Current Topics

Taste and Health: Nutritional and Physiological Significance of Taste Substances in Daily Foods

Role Played by Afferent Signals from Olfactory, Gustatory and Gastrointestinal Sensors in Regulation of Autonomic Nerve Activity

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Afferent signals from the olfactory system, gustatory system and gastrointestinal (GI) tract control visceral functions such as oral and gut secretions and several digestive, endocrine, thermogenic, cardiovascular and renal responses *via* autonomic reflexes. It is well known that odors and tastes, such as umami, can stimulate oral and GI secretions to improve food intake and digestion in a process termed the cephalic phase response. The perception of GI nutrients, such as carbohydrates and amino acids, can control food digestion, absorption and utilization *via* the vago-vagal reflex during a meal. Recent advances in understanding the molecular physiology of taste indicate that taste receptors able to sense such nutrients are widely distributed in the GI tract, including the oral cavity. These receptors act as nutrient sensors to trigger food digestion, the release of GI peptides and the formation of food preferences. In this paper, we review recent evidence on the regulation of GI functions by the autonomic nervous system *via* peripheral odor and nutrient sensors.

Key words autonomic reflex; vagus nerve; sympathetic nerve; gastrointestinal; olfactory; gustatory

1. INTRODUCTION

The autonomic nervous system is composed of the sympathetic nervous system and the parasympathetic (vagal) nervous system and regulates the involuntary functions of various organs. These regulations are mediated by sensory stimulations, such as olfactory, gustatory, gastrointestinal stimuli and others, which make up the autonomic reflex and contribute to the maintenance of body homeostasis. Generally, it is understood that the cephalic phase response is mainly caused by the taste and smell of food and controls several visceral functions *via* the autonomic reflex, but this reflex is also caused by general stimulation from light and auditory stimuli. Nijima *et al.* reported that in anesthetized rats, exposure of one eye to light enhanced the efferent activities of the pancreatic, hepatic, splenic, adrenal, and renal branches of the sympathetic nervous system and suppressed those of the vagal pancreatic, hepatic, and gastric branches of the vagus nerve. However, no change in the activity of these nerves was observed upon light stimulation in rats with lesions of the hypothalamic suprachiasmatic nucleus (SCN).^{1,2)} In addition, light stimulation significantly elevated both renal sympathetic nerve activity and plasma corticosterone levels in wild-type mice; however, both responses were almost completely abolished in mice that were deficient in the pituitary adenylate cyclase-activating polypeptide, which is a transmitter involved in the signal transduction of light stimulation in the SCN.³⁾ These observations suggest that light stimulation modulates visceral functions, including metabolic processes, through the retino-hypothalamic tract, SCN, and vagal and sympathetic efferent pathways that innervate the pancreas, liver, stomach, spleen, adrenal medulla, and kidney. Thus, the autonomic reflex plays a role in the regula-

tion of visceral functions. In this paper, we describe a role for olfactory, gustatory and gastrointestinal stimulation, which are closely associated with daily diet, in the regulation of autonomic nervous system activity.

2. OLFACTORY STIMULI REGULATE AUTONOMIC NERVOUS SYSTEM ACTIVITY

The act of smelling produces physiological effects such as salivation, increasing appetite, and improving the emotional state. Because food smells are composed of many odorants, we will focus on two odorants that cause different autonomic reflex responses. One is grapefruit oil, which has excitatory effects, and the other is lavender oil, which has inhibitory effects. Olfactory stimulation with the scent of grapefruit oil (SGFO) or the scent of limonene, a component of grapefruit oil, excited the sympathetic efferent nerve that innervates the white adipose tissue (WAT), the brown adipose tissue (BAT), adrenal gland and kidney and inhibited vagal gastric efferent (VGE) nerve activity in rats⁴⁻⁶⁾ (Fig. 1) and mice.⁷⁾ Moreover, stimulation with the SGFO and the scent of limonene elevated plasma glycerol levels and blood pressure (BP). Treatment with either ZnSO₄ (used for treatment of anosmia) or intraperitoneal or intracranial injection of diphenhydramine (a histamine H1 receptor-antagonist) abolished the SGFO- or scent of limonene-mediated increases in plasma glycerol, sympathetic renal efferent (SRE) nerve activity and BP, as well as the decrease in VGE activity in rats.^{5,6)} Furthermore, a 15-min exposure to the SGFO or the scent of limonene three times a week reduced food intake and body weight.^{5,6)} Interestingly, bilateral lesions of the SCN eliminated these SGFO- and limonene-mediated effects.⁶⁾ In fact, studies that utilized the pseudorabies virus, which is trans-

