Basic Characteristics of Glutamate and Umami Sensing in the Oral Cavity and Gut

Reflex Effects of Oral, Gastrointestinal and Hepatoportal Glutamate Sensors on Vagal Nerve Activity 1

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ABSTRACT Glutamate sensors in the oral cavity, gastrointestinal canal and hepatoportal region are thought to function in the reflex regulation of vagal activity to the gastrointestinal tract and pancreas. In support of this notion, the findings summarized in this report demonstrate that the infusion of monosodium glutamate (MSG) into the stomach (150 mmol/L, 3 mL), duodenum (150 mmol/L, 3 mL) and portal vein (10 mmol/L, 0.1 mL) increases afferent activity in the vagal gastric, celiac and hepatic nerves, suggesting the existence of glutamate sensors in the gastric wall, intestinal wall and hepatoportal region. Further, oral, gastric and intestinal infusions of MSG (150 mmol/L, isotonic solution) and the infusion of MSG (10 mmol/L, 0.1 mL) into the portal vein resulted in reflex activation of the efferent gastric and pancreatic branches of the vagus. The intravenous injection of 10 mmol/L MSG (0.1 mL) also induced a reflex activation of the efferent discharges of the gastric branch of the vagus; however, in hepatic and celiac vagotomized rats, the intravenous injection of MSG (1 or 3 mol/L, 1 mL) produced no effect on gastric vagal activity. The results of these experiments demonstrate the importance of the afferent nerve signals from visceral glutamate sensors in generating the reflex activation of gastrointestinal and pancreatic functions in response to MSG administration. J. Nutr. 130: 971S–973S, 2000.

KEY WORDS: • monosodium L-glutamate • vagus nerve • stomach • pancreas • neurophysiology • rats

Monosodium L-glutamate (MSG) is a popular food additive that produces the umami taste (savory), which may be a marker for protein-rich foods (just as sweetness is thought to be the marker for carbohydrate-rich foods). Recently, we reported that umami taste stimulation activates the efferent limbs of the gastric (Niijima 1991a), pancreatic and hepatic branches of the vagus nerve (Niijima 1991b), in association with an increase in insulin secretion (Niijima et al. 1990). Jeannigros (1982) identified the existence of amino acid receptors in the duodenointestinal canal, using extracellular recordings of afferent activity of vagal nodosal neurons. The report described many receptors that were sensitive to arginine and leucine, and others that were sensitive to glutamine. In relation to the function of intestinal amino acid receptors, Meyer et al. (1976) reported that continuous intraduodenal infusion of amino acids stimulates pancreatic secretion in the dog. Such results indicate that a reflex increase in efferent activity has occurred in the pancreatic branch of the vagus. Still other findings suggest that amino acid sensors exist in the hepatoportal region; these sensors send signals through the hepatic branch of the vagus nerve to the central nervous system (Niijima and Meguid 1995). A reflex modulation of autonomic outflow, originated by glutamate sensors in the hepatoportal region, may thus exist. This paper continues an examination of these issues, and considers primarily the reflex effects of oral, gastric, intestinal and hepatoportal glutamate sensor stimulation on vagal gastric and pancreatic nerve activity.

MATERIALS AND METHODS

Male Wistar rats (300 g) were acclimated to our animal facilities for 1 wk before experimentation. During this time, they had free access to food and water. They were anesthetized with urethane (1g/kg, intraperitoneal), and tracheal cannulas were inserted. Under a dissecting microscope, a nerve filament was dissected from the peripheral cut end of the gastric, celiac or hepatic branch of the vagus nerve to record afferent nerve activity via a pair of silver wire electrodes. Efferent nerve activity was similarly recorded from a nerve filament dissected from the central cut end of the gastric or pancreatic branch of the vagus nerve (Niijima 1991a and 1991b, Niijima and Meguid 1995). A rate meter with a reset time of 5 s was used to observe the time course of nerve activity. Discharge rate is expressed as means ± SEM (n = 10). For taste stimulation, a solution of 150 mmol/L MSG (Ajinomoto, Tokyo) was applied to the tongue surface for 10 min; the tongue was flushed with distilled water at the con-
Vagal gastric afferents (gastric glutamate sensors)

Vagal celiac afferents (intestinal glutamate sensors)

Vagal hepatic afferents (hepatoportal glutamate sensors)

**FIGURE 1** Upper panel: the effect of monosodium glutamate (MSG) administration on theafferent activities of vagal gastric, intestinal and hepatoportal glutamate sensors. Lower panel: the effect of reflex activation of vagal gastric and pancreatic nerve activity from oral, gastric, intestinal and hepatoportal glutamate sensors. (Nijima, A., unpublished observations.)

