THE IMPORTANCE OF SMELL AND TASTE IN EVERYDAY LIFE: DYSFUNCTION IN COVID-19 PATIENTS

ZNAČAJ MIRISA I UKUSA U SVAKODNEVNOM ŽIVOTU: PROMENE KOD PACIJENATA SA COVID-19

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Abstract

Human-to-human transmission of coronavirus (SARS-CoV-2) - COVID-19 (corona virus disease 2019) - is characterized by a pandemic exponential rate and the patients with mild to moderate infection have odor and taste problems that represent a new atypical disease. A new viral syndrome of acute anosmia or "new loss of taste or smell" without rhinitis and nasal obstruction or rhinorrhea has been placed on the list of symptoms that may occur 2 to 14 days after exposure to the COVID-19 virus. Two months after declaring the COVID-19 pandemic in May 2020, the World Health Organization (WHO) has recognized changes in the perception of smell and taste as symptoms of this disease. The described cardinal symptoms are more common in the population of young patients and able-bodied people which facilitates the spread of disease. Significantly higher prevalence of patients with COVID-19 who have lost their taste and smell is treated at home (rare hospitalization), lung damage is rare, as well as oxygen therapy with mild lymphopenia. Different scenarios of SARS-CoV-2 viral infection can be assumed: it is probable that the virus does not enter directly into olfactory sensory neurons (they do not have ACE2 and TMPRSS2 receptors), but it is localized to vascular pericytes and causes inflammatory processes and vasculopathies. On the other hand, direct infection of non-neuronal cells which contain said receptors is possible. Those are specific cell types in the olfactory epithelium such as sustentacular, horizontal basal cells, as well as Bowman's glands, which leads to massive degeneration and loss of olfactory neurons. The sense of taste is a complex sensation that is the result of the interaction of smell, taste, temperature and texture of food. The virus damages cranial nerves, epithelial receptors and blood vessels leading to taste damage (ageusia or dysgeusia).

A multidisciplinary approach with epidemiological, clinical and basic research is needed to elucidate the mechanism of sensorineural odor and taste loss caused by coronavirus.

Sažetak

Prenos koronavirusa (SARS-CoV-2), COVID-19 (bolest koronavirusa 2019) sa čoveka na čoveka karakteriše pandemijska eksponencijalna stopa, a pacijenti sa blagom do umerenom infekcijom imaju problema sa mirisom i ukusom, što predstavlja novu, atipičnu bolest. Novi virusni sindrom akutne anosmije ili „novi gubitak ukusa ili mirisa", bez rinitisa i nazalne opstrukcije ili rinoreje, stavljen je na listu simptoma koji se mogu javiti 2 do 14 dana nakon izlaganja virusu COVID-19. Dva meseca nakon što je maja 2020. proglasila pandemiju COVID-19, Svetska zdravstvena organizacija (WHO) prepoznala je promene u percepciji mirisa i ukusa kao simptome ove bolesti. Opisani kardinalni simptomi češće se primećuju u populaciji mladih pacijentkinja i radno sposobnih ljudi, što utiče na lakše širenje bolesti. Značajno veći broj osoba pacijenata sa COVID-19 koji su izgubili ukus i miris leči se kod kuće (retka hospitalizacija), retko je oštećenje pluća, kao i terapija kiseonikom uz blagu limfopeniju. Mogu se pretpostaviti različiti scenariji virusne infekcije SARS-CoV-2: verovatno je da virus ne ulazi direktno u olfaktorne senzorne neurone (ne poseduju receptore *ACE2* i *TMPRSS2*) već se lokalizuje na vaskularnim pericitima i uzrokuje zapaljenske procese i vaskulopatije. S druge strane, moguća je direktna infekcija neneuronskih ćelija koje sadrže pomenute receptore, koje čine specifični tipovi ćelija u olfaktornom epitelu kao što su sustentakularne, horizontalne bazalne ćelije i Boumanove žlezde koje mogu dovesti do masivne degeneracije i gubitka olfaktornih neurona. Osećaj ukusa je složena senzacija koja je rezultat interakcije mirisa, ukusa, temperature i teksture hrane. Virus oštećuje kranijalne nerve, epitel receptora i krvne sudove, što dovodi do oštećenja ukusa (ageuzija ili disgeuzija).

Potreban je multidisciplinarni pristup sa epidemiološkim, kliničkim i osnovnim istraživanjima kako bi se razjasnio mehanizam senzorineuralnog gubitka mirisa i ukusa izazvanog koronavirusom.

Ključne reči:
SARS-CoV-2,
anosmija,
ageuzija,
ACE2

Marker of SARS-CoV-2 infection or related anosmia and ageusia

Coronaviruses (SARS-CoV-2) are a family of large single-stranded RNA viruses. Specifically, SARS-CoV-2 is transmitted from person to person through respiratory droplets, which leads to respiratory tract infection that can progress to severe pneumonia, multiple infections of vital organs and fatal outcomes. The infectivity is high and the mortality rate is ~ 7%. The syndromes described in the current SARS-CoV-2 epidemic (COVID-19) are asymptomatic, mild, moderate and severe or (critical) disease, such as bilateral interstitial pneumonia (1-4). Human-to-human transmission of the corona virus, or COVID-19 (corona virus disease 2019), is characterized by a pandemic exponential rate, patients with mild-to-moderate COVID-19 infection have problems with smell and taste which represents a new atypical disease. Prominent symptoms induced by coronavirus are anosmia (together with phantosmia and malodours) and ageusia (parageusia, and hypogeusia), in combination with other symptoms (fever, cough, fatigue, diarrhea, abdominal pain and loss of appetite etc.) that can be used to predict COVID-19 test or positive COVID-19 (5-7). It causes a disorder of smell, taste and often a combination of it, since the experience of taste is associated with a disorder of smell that manifests itself during a meal. Chemosensory deficit or asymptomatic loss of smell (anosmia, 51.5 - 70.2%) and taste (47.1 - 67.8%) is an invisible and new disease and an emerging symptom and subsequently a marker of SARS-CoV-2 infection

