LITERATURE REVIEW

Taste and smell disorders

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ABSTRACT

Both smell and taste are integral part of daily life, from the pleasure of perfumes and foods to detecting life-threatening situations, fire or toxic gases. The quality and intensity of odours or taste perception depend on the anatomic and functional status of the olfactory and gustatory epithelium, as well as of the peripheral and central nervous system, since smell or taste sensations are the result of stimulation of the olfactory, trigeminal, glossopharyngeal and vagus nerves.

KEYWORDS: taste disorders, smell disorders, hypoguesia, anosmia, hiposmia, aguesia

INTRODUCTION

Why talking about taste and smell since modern society is dominated at a sensory level by audio-visual?

Both smell and taste are integral part of daily life, from the pleasure of perfumes and foods to detecting life-threatening situations, fire or toxic gases. A 1994 study revealed that in America there were 2.7 million adults with an olfactory pathology and 1.1 million with a gustatory pathology[1]. According to a study conducted between 1998 and 2000, 14 million adults aged 53-97 years old had olfactory problems[2].

The quality and intensity of odours or taste perception depend on the anatomic and functional status of the olfactory and gustatory epithelium, as well as of the peripheral and central nervous system, since smell or taste sensations are the result of stimulation of the olfactory, trigeminal, glossopharyngeal and vagus nerves. Olfactory stimulation depends on odoriferous particles reaching the olfactory mucosa, a certain type of nasal – orthonasal airflow being necessary. During feeding, apart from the gustatory sensation, a retronasal flow of odorous particles is also achieved.

NOTIONS OF ANATOMY AND PHYSIOLOGY

The olfactory epithelium is located on the upper section of the nasal cavities, at the junction between the upper nose cone, the ethmoid riddled blade and the upper part of the septal mucosa (Figure 1). We are talking about a pseudostratified columnar epithelium, consisting of sensory cells, supporting cells and Bowman's glands. On this epithelium, it is located the first olfactory receptor - the first neuron of the olfactory pathway. In newborns, the nasal olfactory area consists of a very dense network of neurons. Their number decreases with age, so that in adults the nasal olfactory area measures approximately 1 cm^{2-4}.

The effect that the olfactory stimulus has on the receptors in the olfactory area depends on several factors, such as: duration of exposure to the olfactory stimulus, volume and velocity of inspiration.

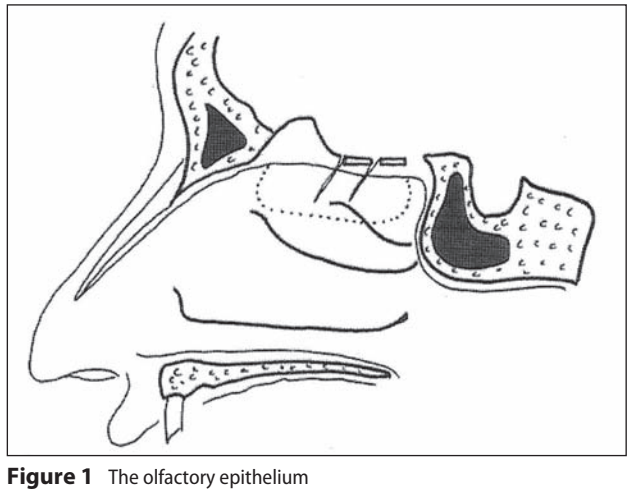

Figure 1 The olfactory epithelium

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Each receptor cell is a bipolar primary sensory neuron which arises from the nasal cells. The nasal cavity contains more than 100 million such neurons. The new receptors appear every 30-60 years, which explains the high frequency of olfactory pathology in the elderly population.

The sensory cells are bipolar olfactory neurons that, anatomically, have two endings: a peripheral one - short, a central one - long. The peripheral ending - the dendrite, the receptor - reaches the mucosa where it ends by cilia, which in turn are the first to be stimulated by odorous substances. Dendrites are the only nerve extensions coming into direct contact with the outside. The central ending - the axon - is a thin, amyelinated structure; it forms a plexiform network, that then condenses into 15-20 fascicles which cross the ethmoid riddled blade, and it reaches the ipsilateral olfactory bulb, forming the olfactory nerves. The sketch of the first olfactory map is formed at this level.

