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Review Article

TASTE PERCEPTION: FROM ANATOMICAL TO MOLECULAR LEVEL

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Summary: Taste plays an essential role in food selection and consequently overall nutrition. Our sense of taste helps us to gain information to form a picture of the world by sampling chemicals from our environment. Till now five basic taste modalities have been elucidated: sweet, sour, salty, bitter and umami, however in last years also fatty acid taste is perhaps becoming six scent of taste and existence of more basic tastes is still under debate. Each of these basic tastes has distinct functions. Umami and sweet taste are caloric detectors, eliciting positive hedonic tone, salt taste is important in maintaining sodium levels and is especially important in herbivores, sour taste contributes to recognition of unripe and spoiled food and bitter taste is assumed to detect toxins in the food. We can sense sweet (carbohydrates) and umami (proteins), therefore it would be sensibly to expect that we can sense fat. Each of the taste modalities is eliciting responses through its type of receptors, which are located in different taste buds, on different papillae in diverse areas of the tongue and its surroundings and influencing different nerves to activate taste recognition. Different channels and receptors, including seven transmembrane receptors (7TM receptors) on their own or by group effort, on example heterodimerization, are involved in taste perception by triggering diverse signaling pathways simultaneously in parallel or diametrically. This article reviews all by now known taste modalities from anatomical basis of taste perception till molecular mechanisms.

Key words: taste; sweet; sour; bitter; salty, umami; dietary lipid perception; anatomy; 7TM receptors; channels; taste transduction

Introduction

The sense of taste is a chemical sense for food quality and plays critical role in life and nutritional status of humans and animals. Although sight and chemical sense of smell is very important for food recognition and selection, the final choice of food is made by chemoreception of inorganic ions, sugars, amino acids, peptides and as well xenobiotics and toxins in the mouth, which are all subjected to nutritional chemoreception, followed by adaptive behavior. Taste is important for detecting chemicals in the environment, which directly influence organism, its specific taste receptor cells (TRC) (1).

We enjoy sweet taste, because we have a need of carbohydrates, we crave for salt, because when sodium chloride level is too low in our diet or we call for certain amino acids, which taste sense we entitle umami. On the other hand bitter and sour taste diverts us from most toxins, since majority of noxious substances are bitter and decaying food becomes sour (2). All life forms from bacteria to mammals check its intake by chemoreceptive examination. Already worms, nematode *Caenorhabditis elegans*, distinct between olfaction and taste (3). Both chemoreceptive senses are more clearly separated in arthropods and are distinct in vertebrates. In the fruit fly *Drosophila melanogaster* taste sensations are mediated by nerve cells. Their sensory dendrites are located in “hairs” found on the body surface. Other taste neurons, found on labellum and clustered around pharynx, express GR3 family receptors, belonging to superfamily of seven transmembrane (7TM receptors), as well designated as G-protein coupled receptors (GPCRs) (4). However, the taste receptor cells (TRCs) of vertebrates are not neurons, they have an epithelial origin (5) and are bounded on oral epithe-

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lium, typically tongue, palate and pharynx. On the tongue, the taste buds are located in special folds and protrusions called papillae, which contain large number of specialized bipolar TRCs. TRC express membrane proteins, identified as receptors for bitter, salty, sweet, sour and umami taste.

Taste is unique and can not be mimicked by mixtures of other taste qualities. Whether taste can be described as primary it depends on multiple criteria. Psychophysical and descriptive data isolate one primary taste from another on the basis of statistics, electrophysiological evidence that reports unique neural transduction features on putative taste modality and biochemical and molecular evidence that identifies and localizes unique receptors and cellular responses to the candidate primary modality. And by these criteria five basic modalities have been elucidated: salt, sour, bitter, sweet and umami (6). Through the history of taste research, there were many methods used to understand our taste perception. One of the first was sensory physiology approach that employed methods of psychophysics, initially developed for studying vision and audition and was mainly focusing on discriminating one taste stimulus from another and differences between intensities in distinct subjects. Human psychophysics used three methods to assess taste: absolute threshold measures, recognition threshold measures and suprathreshold measures. In absolute threshold method the lowest concentration of tastant can be detected by a subject as some kind of taste, while receiving three samples, one containing tastant and the others water. Similar method is a recognition threshold method, in which the lowest concentration that subject reports as having specific taste is determined. The suprathreshold measures attempt to quantify taste stimulus intensity, which is complicated by the fact, that perceived intensity of the taste stimulus can vary substantially between individuals (7). In last years animal models have become significant for taste studies. The most commonly used test performed on mainly rats is: two-bottle taste preference experiment, brief access taste assay and operant taste discrimination. In two-bottle taste preference experiment animals receive free access to two bottles, containing water or tastant solution. To measure what is the preference of the animal, the missing volume is measured; however it is important to be aware of strain differences. In the second model - brief access taste assay animals are mildly water deprived and therefore motivated to try one of the multiple spouts presented, which in random order contain a small amount of either water of tastant solution and animal has only a short period of time possibility to sample solution. Every lick of animal tongue is counted for different taste solutions (8). Operant taste discrimination model represents a more direct assessment of the taste by training a standard tastant solution as a discriminative stimulus for food or water reinforcement of an operant task, such as licking water spout (9).

To advance the knowledge of the process of sensation of the taste, knowledge of the sensory organ, the tongue, became more and more important. Therefore studies focused on the anatomy of the tongue, the organization of sensory apparatus and defining physiological-anatomical unit of sensory reception, the taste bud. Furthermore, different forms of receptors have been identified in the taste buds, interacting with the chemical signal - tastant. Next important step was discovery of G-proteins, specifically expressed in the TRCs (10) and later determined as important for perception of sweet, bitter and umami taste. These discoveries lead to assumption that there must be 7TM receptors involved in the process of recognition. 7TM receptors were identified for sweet, bitter and umami taste, although it was found out that for some taste modalities G-proteins are sufficient in eliciting response. First receptor candidates cloned from TRCs, T1R and T2R, were members of class C 7TM receptors. For salty and sour taste diverse mechanisms, eliciting responses through channels were identified (reviewed in 11). Research is now oriented in identifying different signaling pathways through 7TM receptors and new ligands, to either activate or block taste receptors for different signaling pathways. As well in these cases animal studies are present, mostly on genetically modified mice. In studying taste, also genetic approaches and inherited variation in taste abilities studies yielded new information about sense of taste by molecular studies of genes encoding taste receptors and other taste-signaling components. These studies were especially interesting from the fact that for some substances individuals show great differences in their taste thresholds (12). When stimulus activates TRC, receptors are activated, signal transduction cascades are initiated and through synapse and neurons an electrical impulse to the gustatory region of the cerebral cortex of the brain is transmitted, that interprets the sensation of taste.

Anatomy, histology, physiology and map of taste

Tongue lies in oral cavity and is consisted of skeletal musculature, connective tissue, fat tissue, glands and is covered with cutaneus mucous membrane. Mucous membrane helps to block microbes and pathogens from entering the digestive system and helps to moisten the mouth and food. The tongue is able to move in nearly every direction, expand, compress and display a fine degree of articulation. It is important as a tool for consuming and sorting different types of solid and liquid food, influences action of chewing and swallowing, grabbing, palpating, speaking, in animals is involved in fur and skin cleaning and very importantly for gustatory (taste) perception as a carrier of taste organelles (13).

The organ's ability to transform into a variety of shapes comes from its composition of skeletal muscle interspersed with fat. The tongue and its muscles are laterally symmetrical: a median septum divides the organ into two halves. The tongue is consisted of two types of muscles: extrinsic and intrinsic. Extrinsic muscles originate from elsewhere in the body and attach to the tongue. They connect with surrounding bones and help the organ to move up and down, from side to side and in and out. The tongue's extrinsic muscles all end in "glossus," which, unsurprisingly, means "tongue." The genioglossus depresses the tongue and thrusts it out. The styloglossus raises and withdraws the tongue. The palatoglossus raises its back. And, the hyoglossus lowers the tongue's sides. Despite the tongue's fine degree of articulation, the extrinsic muscles also keep it firmly lashed in place. The muscles connect to the mandible, or jawbone, the hyoid bone, a U-shaped structure that supports the tongue, and the styloid processes of the temporal lobes. The styloid processes suspend the hyoid bone with muscles and ligaments, therefore we sort it into the group of bones, that does not come into contact with another. Unlike extrinsic muscles, intrinsic muscles originate within the tongue. They allow it to expand and contract, altering its shape and size. The tongue's intrinsic muscles, which include the longitudinalis superior, longitudinalis inferior, transversus linguae and verticalis linguae, are especially important for speech and swallowing food. The primary blood supply to the tongue is through the paired lingual arteries with return via lingual vein (14, 15). Tongue surface is covered, especially at the palatal and side surface with tongue or gustatory papillae containing taste buds, special ovoid-shaped structures. They are joints of 30-100 small bipolar neuroepithelial cells together with basal and supporting cells and measure (50-60 x 30-70 μm). Total number of taste buds on the tongue is around 4600. Bipolar neuroepithelial cells are also named TRCs. We can find them at low densities on the soft palate, larynx, pharynx, and upper part of the esophagus (Wiggs, 1997).

