THE IMPACT OF OLFACTORY AND GUSTATORY PERCEPTION ON METABOLIC HOMEOSTASIS IN OBESE PATIENTS

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ABSTRACT

Obesity is currently a major global public health problem. As a result, in recent decades there has been a growing interest in studying the impact of this disease on the functioning of the central nervous system. One of the least understood aspects is the impact that obesity has on sensory systems.
The olfactory and gustatory systems are closely related to various vital functions, such as the nocifensors activation, the stimulation of digestive reflexes. In addition, these sensory systems are known to play an important role in the mechanisms of food consumption through the regulation of appetite and satiety, influencing food choice and, therefore, they are involved in the development of obesity. A number of clinical studies have shown that obese patients are more likely to suffer from hyposmia compared to lean people of the same age.
The reasons why this relationship exists remain largely unclear. The aim of this review is to assess the available data on this topic and to identify new promising areas for further research. The review was conducted in the PubMed databases for 2017–2023.

Key words: *obesity, olfaction, taste, sensory systems*

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ВЛИЯНИЕ ОБОНЯТЕЛЬНОГО И ВКУСОВОГО ВОСПРИЯТИЯ НА МЕТАБОЛИЧЕСКИЙ ГОМЕОСТАЗ У ПАЦИЕНТОВ С ОЖИРЕНИЕМ

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РЕЗЮМЕ

В настоящее время ожирение представляет собой серьёзную глобальную проблему общественного здравоохранения. В результате в последние десятилетия наблюдается рост интереса к изучению влияния этого заболевания на функционирование центральной нервной системы. К одному из наименее изученных аспектов можно отнести влияние, которое ожирение оказывает на сенсорные системы.
Системы обоняния и вкуса тесно связаны с различными жизненно важными функциями, такими как активация защитных механизмов организма, стимуляция пищеварительных рефлексов. Кроме того, известно, что данные сенсорные системы играют важную роль в механизмах потребления пищи за счёт регуляции аппетита и насыщения, влияния на выбор продуктов и, следовательно, участвуют в развитии ожирения. Ряд клинических исследований продемонстрировали, что пациенты с ожирением чаще страдают от гипосмии по сравнению с худыми людьми того же возраста.
Причины, по которым существует эта взаимосвязь, во многом остаются неясными. Целью данного обзора является оценка имеющихся данных по этой тематике и определение новых перспективных областей для дальнейших исследований. Обзор проведён в базах PubMed за 2017–2023 гг.

Ключевые слова: *ожирение, обоняние, вкус, сенсорные системы*

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Obesity is a complex multifactorial disease defined by excess fat mass that poses a health risk [1]. As a serious global public health problem and a major determinant of disability and mortality, obesity increases the risk of developing chronic non-communicable diseases such as type 2 diabetes mellitus, metabolic syndrome, arterial hypertension and many others.

According to the World Health Organization (WHO), more than 1 billion people worldwide suffer from obesity: 650 million adults, 340 million adolescents and 39 million children. This number continues to grow and experts estimate that by 2025, approximately 167 million people (adults and children) will have obesity complications.[1]

For a long time, the effects on the central nervous system caused by metabolic disorders were ignored. In the 1950s, the effects of diabetes on brain function began to be studied and it was noted that this organ was also affected by hyperglycemia, leading to the development of behavioral and cognitive changes. More recently, its effects on sensory systems have been studied [2].

The brain is in charge of food odor processing and has receptors for most of the hormones, neuropeptides and nutrients responsible for eating behavior. The consequences of modifications in homeostasis, nutrient overload and sensory system changes in the development and maintenance of obesity have not yet been studied.

CURRENT STATE OF THE PROBLEM

Gustation and olfaction are polymodal sensory systems that provide communication with many brain structures that regulate essential visceral functions, including metabolism, as well as the endocrine, cardiovascular, respiratory, and immune systems.

In everyday life, gustation and olfaction are considered relatively unimportant to many people. In fact, disorders in this area may not even be recognized by the patients themselves [3].

