— Current Topics —

Taste and Health: New Frontiers in Oral Physiology and Rehabilitation

Hyposalivation Strongly Influences Hypogeusia in the Elderly

Shizuko Satoh-Kuriwada,*, [a] Noriaki Shoji,[a] Misako Kawai,[b] Hisayuki Uneyama,[b] Naoto Kaneta,[a] and Takashi Sasano[a]

[a]*Division of Oral Diagnosis and Radiology, Department of Oral Medicine and Surgery, Tohoku University Graduate School of Dentistry, 4–1 Seiryo-machi, Aoba-ku, Sendai 980–8575, Japan and* [b]*Institute of Life Sciences, Ajinomoto Co., Inc., 1–1 Suzuki-cho, Kawasaki-ku, Kawasaki 210–8681, Japan*

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Aging is sometimes associated with decreased sensitivity to tastants, *i.e.*, hypogeusia. The loss of taste sense induces not only the decreased quality of life (QOL), but also weight loss or health problems in the elderly. In our recent study, whole saliva secretion including minor salivary secretion, was found to be significantly decreased in the elderly with gustatory impairment, while it was normal in all of the elderly with normal taste thresholds, indicating that hyposalivation is closely related to hypogeusia. Moreover, clinical studies have shown that treatment for hyposalivation alleviates hypogeusia, even that due to the side effects of prescribed drugs or the effects of disease, *e.g.*, nervous disorders or endocrine disorders. Thus, salivation is essential for maintenance of the normal taste function. Many medications for relief of dry mouth, primarily parasympathomimetic drugs, have serious adverse effects such as palpitation, sweating, nausea, diarrhea or dizziness, particularly in the elderly. To circumvent this problem, we use glutamate (umami taste) in an attempt to increase salivary secretion and to alleviate hypogeusia. An umami stimulus might be an effective method for the alleviation of hypogeusia through improvement of hyposalivation or dry mouth without side effects in aged patients. Consequently, attempts should be made to remedy hypogeusia by alleviation of hyposalivation so as to maintain and promote the health of the elderly.

Key words —— hypogeusia, hyposalivation, elderly, whole saliva, minor salivary gland

INTRODUCTION

Aging is associated with a decrease in taste sensitivity.[1–5] Clinically, such decreased sensitivity to tastants, *i.e.*, hypogeusia, is one of the most common complaints in the elderly. Recently, paralleling the increase in the life span of the Japanese population, the number of patients with hypogeusia has been rising.[6–8] Since taste dysfunction due to aging gradually develops, some elderly are not aware of their abnormality of taste perception. Such unawareness may result in weight loss, leading to destruction of the body's resistance or immune system in an extreme case because the taste sense is related to food palatability, which promotes the appetite, intake, absorption and digestion.

Although hypogeusia is due to various factors, it is strongly related to dry mouth,[9] including hyposalivation. Dry mouth is a frequently occurring problem found primarily among the elderly. In a previous study, the percentage of the population who complained of dry mouth was estimated to be 29% in the U.S.A.[10] and 46% in Finland.[11] As for Japanese individuals, according to one report oral dryness was found to occur in 24% of individuals over 65 years of age,[12] while another report put the figure at 56%,[13] indicating a significantly higher

*To whom correspondence should be addressed: Division of Oral Diagnosis and Radiology, Department of Oral Medicine and Surgery, Tohoku University Graduate School of Dentistry, 4–1 Seiryo-machi, Aoba-ku, Sendai 980–8575, Japan. Tel.: +81-22-717-8390; Fax: +81-22-717-8393; E-mail: kurishu@mail.tains.tohoku.ac.jp

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occurrence than for younger individuals. Oral dryness is almost always accompanied by a reduction in the secretion of saliva, *i.e.*, hyposalivation, a condition which predisposes individuals to oral disease, including dental caries and periodontitis, and which often induces dysfunction of speech, chewing and swallowing, as well as decreased taste sensation.[14–17] Accordingly, the quality of life (QOL) of such individuals is significantly disturbed. Realization of the relationship between hypogeusia and hyposalivation is important for preservation and promotion of health in the elderly. Thus, we herein review our previous studies on hypogeusia and hyposalivation in the elderly and propose future research.

EPIDEMIOLOCAL EVIDENCE SUPPORTING A LINK BETWEEN HYPOGEUSIA AND HYPOSALIVATION IN THE ELDERLY

Taste sensory changes associated with advancing age may arise from alterations that are part of normal physiologic aging, or may occur in response to secondary influences such as the side effects of drugs or the effects of some diseases, the latter including periodontal disease/oral infections, nervous disorders including cerebral infarction, nutritional impairment and endocrine disorders.[2, 18, 19] Some drugs may impact taste sensitivity by their direct stimulation of taste receptors, not only by altering the normal transduction process and cellular functions, but also by altering the salivary flow.[20–22] The reduction of saliva seems to be highly related to the decline of taste perception in the elderly because of the high prevalence of systemic disease and its treatment with drugs in such individuals.[23, 24] It is well known that most drugs prescribed for aged people reduce salivary flow as a side effect, including remedies for stomach and bowel disorders, antihypertensives, muscarine blockers, antihistamines, antidepressives, and so on.[25–28]

