intake. Studies have shown that pleasant smells, such as those from cookies or warm pizza, can induce salivation and appetite, leading to increased food intake [108, 109].

Given the obesity epidemic, understanding food perceptions through the senses and fostering a better relationship with food in our modern obesogenic environment is crucial for designing effective policy-level interventions [110]. The sensory properties of food not only determine preferences but also play a functional role in guiding food choice and intake behaviour, beyond simply promoting "liking" [56].

5.2 Food palatability

Palatability is a fundamental concept in the study of appetitive behavior and plays a crucial role in food intake across species [111]. Despite ongoing debates about its exact definition, the Encyclopedia of Human Nutrition (Third Edition, 2013) defines food palatability as the "subjective preference for a food, its subjective pleasantness, or the amount (in grams) of a food a subject eats" [112].

Palatability is closely linked to the nature of the food (such as its smell, taste, texture, and form), the sensory capabilities and metabolic state of the individual, and the environment in which the food and the individual interact. Therefore, palatability is not a fixed attribute [112]. High palatability often serves as a strong incentive to eat, as the consumption of "good-tasting foods" is associated with multiple positive emotions [113]. Furthermore, highly palatable foods are chosen more frequently from a range of options [114], which can lead to increased food and energy intake [115].

In addition to the characteristics of the food, palatability is influenced by the sensory capabilities and metabolic state of the individual, as well as the environment in which the food is consumed. Palatability tends to decrease as the intake of the food progresses, increasing with periods of food deprivation [116].

Given its variable nature, the precise role of palatability in contributing to overweight and obesity remains unclear. A hallmark of the Western obesogenic food environment is the widespread availability of highly palatable and varied food options [117, 118]. Laboratory studies have shown a strong relationship between food palatability and short-term food intake, as well as weight gain in animal models [110]. However, these findings do not fully capture the complexity of human eating behaviors in natural settings, and there is limited evidence quantifying the impact of palatability on human weight. Thus, there is a critical need for epidemiologic and intervention studies to better understand the association between palatable diets and weight changes.

Additionally, highly palatable foods affect the brain's reward system [85]. Frequent consumption of such foods can lead to a state of reward hyposensitivity, similar to drug addiction [86]. This condition affects eating behaviour, leading to a progressive increase in food intake [87], analogous to the adaptation seen with drug use [88,89]. A classic example is the cafeteria diet [90],

which includes palatable high-fat foods like hot dogs and muffins. Long-term consumption of these foods may result in addiction-like deficits in brain reward function, leading to overeating and, consequently, obesity [91,92].

5.3 Prior beliefs & associations & hedonic behaviour

New strategies aimed at reducing FI and enhance satiety during meals are crucial for effective weight management [93]. Beliefs and expectations about a recently consumed food not only significantly influence satiety but can also persist into the inter-meal interval [94]. To address the extent to which prior belief and expectation affect FI, Brunstrom *et al* manipulated beliefs about a food incidentally by showing either a large or small portion of fruit as the contents of a fruit smoothie, without exposing participants to explicit satiety-related information. In addition, they analysed the expected satiety associated with a test food immediately prior to consumption, in order to determine the effects of the manipulation [93]. They found that greater satiety was experienced when participants believed that the smoothie contained a large amount of fruit [93]. According to previous studies [95] this study confirmed that beliefs about a food can influence subsequent feelings of fullness. In addition, they suggested that effect of this manipulations persist at least three hours into the inter-meal interval, as hunger and fullness ratings were significantly different between groups at each time point [93].

Indeed, manipulation was also correlated with the expected satiety of the smoothie, before the meal began, as participants strongly believed the smoothie would provide more satiety when they thought it contained a large amount of fruit. These findings support those from previous studies [95,96], which suggest that predictions regard the energy content of a food differentially affected post-meal hunger. Moreover, they provide additional evidence regarding the correlation between expected satiety and the actual satiety experienced.

Notably, the regulation of FI in humans is much more complex than purely physiological need. In fact, people experience subjective pleasure when eating or enjoying the presentation of the meal, its aroma, texture and even the sound of chewing crunchy foods [97–99]. Consistent with sexual pleasure, eating generated satisfaction and well-being leading an individual to eat compulsively, given by the brain reinforcement system [100].

