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Review

Sweet Taste: From Reception to Perception

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Sweet taste is the most powerful taste modality shaping feeding behavior and influencing homeostasis. This review summarizes data on the reception and encoding of taste signals at the level of taste buds and cerebral centers during the consumption of sweet substances. The main focus of attention is on the molecular and cellular mechanisms underlying identification of sweet taste and detection of the caloric composition of food, including the role of T1R2/T1R3 membrane protein receptors and the associated intracellular enzyme cascade, along with the metabolic mechanism assessing the concentration of glucose entering the cytoplasm. The genetic aspects of sensitivity to sweetness and the influence of sweet taste receptor gene polymorphism on sensitivity to sugars and low-calorie sweeteners are described. We present results from current studies of the endocrine, paracrine, and autocrine modulation of the reception and perception of sweet taste depending on the metabolic status of the body. A suggestion is made regarding a promising direction of research in this area.

Keywords: sweet taste buds, T1R2 and T1R3 proteins, brain, neuropeptides, homeostasis.

Abbreviations: AB – body of the amygdala; GPv – ventral nucleus of the globus pallidus; VTN – ventral tegmental nucleus; GE – glucose-excitable neurons; GI – glucose-inhibitory neurons; DA – dopamine, dopamine system; IC – insular cortex; LH – lateral hypothalamus; PPN – parabrachial pontine nucleus; VPTN – ventral posteromedial thalamic nucleus; PFC – prefrontal cortex; NA – nucleus accumbens; STN – solitary tract nucleus; CCK – cholecystokinin; Cdh4, Cdh13 – cadherin 4 and 13; DPP-IV – dipeptidase IV; GABA – γ-aminobutyric acid; GalR2 – galanin receptor; GG – geniculate ganglion; GLP-1 – glucagon-like peptide 1; GLP-1R – receptors for GLP-1; GLU – glutamic acid; GLUT2, GLUT4, etc. – glucose transport protein isoforms 2, 4, etc.; NG – nodular ganglion; PG – petrosal ganglion; Gα – α-gastducin; K_{ATP} – ATP-sensitive potassium channel; L-Asp – aspartic acid; L-Glu – glutamic acid; mGLUR – metabotropic glutamate receptor; NPY – neuropeptide Y; OP – opioids; PC1/3 – protein convertase; Perk – proenkephalin gene; PLCβ – phospholipase Cβ; POMC – proopiomelanocortin; SGLT1 – sodium-glucose cotransporter 1; SNP – single nucleotide substitution; spon1 – spondin-1; T1R1, T1R2, T1R3 – type 1 taste receptors subtypes 1–3; T2R – type 2 taste receptor; *Tas1r1*, *Tas1r2*, *Tas1r3* – genes for type 1 taste receptors subtypes 1–3; *Tas2r* – gene for type 2 taste receptor; VIP – vasoactive intestinal polypeptide; VPAC1 and VPAC2 – VIP receptors; Y1, 2, 4, 5 – NPY receptors.

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Introduction. Carbohydrates are the main easily metabolized source of energy and are also a source of glucose, a metabolite which is required for brain function, such that sweet taste has clearly acquired a maximum level of hedonic appeal [41, 171]. Emotions accompanying the consumption of sweet substances reflect complex processes mediated by taste receptors in the periphery and numerous brain structures, which have been very thoroughly mapped out phylogenetically in vertebrates [19].

Significant variation in sweet taste perception and preference has now been identified, both within and between species. Although learning and homeostatic mechanisms [133, 184, 199] contribute to responses to sweet taste, most of the variation is heritable in nature. Recent studies have shown that polymorphism of the *Tas1r* genes, which encode the subunits of dimeric sweet taste receptors, underlies many within-species and between-species differences in the perception of sweetness [2, 4, 5, 203]. Work using inbred strains of mice has found that some of the variation in preferences for sugars and non-nutritive sweeteners also depends on genes which are not directly involved in peripheral processing of taste signals but probably influence the central mechanisms of analysis, reward, and/or motivation [4].

The central nervous system plays a fundamental role in sensory perception, though increasing evidence indicates

that taste information undergoes significant transformation in the periphery, i.e., in taste buds. Mammalian taste sensory cells express a number of peptide receptors and, frequently, their ligands. Peptides produced in taste buds or in remote tissues influence peripheral taste sensitivity via autocrine, paracrine, and even endocrine signaling, modulating taste functions depending on the condition of the animal [46, 68, 168, 178, 195].

Thus, the taste perception of sweetness is not an exact reflection of the qualitative and quantitative characteristics of a stimulus received from the environment, but is formed as a result of several levels of information processing, starting from taste cells and continuing in parts of the peripheral and central nervous system and, in the context of other sensory information, as well as the animal's experience, motivation, and physiological condition, may be important [42].

Recent decades have seen particular importance attached to the pathophysiological aspects of research into the molecular, cellular, and neurophysiological mechanisms of sensation and the perception of sweet taste. The widespread availability of refined sugars has had the result that in modern humans, the taste sensory system, which is responsible for the identification and perception of sweet substances, is used primarily as a reward system, i.e., it stimulates the consumption of sugars and non-nutritive sweeteners. With unlimited access to simple sugars, the innate preference for sweet taste becomes an important factor in overeating, obesity, and known comorbidities [22].

This review summarizes information on the reception and encoding of taste signals accompanying the consumption of sweet substances at the level of taste buds, conducting pathways, and brain centers. The main focus of attention is on the molecular and cellular mechanisms underlying the identification of sweet substances and the detection of the caloric composition of food, including the role of T1R2/T1R3 membrane protein receptors for the sweet taste, as well as the metabolic mechanism by which the concentration of glucose entering the cytoplasm is evaluated. The genetic aspects of sensitivity to sweet substances and the influence of sweet taste receptor gene polymorphism on sensitivity to sugars and low-calorie sweeteners are highlighted. The review presents the currently known pathways of the endocrine, paracrine, and autocrine modulation of the reception and perception of sweet taste. A suggestion is made regarding further directions of research in this area.

Molecular and Cellular Mechanisms of the Recognition of Sweet Taste. Vertebrates in general are able to distinguish five basic taste modalities: sweet, salty, umami (amino acid taste), bitter, and sour [5, 29, 68, 186]. The presence of specialized receptors for calcium, fats, and starch has also been discussed [102, 182, 192].

The existence of molecular receptors responding directly to the presence of sweet-tasting substances has long been supposed. The actual response to low- or no-calorie sweeteners suggests that receptor function exists independently of metabolism. Protein complexes with sugars were isolated in the 1960s, though the receptors were finally cloned only in the 21st century [5, 7, 113, 131]. The main role in taste sensitivity to sugars and, to a certain extent, amino acids in all vertebrates is played by the T1R family of G-protein-coupled membrane receptors which are encoded by *Tas* (from taste) genes. At least five receptor proteins of this family have now been identified, three of these being found in higher vertebrates: TR1–3 (the *Tas1r1–3* genes). Another related family of membrane taste receptors, T2R (*Tas2r* genes), responsible for the perception of bitter taste, is much more diverse and contains dozens of proteins [5, 186].