We epidermiologically surveyed the prevalence and the causes of gustatory impairment in the elderly in order to elucidate the relationship between age and taste sensitivity. We then examined the relationship between the salivary flow rate and the taste threshold in order to confirm whether hyposalivation influences hypogeusia in the elderly.[7, 8]

The subjects were 71 elderly persons (male: n = 19; female: n = 52), 65 to 94 years of age (mean = 80 year old), in 4 homes for senior citizens with proper daily meals arranged by a nutritionist. We obtained informed consent on this project from each subject. Thresholds of the four basic tastes (sweet, salty, sour, and bitter) were respectively measured using the filter paper disc method[29] (Taste Disc®: Sannwa Chemical Laboratory Inc., Aichi, Japan). Salivary flow rate was measured by the gum test,[30] in which saliva secreted upon the chewing of gum was collected for ten minutes. As a result, 24 of the 71 subjects (33.8%) showed slight hypogeusia and 2 subjects (2.8%) showed medium hypogeusia by the filter paper disc method, the taste threshold being high (Fig. 1). All of the subjects with gustatory impairment had some chronic systemic disease, such as gastroenteritis, cerebral infarction, diabetes, hypertension and so on, and had been under appropriate medication. Whole saliva secretion in the subjects with gustatory impairment was significantly decreased, while it was normal in all of the subjects with normal taste thresholds (> 10 ml/10 min: gum test) (Fig. 2). There were no significant sex or age differences in whole saliva secretion in the subjects with gustatory impairment. These results suggest that hyposalivation is closely related to gustatory impairment in the elderly. Consequently, we concluded that saliva is essential for normal taste function. It is usually difficult to taste food in the case of hyposalivation since saliva not only acts as a solvent for chemical stimuli in food but also conveys such stimuli to the taste receptors. Gustatory receptors are covered with a layer of fluid that extends into the taste pores and bathes the receptor surface of the microvilli, resulting in the ability to sense the taste.[31] Our epidemiological study is supported by findings of a basic examination showing that artificial hyposalivation produced by removal of the major salivary glands induced altered taste perception.[32]

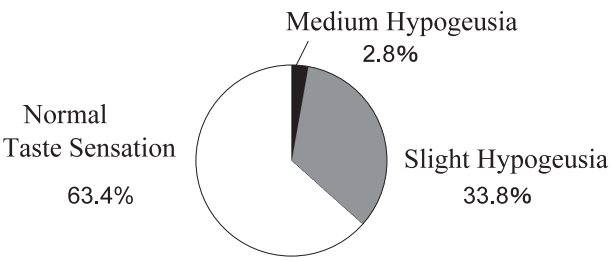

Fig. 1. Results of Gustatory Examination of Elderly People by Means of the Filter Paper Disc Method

Table 1. Results of Initial Gustatory Examination of a Patient with Diabetes Mellitus (Case 1)

Gustatory Examination—Case 1. Initial Examination—										
Electrical Gustatory Method (*dB)			Taste Disc® Method							
			Sweet		Salty		Sour		Bitter	
Measurement Areas	R(Right)	L(Left)	R	L	R	L	R	L	R	L
Chorda tympani N. (Ch. N.)	28	28	5	5	5	5	5	4	5	4
Great.petrosal N. (Gr. N.)	no response		5	5	5	5	5	5	5	4
Glossopharyng. N. (Glo. N.)	no response		5	5	5	5	5	5	4	5

- Normal level of electrical gustatory method: Ch. N. ≦ 8, Gr. N. ≦ 14, Glo. N. ≦ 22
- Normal level of taste disc method
  - No.1–3: normal
  - No.4: slight hypogeusia
  - No.5: medium hypogeusia
  - no response: severe hypoguesia

The underlined numbers show abnormal measurements. *dB: decibel.

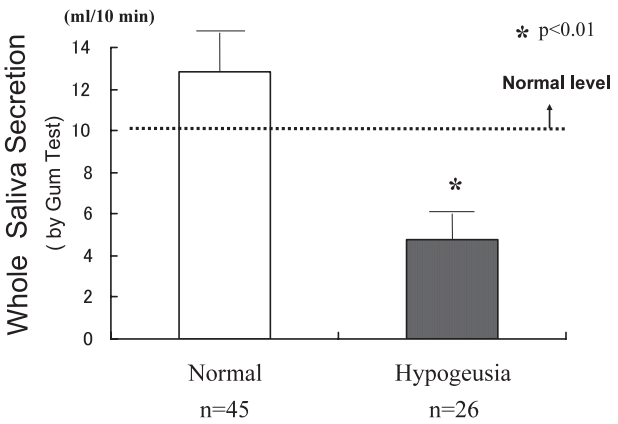

Fig. 2. Relationship between Whole Saliva Secretion and Taste Sensitivity in the Elderly

Whole saliva secretion in subjects with hypogeusia was significantly decreased as compared with that in those with normal taste sensation ($p < 0.01$). Whole saliva secretion was measured by means of the gum test.

CLINICAL CASES OF HYPOGEUSIA IMPROVED BY TREATMENT OF HYPOSALIVATION

We have experienced some cases of hypogeusia which improved as the result of treatment that increased the amount of saliva. In this section, we present two cases of hypogeusia related to systemic diseases and suggest that clinical improvement of the salivary secretion function could be an efficacious remedy not only for improvement of the gustatory disorder, but also for maintenance of healthy life, especially in elderly patients.