There is a medial group of olfactory nerves in the nasal septum, and a lateral one in the upper nose cone. The olfactory nerves make synapse with the deutoneuron in the olfactory bulbs. The latter are ovoid masses of about 15/3 mm located on the upper side of the ethmoid riddled blade; they are in relation to the right gyrus in the upper part and with the medial orbital gyrus laterally.

Olfactory tracts are narrow bands of white substance, with a length of about 20 mm, located between the right gyrus and the medial orbital gyrus. On their path, these tracts are divided into:

- The lateral olfactory stria, whose fibers reach the prepyriform and the peritonsillar areas, the corticomedial nuclei of the tonsillar complex of the entorhinal cortex.
- The intermediate olfactory stria, which passes through the anterior perforated substance.
- The medial olfactory stria, whose fibers end in the paraolfactory area (Broca) and in the paraterminal gyrus.

The primary neuron of the olfactory bulbs is represented by the glomerular cells, whose axons form the olfactory tracts that are distributed up to the olfactory cortex. The latter is divided in five parts:

1. Anterior olfactory nucleus that connects the two olfactory bulbs
2. Olfactory tubercle
3. Piriform cortex – represents the main discrimination olfactory area
4. Cortical nucleus of the amygdala
5. Entorhinal area that is projected into the hippocampus.

The olfactory information reaches the olfactory tubercle, then the piriform cortex. From this level, impulses can be transmitted either to the medial dorsal nucleus of the thalamus, or to other olfactory cortical regions. All these structures are involved in the process of awareness of odorous substances.

On the other hand, the cortical nucleus of the amygdala and the entorhinal area are components of the limbic system, being involved in the manifestation of the emotional, hedonic component of odorous substances.

Another important role in the olfactory function is assigned to the vomeronasal organ - VNO (Jacobson's organ), a membranous structure located in the anterior nasal septum, in the depth of the respiratory mucous, near the septal perichondrium. In 91-97% of the cases, the opening of this organ may be visible in the nasal vestibule. The VNO is involved in the perception of the chemical smell of pheromones.

It is worth remembering that the olfactory epithelium has the ability to regenerate. This process does not take place in those cases where total or almost total destruction of the basement membrane occurs. Neurogenesis occurs in the basal layer of the olfactory epithelium, receptors at this level being replaced only after their total destruction[5]. Death of the receptor cells, as well as their regeneration, is under the influence of both endogenous and exogenous factors[6]. Therefore, apoptosis may occur in cells in various stages of development and regeneration - biochemical mechanism[7,8].

Structurally, the **gustatory system** is somewhat similar to the olfactory system. There is a layer of basal cells that form the sensory receptor cells. Unlike the olfactory system, gustatory receptors are not neurons.

The sensory cell is located in the sensory ganglion of the facial nerve (in the case of taste buds situated in the anterior two-thirds of the tongue), of the glossopharyngeal nerve (for the taste buds at the base of the tongue and the pharynx) and of the vagus nerve (for the taste buds located in the larynx). The dendrites of this cell reach the taste buds, where they are stimulated by taste sensations.

Taste buds are variably distributed in the tongue, the soft palate, the pharynx and even in the larynx.

The taste buds in the tongue occupy different areas and are arranged in the form of gustatory papillae. At the base of the tongue, there is the greatest number of papillae. In the anterior two-thirds of the tongue, there are approximately 20-33 fungiform papillae, whose innervation is given by the facial nerve through the tympanic cord nerve. Each fungiform papilla contains about 114 buds[9].

In the posterior two-thirds of the tongue, the circumvallate papillae are distributed; there are 8-12 papillae that contain approximately 250 buds per papilla and are arranged in the form of the letter V. The sides of the tongue are occupied by the foliate papillae. The innervation of these taste buds is made by the glossopharyngeal nerve.

The axons of the sensory cell in the ganglia of the cranial nerves have an upward trajectory and get to make synapse with the solitary tract neurons in the cerebral substance. In turn, the axons of the neurons at this level reach the central tegmental tract and make synapse in the medial portion of the thalamus that subsequently projects itself in the postcentral gyrus.