The ongoing COVID-19 pandemic has sparked interest in the study of the gustatory and olfactory senses, but even so, anosmia and dysgeusia are considered to be symptoms that may contribute to the early differential diagnosis of benign respiratory tract infections [4]. They may also be a likely sign of subsequent central nervous system (CNS) involvement associated with so-called Long-COVID, being a manifestation of cognitive impairment [5].

Studies have reported that anosmia, i. e., loss of sense of smell, during COVID-19 occurred in a range of 11 to 84 % of cases. This variation is due to the use of different diagnostic techniques [6]. Psychophysical testing is more reliable than results obtained through subjective assessment [7, 8].

Therefore, the actual prevalence of these disorders is unlikely to be studied because patients may not report being asymptomatic or aware of these abnormalities [8].

The majority of patients with COVID-19 have impaired olfaction and gustation, representing only a small part of diffuse chemosensory disorder. Dysregulation of chemosensory systems may underlie the much higher mortality rate of acute respiratory distress syndrome COVID-19 in comparison with acute respiratory syndrome of various origins.

CORRELATION BETWEEN GUSTATORY, OLFACTORY DYSFUNCTIONS AND SOMATIC DISEASES

Although olfactory and/or gustatory disorders have become widely studied due to the COVID-19 pandemic, they are also detected in various physiological and pathological conditions such as aging [9], neurodegenerative diseases [10, 11], autoimmune diseases [12, 13], cancer [14], and dysmetabolic disorders [15–18].

It should be noted that some of the aforementioned conditions that may correlate with gustatory/olfactory dysfunction are risk factors for fatal SARS-CoV-2 virus infection, such as obesity [19], advanced age, cardiovascular disease, dementia, diabetes mellitus, and chronic liver or kidney disease [20, 21].

Deterioration of gustation and/or olfaction has been consistently reported by people with chronic non-communicable diseases such as arterial hypertension, diabetes mellitus or cancer. This may be an indicator of diffuse chemosensory disorder, possibly aggravating the prognosis of these patients.

Under normal conditions, chemoreceptor dysfunction of one system does not seem to lead to the progression of chronic non-communicable diseases. This impairment is presumably largely compensated for by other chemosensory mechanisms. However, under conditions of stress, such as during COVID-19 pneumonia and metabolic imbalance [22, 23], this system may become vital for the brain to organize an effective functional homeostatic response that can significantly increase life expectancy. This means that dysfunction of several chemosensory systems can lead to severe consequences during a number of diseases [23].

INFLUENCE OF CHEMOSENSORY SYSTEMS ON METABOLIC PROCESSES IN THE BODY

Olfactory or gustatory dysfunctions can be quantitative or qualitative [24] and have been suggested to influence eating and social behavior, mood, quality of life and performance [25].

[1] https://www.who.int/news/item/04-03-2022-world-obesity-day-2022-accelerating-action-to-stop-obesity

In fact, all cells in the human body can detect the presence of various molecules in the environment, but only a few can use this ability to inform the CNS to organize adaptive neural or neuroendocrine responses that can affect the whole system.

In addition to olfaction and gustation, a wide range of chemicals in our body are monitored by other cells: carotid corpuscles, single chemoreceptor cells, pulmonary neuroendocrine cells and enterochromaffin cells [26].

The chemosensory system of olfaction is probably the most studied. Olfactory perception can occur through the nasal mucosa (orthonasal perception) or through the oral cavity (retronasal perception) [27] via seven-transmembrane G-protein-coupled receptors (GPCRs).

Notably, similar receptors are expressed in many other tissues [28] and are deeply involved in angiogenesis and modulation of vascular tone [29], as well as in the regulation of lipid and glucose metabolism [30].

In addition, receptors for many hormones are present in the olfactory mucosa, including receptors for insulin, leptin, orexin, cholecystokinin, adiponectin, neuropeptide Y(NPY) and ghrelin in addition to glucose transporters [31]

Carotid corpuscle/glossopharyngeal nerve dysfunction has also been postulated in the potential pathogenesis of nonrespiratory diseases such as metabolic syndrome, type 2 diabetes mellitus and arterial hypertension [23, 32, 33].

