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Lipids, carbohydrates, or proteins, what do you prefer? An update review of physiological factors for food choice

Lípidos, carbohidratos o proteínas, ¿cuál es tu preferencia? Una actualización de los factores fisiológicos de la selección de alimentos

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ABSTRACT

Obesity is an issue that impacts vulnerable populations worldwide, resulting in significant monetary costs related to health problems. Nutrient intake and preferences for specific foods are major factors that can lead to the development of healthy or poor nutritional habits, which will ultimately define if an individual becomes overweight. Various circumstances influence these preferences, such as physiological needs, emotional, social and hedonic factors, and the expression and signaling of different molecules. It is essential to clarify the diverse mechanisms by which the body "chooses" certain types of food since these choices will recur throughout the lifespan of an individual, potentially causing poor eating habits. Multiple components contribute to nutrient preference. Some of these are aging, variability in taste receptors, flavor perception, hormones, nutrient deficiencies, and gene expression. The purpose of this review is to identify and emphasize the physiological elements that may regulate and affect food preference.

Keywords: Diet. Food preferences. Macronutrients. Nutrition.

RESUMEN

La obesidad es un problema que afecta a las poblaciones vulnerables en todo el mundo, lo que genera costos monetarios significativos relacionados con los problemas de salud. La ingesta de nutrientes y las preferencias por alimentos específicos son factores importantes que pueden conducir al desarrollo de hábitos nutricionales saludables o deficientes, lo que finalmente definirá si una persona tiene sobrepeso. Diversas circunstancias influyen en estas preferencias, tal es el caso de las necesidades fisiológicas, factores emocionales, sociales y hedónicos, y la expresión y señalización de diferentes moléculas. Es fundamental esclarecer los diversos mecanismos por los cuales el cuerpo «elige» ciertos tipos de alimentos, ya que estas elecciones se repetirán a lo largo de la vida de un individuo, pudiendo causar malos hábitos alimentarios. Múltiples componentes contribuyen a la preferencia de nutrientes. Algunos de estos son el envejecimiento, la variabilidad en los receptores del gusto, la percepción del sabor, las hormonas, las deficiencias de nutrientes y la expresión génica. El propósito de esta revisión es identificar y enfatizar los elementos fisiológicos que pueden regular y afectar la preferencia alimentaria.

Palabras clave: Dieta. Preferencia de alimentos. Macronutrientes. Nutrición.

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INTRODUCTION

Feeding is one of the primordial needs of the human body. It is known that the fetus is fed through the placenta through the umbilical cord, which is wrapped by a membrane called the amnion. Initially, this membrane covers the embryo, but around the 5th week, it begins to fill with amniotic fluid. The amniotic fluid contains glucose and amino acids, as well as chemicals associated to flavors from the mother's diet. The development of the gastrointestinal tract begins between weeks 3 and 4, but it is not until the past weeks of the first trimester that the developing fetus will start to swallow amniotic fluid. In addition, by the end of the second trimester, the taste buds will have formed, but the gustatory and olfactory systems won't reach its full maturity until the end of pregnancy[1]. Flavor receptors in the fetus are not only found in the tongue, but also throughout the gastrointestinal epithelium, generating the first connection between the intestine and the brain[2]. Some of the most important sensory organs involved in flavor perception are the taste buds. These contain flavor receptors that send signals through cranial nerves (VII, IX, and X) to fungiform papillae located on the anterior part of the tongue, foliated papillae on the back of the tongue, the soft palate, and the pharynx[2].

The oral cavity can perceive sweet, sour, salty, bitter, and umami flavors. Sweetness originates from foods rich in sugars, the umami flavor is associated with protein consumption, in particular to the taste of monosodium glutamate, saltiness is attributed to sodium chloride (table salt), whose receptors can be considered as electrolyte sensors, sourness is caused by acidic foods and drinks such as lemon, and bitterness, which is one of the most sensitive tastes, is often associated with coffee. Our heightened sense of bitterness is particularly useful since it allows us to identify spoiled foods or harmful substances that should not be consumed[2,3]. The salty and sour tastes are detected by ion channels, whereas sweet, umami, and bitter are detected by taste GPCRs[3].

The first taste receptors that were discovered were the TAS1R1, TAS1R2, and TAS1R3 (Taste receptor type 1 member 1/2/3), which are products of the Tas1r genes. The TAS1R1/TAS1R3 dimer detects the umami taste, while the TAS1R2/TAS1R3 dimer detects the sweet taste[3]. Subsequently, the TAS2R (taste receptors type 2), which is able to identify bitterness, was identified in mice and humans (35 members in mouse and ~25 members in human); TAS2R is classified according to their range of adjustment into "generalists, moderates, and specialists." According to Tole et al., generalist receptors are the most important since these detect about 50% of the bitter compounds[3].

At birth, babies present an increased acceptance for sweetness and saltiness. In particular, saltiness acceptance clearly increases in the 1st year of life[4]. These are adaptive responses to foods with these flavors due to developmental needs, for example, milk with sweet taste due to its high lactose content, and amino acids with salty taste caused by glutamate[3]. Besides this, during flavor learning, sensation and perception may differ from periods and rejection to certain foods may occur[4].

The first thousand days of life (~3 years) are essential for the development of healthy eating habits[4]. Moreover, this period seems to predict eating behaviors that may last even into adulthood[5]. Early and repeated exposure to healthy (minimally processed) foods has a serious impact from the prenatal period. This exposure favors the child's future acceptance of new foods. For example, breastfed children of mothers who consumed a varied diet presented a greater desire to eat new food during childhood, whereas children who were fed with formula showed a considerable degree of neophobia to food[4].

It has been suggested that children fed with breast milk for periods longer than 3 months have higher vegetable intakes in later childhood years[6]. However, during ablactation (weaning of an infant), the acceptance of new vegetables is variable, and offering at least 8 times a new green vegetable is recommended to increase its acceptance[4]. Thus, ablactation is considered one of the most important phases to induce food preferences[5].