There are four fundamental tastes: sweet, sour, salty and bitter. Each of them is perceived in different parts of the tongue. Studies performed over the years show that taste receptors can be stimulated preferentially by one of the four fundamental tastes. These observations led to the conclusion that a certain pattern of neural stimulation is responsible for taste recognition[10].

OLFACTORY SYSTEM PATHOLOGY

Smell is an early semiological marker of systemic or neuropsychological diseases. Smell disorders can also result from trauma, surgical interventions or drug therapy.

Smell disorders can be classified as:

Quantitative – hyposmia (reduced olfactory acuity), anosmia (inability to perceive olfactory stimuli) or hyperosmia (exaggerated sense of smell: the individual perceives, strongly unpleasantly, low intensity odours).

Anosmia has diagnostic value when it is unilateral and installs progressively. It is also very important the moment when anosmia occurs in relation to the other symptoms.

Hyperosmia appears in certain physiological states (pregnancy, elderly persons, early childhood etc.). Hyperosmia often occurs in early pregnancy, during the menstrual cycle, in migraine patients or in case of allergic conditions.

Qualitative:

- parosmia, dysosmia (false olfactory impression)
- cacosmia is an entity characterized by a fetid odour emanating from a sick person.

Olfactory hallucinations - olfactory perceptions that do not have any objective generating cause. Patients perceive certain odours, most of the time unpleasant ones. The uncinate crisis is a particular form of olfactory hallucination that is associated with olfactory and visual hallucinations, with a state of unreality. The patient has the impression he knows certain places, experiences a "déjà vu" feeling or familiar things look foreign to him. These manifestations can guide the diagnosis towards a lesion in the hippocampus uncus.

Similarly to hearing losses, olfactory disorders may be classified into conductive or neurosensory dysfunctions, there being multiple **causes**.

In case of the **conductive olfactory dysfunction**, stimulus transmission towards the olfactory epithelium is disrupted or interrupted, and it can be determined by:

- Inflammatory processes - chronic allergic and non-allergic rhinitis, acute or chronic rhinosinusitis - inflammation of the nasal mucosa;
- Tumors - benign (nasal polyposis[11], sinuso-choanal polyp, reversed papilloma) or malignant;
- Laryngectomized patients and carriers of tracheal cannula - due to lack of nasal airflow[12].

Neurosensory olfactory dysfunction involves damage to the central nervous structures and can be determined by:

- Infectious and inflammatory pathology - viral etiology through damage of the neuroepithelium, sarcoidosis, Wegener's granulomatosis, multiple sclerosis.
- Craniocerebral trauma - the percentage of cranial posttraumatic dysosmias varies, since their occurrence can be directly related to the severity of head injury: up to 16% in case of minor head traumas, 15-19% in moderate head traumas and 24-30% in case of severe head traumas[13-15].
- Postoperatively or by the subarachnoid hemorrhage (causes destruction of nervous fillets or the parenchyma, giving rise to anosmia[16]).
- Endocrine causes - hypothyroidism, diabetes mellitus[17], hypogonadism (Turner syndrome, Kallman syndrome)[18], adrenal insufficiency and pseudohypoparathyroidism[19,20].
- Toxic cause - medicines and drugs represent an important category of olfactory disorders. Medicines known as having an undesirable effect on the smell and the pituitary mucosa are: Amlodipine, some anesthetics (ketamine-propofol, benzodiazepines), Captopril, Ciprofloxacin, Carbimazole, Diltiazem, Doxycycline, D-penicillamine, Enalapril, Metoprolol. Tobacco and cocaine have a harmful effect on the olfactory analyzer[21]; exposure to arsenic, benzene, cadmium etc.[22].
- Neurological degenerative processes - dysosmia in Alzheimer's disease is determined by cerebral aging, the evolution being slow and varying from one individual to another[23,24]. Dysosmia in Parkinson's disease remains fix once appeared, as its evolution is not concomitant with the basic disease[25]. Dysosmia appeared in Huntington's disease is due to a progressive and elective degeneration of the neurons and of the nerve fascicles[26].
- Brain tumors - located in the anterior temporal lobe.
- Destruction of the olfactory bulbs - there are studies showing that every year we lose about 520 cells, with a reduction of 0.19 cm^3 of the olfactory bulb volume[27].
- Intranasal application of zinc-based sprays can lead to the onset of anosmia[28].
- Age - almost everyone has some type of smell impairment by age 60 or 70, and half of those in their 80s are anosmic[29].