We differentiate mechanical and taste papillae. Mechanical papillae are divided in filliform, conical and in dogs marginal (they aid nursing to avoid milk spilling) papillae. In the lingual epithelium, taste buds are located in three types of gustatory papillae with different spatial distributions. Taste papillae have different forms and positions and appear in different number and are differentiated in fungiform, circumvallate and foliate papillae. Fungiform papillae cover the front two-thirds of the tongue, are mushroom shaped and have small numbers (1-3) of taste buds on their apical surfaces. On the average, there are 41 taste buds per cm^2 of the tongue, are important for sweet and umami taste sensation and are innervated by facial nerve. The circumvallate papillae are located on the posterior third of the tongue, in the central and lateral regions. They are bigger than fungiform papillae; they do not protrude from the tongue, are separated from surroundings by canal and contain several hundred taste buds. Humans have around 10 circumvallate papillae, whereas rodents have only one, positioned centrally. Each of the papillas is consisted from approximately 250 taste buds, which is 2200 on the whole tongue. Near the circumvallate papillae serose Ebner's glands were found. Ebner's glands are also called gustatory glands and their serous secrete is secreted in the canal surrounding papillas and washing away already tested substances and therefore preparing taste buds for new tasting experiences. They are consisted of TRCs important for recognition of sour and bitter taste and are innervated by glossopharyngeal and facial nerve. Foliate papillae are located at the posterior lateral edge of the tongue and contain several hundred of taste buds. They are mostly reacting on sour taste and are innervated by glossopharyngeal and facial nerve. In humans there are on average 5.4 found in one side of the tongue. Each papilla is consisted froma round 120 taste buds, which are all together 1300 on the tongue. 2500 of foliate papillae can be found on soft palate larynx, pharynx, and upper part of the esophagus. Vagal nerve innervates taste buds in the pharyngeal region (16-18).

The life-span of TRC is around 10 days and every 10 days basal cells, which lay in the vicinity of TRCs differentiate into TRCs. Interesting is the fact that the number of TRCs is decreasing by age. The existing explanation is that every nerve ending can not find new proper TRC in development for the same taste modality, specific for the same type of taste and form new synapse.

Bipolar TRC have two specializations, which are highly important from functional point of view: microvilli, which are in the contact with the oral cavity and synapses with sensory nerve fibers. Taste receptors are mounted on the top of microvilli, working as molecular antennas in the chemical environment. They extend from a small opening, or taste pore, and mingle with molecules of food introduced by saliva. The saliva solution contains digestive enzymes that help to break down foods chemically, which are therefore able to reach receptors. Saliva is secreted by three major salivary glands - the parotid, mandibular and sublingual, as well as other small salivary glands contained within the tongue and mouth. Saliva is also important protector before drying and bacterial infection. Basal part of TRC is connected to fibers of different sensory taste nerves. On the base of TRC afferent dendrites branch into taste buds. When taste molecules bind, receptors trigger transduction cascades that activate synapses and therefore cause excitation of nerve fibers. These carry signal to the brain stream, where central taste processing begins, and elicit responses. The first molecular encounter with tastants by membrane receptors, enables molecular specificity of the taste response and triggers downstream transduction events in TRCs (19).

Neurophysiological studies in several species of mammals have shown four major branches of cranial nerves innervating taste buds and tongue muscles. Taste sensory and muscle innervation is brought to the brainstem by hypoglossal nerve, facial nerve, glossopharyngeal nerve and vagus nerve. Hypoglossal nerve is important for motorical movement of the tongue, while others are important for taste sensation, sense of touch, pain and warmth. Hypoglossal nerve provides motor innervation to the muscles of the tongue (except for the palatoglossus, which is innervated by the vagus nerve) and other glossal muscles and is important for swallowing and speech articulation. First two anterior thirds of the tongue (sensitivity to sodium salts and sugar) are innervated by facial nerve which is consisted from gustatory and sensory fibers. One of the branches of facial nerve is chorda tympani (CT) nerve, which enters through petrotympanic fissure into facial canal towards geniculate ganglion, from where axon enters internal acoustic canal into the cranium till gustatory nuclei. Gustatory nucleus is a part of solitary nucleus (from Latin: nucleus tractus solitarii (NTS)) in the brainstem, laterally from trapezoid bodies. Taste signals to the thalamus, triggers feeding behaviors and via parasimpatic pathway inducing digestive secretions from different glands. It is also important to provide secretomotor innervation to the salivary glands (except parotid) and the lacrimal gland. Posterior third of the tongue is innervated by glossopharyngeal nerve (responding to quinine, acids, weekly to sugars and salts), which is again leading gustatory and sensory fibers till medulla oblongata. Important is lingual branch of glossopharyngeal nerve and is involved in unspecific innervation. Through jugular foramen enters cranium and leads to distal sensory ganglion, consisted of perikarions and furthermore till medulla oblongata. Vagus nerve covers small area on the epiglottis (17, 20, 21).

Receptors and signal transduction in different type of taste

Specialized receptors are stimulated by the chemical makeup of solutions. They respond to several primary tastes: sweet, salty, bitter, sour and umami (savory). 7TM receptors are class C of receptors and are type 1 taste receptors (T1R1, T1R2 and T1R3), type 2 taste receptors (T2R) and taste metbotropopic glutamate receptors (mGluRs) (22). Besides highly important 7TM receptors for taste recognition, mammalian transient receptor potential (TRP) family of ion channels are higly significant for certain types of taste modalities. This is family of ion channels, consisted of 28 members, which are classified into 6 subfamilies: taste vanilloid receptors (TRPV), transient receptor potential cation channel (TRPC), its subfamily M (TRPM), subfamily P (TRPP), subfamily ML (TRPML) and subfamily A (TRPA). Additionally, there are five additional members, referred as PKD1-like family members, distantly related to TRP channels in amino acid sequence. Many TRP channels play important roles in signal transduction in various sensory systems including vision, smell, pheromone, hearing, touch, osmolarity, thermosensation and sweet, bitter and umami taste of diverse animal species, ranging from mammals and fish to fruit flies and nematodes (23). In certain taste modalities firing of action potentials through voltage-

gated Na^+, K^+ and Ca^{2+} channels is highly important, like epithelial Na^+ channels (ENaC), and Na^+ channels susceptible to tetrodotoxin (24). According to the recent literature fatty acid taste, might be a sixth taste, connected to putative CD36 receptor and fatty acid transporter (FAT) (25).

Salt taste

The most abundant dietary source of salty taste is NaCl, which has essential physiological roles in determining blood volume and indirectly influencing blood pressure and water homeostasis. Although salt taste is elicited by many ionic species, Na^+ has a major impact on physiological processes since it represents 90% of all anorganic ions and is therefore the most studied in mammals (12). Salty taste response is also elicited by NH_{4+} and Li^+ and salty-testing KCl that contributes K^+ to the diet. Some of above mentioned ions participate in important physiological processes, such as nerve and muscle signaling, active transport across the membrane and maintaining cell volume, pH and cellular concentrations of other important ions, such as Ca^{2+}(26).

Basis of salt taste perception has been studied for years; however its molecular mechanism is still not fully elucidated. Taste receptors for salty stimuli include several candidates, consisted of specific and unspecific receptors, such as epithelial Na^+ channels (ENaC) and taste variant of the vanilloid receptor-1 nonselective cation channel (TRPV1t) (Lyall, 2004). ENaC is hetero-oligomeric complex, comprised of three homologous subunits (α-, β- and γ), which together act as specific salt-taste receptor by providing a specific pathway for sodium current into TRC, when Na^+ ions are present in the environment in sufficient concentration. Na^+ ions passively flow through these ion channels in the apical, as well as basolateral membrane of TRC according to the concentration gradient and trigger action potential. ENaC channels form adherent junctions on the apical surface of the membrane. With membrane depolarization Ca^{2+} ions enter through voltage dependent Ca^{2+} channels, sensitive to calcium, which elicits neurotransmitter release and signal transmission on primary afferent fiber and eliciting salt taste response (28). ENaCs are distributed in dorsal lingual epithelium in vallate and fungiform papillae. At least one of the subunits of ENaC is under control of hormone aldosterone (29). In animals in sodium-need the sensitivity in sodium taste is increased by induction of more ENaC channels and adapts the tuning of taste acuity in the state of nutritional deficiency. The Na^+ specific salt taste receptor is especially evident in herbivores, where it plays essential role in their foraging for Na^+ (30). EnaCs are sensitive to channel-blocker amiloride and its potent analog benzamil, both diuretic drugs that inhibit Na^+ transport in various epithelial tissues. Amiloride is a guanidinium group containing pyrazine derivative and is known as potassium-sparing diuretic, first approved for use in 1967 (then known as MK 870), used in the management of hypertension and congestive heart failure (31, 32).