There are three mechanisms by which food preferences are established in infants during ablactation. These are as follows: repeated exposure, exposure to

varieties, and associative conditioning. Repeated exposure refers to trying a particular new food on multiple occasions, exposure to varieties means offering different foods repeatedly, and associative conditioning is combining a new food with one already known or accepted; these last two mechanisms showed greater positive responses than repeated exposure[6]. Food preference also encompasses other factors such as: food selectivity, sensory sensitivity, lack of interest in eating, food aversion, consuming only particular preparations or food presentations, eating small amounts of food, and inappetence. Some of these factors can lead to an insufficient consumption of specific foods necessary for development and growth[5,6].

Inadequate eating habits (influenced mostly by food preferences), in conjunction with other elements such as sedentarism and genetics, predispose people to malnutrition. In this context, obesity, as a form of malnutrition, represents a major global health problem since more than 609 million individuals worldwide suffer from this condition[7]. Hence, there is a dire need to elucidate the underlying mechanisms that take place during the beginning and development of obesity. One such mechanism is related to our food choices, which, at some point in time, could lead to a detrimental lifestyle, affecting health homeostasis. Finally, it is important to recognize that different molecular processes may influence food selection. Consequently, this review also identifies molecular elements that regulate macronutrient intake processes, emphasizing sensorial elements that affect food preference.

MATERIALS AND METHODS

Search strategy and databases

This review is based on retrospective clinical studies, basic science research, case reports, and review articles associated with diet preferences and conditioning factors for specific foods. The cited works were found in PubMed, Science Direct, and Google Scholar. Pertinent studies were selected from an extensive reference search. The search terms included "Food," OR "Diet," OR "Carbohydrates," OR "sugars," OR "Lipids," OR "Fats," OR "Protein," and combined with "Preference." Result duplicates and patient studies were removed. Only full-text articles were considered, and the publication date of the selected studies ranged from 2000 to 2021. In addition, in a second round, we searched specifically for each macronutrient with "food preference" to augment the scope of the research. Studies of patients undergoing surgical procedures, pharmaceutical trials, or supplementation were excluded from the study. Eligible research was analyzed regardless of its duration.

Data analysis and synthesis

Data were narratively reported for each macronutrient. Results of the selection criteria were displayed in a flowchart (Fig. 1). Potential future research directions were suggested in the conclusion.

ELEMENTS INVOLVED IN CHOOSING HIGH-FAT FOODS

Dietary fats add palatability to meals, stimulate the satiety response, increase the energy density of foods, and are often preferred by individuals with obesity. The perception of this nutrient depends on lipid receptors, which have been identified in the taste buds of rodents and humans[8]. Interestingly, a partial or total absence of these receptors (CD36/SR-B2, GPCRs) will lead to the preference toward fat consumption[9]. Another variable that plays an important role in dietary fat perception is the nutritional state of an individual. For example, obesity alters the orosensory perception of signals, impairs the appetite and satiety circuitry, and may eventually produce outcomes such as neuronal desensitization, endocrine abnormalities, chronic inflammation, and dominant hedonic hunger. Ultimately, these factors can cause unhealthy eating behaviors. Some studies have tried to illustrate the endocrine role in dietary fat preference. For example, glucagon-like peptide-1 receptor (GLP-1) and peptide YY (PYY_{1-36}) knock-out mice showed a decreased response to lipids[8,9].

Figure 1. Algorithm for the selection of dietary preference studies.

CD36 (a lingual lipid receptor) is a glycoprotein receptor that has an affinity for long chain fatty acids. According to Bricio-Barrios et al., people with mutations in CD36 have a lower perception of lipids, causing a greater preference for fats and oils. Moreover, the combination of low levels of this receptor with a high sensitivity threshold for fatty acids was observed in overweight and obese people, which is evidence of an inadequate lipid taste perception[10]. Another important factor is taste receptors. For example, TAS1R knock-out murine models responded differently to high-fat food, consuming less due to the poor palatability experience. These animals also showed lower levels of fat mass and triglycerides

