

# Neurological Aspects of Taste Disorders

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**T**he sense of taste is generally regarded as less important compared with vision and hearing. However, gustatory disorders considerably diminish the pleasures of life and can lead to work-related problems. At its worst, this deficit may become a life-threatening hazard. However, few studies are found in the medical literature on taste disorders, including authoritative textbooks of neurology and internal medicine.<sup>1</sup> One reason for this may be that gustatory functions are tied to the sense of smell, the somatosensory system, and the perception of pain (eg, when spicy food is eaten), which makes it difficult to examine sensations mediated through an individual system. In addition, gustatory dysfunction is rare, eg, compared with olfactory disorders.<sup>2,3</sup> Therefore, the scope of this review from a neurological viewpoint is to alert physicians to the problem of taste disorders and to help in the diagnosis.

The sense of taste is based on the detection of chemicals by specialized taste cells in the mouth. Gustatory receptor cells are located within taste buds, which are contained in the papillae (approximately 250 buds per circumvallate papilla). Taste cells are known to have regenerative capabilities, with an approximate life span of 10 to 20 days.<sup>4</sup> The actual taste organ consists of approximately 10000 taste buds, which are situated predominantly on the tongue and soft palate, each with 50 to 150 receptor cells.<sup>5</sup> Afferent nerves make contact with the receptor cells at the base of the taste bud. A single taste bud may be innervated by several afferents, while a single fiber may innervate several taste buds. Fungiform papillae are found on the anterior portion of the tongue; circumvallate and foliate papillae are located on the posterior portion of the tongue.

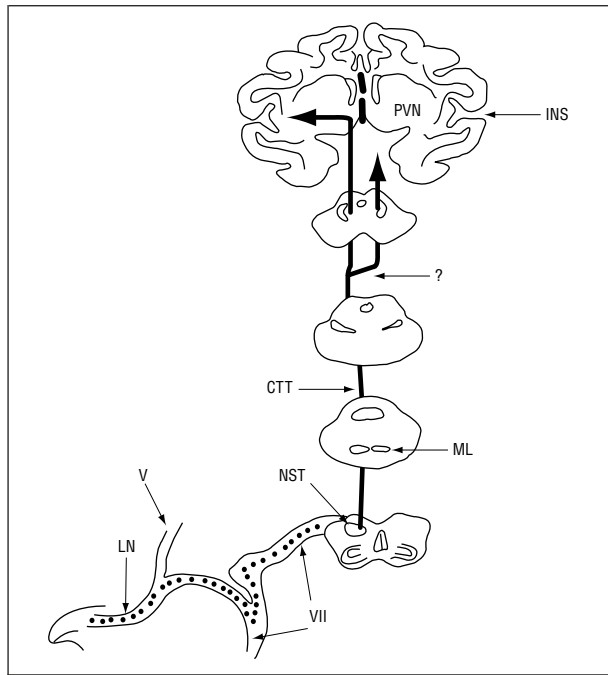
Taste sensations are described as sweet, sour, bitter, and salty. Recently, *umami* (the taste of glutamate) was added

as a fifth quality.<sup>5</sup> Furthermore, there may be specific taste receptors for fatty acids.<sup>6</sup>

According to current knowledge, the former theory of specified receptor cells that respond to only one of the basic tastes has been abandoned. There is now evidence that a receptor cell may respond to a particular taste, but the same cell may also respond to other tastes.<sup>7</sup> This means that there is not always a correlation between chemical stimulant and perceived taste quality; in turn, different types of chemicals can evoke similar sensations.

Chemicals that produce a salty or sour taste are mostly ions and act through ion channels. The chemicals that produce sweet or bitter taste typically bind to surface receptors, triggering a cascade of signals that results in conformational changes in ion channels.<sup>8</sup> A key member of this cascade is gustducin.<sup>9</sup> Following activation of the taste buds, gustatory information is carried primarily by specific branches of 3 cranial nerves (CNs). The facial nerve (CN VII) innervates the anterior two thirds of the tongue, the glossopharyngeal nerve (CN IX) innervates the posterior one third of the tongue, and the vagal nerve (CN X) carries taste information from the back part of the mouth, including the upper third