Role of ENaC in Na^+ ion transport and specific taste reception was shown by studies on isolated rat and hamster taste buds by showing that amiloride blocks Na^+ current across TRC membranes and that taste nerve responses to NaCl are significantly inhibited by amiloride or its analog. Results revealed that taste responses to NaCl recorded in the afferent CT nerve or in the NTS of various species are significantly inhibited by amiloride without effect on responses to stimuli of other taste modalities (reviewed in 26). Rodents are the species, which are the most sensitive to amiloride and ENaC play important role in perception of NaCl. Since amiloride sensitivity of salt taste is less pronounced in humans, the involvement of other channels was proposed besides ENaCs that may affect NaCl perception (33). It is interesting that TRCs from rat circumvallate papillae in the posterior part of the tongue, innervated by glossopharyngeal nerve give only amiloride-insenitive neural responses to NaCl. However, ENaC can be detected in circumvallatae TRCs.

It was also observed that one of the amiloride or benzamil insensitive salt taste receptors in fungiform papillae taste buds are taste variant of vanilloid receptor 1 (VR1), also designated as TRPV1 (TRPV1t) and are hypothesized to respond to various cations, including Na^+, K^+, NH_4^+ and Ca^{2+}, and therefore described as cation unspecific channels (26). It is one of the non-selective cation channels in nociceptive neurons that mediate terminal pain including the noxious thermal pain produced by vanilloids such as capsacein and resinferatoxin. The amiloride-insensitive component of NaCl CT nerve response, as well as responses to KCl, NH_4Cl and $CaCl_2$ in rat are enhanced by resinferatoxin and capsaicin with increasing concentration up to a maximum enhancement and at higher vanilloid concentrations in neural responses are suppressed (34). The tonic part of the amiloride-insensitive NaCl CT nerve response

are completely inhibited by a TRPV1t inhibitor. The structure of TRPV1t is still undetermined, but it was observed it is constitutively active in comparison to TRPV1 channel, which is not conducting, unless activated by heat, acidic pH or the presence of vanilloids. Also decrease of pH has no effect on TRPV1t, whereas lower pH activates TRPV1. The taste variant TRPV1t cannot detect an increase in food acidity and can therefore function as salt taste receptor, but not as sour taste receptor (35). However, the importance of this protein has been questioned because knock out mice lacking the receptor are nonetheless responsive to salt taste (36). The second proposed option are Na^+ channels, which are susceptible on tetrodotoxin (TTX), which is a neurotoxin found in fish species Tetraodontiformes (pufferfish, porcupinefish, ocean sunfish and triggerfish) (37).

Taste sensitivity to salty stimuli appears to develop postnatally in humans and laboratory rats (38). The hedonic value of NaCl, physiologically the most important dietary salt, varies to some extent with the subject's sodium needs. Salt taste sensation is affected by systemic conditions, that result in increased level of aldosterone and suggests that salt taste reception may involve one of the sodium transporter targets (26). Because salt taste is appetitive, humans ingest more salt than they need. The global high prevalence of hypertension and cardiovascular disease has raised concerns regarding the sodium content of the foods which we consume. Over 75% of sodium intake in industrialized diets is likely to come from processed and restaurant foods. Therefore international authorities, such as the World Health Organization, are encouraging the food industry to reduce sodium levels in their products (39). On the other hand in the state of hiponatremia, Na^+ becomes inaccessible for action potential transmission, which causes hypovolemia and shock and in a rarer cases pathological neurological signs, excitations, convulsions and coma. For this reason it is important to maintain proper sodium concentration.

Sour taste

Sourness is evoked by acids. Sour taste is acceptable or interesting when mild; thereby aiding the recognition of complex food, but it becomes increasingly unpleasant when strong. It serves to detect unripe fruit and rotten food and helps us to prevent tissue damage with acids and problems with acid-base regulation (12). Sources of sour tastants include anorganic molecules such as hydrochloric acid and organic compounds such as acetic, citric, lactic or tartaric acid, which are either natural products of fermentation or basic metabolic pathways such as citric acid cycle. They can be found in most fruits and vegetables, as well as animal products and man-made products, such as wine (40). Limiting the indigestion of acids from food is body strategy to maintain acid-base homeostasis. If sourness is masked by sweet- or salty-tasting substances on example by addition of artificial and natural sweeteners to soft drinks or other acidic beverages, indigestion of acids is tolerable and can be consumed in large quantities. However, by masking sour taste, we ingest large quantities of acids daily, probably more than we are supposed to, given that sour taste is repulsive *per se*. Besides all negative effects for lungs and kidneys, combination of increased acid and sugar in food leads to too low pH in the oral cavity, which promotes tooth enamel demineralization directly and indirectly by encouraging the growth of acid-tolerant bacteria, that are by themselves strong acid secretors (26).

The large variety of mechanisms involved in eliciting sour taste highlights the complexity of taste transduction. A number of candidate receptors for sour stimuli have been proposed, including ENaC, acid-sensing ion channel-2 (ASIC-2), hyperpolarization activated, cyclic nucleotide-gated channels (HCN1 and HCN4) (41). Furthermore, possible candidates would be two pore domain potassium (K^+) channels, which include apical K^+ channel in Mudpuppy necturus (MDEG1), H^+-gated Ca^{2+} channel, proton conduction through apical amiloride-blockable Na^+ channels, a Cl-conductance blocked by 5-nitro 2-(3-phenylpropylamine) benzoic acid (NPPB) and the activation of proton gated channel, BNC-1, a member of the Na^+ channel/degenerin superfamily (reviewed in 12, 24, 42). Sour taste perception is triggered when acidic substances stimulate TRCs, causing depolarization-induced Ca^{2+} entry into TRC (43). Blockade of the H^+-gated Ca^{2+} channels starts depolarization, enables Ca^{2+} ions entrance, which leads to neurotransmitter release and transfer of signal into the primary afferent nerve. To some extent the intracellular pH of TRCs follows extracellular changes in pH, which occurs probably because of the tight junction, which closes the extracellular space of taste bud towards oral space, however is permeable to H^+ ions. The second mechanism is enabled through channels inhibited by amilorid. H^+ ions can use the same channels important for salt and sour taste (12).

In last years two transient receptor potential (TRP) ion channels have gathered strong evidence as putative sour taste receptors and are a focus of additional interest (24). Two receptors - polycystic kidney disease 1-like 3 (PKD1L3) and polycystic kidney disease 2-like 1 (PKD2L1) belong to polycystic kidney disease-like (PKDL) subfamily of TRPs, consisted of 5 members, some of which act as non-selective cation channels and are permeable to both Na^+ and Ca^{2+}. Polycystins (PKD) consist of polycystin-1 (PKD1) and polycystin-2 (PKD2), whose mutations cause an autosomal dominant polycystic kidney disease (ADPKD) (44), one of the most common inherited diseases. ADPKD in humans is manifested with progressive development of fluid-filled cysts from the tubules and collecting ducts of affected kidneys. Association of PKD1 and PKD2 as heteromer appears to be required for formation of a functional receptor that sense mechanical flow, osmolarity and/or unknown extracellular ligands. For both it was shown to be abundantly expressed only in taste tissue and testises (45). PKD2L1 is expressed in all taste areas, while PKD1L3 is expressed only in circumvallate and foliate papillae, but not in fungiform papillae. Both receptors are co-expressed in circumvallatae and foliate papillae, in the same subset of TRCs, distant from sweet, umami or bitter sensing cells, which suggests their involvement in salt or sour taste modality. When studying activation of PKD1L3- and PKD2L1-mediated currents, it was shown that they are delayed in comparison with the onset of sour stimulation (45) and concluded that PKD1L3/PKD2L1 channel has unique off-response property, meaning that the channel is gated open only after the removal of acid stimulus, although initial acid exposure is essential. This type of channel is activated during stimulus application, but not gated open until removal of the stimulus. This could be physiologically significant to enable sour taste sensation regulated by on- and off-response mechanisms. Off-response would be maintained by these described receptors and was also proven in CT nerves. And for on-response other receptors/channels may play their role (24).