Case 1. A Diabetes Mellitus Patient with Hypogeusia

Diabetics are known to suffer from gustatory impairment. They have increased electrical and chemical gustometric thresholds compared with controls.[33] It has clinically been shown that partial improvement of hypogeusia was noted after initiation of antihyperglycemic therapy, indicating the association between gustatory deficits and neuropathy in diabetics.[34] We have recently treated a patient with gustatory deficit who complained of marked decreases in whole salivary flow rate.[35] The taste thresholds for the four basic tastes were obviously high (Table 1), and whole saliva was severely decreased (2.0 ml/10 min: gum test). As blood examination revealed high blood sugar (461 mg/dl), the patient was referred to the Internal Medicine Department with a diagnosis of diabetes mellitus and was immediately admitted to the hospital. Before we determined the patient to be diabetic, we had already started treatment for hyposalivation with a Chinese herbal medicine (*juzen-taiho-to*). Five weeks after commencement of the Chinese herbal remedy (no treatment for diabetes mellitus), his whole salivary flow rate increased (8.0 ml/10 min: gum test) and his abnormal high taste threshold was slightly improved (Table 2, Fig. 3). Furthermore, 7 weeks after commencement of the remedy, his whole salivary flow rate had entirely recovered (10.0 ml/10 min: gum test) and his ability to dis-

Table 2. Results of Gustatory Examination of a Patient with Diabetes Mellitus (Case 1)

Gustatory Examination—Case 1. 5 Weeks After Chinese Herbal Remedy—										
Electrical Gustatory Method (*dB)			Taste Disc® Method							
			Sweet		Salty		Sour		Bitter	
Measurement Areas	R(Right)	L(Left)	R	L	R	L	R	L	R	L
Chorda tympani N. (Ch. N.)	18	18	4	3	3	4	3	3	4	3
Great.petrosal N. (Gr. N.)	22	22	4	3	4	4	3	4	3	3
Glossopharyng. N. (Glo. N.)	28	26	4	4	4	4	4	4	3	3

- Normal level of electrical gustatory method: Ch. N. ≦ 8, Gr. N. ≦ 14, Glo. N. ≦ 22
- Normal level of taste disc method
  - No.1–3: normal
  - No.4: slight hypogeusia
  - No.5: medium hypogeusia
  - no response: severe hypoguesia

5 weeks after treatment for hyposalivation by means of a Chinese herbal medicine. The underlined numbers show abnormal measurements. The taste threshold was slightly improved compared with the initial measurements. *dB: decibel.

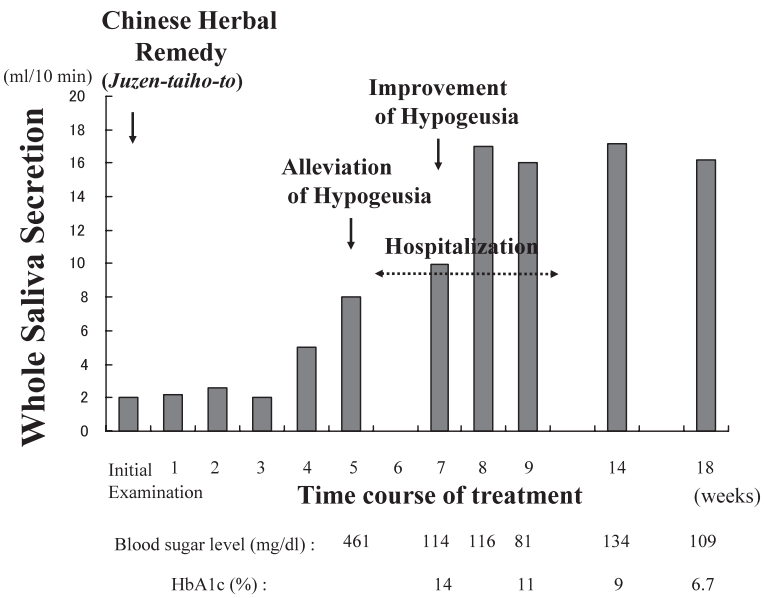

Fig. 3. Improvement of Hypogeusia Following the Increase in Whole Saliva Secretion by Means of a Chinese Herbal Remedy in a Patient with Diabetes Mellitus

Whole saliva secretion was measured by means of the gum test.

tinguish basic tastes had become normal. His taste threshold was then perfectly improved 8 weeks after the remedy for hyposalivation (Table 3, Fig. 3). As shown, it was of interest that patient's taste dysfunction was alleviated before the patient's sugar level became normal following the remedy for diabetes mellitus. This case suggests that the reduced salivary flow rate in patients with diabetes mellitus might be a contributory factor to hypogeusia. This idea is in line with the epidemiologic demonstration by Moor *et al.* in 406 patients with diabetes mellitus and in 268 control subjects, in which the subjects with type 1 diabetes who had developed neuropathy often manifested hypogeusia as well as decreased salivary flow rates.[36)]

Case 2. A Sjögren's Syndrome Patient with Hypogeusia

Sjögren's syndrome (SS) is an autoimmune disease, which predominantly afflicts women after

Table 3. Results of Gustatory Examination of a Patient with Diabetes Mellitus (Case 1)