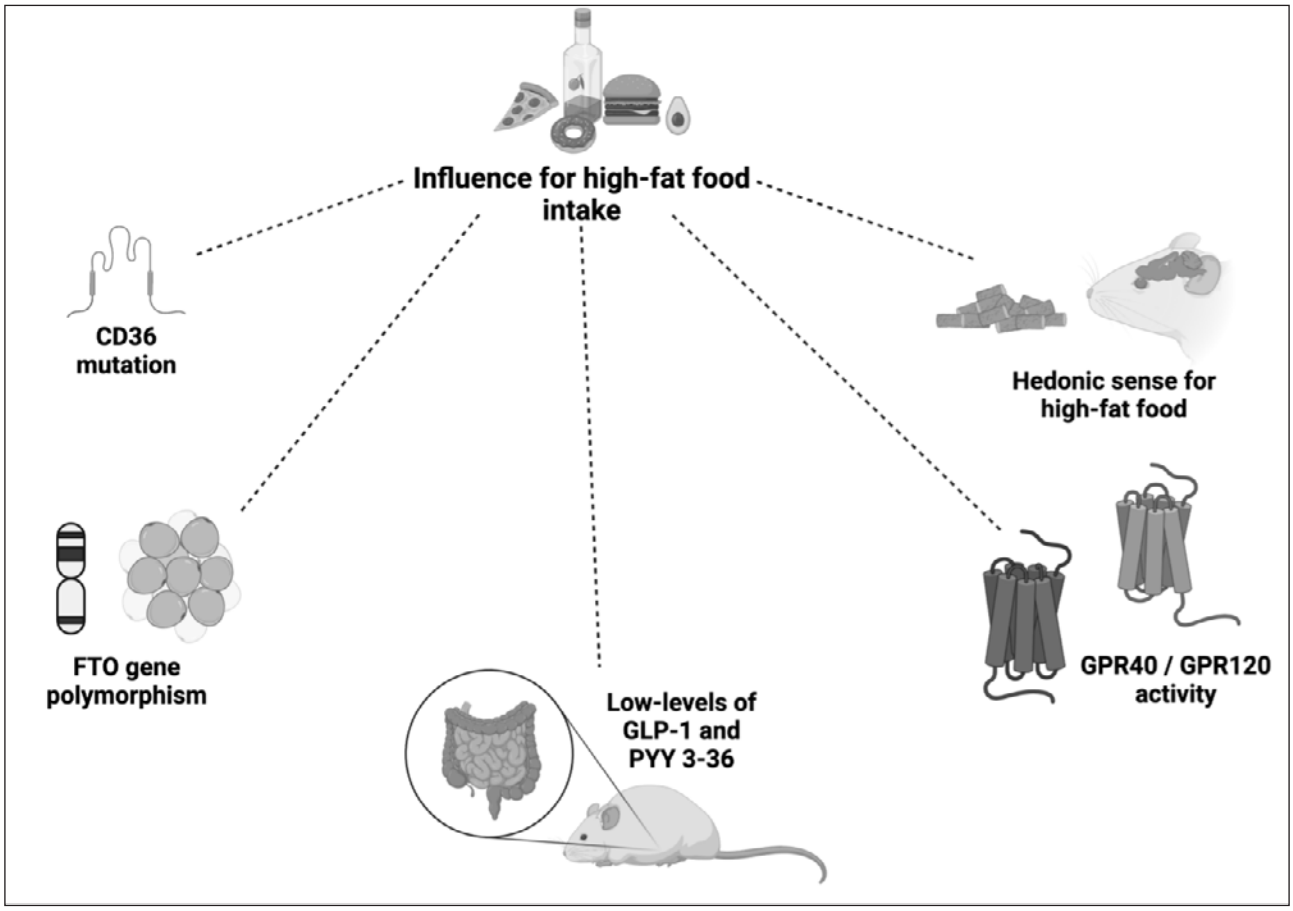

Figure 2. Putative events that influence high-fat food intake. *Created with BioRender.com.*

stored in the liver. It has been hypothesized that the ablation of these receptors reduced the activity in adipocytes (lipid metabolism alteration) and the pancreas (diminished hyperinsulinemia), conferring a protective effect against fat accumulation[10].

Nucleotide polymorphisms may also play a role in lipid perception. For instance, the AT/AA genotype of the FTO rs9939609 gene, which is associated with fat mass, obesity, appetite regulation, and the preference for energy-dense foods, is believed to cause increased dietary fat intakes[11]. However, this remains controversial.

Another aspect to be considered is the endocannabinoid system, which has been linked to food consumption through the cannabinoid receptor 1 (CB1R). This receptor has been shown to play an important role in the fat taste perception. The activation of CB1R induces a Ca^{2+} response, which increases the perception linked to CD36 activity[12]. Similarly, GPR120 was also found to be implicated by regulating fat-related satiety in mice models. This suggests that GPR120, along with the secretion of the peptide hormone GLP-1 in taste bud cells, plays a role during postprandial fat taste sensitivity (Fig. 2). Furthermore, relevant is how the fatty acid sensors GPR40 and GPR120, which are expressed in intestinal enteroendocrine cells, are activated after oral intake of fats, conditioning the preference toward this nutrient and suppressing the secretion of other molecules such as ghrelin through GPR120. However, the mechanism of action of these receptors has not yet been elucidated[12,13].

Downregulating the preference of a high-fat diet (HFD) is a potential target in the treatment for obesity. Miyake et al. (2021) described the effect of adipocyte activation during the integrated stress

response pathway, which induced the secretion of the adipokine growth differentiation factor 15, an adipokine associated with a decreased preference for a HFD in murine models[14].

The influence of the ventral tegmental area has also been studied. This region becomes sensitized (specifically in dopaminergic neurons) after the chronic consumption of a HFD, leading to the preference toward this type of foods through the blunted release of dopamine in the nucleus accumbens (NAc) during the time of ingestion. This preference has been associated with the parallel increase in activity in glutamatergic and GABAergic neuronal subpopulations[15].

Lactation can also influence food choices. It has been observed in murine models that early weaning can result in elevated corticosterone levels, favoring the appearance of anxiety-like behaviors, and consequently increasing the intake of fat in the diet. Moreover, low expressions of the brain-derived neurotrophic factor and the 5HT-1B receptor, which are molecules that modulate the mesolimbic dopamine system, can also cause individuals to increase the intake of more palatable foods, impacting directly the hedonic feeding[15].

Stress certainly plays a role in our diet and, therefore, the associated coping mechanisms too. For example, beta-endorphin, which is a neuropeptide produced in the pituitary gland capable of blocking the sensation of pain and other forms of stress, has been shown to regulate fat consumption. Concretely, murine studies have confirmed that after ingesting corn oil, there is a release of this neuropeptide in the hypothalamus, generating satiety in the short term, but potentially increasing the appetite at high doses in specific loci of the brain[16].

The last example in this section is the neuromedin-U receptor 2. This G-protein coupled receptor is located in the paraventricular nucleus and a reduction in its expression is associated with obesogenic eating. It has been proposed that neuromedin neurons may project to different regions such as the arcuate nucleus and the parabrachial nucleus, which are associated with feeding behaviors. This mechanism could involve different neuronal populations, and chemicals, such as -melanocyte-stimulating hormones, dopamine, and the melanocortin system[17].

FACTORS INVOLVED IN CARBOHYDRATES INTAKE PREFERENCE

Carbohydrates are an important source of energy and contribute more than 50% of the daily caloric intake suggested by the FDA; in the last decade, high-carbohydrate diets have been analyzed to clarify diverse observations. For example, persons who perceive sweet taste with greater intensity tend to consume less carbohydrates and overall less calories. However, people with a stronger hedonic taste of foods high in sugar usually eat more carbohydrates and calories[18]. It is important to mention that in contrast to other receptors, sweet receptors are expressed in several tissues such as the mouth, gut and pancreas, and some of these tissues can even distinguish between different sweeteners[19].