(8-10). The World Health Organization (WHO), two months after it declared the COVID-19 pandemic on May 2020, recognized alterations in the perception of smell and taste as symptoms of this disease (11). The described cardinal symptoms are more often observed in the population of young (not yet explained why) female patients (more frequently than males) and able-bodied, where the disease spreads more easily (12,13). A significantly higher prevalence of patients with COVID-19 who have lost their taste and smell is treated at home (rare hospitalization), they are less likely to have lung damage, less likely to receive oxygen therapy and they have mild lymphopenia (4,9). In the literature, the opinion is represented for all the above, that the loss of odor is a prognostic and predictive sign of a less severe form of coronavirus infection (12-14). But there are studies that have the opposite opinion and advocate the view that there is no difference in the rate of hospitalization or in the severity of the disease between patients with and without sensory disorders in smell and taste (9,15). Most of the patients belong to a group that has mild flu syndrome (nasal obstruction, headache, and myalgia). On the other hand, there are patients with a more severe clinical picture (fever, cough and dyspnea) and were hospitalized (12,16).

The time and duration of sensory deficits are so unique in COVID-19 that people with odor loss differ from people with other virus-related deficits. They have a sudden onset of illness, a short duration, and in most cases a speedy recovery. The fact is that anosmia (phantosmia and parosmia) and taste dysfunction may be the

only symptoms in a large number of patients (6,7,17). Chemosensory deficit is transient; odor recovery and recovery time from gustatory dysfunction occur in the range of a few days to 2 weeks after the resolution of general symptoms. It seemed that some patients recovered the smell, but not the taste, and *vice versa*, but there are cases when the smell did not return to normal, eight weeks after the illness (9,12,18). Monitoring of post viral patients with odor loss in over 96.1% of patients reported subjective recovery by 12 months (6,7,19).

Smell and taste systems, as well as parts of the somatosensory system, are separated by different peripheral and central neural mechanisms (5,19,20).

Smell and taste are specialized sensory visceral senses that belong to chemoreceptors and enable recognition of the world in numerous ways (**figure 1**). Immediately after birth, the baby recognizes its mother by the sense of smell. Smell is a natural function that is performed unnoticed and continuously, it is similar to swallowing, breathing, blinking, actions that happen continuously without conscious effort. The processing of the olfactory sensation includes the detection, perception, differentiation and identification of odors (21,22). Powerful messages can be delivered by smell by pheromones, odors that are specific for the animal species and through a highly specialized and functionally integrated olfactory system; it is possible for vital activities to be performed in the animal world for the purpose of survival, nutrition, reproduction, etc. (23). In the human population, of all the five senses, smell is the most exciting and least understood or "forgotten" first cranial nerve or *n.olfactorius*. The olfactory system is described as the most primitive, and the physiological significance of odor is minimized in the identification of environmental factors and potential threats. Due to early phylogenetic development and simultaneous involvement of numerous and oldest and subconscious brain structures in the processing of olfactory sensations (without a hierarchical organization), the olfactory system is specific and differs from other sensory systems (24-26).

Patients often find it difficult to distinguish between olfactory and flavor disorders, due to tight olfactory-gustatory interactions and symptoms that are often reported together. The neural systems of the two chemical senses participate in the recognition of thousands of different odors and tastes as a result of combining different complex substances. Pleasant and unpleasant chemosensions alter behavioral, emotional, and cognitive aspects that can improve quality of life, reduce anxiety and increase alertness and work activity (24,27,28). Man detects more than 10,000 odors, but recognizes about 5,000. Molecules of odor in the nose and from food in the mouth dissolve in the mucosa soaked in water and activate membrane receptors on the cilia of specialized neuroepithelium (smell) and epithelium (taste) (24,26,29). Odors from the external environment through the nostrils lead to continuous, automatic and passive odor. In order to recognize odor (odorant) small volatile molecules and soluble substances (water-soluble and liposoluble) during eating and drinking

enter the nasal cavities by air current during inhalation (orthonasal air flow) and come into contact with the nasal olfactory neuroepithelium and chemoreceptors (27,30,31). There are ten **basic scents**: 1. fragrant, 2. fruit (all except citrus lemon), 3. citrus (lemon), 4. mint and peppermint (menthol), 5. sharp (cigarette smoke, etc.), 6. smell of rotten meat (thiols, etc.), 7. sweet (chocolate, etc.), 8. chemicals (ammonia, etc.), 9. woody and resinous (fresh cut grass, etc.), 10. toasted and nutty (almonds etc.) (27,29). Smell-sharpness increases with age, and peaks in people in their 30's, but it decreases rapidly after the age of 60, when cognitive decline (especially episodic memory) occurs. Half of the population aged 65 to 80 suffers from olfactory disorders, which are manifested by an increase in the smell threshold, which can affect the reduction of a quality of life. In people older than 80 that number is much higher (75%). Active smokers have a significantly lower olfactory function (32,33).