Gustatory Examination—Case 1. 8 Weeks After Chinese Herbal Remedy—										
Electrical Gustatory Method (*dB)			Taste Disc® Method							
			Sweet		Salty		Sour		Bitter	
Measurement Areas										
	R(Right)	L(Left)	R	L	R	L	R	L	R	L
Chorda tympani N. (Ch. N.)	6	6	2	3	2	2	3	3	2	2
Great.petrosal N. (Gr. N.)	14	14	3	3	2	2	3	3	2	2
Glossopharyng. N. (Glo. N.)	16	16	3	3	3	2	3	3	3	3

- Normal level of electrical gustatory method: Ch. N. ≦ 8, Gr. N. ≦ 14, Glo. N. ≦ 22
- Normal level of taste disc method
  - No.1–3: normal
  - No.4: slight hypogeusia
  - No.5: medium hypogeusia
  - no response: severe hypoguesia

8 weeks after treatment for hyposalivation by means of a Chinese herbal medicine. The taste threshold was completely improved. *dB: decibel.

Table 4. Results of Gustatory Examination of a Patient with Sjögren's Syndrome (SS) (Case 2) on the Initial Examination

Gustatory Examination—Case 2. Initial Examination—										
Electrical Gustatory Method (*dB)			Taste Disc® Method							
			Sweet		Salty		Sour		Bitter	
Measurement Areas										
	R(Right)	L(Left)	R	L	R	L	R	L	R	L
Chorda tympani N. (Ch. N.)	14	16	4	5	4	4	4	4	4	5
Great.petrosal N. (Gr. N.)	22	20	4	4	4	4	4	4	4	5
Glossopharyng. N. (Glo. N.)	no response		4	4	4	4	4	4	4	5

- Normal level of electrical gustatory method: Ch. N. ≦ 8, Gr. N. ≦ 14, Glo. N. ≦ 22
- Normal level of taste disc method
  - No.1–3: normal
  - No.4: slight hypogeusia
  - No.5: medium hypogeusia
  - no response: severe hypoguesia

The underlined numbers show abnormal measurements. *dB: decibel.

middle age. This disease is characterized by progressive destruction of the exocrine glands, including the salivary glands, which results from both lymphocytic infiltration and immune complex deposition. Regarding the relationship between hyposalivation and hypogeusia in SS patients, it has been reported that there is a rather poor correlation between the salivary flow and the degree of taste disturbance, suggesting that a mechanism other than reduced salivary flow alone may be present.[37] Contrary to this report, we encountered a patient with SS (female, 71 years old) whose hypogeusia was remarkably improved following treatment for hyposalivation. Her chief complaint was severe defective taste and mucosal pain, which had lasted for a few decades. The taste thresholds for the four basic tastes were obviously high (Table 4), and the salivary flow rate was severely low (2.0 ml/10 min: gum test). We usually prescribe cevimeline hydrochroride hydrate, an agonist of muscarinic type 1 and 3 receptors,[38] for SS patients based on evidence showing its clinical efficacy in increasing saliva pro-

Table 5. Result of Gustatory Examination of a Patient with SS (Case 2)

Gustatory Examination—Case 2. 12 Months After Treatment—										
Electrical Gustatory Method (*dB)			Taste Disc® Method							
			Sweet		Salty		Sour		Bitter	
Measurement Areas										
	R(Right)	L(Left)	R	L	R	L	R	L	R	L
Chorda tympani N. (Ch. N.)	8	6	3	3	3	3	3	3	3	3
Great.petrosal N. (Gr. N.)	12	14	3	2	3	3	3	3	3	3
Glossopharyng. N. (Glo. N.)	22	22	3	2	3	2	2	3	3	3

- Normal level of electrical gustatory method: Ch. N. ≦ 8, Gr. N. ≦ 14, Glo. N. ≦ 22
- Normal level of taste disc method
  - No.1–3: normal
  - No.4: slight hypogeusia
  - No.5: medium hypogeusia
  - no response: severe hypoguesia

12 months after treatment for hyposalivation by means of cevimeline hydrochloride hydrate. The abnormal taste threshold was completely improved. *dB: decibel.

duction and improving the subjective perception of oral dryness in SS patients.[39,40] After 2 months of the administration, the taste dysfunction and mucosal pain of the patient were mitigated, and after 6 months of the administration, the abnormal high taste threshold had fallen. Then, by 12 months after the administration, the taste threshold had returned to the normal level (Table 5) and mucosal pain was almost completely relieved. However, the whole saliva flow rate did not change and remained at a low level (data not shown). Regarding this result, we considered the salivary flow rate from the minor salivary gland to be more important for improvement of the patient's oral dryness rather than the flow from the major salivary gland. To measure the secretion rate of the minor salivary gland, we have recently reported a new method, the iodine-starch filter paper method.[41] Measurement in this patient using this method showed that minor salivary secretion had increased, accompanied by lessening of both the feelings of dry mouth and hypogeusia (Fig. 4). Thus, this case suggests that increased salivation by the minor salivary gland is effective and important for alleviating hypogeusia.