The innate preference for sweet flavors comes from the need to obtain energy, whereas the rejection of acidic or bitter foods is a defense mechanism to prevent us from consuming poisonous substances[1]. At the intrauterine level, the connection between food preference and the mesolimbic dopaminergic system has been investigated by Dalle Molle et al. They observed that when number of dopamine receptors (D2) is reduced, the palatability of food is also reduced, which could favor the excessive consumption of foods rich in sugars and fats[20]. In the same context, data from Dugas et al. (2019) showed that children who were exposed to gestational diabetes mellitus (GDM) had a predilection for sweet foods and beverages if exposed to them during the first 9 months postpartum. This supports the hypothesis that GDM can predispose the fetus to prefer certain foods[21]. Interestingly, it has been suggested that in elderly, this preference increases again, possibly, due poor taste perception and functional and structural changes in the brain[22].

The role of the gut-brain axis in food preference has been studied in recent years. For example, it has been observed that the gut-brain axis acts as a pathway to activate populations of neurons responsible for developing a preference for sweet foods[23]. This process requires the presence of sugar in the gut, stimulating the expression of the

sodium-glucose-linked transporter 1 in neurons of the caudal nucleus of the solitary, which results in an enhanced preference for sugar. However, additional factors have to be considered. For instance, since the 80s, serotonin disturbances have been extensively analyzed to explain the development of sugar cravings. Serotonin is a neurotransmitter involved in depression management, emotions, and personality. Serotonin transporters have been shown to be increased in the hypothalamus of male Wistar rats as a consequence of a high-carbohydrate diet. These physiological modifications can further aggravate the eating behavior and produce physical and metabolic changes[24].

Orexigenic and anorexigenic molecules are also involved in the predilection for carbohydrates. For instance, ghrelin activates the mesolimbic dopamine system, promoting the consumption of sugary foods by increasing dopamine turnover in the NAc[25]. Another relevant molecule is leptin, which can regulate flavor perception by inhibiting the response to sweetness, increasing the perception threshold for glucose and sucrose. Thus, low leptin levels would increase the sensitivity to sweetness[26].

Studies trying to establish a connection between hormonal activity and food choices have produced opposing results. For example, some authors have claimed that there is no correlation between the preference for sugary foods and puberty. In contrast, other researchers have found that high levels of progesterone, which tend to rise during puberty, have been associated with an increase in the consumption of sweet foods. Similarly, Krishnan et al. showed that high levels of estradiol generate comparable results in the selection of food. However, the role of these hormones in food choice has not yet been fully characterized[27]. Another hormone related to sugar cravings is oxytocin (OT). Low levels of this molecule are associated with a reduced appetite for carbohydrates, regardless of their sweetness. This may be explained through the "relaxing" effect of OT, which decreases anxiety[28].

Endocannabinoids have also been shown to increase the sensitivity to sweet taste. For instance, the CB1R gene polymorphisms seem to be involved in the perception and preference for sweet taste.

Table 1. Single-nucleotide polymorphisms involved in macronutrients selection[30]

Macronutrient	Gene	SNP
Lipids	CD36	rs3211908
		rs3211828
		rs1527483
Carbohydrates	TAS1R2	rs4920564
		rs35744813
Proteins	TAS1R1	rs11122100
		rs12080675
	GRM4	rs9469718
		rs10947476
		rs11759763

CD36: cluster of differentiation 36; GRM4: glutamate metabotropic receptor 4; TAS1R1: taste receptor type 1 member 2; TAS1R2: taste receptor type 1 member 2; SNPs: single-nucleotide polymorphisms.

This is caused by the short tandem repeats $(ATT)_n$ that lower the sweetness threshold in people with obesity carrying this anomaly[29]. Furthermore, single-nucleotide polymorphisms (SNPs) such as rs9701796, rs35744813, and rs4920564 in the TAS1R2 and TAS1R3 genes were related to higher intakes of sugary foods by increasing the sensitivity threshold to sucrose (Table 1)[30].

The FGF21 (Fibroblast growth factor 21) signaling in oxytocin neurons has been suggested to suppress sugar intake[31]. However, recent studies by Jensen-Cody et al. demonstrated that the suppression could take place in the absence this neuronal population. Instead, this process is regulated by the ventromedial hypothalamic nucleus (VMH), which decreases the sugar intake by communicating with the gut-to-brain axis[32]. Phase 1 studies have been initiated to test subcutaneous FGF21 implants in persons with obesity, and preliminary results showed a reduction in cravings for sweet foods in patients who received doses of 39 mg or more. However, most of the participants presented gastrointestinal symptoms. Further studies of this molecule and its effects in humans are needed[33].

As mentioned before, the TIR family of receptors (1, 2, and 3) is present in the lingual epithelium[34]. Both, nutritive and low-calorie/non-nutritive sweeteners,