Little is known about inter-individual and inter-population variation in sour taste perception and how such variation may be linked to genetic variation. European population was described as fairly narrow in tasting different types of acids (34). Existing twin studies have shown strong heritability component of sour taste sensitivity (46). In future PKD2L1/PKD1L3 could provide a startup for genetic studies for exploring inter-individual variation. Both receptors contain single nucleotide polymorphisms (SNPs) and it is possible that these polymorphisms may affect sour taste perception, but the potential relationship between polymorphisms in these genes, sour taste perception, and subsequent food choices remains to be explored (34).

Neuronal response to all taste modalities consists of rapid phasic burst of action potentials peaking in frequency and is followed by tonic response, which is a rapid decline to pseudo-steady state. Phasic and tonic components of sour taste neural response are well described. The proximate stimulus for sour taste is a decrease in the intracellular pH of a subset of acid-sensing TRCs for week and strong acids alike, which serves as the input to separate transduction pathways for the phasic and tonic parts of the sour neural response. This causes a shift in the cytoskeletal F-actin to G-actin, equilibrium in the G-actin direction, resulting in cell shrinkage, which was also observed from imaging studies of fungiform papillae. This activates acid-sensitive shrinkage-activated nonselective cation channel (SANSCC) in the basolateral membrane of TRCs that results in cell depolarization and leading to phasic neural response. SANSCC is involved in eliciting the phasic part of the CT nerve to acidic stimulation. In the subset of TRCs a decrease in pH induces an increase in intracellular Ca^{2+} concentration, which is necessary to sustain tonic phase response. Ca^{2+} ions activate basolateral Na^+-H^+ exchanger isoform 1 (NHE-1), which is responsible for pH and cell volume recovery and for the observed level of neural adaptation (tonic response) in CT nerve in response to acid stimuli (26). In support of this mechanism, complete elimination of the phasic response is achieved by disrupting the depolarization of F-actin to G-actin, which was performed in rat tongue with cytochalasin B and furthermore restored by treating rat tongue with phalloidin, which binds to F-actin and stabilizes the actin cytoskeleton (47). To prove that Ca^{2+}-activated NHE1 represents the molecular basis of TCR sour adaptation; it was published that by increasing taste cell intracellular Ca^{2+} *in vivo* by lingual application of ionomycin increases the level of neural adaptation and decreased tonic response level to an acidic stimulus (48). Adaptation to sour arises from the activation of the basolateral sodium-hydrogen exchanger isoform-1 by an increase in intracellular calcium that sustains the tonic phase of the sour taste response.

Bitter taste

Bitter taste is bearable when week and therefore helps us to recognize complex food, however when strong, becomes repulsive and has strong negative hedonic tone. Bitter taste is effective warning that we should not use potentially dangerous ingredients. Therefore one of the important and interesting challenges in bitter taste research is to understand how the receptors involved in recognition of bitter taste have formed during evolution to serve this mission. Many organic molecules, originating from plants are bitter, including caffeine, nicotine, strychnine, as well as industrial drugs (49). Around 10% of plants may contain toxic glycosides or alkaloids, which are in plants chemical defense systems against herbivores and pathogens. Also insects can synthesize cyanogenic glycosides for their defense (50).

Searching through databases has revealed that 7TM receptors, with short amino-terminal domain, comprised from at least 40 members, designated as T2R family lie on mouse chromosome 6, near the locus for bitter taste (51) and are expressed on the subset of specific TRCs on the front thirds of the tongue and palate epithelium. At least 24 of these receptors are involved in responding to bitter agents. First deorphanied was murine T2R5 (mT2R5) by responding to cyclohexamide in brief access taste aversion assay. It was shown that a single taste TRC expresses a large repertoire of T2Rs, suggesting it has ability to recognize multiple tastants, however single taste nerve fibers carries signals that discriminate between bitter compounds (52). It was also found out that mouse strains vary in sensitivity to specific bitter substances, such as cyclohexamide and sucrose octaacetate, and is connected to genetic variation on chromosome 6. Bitter taste seems to be the most complex taste quality in humans, based on the variety of chemical structures that elicit bitterness and on the large number of genes, encoding receptors for this taste modality. Bitter taste genes were designated as T2R or TAS2R genes. In humans there are 24 potentially functional T2R genes and several T2R pseudogenes, which differentiate between each other in 25-89% amino acid residues, and reside on three different locations (12p13, 7q31 and 5p15) (12).

Interesting for bitter taste modality is that responses of humans to some bitter compounds show a bimodal distribution that distinguishes two phenotypes, tasters and non-tasters and the compounds the most studied in this respect are phenylthiocarbamide (PTC) and similar 6-n-propyl-2-thiouracil (PROP), since some of the population taste it as bitter and some of the population is "taste blind" for PTC. Initial studies have shown that ability to detect PTC was inherited by classic recessive Mendelian mode of inheritance. Further genetic differences for T2R bitter receptors were provided by the variable ability in humans to intensively sense bitter taste of PROP and PTC. On this basis taste subjects have been identified as non-tasters, tasters or super-tasters according to the intensity of their responses to substances (53). The variation in taste sensitivity was mapped to chromosomes 5 and 7 and differs at 3 amino acid positions. Later on human candidate receptor for these substances were cloned, designated as T2R38 and was responding to both, PROP and PTC. Additionally, variation of human threshold sensitivity to test these substances was linked to mutations in the gene for receptor (12). In humans also T2R16 was identified by calcium signaling assay as the receptor that mediates bitter taste (54) and furthermore more receptors in different species were cloned. Later also 3 other forms of this gene were observed, mostly in sub-Saharan African populations (12). For these genes it was demonstrated that they show a broad range of variation, including a substantial number of SNPs and many of them are non-synonymous and change amino acid encoded in the protein, which is important for elucidating important sites for bitter transduction within these proteins (12, 55). The non-tester alleles reside on a small chromosomal region identical by descent, indicating that non-tasters are descended from an ancient founder individual and consistent with an origin of the non-taster allele preceding the emergence of modern humans out of Africa. The two major forms differ from each other at three amino acid positions and both alleles have been maintained at high frequency by balancing natural selection, suggesting that the non-taster allele serves some function on example serve as a receptor for another, yet unidentified toxic bitter substance (55). 75% of individuals worldwide perceive PTC intensely bitter, while to others it is relatively tasteless and this difference is stable over lifetime of a given individual (12).

Data obtained from *in situ* hybridization showed that one TRC expresses a huge repertoire of T2Rs, which shows that every TRC is capable of recognizing more taste modalities. Members of T2R family have been found co-expressed with $G\alpha_{gustucin}$. Mice

models with knock out gene for $G\alpha_{gustucin}$ have shown lower sensitivity for bitter substances and as well for sweet substances, such as saccharin and sucrose. Bitter compound binds to T2R $G\alpha_{gustucin}$ and amplifies the signal, which leads to activation of intracellular phosphodiesterase (PDE), which lowers the activity of cyclic adenosine monophosphate (cAMP), interrupts normal cation release through channels that act through cAMP leading to cell depolarization. These complex events lead to transient elevation of cyclic guanosine monophosphate (cGMP) (56). The second signal transduction cascade is generated through phospholipase C-inositol trisphosphate (PLC-IP_3) activation system. Bitter tastant stimulates 7TM receptor, which activates PLC that leads to IP_3 release, and Ca^{2+} ions release from intracellular storage and subsequently to depolarization and neurotransmitter release on the afferent nerve fiber. Also βγ subunit of the heterotrimer protein gustducin (G $\beta_3\gamma_{13}$) is able to activate PLC $C\beta_2$. It is interesting; however still unclear, that both pathways are activated simultaneously, whether this is needed for bitter taste recognition or it is just parallel amplification (57). It is known that human Gγ13 is participating in bitter taste signaling (55, 58).

Interesting is the finding that some bitter peptides with amphipatic properties do not need 7TM receptors, they interact directly with G-proteins, like quinine (59). General structural characteristics of hydrophobicity and hidrophility enable compounds to rapidly insert into cell membranes where they directly activate G-proteins or other signaling molecules independent of receptor occupancy. Quinine activates $G\alpha_{transducin}$ and $G\alpha_{i/o}$ proteins *in vitro*. The second example is caffeine and other metilksantins, which penetrate cell membrane and block intracellular PDE. In both, further signalization could be under the control of nitric oxide, since nitric oxide synthetase was found in TRCs (60).

Transgenic animals deficient of critical components of bitter receptor signaling pathways still avoid high concentrations of the bitter compounds denatonium benzoate and quinine (61). One of the animal experiment regarding bitter taste has shown that mice engineered to express bitter taste receptor for β-glucopyranosides in »sweet cells« become strongly attracted to bitter compound, showing that the taste of bitter or sweet compound (that is, the perception of sweet and bitter) is reflection of the selective activation of T1R-expressing vs. T2R expressing cells, rather than a property of the receptors or even tastant molecules (49).