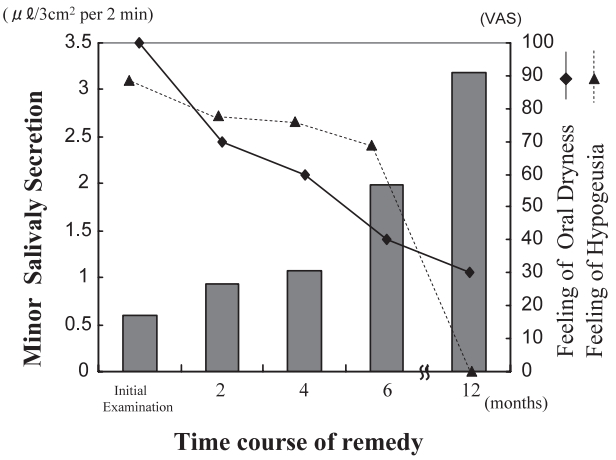

Fig. 4. Improvement of Both the Feeling of Oral Dryness and Hypogeusia Following the Increase in Minor Salivary Secretion by Means of Cevimeline Hydrochloride Hydrate in a Patient with Sjögren's Syndrome

The feeling of oral dryness and hypogeusia were measured by means of VAS, and minor salivary secretion was determined by means of the iodine-starch filter paper method.

ROLE OF SALIVA FOR ORAL TISSUES

As described above, even hypogeusia related to some systemic diseases might be improved by treatment of hyposalivation. Saliva contains many organic components with diverse functions, such as enzymatic action, coating of tissue surfaces, protection of oral tissue, and control of tissue growth, including the tissues having taste receptors (Table 6).[42] For example, there are several proteolytic enzymes (lysozyme, peroxidase, histatin, and so on) as well as thiocyanate ions that attack the bacteria, and aid the thiocyanate ions in entering the bacteria where they become bactericidal. Histatine functions to attack and suppress the growth of

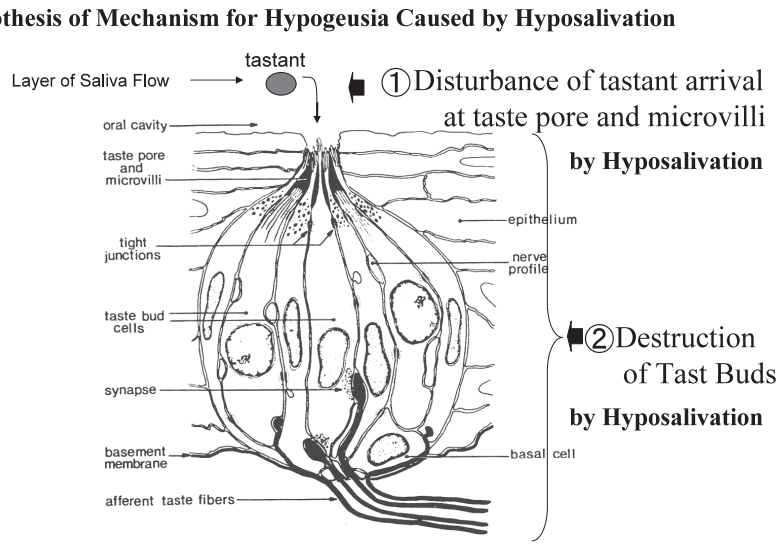

Fig. 5. Hypothesized Mechanisms of Hypogeusia Caused by Hyposalivation

Hypogeusia might be caused by ①Disturbance of tastant arrival at the taste pore and microvili following loss of saliva flow, and/or by ②Destruction of taste receptors based on lack of salivary organic components (mucous glycoproteins, lysozyme, Ig A and so on) contained in saliva.

Table 6. Organic Components of Saliva[42)]

Proteins of acinar cell origin
Amylase
Lipase
Mucous glycoproteins
Proline-rich glycoproteins
Basic glycoprotein
Acidic protein
Tyrosine-rich protein (statherin)
Histidine-rich protein
Peroxidase
Proteins of nonacinar cell origin
Lysozyme
Secretory lgA
Growth factors
Regulatory peptides

candida albicans[43)] and bacteria in periodontal lesions.[44)] Candida is well known to be often related to hyposalivation in the oral cavity of the elderly and to induce various symptoms (hypoguesia, xerostomia, periodontal disease or oral lichen planus).

Patients who have suffered from xerostomia for a long time manifest oral mucous infection with easy bleeding under extreme oral dryness. Mucous glycoproteins secreted in saliva have a high molecular weight. All soft oral tissues are coated with mucous glycoproteins, which are thought to act as a trap for bacteria and a regulator of the interaction and interchange between surface epithelial cells and the oral environment,[42)] in concert with immunoglobulin A,[45)] lysozyme[42)] and other salivary components. Therefore, the decline (or the absence) of salivation often causes infection, resulting in characteristic oral stomatitis, including ulceration of oral tissues, which may predispose to the destruction of taste receptors (Fig. 5).[46)]

EFFECT OF UMAMI TASTE ON SALIVA SECRETION

A large number of systemic agents have been proposed as secretagogues, but only a few have been shown to have consistent salivary enhancing properties in well-designed control trials.[47)] In this situation, some medications (*e.g.*, pilocarpine, bethanecol and cevimeline)[39, 40, 48, 49)] have been clinically selected to activate the pathway of saliva secretion. However, many of these drugs have various adverse effects such as palpitation, sweating, nausea, diarrhea and dizziness due to activation of the receptors for autonomic neurotransmitters (*i.e.*, acetylcholine and noradrenalin), especially in the elderly.[39, 40)]

