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Changes in eating behavior, taste and food preferences and the effects of gastrointestinal hormones

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SUMMARY

Eating behavior is a complex response to different internal and external factors and whose aim is to preserve the homeostasis of energy intake, the stability of body weight and ultimately health. Although under physiological conditions, energy intake is relatively stable over the long period, many stimuli (i.e., mechanical, metabolic, environmental, etc.) may acutely influence energy intake. To offset or minimize the effects of such stimuli on energy homeostasis, humans are equipped with neuronal complex mechanisms integrating peripheral and environmental signals. In particular, eating behavior is determined by homeostatic feeding and hedonic feeding. In the presence of changes in taste or smell, these mechanisms interact with peripheral effectors, including gastrointestinal peptides, to preserve energy intake and ultimately body weight. Aging is associated with a progressive inability of these systems to protect net food intake. Also, changes of eating behavior during disease appear to be related to the activation of a specific neuronal emergency circuit, which promotes anorexia. The persistence during evolution of the emergency pathway suggests that still unidentified component of anorexia and fasting metabolism could be exploited to enhance recovery of patients with acute and possibly chronic diseases.

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1. Introduction

Food intake is a priority for humans since the ability to sustain long periods of starvation is limited and almost abolished during disease. However, measuring energy and protein intake describes only a fraction of the complexity of the decision process leading to eating and stop eating. Therefore, the term eating behavior more precisely characterizes the process of eating in humans, since it encompasses the complex mechanisms behind the decision to eat and to stop eating. Indeed, the number of meals and their sizes, as well the selection of different foods, are under the variable influence of many internal and external factors, including taste changes, gut motility, psychological distress, and pain among others. Consequently, prevention and treatment of primary and disease-related changes of eating behavior should be based on a thorough assessment of the different influencing factors [1].

2. Homeostatic control of eating behavior

Under physiological condition, the intake of energy, proteins and nutrients with the diet is stable over the long period, although significant variations may occur on a day-to-day basis. An example is provided by observing the food intake of female rats during their estrous cycle, whose food intake is relatively stable despite cyclically and reciprocally recurring changes in meal number and meal size (i.e., proxies for satiety and satiation, respectively), which are synchronized with the estrous cycle [2]. Therefore, under physiological conditions, net food intake is a dynamic process and the homeostasis of energy intake in response to external as well as internal stimuli is maintained via the modulation of satiety and satiation.

The homeostatic control of eating behavior is a complex mechanism mainly integrated in the brain, at the hypothalamic level. Robust evidence point to hypothalamic nuclei as the site of integration of metabolic, hedonic and mechanical signals arising from peripheral and central areas [3]. In particular, activation/inhibition of NPY neurons and/or melanocortin neurons increase/reduce the drive to eating. Of interest, these two sets of neurons are reciprocally innervated, and therefore the prophagic drive activated by the stimulation of NPY neurons is simultaneously reinforced by the concurrent inhibition of melanocortin neurons [4].

As previously mentioned, different factors contribute to modulate the concerted activity of hypothalamic nuclei involved in the homeostatic regulation of eating behavior. Among them, mechanical stimuli from gastrointestinal tract have been extensively studied. Experimental imaging studies revealed that distention of the stomach with an intragastric balloon resulted in significant reduction in food intake [5]. More importantly, gastric distention increased functional activity, as revealed by BOLD fMRI, within homeostatic regions such as the hypothalamus, as well as non homeostatic regions including the hippocampus, amygdala, thalamus, cerebellum and the cortex [5]. These results indicate that gastric distention increases neuronal activity in both homeostatic and non homeostatic brain circuits which regulate food intake. Similarly to mechanical signals, metabolic signals also influence homeostatic eating behavior. To preserve body weight, it is assumed that changes in metabolic rate modulate appetite and food intake. To address this issue, Mc Neil et al. studied the relationship between body composition and resting metabolic rate with acute (1 meal) and daily energy intake [6]. They observed that fat-free mass is the best predictor of acute energy intake whereas resting metabolic rate is a good predictor of daily energy intake in weight stable individuals [6]. However, greater error variance in acute and daily energy intake with increasing resting metabolic rate values was observed, suggesting that the influence of energy metabolism may not be linear across the spectrum of its possible changes.

3. Hedonic control of eating behavior

Food is a potent inducer of metabolic response but also triggers specific rewarding neural circuits. Consequently, the hedonic properties of food contribute to modeling individual eating behavior and may also override the precise balance of the homeostatic control of eating. In fact, many neural circuits that are thought to orchestrate feeding behavior overlap with the brain's reward circuitry both

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anatomically and functionally [3]. Therefore, homeostatic feeding and hedonic feeding are not completely dissociable although addressing different needs of the living organisms, because of their functional and anatomical overlap.