Diagnosis of olfactory disorders may be difficult and it starts with the clinical and paraclinical explora-

tion, the radiological one and that of the respiratory function of the nasal fossae, in order to eliminate the potential pathological obstacles.

Evaluation of patients with disorders of smell must follow the following steps: complete and accurate anamnesis, olfactory function tests and head and neck clinical examination[8,30].

ENT clinical examination involves anterior and posterior rhinoscopy, as well as nasal endoscopic examination. These can reveal the existence of rhinosinusal pathology that determines the olfactory disorder (e.g. nasal septum deviation, nasal polyposis, rhinosinusal tumors, sinuso-choanal polyp, hypertrophy of the middle nasal turbinate - concha bullosa etc.)

Olfactory function tests can be made by subjective or objective methods.

Subjective exploration methods aim to determine the olfactory threshold. The olfactory threshold is defined as the minimum concentration of an olfactory molecule which can be perceived.

According to guidelines published in 2011 for the diagnosis of rhinosinusal disorders by the EAACI[31], there are numerous tests that can assess the olfactory function. Of these, the most commonly used are: UPSIT (University of Pennsylvania Smell Identification Test), diskettes test, Eloit-Trotier test, T&T olfactometry, sniff test.

UPSIT is a quick test, based on the quantitative testing of the olfactory function[8, 32-34]. It uses 4 tests with 10 odorants each, the patient having to choose from several variants existing on each odorant separately.

Smell diskettes contain 8 odorants – coffee, vanilla, smoke, pineapple, coconut, peach, rose, grape[30,35].

The method of limits or T&T olfactometry[30,35] is the most commonly used clinical method. The patient is given five olfactory stimuli with increasing concentrations. In the ascending phase, one stops at the concentration that determines odour perception, this being the olfactory threshold. In the descending phase, one stops at the concentration that does no longer determine odour.

During the constant stimulation test (sniff test) the patient is given to smell odorant stimuli ranked between imperceptible and perceptible. The olfactory threshold is considered to be 75% correct answers[36-38]. It is a precise method, but it may tire the patient.

The ascending-descending method developed by Deems and Doty[39] involves alternative olfactory stimulation with two vials: one with mineral oil smelling of roses, the other with simple mineral oil[40]. Determination of the olfactory threshold is made by a logarithmic calculation of the patient's answers.

The Eloit-Trotier olfactory test is performed with the Trotier olfactometer that contains five categories of odorant factors similar to the natural ones: PEA (beta-phenylethyl) smelling of flowers, UND (gamma-undecalactone) with fruity odour, IVA (isovaleric acid) with cheese odour, CYC (cyclotene) with the smell of cake, SKA (skatole) with fecal odour[41-43]. Each substance is found in seven different concentrations. The patient had to identify each odorant separately. Detection level was considered as the highest concentration of the odorant not perceived plus one. The identification level was considered the lowest concentration correctly identified in a series of correct identifications, beginning with the highest concentration[31,42].

Objective exploration methods

The electro-olfactogram (EOG) detects the olfactory potential by applying an electrode directly on the olfactory mucosa, with a graphic recording of the response to the olfactory stimulus[44,45].

Recording of olfactory evoked potentials (OEP) is a non-invasive method of investigation of the olfactory function. It monitors brain electrical activity (EEG) induced by repeated exposure to odorous substances[46]. Electrodes are placed on the vertex, mastoids and forehead. The examination requires auditory masking. A stimulus is applied with controlled regularity and comparative graphs between the stimulation and the resting period are made. It provides certain diagnosis of hyposmias, but not of anosmias and parosmias. This test is really helpful in evaluating patients with Alzheimer's disease[47].

The contingent negative variation or Auffermann method is an electrophysiological examination used to test parosmias[48,49]. The method records negative potentials through discrimination between two odorous substances. It thus allows establishing the diagnosis of parosmia, as well as differentiating between parosmia and hyposmia.