This system is defined as the hedonic system and is linked with the activation of the neuronal reward system in response to any highly palatable food or any food which independently of its nutritional value, produces a pleasurable sensation [101–103].

In the same cases, this system may override the homeostatic system, leading to increased consumption of highly palatable, energy-dense foods, , even when there is no physiological need and the energy reserves have already been restored [102–104].For instance, the obesogenic food environment, characterized by palatable and energy-dense foods may induce some individuals to think frequently about food [103].

5.4 Rewards

Eating is inherently pleasurable and rewarding, which explains why brain centers related to pleasure and reward are activated during food consumption. For instance, highly palatable diets, such as those rich in fats and sugars (e.g., cafeteria diets and chocolate), can stimulate food intake

even when one is already satiated [105]. Neuroscience research has significantly advanced our understanding of the neurobiological mechanisms underlying both the hedonic and motivational components of reward, which are crucial for regulating body weight in both health and disease [106].

The reward system comprises two distinct components: 'liking' and 'wanting' [106]. Although these terms are often used interchangeably, they represent separate psychological processes. "Liking" pertains to the hedonic aspect, which involves the immediate pleasure or anticipated enjoyment derived from consuming a palatable food, particularly through orosensory stimulation [107,108]. In contrast, "wanting" is related to the incentive motivation component, driving increased appetite, food cravings, and behaviours aimed at acquiring food [109].

The 'liking' component is mediated by mesolimbic circuitry, while the 'wanting' component relies on cortically-weighted circuitry that is triggered by cues. Specifically, the hypothalamus and caudal brainstem play critical roles in homeostatic functions, while the mesocorticolimbic circuitry—including the prefrontal cortex, hippocampus subiculum, amygdala, midbrain ventral tegmental area, and nucleus accumbens—processes information related to prior food experiences, reward, emotion, and the social and environmental context [110].

Within the mesocorticolimbic circuitry are brain regions that produce 'liking' and can induce the incentive salience of 'wanting,' illustrating the close interconnection between these functions in the reward system. For example, describing a taste as having a "rich, delicious flavor" leads to greater activation in the reward-related orbitofrontal and pregenual cingulate cortex compared to when the same taste is described as "boiled vegetable water." This demonstrates the potential role of cognitive interventions in shaping sensory perceptions of palatable foods.

Dopamine, a neurotransmitter crucial for incentive motivation, plays a key role in this system, particularly through the mesoaccumbal projection from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAcc) [111]. Studies in rodents have shown that sweet-tasting substances, such as corn oil and sugar, activate the mesoaccumbal dopamine pathway and stimulate motivated behavior for food rewards [112,113]. Similar effects on the dopamine system can lead to increased motivated behavior for food rewards [114,115]. Previous reviews have clarified that the mesolimbic dopamine system is not primarily responsible for the 'liking' of sweet tastes but is instead essential for the 'wanting' or incentive-driven behavior [116,117]. Animals often repeat behaviors that increase accumbal dopamine levels, such as consuming food rewards. For instance, in a model of enhanced dopamine signaling in mice, there was no increase in 'liking' reactions to sucrose, but there was an increased motivated behavior for sweet rewards [118,119]. Thus, the consumption of palatable foods activates the reward center in the nucleus accumbens, leading to increased dopamine levels and consequently, increased food intake [120,121].

Furthermore, taste is not essential for food reward. Mice that cannot process sweet tastes still exhibit a preference for sucrose, demonstrating that sucrose can activate the mesoaccumbal system even in the absence of taste perception [122]. Food palatability and hedonic value play central roles in nutrient intake. However, postingestive effects can influence food preferences independently of palatability, although the neurobiological bases of such mechanisms remain poorly understood. Of central interest is whether the same brain reward circuitry that is responsive to palatable rewards also encodes metabolic value independently of taste signaling. Here we show that trpm5−/− mice, which lack the cellular machinery required for sweet taste transduction, can develop a robust preference for sucrose solutions based solely on caloric content. Sucrose intake induced dopamine release in the ventral striatum of these sweet-blind mice, a pattern usually associated with receipt of palatable rewards. Furthermore, single neurons in this same ventral striatal region showed increased sensitivity to caloric intake even in the absence of gustatory inputs. Our findings suggest that calorie-rich nutrients can directly influence brain reward circuits that

control food intake independently of palatability or functional taste transduction [122]. Lastly, an imbalance between the hedonic/rewarding value attributed to food and actual energy needs is often observed in eating disorders, including obesity [123]. In such cases, the brain's reward system, activated by highly palatable 'obesogenic' foods, appears to override homeostatic signals for body weight control [123].