The processing and encoding of primary sensory information begins with four types of taste receptor cells, which are combined in the lingual and pharyngeal epithelium to form taste buds, distributed singly or, more often, in papillae of different types (fungiform, circumvallate, foliate). Type I glia-like cells recognize salty taste. Type II cells express G protein-coupled receptors which respond to sweet, umami, and bitter molecules. Type III includes cells responding to acidic stimuli. Type IV includes stem cells, i.e., the precursors of other types of taste cells [96].

The sensitivity of type II taste cells to sweet substances is mediated by membrane proteins T1R2 and T1R3. These have typical structures for G protein-coupled receptors: the molecule's seven-turn transmembrane domain combines a large extracellular domain (the N terminus) with a characteristic configuration called the Venus flytrap, which is primarily responsible for receptor function, and an intracellular C terminus which mediates interaction with G proteins [5, 7, 29, 68, 124, 186]. The perception of sweet taste is mediated mainly by a heterodimer consisting of T1R2 and T1R3 subunits [29]. More than 50 substances with different chemical structures cause the sweet taste sensation in humans; this set includes mono- and disaccharides of natural origin, alcohols, a wide range of artificial low-calorie sweeteners, and some alkaloids, as well as divalent metal salts such as $FeSO_4$ and $ZnSO_4$ [43, 68, 148, 186].

Glucose, sucrose, the synthetic sweetener sucralose, and amino acids interact with the extracellular domains of the receptors, with T1R3 having a greater affinity for sucrose and T1R2 for glucose. Cyclamate and the sweet polypeptide monellin interact with the transmembrane domain of T1R3 [132]. However, not all sweet taste stimulants bind to the Venus flytrap receptor site. Thaumatin protein binds to a short cysteine-rich region connecting the transmembrane and N-terminal domains of hT1R3 [43]. Finally, brazzein protein interacts simultaneously with many sites of both hT1R2/hT1R3 subunits [34, 132]. A special population of type II taste cells (about 6%), located in the fungiform papillae, expresses only T1R3 protein, so low-affinity T1R3/T1R3 homodimers are formed in the membranes of these cells and appear to respond to high concentrations of mono- and disaccharides [16, 131]. It has been suggested that homodimeric T1R2/T1R2 receptors can also perform

sensory functions [35, 203]. Between-species differences in sensitivity to sweet substances are known; in particular, mice do not mount responses to the sweetener cyclamate and some amino acids [179].

The T1R3 protein is also part of the T1R1/T1R3 receptor, which responds to amino acids and flavor enhancers such as inosine and guanosine monophosphate [5, 29]. The human form hT1R1/hT1R3 recognizes glutamic acid L-Glu and aspartic acid L-Asp, while the mouse mT1R1/mT1R3 recognizes other L-amino acids: alanine, serine, glutamine, threonine, glycine, methionine, arginine, and asparagine [179].

In type II taste cells, the T1R2/T1R3 receptor is associated with a G-protein heterodimer consisting of the Gα subunit of gastducin $G\alpha_{gust}$ (Gαt3), which belongs to the Gαi/o subfamily (the GNAT3 gene) and is specific to the taste system, the β-subunit $G_{\beta}1$ or $G_{\beta}3$ (GNB1/3), and the γ-subunit Gγ13 (GNG13) [120, 153, 186]. The intracellular signal cascade responds to the interaction of the receptor with the ligand, which leads to the dissociation of the Gβγ-dimer and activation of α-gastducin, which stimulates phospholipase C-β2, which cleaves membrane phosphatidylinositol-4,5-bisphosphate into two molecules: inositol 1,4,5-triphosphate and diacylglycerol. Inositol 1,4,5-triphosphate activates ryanodine receptors, which leads to the release of Ca^{2+} from intracellular depots. An increase in $[Ca^{2+}]_i$ stimulates non-selective transient receptor potential TRPM5 cation channels on the basolateral cell membrane and, according to new data, TRPM4 [13], which allows Na^+ to enter the cell and leads to action potential generation and the release of a transmitter (ATP) from specialized channels formed from two molecules of the pannexin 1 protein [52, 29, 84, 120, 151, 152, 186]. ATP interacts with P2X2/P2X3 purine receptors on afferent nerve endings, which transmit a signal identifying contact with the substance to the CNS [53]. In addition to α-gastducin, T1R can be associated with other α-subunits which are members of the Gαi/o family, particularly α-transducin, Gαi2, and Gαi3, as well as other subfamilies – Gαq, Gα12/13 or GαS [120, 153, 186, 200]. In particular, Gα14 protein, a member of the Gαq subfamily, is expressed in the root regions of the tongue in place of gastducin [186]. The result of this is that a link can be formed with other intracellular signaling cascades, as happens when transmitting signals relating to a variety of sugar substitutes. Thus, T1R receptors are able to activate adenylate cyclase, which leads to an increase in the concentration of cAMP [120, 186].

Type II taste cells also release acetylcholine [36, 134]. While ATP performs the main transmitter function, sending signals from taste cells to afferent nerves, other transmitters probably modulate the activity of taste cells through autocrine and paracrine pathways [30]. A number of recent studies have shown that the expression of taste receptors is associated with blood nutrient levels, and this has been demonstrated both for glucose and for amino acids, salts, and other classes of taste substances [31, 161].

The actions of a number of plant alkaloids target the T1R system. For example, plants of the South American *Stevia*, especially *S. rebaudiana*, contain sweet glycosides, i.e., steviosides, which are now widely used as natural sweeteners [111]. The opposite effect has been shown for the protein gurmarin, isolated from the Indian plant *Gymnema sylvestre*, which is an inhibitor of sweet taste receptors in rodents [172]. In humans, the sweet taste inhibitor lactisol (2,4-methoxyphenol-propionic acid), found in roasted coffee beans, has been discovered and is already actively used in the food industry [70, 85].

Perception of Sweet Taste – a Polymorphic Trait. Early psychophysical experiments on sweet perception found that people are divided into so-called "sweet-likers," in whom preference (the hedonic reaction) increases with the concentration of the sweet substance, and "sweet-dislikers," who develop aversion with increasing concentration [116]. More complex reactions were also observed, where the increase in preference slowed with increasing concentration and fell to a near-neutral level after reaching a maximum [117]. Recent testing of a wide range of sucrose concentrations (1–35%) showed that this type of reaction was characteristic of the majority (50%) of subjects [80, 81].