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Fig. 1. Effects of Olfactory Stimulation with the Scent of Grapefruit Oil (SGFO) and Lavender Oil (SLVO) on Neuronal Activity of the Vagal Gastric Nerve and the Sympathetic Nerves That Innervate the Epididymal Adipose Tissue, Interscapular Adipose Tissue, and Adrenal Gland

Representative recordings of nerve activity in a rat stimulated with water, grapefruit oil (GF) or lavender oil (LV) are shown. Upper bars indicate the 10-min stimulation period, lower bars represent 30 min, and vertical scale bars to the left of the recordings represent neuronal discharge rates of 100 spikes/5 s. Figure reproduced from Shen *et al.*^{5,10}

ported into the brain in a retrograde and polysynaptic manner, provide evidence that the SCN is a control center for autonomic nerves.^{8,9}

Olfactory stimulation with the scent of lavender oil (SLVO) or the scent of linalool, a component of lavender oil, inhibits the activity of the sympathetic efferent nerves that innervate WAT, BAT, adrenal glands and kidneys and excites VGE activity in both rats^{10,11} (Fig. 1) and mice.⁷ Treatment with ZnSO₄ eliminated the autonomic changes caused by the SLVO and the scent of linalool in rats.¹⁰ Moreover, stimulation with the SLVO and the scent of linalool lowered plasma glycerol levels and BP, and treatment with either ZnSO₄ or an intracranial injection of thioperamide (a histamine H3 receptor-antagonist) abolished these effects.^{10,11} Furthermore, a 15-min daily exposure to the SLVO and the scent of linalool increased food intake and body weight.¹⁰ Bilateral lesions of the SCN eliminated the suppression of SRE activity and BP and the elevation of VGE activity caused by the SLVO or linalool.¹¹

Both SGFO- and SLVO-induced reflexes were abolished by bilateral lesions of the SCN. Therefore, using clock gene knockout mice, Tanida *et al.* examined whether molecular mechanisms in the SCN are responsible for control of the autonomic reflex.^{7,12} SGFO-induced elevations in SRE activity and BP and SLVO-induced increases in VGE activity were not observed in cryptochrome (Cry)-deficient mice, which harbor mutations in both *cry1* and *cry2* and lack normal circadian rhythms.⁷ This finding suggests that the molecular clock mechanism in the SCN, which involves the *cry1* and *cry2* genes, is partially involved in mediating the autonomic and cardiovascular effects of the SGFO and the SLVO. Interestingly, SGFO-induced elevations in SRE activity and BP were not observed in *Clock* mutant mice, which lack normal circadian rhythms, whereas SLVO-based suppressions were preserved.¹² This finding implicates the *Clock* gene in elevating autonomic and cardiovascular functions to olfactory stimulation in response to the SGFO. These observations indicate that olfactory stimulation modulates visceral functions including metabolic processes through the SCN and that the *Clock* gene, histaminergic neurons, and the vagal and sympathetic efferent pathways that innervate WAT, BAT, stomach, spleen, adrenal medulla and kidney are involved.