On the other hand, perceptual areas of the senses of smell and taste differ from each other, but are closely connected and integrated with sensory systems that participate in homeostatic, visceral processes (27,34). The sense of taste has evolved in humans over millions of years in a dominant food shortage. Perception of odors of food and drink emanating from the oral cavity is caused by the flow of air through the nasopharynx (retronasal olfactory). Retronasal airflow is caused by movements of the mouth and tongue during chewing and swallowing food that is in contact with chemoreceptors (29). Taste is a combination of signals we receive from all our senses (nose, eyes, ears) by retronasal olfaction. Cranial nerves VII, IX and X innervate taste buds on the tongue, which recognize five basic flavors (salty, sweet, bitter, sour and "umami"). In humans, the sharpness of the senses of taste decreases physiologically and decreases dramatically from the age of 50, so that the child thinks that the food is too spicy while for an older person the same food is bland (14,33,35).

The rhinencephalon (olfactory brain) is made up of brain structures responsible for smell, which consists of the brainstem, limbic system, hypothalamus and cortex. The primary olfactory areas interact with other cortical areas to process and integrate higher-order olfactory information because it contains a complex system of functioning. Piriform cortical processing of olfactory sensory neurons creates a conscious and unconscious reaction (27,36).

One of the main pathways of olfactory information is to the limbic system (hippocampus, amygdala, hypothalamus, etc.) which processes emotions, creates memory, as well as specific behavior. Smell memory is a form of implicit or reflex memory that has a very special role in ignoring well-known smells and thus increases a person's readiness to be able to detect new smell stimuli. Smelly perception conditions the consolidation of memory, whereby temporary traces are coded and become long-lasting (declarative and autobiographical memory). Thus, previous experiences affect later odor-related behaviors (25,27,37).

The second main sensory olfactory ending is in the frontal cortex, finally in the "higher" areas, where sensations

are consciously recognized (25,31,36). The conscious sensory perception of smell and the processing of complex olfactory elements, which consists of identification and discrimination, are primarily affected by experience (reaction of pleasure or disgust), as well as olfactory working memory to a certain smell, as well as short-term adaptation to odors (30,38).

The influence of smell on the sense of taste is caused by the spectrum of emotions from hedonism to depression

A common feature of taste and smell is the affective nature that provides the quality of pleasure or discomfort, as well as the aversive reaction (avoiding spoiled food), which is vital (36). Occupations that require a good olfactory system are cooks, perfumery workers, oenologists, fire fighters, beverage tasters including the chemical industries and others.

The senses through which we receive altered odors and tastes in food choices are vital to detecting and avoiding potentially toxic and harmful foods. In fact, unpleasant odors, as well as the taste of rotting spoiled food can reduce pleasure and initiate avoidance of this type of food. Also, timely detection of smoke by smell (poisonous vapors or gas leaks) creates a sense of danger, causes fear and timely reactions (30,31). The fragrance has a hedonistic and social function since it acts on emotions, which is why the cosmetics and perfume industries are successful. The presence or memory of certain tastes and smells (food, flowers, essential oils, soaps and perfumes etc.) has a stimulating effect on increasing appetite and causes feelings of pleasure and enjoyment. In the absence of the smell and taste of food and drink, all glands (salivary, gastric and intestinal) reduce their secretory function, which makes digestion difficult (14,37). On the other hand, the physiological needs associated with smell are sexual instinct, love, which together with psychological processes (lust, belonging and mood) affect the behavior of the partner (increase or loss of sexual desire). There is also a commercial component, satisfying aesthetic needs that provoke people to buy, because some shopping malls and stores nurture certain scents (30,39).

Senses of smell and taste participate in the consolidation of memory and recollection of places and events associated with olfactory (fragrant) and delicious (tasty) sensations. Due to numerous anatomical connections, they show activation in the prefrontal cortex and amygdala, hippocampus and rhinal cortex in the temporal lobe. Olfactory memory is multisensory, through glutamatergic synapses it causes short-term and long-term plasticity, olfactory working memory is coded, and all of the above affects daily activities and the creation of memories of smells that are remembered and later recognized (25,31,37). The smell of freshly baked bread evokes different memories from grandmother's kitchen and childhood - it creates a pleasant feeling of security with abundant salivation (31).

Odor perception began with relationship between odor receptor and molecules

The nasal epithelium is divided into a respiratory epithelium and olfactory epithelium, whose functions and cell types differ. The olfactory system begins with the nasal cavities in which there are olfactory neuroepithelial cells in direct contact with the brain (**figure 1**).

A set of olfactory receptor cell axons passes through the openings (perforations) of cribriform plate of the ethmoid bone on the roof of the nasal cavity, which separates it from the olfactory bulb in the cranial cavity. Olfactory sensory neurons with the same protein recipes send signals to a specific group of cells in the brain (38). The olfactory neuroepithelium is a pseudostratified column of epithelium located in the upper part of the nasal septum and on the roof of the nasal cavity (below the lamina cribrose). The olfactory receptor neurons ($10 - 20 \times 10^6$) covers an area of four to eight square centimeters in each nostril and makes up 1.25% of the nasal mucosa, with about 10 – 20 million dendrites that are directly connected to olfactory receptors (36,38,40,41).