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Schematic drawing of the current understanding of the gustatory pathway. In the lower left, the main peripheral gustatory pathway is shown (branch of cranial nerves [CN] V and CN VII; the remaining branches of CN IX and X are not shown); on the right, the central gustatory pathways are given. LN indicates lingual nerve; PVN, posterior medial ventral nucleus of the thalamus; INS, insula; ?, some fibers cross at the mesencephalon level; CTT, central tegmental tract; ML, medial lemniscus; and NST, nucleus of the solitary tract. Adapted from Lee et al<sup>10</sup> and Sanchez-Juan and Combarros.<sup>1</sup>

of the esophagus. The tongue is also innervated by the trigeminal nerve, which is involved in tasting through the perception of touch, pressure, temperature, and pain (eg, spicy foods). The first nuclear region in the brainstem is the nucleus of the solitary tract of the medulla, from which the information runs ipsilaterally via the central tegmental tract to the posteromedial ventral nucleus of the thalamus, and then to the cortex (**Figure**).

Crossing of gustatory fibers may occur at the lower midbrain level.<sup>1</sup> Analogous to the olfactory pathway, taste information also connects to the amygdala and hippocampus. Although the perception of a flavor, eg, cherry, is complex and integrates gustatory, olfactory, and somatosensory perceptions, for didactic reasons, we will focus in this review on gustatory disorders from a neurological viewpoint.

## CLINICAL MANIFESTATION AND EXAMINATION

Many patients do not spontaneously report on their taste disorder, particularly if other symptoms are present.<sup>11</sup> Therefore, it is important to specifically ask the patient about any taste-related clinical problems. Among patients who denied the question “Do you have difficulties in recognizing food or beverages as sweet, sour, bitter, or salty?” no taste disorder was confirmed in 94%.<sup>12</sup> In contrast, the question “Do you have a taste problem?” identified only 10% of the patients with a taste problem. Furthermore, patients should be questioned with regard to salivation, swallowing, chewing, oral pain, previous ear infections (possibly indicated by hearing or bal-

ance problems), oral hygiene, and stomach problems. The history should also focus on the possibility of accompanying diseases, eg, diabetes mellitus, hypothyroidism, or cancer.<sup>13</sup> Clinical examination includes inspection of the tongue and the oral cavity. Furthermore, the ear canal should be inspected, as lesions of the chorda tympani have a predilection for this site.

Gustatory testing is performed as a whole-mouth procedure or as a regional test.<sup>14</sup> Natural and electrical stimuli are used. For regional testing, 20 to 50  $\mu$ L of liquid stimuli may be presented to the anterior and posterior tongue using a pipette; other methods are based on the use of soaked filter-paper disks or cotton swabs. For whole mouth testing, small quantities (2-10 mL) of solution are administered, and the patient swishes them around in the mouth. Typically, after a couple of seconds, the solutions are spit out and the patient rinses the mouth with tap water.<sup>3</sup>

Threshold tests for sucrose (sweet), citric acid (sour), sodium chloride (salty), and quinine or caffeine (bitter) are frequently performed with natural stimuli.<sup>3</sup> One of the most frequently used techniques is the “3-drop test.”<sup>3,14</sup> In this test, 3 drops of liquid are presented to the subject (one of them being the taste stimulus and 2 being pure water; volume, <0.1 mL). Threshold is defined as the concentration at which the patient correctly identifies the taste 3 times consecutively. In addition, tests are being developed that are based on impregnated filter-paper strips.<sup>15</sup> This test has a long shelf life, can be used for testing each site separately, and is used with a range of different concentrations of 4 tastes. It has been shown to be useful in the identification of gustatory deficits in patients with burning mouth syndrome.<sup>16</sup>

Suprathreshold tests are used to assess the patient’s ability to differentiate between different intensities and to estimate the magnitude of suprathreshold loss. Ratings of pleasantness may be of value in the diagnosis of dysgeusia. Although many of the tests are based on ratings using visual analog scales, some of these methods use magnitude-matching procedures. Other tests include identification or discrimination of common taste substances. In addition, gustatory-evoked potentials<sup>17</sup> may be useful in the diagnosis of taste loss, especially in medicolegal cases. Topical anesthesia of the tongue has been reported to be of use in the diagnosis of dysgeusia.<sup>3</sup>