Fig. 2. The Effect of Reflex Activation of Vagal Gastric and Pancreatic Nerve Activity from Oral, Gastric, Intestinal and Hepatoportal Glutamate Sensors

Figure was cited from Nijijima.²⁴

3. GUSTATORY STIMULI REGULATE AUTONOMIC NERVE ACTIVITY

Similar to olfactory stimulation, taste sensations affect various visceral efferent nerve activities and functions. Salivary secretion is well known to be one of the taste-induced autonomic reflexes.¹³ The role of saliva is not only to lubricate food for swallowing but also to initiate the digestion of starch and fats because it contains the enzymes amylase and lipase. In addition, there are various reports describing taste-induced reflexes. Sweet taste stimulation with sucrose and glucose solution increases the efferent activity of the pancreatic and the hepatic vagus nerve in rats, whereas a salty taste solution containing a high concentration of sodium chloride (NaCl) suppresses such activity.^{14–17} In addition, sweet taste stimulation elicits insulin release prior to increasing plasma glucose levels, a process called cephalic phase insulin release.^{18–20} In contrast, sweet taste stimulation was observed to suppress VGE activity and the efferent activity of the adrenal, pancreatic and hepatic sympathetic nerves, whereas salty taste stimulation was shown to increase these activities.^{16,21} Moreover, sweet taste signals stimulate gastric acid secretion *via* the vagus nerve.²² Another taste stimulation, umami, produced by a monosodium glutamate (MSG) solution, was able to activate VGE activity and the efferent activity of the pancreatic and hepatic vagus nerves^{17,23,24} (Fig. 2), in association with an increase in insulin secretion.²⁵ However, it has been reported that MSG does not elicit cephalic phase insulin release,²⁶ so further study will be necessary. Altogether, taste sensation induces the reflex of salivary, gastric, and insulin secretion, which is important for metabolism and the digestion and absorption of food.

4. GASTROINTESTINAL STIMULI REGULATE AUTONOMIC NERVOUS SYSTEM ACTIVITY

In the gastrointestinal (GI) tract, various nutrients are detected and absorbed through the luminal mucosa. Nutrients also regulate the activity of vagal afferent nerves and the release of GI peptides, including cholecystokinin, peptide YY, glucagon-like peptide-1, leptin, ghrelin and others.^{27–30}

It was thought for a long time that the vagal gastric affer-

ents in the stomach could detect only gastric distension and not individual nutrients. Glucose and isotonic NaCl solutions did not activate the vagal gastric afferent nerve in rats.^{31,32} Mathis *et al.* also reported that rat gastric afferents were activated in a volume-dependent manner by intragastric liquid loading, but the intensity of the afferent activation was not changed by nutrient composition (saline, carbohydrate or protein).³³ However, we have reported that glutamate evoked visceral sensation in the stomach.²⁴ This report is impressive to the field of gastric nutrient perception, because these data strongly suggest that chemical perception, and in particular an amino acid-sensing system, exists in the gastric mucosa. Interestingly, among the 20 amino acids, rat gastric afferents can be stimulated only by glutamate (Fig. 3). Luminal perfusion with the local anesthetic lidocaine abolished the glutamate-evoked gastric afferent activation, indicating that this response is a chemical event within the gastric mucosa. Furthermore, the glutamate response was blocked by depletion of serotonin (5-HT) and by inhibition of 5-HT₃ receptors or the nitric oxide (NO) synthase enzyme. The afferent response was also mimicked by luminal perfusion with the NO donor sodium nitroprusside. In addition, NO donor-induced afferent activation was abolished by 5-HT₃ receptor blockage.³² This finding strongly supports the possibility of intercellular communication between mucosal cells and the vagus nerve using NO and 5-HT in the rat gastric mucosa. More than 90% of 5-HT throughout the body is localized in the enterochromaffin (EC) cells of the GI mucosa. The physiological role of mucosal 5-HT released from EC cells serves a paracrine function by specifically recognizing glutamate in the lumen of the stomach, similarly to the role reported in duodenal glucose-sensing.