Umami taste, including glutamate, has been identified as the fifth basic taste[50–52)] and is reported to improve taste perception and palatability.[53)] Recent studies have shown that umami taste is the most potent taste stimulus for saliva secretion from the parotid gland, followed by sour taste.[54, 55)] In addition, the increase in whole salivary secretion

produced by umami taste is the most long-lasting among the five taste stimuli.[56] Recently we have found saliva from the minor salivary gland to be increased by umami taste stimuli to the tongue (data not shown). Consequently, umami stimuli might be considered to be an effective remedy for hypogeusia in the elderly based on improvement of hyposalivation without side effects.

Recently, glutamate receptors have been shown to also exist in the stomach and to act beneficially for the gut function linked to the gastric vagus nerve.[57,58] In this sense, umami is considered to maintain health conditions in the elderly since the nutritional status of such individuals is linked to insufficient energy and nutrient intake. Schiffman has shown that the immune function in the elderly is also improved with the use of monosodium glutamate.[59,60] Thus, application of umami taste for the aged might be a safe and effective remedy to maintain their health condition, including oral health.

CONCLUSION

Decreased sensitivity to tastants (*i.e.*, hypogeusia) is sometimes associated with aging. This consequently affects the quality of life, the primary effect being impairment of the perception of food, and a secondary effect being a lack of nutrition. Age-related deficits in taste sensation also compromise the body's chemosensory resistance and/or the immune system, resulting in health problems. Decline of the taste sense is indisputably related to hyposalivation. Consequently, attempts should be made to remedy hypogeusia based on alleviation of hyposalivation in order to maintain and promote health in the elderly. Umami taste stimulation might be a safe and effective treatment method for this.

REFERENCES

1) Murphy, C. and Gilmore, M. M. (1989) Quality-specific effects og aging on the human taste system. *Percept. Psychophys.*, **45**, 121–128.
2) Schiffman, S. S. and Gatlin, C. A. (1993) Clinical physiology of taste and smell. *Annu. Rev. Nutr.*, **13**, 405–436.
3) Stevens, J. C. (1996) Detection of tastes in mixture with other tastes: issues of making and aging. *Chem. Senses*, **21**, 211–221.
4) Weiffenbach, J. M., Baum, B. J. and Burghauser, R. (1982) Taste thresholds: quality specific variation with human aging. *J. Gerontol.*, **37**, 372–377.
5) Weiffenbach, J. M., Cowart, B. J. and Baum, B. J. (1986) Taste intensity perception in aging. *J. Gerontol.*, **41**, 460–468.
6) Hamada, K., Endo, S. and Tomita, H. (1995) A clinical analysis of patients with taste disorders at our university hospital: with special reference to age and sex distribution. *J. Nihon Univ. Med. Assoc.*, **54**, 529–535.
7) Satoh-Kuriwada, S., Sasano, T., Saito, M., Hasimoto, K., Simeno, Y., Oba, M., Sakamoto, M., Aizawa, K. and Watanabe, M. (2003) Epidemiological study on taste disorders in the elderly. Part 1: Influence of systemic disease and medication on gustatory disorder. *Jpn. J. Oral Diag. Oral Med.*, **16**, 1–8.
8) Satoh-Kuriwada, S., Sasano, T., Saito, M., Simeno, Y., Oba, M., Sakamoto, M., Aizawa, K. and Watanabe, M. (2005) Epidemiological study on gustatory disorders in the elderly. Part 2: Influence of hyposalivation on gustatory disorder. *Jpn. J. Oral Diag. Oral Med.*, **18**, 14–18.
9) Snow, J. B., Jr., Doty, R. L., Bartshuk, L. M. and Getchell, T. V. (1991) Categorization of chemosensory disorders. In *Getchell TV, Doty RL* (Bartshuk, L. M. and Snow, J. B., Jr. Eds.), Smell and taste in health and disease, Raven Press, New York, pp. 445–447.
10) Sreebny, L. M. (1989) Xerostomia (dry mouth). In *The salivary system* (Sreebny, L. M. and Boca Raton, F. L. Eds.), CRC Press, U.S.A., pp. 179–202.
11) Närhi, T. O. (1994) Prevalence of subjective feelings of dry mouth in the elderly. *J. Dent. Res.*, **73**, 20–25.
12) Sakamoto, M., Satoh-Kuriwada, S. and Marumo, M. (1996) Epidemiological study of dry mouth in the elderly. *Jpn. J. Gerodont.*, **11**, 81–87.
13) Kakiki, Y. (2006) Xerostomia in aged persons. *J. Kyushu Dent. Soc.*, **60**, 43–50.
14) Fox, P. C., Busch, K. A. and Baum, B. J. (1987) Subjective reports of xerostomia and objective measures of salivary gland performance. *J. Am. Dent. Assoc.*, **115**, 581–584.
15) Sreebny, L. M. and Valdini, A. (1988) Xerostomia. Part 1: Relationship to nonoral symptoms, drug, and diseases. *Oral Surg. Oral Med. Oral Pathol.*, **68**, 419–427.
16) MacFarlene, T. W. (1990) Ecology and epidemiology of Candida. In *Oral candidosis* (Samaranayake, L. P. and MacFarlane, T. W. Eds.), Wright, London, pp. 21–46.
17) Papas, A. S., Joshi, A., MacDonald, S. L., Maravelis-Splagounias, L., Pretara-Spanedda, P.