Sweet taste

Sweet taste is strongly pleasant and it corresponds to soluble carbohydrates, which are present in sufficient concentrations in the oral cavity. However, a wide diversity of non-carbohydrate molecules is also sweet. Extensive research has been made to define characteristics of "sweet" molecule and its "sweet" receptor, to be able on the basis of existing binding models, predict new high-potency sweeteners. First 7TM receptor identified, involved as being a candidate for trehalose receptor was found in *Drosophila* (62). Further on it was found out that in mouse genome receptors for sweet taste are located on the chromosome 4, in two taste-related locations, the *Dpa* and *Sac* locus (63). Mutations in the Dpa locus resulted in a partial loss of taste acuity for the sweet amino acid D-phenylalanine, whereas mutations in the Sac locus caused partial loss of taste acuity for sucrose, saccharin and other sweeteners. The chemical structure of substances that taste sweet is almost as broad as the set of compounds that taste bitter, from natural (sugar, glycerol, amino acids, aspartame, thaumatin, monellin) to whole set of artificial sweeteners (Na saccharin, Na cyclamate, dulcin and Pb and Be salts).

Inter-individual differences in response to sweet compounds are not yet fully characterized and intersubject differences are relatively modest. The names for associated genes for sweet receptors are *Tas1r2* and *Tas1r3* in mice and in humans *TAS1R1* and *TAS1R2* and were delineated through gene-mapping experiments in mice and humans (12). Furthermore, it was expected that more genes for perception of sweet taste would be found near these locuses and strategy was shown to be successful. 7TM receptor with large terminal domain (T1R3) was found (64), similar to T1R1 and T2R, described previously (65).

T1R1 was found on the buds of anterior, lateral and posterior tongue and in the same TRCs that express T1R2, suggesting they might elicit response by forming heterodimers (66). Since *Tas1r3* gene is the only 7TM receptor coding gene at Sac locus, therefore its product T1R3 is a strong candidate for a sweet receptor, practically confirmed by observations in mice, that differ in taste-ability also differ in several point mutations in *Tas1r3*, displayed mainly as decline in function. Finally, when T1R3 was expressed in oocytes, it was shown that receptor does not respond to sweetners by its own, just after coexpression with T1R2, showing that receptors functionally work as heterodimers and as well shown as

first functional sweet receptor found in mammals as a heterodimer (67).

Interesting is the observation that receptor for sweet taste, functionally being heterodimer, is also often written as T1R2/T1R3. As Class C 7TM receptor member is unique in the case of N-terminal Venus flytrap-like domains (VFDs). Like in the metabotropic glutamate receptor also T1R2/T1R3 receptors are likely to bind sweeteners in the VFD on T1R2 (aspartame and artificial sweetner neotame), however cyclamate binds within the 7TM domain of T1R3. T1R2/T1R3 heterodimer is the first functional 7TM receptor unit demonstrated to have more than one agonist binding site (orthosteric sites) (68). This leads to further questions whether VFD on T1R2 is perhaps ortosteric site for sucrose and other carbohydrates. Kniazeff and al. (69) has demonstrated that both VFDs of the homodimeric metabotrophic glutamate receptor must be populated by glutamate to give a maximal response, however in the other representatives of family C 7TM receptors γ-aminobutyric acid type B ($GABA_BR$), GABA binds only to one receptor type. Therefore more options of dimer activation by ligands exists, one is that sucrose and other sweeteners bind to the VFDs of T1R2, they might also bind to VFDs of T1R3, second would be that VFDs are different and they can bind just to one or two carbohydrate sweetener molecules in each VFD and leading to high state of activation. Also it is not known whether there is synergy existing between different sweeteners on example aspartame and cyclamate and since they bind on separate orthosteric sites they could have cooperative binding effect. Given that there is also synergy existing between saccharin and cyclamate, it is possible that more orthosteric sites exist (68).

Sweet taste receptor needs many G-proteins. Especially important is $G\alpha_{gustucin}$, which is besides for sweet perception important also to percept bitter taste. $G\alpha_{gustucin}$ is active through adenyl cyclase (AC) and cAMP through K^+ ion channels at the basolateral side of membrane. T1R3 is expressed in 20% of the TRCs, some of which also express $G\alpha_{gustucin}$. Data from knock-out mice showed that co-expression of both is compatible, with a role in $G\alpha_{gustucin}$ in sweet taste (70). Signal transduction in sweet-responsive cells is complex and questionable. At least two pathways have been described, one mediated through cGMP or cAMP and the second through elevating the level of IP_3, as second messengers.

On the apical membrane of TRCs are receptors binding glucose, sucrose or other carbohydrates. Transduction mechanism runs through the blockage of K^+ channels. Binding of sugar on the receptor activates AC, which leads to elevated level of cAMP and furthermore with protein kinase A (PKA) activated phosphorylation of K^+ ion channels and inhibits them. After depolarization Ca^{2+} ions enter the cell with depolarization of activated Ca^{2+} channels, leading to transmitter release and further to transmission of the signal. It was thought that inhibition of K^+ conductance was occurring through PKA, but cyclic nucleotide-gated channel (CNGgust) was found in TRCs, important for membrane depolarization and Ca^{2+} inflow, when cAMP increases.

It was shown that sugars activate cyclic nucleotide cascade, leading to an increase of cAMP, membrane depolarization and Ca^{2+} uptake, whereas non-sugar sweeteners activate IP_3 cascade in the same cell (71). Membrane depolarization by inhibition of K^+ conductance may be a common feature for both pathways. An increase in the cytosolic Ca^{2+} concentration occurs in both pathways; even the source of Ca^{2+} ions is different. It looks like there is variability in utilizing different pathways across the posterior and anterior part of the tongue and across sweeteners in animal species.

The second pathway through IP_3 causes intracellular release of Ca^{2+} ions. Released Ca^{2+} ions enable neurotransmitter release. This group includes artificial sweeteners, such as saccharin, which is sweet only to human, but not to bees and butterflies, cyclamate and aspartame, which is a combination of two natural amino acids – asparate and phenylalanine and it is 2000-fold sweeter than sugar. In this group we can also include sucralosa, which is a chloride, including carbohydrates and it is 600-fold sweeter than sugar. Also lead and berilium salts are sweet. It was shown in hamster that PKA inhibitors do not inhibit sugars-sweet response in the posterior part of the tongue; on the contrary they accelerate it, which shows that PKA is not directly involved in the response to sugars, but may be involved in the adaptation. On the contrary inhibition of PKC did not affect responses to sucrose, but inhibited responses to artificial sweeteners, which showed that transduction of two kinds of sweeteners differs. Inhibition of the cAMP enhanced the responses to sucrose but not to synthetic sweetners, indicating that Ca^{2+} ions release during stimulation with synthetic sweeteners may depress a simultaneous response to sucrose by activation of this enzyme (72, 73).

Sweet taste is modified by circulating hormones. Leptin, a protein hormone (reviewed in 74) has gath-

ered much interest on sweet-responding cells. Leptin is secreted mainly by adipocytes and regulates body mass. A full length leptin receptor is expressed in various tissues and among others also in TRCs and it suppresses insulin secretion by activation of ATP sensitive K^+ channels. Its inhibitory effect on TRCs also involves the activation of a K^+ conductance and membrane hyperpolarization (75). Thereby the hormone partially blunts nerve signals indicating sweet taste, which presumably makes food less attractive. During the starvation the production of leptin is decreased and the resulting disinhibition in the target tissues diminishes energy expenditure and leads to motivational state of hunger. At the same time, disinhibition of sweet-responsive TRCs enhances sensitivity to sweet taste and makes food more attractive and therefore supporting its role in whole organism (63).

Umami taste

Umami – the "meaty" taste of glutamate and some other L-amino acids is dominant flavor of the food, which contains L-glutamate, an amino acid that is abundantly found in food and often occurs as monosodium glutamate (MSG), consisted from two tasting stimuli: Na^{2+} ions and glutamate. L-glutamate guides the intake of peptides and proteins, from which it is released by proteolysis (curing and decay). Animals are attracted to this taste. The characterizing taste is enhanced by purine nucleotides 5'-ribonucleotides such as inosine 5'-monophosphate (IMP) and guanosine-5'-monophosphate (GMP), which are also present in decaying tissues, that is why some people misconcepted that glutamate contained food might be harmful (77, 78). L-glutamate is a cleavage product of all proteins. The synergism between MSG and the nucleotides was explained by an allosteric effect (79).