Our understanding of the sensing of nutrients by the gut is based on the "intestinal sensor cell hypothesis" originally proposed in the 1970s by Fujita *et al.*³⁴ This hypothesis states that nutrient-sensing cells are distributed in the gastric antrum or duodenal mucosa and that when these cells interact with luminal nutrients, they release hormones in an en-

docrine or paracrine manner to transfer information about luminal nutrient content to other organs, including the brain, via endocrine or vagal pathways. However, the cells involved in gut nutrient perception remained unidentified for a long time. In 1996, Höfer *et al.* suggested that taste-like cells similar to the taste cells in the oral cavity are distributed in the gastric and intestinal mucosa and proposed that these taste-like cells represent the unknown sensor cells.³⁵ Subsequently, with the development of molecular biology techniques in the field of taste research, several taste receptors that sense amino acids have been identified. We now know that metabotropic glutamate receptors (mGluRs), such as mGluR1 and mGluR4, a calcium sensing receptor (CaSR), and a taste receptor (the T1R1/T1R3 complex) are linked to amino acid sensation in the tongue. These receptors are also candidates for luminal amino acid sensors. San Gabriel *et al.* reported that mGluR1 is located in the glandular stomach. Their report suggested the possibility that glutamate is sensed by mGluR1, which conveys sensory information to vagal afferent nerves.³⁶ Although the molecule that senses glutamate in the gastric mucosa is still unknown, intragastric infusion of MSG causes a vago-vagal reflex, which increases VGE and vagal pancreatic efferent nerve activity²⁴ (Fig. 2). In addition, using a functional magnetic resonance imaging (fMRI) technique, it has been revealed that the intragastric infusion of MSG induces activation in forebrain regions, including the cortex, hypothalamus, and limbic areas in rats.³⁷ Assuming there is a universal coexistence of free glutamate with dietary protein, these findings suggest that a glutamate-sensing system in the stomach could contribute to the gastric phase of protein digestion, and integrating nutrient information in the brain.

In contrast to what occurs in the small intestine, there are many reports that intraduodenal infusion of amino acids or oligopeptides alters vagal celiac afferent activity. Sharma and Nasset observed an apparent increase in mesenteric afferent activity in either whole-nerve or multifiber preparations from the GI tract following amino acid infusions in cats.³⁸ Using a unitary recording technique in the nodose ganglion, Jeannigros and colleagues subsequently revealed the response of the vagal celiac afferent nerve to amino acid infusions in the cat small intestine in detail. Their report described many sensors sensitive to arginine, leucine and other amino acids.^{39,40} Recently, we re-examined the luminal amino acid sensitivity of vagal celiac afferents in rats. Intraintestinal infusion of MSG, lysine, leucine, and other amino acids evoked excitatory responses in vagal celiac afferents.⁴¹ In contrast to these amino acids, intraintestinal infusion of glycine, methionine, and certain other amino acids led to the depression of afferent nerve activity.⁴¹ In rats, duodenal infusions of protein hydrolysates also increased mesenteric afferent activity.^{42,43} Schwartz *et al.* revealed that duodenal protein hydrolysates (*i.e.*, peptone) stimulated celiac afferents, indicating that an amino acid or oligopeptide sensor might exist in the rat duodenum.⁴³ However, the mechanisms underlying such sensation are not fully understood, and further research will be needed.

Changes in vagal celiac afferent activity induce the autonomic reflex and regulate visceral functions along with other stimulations. Intraintestinal infusions of MSG resulted in an increase in VGE, vagal pancreatic efferent activity,^{23,24} and

Fig. 3. Vagal Gastric Afferent Responses to Intragastric Infusion of Various Amino Acids

Each aqueous solution (150 mmol/l, 2 ml) was introduced into the rat stomach, and the mean discharge rate above baseline at 20 min was plotted. Each column and horizontal bar represents mean $\pm$ S.E.M. from 5 rats. ** $p < 0.05$ vs. saline (Kruskal-Wallis test). Figure was cited from Uneyama *et al.*³²

Fig. 4. Afferent Signals from Olfactory, Gustatory and Gastrointestinal Sensors Regulate Efferent Autonomic Nerve Activity

Sensory stimulations from food lead to the activation of physiologic processes in visceral organs, helping to optimize the digestion, absorption, and use of ingested nutrients.