Imaging is another important step to be performed for patients with smell disorders. In order to evaluate soft tissues (olfactory bulbs, olfactory tract, cortical parenchyma etc.), magnetic resonance imaging (MRI) is the most reliable method. Computed tomography examination (CT) is the most effective method of assessing the craniofacial bone structure and the rhinosinusal system[50].

Treatment of olfactory disorders begins, first of all, with treating the pathology identified through the clinical and paraclinical tests performed.

In the case of rhinosinusal pathology, treatment may consist of nasal irrigation with saline sprays, topical corticosteroids, antibiotherapy, steroidal or non-steroidal anti-inflammatory, antihistamines. In case of benign or malignant tumors and nasal septum deviation, surgery is performed.

Full recovery is more likely to occur in recent smell disorders caused by inflammations, where we quickly intervene with intranasal corticosteroids, vitamins B1 and B6, antihistamines and even systemic corticosteroids.

In the case of dysosmias caused by an infection of the upper airways, drug therapy has not increased effectiveness in the recovery of the olfactory epithelium. However, there are studies showing a restoration of smell, of various degrees, after a certain period of time, without special treatment[51-53].

If loss of smell is caused by craniocerebral trauma, chances of recovery are very low, since sectioning of the nerve fillets can occur in these cases[54,55].

In the case of patients who quit smoking, an improvement in the olfactory and gustatory functions has been noticed after a period of time dependent on the period of smoking status[56].

Moreover, one may observe an improvement in smell in people working in toxic environment, after cessation of exposure to it.

GUSTATORY SYSTEM PATHOLOGY

The gustatory pathology is closely related to the olfactory pathology, between the two being a directly proportional connection.

Gustatory disorders can manifest by changing the properties of food, beginning with taste, texture and up to temperature perception. Taste loss may occur in case of an anomaly in quantity and quality of saliva, as well as a change in papillae and taste buds[57].

There are multiple **causes** that may underlie the occurrence of a gustatory pathology:

1. upper airway infections, which results most commonly in olfactory disorders, may be accompanied by changes in taste;

2. oral cavity disorders - inflammations, lesions, bacterial or fungal infections - that may be accompanied by destruction of papillae or taste buds;

3. poor oral hygiene;

4. dental prostheses or braces;

5. cranial nerves damage (post virally - facial nerve paralysis, dental treatments[58]). In case of facial nerve paralysis, the gustatory-salivary reflex arc may be affected. Changes in the sense of taste have also been described in Ramsay Hunt Syndrome (herpes zoster oticus), that occur due to viral injury of the geniculate ganglion[59];

6. although sense of taste decreases with age, this change is not so striking as in the case of olfactory disorders[60]. In elderly patients, there is a decrease in sense of taste that may lead in time to anxiety, depression, malnutrition, weight loss[8,61]. Changes appear due to the impaired function of ionic channels and taste receptors[62,63];

7. gastroesophageal reflux disease;

8. endocrine disorders - Sjogren syndrome[64,65], diabetes mellitus, hypogonadism can lead to a decrease in sense of taste, while hypothyroidism or cortico-renal insufficiency result in accentuated sense of taste. Also, pregnancy or menstruation can influence taste perception;

9. cranio-cerebral trauma may cause taste disorders with a low frequency, as compared to posttraumatic olfactory disorders[66]. Temporal bone fractures also involving the inner ear may damage the tympanic cord nerve, causing unilateral taste change, as well as decreased saliva secretion. Auriculo-temporal nerve damage can determine the occurrence of gustatory neuralgia, characterized by paroxysmal facial pain followed by gustatory stimulation[67,68];

10. tumors or central nervous system lesions - there are taste disorders associated with acoustic neuroma, pituitary tumors, facial nerve neuromas. Contralateral dysgeusia has been reported in patients with ischemic lesions in the thalamus and corona radiata[69]. In patients with multiple sclerosis, an association of hemiageusia has been reported[70];

11. post-operative gustatory disorders or after certain invasive maneuvers. Glossopharyngeal nerve lesion may occur after amigdalectomy, bronchoscopy or even laryngoscopy[71,72]. In the literature, there are cases of altered sense of taste after uvuloveloplasty[73] or even after endotracheal intubation, caused by lingual nerve injury[74]. Tympanic nerve cord damage after tympanoplasties, mastoidectomies or stapedectomies[75] may lead to a gustatory pathology. General anesthesia can cause taste disorders[76];