The olfactory neuroepithelium contains at least five cell types:

1. The bodies of olfactory sensory neurons are specialized bipolar cells that at one end contain dendrites with hairs or cilia (10 – 30 cilia) that immerse in a mucous film on the surface of the epithelium of the nasal cavities. Small amyelin axonal bundles of the primary olfactory neurons originating in the basal pole (formed *fila olfactoria*). The **first and shortest** cranial nerve the *n.olfactorius* (CN I) is special visceral afferent nerve that transmits information related to smell. It is one of two nerves that do not emerge from brainstem; it joins into thin bundles which projects into the olfactory glomeruli of olfactory bulbs (9,42);

2. Sustentacular cells (sustentaculocytes) or supporting cells on the apical part are covered with microvilli that are located in the mucous film provide structurally support sensory neurons, neurotrophic and physical, secretory, absorption as well as phagocytic support to olfactory sensory neurons. It is believed that these cells are partly epithelial and partly glial and perform high energy requirements (glucose metabolism) together with detoxifying activity due to phagocytosis of toxic inhaled substances (1,14);

3. The cells of the channels of the **olfactory glands** (Bowman's) are distributed throughout the glands of the olfactory epithelium, projecting narrow channels on the surface of the epithelium, through which they secrete sero-mucous mucus that covers the epithelium. Mucus contains water, mucin glycoproteins, enzymes, antibodies, salts and odorant-binding proteins which help carry certain hydrophobic olfactory molecules (14,42);

4. Microviral cells are non-neuronal cells, like support cells underlying the olfactory stem cells, actively proliferating stem cells show a multipotent progenitor phenotype and are responsible for the constant regeneration and
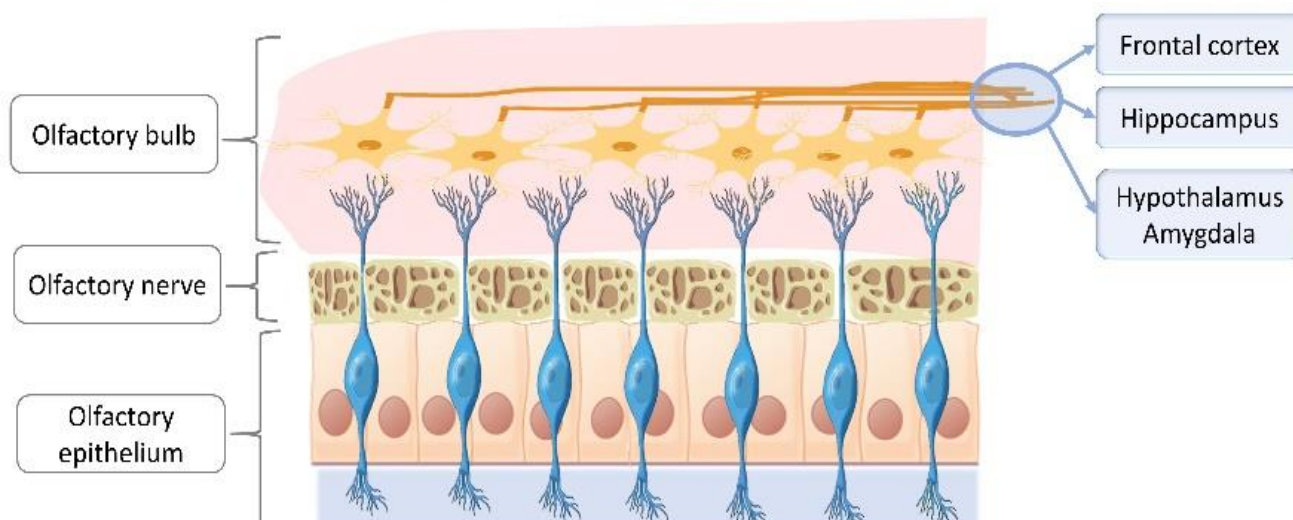
Figure 1. Olfactory pathway: from the olfactory epithelium through the olfactory bulb (first relay station), without passing through the thalamus, the pathway goes to the limbic and frontal cortex.

recovery of odors. Basal cells can divide and differentiate and can replace olfactory sensory neurons and all other cell types after a severe injury;

5. globose basal cells are primarily responsible for regenerating and proliferate in uninjured olfactory epithelium during normal epithelial turnover. Horizontal basal cells act as reserve stem cells activated upon tissue damage proliferate in response to sustentacular cell death (36,43,44).

Olfactory receptors

Olfactory receptors were found 30 years ago (42). Receptor behavior is improved: one neuron - one olfactory receptor that acts on the principle of "key and lock". Each olfactory cell carries only one type of receptor protein for a particular substance (smell) or "lock", while the smell floats in the air, fits into the "lock" and thus activates the cell. An olfactory cell neuron that does not express the olfactory receptor will die, and on the other hand, if more than one olfactory receptor is expressed, negative selection of the olfactory neuron is induced (45,46). Smell sensation creates an electrical receptor potential in response to the olfactory nerves: an odor molecule binds to a receptor belonging to receptors associated with the G protein/cAMP cascade, located in the cilia of bipolar neurons in the olfactory mucosa. After that, olfactory receptors open non-specific cation channels permeable to Ca^{2+} and induce receptor potential. This is how odor receptors play a crucial role in recognizing thousands of odor molecules. Odor receptors have a unique ability to regenerate from stem cells when they are injured or old (45,47).

Olfactory bulb is the first relay station of the olfactory pathway

The olfactory bulb is the first relay station of the olfactory pathway that contains specialized neurons, divided into five layers and located below the cerebral cortex and frontal lobe. The olfactory bulb contains two specialized types of projection neurons, called mitral and tufted cells that make synapses (or glomeruli). The dendrites of primary olfactory neurons are highly convergent and bind to only 1 – 4 glomeruli of the olfactory bulb and provide odor impulse conversion (**figure 1**). Local interneurons participate in the formation of glomeruli within the olfactory bulb, containing about 8000 glomeruli (46,48). Secondary dendrites of mitral and tufted cells are elongated in the outer plexiform layer, while long single primary dendrites go into the glomerulus (glomerular layer) (21,36). Granulated cells are without axons, they are inhibitory GABAergic interneurons that apically extend the dendrites into the secondary dendrites of mitral cells, forming dendrodendritic synapses. Granular cells and their interaction with mitral cells play an important role in odor discrimination (38,46,48).