lysine evoked long-lasting enhancement of VGE activity.⁴¹⁾ On the other hand, the intrainestinal infusion of glycine inhibited VGE activity.⁴¹⁾ In addition, introduction of a glucose solution into the intestine increased vagal celiac afferent activity; the sensing mechanism underlying glucose effects has been described in another review.⁴⁴⁾ Glucose solution also suppressed sympathetic adrenal efferent activity and enhanced vagal pancreatic efferent activity.⁴¹⁾ These observations support the hypothesis that vagal GI afferent signals regulate gastrointestinal motility, metabolic activity, and food intake.^{45,46)}

5. CONCLUSIONS

In a daily diet, smell- and taste-inducing chemicals in food activate olfactory, gustatory and GI sensors and trigger the autonomic reflex, which contributes to the processes of metabolism, digestion, absorption and other physiological functions (Fig. 4). Therefore, it is very important that we enjoy the smell of food and eat foods rich in flavor. The environment of the meal is also important; recent reports have shown that music (*Träumerei*, composed by Schumann) decreased SRE activity and BP and increased VGE activity in rats.^{47,48)} This finding suggests that eating meals in a relaxing environment is beneficial for food digestion. The processes of the autonomic reflex suggest that we should take special care to enjoy our meals and to eat and live healthily.

REFERENCES

- Nijijima A., Nagai K., Nagai N., Nakagawa H., *J. Auton. Nerv. Syst.*, **40**, 155–160 (1992).
- Nijijima A., Nagai K., Nagai N., Akagawa H., *Physiol. Behav.*, **54**, 555–561 (1993).
- Hatanaka M., Tanida M., Shintani N., Isojima Y., Kawaguchi C., Hashimoto H., Kakuda M., Haba Y., Nagai K., Baba A., *Neurosci. Lett.*, **444**, 153–156 (2008).
- Nijijima A., Nagai K., *Exp. Biol. Med.*, **228**, 1190–1192 (2003).
- Shen J., Nijijima A., Tanida M., Horii Y., Maeda K., Nagai K., *Neurosci. Lett.*, **380**, 289–294 (2005).
- Tanida M., Nijijima A., Shen J., Nakamura T., Nagai K., *Brain Res.*, **1058**, 44–55 (2005).
- Tanida M., Yamatodani A., Nijijima A., Shen J., Todo T., Nagai K., *Neurosci. Lett.*, **413**, 177–182 (2007).
- Buijs R. M., Chun S. J., Nijijima A., Romijn H. J., Nagai K., *J. Comp. Neurol.*, **431**, 405–423 (2001).
- Buijs R. M., La Fleur S. E., Wortel J., Van Heyningen C., Zuiddam L., Mettenleiter T. C., Kalsbeek A., Nagai K., Nijijima A., *J. Comp. Neurol.*, **464**, 36–48 (2003).
- Shen J., Nijijima A., Tanida M., Horii Y., Maeda K., Nagai K., *Neurosci. Lett.*, **383**, 188–193 (2005).
- Tanida M., Nijijima A., Shen J., Nakamura T., Nagai K., *Neurosci. Lett.*, **398**, 155–160 (2006).
- Tanida M., Shen J., Nijijima A., Yamatodani A., Oishi K., Ishida N., Nagai K., *Auton. Neurosci.*, **139**, 1–8 (2008).
- Hector M. P., Linden R. W., “Neural Mechanisms of Salivary Secretion,” ed. by Garrett J. R., Ekstrom J., Anderson L. C., Karger, Basel, 1999, pp. 196–217.
- Nijijima A., “Integrative Functions of the Autonomic Nervous System,” ed. by Brooks C. McC., Koizumi K., Sato A., University of Tokyo Press, Tokyo and Elsevier/North-Holland Biomedical Press, Amsterdam, 1979, pp. 68–83.
- Nijijima A., *Brain Res. Bull.*, **26**, 161–164 (1991).
- Nijijima A., *Brain Res. Bull.*, **26**, 165–167 (1991).
- Nijijima A., *Brain Res. Bull.*, **27**, 393–396 (1991).
- Louis-Sylvestre J., *Am. J. Physiol.*, **230**, 56–60 (1976).
- Steffens A. B., *Am. J. Physiol.*, **230**, 1411–1415 (1976).
- Strubbe J. H., Steffens A. B., *Am. J. Physiol.*, **229**, 1019–1022 (1975).
- Jiang Z. Y., Nijijima A., *Neurosci. Lett.*, **69**, 42–46 (1986).
- Ikuno H., Sakaguchi T., *Brain Res. Bull.*, **25**, 429–431 (1990).
- Nijijima A., *Physiol. Behav.*, **49**, 1025–1028 (1991).
- Nijijima A., *J. Nutr.*, **130**, 971S–973S (2000).
- Nijijima A., Togiya T., Adachi A., *Physiol. Behav.*, **48**, 905–908 (1990).
- Tonosaki K., Hori Y., Shimizu Y., Tonosaki K., *Biomed. Res.*, **28**, 79–83 (2007).
- deFonseca A., Kaunitz J., *Curr. Gastroenterol. Rep.*, **11**, 442–447 (2009).
- Kitamura A., Nijijima A., Torii K., Uneyama H., “Horizons in Neuroscience Research,” Volume 1, ed. by Costa A., Villalba E., Nova Science Publishers, Inc., New York, 2010, pp. 367–377.
- Raybould H. E., Glatzle J., Freeman S. L., Whited K., Dracel N., Liou A., Bohan D., *Auton. Neurosci.*, **125**, 28–33 (2006).
- Rozengurt E., Sternini C., *Curr. Opin. Pharmacol.*, **7**, 557–562 (2007).