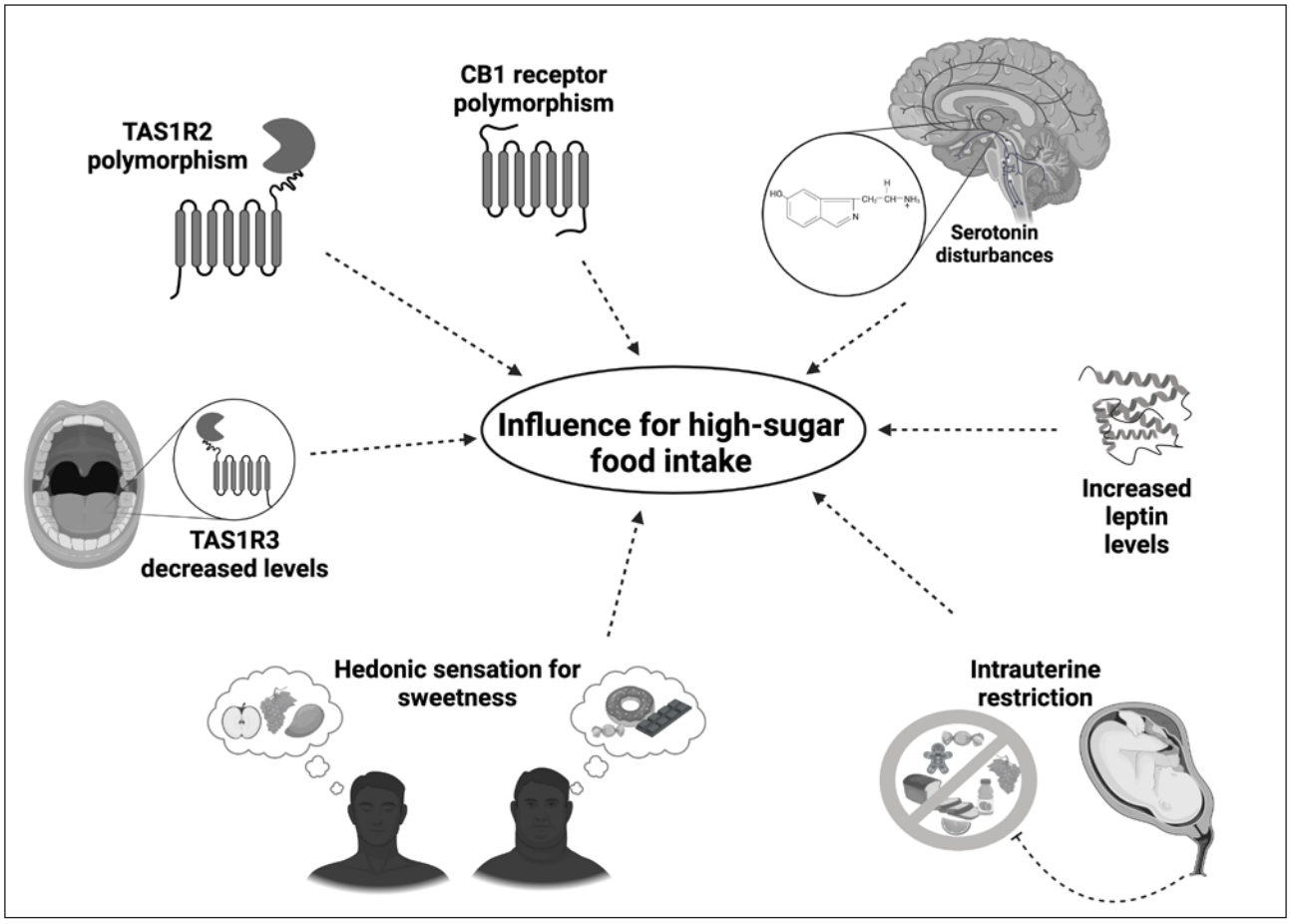

Figure 3. Factors that contribute to high-carbohydrate food preference. Created with BioRender.com.

can activate the G-protein-coupled receptor TIR2/3, which is normally found in the membrane of enterocytes, possesses endocrine functions. These functions mediate the secretion of the incretin hormones GLP-1 and GIP in response to the presence of glucose[19,33,35].

Differences in preferences between simple and complex carbohydrates have also been investigated. For example, studies in women have shown that regardless of their level of sensitivity toward glucose, participants who preferred complex carbohydrates consumed higher amounts of these, and similarly, those who preferred simple carbohydrates also consumed them in greater quantity[36]. In murine models, a preference for polysaccharides, sucrose, and starch suspensions has also been observed. This is linked to taste-signaling proteins such as α-gustducin, Transient Receptor Potential Cation Channel Subfamily M Member 5, and the sweet taste receptor subunit T1r3, which act as gustatory mediators. Expectedly, the lack or deficiency of these proteins is related to inappetence or indifference toward carbohydrates and fats[37].

Finally, caloric restriction and physical activity also play a role in food choices, triggering a greater desire for sugars. This is related to the expression of hypothalamic neuropeptides, hormone release, and -aminobutyric acid activity, which is associated with circulating glucose and corticosterone levels[38]. However, opposite results have been reported in overweight or obese subjects, who showed no predilection for carbohydrates or any other macronutrient during or after exercise, regardless of the type of workout, its duration, or intensity [39]. A summary of relevant factors involved in the preference for sugars is given in figure 3.