and Curro, F. A. (1993) Caries prevalence in xerostomic individuals. *J. Can. Dent. Assoc.*, **59**, 171–179.
18) Wrobel, B. B. and Leopold, D. A. (2004) Clinical assessment of patients with smell and taste disorders. *Otolaryngol. Clin. North Am.*, **37**, 1127–1142.
19) Wrobel, B. B. and Leopold, D. A. (2004) Smell and taste disorders. *Facial Plast. Surg. Clin. North Am.*, **12**, 459–468.
20) Doty, R. L. and Bromley, S. M. (2004) Effects of drugs on olfaction and taste. *Otolaryngol. Clin. North Am.*, **37**, 1229–1254.
21) Cowart, B. J., Young, I. M., Feldman, R. S. and Lowry, L. D. (1997) Clinical disorders of smell and taste. In *Tasting and smelling* (Beauchamp, G. K. and Bartshuk, L. M. Eds.), New York, Academic Press, pp. 175–198.
22) Ackerman, B. H. and Kasbekar, N. (1997) Disturbances of taste and smell induced by drugs. *Pharmacotherapy*, **17**, 482–496.
23) Yui, S., Komori, T., Ito, D., Kobayashi, M., Nakatsuru, M., Tanaka, T., Yanagi, B. and Akagawa, T. (1993) Clinico-statistical observation of the patients during past two years at department of oral surgery. *Jpn. J. Oral Diag. Oral Med.*, **6**, 12–16.
24) Iikubo, M., Kuribara, N., Inukai, K., Onodera, D., Komai, S., Shoji, N., Sugawara, Y., Satoh-Kuriwada, S., Furuuchi, T., Sakamoto, M., Takahashi, K., Kobayashi, K., Marumo, M. and Sasano, T. (1999) Trends of patients newly presenting at our hospital. Part 2. Clinico-statistical study of new patients with systemic disease. *Tohoku Univ. Dent. J.*, **18**, 73–82.
25) Johan, K. M. and Luc, C. M. (2005) Review: The physiology of saliva and transfer of drugs into saliva. *Forensic Sci. Int.*, **150**, 119–131.
26) Kujirai, M., Sawaki, K. and Kawaguchi, M. (2002) Inhibitory effect of diazepam on muscarinic receptor-stimulated inositol 1,4,5-triphosphate production in rat parotid acinar cells. *Br. J. Pharmacol.*, **137**, 945–952.
27) Schubert, M. M. and Izutsu, K. T. (1987) Iatrogenic causes of salivary gland dysfunction. J. Dent. Res., **66**(Spec. Iss.), 680–688.
28) Galili, D., Mallr, O. and Brightman, V. J. (1978) Effects of drug-desalivation on feeding and taste preferences in the rat. *Arch. Oral Biol.*, **23**, 459–464.
29) Tomita, H., Ikeda, M. and Okuda, Y. (1986) Basis and pracice of clinical taste examinations. *Auris Nasus Larynx*, **13**(Suppl.1), S1–S15.
30) Oofuji, T. (1977) Annual report of the ministry of health and welfare sjögren's disease research committee, Japan.
31) Bradley, R. M. (1991) *Salivary secretion*. In *Smell and taste in health and disease* (Getchell, T. V., Doty, R. L., Bartoshuk, L. M. and Snow, Jr., J. B. Eds.), New York, Raven Press, pp. 127–144.
32) Galili, D., Maller, O. and Brightman, V. J. (1981) The effects of desalivation by duct ligation or salivary gland extirpation on taste preference in rats. *Arch. Oral Biol.*, **26**, 853–858.
33) Le Floch, J. P., Le Lievre, G., Verroust, J., Philippon, C., Peynegre, R. and Perlemuter, L. (1990) Factors related to the electric taste threshold in type 1 diabetic patients. *Diabet. Med.*, **7**, 526–531.
34) Perros, P., MacFarlane, T. W., Counsell, C. and Frier, B. M. (1996) Altered taste sensation in newly-diagnosed NLDDM. *Diabetes Care*, **19**, 768–770.
35) Satoh-Kuriwada, S., Sasano, T. and Sakamoto, M. (2006) A case of taste disorder following diabetes mellitus improved by juzen-taiho-to. *Jpn. J. Oral Diag. Oral Med.*, **19**, 109–114.
36) Moore, P. A., Guggenheimer, J., Etzel, K. R., Weyant, R. J. and Orchard, T. (2001) Type 1 diabetes mellitus, xerostomia, and salivary flow rates. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.*, **92**, 281–291.
37) Weiffenbach, J. M., Schwartz, L. K., Atkinson, J. C. and Fox, P. C. (1995) Taste performance in Sjögren's syndrome. *Physiol. Behav.*, **57**, 89–96.
38) Iwabuchi, Y., Katagiri, M. and Masuhara, T. (1994) Salivary secretion and histopathological effects after single administration of the muscarinic agonist SNI-2011 in MRL/lpr mice. *Arch. Int. Pharmacodyn. Ther.*, **328**, 315–325.
39) Fife, R. S., Chase, W. F., Dore, R. K., Wiesenhutter, C. W., Lockhart, P. B., Tindall, E. and Suen, J. Y. (2002) Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. *Arch. Intern. Med.*, **162**, 1293–1300.
40) Petrone, D., Condemi, J. J., Fife, R., Gluck, O., Cohen, S. and Dalgin, P. (2002) A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum.*, **46**, 748–754.
41) Shoji, N., Sasano, T., Inukai, K., Satoh-Kuriwada, S., Iikubo, M., Furuuchi, T. and Sakamoto, M. (2003) A simple, yet accurate method for detecting and quantifying secretions from human minor salivary glands using the iodine-starch reaction. *Arch. Oral Biol.*, **48**, 761–765.
42) Ellison, S. A. (1979) Identification of salivary components. In *Saliva and dental caries* (Kleinberg, I., Ellison, S. A. and Mandel, I. D. Eds.), Information Retrieval, New York, pp. 13–29.