Inbred strains of laboratory mice also differ in terms of sensitivity thresholds and levels of sweet consumption, and it is now long since they have been characterized as having so-called sensitive and insensitive ("taster" and "nontaster") alleles of the putative receptor gene [4, 8, 9]. Studies in mice at the end of the 1970s showed that preference for saccharine solution is determined by allelic variants of a single autosomal locus, named *Sac* (saccharine), for the ligand. The dominant allele of this locus, Sac^b, originally discovered in C57BL/6 mice, determines an increased preference for saccharine and, as shown later, other sweet substances, as well as amino acids, while the recessive allele, Sac^d, present in the strains DBA/2, 129P3/J, etc., is associated with lower consumption [9]. Data accumulated over years of investigations led several research teams to show independently, by the beginning of the 21st century, that the *Sac* locus is identical to the *Tas1r3* gene located in the distal part of the short arm of mouse chromosome 4, encoding T1R3 receptor protein [7, 113, 131]. In humans, the ortholog of this gene, TAS1R3, is located on the short arm of chromosome 1 [4].

Cases of loss of *Tas1r* genes or transcriptional disturbances (pseudogenization) have been identified in different taxa: pandas, chickens, cetaceans, pinnipeds, and felids, confirming the connection between species-specific characteristics of sweet preference and amino acid taste on the one hand with loss of these genes on the other [2, 4]. Thus, the well-known loss of sensitivity to sweets in felines results from pseudogenization of *Tas1r2* [4]. The specific diet of the giant panda *Ailuropoda melanoleuca*, consisting of 99% bamboo shoots, is associated with loss of sensitivity to amino acids caused by pseudogenization of the *Tas1r1* gene [4, 5]. The food preferences of such obligate predators

as sea lions, seals, and baleen and toothed whales [86], as well as penguins [201], are combined with inactivation of all three genes, *Tas1r1–3*. Finally, some frogs completely lack receptor genes of the T1R family [4, 5]. A good illustration of the biological importance of the T1 receptor system is provided by the fact that, on the background of the loss of the T1R2 receptor protein in most modern birds, the nectar-eating hummingbird *Archilochus colibris* regained its function due to a mutation in the *Tas1r1* gene encoding the T1R1 receptor, which stopped responding to amino acids and acquired an affinity for sugars [12].

Studies in mice showed that deletion of the *Tas1r2* and *Tas1r3* genes suppresses neuronal responses to sweet substances in the brief access test and completely suppresses the behavioral preference for natural sugars and low-calorie artificial sweeteners. On the background of long-term exposure to sweet substances, gene knockout eliminates the consumption of non-nutritive sweeteners and reduces the consumption of low, but not high concentrations of natural sugars, increasing the hedonic response threshold [35, 63, 127, 203]. The difference between the effects of sweeteners and sugars is due to the fact that alternative sensory pathways exist in addition to T1R-mediated pathways [135, 186]. In addition, the postabsorption effects of food are just as important as the initial perception of its taste and can determine the consumption of initially non-preferred high-calorie foods without a particularly sweet or otherwise attractive taste [157, 158]. At the same time, deletion of *Tas1r1* alters the food preference for amino acids, but does not eliminate it completely, as other signal pathways presumably associated with metabotropic glutamate receptors (mGLUR) exist [5, 29, 123].

Variation in the amino acid sequences of T1R2/T1R3 receptor heterodimer subunits has a significant impact on the qualitative and quantitative perception of sweet substances. Although the structure of T1 receptors is phylogenetically relatively constant across species, with 70% homology between rodents and humans [131], the differences appear to be sufficient to alter the perception of sweet taste. Thus, rodents are virtually insensitive to many artificial sweeteners perceived as sweet by humans, such as aspartame, neotame, cyclamate, and neohesperidin dihydrochalcone, as well as the sweet proteins brazzein, monellin, and thaumatin. Similarly, rodents do not prefer sucralose as strongly as humans [115]. These changes in the structure of taste genes were fixed in evolution as adaptations to diet [2].

Evolutionarily fixed allelic variants of *Tas1r2* and *Tas1r3* determine within-species quantitative differences in sensitivity and preference for sweets. Analysis of saccharine preference in 30 strains of laboratory mice showed that *Tas1r3* polymorphism is associated with three nonsynonymous single nucleotide substitutions (SNP), among which T179C, leading to the substitution of isoleucine by threonine at position 60 in the extracellular N domain of T1R3 protein, had the greatest effect on behavioral preference for sweetness due to the formation of a recessive (low-sensitivity) allele, and this is apparently the cause of the previously identified *Sac* polymorphism [146]. Phenotypic manifestations of *Tas1r3* polymorphism have been studied in vitro and in vivo. The T179C substitution, as demonstrated in vitro, limits conformational changes and reduces the affinity of the T1R3 receptor for sucrose, glucose, and sucralose, which significantly (up to 10-fold in the case of sucrose) increases the effective dose of tastant [132]. In in vivo studies, congenic mouse strains 129P3/J-C57BL/6-*Tas1r3* [83] or hybrids 129S2B6F1 [128], carrying the dominant B6-*Tas1r3* gene, demonstrated a greater preference for sugars and artificial sweeteners than carriers of the recessive allele alone.

Synonymous and nonsynonymous SNP of *TAS1R* genes have also identified in humans, as have haplotypes characteristic of individual populations; the *TAS1R3* gene was found to be more evolutionarily conservative, the greatest level of variability being detected in *TAS1R2*. The African population has been noted to be characterized by a larger number of SNP in *TAS1R3* [95]. Two identified SNP polymorphisms in the promoter of the TAS1R3 receptor [59] affect the evaluation of the sweetness of sucrose and occur at different frequencies in different parts of the world, explaining 16% of the variation in the perception of sucrose in the population. The effects of so-called C-substitutions, which determine an enhanced reaction, are seen in all regions except Africa, and the frequency of the T-allele with low evaluations is lowest in the European population. Identified *TAS1R2* polymorphisms influence carbohydrate intake and sucrose discrimination thresholds depending on body mass index [39, 47] and blood triglyceride concentrations [144]. In addition, a connection has been demonstrated between the *TAS1R2* polymorphism and *GLUT2* and the incidence of dental caries [149].

Thus, the significant amount of experimental data obtained to date allow us to be confident in the views that the taste preferences of vertebrates depend largely on the presence of Tas genes, which encode different taste receptors, and that receptor sensitivity is directly related to polymorphisms of these genes.