Odor discrimination

Odor discrimination begins with the binding of olfactory molecules to receptors. Olfactory receptor neurons express the same type of receptor for a specific scent and send signals through axons to a specific group of cells that further converge to the same glomerulus in the olfactory bulb. Each glomerulus represents one odorant receptor therefore its role is crucial for detecting and differentiating olfactory stimuli. Individual mitral cells receive excitatory input from a single glomerulus and thus input from a homogeneous population of sensory neurons (45,48).

The olfactory pathway

One of the oldest sensory systems is the olfactory pathway associated with phylogenetically old brain structures that belong to the limbic system. The olfactory tract arises from the axons of mitral and tufted cells of relay neurons (second-order olfactory neurons). Mitral cell axons are projected onto the primary olfactory areas: anterior olfactory nucleus, piriform cortex, anterior cortical amygdaloid nucleus, periamygdaloid cortex and entorhinal cortex.

It is the only afferent sensory system that does not pass through relay neurons in the thalamus on its way to the primary cerebral cortex. The olfactory tract passes inferiorly to the frontal lobe and exits the ipsilateral olfactory cortex through the lateral olfactory tract (21,36,46).

In response to different odors of different receptors on olfactory sensory neurons, spatial patterns are activated that allow different mitral glomerular cells to overlap and converge into cortical areas. There are local effects at all levels of the olfactory tract (42,45).

Adult neurogenesis

In the central nervous system (CNS), the neurogenesis of adults in mammals exists and is limited to two areas of the brain. Structures such as the olfactory bulb and the dentate gyrus of the hippocampus are involved in the processes of neurogenesis or plasticity (49,50). Neurogenesis creates new neurons from basal cells and maintains this process throughout life. All structures of the olfactory pathway (from epithelium, neuronal receptors, olfactory bulb, glomeruli, periglomerular and granular cells etc.) participate in neurogenesis. Subpopulations of interneurons (periglomerular and granular cells), as well as mitral and tufted cells (forming the lateral olfactory tract) in the olfactory bulb are constantly replaced during life by differentiation of neuroblasts originating from the sub ventricular zone (ventro-lateral part of the telencephalon). There is a modification of the sensitivity of the olfactory system in terms of sharpness and ability to olfactory learning. Neurogenesis in the olfactory bulb enables learning, while the hippocampus is associated with the consolidation of long-term memory (21,30,31,49). Taste perception and odor recognition are maintained in the midst of the growth and replacement of a new axon. After about ten days, the epithelial cells of the taste buds die and are being replaced by new cells.

Olfactory cortex in the processing and perception of odors

Most projections of the olfactory pathway end in the primary olfactory areas: anterior olfactory nucleus, piriform cortex (area 51), anterior amygdaloid nucleus, periamygdaloid cortex and entorhinal cortex, as well as the orbitofrontal cortex (**figure 1**). The primary olfactory cortex (piriform cortex) is the largest and is defined as the cortical region of the brain that receives afferent fibers directly from the olfactory bulb but there are also multiple cortical sub regions (orbitofrontal, entorial, several amygdaloid nuclei etc.) (51). The piriform cortex differs from the rest of the neocortex in numerous features: 1. individual pyramidal cells receive certain patterns from mitral cells in it and at the same time send efferent feedback to the same cells (25); 2. unlike most sensory systems in the pyriform cortex, spatial organization is absent; 3. also, in relation to one primary sensory cortical part (e.g. somstosensory etc.) that processes one sensory information, different sensory information arrive in the piriform cortex and are processed within regional corticocortical projections with structures of other sensory modalities; 4. all sensory afferents on the way to the neocortex go through thalamic relay nuclei, only the piriform cortex receives monosynaptic fibers from the olfactory bulb (52); 5. the six-layered neocortex is typical of all sensory modalities versus the olfactory paleocortex, which contains three cell layers; 6. central cortical neurogenesis in adults exists only in the piriform cortex (hippocampus) throughout life, primary cortex (hearing, sight, touch, etc.); 7. due to the connection of the piriform olfactory cortex with different limbic and other cortical areas, it functions as an associative multimodal cortex (52); 8. due to dense two-way connections (entrance/exit) the piriform cortex can change higher order processes in terms of central adaptation which is faster and stronger in relation to the adaptation of olfactory receptors (the smell of tobacco smoke in the room is soon not felt), piriform cortical adaptation to long exposure to known odors is very rapid (53); 9. experience related to smell, olfactory memory etc. can activate piriform cortical surfaces in odor processing (30,31); and 10. an integrated response in the piriform cortex can elicit olfactory responses that can be - emotional, behavioral and memory (working memory) (25).

Olfactory dysfunction and clinical picture severity

Chemosensory disorders range from a slight change in normal taste and smell to a loss or distortion of the perception of taste or smell. Olfactory nerve and olfactory function, although somewhat neglected in clinical trials, may be a valid indicator of how old the brain is and subtle cognitive and sensory impairment during aging, as well as the progression of neurodegenerative diseases. Olfactory dysfunction is manifested by long latency, poor identification or loss of sense of smell. Olfactory perception dysfunctions occur due to damage to olfactory neurons that reduce the reception and processing of stimuli in olfactory receptors, pathways, or brain centers (54,55). Taste and odor disorders are difficult to separate due to their mutual activity. Changes in patients' sense of smell and taste affect well-being and quality of life and open up a spectrum of discomfort: depression, anxiety, feelings of insecurity and loneliness (54,56), problems with food preparation and decreased appetite (reduced enjoyment of food), excessive use of perfume or shaving products as well as excessive showering or cleaning (53,55,57), social insecurity and a sense of social isolation, loss of interest etc. (58).