5.5 *Sensory-specific satiety*

Sensory-specific satiety (SSS) refers to the reduction in pleasantness of a food that has been consumed relative to foods that have not been eaten [124,125]. SSS is associated with both the end of an eating episode and the desire to resume eating when different foods become available (e.g., desserts) [126]. Research by Higgs et al. in 2008 demonstrated that SSS can occur even in the absence of a 'memory for recent eating,' as observed in amnesic patients who experienced SSS across multiple meals [127].

Conversely, some researchers suggest that SSS may be influenced by 'top-down' factors, such as contextual processing, motivation, and broader beliefs about a meal [128]. Rolls and colleagues found that after consuming chocolates of one color, the pleasantness of the taste of the consumed color declined more than that of the uneaten colors, despite these chocolates differing only in appearance [101].

Supporting this finding, other studies have indicated that merely giving participants the impression of consuming a greater variety of flavored test foods can delay satiation [128]. To explore the hypothesis that 'top-down' cognitive processes affect SSS, Wilkinson et al. conducted an experiment where they manipulated participants' expectations about the availability of alternative test foods (uneaten foods) after consuming a test meal (eaten food) [128]. They hypothesized that a decrease in the pleasantness and desire to eat the eaten food would be more pronounced when uneaten foods were not available. However, their findings did not support this hypothesis, and they found no evidence that SSS depends on top-down processes related to the availability of other uneaten test foods [128]. Additionally, Weijzen et al. examined the effects of food complexity and intensity on sensory-specific satiety (SSA), finding that intensity plays a crucial role in SSS, while complexity has a slightly diminishing effect on SSS [102]. Despite these insights, further research is needed to fully understand the complexity of SSA.

5.7 Social context

Human eating behavior is strongly influenced not only by food availability but also by social and cultural contexts, as well as concerns about health and appearance. In situations where social, cultural, and environmental factors exert their own pressures, the reward value of food may not always be the primary determinant of food intake [129,130].

For instance, numerous studies have demonstrated a socioeconomic gradient in obesity rates. In industrialized Western societies, obesity is more prevalent among individuals from disadvantaged social backgrounds [131,132]. Survey data from England and the United States confirm a negative correlation between socioeconomic factors-such as income and education levels-and obesity rates [133].

One possible explanation for the link between poverty and obesity is the affordability of energy-dense foods, which are often high in sugar and fat. In addition to the cost of food, socioeconomic challenges such as low income, limited education, or divorce can increase stress levels, which significantly influence eating behavior and food intake [134]. Studies have linked social disadvantage to disrupted cortisol secretion, neuroendocrine–autonomic imbalance, and increased visceral obesity [135]. Higher socioeconomic status is associated with reduced stress-induced

cortisol secretion, whereas lower socioeconomic status is linked to more stable daily cortisol levels and diminished suppression following dexamethasone treatment [136].

Moreover, atypical stress responses, particularly those involving the hypothalamic–pituitary–adrenal (HPA) axis, may lead to specific addictions. Consuming highly palatable, high-fat foods might mitigate the adverse emotional impacts of stress by affecting the HPA axis in the central nervous system [125,127,128]. Consequently, seeking out foods with high reward properties can be viewed as a form of self-medication, suggesting that some forms of obesity may share similarities with substance dependence [137–139].

Animal studies have supported this notion by demonstrating that rodents and monkeys in lower social hierarchies, who experience higher levels of stress and anxiety, tend to shift their diets toward higher-calorie foods [135]. However, translating these findings to human behavior is complex. Ramani et al. investigated the effect of disadvantageous social contexts on food choice among healthy, non-dieting participants. Despite using experimental methods to create various social contexts in a controlled environment, they found no significant effect of the induced social context on food choice, even when accounting for individual differences [140].