The Sweet Component of the Taste of Ethanol. Low concentrations of ethanol can be regarded as a natural chemical stimulus generated during the fermentation process with the ability to serve as an indicator of the ripening of fruit [44]. Ethanol is a complex chemical irritant which acts on taste, olfactory, and somatosensory (heating and burning sensations) receptors [6]. First contacts with alcohol should produce the maximal influence of innate chemoreceptor reactions; in some cases, for example, when the influences of social factors such as imitation are weak, this influence should be decisive in relation to further consumption and the rejection reaction. The connection between taste perception and preference for sweetness on the one hand and the development of alcoholism on the other was substantiated in early studies demonstrating that alcohol dependence correlates with hedonic reactions to sweet, but not bitter, solutions [87–89]. A hereditary associa-

tion was also found between the tendency to consume sweets and increased consumption of alcohol solutions in inbred mouse strains [6, 8, 20]. It has long been known that some mammalian species, including humans, are able to distinguish sweet and bitter components in the taste of ethanol [140]. C57BL/6J mice [21] and rats transferred acquired conditioned taste avoidance of ethanol to sucrose and mixtures of sweet and bitter solutions, i.e., the sweet component of the taste of ethanol has a signal value for them [93, 94, 105]. Application of an ethanol solution to the tongue of mice has been shown to cause an increase in spike activity primarily in the sweet-sensitive fibers of the taste nerves [73, 154] and neurons of the solitary tract nucleus, which can be blocked by gurmarin, a specific inhibitor of sweet taste in rodents [40, 109]. In addition, some overlap has been identified between the central mechanisms of hedonic responses to ethanol and sweeteners, including the opiate, serotonergic, and dopaminergic pathways [27, 56, 62, 66, 78, 143]. A comparative analysis of ethanol preference in about 20 inbred mouse strains and their F1 and F2 hybrids showed that C57BL/6 mice, with high sensitivity to sweetness (carriers of the *Sac*^{b} taster allele) demonstrated that they had the greatest preference for ethanol, while the DBA and 129 strains, with weaker preference for sweeteners (the nontaster allele *Sac*^{d}), had the lowest ethanol preference [6, 8, 17, 129]. Genetic analysis of hybrids obtained by crossing C57BL6/ByJ mice with 129P3/J mice showed that differences in the consumption of sweets and ethanol are due to a relatively small and partially overlapping group of genes [8]. One of these genetic loci, *Ap3q*, was mapped to chromosome 4 and overlapped with the *Tas1r3* gene, which served as the basis for the conclusion that they were identical. Subsequent behavioral testing showed that allelic variants of the *Tas1r3* gene in congenic and knockout mice have pleiotropic effects on the perception and consumption of sweeteners and ethanol [4].

At the same time, the influence of the olfactory component of the action of ethanol must be taken into account. The odor of alcohol and its irritating effect are stimuli which most animals absolutely reject [93, 94]. Experiments employing olfactory impairment have shown that the role of odor in the response to ethanol varies depending on *Tas1r3* genotype. 129P3/J mice, with low sensitivity to sweetness, perceive low concentrations of ethanol by smell and avoid high concentrations on the basis of odor rather than taste. In the case of the highly sensitive strain C57BL/6ByJ, the negative olfactory effect of ethanol was significantly smaller [1].

Taste Sensitivity to Sweetness Not Related to T1R Receptors. Some of the processes occurring in type II receptor cells on contact with simple sugars are not directly related to the activity of T1R receptors. The enzyme sucrase-isomaltase, which is expressed in T1R3-positive type II taste cells, breaks down disaccharides on the surface of the lingual epithelium, for example, converting sucrose into glucose and fructose [176]. The resulting glucose is at least partially transported into sensory cells by glucose transporters; the set of these proteins identified is similar to that of intestinal absorptive cells and includes high-affinity sodium-glucose cotransporter 1 (SGLT1), insulin-independent and -dependent glucose transporters types 2 and 4 (GLUT2, 4), and a number of others [125, 194]. Recent studies have shown that SGLT1 in taste cells may be directly involved in glucose reception, which explains the well-known phenomenon of potentiation of the response to sweets by salt [193]. In humans, polymorphism of the GLUT2 and GLUT4 transporters correlates with the taste preference for sweetness and sensitivity thresholds, as well as with the consumption of sweet foods and caries [50].

An increase in the glucose concentration in the receptor cell cytoplasm, which contains a special form of glucokinase (hexokinase IV), stimulates ATP synthesis, which binds to K_{ATP} channels and closes them, leading to receptor cell depolarization. This process is regarded as a T1R-independent mechanism of glucose sensitivity [35, 125, 194]. The T1R-independent response of receptor cells to sugars was found to be more marked on application of monosaccharides, which confirms the involvement of glucose transporters and/or K_{ATP} channels in reception [194]. These points allow us to explain why knockout of the *Tas1r3* gene in mice does not completely eliminate neuronal responses to sweetness. Thus, when high-calorie sugars are applied to the tongue, an increase in spike activity and a change in its pattern are seen in the chorda tympani and glossopharyngeal nerve, as well as in the neurons of the solitary tract nucleus, and this is interpreted as the presence of residual sensitivity to sugars [35, 110, 186, 203]. It should be noted that this suggests that blood glucose levels influence receptor sensitivity. The reactions of taste cells themselves have been shown to require the presence of some particular glucose concentration in the extracellular environment at which the K_{ATP} system maintains an optimal level of membrane depolarization. At the same time, long-lasting exposure to an elevated glucose concentration can induce depolarization block and disruption of the responses of taste cells [194].

Thus, taste bud receptor cells also contain a caloric sensor, whose operation involves glucose transporters [38, 159]. This mechanism makes it possible to discriminate between caloric substrates and artificial non-nutritive sweeteners at a level as early as receptors [176]. T1R-independent glucose transporters in taste cells are known to be the trigger of the cerebral phase of the insulin secretion reflex. Sugar applied within the oral cavity for 5 min, i.e., long before glucose is absorbed the intestine, stimulate a slight increase in the plasma insulin concentration. At the same time, the cerebral phase of insulin secretion is preserved in *Tas1r3* knockout mice [64]. Mice lacking sweet taste perception due to TRPM5 knockout also retain a preference for high-calorie sucrose [37].

Peptide Regulators of Taste Sensory Cells. Taste information undergoes initial processing in the taste buds, by mechanisms including synaptic transmission. Mammalian

taste cells have been shown to express a number of peptide hormones and receptors which were previously believed to be related exclusively to the functioning of the nervous or digestive systems. The roles of these peptides in autocrine regulation and intercellular communication in taste buds have been discussed in some detail [76]. Some peptides from taste buds may enter the brain or peripheral organs, while taste cell receptors respond to circulating hormones, i.e., taste responses may depend on the metabolic status of the body or may prepare the body to process consumed nutrients or toxins [31, 92, 106, 130, 168, 169, 183].