Detection disorders

Marking the appropriate smell is called normosmia, and the other extreme is the impossibility of perceiving the sense of smell or anosmia. There are also disorders in the direction of increased ability to perceive odors (hyperosmia) or decrease (hyposmia) (21,53,57).

Identification disorders (dysosmia)

We are talking about the impossibility of identifying or classifying the sense of smell (odor agnosia), as well as distorted odor in the presence of a known source of odor (parosmia), sense of smell in the absence of odor source (phantosmia) and discouragement sense of unpleasant odors (21). Numerous pathological reasons are associated with conductive odor dysfunction such as congenital anosmia (30,31) or inflammatory sinonasal diseases (allergic rhinitis, chronic rhinosinusitis etc.) (59). Upper respiratory tract infections cause viral hypoosmia or anosmia (rhinoviruses, parainfluenza, coronavirus and Epstein-Barr virus etc.) or persistent odor dysfunction without neurological diseases (60,61). Olfactory system weakness is a warning for timely diagnosis and early treatment of neurodegenerative diseases and it can be said that impaired olfactory function is a biomarker for timely neuroprotective treatment (62,63). Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's disease and multiple sclerosis (32,40,50), as well as brain injuries due to trauma, cause neurosensory disorders and loss of smell (41,62,64). Olfactory deficits such as reduced ability to identify, recognize and odor discrimination, together with brief hallucinations prior to seizures, have been reported in patients with mesial temporal lobe epilepsy (Jackson described the olfactory aura for unpleasant odors) (65-69). The same symptoms hold true, in patients with schizophrenia (olfactory hallucinations (70,71) and psychiatric disorders (21,72).

Impaired recognition of the threshold and intensity of taste (**ageusia or dysgeusia**) can occur after trauma and injury to the tongue (papilla fungus), dentures, smoking, cranial nerve damage, brain contusion, dementia, colds, head injuries or bleeding. External factors (toxic and industrial agents) or internal (liver and kidney failure, uremia, diabetes, etc.) negatively affect the perception of taste; interfere with the chemical composition and amount of saliva. Numerous drugs (antifungals, antibiotics, anti-inflammatory substances, immunosuppressants and psychiatric drugs) reduce the perception of taste and behavior in the diet, which also occurs due to malnutrition (20,73,74). A long-distorted sense of taste can affect health complications due to changes in diet and unhealthy diet. This occurs due to a reduced salt perception threshold, which leads to increased intake and thus increases the risk of cardiovascular disease (hypertension), especially in the group of patients with diabetes, celiac disease, metabolic and other diseases (20,75). Radiation therapy in patients with head and neck cancer significantly affects taste function. Postoperative causes (middle ear, head and neck surgery and after general anesthesia) have been described as causes of impaired taste. High alcohol consumption and reduced absorption of trace elements (vitamins B and A) and *Zn* are definitely possible causes of altered taste (74,75).

Odor testing (subjective reports or objective testing or combination)

There are techniques and tools for researching chemosensory abilities. Odor testing in routine clinical practice can serve as a biomarker for various neurological diagnoses and could be a way to detect subtle cognitive and sensory impairments (64). Psychophysical olfactory tests: detection test, discrimination, identification test, explicit and implicit memory tests and other (39,53,57). Taste, sensation, and odor descriptors can all be ranked in relative intensity on a 0 to 5 scale (faint to strong). Electrophysiological tests for odor testing (identify odors, smell discrimination, and odor thresholds) are electro-olfactogram (records the magnitude of the electrical activity of the nasal olfactory epithelium), and olfactory evoked potentials (collect electrical activity from olfactory bulb or frontal cortex) (76), which together with biopsy of the olfactory region give a full profile (77, 78). Olfactory evoked potentials depend on the subjective factors of the patient (age, sex, alcohol, tobacco, cocaine, culture, etc.) and environmental factors (social aspects).

SARS-CoV-2 or COVID-19 and olfactory/ taste dysfunction

A new viral syndrome of acute anosmia or "new loss of taste or smell" without rhinitis and nasal obstruction or rhinorrhea has been placed on the list of symptoms that may occur 2 to 14 days after exposure to COVID-19 virus patients in a mild-moderate way (**figure 2**). Patients with confirmed COVID-19 infection have decreased or lost odor or retronasal odor dysfunction and loss of taste (hypogeusia and ageusia) up to 47.1 - 70.2%, and varies in different studies (7,10).

Loss of odor is a symptom with high prevalence, which is especially relevant for the younger ages and able-bodied population that will spread the disease faster. Olfactory dysfunction may appear before, during or after the general symptoms (1,2). The highest susceptibility of females to develop olfactory and gustatory dysfunctions would be related to the gender-related differences in the inflammatory reaction process. It can be a key symptom, potentially effective tool to assess the prevalence of positive cases and a marker for detecting COVID19 virus infection in the population (4,9,20).