In addition to techniques based on administration of chemicals to the tongue, electrogustometry is frequently used.<sup>18</sup> It is based on the induction of gustatory sensations by means of an anodal electrical direct current. Patients usually report sour or metallic sensations similar to those associated with touching a battery with the tongue. However, although electrogustometry is widely used, there seems to be a poor correlation between electrically and chemically induced sensations.<sup>19</sup>

## ANCILLARY EXAMINATIONS

With the finding of gustatory dysfunction, several electrophysiological tests may be applied to identify abnormalities in the nerve to brainstem pathways, which is of importance in cases of trigeminal neuropathy, multiple sclerosis, and pontine lesions. For example, the blink re-

flex may be used to evaluate the integrity of the pathway trigeminal nerve–pontine brainstem–facial nerve.<sup>20</sup>

Structural imaging is routinely used to investigate lesions in the taste pathway. In particular, using special sequences, magnetic resonance imaging allows visualization of the CNs.<sup>21</sup> Furthermore, it provides significant information in terms of the type and cause of a lesion. Analysis of mucosal blood flow in the oral cavity in combination with the assessment of autonomous cardiovascular factors appears to be useful in the diagnosis of autonomic disorders in burning mouth syndrome<sup>16,22</sup> and in patients with inborn autonomic disorder,<sup>1</sup> both of which are associated with gustatory dysfunction. Cultures are indicated when fungal or bacterial infections are suspected.

In addition, the analysis of saliva should be performed, as it constitutes the environment of taste receptors, including transport of tastes to the receptor and protection of the taste receptor. Typical clinical investigations involve sialometry and sialochemistry.<sup>23</sup>

Compared with other sensory dysfunctions, an interdisciplinary approach combining dental, neurological, and otorhinolaryngological expertise seems to be especially important to effectively diagnose and treat disorders of the sense of taste.<sup>24</sup> Based on teamwork, causes such as sarcoidosis, rheumatoid arthritis, immunological disorders, vitamin B<sub>12</sub> deficiency, dental disorders, salivary dysfunction, and infections are easily diagnosed and treated using an interdisciplinary approach.<sup>13</sup>

#### CLASSIFICATION OF GUSTATORY DYSFUNCTION

Using quantitative measures, taste disorders can be described as ageusia (complete loss of taste), hypogeusia (diminished sense of taste), or hypergeusia (enhanced gustatory sensitivity). Dysgeusia is a qualitative gustatory disturbance relating to a distorted taste perception or to a persistent taste sensation in the absence of stimulation.<sup>5</sup> It seems to be the most common and annoying complaint in self-identified patients with gustatory disorders. Frequently, gustatory stimuli are reported to be different from what they used to be; they are perceived as bitter, sour, or metallic. Taste phantoms (phantogeusia) have been reported in patients with epilepsy and schizophrenia.<sup>25</sup> In clinical practice, many patients are found to have quantitative and qualitative taste disorders.<sup>16</sup>

#### NEUROLOGICAL ENTITIES CAUSING TASTE DISORDERS

The search for the cause of taste dysfunction should bear in mind the following considerations: (1) Is it caused by drugs? (2) Is it caused by local factors, eg, atrophy, injury, or alteration of saliva composition? (3) Is it caused by damage to the peripheral or central nervous system? (4) Is it caused by systemic disease?

#### DRUG-INDUCED GUSTATORY DYSFUNCTION

Many gustatory disorders are induced by drugs. Frequently, patients are aware of this relationship and re-

port on the close temporal relationship between occurrence of the taste disorder and drug intake. Numerous mechanisms of drug-induced gustatory dysfunction have been identified, including deposition of silver sulfate, altered influx of calcium and other ions, chelation or depletion of zinc, disturbed bradykinin catabolism, alteration of second messenger synthesis, and altered prostaglandin metabolism.<sup>26</sup> Lists of drugs that may cause taste problems have been compiled by Schiffman<sup>13</sup> and by Ackerman and Kasbekar.<sup>26</sup> Among others, drugs used to treat epilepsy (carbamazepine, phenytoin sodium, and lamotrigine<sup>27</sup>), spasticity (baclofen), Parkinson disease (levodopa), pseudotumor cerebri (acetazolamide), migraine (triptans<sup>28</sup>), diabetes mellitus (glipizide), and arterial hypertension (captopril and losartan potassium<sup>29</sup>) should be considered as candidates responsible for gustatory dysfunction.