Another critical aspect to consider is the role of social influence in eating behavior. People tend to consume more food when dining with acquaintances or close friends, such as during family meals or social gatherings. This phenomenon, known as 'social facilitation,' is thought to be rooted in basic human behaviors that historically improved survival rates [141]. Previous reports have shown that, in such settings, food intake can increase by as much as 48% in some cases.

Additionally, research by Nisbett and Storms revealed that young males ate more when the person next to them consumed a larger number of crackers and less when the person beside them ate fewer [142,143].

Similarly, a study on women with obesity demonstrated that food intake was about 30% higher during social eating compared to eating alone, and that obesity often clusters within social networks [144]. The extended duration of meals typically associated with shared dining and the social expectation to eat in such settings may also contribute to increased individual food intake compared to eating alone [144].

Finally, research indicates that food behavior can be partially predicted by peers and family [104,119,122–124], with social modeling significantly affecting eating behaviour. In conclusion, while the relationship between social context and food intake is not yet fully understood, gaining a better understanding of how social disadvantage influences unhealthy food choices will be crucial for designing and implementing effective policies to combat obesity and related eating disorders.

6. Complex factors

6.1 Exercise and muscle tissue

Currently, exercise and dietary behaviors are two well-established strategies affecting body composition and weight control.

Exercise’s timing, duration and intensity are essential parameters to optimize energy balance (EB), energy intake (EI) and, consequently, appetite response to physical activity (PA).

During acute exercise, it has been observed that EI does not increase, leading to a short-term negative EB. Forced and vigorous PA, in particular, can result in a temporary appetite suppression, a phenomenon known as ‘exercise-induced anorexia’. At the same time, intense exercises influence appetite-related hormonal fluctuations: ghrelin O-acyltransferase (GOAT) circulating concentrations are suppressed whilst PYY and GLP-1 plasma levels are elevated, returning typically to control values within hours after exercise completion [119,122].

Specifically, muscle contraction resulting from regular PA induces several physiological adaptations on energy demand, muscle fibers conversion (from slow to fast ones), ATP production and skeletal muscle glucose uptake, which increases glucose transporter 4 (GLUT-4) levels.

Moreover, activated muscle tissue induces myokines secretion playing a critical role in weight control. Indeed, as a result of prolonged exercise, muscle cells produce interleukin-6 (IL-6) which stimulates intestinal endocrine cells to release PYY and GLP-1, increasing lipolysis and exercise-induced hepatic neoglucogenesis [29,145].

In contrast, during exercise myostatin is the only reduced myokine which limits muscle growth during embryogenetic development [146].

Another important hormone secreted in response to exercise is irisin involved into browning of subcutaneous adipose tissue [147]. However, research on irisin levels during exercise has produced mixed results [148]. Moreover, irisin increase lipid metabolism and glucose homeostasis reducing insulin-resistance and adipose tissue inflammation[149].

Collectively, these findings all point in the same direction: following a regular exercise program alters appetite sensitivity, gastric emptying rate and glycemic response to meals generating a long-term energy balance.

Indeed, given the crosstalk among exercise, skeletal muscle plasticity and nutritional interventions, these factors are crucial in modulating chronic adaptation to both endurance and resistance exercise.

7.1. Microbiota

An increasingly important impact is played by the gut microbiota comprising a huge diversity of microbes influencing homeostasis maintenance through mutual communication between the GI tract, brain and intestinal bacteria [150,151].

Lactobacillus, *Clostridium*, *Enterococcus* and *Bacteroides* are the main type of intestinal microorganisms in human population [150]. Malnutrition, medications, host genetics and day-to-day diet are some of the factors affecting microbiota composition.

Diet-derived gut microbial metabolites, such as short chain fatty acids (SCFAs), bile acids (BAs) and lipopolysaccharide (LPS) supply essential energy needed forbrain and GI tract biochemical functions.