12. medicines - diuretics, antihypertensive medication, cytostatics, antibiotics, antifungals, antilipemiants[77]. Studies have shown that interruption or replacement of medication can lead in time to restoration of taste sensation[78-80];

13. hormone deficiencies (estrogens) or nutritional deficits (zinc, vitamin B, folic acid), geographic tongue may lead to the so-called “burning mouth”. This sensation starts during the morning and persists all day[81,82];

14. in case of radiotherapy, changes in taste sensation occur early, even from the beginning of treatment, subsequent recovery lasting up to several months or even years[83]. Chemotherapeutic agents – 5-fluorouracil, cisplatin etc. – can determine taste change[84-86]. Patients most frequently report the occurrence of a metallic taste[87,88];

15. pesticide exposure[89].

In terms of **classification**, when we refer to a disturbance of taste sensation, we can talk about:

- Hypogeusia – reduced sense of taste
- Dysgeusia – taste sensation disturbance (pleasant or unpleasant taste)
- Phantogeusia – perception of an unpleasant taste in the absence of a stimulus
- Ageusia – absence of taste – it is rare and, most of the times, is the result of a central nervous system disorder[90,91]
- Glossodynia – burning sensation.

Diagnosis of taste disorders, as in the olfactory pathology, is very complex and should include a meticulous anamnesis, complete ENT examina-

tion, neurological examination, taste testing and imaging.

Anamnesis must be meticulous, carefully performed and must obtain information about the type of taste change, if it is associated with salivation or swallowing disorders, pain in the oral cavity, odynophagia, digestive disorders, weight loss or cranio-facial trauma.

ENT clinical examination is very important in identifying the probable cause of the gustatory pathology[30]. The existence of facial asymmetry should take into account the existence of facial nerve paralysis, accompanied by gustatory sensitivity disorders. Examination of the oral cavity may reveal changes in the gustatory papillae, the existence of inflammatory, erosive, ulcerative lesions or their atrophy. Dental examination should not be absent from the clinical balance.

As additional investigation, bioptic examination of circumvallate or fungiform papillae can be performed, taking into consideration that there is a close correlation between the number of fungiform papillae and the number of taste buds[92].

Taste sensitivity testing can be performed using two methods: gustometry or electrogustometry.

Gustometry involves application of various substances on the tongue or in the oral cavity: citric acid - sour, caffeine - bitter, sodium chloride - salty, sucrose - sweet. After each substance, the patient should thoroughly rinse the mouth. The test takes a long time and can be subjective.

Electrogustometry is useful in determining taste sensitivity and involves presentation of currents, μA, to small regions of the tongue for a certain period of time[93,94]. The stimuli have low intensities and may activate trigeminal afferents, not the efferents, testing in this way the effectiveness of gustatory pathways.

For an individual assessment of taste (sour, salty, sweet, bitter), the most useful is gustometry, this test using physiological gustatory stimulation[95].

Imaging of the gustatory pathways is extremely useful in explaining several symptoms. MRI examination may reveal lesions or tumors in the central nervous system, knowing that ischemic lesions in the bridge can be associated with the presence of ageusia or dysgeusia[96].

Treatment of gustatory disorders

A great number of gustatory function disorders can resolve spontaneously after several years[97]. In case of post-radiotherapy disorders or facial nerve paralysis, sense of taste improves once symptoms disappear.

In the case of gustatory pathology caused by medicines, symptomatology improves from the moment medication is interrupted. In case of xerostomia, artificial saliva can be used.

There are studies showing that mouthwash containing chlorhexidine would be effective in some cases of disgeusia for salty or sour[98].

In patients with hypothyroidism, it has been observed that administration of thyroxine substitutes led to normal reappearance of taste sensation[99].

The "burning mouth" sensation in postmenopausal patients can lead to anxiety, depression. Therefore, besides estrogenic medication, tricyclic antidepressants may play a role in improving taste perception[99,100].

CONCLUSIONS

Beside the anatomic and functional role of the olfactory and gustatory systems, both taste and smell play an important part in the psycho-social individual behavior. This is why a correct diagnosis and treatment strategy are important in case of taste in smell disorders.

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