Whether the nose acts as a reservoir for SARS-CoV-2, ACE2 receptors, devil and angels in the renin angiotensin system

To enter the SARS-CoV-2 virus host cell, the target is a receptor protein human enzyme that converts angiotensin (ACE2) and the proteolytic action of host proteases such as transmembrane serine protease 2 (TMPRSS2) (79-81). The SARS-CoV-2-mediated infection requires
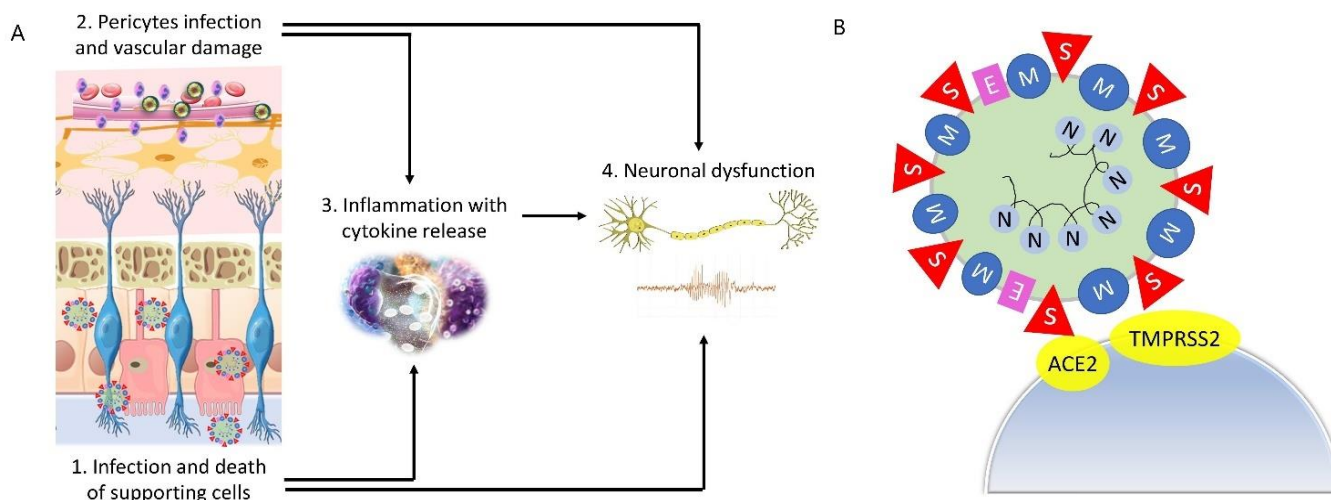
Figure 2. A. Different scenarios show how the SARS-CoV-2 virus may result in a quantitative reduction in odor: 1. infection of supporting cells, 2. infection of pericytes and vascular damage or 3. cytokine release **B.** To enter the SARS-CoV-2 virus host cell, the targets are: **ACE2** (human enzyme that converts angiotensin) and transmembrane serine protease 2 (TMPRSS2), SARS-CoV-2 virus S (spike protein), M (membrane protein, E (envelope) and N (nucleoprotein).

subsequent cleavage of the S protein by the serine protease of the TMPRSS2 host cell and other proteases (**figure 2**). Analyzes revealed that both ACE2 as a key cell receptor and TMPRSS2 are used and recognized in neuronal and non-neuronal cells to which the SARS-CoV-2 virus binds (5,15,43). The respiratory tract is the main site of infection and morbidity with the SARS-CoV virus. Neurons (carrier cells in the olfactory mucosa and olfactory bulb) and non-neuronal cells containing ACE2 receptors and the protein protease TMPRSS2 include specific cell types in the olfactory epithelium (sustentacular and horizontal basal cells of the Bowman glands, secreting neuronal mucus, vascular pericytes) that may alter the function of olfactory neurons. Sustentacular cells showed the highest frequency of ACE2 expression in the olfactory epithelium (2.9% of cells) (43,79,81). All of this suggests that infection of these non-neuronal cell types expresses ACE2 at a level that allows direct infection and then contributes to anosmia in patients with COVID-19 (14,82). However, sensitive sensory neurons and mitral cell of olfactory bulb neurons do not express ACE2 and TMPRSS2. In the brain, the ACE2 protein is predominantly expressed in vascular cells (pericytes), which is the cause of vasculopathy, stroke or altered consciousness. The SARS-CoV-2 can directly affect taste buds or ACE2 receptors that are diffusely expressed in the oral mucosa, epithelial cells of the tongue, taste buds and salivary glands, blood vessel cells, especially pericytes (79,83,84). The SARS-CoV-2 virus binds to ACE2 receptors and triggers an inflammatory response that leads to cellular and genetic changes that can change the taste (15,82). No significant differences in the level of ACE2 expression were observed between men and women or younger and older people in any tissue (81,82).

The ACE is a zinc-dependent peptidase and its homologue ACE2 are two key enzymes involved in the synthesis of bioactive components of the renin angiotensin (Ang I and II) system. The renin angiotensin system is the main regulator of human physiology, playing a key role in maintaining blood pressure homeostasis, regulating fluid and salt balance by coordinating the work of the heart, kidneys, blood vessels and brain. The ACE conversion of Ang I is into vasoconstrictive Ang II, while unlike that, the ACE2 counteracts the activity of ACE by reducing the amount of Ang II, increasing Ang (85,86). On the other hand the mechanism of SARS-CoV-2 infection requires binding of the virus to the membrane form of the angiotensin-converting enzyme 2 (ACE2) receptor (87,88). The entry of SARS-Cov-2 into the cell depends on ACE2, which reduces the activity after the virus enters. Through the imbalance of renin and angiotensin II, COVID-19 can result in a huge number of chronic problems. Due to the loss of ACE2 receptor activity, disorders of regulation and accumulation of undegraded angiotensin II, development of atherosclerosis, systemic activation of fibroblasts, and initiation of fibrosis of the lungs, kidneys, heart and liver occur. Consequently, the ACE2 performs its functions by cleaving either angiotensin I or Ang II into inactive peptides Ang (1 – 9) and Ang (1 – 7), respectively. In this regard, it could be considered that the classical axis of the ACE -Ang II- AT1 receptor plays the role of "devil" and ACE2 -Ang- (1 - 7) - Mass axis plays the role of "angels" in the renin angiotensin system (88, 89).