Studies in recent years have hypothesized that vagal nerve dysfunction is significant for the development of obesity and metabolic syndrome [34], but in general, the involvement of chemosensory systems in these diseases is currently receiving little attention in clinical practice. A possible explanation is that the levels of this hormone are not considered vital for humans. Therefore, the hormone study is insignificant for the routine medical examination [23].

Perhaps two strikingly opposite conditions need to be considered: cachexia (which involves elevated resting energy expenditure, anorexia) and obesity.

These multifactorial syndromes share common biochemical characteristics. In addition to altered food intake, similar metabolic changes are present, such as insulin resistance, loss of muscle tissue, altered energy expenditure (in both increased or decreased diseases depending on the patient), increased lipolysis, unregulated excess protein catabolism, chronic inflammation [35], and dysregulation of the immune system [36, 37]. Most patients present similar multiple endocrine dysfunctions and, in particular, elevated peripheral serotonin levels [38]. Both central and peripheral levels of this hormone from enterochromaffin cells are a major component of metabolic regulation [39]. All of these parameters are largely under the control of chemosensory systems. The cause-and-effect relationships have not yet been established, but they are worth studying.

INFLUENCE OF GUSTATORY RECEPTIVITY ON NEUROENDOCRINE MECHANISMS OF APPETITE REGULATION

Gustatory receptors of the tongue respond to different taste stimuli by releasing different combinations of neuropeptides. These peptides are recognized by receptors located on the taste bud cells themselves for intercellular communication (autocrine/paracrine) or on adjacent afferent sensory nerve fibers to transmit taste information to the brain [40]. Examples of neuropeptides produced by gustatory receptor cells are glucagon, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), NPY, peptide tyrosine tyrosine (PYY), vasoactive intestinal peptide, ghrelin and galanin [40]. Although adenosine triphosphate (ATP) is the main neurotransmitter that transmits signals to afferent nerve fibers. These peptides can function as cotransmitters that form the physiological response to various stimuli [41].

Some of these peptides are involved in food intake and energy utilization, suggesting that oral nutrient perception may influence whole body metabolism through neural and endocrine pathways. When these hormones enter the extracellular space of the lamina propria, they can affect neighboring cells (paracrine) or penetrate intestinal capillaries and lymphatic vessels to affect other peripheral organs (endocrine) [42].

However, it is still unclear whether these gustatory receptor peptides actually cause endocrine effects by entering the bloodstream and affecting other organs [41]. Interestingly, peptide receptors on gustatory cells can also be a target for peptides produced in the intestine, adipose tissue or other tissues [41]. Leptin receptors on gustatory cells have been shown to respond to systemic leptin content, causing decreased sensitivity to sweet stimuli without affecting the response to sour, salty and bitter substances [43]. The above suggests that postingestin hormone release is capable of regulating the peripheral gustatory apparatus, for example, by modulating the response to sweet stimuli [41].

Animal and human studies demonstrate an inverse correlation between fatty acid sensitivity and fat intake [42].

Recognition of fatty acids by intestinal lipid-sensitive receptors triggers signaling cascades that lead to the release of hormones such as GLP-1, CCK and PYY [42]. However, obese patients have impaired sensitivity to dietary fat in the oral cavity and gastrointestinal tract [42]. Desensitization of these receptors in response to chronic dietary fat intake may be a potential mechanism that contributes to decreased receptor sensitivity to consumed fat. Therefore, fatty acid recognition dysfunction in the gastrointestinal tract may contribute to satiety response dysfunction, leading to overeating and obesity.

Therefore, future studies should investigate how these gustatory receptors and their signaling pathways are altered by impaired metabolism and what signaling

molecules may be targeted to restore gustatory receptor function.