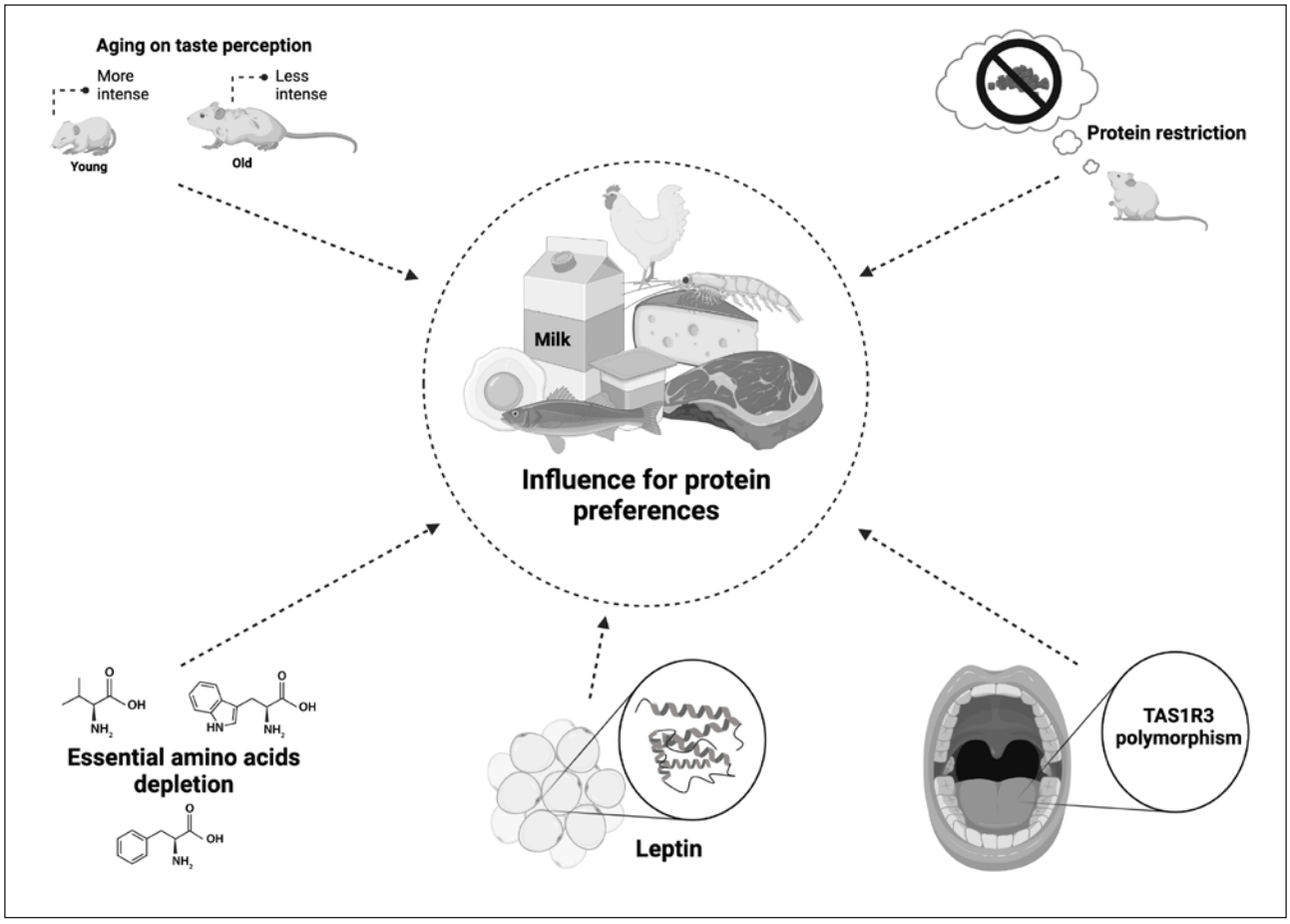

Figure 4. Elements associated to dietary protein intake preference. Created with BioRender.com.

DEVELOPMENT OF PROTEIN INTAKE PREFERENCE

Dietary protein is a cornerstone of human nutrition, from conception to late adulthood, involved in every stage of life and necessary for a proper development. A deficiency of this nutrient is related to sarcopenia, undernourishment, kwashiorkor, alterations of the immune system, and other complications. Protein preference may be influenced by genetic inheritance. Twin studies have been conducted and a modest correlation was observed by Breen et al.[40]. However, more studies connecting genotypes to phenotypes associated with protein preference are required.

It is important to mention that TASR1 and TASR3, two G-protein coupled receptors, respond to the umami taste[41]. This taste, which is characteristic of cooked meats and broths, is elicited by the amino acid L-Glutamate (anionic form of glutamic acid)[41]. Glutamate can also act as a reinforcer for eating behaviors, activating several forebrain regions like the amygdala and the lateral hypothalamus. This occurs through the activation of vagal afferents and was observed on Sprague–Dawley rats[42].

Several factors mediate protein intake (Fig. 4). One of them is aging, which impacts the preference for high-protein diets. Physiologically, the greater petrosal and the chorda tympani nerves are mainly involved in the perception of the umami flavor. Based on this, Miura et al. noted that the preference for substances with umami flavor (inosinic acid and monosodium glutamate) was more intense in young rats, and as time progressed, the perception diminished

with age. The researchers hypothesized that this process involved modifications in brain cell populations and neural responses[43].

Restricting protein in the diet, specifically casein, has been shown to cause an enhanced gustatory experience and preference for proteins, surpassing even that for carbohydrates. This was illustrated in murine models where the treatment group had a 4% casein diet (4% of the total calories come from casein) and the control group one with 18% casein. Clinical trials have also reported similar results. For example, in one study, the preference for proteins increased after a period of low-protein consumption. However, further experiments are required to support these findings[39,44].

Research on C57BL/6 mice has tested the effect of the hormone FGF21 through the coreceptor Beta-Klotho (K1Beta), a molecule that could mediate metabolic adaptations and reduce growth when a low protein diet is administered. When mice have access to protein sources, FGF21 induces a change, increasing protein intake without increasing total food consumption[45].

FGF21 has already been identified as a regulator of complex responses to protein restriction in murine models[31,45]. In particular, it has been observed that the plasma concentration of FGF21 increases exponentially when the protein intake is below a certain threshold to preserve nitrogen balance[46]. For example, Gehring et al. worked with Wistar male rats and noted that when they are offered the option to choose between a 100% protein diet and one with variable percentages of carbohydrates their FGF21 plasma values remained fairly constant, but when fed a 5% protein diet, the FGF21 concentration tripled. Protein intake increases as a means to maintain a high protein-carbohydrate ratio, thus reducing the dependence on the metabolism of sugars. This is connected to the "protein-leverage" hypothesis in mice[47]. Moreover, Sørensen et al. analyzed several aspects of mice fed with different diets. They noticed that low-protein diets were related to higher intakes of food until protein requirements had been fulfilled, regardless of the energy content of the food. This suggests that certain food choices are conditioned on macronutrient requirements[48], denoting that they could prioritize this preference when the ratio with carbohydrates is stable. .

Bachmanov et al. proposed that the pleasant taste of certain amino acids is due to their sucrose-like taste and possibly to the genetic variations that influence the peripheral taste response. The perception of some sweet-tasting amino acids depends on TAS1R3 gene polymorphisms, which involve different peripheral taste sensitivities[49]. In the anterior pyriform cortex (APC), a chemosensor for essential amino acids is located, whose activation is triggered during depletion periods. This has been associated with protein intake regulation. Feeding from a diet deficient on essential amino acids was linked to the activation of the APC, which prompted the rejection of the inadequate diet and stimulated the need for foods containing the indispensable amino acids. Rats presenting APC damage could not refuse diets deficient in essential amino acids[49,50].