Different scenarios how the SARS-CoV-2 virus may result in a quantitative reduction in odor a qualitative change

In the short time of the pandemic, several mechanisms of odor loss have been described. Viral direct and indirect penetration into nerve tissue or non-neural cells causes odor damage (**figure 2**) as the following:
a. Conductive disorders are caused by nasal obstruction due to congestion, while rhinorrhea mechanically prevents

access to olfactory substances and their binding to sensory epithelial receptors (84,90);

b. Sensory-neuronal disorders or odor transmission disorders can be the result of damage to neural structures. It is assumed that this type of disorder occurs due to the death of the most commonly olfactory sensory neurons, olfactory bulbs or damage to the first cranial nerve (5,14). Thanks to neurogenesis, new mature olfactory sensory neurons are created and renewed and ACE2 receptors are expressed, which lasts 8 to 10 days;

c. The direct neuroinvasive potential of the virus plays a key role in the respiratory failure of patients with COVID-19 leading to neurological outbursts. Due to viral infiltration in brain neurons (olfactory neurons and centers, peripheral cranial nerve endings, and neuromuscular synapses), COVID-19 symptoms can be association with numerous neurological outbursts (such as rhinolaryngological symptoms of tinnitus, sudden sensorineural hearing loss, dizziness and headache etc.) (1,14,90). One of the hypotheses about the infection of the brain with the SARS-CoV-2 virus is the olfactory pathway. As a matter of fact, virus could invade the CNS *via* the olfactory nerve and possibly other cranial nerves. The second central extension of the pseudo-monopolar ganglion cell allows a death of neuroepithelium, olfactory bulb or olfactory cortex and reduces sense of smell (12,91,92). There is another hypothesis that SARS-CoV-2 can pass from non-neuronal olfactory epithelial cells directly into the cerebrospinal fluid and then spread to the brainstem, respiratory center or vasomotor center (85,93);

d. Primary infection in non-neuronal cells in patients with COVID-19 leading to ansosmia is very likely. The virus does not enter directly into the olfactory sensory neurons, but instead can be localized exclusively to sensitive cells and vascular pericytes and causes inflammatory processes and massive degeneration and loss of the olfactory epithelium. After entering sensitive cells, SARS-CoV-2 can cause permanent damage due to changes in stem cells, which help odor receptor cells because there is a reduced function of cleansing from odorant. This mechanism is supported by the abundant expression of two input proteins, ACE2 and TMPRSS2, in susceptible cells in the olfactory epithelium (79,94);

e. There is a hypothesis of neuronal damage and hypoperfusion due to the inflammatory response and immune-mediated vascular damage of vascular pericytes and endothelial cells expressing ACE-2 in the nose and bulb, by the release of cytokines and neurotoxic compounds (1,95).

Hypotheses of taste dysfunction in COVID-19

The sense of taste is a complex sensation, created by the interaction of smell, taste, temperature and texture of food, as well as sound stimuli (**figure 2**). The prevalence of density dysfunction is higher than odor dysfunction in almost all studies. Due to the intimate functional correlation of the two chemosensory systems, taste perception in patients with lost sense of taste is aggravated by odor

disorder (7,8). Mentioned sensory stimuli have a unique meaning when we take a meal (18,85).

Patients with COVID-19 reported gustatory disorders consisting of acute symptoms of ageusia without odor dysfunction, hypogeusia, parageusia (5,35). Epithelial cells of the tongue and buccal mucosa as a gateway for SARS-CoV-2 contain ACE-2 receptors in large numbers. Viral infection and inflammatory response can lead to disturbances in the nerve endings of taste buds in the oral cavity and saliva composition, resulting in anosmia and ageusia in patients with COVID-19 (5,14,18). Prevalence olfactory dysfunction in patients with COVID-19 varies from approximately 5 to 85% (35,93). There are a number of explanations for the mechanisms by which taste receptors are damaged and their reduced expression caused by COVID-19 infection: **a.** Direct infection of tongue cells that damage taste cells and neurosensory chemoreceptors with ACE2 receptors (17,96); **b.** Inflammation or direct damage to any cranial nerve (CN V, VII, IX or X) is a responsible for taste disorder (81,93,95); **c.** Damage to the tympanic chord through the eustachian tube; **d.** Due to the release of inflammatory cytokines (interferon) (97); **e.** Tissue hypoxia in patients can lead to taste disorders (97); **f.** Due to inflammatory processes, localized changes occur in the cellular homeostasis of zinc and oral gustatory cells as a result of infection with the SARS-CoV-2 virus (14); **g.** Salivary gland dysfunction with impaired salivary flow is the reason for dysgeusia in asymptomatic patients with COVID-19 (80,93); **h.** Infection with SARS-CoV- 2 by binding to sialic acid which has a protective role against enzymatic degradation to taste molecules, on taste buds reducing sialic acid in saliva and increasing the taste threshold (8).

The only manifestation of COVID-19 in a small number of patients is asymptomatic loss of smell and taste. Testing of patients with confirmed COVID-19 provides quantitative data on the frequency and severity of sensory losses. The intensity and duration of the disease, as well as the time during which the fragrant and tasty functions completely recover, remain unknown for now. A multidisciplinary approach with epidemiological, clinical and basic research is needed in order to elucidate the mechanism of sensorineural odor and taste loss caused by coronavirus.

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