OBESITY AND AFFERENT CONDUCTION DYSFUNCTION

In addition to impaired nutrient transport, obesity also shows changes in vagus nerve responses to appetite-regulating hormones [42, 44]. Obese mice on high-fat diet have a reduced vagus nerve response to leptin [42, 45]. M. Covasa and R. Ritter in 2000 demonstrated a decrease in sensitivity to CCK in obesity models on rats [42, 46]. In a study by D. Daly et al. (2011) long-term feeding of mice with a high-fat diet led to a decrease in mechanosensitivity of intestinal afferents and a decrease in excitability of membranes of nodose ganglion neurons [42, 47]. Therefore, dysfunction of afferent excitability of the vagus nerve may be a mechanism for loss of sensitivity to hormones.

Like vagus nerve afferents, the primary afferents of the enteric nervous system (ENS) are also able to perceive intestinal hormones such as GLP-1, GLP-2, CCK and PYY due to their close proximity to enteroendocrine cells (EECs) and expression of the corresponding receptors [48]. The ENS is a network of nerves and glial cells organized into two main plexuses: the submucosal plexus, located between the submucosa and the circular muscle, and the myenteric plexus, located between the circular and longitudinal muscles. It functions to regulate gastric motor activity.

Changes in ENS during a high-fat diet also resulted in decreased sensitivity to gastrointestinal hormones. E. Grasset et al. (2017) found that the lack of response to GLP-1 in mice fed on a high-fat diet is due to the abundance of a particular set of intestinal bacteria that disrupt GLP-1-induced nitric oxide production in enteric neurons, which prevents activation of the intestine-brain-peripheral release axis to control insulin secretion [49].

In addition, these peptides can activate sensory afferent nerve fibers. Vagal nerve fibers do not project into the intestinal lumen but have been shown to respond to nutrients including glucose, amino acids and lipids in a postabsorptive manner [50]. The additional regulation of their neural signaling by nutrient-stimulated hormones from the intestine is supported by the presence of intestinal peptide receptors on afferent fibers (such as CCK and GLP-1R receptors) and the dependence of the effects of gastric emptying and CCK saturation on vagal signaling [51].

In conclusion, receptor perception of nutrients in the intestine and vagus nerve responses to them serve as important mediators of energy homeostasis and represent distinct steps in which high-fat diets and obesity can disrupt proper functioning.

ASSESSMENT OF GUSTATORY AND OLFACTORY FUNCTIONS IN CLINICAL PRACTICE

Unfortunately, quantitative testing of gustation and olfaction is rarely performed in clinical practice. The accuracy of a patient's chemosensory complaint cannot be definitively established without diagnosis. Indeed, most people do not accurately assess the nature and extent of their sense of different tastes and smells, and significant recovery of function can occur, often without patients being aware of it [52]. For example, the study by H. Tomita et al. (2002) showed that only 18 % of patients with bilateral taste loss after transection of both *chorda tympani* nerves were aware of their deficit [52, 53]. It is almost impossible to detect gustatory and olfactory dysfunctions without testing [52, 54], nor is it possible to determine whether the perceived decline in function is normal for the patient's age and gender [52, 55]. Without testing, the efficacy of pharmacological, surgical, or other therapeutic interventions cannot be accurately established.

Quantitative evaluation has shown that olfactory dysfunction is more prevalent than gustatory dysfunction [52]. In fact, most patients who clinically complain of gustatory dysfunction have pathology related to olfactory function [52]. The taste of foods, which is often interpreted as "flavor", is largely dependent on volatile substances that reach olfactory receptors through the nasopharynx during swallowing [52].

Along with sweet, sour, bitter, salty, savory ("umami"), it is likely that chalky or metallic sensations in the oral cavity are olfactory sensations [52].

CORRELATION BETWEEN OBESITY AND OLFACTORY AND GUSTATORY DYSFUNCTIONS

Reduced gustatory and olfactory perception causes high consumption of palatable foods, which will either lead to obesity or aggravate existing obesity [19, 56, 57], although the consequences of the food addiction component should not be ignored, especially for sweet and fatty food [19, 58].