Smell is a key component of food informing on its quality and safety, and driving selection and duration of the meal. Olfactory bulbectomized rats acutely decrease meal size, but net food intake is not compromised due to increased meal number [7]. However, 40 days after olfactory bulbectomy, baseline differences between meal size and number no longer exist [7]. These results suggest a functional adaptation of food intake regulatory mechanism despite the loss of smell, to preserve homeostasis of energy intake. When hedonic feeding dysregulates homeostasis of energy intake, olfaction plays a key role. Mice upon conditional ablation of mature olfactory sensory neurons are resistant to diet-induced obesity accompanied by increased thermogenesis [8]. After obesity onset, acute loss of olfaction abrogated further weight gain and improved body composition and metabolic abnormalities [8]. Also, increased sympathetic nerve activity was also registered, leading to activation of beta-adrenergic receptors on white and brown adipocytes to promote lipolysis. In contrast, enhanced olfactory performance leads to increased adiposity and insulin resistance [8].

Whether hedonic feeding has developed and evolved as a reinforce for homeostatic feeding or plays a more substantial role in maintaining health remains a debated issue. Recent experimental data suggest that hedonic feeding, by activating brain rewarding circuits, may actually enhance immune competence thereby providing biological insights into the association between psychological and physical well-being. Ben-Shaanan et al. reported that activation of the ventral tegmental area, a key component of the reward system, strengthens immunological host defense as manifested by enhanced antibacterial activity of monocytes and macrophages, reduced in vivo bacterial load and a heightened T cell response in the mouse model of delayed-type hypersensitivity [9]. Also, ablation of the sympathetic nervous system reduces the magnitude of the immune-enhancing effects of activation of the ventral tegmental area [9].

4. Taste changes and eating behavior

Sensorial inputs modulate eating behavior. During lifetime, the acuity and discriminating ability of senses significantly change, leading to changes in taste and smell perceptions and consequently to modifications of food preferences and eating behavior. Interestingly, changes in taste/smell do modify energy intake when they occur in late life, whereas they are almost completely compensated when they occur in early adulthood. This suggests that the homeostatic mechanisms maintaining adequate energy intake fail in older adults, contributing to the onset of secondary anorexia and sarcopenia of aging [10].

Taste is a key sensation informing food selection. Taste receptors are located through the body, but extensive research has been devoted to the functional role of those located on the tongue. In this anatomical area, taste receptors are organized in taste buds [11]. Aging modifies taste sensitivity. The pathogenesis of taste changes is related to decreased expression and function of peripheral taste receptors although animal studies revealed that the profile of the gustatory nerve responses is inconsistent with the profile of the behavioral responses [12]. Also, the mRNA expressions of signaling effectors were slightly, but significantly, decreased in old mice [12]. Finally, no significant differences in the turnover rates of tastebud cells has been observed between the young and old mice [12]. Consequently, changes in taste sensitivity with aging may not be solely caused by aging-related degradation of peripheral taste organs. These results point to a contributory role of altered neuronal circuits.

By applying psychophysics and gustatory event-related potentials (gERPs) to explore age-related differences in the processing of gustatory information as indicated by the cerebral sources of the gERP, Iannilli et al. reported that psychophysical testing for smell and taste function exhibited a significant decrease with age [13]. Topographical analyses of the EEG delineated four basic topographical maps that explained the processing of taste in the pre-decline age range, with sources inside the relevant gustatory areas. The age-related change of gustatory processing was associated with the absence of a specific map with sources inside the cerebellum and posterior insula, and the temporal broadening of a map with sources in the bilateral inferior frontal gyrus. These results confirm the

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hypothesis that the reduction of taste function with aging is not only due to degradation of gustatory peripheral tissues but is also related to different neural signatures in the central nervous system.

5. Role of gastrointestinal peptides in eating behavior and its changes

The gut controls eating behavior, digestion and absorption of nutrients by producing a number of peptides which modulate the interest in food, satiation, satiety and gut motility among other functions (Table 1).

The gastrointestinal tract is the primary source of the hormones ghrelin and motilin [14]. Both hormones act on structurally similar G protein-coupled receptors. The function of endogenous ghrelin and motilin is to increase appetite or hedonic eating (ghrelin) and initiate phase III of gastric migrating myoelectric complexes (motilin). In clinical trials, the use of a motilin receptor agonist increases gastric emptying, but at lower doses reduces gastroparesis symptoms and improves appetite. Ghrelin analog agonists have been tested for the treatment of diabetic gastroparesis because of their ability to increase gastric emptying, but with mixed results; however, relamorelin, a ghrelin agonist, reduced nausea and vomiting in patients with this disorder. Ghrelin and ghrelin analogs (i.e., anamorelin) have been also tested in cancer patients to treat anorexia-cachexia. Results obtained showed that ghrelin improves eating behavior and food intake of cancer patients, but has no effect on physical function [15,16].