43) Helmerhorst, E. J., Breeuwer, P., van't Hof, W., Walgreen-Weterings, E., Oomen, L. C., Veerman, E. C., Amerongen, A. V. and Abee, T. (1999) The cellular target of histatin 5 on *Candida albicans* is the energized mitochondrion. *J. Biol. Chem.*, **274**, 7286–7291.
44) Gusman, H., Leon, C., Helmerhorst, E. J., Potempa, J., Troxler, R. F. and Oppenheim, F. G. (2001) Salivary histatin 5 is an inhibitor of both host and bacterial enzymes implicated in periodontal disease. *Infect. Immun.*, **69**, 1402–1408.
45) Sivarajasingam, V. and Drummond, J. R. (1995) Measurements of human minor salivary gland secretions from different oral sites. *Arch. Oral Biol.*, **40**, 723–730.
46) Mistrerra, C. M. (1989) Anatomy and neurophysiology of the taste system in aged animals. *Ann. N. Y. Acad. Sci.*, **561**, 277–290.
47) Fox, P. C. (2004) Salivary enhancement therapies. *Caries Res.*, **38**, 241–246.
48) Fox, P. C., Baum, van der Ven, B. J. and Mandel, I. D. (1986) Pilocarpine for the treatment of xerostomia associated with salivary gland dysfunction. *Oral Surg. Oral Med. Oral Pathol.*, **61**, 243–245.
49) Bymaster, F. P., Carter, P. A., Yamada, M., Gomeza, J., Wess, J., Hamilton, S. E., Nathanson, M. M., Mckinzie, D. L. and Felder, C. C. (2003) Role of specific muscarinic receptor subtypes in cholinergic parasympathometic responses, in vivo phosphoinositide hydrolysis, and pilocarpine-induced seizure activity. *Eur. J. Neurosci.*, **17**, 1403–1410.
50) Ikeda, K. (1908) Japanese patent 14805.
51) Nelson, G., Chandrashekar, J., Hoon, M. A., Feng, L., Zhao, G., Ryba, N. J. and Zuker, C. S. (2002) An amino-acid taste receptor. *Nature*, **416**, 199–202.
52) Li, X., Staszewski, L., Xu, H., Durick, K., Zoller, M. and Adler, E. (2002) Human receptors for sweet and umami taste. *Proc. Natl. Acad. Sci. U.S.A.*, **99**, 4692–4696.
53) Yamaguchi, S. and Kimizuka, A. (1979) Psychometric studies on the taste of monosodium glutamate. In *Glutamic Acid: Advances in Biochemistry and Phusiology* (Fler, L. J. Jr., Garattini, S., Kare, M. R., Reynolds, W. A. and Wurtman, R, J. Eds.), Raven Press, New York, pp. 35–54.
54) Hodson, N. and Linden, R. (2006) The effect of monosodium glutamate on parotid salivary flow in comparison to the response to representatives of the other four basic tastes. *Physiol. Behav.*, **89**, 711–717.
55) Horio, T. and Kawamura, Y. (1989) Salivary secretion induced by umami taste. *Jpn. J. Oral Biol.*, **31**, 107–111.
56) Hayakawa, Y., Kawai, M., Torii, K. and Uneyama, H. (2008) The effect of umami taste on saliva secretion. *Jpn. J. Taste Smell Res.*, **15**, 367–370.
57) Uneyama, H., Niijima, A., San Gabriel, A. and Torii, K. (2006) Luminal amino acid sensing in the rat gastric mucosa. *Am. J. Physiol.*, **291**, G1163–G1170.
58) Somekawa, S., Yamada, M., Hayashi, N. and Kokubo, Y. (2007) Diretary free glutamate preventdiarrhea during intragastric tube feeding in rat model. *J. Parenter. Enteral. Nutr.*, **31**, S48–S49.
59) Schiffman, S. S. and Warwock, Z. S. (1993) Effect of flavor enhancement of foods for the elderly on nutritional status: food intake, biochemical indices, and anthroropometric measures. *Physiol. Behav.*, **53**, 395–402.
60) Schiffman, S. S. (1998) Sensory enhancement of foods for the elderly with monosodium glutamate and flavors. *Food Rev. Int.*, **14**, 321–333.