The effect of MSG administration to gastric, intestinal and hepatoportal MSG sensors on vagal afferent activity. In the upper three traces of Figure 1, the top trace shows an example of the effect of MSG stimulation of the gastric wall on afferent activity of the vagal gastric nerve fibers. After infusion of the MSG solution (150 mmol/L, 3 mL), a long-lasting increase in afferent activity was observed. The discharge rate just before and 30, 60 and 90 min after infusion was 57.4 ± 3.9, 137.6 ± 5.0*, 112.0 ± 3.3* and 96.6 ± 3.9* impulses/5 s, respectively. The bottom trace indicates the afferent activity of the hepatic branch of the vagus nerve in response to an injection of 10 mmol/L MSG (0.1 mL) into the portal vein. The discharge rates before and after injection were 67.0 ± 2.7, 76.7 ± 2.2*, 92.5 ± 2.5* and 88.5 ± 2.1* impulses/5 s (same time sequence as indicated above). A gradual and clear increase in discharge rate occurred.

**Vagal efferent activity after MSG administration.** Figure 1 (lower panel) presents the efferent vagal responses to administration of peripheral MSG sensors. As shown in the top traces, taste stimulation by 150 mmol/L MSG for 10 min clearly increased efferent activity of the vagal gastric and pancreatic nerves. The efferent discharge rate in the vagal gastric nerve before and 30, 60 and 90 min after taste stimulation was 73.8 ± 3.8, 86.4 ± 3.1*, 100.9 ± 2.6* and 142.1 ± 5.2* impulses/5 s, and that in the vagal pancreatic nerve was 63.7 ± 2.2, 113.3 ± 2.0*, 129.2 ± 2.3* and 178.1 ± 3.1* impulses/5 s, respectively. The efferent discharge rates before and 30, 60 and 90 min after intragastric MSG infusion on vagal gastric and vagal pancreatic nerve activity were 60.0 ± 2.6, 63.9 ± 1.3, 72.2 ± 1.8*, 82.8 ± 2.9*, and 63.6 ± 2.0, 70.6 ± 2.3*, 87.1 ± 2.3*, 98.2 ± 2.1* impulses/5 s, respectively (second trace from the top). The efferent discharge rates before and 30, 60 and 90 min after intraduodenal infusion of 150 mmol/L MSG solution (3 mL) were 61.8 ± 1.5, 51.0 ± 1.2, 87.7 ± 1.8*, 96.7 ± 2.6* impulses/5 s, respectively, in the gastric vagus nerve, and 71.8 ± 3.8, 77.7 ± 2.0, 78.7 ± 3.0, 82.8 ± 4.1* impulses/5 s, respectively, in the vagal pancreatic nerve (third trace from the top). The intraportal injection of a small amount of an MSG solution (10 mmol/L, 0.1 mL) also increased efferent nerve activity in the gastric and pancreatic branches of the vagus nerve. The discharge rates before and 30, 60 and 90 min after intraportal injection were 69.0 ± 2.2, 96.8 ± 3.0*, 117.2 ± 2.9*, and 135.8 ± 3.4* impulses/5 s (vagal gastric efferents), and 63.4 ± 1.3, 71.2 ± 2.2*, 83.1 ± 3.2*, and 79.9 ± 2.6* impulses/5 s (vagal pancreatic efferents), respectively (bottom traces).