Glucagon-like peptide 1 (GLP-1) is found in mice, rats, and macaques in some type II and type III taste cells, which also contain the enzyme required for its independent synthesis, i.e., the protein convertase PC1/3 [51, 168]. In the circumvallate papillae of mice, approximately half the GLP-1-containing cells show immune reactivity to α-gastducin and T1R3. GLP-1R receptors are absent from the membranes of taste cells but are present on nerve terminals within taste buds, which suggests that hormone synthesized in receptor cells has paracrine actions, though the peptide can also enter the bloodstream. In contrast to blood and intestinal tissue, GLP-1 is inactivated slowly in taste buds due to the minor content of dipeptidase DPP-IV within them [168]. The presence of GLP-1R in taste buds raises questions regarding their role in the formation of taste responses. Behavioral responses to natural and artificial sweeteners were found to be weakened in GLP-1 knockout mice, though the response to umami taste was surprisingly enhanced [121, 168].

Glucagon is produced in type II cells of the foliate, fungiform, and circumvallate taste buds, where it coexists with glucagon receptors. These cells always contain PC2 convertase protein, which converts proglucagon into glucagon, along with its cofactor 7B2 [46, 168]. The vast majority of glucagon-containing cells (95%) express phospholipase Cβ2 (PLCβ2), while 93% express T1R3 protein [46]. Thus, glucagon and GLP-1 are synthesized in partially overlapping populations of taste cells. Pharmacological or genetic suppression of glucagon synthesis, like suppression of GLP-1 sythesis, led to weakening of taste responses to sweet substances, though the effect of glucagon, unlike that of GLP-1, was determined by its autocrine action [168].

Expression of another gastrointestinal hormone, cholecystokinin (CCK), was first identified in the taste cells of foliate and circumvallate papillae [75], with about 50% of cells also immunopositive for α-gastducin but only 15% expressing T1R2 [162]. These data suggest that CCK also influences the peripheral perception of sweet and bitter tastes. Colocalization of CCK and CCK_A receptors indicates that the peptide acts primarily by an autocrine mechanism within the taste bud, operating via the phosphoinositide pathway to enhance the excitability of sweet receptors by prolonging depolarization [69, 75, 76].

Rat tongue foliate and circumvallate papillae [74] and human circumvallate papillae [101] contain large numbers of cells with immunoreactivity for vasoactive intestinal polypeptide (VIP). About 60% of VIP-containing cells in rats synthesize α-gastducin and 19% express T1R2 [162]. The localization of VIP receptors (VPAC1 and VPAC2) in the group of PLCβ2-immunoreactive taste cells [122] indicates that VIP signaling occurs within the taste bud, though it is not yet known whether VIP acts as an autocrine or a paracrine factor [202]. The physiological role of VIP in taste buds is not entirely clear. VIP knockout mice showed slight abnormalities in responses to sucrose and bitter and sour substances in a brief access test, though the presence of VIP receptors in type III taste cells remains to be confirmed [122].

Neuropeptide Y (NPY)-positive taste cells are present in the foliate, fungiform, and circumvallate taste buds, as well as in the epithelium of the nasopalatine canal (the incisive canal), while NPY is almost entirely colocated with CCK and VIP. NPY receptors types Y1, 2, 4, and 5 are also found in the membranes of taste cells in mice [76]. In mice, the Y4 receptor is also found in the nerve endings within taste buds [79]. At the same time, there is insufficient knowledge of the functions of NPY in the taste system. Exogenous NPY enhances potassium currents in isolated taste cells, this being mediated mainly by Y1 receptors [202]. By analogy with the olfactory system, it has been suggested that NPY may be a proliferation factor in taste buds [72].

Several components of the ghrelin signal system are also present in taste buds. Ghrelin and its precursor preproghrelin, along with the processing enzyme protein convertase PC1/3, are coexpressed in approximately 13% of all taste cell types (I–IV) in the circumvallate papillae. Deletion of ghrelin led to slight increases in the responses to sour and salty solutions in the brief-access test, but had no effect on responses to sweet and bitter stimuli [169].

Galanin is expressed in many taste cells of the circumvallate papillae along with PLCβ, α-gastducin, and nerve cell adhesion factor. The latter is known as a marker for type III cells. Galanin receptors, GalR2, were also identified in these cells. Galanin has been suggested to be a neurotrophic factor in the taste system [119, 160].

Encoding of Modality, Intensity, and Hedonic Value of Sweet Taste. Stimulation of sweet taste buds leads to the generation of neuron activity at different levels of the peripheral and central nervous system. Signals from the periphery, propagating to the CNS, are ultimately transformed into sensory images carrying information relating to various characteristics of the taste agent, such as taste quality (modality), attractiveness (hedonic value), and intensity (stimulus concentration) [48, 49].

At the periphery, taste quality (sweet, umami, and bitter), at least at low concentrations, is identified by many but not all type II taste receptor cells with narrow tuning [181], i.e., encoding occurs on the labeled line principle [48]. Increasing the concentration of tastant can expand the tuning of certain specialized cells, which are generally classified as a non-persistently labeled line [136]. In fungiform

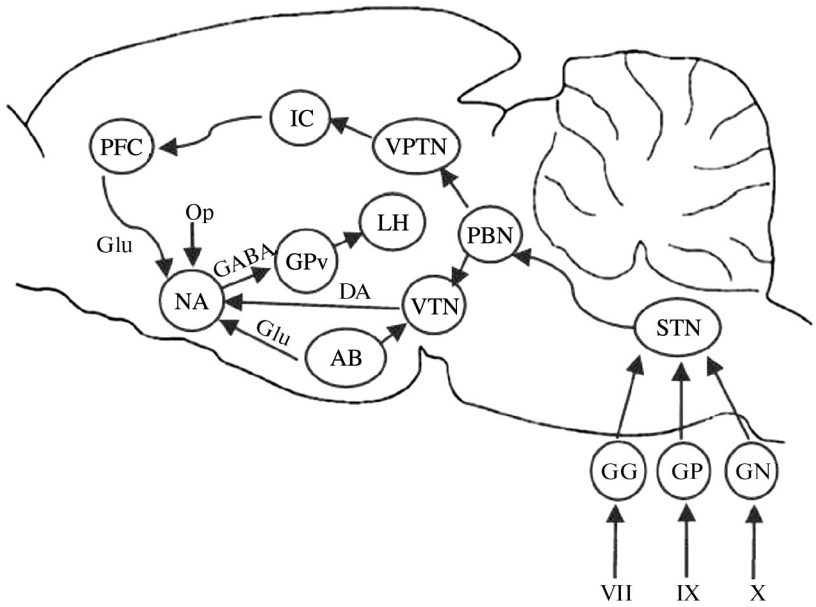

Fig. 1. Interaction of the nerve centers of the taste sensory system with the reinforcement system and homeostatic centers. VII – branch of the facial nerve (chorda tympani); IX – glossopharyngeal nerve; X – vagus nerve; GG – geniculate ganglion; PG – petrosal ganglion; NG – nodular ganglion; STN – solitary tract nucleus; PBN – parabrachial nucleus; PMTN – ventral posteromedial thalamic nucleus; VNT – ventral tegmental nucleus; NA – nucleus accumbens; PFC – prefrontal cortex; IC – insular cortex; AB – body of the amygdala; GPv – ventral nucleus of the globus pallidus; LH – lateral hypothalamus; DA – dopamine; GABA – γ-aminobutyric acid; Glu – glutamic acid; OP – opioids.

taste buds, up to 70% of type II sensory cells are specialized, while 30% are broadly tuned and most frequently respond to two taste qualities, sweet/umami (10%) or salty/other (20%). It is interesting to note that type II sensory cells which respond simultaneously to sweet and bitter signals are not found in taste buds, while neurons with these characteristics are found in the geniculate ganglion and cerebral cortex [71].