The study by A.S. Khan et al. (2020) demonstrated that obese people have a lower sensitivity to sweet-sour taste compared to healthy people [19]. Mice with obesity induced by a 10-week high-fat diet had reduced gustatory sensitivity to the tastes [19, 59]. Similar results have been obtained for bitter and salty tastes in obese patients [19].

Decreased sensitivity to various gustatory stimuli may be related to deficient functionality of gustatory receptors/sensors caused by obesity [59], genetic polymorphisms [19, 59] or epigenetic patterns [19, 60].

A similar situation is characteristic of olfactory function. For example, olfactory threshold increases with body weight of obese individuals [19, 61]. Z. Patel et al. reported that high body mass index (BMI) was associated with subjective olfactory dysfunction of obese patients [62].

Decreased olfactory perception during obesity is a multicomponent phenomenon that involves abnormalities not only of the nasal epithelial receptors but also of various brain regions such as the limbic system, thalamus and piriform cortex, and amygdala, which project to the orbitofrontal cortex [19, 63].

In addition to the above-mentioned factors leading to gustatory and olfactory perception dysfunction, the role of cytokine-induced (generalized or specific) inflammation during obesity cannot be overlooked.

The study by A. Kaufman et al. showed that the increase in the level of tumor necrosis factor α (TNF-α) in the area of tongue papillae of obese mice was associated with a significant decrease in the number of taste bud cells and their precursors [64]. Moreover, TNF-α-null mice were protected from obesity-induced reduction in taste bud cell number, and administration of exogenous TNF-α caused taste buds to degenerate [64]. The Sel1L (Suppressor/Enhancer of Lin-12-like) deletion specific for adipose tissue in mice maintained on a high-fat diet resulted in reduced adipose tissue levels and showed neither an increase in TNF-α concentration nor any evidence of taste bud cell atrophy. These observations clearly indicate that TNF-α released from hyperplastic/inflamed adipose tissue in obesity may cause loss of gustatory perception. Moreover, inflammation has also been found to reduce the lifespan of mature taste bud cells.

It has also been demonstrated that chemosensory perception in mammals is regulated by bacterial metabolites, and the microbiota of the tongue mucosa may also be involved in taste formation by influencing food intake and metabolism [65, 66]. A recent study of the human microbiome showed that commensal bacteria have evolved strategies to stimulate chemosensory receptors and trigger host cell functions [65]. Therefore, the tongue microbiota may influence metabolic systems through interaction with chemosensory receptors, similar to how this process occurs in the intestine [67, 68].

It has been reported that obese children have significantly reduced gustatory discrimination (level of taste recognition) and fewer mushroom papillae have been identified, which is accompanied by a decrease in the α-diversity of the microbiota of the tongue membrane, which may affect gustatory perception [66]. Studies involving healthy subjects showed that the microbiota of the tongue mucosa was associated with gustatory function, thereby influencing dietary habits such as preference for salty baked goods and foods rich in saturated fats [66].

The microbiota of the tongue mucosa, one of the important components of the oral microbiome, is characterized by high sampling stability and is more accessible for research. Therefore, it is a promising subject for studies.

In addition, it has been shown that tongue mucosal microbiota disorders can lead to increased levels of various markers of chronic inflammation, and thus are closely associated with the development of a number of chronic noncommunicable diseases (NCDs) such as obesity, type 2 diabetes mellitus, and cardiovascular pathology [66, 69, 70].

However, the number of studies on the association between the mechanisms of metabolic disorders and microbiota of the tongue mucosa is limited.

Considering the above, it can be hypothesized that the microbiota of the tongue mucosa will be a new, simple and non-invasive biological marker that can contribute to diagnostic and prognostic studies of obesity and other NCDs.

CONCLUSION

Thus, further study of olfactory and gustatory disorders associated with obesity is relevant and may make it possible to predict the risks of developing metabolic disorders and carry out their correction before the realization of the obesity phenotype in the future.

Conflict of interest

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