In particular, SCFAs are produced through the bacterial fermentation of non-digestible polysaccharides, such as dietary fibers and starches [152]. Once in the blood tream, SCFas bind to free fatty acid receptors expressed in skeletal muscle and adipocytes, triggering the release of anorexigenic hormones release (PYY and GLP-1) and subsequently increasing the secretion of peripheral hormones like insulin, leptin and ghrelin) [152–154]. Additionally, SCFAs exert metabolic effects by crossing the blood-brain barrier, directly influencing appetite-regulating neurons [150,152,155]. Therefore, the interaction between microbial metabolites and gut receptors is crucial for modulating the release ofenteric hormones, thus playing a key role in appetite regulation [152,154,156].

Moreover, immunoglobulins (Igs) are involved in the regulation of appetite-related hormones, stimulating the secretion of anorexigenic hormones from enteroendocrine cells [154].

A high-calorie diet and dysbiosis can induce an inflammatory state in the GI tract, resulting in epithelial cells damage, incresed intestinal permeability, and the translocation of bacterial products [152,155].

Consequently, plasma LPS concentrationrises, promoting the growth of gramcausing gram-negative pathogens growth and LPS absorption thus promoting obesity pathogenesis and insulin resistance. From the other side, SCFAs inhibits lipolysis and promotes adipose cells differentiation [150,155,156].

Consequently, brain-gut-microbiota can be considered as a potential regulation factor of energy homeostasis and host metabolism.

7.2. Sleep

Sleep duration, quality, and structure are fundamental to maintaining optimal psycho-physical balance. Aberrations in these sleep aspects, known as "sleep deprivation", detrimentally affect health outcomes and quality of life [157].

An example of such health impacts is the rise in chronic conditions stemming from dysregulation of appetite -namely obesity, metabolic syndrome, and type 2 diabetes [157,158].

Since 2008, studies have established a significant link between inadequate sleep and alterations in body mass index, particularly highlighting an elevated risk of obesity in childrenwith insufficient sleep [159]. Further research indicate a higher consumption of added sugars and sugary beverages among individuals with reduced sleep duration [160].

Chronic sleep deprivation leads to decreased leptin levels and increased ghrelin levels, which enhance hunger and may contribute to weight gain. On the other hand, a diet without restrictions paired with inadequate sleep can suppress the sensation of hunger [157,158].

Moreover, sleep deprivation has been shown to promote the intake of high-calorie foods and encourage hedonic eating behaviors, mediated trough the endocannabinoid system [158,161].

Consequently, circadian rhythms and sleep are critical in regulating metabolism and weight, suggesting that sleep deprivation can alter eating behaviours and increase vulnerability to metabolic disorders.

7.3. Genetic polymorphism

In addition to the previously mentioned environmental and physiological factors, , genetic background plays an important role in appetite regulation.

Historically, obesity has been classified into "monogenic" and "polygenic" forms based on genetic contribution. The first one is typically early-onset and it is caused by single genes mutations which are often loss-of-function alterations in the leptin-melanocortin pathway. The second one, which represent the commonest, is characterized by an interplay among polygenic predisposition and environmental factors. In contrast to monogenic obesity, polygenic obesity is widespread in the general population and involves low penetrance genes [162,163]. Among them, there are single nucleotide polymorphisms (SNPs) in gene involved in hypothalamic FI control and genetic variants in genes coding for GI proteins involved in hunger and satiety [164].

Indeed, it has been demonstrated that extreme obesity is associated with mutations in single genes, such as dose encoding leptin, melanocortin 4 receptor (*MC4R*), *POMC* and the fat mass and obesity-associated (*FTO*) genes, leading to disruption in appetite regulation pathways.. Moreover, SNPs in FTO are linked to variations in energy intake, which result in increased adipogenesis and reduced satiety [165] *FTO* and leptin polymorphisms appear to be involved also in higher saturated fatty acids intake and lipid consumption and seem to be related with improper eating behaviors [165].

Conclusions

In conclusion, the current review delineates a complex interplay of physiological, psychological, and environmental factors in the regulation of hunger, appetite, satiation, and satiety. The rising prevalence of obesity underscores the importance of understanding these multifaceted mechanisms for developing more effective interventions. While pharmacological advances, exemplified by GLP-1 receptor agonists, hold promise, they are not stand-alone solutions. Lifestyle modifications and policy-level changes are equally critical to address the obesogenic environment contributing to the obesity epidemic.