Glucagon-like peptide-1 (GLP-1) has emerged as one of the most important gastrointestinal peptides because of a combination of functions not previously ascribed to any other molecule. GLP-1 potentiates glucose-induced insulin secretion, suppresses glucagon release, slows gastric emptying and may serve as a satiation signal, although the physiological status of the latter function has not been fully established yet [17].

Pancreatic polypeptide (PP) is a potent anorexigenic hormone, which significantly modulates eating behavior and energy homeostasis. Intra-gastric and intra-intestinal nutrients activate PP secretion from the gastrointestinal tract, leading to vagal stimulation that mediates complex actions via the neuropeptide Y4 receptor in the hypothalamus, subsequently activating key hypothalamic nuclei and dorsal vagal complex of the brainstem to influence energy homeostasis and body composition [18]. PP has been demonstrated to have affinity for the neuropeptide Yy6 receptor, mediating actions via the suprachiasmatic nucleus and pathways involving vasoactive intestinal polypeptide and insulin like growth factor 1 [18].

Cholecystokinin (CCK) is a satiety factor, acting at type 1 receptors (CCK1Rs) on vagal afferent neurons [19]. Therefore, its role in the treatment of obesity has been studied in trials with negative results. Of great interest are recent data suggesting that the anorexigenic effects of CCK could be related

Table 1
Site of synthesis/release and function of gastrointestinal peptides.

Gastrointestinal peptide	Site of synthesis/release	Function(s)
Gastrin	Gastric mucosa	Gastric acid secretion Gastric epithelial organization
CCK	Duodenal mucosa	Activation vagal afferents and mechanosensitive fibers Relaxation of proximal stomach Inhibition gastric emptying Gallbladder contraction Reduces meal size
Ghrelin	Stomach	Stimulates release of GH Increases food intake Favors adiposity Stimulates gastric emptying
Gastric leptin	Fundic glands in the stomach	Released after food intake
GLP-1	Intestinal L cells	Increases insulin release Increases satiety
PP	Pancreatic D cells	Reduces appetite
PYY	Intestinal L cells	Appetite suppression

CCK: cholecystokinin; GLP-1: glucagon like peptide-1; PP: pancreatic polypeptide; PYY: peptide tyrosine–tyrosine.

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to the specific metabolic environment of patients. In particular, CCK1R function might be defective due to abnormal membrane composition. Results obtained showed broad ranges of cellular cholesterol and CCK responsiveness, with elevated cholesterol correlated with reduced CCK sensitivity [19]. This was prominent with increasing degrees of obesity and the presence of diabetes, particularly when poorly controlled. Therefore, CCK responsiveness varies widely across the population, with reduced signaling in patients with obesity and diabetes. This could explain the failure of CCK agonists in anti-obesity clinical trials.

6. Changes of eating behavior during disease

Acute and chronic diseases are associated to the development of sickness behavior, a highly evolutionary conserved behavioral and metabolic response. Key component of sickness behavior is the loss of appetite and dysregulation of eating behavior. The better understanding of the pathogenesis of altered eating behavior during disease may contribute to its prevention and treatment, with immediate positive consequences on clinical outcome. For decades, it has been hypothesized that the changes of eating behavior during disease could be secondary to deranged activity of the mechanisms controlling homeostatic and hedonic feeding [4]. Based on this premise, a number of therapies and drugs have been developed to target the melanocortin neurons with limited results. This could suggest that a more complex mechanism control eating behavior during disease.

Using genetically encoded anatomical, optogenetic and pharmacogenetic tools, Carter et al. demonstrated that parabrachial nucleus neurons projecting to the central nucleus of the amygdala suppress appetite [20]. In contrast, inhibition of these neurons increases food intake in circumstances when mice do not normally eat. These results show that this neural circuit from the parabrachial nucleus to the central nucleus of the amygdala mediates appetite suppression in conditions when it is unfavorable to eat, thereby providing an anatomical independent localization to the anorexia of disease.

7. Conclusions

Eating behavior is precisely controlled to maintain the homeostasis of energy intake and preserve health. Different internal factors contribute to this process, each influencing either the homeostatic mechanism of eating or the hedonic mechanism of eating. Therefore, taste, sight, smell modulate meal structure, yet the system appears able to compensate, at least temporarily, for the negative consequences of internal and external factors on the stability of energy intake. A robust contributory role for the preservation of eating behavior is played by the gastrointestinal peptides, whose function is to modulate not only satiety and satiation but also gut motility and food preferences. Interestingly, the ability of the system to compensate for food or smell changes appears to fail in older age, making this population more vulnerable to the development of malnutrition and sarcopenia. During disease, changes of eating behavior appear to be secondary to the activation of a specific emergency pathway rather than the dysregulation of the homeostatic/hedonic feeding. This information may help in developing more effective therapies to counteract the anorexia of disease and the attendant cachexia syndrome.

Conflicts of interest

The authors declare no conflict of interest.

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