Type of food with characteristic umami taste is typically chicken broth, meat (beef, pork and chicken), seafood (fish, oyster, crab, sea urchin, various sea-weeds and others) and aging cheese, however it is also find abundantly in a wide array of vegetables, such as tomatoes, potatoes, mushrooms, carrots, cabbage, soybean and green-tea (80). MSG is added to different sorts of food as a taste enhancer and is the main ingredient of soy sauce and Japanese soup base. It is interesting that taste of boiled crab meet can be reproduced by mixing amino acids: glycine, alanine, arginine, MSG, monophosphate disodium salt (IMP) and salts in particular ratio. When umami constituents are eliminated, the characteristic taste of crab disappears, suggesting that umami substances are essential for producing the unique taste of many foods (81). When umami substances are added to food they enhance food palatability (76). Other amino acid that trigger umami taste is L-aspartate (82), showing umami substances are originally acids, therefore at neutral pH they exist in the salt form. Usually they are sodium salts, i.e. glutamate, disodium inosinate and disodium guanylate. Thus the umami substances contain the sodium ion (80).

Umami taste was the first time identified by Prof. Kikune Ikeda in Tokio more than 100 years ago in 1909 (83), however it was translated in English in 2002 by Ikeda (84). Umami, a term describing meaty, savory flavor, derives from the Japanese *umai* (delicious, good taste) and designates pleasant taste sensation, which is qualitatively different from sweet, salty, sour and bitter taste (84). It was hard to accept this new taste modality, since this taste is mild even in high concentrations of tastants and especially because the umami taste from anionic L-glutamate, was difficult to dissociate from the cationic sodium, which forms salty taste and is also found in MSG (12). However, the umami substances L-glutamate, IMP and GMP are still an object of interest and their taste responses are investigated in humans and animals. Therefore unique taste of umami argues for a specific receptor at taste level. The taste synergism between MSG and certain 5'-ribonucleotides provides a pharmacological mechanism showing that several receptors are involved in umami taste recognition.

It was also discussed whether MSG and umami are the same. It was concluded that since umami was described as delicious, nice and palatable and MSG by itself does not in any sense represent deliciousness, on contrary being rather unpleasant, bitter and soapy, MSG and umami can not be unified. However, when MSG is added in low concentrations to different foods, the flavor, pleasantness and acceptability of food increases, which is a perfect example of distinction between the taste of single testant and the effects upon flavor of tastants in food (85). Two hypotheses seek to explain umami taste transduction through 2 categories of receptors: stimulus-gated ion channels (*N*-methyl-D-aspartate (NMDA)-type glutamate ion channel) and 7TM receptors (truncated and brain forms of metabotropic-type glutamate receptor: mGluR4, mGluR1 and brain forms of mGluR4 and mGluR3, as well as

other 7TM receptors: T1R1 and T1R3 (86). Na^+ ions use separate way of eliciting their response. Umami taste is very different perceptually from sweet taste; however they are closely related phylogenetically. The names for associated genes for umami receptors are *Tas1r1* and *Tas1r3* in mice and in humans *TAS1R1* and *TAS1R3* (12).

In rat fungiform papillae through EnaC Na^+ ions cross, however MSG crosses through metabotropic and ionotropic receptors. ENaC are not directly involved in glutamate signal transduction, however co-localization with glutamate receptors enables substrate to integrate through this pathway. Initial results in support of the glutamate-stimulated ion channels have shown they could be reconstituted into lipid bilayer and that the addition of mM concentrations of L-glutamate led to an increase in conductance of bilayer (86). Further studies monitored intracellular Ca^{2+} and membrane voltage in isolated TRCs from mouse vallate and foliate papillae. Cells responded to L-glutamate with either increase or decrease in the intracellular calcium and membrane depolarization accompanied to increase in the intracellular Ca^{2+} (86). These results show more receptors that activate different pathways exist. There are 2 types of glutamate receptors – stimulus gated-ion channels, which are stimulatory and metabotropic channels. Ionotropic glutamate receptors, connected to ion channels, induce signal transduction by altering ion flux through an ion channel directly coupled to and gated by glutamate binding site. These receptors can be delineated by differential sensitivity to glutamate analogs such as a-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA), kainic acid and *N*-methyl-D-aspartate (NMDA) (86, 87). NMDA receptors are integral receptor non-selective cation channel complexes. When stimulus binds to receptor site on the channel complex and therefore directly gates an ion channel, allows influx of cations - Na^+ and Ca^{2+} ions in the TRC, which leads to the depolarization of TRC. This depolarization induces further modulation of voltage-sensitive channels, leading to cellular depolarization, in the basolateral region of the TRC, sustaining and increasing depolarization sufficient to induce neurotransmitter release.

7TM receptors in which glutamate binding induces changes in intracellular messengers and then alter the balance of intracellular ions were shown to play an important role in umami signal transduction. At least two types of 7TM receptors have been recognized till now. Studies have shown that a subset of TRCs contains metabotropic glutamate receptor (mGLuR4), which differs from brain version in truncated N-terminal domain (NTD), suggesting an important adaptation to high glutamate concentrations occurring in the food (88). The metabotropic receptors are classified in several groups, i.e. I. (mGluR1, mGluR5), II. (mGluR2, mGluR3) and III. (mGluR4, mGluR6, mGluR7 and mGluR8) (89). Umami involved should be mGluR4, mGluR1, brain mGluR4 and mGluR3. Chaudari (90) has reported in 1996 that mGluR4 is expressed in rat papillae-bearing taste buds and suggested that mGluR4 might be a chemosensory receptor responsible for umami taste (Chaudahari, 1996). Binding of MSG on these 7TM receptor activates $G\alpha_{i/o}$ protein, which decreases cAMP by inhibiting the action of AC. Lower levels of cAMP result in a lower activity of PKA, decrease in Ca^{2+} ions and inhibition of voltage sensitive ion channels on the basolateral membrane, bringing about no charge or hyperpolarization of the cell (86). CHO cells transfected with taste-mGLuR4 were responsive to L-2-amino-4-phosphonobutyrate (L-AP4), ligand that elicts umami taste responses in humans and MSG in concentrations similar to the ones that elict umami response *in vivo*. However, it was still apparent that taste mGLuR4 are not the only receptors important for umami taste. One of the important evidence was that taste m-GluR4 receptors lacks a portion of the domain, necessary for glutamate recognition and that mGluR4 knock out mice still respond to umami stimuli (9). It is also possible that ion channel receptors or other 7TM receptors would act in concert, with the mGluR4 providing inhibitory signal in some cells to enhance the contrast with excitable cells. The interesting option is to consider analogy with visual system, where activated cell inhibits surrounding cells, to enhance visual acuity. By this possibility mGluR4 inhibitory response may signal on example through Merkel-like cell, which are also present in taste buds of animals, which would as in visual system transform the initially inhibitory signal into an excitatory one (92). The mGluR4 receptor was originally found in the brain, where it responds to extracellular glutamate by downregulating cAMP. This receptor is expressed on presynaptic terminals of both glutaminergic and GABAnergic neurons, where it mediates glutamate-dependent regulation of neurotransmitter release. In addition mGluR4 is expressed in TRCs, making it a candidate for umami receptor. Glutamate activates mGluR4 at μM concentrations far below the threshold; however alternative transcript mGluR4 variant, with truncated N-terminus can transduce

a response to glutamate. It is actually surprising, since it is known that in family C 7TM receptors are forming N-terminal VFDs (69), where glutamate binds. Alternatively the answer could lie in the receptor additional binding site. This triggered issues whether mGluR4 was really the right receptor. However, evidence has shown by confirming activation of receptor by agoinst L-AP4 and *in situ* hybridization of mGluR4 in the TRCs, that 40% of receptor is expressed in TRCs. Another question which appears is how decrease of cAMP can modulate membrane potential and cause TRC to signal. By electrophysiological experiments it was found out that 60% of TRCs respond to glutamate with sustained hyperpolarization and just 4% of cells respond with transient depolarization, which looks like sustained hyperpolarizing response is what leads to taste signaling. By this model glutamate triggers decrease in cAMP, resulting in the closure of cyclic nucleotide-gated channels and hyperpolarization of TRCs. Since it was shown that MSG induces a large response in the taste nerve, it was postulated that a receptor for umami taste should be an excitatory receptor and therefore speculating mGluR4 can not be a receptor for umami taste or at least the main receptor for umami taste, although L-AP4 has an umami taste (80).