FUTURE CONSIDERATIONS AND CONCLUSIONS

The development of obesity is mainly caused by inadequate eating habits, strongly associated with hypercaloric diets rich in lipids and simple carbohydrates. Oral desensitization and alterations of peptide and hormone secretion may predispose people to prefer foods with high palatability, probably because these foods could stimulate reward and addiction centers in the brain. Most individuals with obesity share some feeding preferences and behaviors such as eating in excess, particularly fats. Satiety and hunger are partially mediated by lipid messengers produced in the small intestine. One of them is oleoylethanolamide, which induces the activation of the transcription factor PPARα after dietary lipids are consumed. This initiates a signaling cascade that enhances the dopamine neurotransmission in the dorsal striatum, producing a reduction in the preference for HFDs. Thus, it is believed that obese people could present an impaired lipid-mediated signaling cascade[50]. Interestingly, some studies have reported that there are no differences in fatty acid

sensitivity between slim and obese or overweight persons. Thus, experiments with greater sample sizes are needed to provide better interpretations of these results[8].

Historically, food preferences have been analyzed using multiple demographic factors such as age, gender, ethnicity, geographic location, customs, and health condition with remarkable findings. Nevertheless, additional clinical research is required to establish the roles of several biomolecules and their relationship with preferences for a specific macronutrient. Moreover, we need to find bioactive compounds capable of regulating the gene expression in the hunger-satiety process and elucidate mechanisms that connect physical activity with the selection of certain foods. Finally, it is also important to understand the diseases that either directly or indirectly impact the above mentioned processes. Problems related to malnutrition clearly persist, mainly in industrialized countries and are aggravated by poor food choices, as well as unhealthy lifestyles like sedentarism. Moreover, hyperreactivity to highly palatable foods and their ease of availability in the market make the situation even more complicated. Thus, it is extremely important to study the aforementioned molecules and mechanisms to identify therapeutic targets and better strategies for this pandemic-like problem. Last but not least, we call for more campaigns that bring awareness to consumers about their food choices and how they can lead to obesity.

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CONFLICTS OF INTEREST

The authors declare that they do not have conflicts of interest.

ETHICAL DISCLOSURES

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

REFERENCES

1. Ventura AK, Worobey J. Early influences on the development of food preferences. Curr Biol. 2013;23:R401-8.
2. Behrens M, Meyerhof W. A role for taste receptors in (neuro) endocrinology? J Neuroendocrinol. 2019;31:e12691.
3. Töle JC, Behrens M, Meyerhof W. Taste receptor function. Handb Clin Neurol. 2019;164:173-85.
4. Nicklaus S, Schwartz C. Early influencing factors on the development of sensory and food preferences. Curr Opin Clin Nutr Metab Care. 2019;22:230-5.
5. De Cosmi V, Scaglioni S, Agostoni C. Early taste experiences and later food choices. Nutrients. 2017;9:107.
6. Nicklaus S. The role of dietary experience in the development of eating behavior during the first years of life. Ann Nutr Metab. 2017;70:241-5.
7. Samuel TM, Musa-Veloso K, Ho M, Venditti C, Shahkhalili-Dulloo Y. A narrative review of childhood picky eating and its relationship to food intakes, nutritional status, and growth. Nutrients. 2018;10:1992.
8. Liu D, Archer N, Duesing K, Hannan G, Keast R. Mechanism of fat taste perception: association with diet and obesity. Prog Lipid Res. 2016;63:41-9.
9. Hertzel AV, O'Connell TD, Bernlohr DA. Lipid receptors and signaling in adipose tissue. Lipid Signal Metab. 2020;6:99-114.
10. Bricio-Barrios JA, Del Toro-Equihua M, Huerta M, Ríos-Silva M, Cárdenas Y, López M, et al. Oral fatty acid taste sensitivity in healthy young individuals of both sexes is related to body mass index and soluble CD36 serum levels. Nutr Hosp. 2019;36:1133-8.
11. Daya M, Pujianto DA, Witjaksono F, Priliani L, Susanto J, Lukito W, et al. Obesity risk and preference for high dietary fat intake are determined by FTO rs9939609 gene polymorphism in selected Indonesian adults. Asia Pac J Clin Nutr. 2019;28:183-91.
12. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CN. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med. 2008;359:2558-66.
13. Brissard L, Leemput J, Hichami A, Passilly-Degrace P, Maquart G, Demizieux L, et al. Orosensory detection of dietary fatty acids is altered in $CB_1R(-/-)$ mice. Nutrients. 2018;10:1347.
14. Miyake M, Zhang J, Yasue A, Hisanaga S, Tsugawa K, Sakaue H, et al. Integrated stress response regulates GDF15 secretion from adipocytes, preferentially suppresses appetite for a high-fat diet and improves obesity. iScience. 2021;24:103448.