Encoding of the sweet modality of a taste stimulus is provided by a population of type II sensory cells containing a combination of T1R2 and T1R3 proteins [131]. A number of questions still remain to be answered. Thus, it is unclear whether stimulation of a small population of type II taste cells expressing only T1R3 – suggesting the existence of a low-affinity T1R3/T1R3 receptor in the taste system [16, 131] – can induce a positive behavioral response to sweetness. It is also unclear whether this group of cells responds to the umami taste.

The rationale for labeled line coding was clearly demonstrated by Zhao et al. [203], who were able to express, along with T1R2 protein, the opiate receptor RASSL, which is activated by taste-free spiradoline, in taste cells. As a result, presentation of spiradoline to transgenic mice caused the same positive behavioral reactions as presentation of sweet solutions. In another equally elegant experiment, the expression of bitter receptors (hT2R16) in sweet-sensitive (T1R2-positive) taste cells stimulated active consumption of a previously rejected bitter substance by animals [126].

The signal from the main primary sensors of the sweet taste, type II cells containing T1R2/T1R3 receptors, is transmitted to primary afferent neurons, which are classified as "better perceiving sweet" ("sweet-best"), though they are also "selective for sweet" ("sweet-selective") [57, 152, 180, 190]. These neurons responded intensely to sweetness in a series of taste stimuli or responded exclusively to sweetness.

Afferent fibers originate from the taste buds of the fungiform papillae and from the foliate papillae concentrated in the anterior part of the tongue and run as part of the chorda tympani – a branch of the facial nerve (cranial nerve VII). The bodies of these sensory neurons are located in the geniculate ganglion (GG). The foliate papillae of the posterior part of the tongue and the circumvallate papillae are innervated by the sensory branch of the glossopharyngeal nerve (cranial nerve IX). The cell bodies of these afferent neurons are located in the ganglion petrosum. The root of the tongue, epiglottis, and larynx are innervated by the superior laryngeal branch of the vagus nerve (cranial nerve X). The superior laryngeal branch and glossopharyngeal nerve are also involved in the swallowing and vomiting reflexes [138, 173]. These taste nerve fibers project to the first relay center of the taste system (Fig. 1), which is the rostral part of the solitary tract nucleus (STN). The second relay point of the bottom-up taste tract in rodents is the parabrachial pontine nucleus (PPN). The third central neuron of the gustatory sensory system is located in the paraventricular part of the ventral posteromedial thalamic nucleus (VPTN). This thalamic nucleus sends projections to the gustatory area of the insular cortex (IC). In monkeys, however, bottom-up gustatory fibers from the STN run directly to the VPTN, bypassing the PPN [15].

Evaluation of the spike responses of taste nerves, as well as calcium imaging data for GG neurons, showed that

they are similar to the responses of type II taste cells, i.e., most neural units at this level are specialized and respond to a specific taste quality, while a minority are characterized by generalized responses to several modalities at the same time [14]. In particular, deletion of T1R3 in mice impaired labeled line responses to sweet and umami tastes [32]. However, neurons with broad tuning are present even at such a low level of sensory taste information processing. An increase in the tastant concentration (stimulus intensity) converts the initially narrow tuning of GG sensory cells into a broad one [189]. Interestingly, relatively recent studies revealed genetic markers for the five main taste modalities in the neurons of this ganglion. Thus, GG neurons preferentially responding to umami taste expressed the cadherin 4 gene (*Cdh4*), while bitter-sensitive neurons expressed cadherin 13 (*Cdh13*); the *spon1* gene (spondin-1) was identified in neurons which differentiate sweet taste; units responding to salty taste were characterized by the transcription factor gene *Egr*, and the proenkephalin gene (*Perk*) was characteristic of cells responding to sour [198].

Neurons with broad tuning predominate in the higher cerebral taste sensory information processing centers and respond to different qualities of taste stimuli, though specialized units are also present. At the same time, it remains unclear which of the neural reactions is necessary for the perception of the quality of the taste signal, particularly in respect of sweet taste. Chen et al. [32] compiled a gustotopic map of the insular cortex of anesthetized mice, which clearly demonstrated concentration of responses to bitter taste in the posterior region of this cortical zone and responses to sweet stimuli in the anterior region, i.e., spatial separation of neural clusters. Mouse strains with knockout of taste receptor genes showed, along with the disappearance of specialized taste receptors, disappearance of zones of preferential response to taste quality, which allows these zones to be regarded as a continuation of the labeled line [32]. Nonetheless, not all researchers have confirmed the existence of specialized zones in the primary gustatory cortex. Calcium imaging and electrophysiological recordings have identified only broadly tuned neurons in the posterior insular cortex [54, 55, 103, 112, 114]. Furthermore, most neurons in the posterior insular cortex have been shown to be multisensory, responding mostly to aversive stimuli, i.e., painful stimuli and bitter substances [61].

The gustotopic concept of the representation of taste modalities in humans has not received sufficient confirmation. Recording of primary taste responses in the human cortex using functional magnetic resonance imaging revealed a more complex picture than seen in mice, with significant overlap of areas with representation of different taste qualities and with extensive individual variability [3]. Changes in the concentration of tastant sometimes completely changed the locations of taste zones [26, 142]. Modalities in both the human primary gustatory insular cortex and the areas determining hedonic and aversive reactions to taste were not represented gustotopically but were implemented through a combinatorial network code [3].

The insular cortex is of great importance for the formation of hedonic reactions. Optogenetic stimulation of sweet and bitter taste clusters in the mouse insular cortex causes both behavioral preference (appetitive) reactions, as well as aversive and anxiety responses, regardless of the presence of the taste stimuli themselves [61, 141].

The perception of sweet taste has a marked emotional aspect which is associated with limbic system activity and is accompanied by a hedonic or appetitive (palatable) response, which is one of the main reasons for the excessive consumption of sugars in the vast majority of species [19, 68]. The behavioral correlate of the hedonic significance of a stimulus is a change in feeding behavior, such as initiating a response, increasing it, or stopping eating or drinking. The most commonly used experimental indicator of preference for a tastant solution is the oromotor response: acceleration or deceleration of licking depending on the concentration [174]. The oromotor response is generally recorded using a brief access test, in which contact with a solution of a particular taste is brief (usually $\leq$ 5 sec), excluding strong post-absorption effects [196].