Emerging research linking genetic factors, the gut microbiome, sleep patterns, and stress responses to appetite regulation offers potential new avenues for targeted therapies. However, these findings must be carefully integrated with clinical and public health strategies to ensure that interventions are culturally sensitive, equitable, and sustainable.

Ultimately, the fight against obesity will be most effective when grounded in a holistic understanding that integrates scientific advancements with behavioral and societal initiatives. Ongoing research and interdisciplinary collaboration are essential to translate these insights into practice, aiming to reduce the burden of obesity and related metabolic diseases.

List of abbreviation

AgRP: agouti-related peptide
AT: adipose tissue
BAs: bile acids
BAT: brown adipose tissue
BDNF: brain-derived neurotrophic factor
CART: cocaine- and amphetamine-regulated transcript
CCK: cholecystokinin
EB: energy balance
EE: energy expenditure
EI: energy intake
EIR: energy intake rate
ER: eating rate
FAs: fatty acids
FED: food energy density
FI: food intake
FGF21: fibroblast growth factor 21
FTO: fat mass and obesity
GHS-R1a: growth hormone secretagogue receptor 1a
GI: gastrointestinal
GIP: glucose-dependent insulinotropic polypeptide
GlyI: glycemic index
GLP1: glucagon-like peptide 1
GLUT4: glucose transporter 4
GOAT: ghrelin O-acyltransferase
HPA: hypothalamic–pituitary–adrenal axis
Igs: immunoglobulins
IL-6: Interleukin-6

LCTs: Long-chain triglycerides
LPS: lipopolysaccharide
MC3R: melanocortin 3 receptor
MC4R: melanocortin 4 receptor
MCT: medium chain triglycerides
MSH-α: Melanocyte Stimulating Hormone alpha
NAcc: nucleus accumbens
NPY: neuropeptide Y
OET: oro-sensory exposure time
OFP: oral food processing
OXM: oxyntomodulin
PA: physical activity
POMC: pro-opiomelanocortin
PYY: peptide YY
SNPs: single nucleotide polymorphisms
SNS: sympathetic nervous system
SCFAs: short chain fatty acids
SSS: sensory specific satiety
TLR4: Toll Like Receptor 4
WAT: white adipose tissue

Table 1. Obesity-associated diseases and conditions

Organ or system	Disease or condition
Mental	Attention deficit diseases Depression Anxiety Panic disorders
Cancer	Many cancer types, including breast, colon, and pancreatic cancer
Cardiovascular	Atherosclerotic cardiovascular disease Hypertension Atrial fibrillation Heart failure
Metabolic	Type 2 diabetes Fatty liver disease Dyslipidemia Gallstones Gout
Coagulation	Thrombosis Lung embolism
Skin	Psoriasis
Reproductive	Male infertility Hypogonadism Polycystic ovary syndrome
Musculoskeletal	Osteoarthritis Fatigue Physical impairment Back pain
Pulmonary	Sleep apnea Asthma Chronic obstructive pulmonary disease
Urogenital	Infection Incontinence

Adapted from Müller T.D. et al. [1]

Table 2. Strategies to increase satiety or satiation

Gastrointestinal factors	
Oral food processing	• Eat foods slowly • Increase the chewing time • Lower the sizes of bites or use smaller silverware
Gastrointestinal stretch	• Consume high-volume low-calories food at the beginning of the meals (e.g., salads)
Food-intrinsic factors	
Food energy density	• Reduce the consume of high energy dense foods (sugar beverages) while increasing low energy dense foods (fresh fruits) • Reduce energy density in food by reducing the caloric content (without affecting food volume) or increasing food volume (without affecting caloric content)
Physical features of foods	• Prefer harder foods (solid > semi-liquids > liquid), elastic foods (squid > crispy potatoes) • Prefer foods with a lower lubrication (e.g., dry, without condiments, low fat content)
Food macronutrients	• Favor balanced meals in terms of macronutrients
Sensory & cognitive factors	
Food perceptions by senses	• Apply sensory cues to encourage the consumption of healthier diets like color odors and texture
Food palatability	• Reduce highly palatable food with an high content in saturated fats, sugars, and refined grains (western diet)
Prior beliefs & associations & hedonic behaviour	• Manipulate beliefs and expectations about food to reduce consumptions
Reward	• Finding sources of pleasure and reward in recreational activities, hobbies, and relationships
Sensory-specific satiety	• Decrease the variety of intrameal food
Social context and complex factors	• Reduce and/or learning to manage stress while maintaining a healthy lifestyle
Other regulators	
Exercise and muscle tissue	• Perform regular aerobic physical activity
Adipose tissue	• Eat a well-balanced diet, increasing fruit and vegetables consumption
Microbiota	• Consume a high amount of vegetables and fiber
Sleep	• Ensure an optimal and restful sleep, providing the regular sleep circle
Genetic polymorphism	• Identify early a potential genetic condition