The effect of an intravenous injection of MSG on gastric vagal nerve activity. Figure 2 (upper panel) shows the effects of an intravenous injection of an MSG solution on the efferent activity of the gastric branch of the vagus nerve. As shown in the top trace, an intravenous injection of 10 mmol/L MSG solution (0.1 mL) produced a rise in the efferent activity of the gastric branch of the vagus nerve. This activation could be blocked by prior hepatic vagotomy, i.e., after sectioning of the hepatic vagus branch, successive intravenous injections of 10 mmol/L, 100 mmol/L and 1 mol/L MSG (0.1 mL each) failed to facilitate efferent nerve activity. Finally, the intravenous injection of a large volume of a concentrated MSG solution (1 mol/L or 3 mol/L, 1 mL) on vagal gastric nerve activity in a hepatic, gastric and celiac vagotomized rat. As shown in the trace, these injections were without effect.

**RESULTS**

The effect of MSG administration to gastric, intestinal and hepatoportal MSG sensors on vagal afferent activity. In the upper three traces of Figure 1, the top trace shows an example of the effect of MSG stimulation of the gastric wall on afferent activity of the vagal gastric nerve fibers. After infusion of the MSG solution (150 mmol/L, 3 mL), a long-lasting increase in afferent activity was observed. The discharge rate just before and 30, 60 and 90 min after infusion was 59.2 ± 3.3, 112.2 ± 3.5*, 109.3 ± 4.0* and 96.0 ± 4.4* impulses/5 s, respectively; the asterisk indicates a significant increase, compared with preinfusion value; *P < 0.05 (ANOVA, Scheffé test). The middle trace indicates an example of vagal celiac afferents, which showed a clear increase after intraduodenal infusion of MSG (150 mmol/L, 3 mL). The discharge rate just before and 30, 60 and 90 min after infusion was 57.4 ± 3.9, 137.6 ± 5.0*, 112.0 ± 3.3* and 96.6 ± 3.9* impulses/5 s, respectively. The bottom trace indicates the afferent activity of the hepatic branch of the vagus nerve in response to an injection of 10 mmol/L MSG (0.1 mL) into the portal vein. The discharge rates before and after injection were 67.0 ± 2.7, 76.7 ± 2.2*, 92.5 ± 2.5* and 88.5 ± 2.1* impulses/5 s (same time sequence as indicated above). A gradual and clear increase in discharge rate occurred.

**DISCUSSION**

The umami (savory) taste is known to be independent of the four classical, basic tastes (Ninomiya and Funakoshi 1987, Schiffman and Gill 1987, Yamaguchi 1987, Yamamoto and...
Asai (1987). MSG stimulates oral glutamate sensors and produces the umami taste. Niijima et al. (1990) reported that umami taste stimulation with MSG increased the efferent activity of the vagal pancreatic nerve and stimulated insulin secretion. Jeannigros (1982) also identified glutamine-sensitive receptors in the duodenointestinal canal using extracellular recordings of vagal nodosal neurons. Niijima and Meguid (1995) subsequently reported the existence of amino acid sensors in the hepatoportal region via recordings of afferent signals from the hepatic branch of the vagus nerve. However, the occurrence of glutamate sensors in the hepatoportal region has not been identified until now (these results). Further, stimulation by MSG solutions of oral and intestinal glutamate sensors enhanced efferent gastric vagus activity (Niijima 1991b).

Thus, the present experimental data demonstrate the existence of glutamate sensors not only in the oral cavity and intestinal wall, but also in the gastric wall and hepatoportal region, as well as a reflex activation of efferent discharges in the vagal gastric and pancreatic nerve from oral, gastric, intestinal and hepatoportal glutamate sensors. Figure 2 (lower panel) presents a schematic representation of the reflex pathway from gastric, intestinal and hepatoportal glutamate sensors to vagal gastric and pancreatic outflow. Figure 2 (upper panel) demonstrates that activation of gastric vagus activity by the intravenous injection of MSG is partially blocked by sectioning the hepatic branch of the vagus nerve, whereas sectioning of the hepatic, gastric and celiac branches of the vagus nerve completely blocks the effects of intravenous MSG. This response suggests that the activation of vagal activity by MSG administration is due mainly to an activation of peripheral glutamate sensors, and not the direct stimulation of autonomic centers within the brain.

**LITERATURE CITED**