Although sweet taste usually induces a positive appetitive response, taste sensations and this type of response do not always develop in parallel. Appetitive reactions can change with experience, for example, when conditioned reflex taste aversion develops. In this situation, the animal continues to perceive the sweet taste of the substance but learns to reduce its consumption [60].

The most important nervous structure in the implementation of the emotional component of taste reactions is the ventral tegmental nucleus (VNT), which is part of the mesolimbic dopamine (DA) system (Fig. 1). In rodents, the spike activity of more than half of the neurons in this nucleus correlates with reward responses on consumption of preferred solutions. At the same time, the responses of these neurons do not reflect taste modality and remain the same as when the animal comes into contact with water [164]. At the level of the VTN, hyperphagia is stimulated by the interaction of the benzodiazepine and opioid systems with the dopamine system. Ablation of the VTN leads to a sharp decrease in the consumption of sucrose solution but does not affect the consumption of less preferred tastants [164, 166].

Another area of the brain important in the gustatory reward system is the nucleus accumbens (NA), which converts motivation (appetitive responses) into consumption (nutrition) [175]. The most marked hyperphagia, caused by the action of opioids, develops after injection of these substances into the shell of the NA [11]. The central taste sensory pathways run to the NA from the STN [147, 155] and insular cortex [24]. Pathways from the gustatory cortex to the prefrontal cortex (PFC) have been described, and neurons in the dorsomedial PFC are known to respond to taste stimuli [91, 118, 163]. PFC neurons in conscious rats

were activated during licking [190]. The PFC is connected with the subcortical nutrition centers, the VTN and the NA [24, 100]. The amygdaloid body (AB) and PFC send glutamatergic nerve fibers to the NA [150]. Glutamatergic fibers in the NA form synapses with GABAergic neurons, which constitute up to 90% of the nerve cells in this nucleus and suppress food intake by inhibiting the activity of cells in the ventral nucleus of the globus pallidus (GPv) [82]. Efferent fibers from the GPv pass to the lateral hypothalamus (LH), which is the center regulating food intake. Microinjection of a GABA-A receptor blocker into the GPv stimulates the consumption of the preferred food but does not affect water consumption [165, 175].

Food preference is of particular importance in regulating consumption. The main structure regulating feeding behavior is the hypothalamus, where numerous neuropeptides with influences on appetite play a major role [156]. Intraventricular administration of orexin, NPY, and melanin-concentrating hormone was found to stimulate the consumption of saccharine solution, while drinking saccharine solution, in turn, increased the expression of mRNA for orexin and NPY. Excessive consumption of sweet solution under the influence of hypothalamic neuropeptides also depended on the level of opioids [58]. This response involves endogenous opioids, such as endorphin, in the arcuate nucleus of the hypothalamus [191].

Glucose Reception in the CNS. Glucose is the main source of energy in the structures of the brain. Of the total amount of glucose consumed by an adult at rest, about 75% is used by the brain. During the active phase, the brain consumes up to 90% of total glucose turnover in the body. Glucose molecules are transported from the bloodstream through the blood–brain barrier and enter neurons and glial cells, where they either accumulate as glycogen or undergo glycolysis and oxidative phosphorylation to form ATP and other metabolites [187].

Glucose concentrations in the brain are maintained within a fairly narrow range, which is achieved through the responses of the population of central glucose-sensitive neurons and glia, along with the combined activity of the pancreas, liver, carotid body, and adipose tissue [177]. Glucose-sensitive cells express T1 taste receptors and a variety of glucose transporters, and also have the corresponding signal cascades, including so-called metabolic sensor enzymes. The diversity of these molecules largely determines the brain's ability to integrate multiple signals to maintain physiological processes in the body at the required levels. In particular, responses to extracellular glucose concentrations influence glucose transport and metabolism and, ultimately, the production of energy and essential substrates, transcriptional activity, and gene expression.

Glucose-sensitive CNS neurons respond to changes in extracellular glucose concentration with changes in spike activity [25, 97, 98]. This population of neurons is divided into glucose-excited (GE), whose activity increases with increasing extracellular glucose concentrations and is inhibited by low concentrations, and glucose-inhibited (GI), whose reactions are inhibited by high extracellular glucose concentrations and are enhanced by low concentrations [97]. These neurons, along with glucose-sensitive astrocytes, are located in the hypothalamus (arcuate nucleus, lateral and ventromedial zone), brainstem (area postrema and STN) [25, 98], nucleus accumbens, amygdala [97], septum [170], and cortex [107]. GE neurons in the arcuate nucleus contain proopiomelanocortin, while those in the LH produce melanin-concentrating hormone. GI neurons are consist of several anatomically and functionally distinct subgroups, including orexin/hypocretin neurons in the lateral hypothalamus, NPY/AgrP cells in the arcuate nucleus, and SF-1 cells in the ventromedial nucleus [99]. A decrease in cerebral glucose levels activates GI neurons in the hypothalamus, perifornical region, and brainstem and initiates a sequence of neurohumoral feedback reactions, including sympathoadrenal activation and increased plasma adrenaline, noradrenaline, and glucagon levels, in turn stimulating gluconeogenesis in the liver and kidneys and inhibiting insulin secretion by the pancreas. Acute increases in glucose levels lead to inhibition of glucose inhibitory neurons and activation of glucose excitatory units, with subsequent stimulation of insulin release and suppression of hepatic glucose production by reducing gluconeogenesis and glycogenolysis [99]. It is clear that the existence of glucose-sensitive cells in the nucleus accumbens and amygdala creates an additional mechanism for the involvement of these structures in reward reactions [97]. In addition, these brain regions coordinate nutrition and energy expenditure [91]. In particular, the arcuate nucleus plays a leading role in the regulation of glucose metabolism. Glucose and hormones from the bloodstream have easier access to the mediobasal region of the hypothalamus, where this nucleus is located, as blood–brain barrier permeability is increased here [18].

The most important role in triggering the reactions of cerebral neurons to changes in the extracellular glucose concentration is played by a well-studied metabolic detection mechanism associated with the presence of a special isoform of the enzyme glucokinase and K_{ATP} channels. The transport of glucose into cells is mediated by transporters GLUT2 and SGLT1 [25, 90]. In addition, several of the enzymes of the intracellular signaling cascade are involved in the metabolic response to changes in glucose concentrations and shifts in ATP levels, for example cAMP-activated protein kinase [33]. However, while K_{ATP} channels in general are widely expressed in the brain, SUR1, a subunit of the pancreatic β-cell K_{ATP} channel, and glucokinase have been found in some – but not all – glucose-excitable neurons [65]. At the same time, these neurons in living slices also respond to a non-metabolizable analog of glucose, 2-deoxy-D-glucose. These and other data clearly support the existence of non-metabolic detection mechanisms independent of K_{ATP}. It has been suggested that the benefit of

direct membrane-associated glucose reception by neurons may be that the perception of glucose levels is "decoupled" from the cell's energy status [65].