#### PERIPHERAL NEUROLOGICAL CAUSES

Lesions of the peripheral nervous system may be associated with syndromes affecting the facial, glossopharyngeal, or vagal nerve, with the facial nerve affected most frequently. In idiopathic CN VII palsy (Bell palsy), gustatory dysfunction can be the predominant and sometimes earliest symptom.<sup>30</sup> Other causes of CN lesions should be considered, eg, neuritis due to neuroborreliosis or herpes zoster, space-occupying processes in the cerebellopontine angle such as meningioma or neurinoma, or neoplastic processes affecting the submandibular region or the skull base.<sup>13,30</sup> A more frequent cause of CN lesions is dissection of the cervical arteries.<sup>31</sup> In this situation, the caudal CN can be affected itself or with other nerves.<sup>32</sup> Rare causes of the peripheral gustatory system include iatrogenic lesions (eg, following laryngoscopic manipulations<sup>33</sup>), neuralgia, and polyneuropathies (eg, due to diphtheria, porphyria, lupus, or amyloidosis<sup>1,13</sup>).

#### CENTRAL NEUROLOGICAL CAUSES

Gustatory dysfunction due to central lesions is, by definition, the result of a disturbance in the taste pathway originating from the level of the brainstem that includes the solitary tract nucleus up to its cortical representation. An isolated taste disorder due to a central nervous system lesion is rare. In most cases, gustatory symptoms are accompanied by signs and symptoms that, during the acute phase of the disease, are typically more serious than the taste disorder.

With the improvement of imaging methods (eg, functional magnetic resonance imaging and positron emission tomography), new insights into the central gustatory pathway have been possible through the analysis of clinical taste disorder phenomena and their neuroanatomical presentation. After entering the ipsilateral medulla oblongata and synapsing the nucleus tractus solitarii, the gustatory pathway ascends in the central tegmental tract (not, as previously thought, in the medial lemniscus) to the mesencephalon. At this level, some fibers cross to the contralateral side. They ascend farther to the thalamus, where the ventral posteromedial nucleus is the synapsing region (Figure). After synaps-

ing at this level, gustatory fibers project to the corresponding hemisphere, where the insular cortex, frontal operculum, opercular part of the superior temporal gyrus, and inferior part of the precentral and postcentral gyri are crucial projection zones of cortical representations. Therefore, it may be practical to differentiate 3 types of central taste disorders with lesions at the level of the brainstem, thalamus, or cortex.<sup>1</sup>

Brainstem taste disorders appear as ipsilateral hemiageusia or hemihyposgeusia due to lesions of the bulbar tegmentum at the level of the solitary tract or due to a pontine lesion. Frequent causes are demyelinating processes or ischemia and hemorrhage; vascular and traumatic lesion sources should be considered.<sup>1,10</sup> Lesions in the mesencephalon rarely lead to hypogeusia or ageusia.

Thalamic taste disorders have been recognized since 1934, when Adler<sup>34</sup> described a patient with right-sided hemihyposgeusia of the face and right-sided hypogeusia due to an idiopathically diagnosed glioblastoma that infiltrated the left nucleus ventralis posteromedially. This finding indicates that the gustatory pathway is contralaterally represented in the thalamus. More recent investigations in patients who have had strokes indicated that dysgeusia was present contralaterally to a thalamic or corona radiata infarction, thus supporting the idea that gustatory fibers ascend contralaterally in the cerebral hemisphere and that the pathway ascends from the thalamus to the cerebral cortex via the posterior part of the corona radiata.<sup>1</sup> However, there are reports indicating that an ipsilateral lesion of the thalamus can result in hemihyposgeusia,<sup>1</sup> thus supporting the theory that crossing of fibers occurs at the lower brainstem level.