More recently other receptors, members of 7TM receptors were discovered and molecular methods have shown that umami processing seems to be closely related to sweet taste processing at the molecular level. 7TM receptors, T1R1 and T1R3, cloned both from humans and rats appear to form a heteromeric umami taste receptor. Co-expression of T1R1 and T1R3 responded exclusively to umami L-amino acids, such as L-glutamate in rodents and specifically to L-glutamate in humans. Human and rodent receptors show strong synergy when co-treated with IMP or GMP (93). In mice this heteromers responds to many amino acids contained in the food, but in humans its response is preferentially to L-glutamate and is enhanced by IMP (94, 95), which perhaps reflects differences between two species in their natural diets. Expressed singly, the T1Rs express weakly, if at all to tastant *in vitro* (94). T1R1/T1R3 heterodimer is coupled to a G-protein, consisted from Gα subunit, that modulates cAMP levels and Gβγ subunit that stimulates PLC. Through Gβγ transduced part of the pathway appears to be necessary for umami transduction and therefore considered as dominant pathway (96). Upon receptor binding Gβγ stimulates $PLC\beta_2$, causing production of second messengers IP_3 and DAG. IP_3 causes release of Ca^{2+} from intracellular stores and Ca^{2+}-dependent activation of monovalent cation channel, TRPM5. This leads to membrane depolarization, action potential generation and release of transmitter, believed to be ATP (97). Evidence for this hypothesis comes from molecular and immunocytochemical studies, showing that relevant effectors are co-expressed with T1R1/T1R3 (93). It is interesting that Gα subunit that couples to T1R1/T1R3 heterodimer differs with respect to taste fields. In fungiform and palatal taste buds receptors are co-expressed with $G\alpha_{gustducin}$ and/or $G\alpha_{transducin}$, however in vallate and foliate taste buds Gα associated with T1R1/T1R3 has not been identified, but decrease in cAMP suggests the involvement of $G\alpha_i$. (93). It was also reported that umami taste responses are mediated through $G\alpha_{transducin}$ and $G\alpha_{gustducin}$ in anteriorly placed taste buds, however TRCs at the back of the tongue respond to umami compounds independently of these two G-protein subunits (98, 99).

Results based on reports from cDNA library derived from rat vallatae papillae, *in situ* hybridization studies have pointed on mGLuR4 family of receptors. Use of agoinst of mGLuR4 receptor L-AP4 in patch recording studies displayed a transient inward current, induced by glutamate (100). Biochemical studies to characterize receptor for glutamate were performed on membrane preparations from bovine circumvallatae papillae, where L-gutamate binding was observed and as well enhanced by 5'-ribonucleotides. First *in vivo* data were performed on Scl:ICR strain of mouse, which was able to discriminate MSG from other basic tastes. Information was based on information from glossopharyngeal nerve, since fibers of the nerve were uniquely sensitive to MSN (100). The physiological roles of these receptor heterodimers was established in studies with transgenic mice. *Tas1R1* and *Tas1R3* knock out mice were generated and the sensitivity to either umami or sweet taste was compared to results obtained in cell-based assays. Mice were characterized through behavioral tests and by measuring activity of the gustatory CT nerve after exposure to different taste stimuli (101). As expected, results have shown that *Tas1R1* and *Tas1R3* knock out mice showed a complete loss of preference for umami, since they have exhibited no CT nerve activity after stimulation with glutamate and clearly showed that umami taste is preceded by heteromeric T1R1/T1R3 receptor (94, 95). Another study on dogs showed that not every dog responded to 5'-oligonuclotides and that sensi-

tivity to MSN varied. In dogs, CT nerve is sensitive to MSG and 5'-oligonuclotides, such as guanosine-5'-monophosphate (GMP), since AMP was effective only in beagles (102). The same nerve is also sensitive in chimpanzees, however further representations for umami stimuli were localized in orbitofrontal cortex. Nevertheless, species, strain and individual differences were observed, however the basic postulates remained the same. Furthermore, both, kinetics of the binding data and *in vivo* data suggested that GMP increased number of binding sites for L-glutamate or increase in affinity for L-glutamate as a result of nucleotide interaction with a closely associated site proposed was observed and therefore an allosteric-type model for MSG/5'ribonucleotode binding interaction was proposed (79).

Human variability of umami taste is still poorly understood. In European adults responses to L-glutamate have been tested and only 27% subjects were unable to distinguish MSG vs. NaCl and were therefore unable to distinguish salty umami taste component from the salty component of MSG, which suggests reduced ability to taste umami (103). Regarding genetic basis underlying these mechanism, sequence of *Tas1R* gene was compared between different populations (e.g. Asian, African, Auropean and others) and several SNPs were identified within extracellular domain of *TAS1R1* and *TAS1R3* and their frequencies varied between populations suggesting interindividual variability (104). Regarding taste enhancement with IMP it was found out by psychophysical method that taste enhancement occurred when IMP was added to several sweet amino acids, such as L-alanine, L-serine and glycine. The enhanced quality of taste was recognized as umami and was not blocked by the sweetness inhibitor. The connection appears to exist through T1R3 subunit, which is shared with sweet taste receptor (75).

Is there a fatty acid taste?

Fatty foods are very palatable and most people prefer high-fat food, such as ice cream, hamburgers, steaks and mayonnaise to low-fat food, although that dietary fat is tasteless. It is interesting that although people can not feel the taste or smell of dietary oil and fats clearly, fat is interestingly tasty. Neuropeptides and neurotransmitters, related to hedonic or aversive response in the brain are released after basic tastants, described under five basic tastes and accepted by taste receptors in the TRCs. Paradoxically, dietary oils and fats do not stimulate the taste in the classic sense of tasting, however recently some resemblance to other taste modalities has been described (19).

Obesity is recognized as a worldwide health problem and overconsumption of fatty foods significantly contributes to this phenomenon. Therefore gaining knowledge about molecular mechanisms of fat preference and overeating might help to lower the risk of obesity. The disturbing data is also that chronic high-fat diets promote greater daily intake by eliciting larger and more frequent meals and increase the risk of obesity. When lipids indigested, they trigger set of regulatory events that limit food intake. Lipid-mediated regulation of food intake results from integration of multiple short-acting early (oral) satiety signals and long-acting, delayed (postabsortive) homeostatic signals. Early events are consisted from olfactory, textural and gustatory cues. Olfactory information is mediated through olfactory nerve, texture of foods through trigeminal nerve and gustatory information via the facial (branch CT nerve), glossopharyngeal and vagus nerve. A key early regulator is cholecystokinin (CKK), which is released by proximal intestine in response to dietary lipid loads and is sending meal-reducing signals through vagal afferent pathway, which express receptors for CCK, designated as CCK1R. A short-term satiety agent include glucagon-like protein 1 (GLP1) and peptide YY (PYY), released by ileal enteroendocrine cells in response to fat (105). Delayed events are associated with postindigestive and postabsortive signals. Postindigetsive/absorptive information via nerves converge on the NTS in the brain steam that connects to central regulatory areas like nucleus accumbens (Nac) and hypothalamus (HT), both of which are constitutes of metabolic and pleasure pathways. The NTS also projects efferent nerves toward indigestive tract, which accounts for the cephalic phase of indigestion, triggered by oral lipid stimulation facilitating fat digestion and absorption. HT activity is modulated by plasma factors (hormones, regulatory peptides, lipids). Satiation, which largely determines the size of meals, mainly depends on postidigestive signals. Postprandial satiety is largely responsible for meal frequency and essentially related to post-absorptive signals. Alipoprotein A-IV (ApoA-IV) promotes satiety and it was shown in rats that peripheral or cerebroventricular injections decrease food intake in dose-dependent manner and it becomes less efficient when subjected to chronic high-fat diets. Long-term satiety agents include leptin, which is produced by adipose tissue (74). It was shown that

high levels of leptin during obesity might contribute to reduce satiety sensitivity observed during chronic exposure to fatty foods. Such reduced satiety might help to explain the overfeeding frequently found in obese animals and humans. Although there are several factors in blood preventing high foods intake, it was shown that free fatty acids (FFA) can modulate feeding behaviors through direct actions on the brain through acting on the ion channels or binding to specific receptors in fatty acid (FA)-sensitive hypothalamic neurons (106). »Fat taste« perception was supposed to be evolved from evolutionary perspective to detect high energy foods and to select foods containing fat soluble vitamins and essential FAs (107). Important function of fat detection in cephalic phase would be to aid digestive system for lipid metabolism. It was seen that both rats and mice select high fat diet over a low-fat diet. Since preference on low or high-fat diet is based on animal instinct, using laboratory animals to get new insight is relevant (19). Rodents, like humans display preference for lipid-rich foods and therefore provide useful models to explore the mechanisms of fat preference and also overeating. The mechanisms guiding fat detection have traditionally been attributed to texture and olfaction, however also oral detection is very important. First "fat taste" receptor evidence have come from evidence that FAs, specifically unsaturated long-chain fatty acids (LCFAs) were prolonging cell depolarization by influencing K^+ channels on TRCs (108). Candidate for "fat taste" receptor is proposed to be an oral lipid sensor CD36 (107).