Table 3. Selected hormones involved in hunger, appetite, satiety, and energy regulation. CCK: cholecystokinin, GLP1: glucagon-like peptide 1, OXM: oxyntomodulin, PYY: peptide YY. *Adapted and modified from Advanced Nutrition and Human Metabolism 8th edition.*

Hormone	Site of production	Stimulus	Action
Leptin	White adipose tissue	Overfeeding or increased adipose tissue	Impair the drive to eat and stimulates physical activity; chronic overfeeding and obesity can cause leptin resistance
Insulin	Beta-cells of pancreas	Blood glucose levels	Reduces blood glucose levels, suppress hunger, and stimulates the deposition of triacylglycerols in adipose tissue
Amylin	Beta-cells of pancreas	Blood glucose levels	Suppress hunger

Adiponectin	Adipocytes	Decreased adipose tissue	Protect against insulin resistance
Ghrelin	Stomach and duodenum	Fasting and acute stress	Stimulates food intake
CKK	Intestine	Food ingestion	Suppress hunger
GLP-1	Intestine	Food ingestion	Suppress hunger and inhibits glucagon synthesis
OXM	Intestine	Food ingestion	Suppress hunger
PYY	Intestine	Food ingestion	Reduce gastric motility and suppress hunger

***Figure 1**: The satiety cascade*

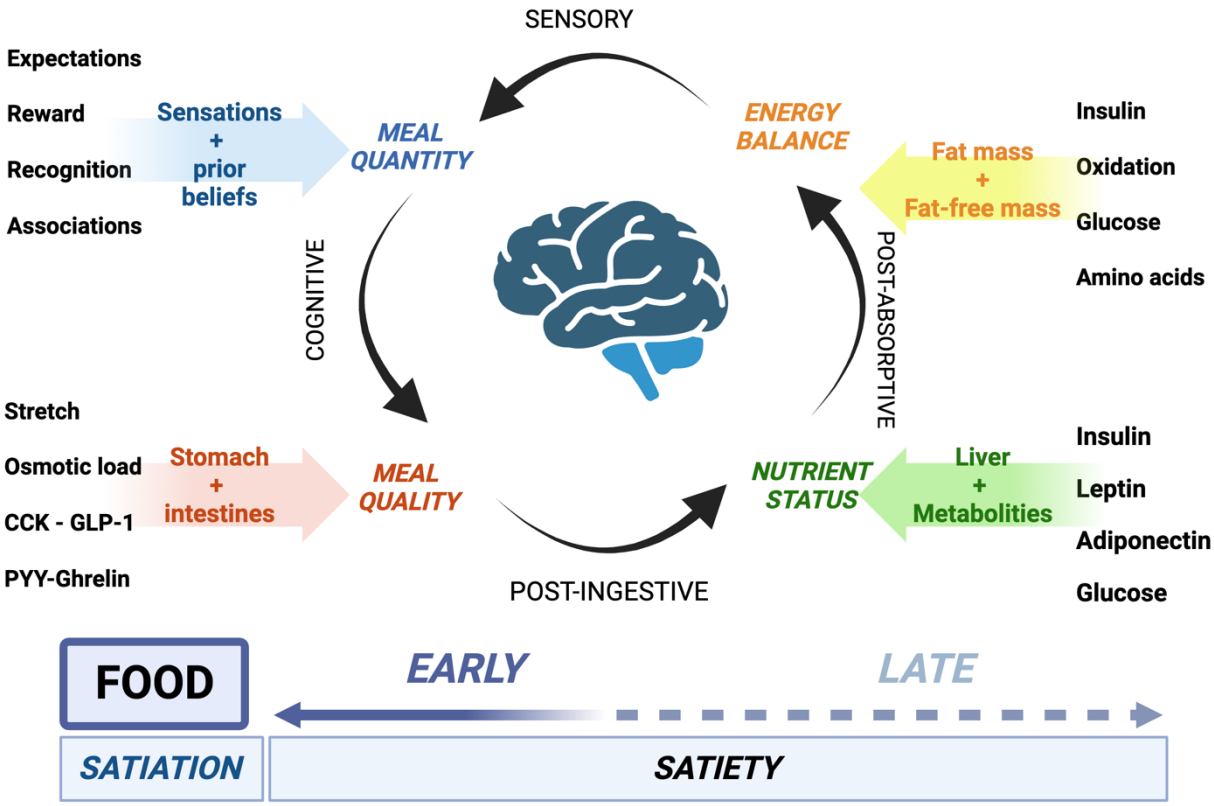
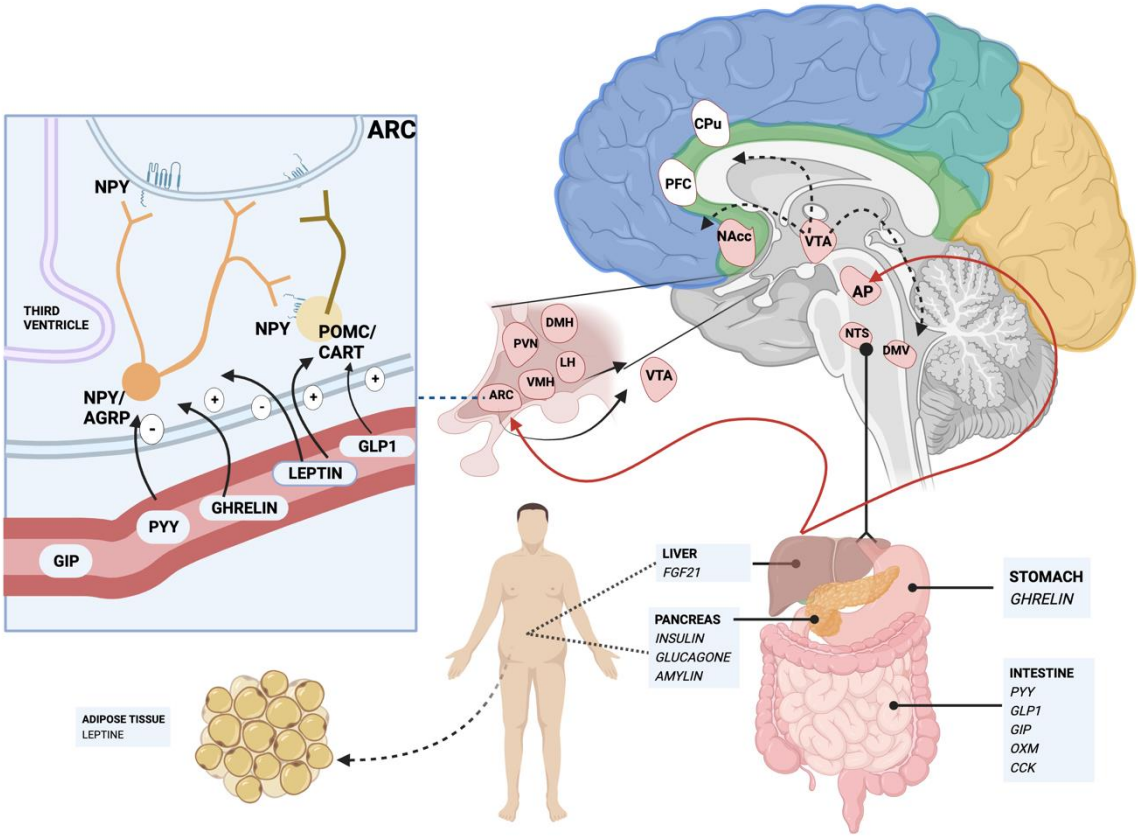


***Figure 2**. Gut-brain neuronal feedback: Mechanisms of action of peripheral hormones in the central regulation of eating behavior.*



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