With thalamic lesions, hedonic aspects have to be considered. Particularly in patients with bilateral lesions, the loss of hedonism may result in impaired appreciation of foods, which, in turn, leads to changes in food intake, followed by clinically significant weight loss.<sup>33</sup>

Cortical taste disorder is difficult to detect through patient history or clinical examination. In pharmacoresistant epilepsy, approximately 4% of patients report gustatory auras, probably due to focal abnormalities in the opercular parietal region.<sup>25</sup> These auras are mainly bilateral. In patients treated surgically for hippocampal sclerosis, gustatory auras persisted in many cases.<sup>1</sup> In drug-resistant temporal lobe epilepsy, seizures in all investigated cases were found to invade the insular cortex; a few seizures originated in the insula itself. Clinically, it was not possible to differentiate ictal symptoms between the 2 types of seizures. However, a less accurate estimate of taste intensity was observed in patients with excisions from the left or right anteromedial temporal lobe. This emphasizes the importance of the anterior temporal lobe in gustatory perception; furthermore, in terms of recognition of bitter taste, the right temporal lobe was superior to the left one.<sup>35</sup> Apart from epilepsy, other causes, mainly cerebrovascular and neoplastic, should be considered.<sup>36-39</sup> It is unclear the extent to which gustatory dysfunction related to migraine,<sup>40</sup> schizophrenia, major depression,<sup>1</sup> dementia,<sup>41,42</sup> or eating disorders<sup>43</sup> is based on cortical dysfunction.

## AGING

A discrete taste loss in older persons is frequent but rarely causes significant clinical problems.<sup>44</sup> Following quantitative gustatory testing and appropriate clinical examinations, patients usually can be counseled such that the problem has no life-threatening cause and that the addition of seasonings to foods, tongue cleansing, or cessation of smoking may be helpful remedies.<sup>45</sup>

## NEUROLOGICAL CAUSES WITH UNDETERMINED LOCALIZATION

There are numerous conditions presenting with gustatory dysfunction in which exact localization in the nervous system is not possible. For example, taste disorders have been reported in familial dysautonomia,<sup>1,13</sup> hereditary ataxia,<sup>1</sup> Machado-Joseph disease,<sup>46</sup> and Guillain-Barré syndrome,<sup>1</sup> probably due to dysfunction of small nerve fibers. Taste disorders due to high altitude sickness are hypothesized to be related to hypoxic damage of nerve fibers.<sup>1</sup> Taste disorders are also observed in craniofacial trauma, albeit much less frequently than olfactory disorders.<sup>11</sup> Recently, hypogeusia has been described as a prominent early feature of the new variant of Creutzfeldt-Jakob disease, probably caused by deposits of prions in the central gustatory pathway.<sup>47</sup> Finally, in human rabies virus, antigen was demonstrated in the plexuses of the salivary glands. Therefore, it can be speculated that taste disorder exists in early rabies before fatal encephalomyelitis progresses.<sup>48</sup>

## TREATMENT OF TASTE DISORDERS

As with olfactory disturbances, there are few therapeutic options for gustatory dysfunction. Treatment with zinc sulfate is frequently tried, despite conflicting results of clinical investigations.<sup>49</sup> In addition, corticoids and vitamin A have been used to treat taste disorders, despite a lack of convincing clinical studies. Therefore, in gustatory disorders, the focus is on the search and therapy for possible underlying diseases. For example, local causes need appropriate dental, dermatological, or otorhinolaryngological care; underlying schizophrenia or depression requires psychiatric treatment. This approach also includes a thorough review of drugs taken by the patient. If there is no specific treatment option, zinc gluconate (140 mg/d for 4 months) may provide promising results in idiopathic dysgeusia, according to preliminary data.<sup>50</sup>

In conclusion, a diagnostic armamentarium is available to determine the cause and severity of gustatory dysfunction. However, with few exceptions, appropriate studies on the treatment of gustatory dysfunction are notably missing, a void that should be filled in the near future.

*Accepted for publication December 5, 2002.*

**Author contributions:** *Study concept and design* (Drs J. G. Heckmann, Lang, and Hummel); *drafting of the manuscript* (Dr J. G. Heckmann); *critical revision of the manuscript for important intellectual content* (Drs S. M. Heck-

mann, Lang, and Hummel); *study supervision* (Drs J. G. Heckmann, S. M. Heckmann, Lang, and Hummel).

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