Hyperglycemia and hypoglycemia affect the expression of the low-affinity glucose transporters GLUT2 [108] and SGLT3 [45, 139] in neurons and astrocytes in the hypothalamus and brainstem [18, 97, 98, 145], as well as the AB and NA [97]. The highest level of expression of GLUT2 was found in astrocytes and tanycytes, a variant ependymal and hypothalamic glial cell type [90, 177]. Operating in the STN and the dorsal motor nucleus of the vagus nerve, GLUT2 mediates increases in the spike activity of parasympathetic fibers and glucagon secretion [177]. Eating behavior disorders are known to occur in mice with GLUT2 deficiency [10].

Sodium-glucose transporter 1 (SGLT1) is present in glucose-sensing neurons in a variety of brain structures, mainly in the hypothalamus, midbrain, and brainstem [90, 185, 188, 197]. There is also evidence that SGLT3 functions as a glucose sensor in the hypothalamus [137, 188]. Entry of glucose into the cell through SGLT, which is accompanied by an influx Na^+ ion current with simultaneous activation of the Na^+/K^+ pump and a hyperpolarizing Cl^- current, can shift the membrane potential both towards hyperpolarization (GI neurons) and depolarization (GE neurons) [25, 38].

Of particular interest is the presence of T1 taste receptors in cerebral neurons and astrocytes [18, 28, 77, 97, 98, 104, 145]. The *Tas1r2* and *Tas1r3* genes, as well as the α-gastducin gene (*Gnat3*), are expressed in many structures in the brain. Their expression in the hypothalamus has been reported to be much higher than in the cortex and hippocampus [77, 145]. Intracerebroventricular administration of sucralose, a synthetic sweet taste receptor ligand, to mice after a 24-h fast resulted in a dose-dependent reduction in food intake, which was also accompanied by increases in the intracytoplasmic calcium concentration and c-Fos expression in the arcuate nucleus. The responses of approximately 70% of GE neurons were suppressed in the presence of the sweet taste receptor blocker gurmarin. The majority of arcuate nucleus neurons responding to sucralose did not express proopiomelanocortin (POMC). Nonetheless, T1R2 and T1R3 proteins were still present in approximately 20% of POMC neurons [98].

The level of expression of T1R2 and T1R3 in the hypothalamus is associated with the metabolic status of the body. The level of T1R2 mRNA has been shown to increase after fasting, while there are no changes in T1R2 and T1R3 expression in the hippocampus or cortex [145]. T1R2 and T1R3 mRNA levels in mHypoA-2/12 mouse hypothalamic cell cultures decreased in response to administration of the satiation hormone leptin [28]. Similarly, exposure to high extracellular glucose concentrations leads to decreases in T1R2 mRNA in cultured mouse hypothalamic N38 and mHypoA-2/12 cells [77]. Expression of T1R2 and T1R3 has been shown to be reduced in mice on a high-calorie diet and was also lower in the leptin-deficient strain ob/ob [77, 145]. Overall, these data indicate that the expression of sweet taste receptor T1R2 and T1R3 subunits in the hypothalamus is closely related to ligand concentration and metabolic status. Excess ligand in the hypothalamus leads to a decrease in the expression of the sweet taste receptor and desensitization of the neural pathways associated with it. During fasting, conversely, there is an increase in the expression of T1R2/T1R3. A decrease in the intensity of the signal from sweet taste receptors in the hypothalamus in obesity can provoke hyperphagia and disruption of glucose homeostasis. Studies in animals have shown that hypothalamic sweet taste receptors (T1R2 + T1R3) are involved in regulating central and peripheral insulin secretion. It has been suggested that stimulation of these receptors can be used in the treatment of disorders of hormonal secretion and neural transmission [64].

Conclusions. Sweet is the most powerful taste modality and largely shapes eating behavior and influences homeostasis. Contact of a type II taste receptor cell with a substance characterized organoleptically by a person as sweet activates a complex ensemble of nerve centers in the taste analyzer and the mesolimbic and homeostatic nuclei of the brain. The gustotopic and combinatorial reactions of these structures forms an image of a sweet taste stimulus with a characteristic modality, intensity, and hedonic value.

Modern studies of the mechanisms of taste signal analysis have received a significant impetus as a result of the discovery of the heterodimeric membrane sweet taste receptor proteins T1R2 and T1R3 in most mammals, as well as the genes encoding them – *Tas1r2* and *Tas1r3*. Due to the complex structure of the supramembrane and transmembrane domains, the T1R2/T1R3 receptor has acquired an extremely broad configuration, i.e., affinity for multiple classes of substances (carbohydrates, amino acids, metal salts, various synthetic sweeteners, and, probably, alcohols), supporting maximal utilization of easily metabolized high-calorie foods. At the same time, evolutionary selection has preserved significant variation in the sensitivity of the T1R2/T1R3 receptor, reflected, for example, in rodents and humans, in the separation of populations with greater or lesser sensitivity to low concentrations of sweet substances. The adaptive significance of such selection is not entirely clear.

At all levels of the taste analyzer, membrane T1R2/T1R3-mediated sweet reception functions synergistically with the so-called metabolic glucose sensor, a glucokinase-K_{ATP}-dependent process leading to depolarization of the cell membrane. Membrane T1R2/T1R3-mediated sweet perception predominates in the periphery, where metabolic mechanisms provide only residual arousal of type II taste receptor cells. The importance of the metabolic mechanism of responses to the entry of glucose into the cytoplasm from the outside increases in CNS neurons and astrocytes. However, the characteristic taste bud receptor proteins T1R2 and T1R3 are present in the central nuclei, with the highest concentrations reported in the hypothalamus. Their

roles in modulating the responses of orexigenic and anorexigenic hypothalamic neurons and their effect on insulin production and interaction with leptin are discussed.

An important property from the physiological and pathophysiological point of view of the reactions of the taste system to sweetness at all levels consists of changes in their tuning depending on the metabolic status of the body. This is achieved through endocrine, paracrine, and autocrine effects mainly from neuropeptides of the digestive system.

Possible directions of further research in this area can be judged from current work which has demonstrated the presence of sweet taste receptors, despite their name, outside the oral cavity and brain. High concentrations of T1R2 and T1R3 receptor proteins are found in the intestinal epithelium, pancreas, liver, adipose tissue, and bone, where they play a role in local regulation of metabolism and have systemic effects on glucose homeostasis and fat metabolism, which the authors hope to present in their next scientific review.

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