CD36 is a receptor-like protein that binds saturated and unsaturated LCFA with affinities in nM range and has structural and functional features required for putative taste-based lipid receptor. It belongs to family of class-B scavenger receptors. It increases uptake of LCFA by cardiomyocytes and adipocytes and uptake of oxidized-low-density lipoproteins (LDL) by macrofages, it modifies platelet aggregation by binding to thrombospondin and collagen, facilitates phagocytosis of apoptotic cells by macrophages and plays role of taste reception of dietary lipids on the tongue (106). CD36 is an integral membrane protein creating large extracellular hydrophobic loop (likely the site interacting with FAs) and two short cytoplasmic tails, that has a high affinity for LCFA and having a role in facilitating FFA transport across the cell membrane (109). It was also isolated on the apical surface of TRC on the tongue, stomach, intestine and on the surface of macrophages, adipocytes, muscle cells, endothelial cells and platelets. Interesting is also data that CD36 specific inhibitor, sulfo-N-succinimidyl oleic acid ester attenuates its response (108). As well CD36 knock out mice have been generated for which it was shown they lose the ability to distinguish between FFA containing diet over control (107). These mice were able to distinguish a FA solution over gum vesicle, indicating that CD36 is required to distinguish these texturally comparable choices (111). However, role of CD36 in humans is not yet known. Many sequence variations have been identified in human CD36 gene, located on the chromosome 7q11.2 (112), which would be important from genetic point of view, showing that genetic variation in CD36 affects our ability to sense or taste FFA and therefore showing variation in preferences for fatty foods. Thus, examining the relationship between inherited variations of CD36 with fat consumption and oral chemosensory response to fat may help identify individuals predisposed to prefer foods higher in dietary fat. Working model for gustatory perception of LCFA in mouse would be: LCFA released from triglycerides (TG) by lingual lipase bind to CD36, which acts as gustatory lipid receptor in TRCs, which triggers increase in intracellular free Ca^{2+}, which causes release of neurotransmitters by TRC. Animal experiments on rats, including three long chain fatty acids (oleic, linoleic, α-linolenic) suggested that stimulation by fatty acids (FAs) in the oral cavity may provide the chemical information underlying selective behavior toward FFA (19). Electrophysiological recordings on FA chemical information was performed on twins. Dripping FAs on the tongue failed to trigger any electrical response from the CT nerve leading from the fungiform papillae distributed on the lower anterior portion of the tongue (113). However, it was reported in rats, that FFA trigger chemical sensitivity in oral cavity and that glossopharyngeal nerve transmit information to the brain (114). It was also shown that chemical reception of fat centers is triggered by FFA and not by the triglycerides, which actually constitute the bulk of fats. One explanation would be that Ebner's gland, lying in the vicinity of the circumvallatae papillae, where gustatory cells including FAT and CD36 are located, are immersed by lingual lipase in their secret that would split triglicerides to FFA before they would reach these points (12).

Besides CD36 receptor also fatty acid transporter (FAT) was found on the apical part of TRCs in the circumvallatae papillae (12). In CD36/FAT null mice it was shown that they do not recognize FFA (113), which suggested that CD36/FAT acts as a sensor

for LCFAs, which are a major form of fat involved in preferable taste. Recently it was proposed that FFAs in dietary fat may be perceived chemically in TRCs as a basic tastant, accepted into CD36/FAT receptor in the circumvallatae papillae on the tongue, which would serve to recognize LCFAs on the tongue and neuropeptidies, such as β-endorphin or dopamine are released in the brain (12). β-endorphin was shown to be released 15 min after fat intake (111) and dopamine in the Nac was released during sham licking of 100% corn oil (12), which clearly and altogether with described studies show that signals of dietary fat are accepted in the oral cavity and transmitted to the brain, and neuropeptides and neurotransmitters, such as β-endorphin and dopamine were released just after fat intake.

Interestingly chronic fat diet is associated with reduced vagal sensitivity in rodents. This desensitization could be due to dynamic regulation of CCK1R in vagal afferent neurons, since the number of receptors decrease rapidly in the response to fat indigestion. Also expression levels of receptors for GLP1 and leptin by vagal neurons seems to be downregulated by lipids as found for CCK1R (110, 115). This dynamic regulation might account for some of the reduced ability for lipids to satiate in comparison to carbohydrates and proteins.

Interestingly also dopaminergic system plays an important role in lipid preference. Pharmacological inhibition of D1R and D2R in rats has shown food increases reference for fatty foods in dose-response manner, which is important because it was shown that feeding with such food increases dopamine levels in Nac, which is a key component of pleasure and reward circuits and this is decreased by antagonists (116).

Conclusion or making sense of taste

Over the years knowledge about taste perception has raised rapidly. Many candidate receptors are already known to be mediating different taste modalities, however exact pathways and their cooperativity in different pathways still remains unknown. By expanding knowledge about receptors and signal transduction mechanism they are eliciting many options are open to use the knowledge in applicative way. One of the options is to precisely control perception of taste by maneuver the peripheral sensory apparatus and its function directly with small molecules, similarly as have been done in an imprecise way by adjusting the flavors of foods. Basically each flavoring ingredient can be regarded as an agonist or perhaps allosteric modulator. By precisely controlling taste sensation on the level of the sensory receptors in the tongue, we might be able to modulate, turn on off or fine tune taste sensations. Blockers of aversive tastes would be appreciated to help improve patient compliance with unpalatable orally administered therapeutics by influencing 7TM receptors or ion channels as targets. Secondly, important is also interface between taste and indigestion, especially in the case of sweet taste, in connection to obesity and diabetes. By defining why some people are more sensitive to fat taste than the others and modulating the perception high, daily intake of fat could be prevented. On the other hand appetite could be increased in the anorexia as a consequence of manifestation of disease. For example not only in human medicine also in veterinary medicine lack of pet's appetite is evidence that pet is suffering. Especially cats are subjected to anorexia. Mechanisms underlying decreased food intake are complex and not completely understood and one segment is regulation of appetite and mechanisms underlying it. By knowing more about taste mechanisms, "mouth feel", extremely significant factor influencing dietary preference in cats could be influenced and preparing more appealing, masked food.

An important aspect of taste research in future should also be performed in the area of taste receptor genes. The important question to be addressed include finding genes that encode a complete repertoire of taste receptors for different taste qualities, as well as genes that encode proteins involved in taste transduction and transmission, taste bud cell turnover and connectivity between TRCs and afferent nerves. Studies of allelic variation of taste receptors would be helpful to elucidate individual differences in taste perception, food choice, nutrition, and health and to understand functional organization of receptor domains and their ligand specificities.

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ZAZNAVANJE OKUSA: ANATOMSKI IN MOLEKULARNI MEHANIZMI

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Povzetek: Zaznavanje okusa igra ključno vlogo pri izbiri hrane in posledično vpliva na način prehranjevanja. Dojemanje okusa nam pomaga izbirati informacije o različnih kemikalijah v okolju. Do sedaj je opisanih pet osnovnih vrst okusa: sladek, kisel, slan, grenek in umami. V zadnjem času se pojavlja vedno več raziskav in člankov o zaznavanju maščobnih kislin v hrani, t.i. maščobnokislinskem okusu, ki morda postaja šesti osnovni okus, obstoj novih kategorij okusa se še vedno raziskuje. Vsak od osnovnih okusov ima različne funkcije. Umami in sladek okus sta kalorična detektorja, ki nam potešita hedonske čute, sposobnost zaznavanja slanega okusa je pomembna za uravnavanje količine natrija v organizmu in tako še posebej pomembna pri rastlinojedih živalih, kisel okus nam pomaga zaznati nezrelo in pokvarjeno hrano, grenak okus pa prispeva k zaznavi toksinov v hrani. Tako bi lahko bili izsledki raziskav na področju zaznave maščobnih kislin čisto logični: če lahko zaznavamo sladko (ogljikove hidrate) in umami (proteine), je smiselno pričakovati, da imamo tudi sposobnost okušanja maščob. Pri vsakem načinu zaznavanja okusa gre za prenos znotrajceličnega signala preko različnih tipov receptorjev, ki so na različnih okušalnih celicah različnih okušalnih brbončic. Obstajajo na različnih regijah jezika in njegove okolice in z draženjem živčnih vlaken sodelujejo pri zaznavi okusa. Različni kanalčki in receptorji, ki vključujejo tudi receptorje s sedmimi transmembranskimi območji (receptorji 7TM) so posamič ali v sodelovanju (npr. kot heterodimeri) vključeni v zaznavo okusa s sprožanjem različnih poti znotrajceličnega signaliziranja istočasno ali pa vsaka s svojim namenom. V preglednem članku so opisani do sedaj poznani okusi, od anatomskih osnov do molekularnih mehanizmov.

Ključne besede: okus; sladko; kislo; grenko; slano; umami; zaznavanje maščob v prehrani; anatomija; receptorji 7TM; kanalčki; prenos signala