- (2007).
- 31) Clarke G. D., Davison J. S., *J. Physiol.*, **284**, 55—67 (1978).
- 32) Uneyama H., Nijima A., San Gabriel A., Torii K., *Am. J. Physiol.*, **291**, G1163—G1170 (2006).
- 33) Mathis C., Moran T. H., Schwartz G. J., *Am. J. Physiol.*, **274**, R280—R286 (1998).
- 34) Fujita T., Kobayashi S., Yui R., *Adv. Biochem. Psychopharmacol.*, **25**, 321—325 (1980).
- 35) Höfer D., Püschel B., Drenckhahn D., *Proc. Natl. Acad. Sci. U.S.A.*, **93**, 6631—6634 (1996).
- 36) San Gabriel A. M., Maekawa T., Uneyama H., Yoshie S., Torii K., *FEBS Lett.*, **581**, 1119—1123 (2007).
- 37) Tsurugizawa T., Uematsu A., Nakamura E., Hasumura M., Hirota M., Kondoh T., Uneyama H., Torii K., *Gastroenterology*, **137**, 262—273 (2009).
- 38) Sharma K. N., Nasset E. S., *Am. J. Physiol.*, **202**, 725—730 (1962).
- 39) Jeanningros R., Mei N., *Reprod. Nutr. Dévelop.*, **20**, 1615—1619 (1980).
- 40) Jeanningros R., *Physiol. Behav.*, **28**, 9—21 (1982).
- 41) Nijima A., Torii K., Uneyama H., *Chem. Senses*, **30** (Suppl. 1), i178—i179 (2005).
- 42) Eastwood C., Maubach K., Kirkup A. J., Grundy D., *Neurosci. Lett.*, **254**, 145—148 (1998).
- 43) Schwartz G. J., Moran T. H., *Am. J. Physiol.*, **274**, R1236—R1242 (1998).
- 44) Raybould H. E., *Auton. Neurosci.*, **133**, 86—90 (2007).
- 45) Mei N., *Physiol. Rev.*, **65**, 211—237 (1985).
- 46) Schwartz G. J., *Nutrition*, **16**, 866—873 (2000).
- 47) Nakamura T., Tanida M., Nijima A., Hibino H., Shen J., Nagai K., *Neurosci. Lett.*, **416**, 107—112 (2007).
- 48) Nakamura T., Tanida M., Nijima A., Nagai K., *in vivo*, **23**, 415—420 (2009).