15. Altherr E, Rainwater A, Kaviani D, Tang Q, Güler AD. Long-term high fat diet consumption reversibly alters feeding behavior via a dopamine-associated mechanism in mice. Behav Brain Res. 2021;414:113470.
16. Oliveira LS, de Lima DP, da Silva AA, da Silva MC, de Souza SL Mizushige T, et al. Preference for dietary fat induced by release of beta-endorphin in rats. Life Sci. 2009;84:760-5.
17. Benzon CR, Johnson SB, McCue DL, Li D, Green TA, Hommel JD. Neuromedin U receptor 2 knockdown in the paraventricular nucleus modifies behavioral responses to obesogenic high-fat food and leads to increased body weight. Neuroscience. 2014;258:270-9.
18. Jayasinghe SN, Kruger R, Walsh DC, Cao G, Rivers S, Richter M, et al. Is sweet taste perception associated with sweet food liking and intake? Nutrients. 2017;9:750.
19. Kyriazis GA, Soundarapandian MM, Tyrberg B. Sweet taste receptor signaling in beta cells mediates fructose-induced potentiation of glucose-stimulated insulin secretion. Proc Natl Acad Sci U S A. 2012;109:E524-32.
20. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci U S A. 2007;104:15069-74.
21. Dalle Molle R, Laureano DP, Alves MB, Reis TM, Desai M, Ross MG, et al. Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. Brain Res. 2015;1618:41-9.
22. Dugas C, Perron J, Marc I, Weisnagel SJ, Robitaille J. Association between early introduction of fruit juice during infancy and childhood consumption of sweet-tasting foods and beverages among children exposed and unexposed to gestational diabetes mellitus *in utero*. Appetite. 2019;132:190-5.
23. Tan HE, Sisti AC, Jin H, Vignovich M, Villavicencio M, Tsang KS, et al. The gut-brain axis mediates sugar preference. Nature. 2020;580:511-6.
24. Jenkins TA, Nguyen JC, Polglaze KE, Bertrand PP. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. Nutrients. 2016;8:56.
25. Disse E, Bussier AL, Veyrat-Durebex C, Deblon N, Pfluger PT, Tschöp MH, et al. Peripheral ghrelin enhances sweet taste food consumption and preference, regardless of its caloric content. Physiol Behav. 2010;101:277-81.
26. Nakamura Y, Sanematsu K, Ohta R, Shirosaki S, Koyano K, Nonaka K, et al. Diurnal variation of human sweet taste recognition thresholds is correlated with plasma leptin levels. Diabetes. 2008;57:2661-5.
27. Krishnan S, Tryon RR, Horn WF, Welch L, Keim NL. Estradiol, SHBG and leptin interplay with food craving and intake across the menstrual cycle. Physiol Behav. 2016;165:304-12.
28. Herisson FM, Brooks LL, Waas JR, Levine AS, Olszewski PK. Functional relationship between oxytocin and appetite for carbohydrates versus saccharin. Neuroreport. 2014;25:909-14.
29. Tarragon E, Moreno JJ. Role of endocannabinoids on sweet taste perception, food preference, and obesity-related disorders. Chem Senses. 2017;43:3-16.
30. Chamoun E, Liu AS, Duizer LM, Feng Z, Darlington G, Duncan AM, et al. Single nucleotide polymorphisms in sweet, fat, umami, salt, bitter and sour taste receptor genes are associated with gustatory function and taste preferences in young adults. Nutr Res. 2021;85:40-6.
31. Matsui S, Sasaki T, Kohno D, Yaku K, Inutsuka A, Yokota-Hashimoto H, et al. Neuronal SIRT1 regulates macronutrient-based diet selection through FGF21 and oxytocin signalling in mice. Nat Commun. 2018;9:4604.
32. Jensen-Cody SO, Flippo KH, Claflin KE, Yavuz Y, Sapouckey SA, Walters GC, et al. FGF21 Signals to glutamatergic neurons in the ventromedial hypothalamus to suppress carbohydrate intake. Cell Metab. 2020;32:273-86.e6.
33. Hill CM, Qualls-Creekmore E, Berthoud HR, Soto P, Yu S, McDougal DH, et al. FGF21 and the physiological regulation of macronutrient preference. Endocrinology. 2020;161:bqaa019.
34. Chandrashekar J, Hoon MA, Ryba NJP, Zuker CS. The receptors and cells for mammalian taste. Nature. 2006;444:288-94.
35. Shirazi-Beechey SP, Daly K, Al-Rammahi M, Moran AW, Bravo D. Role of nutrient-sensing taste 1 receptor (T1R) family members in gastrointestinal chemosensing. Br J Nutr. 2014;111 Suppl 1:S8-15.
36. Low JY, Lacy KE, McBride RL, Keast RS. The Associations between oral complex carbohydrate sensitivity, BMI, liking, and consumption of complex carbohydrate based foods. J Food Sci. 2018;83:2227-36.
37. Sclafani A, Zukerman S, Glendinning JI, Margolskee RF. Fat and carbohydrate preferences in mice: the contribution of alpha-gustducin and Trpm5 taste-signaling proteins. Am J Physiol Regul Integr Comp Physiol. 2007;293:R1504-13.
38. de Sá Ramalho M, de Oliveira Melo NC, Araújo AP, de Santana Muniz G, do Nascimento E. Mild energy restriction and physical swimming activity: biochemical effects and food preference in male rats. Sport Sci Health. 2018;15:319-28.
39. Castro EA, Carraça EV, Cupeiro R, López-Plaza B, Teixeira PJ, González-Lamuño D, et al. The effects of the type of exercise and physical activity on eating behavior and body composition in overweight and obese subjects. Nutrients. 2020;12:557.
40. Breen FM, Plomin R, Wardle J. Heritability of food preferences in young children. Physiol Behav. 2006;88:443-7.
41. Kinnamon SC. Umami taste transduction mechanisms. Am J Clin Nutr. 2009;90:753S-5.
42. Uematsu A, Tsurugizawa T, Kondoh T, Torii K. Conditioned flavor preference learning by intragastric administration of L-glutamate in rats. Neurosci Lett. 2009;451:190-3.
43. Miura H, Ooki M, Kanemaru N, Harada S. Decline of umami preference in aged rats. Neurosci Lett. 2014;577:56-60.
44. Griffioen-Roose S, Mars M, Siebelink E, Finlayson G, Tomé D, de Graaf C. Protein status elicits compensatory changes in food intake and food preferences. Am J Clin Nutr. 2012;95:32-8.
45. Talukdar S, Owen BM, Song P, Hernandez G, Zhang Y, Zhou Y, et al. FGF21 Regulates sweet and alcohol preference. Cell Metab. 2016;23:344-9.
46. Gehring J, Azzout-Marniche D, Chaumontet C, Piedcoq J, Gaudichon C, Even PC. Rats self-select a constant protein-to-carbohydrate ratio rather than a constant protein-to-energy ratio and have low plasma FGF21 concentrations. J Nutr. 2021;151:1921-36.
47. Raubenheimer D, Simpson SJ. Protein leverage: theoretical foundations and ten points of clarification. Obesity (Silver Spring). 2019;27:1225-38.
48. Sørensen A, Mayntz D, Raubenheimer D, Simpson SJ. Protein-leverage in mice: the geometry of macronutrient balancing and consequences for fat deposition. Obesity (Silver Spring). 2008;16:566-71.
49. Bachmanov AA, Bosak NP, Glendinning JI, Inoue M, Li X, Manita S, et al. Genetics of amino acid taste and appetite. Adv Nutr. 2016;7:806S-22.
50. Raghow R. Gut-brain crosstalk regulates craving for fatty food. World J Diabetes. 2017;8:484-8.