Chewing and taste increase blood velocity in the celiac but not the superior mesenteric arteries

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Running title: Splanchnic blood flow response to sham feeding

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Abstract

To investigate the role of chewing and taste in the meal-induced rapid increase in splanchnic blood flow, we compared the blood flow responses in the celiac artery (CA) and superior mesenteric artery (SMA) to chewing solid food with a chocolate taste (FOOD) and paraffin wax without taste (WAX). After 5 min of baseline measurement, 15 healthy subjects repeated chewing and expectorating the FOOD or WAX every 20 s for 4 min followed by 10 min of recovery measurement. We measured the mean blood velocity (MBV) in the CA and SMA. The baseline MBVs in the CA and SMA did not differ between the FOOD and WAX trials. The MBV in the CA was lower than baseline at the 1st min of chewing in both trials. It was higher than baseline at the 3rd min of FOOD chewing, whereas it did not increase during and after WAX chewing. The MBV in the CA was higher in the FOOD trial than in the WAX trial at the 3rd min of chewing and thereafter. In contrast, the MBV in the SMA did not change throughout the protocols. These results suggest that the taste of food plays a role in meal-induced hyperemia in the CA but not the SMA.
Introduction

We have previously reported that the mean blood velocity (MBV) in splanchnic arteries increases within 1 min after beginning to ingest solid food, and suggested that the increase in blood flow (BF) in some parts of the gastrointestinal tract precedes the arrival of chyme (23). The splanchnic circulation provides nutrition and oxygen to the organs it supplies, and removes absorptive substances and waste products from these organs (6). It is therefore important for the splanchnic BF, as well as the secretion and motility to increase when ingested food is digested and absorbed.

Factors increasing the splanchnic BF during this early phase have not been investigated previously. A candidate mechanism might be present during the cephalic phase of digestion, which refers to the autonomic and endocrine responses of the digestive system that result from stimulation of the sensory system at the cephalic level (30). Since many malfunctions are induced by the absence of the cephalic phase, these responses appear necessary to prepare the digestive system for food reception (10, 11, 26, 28). Many studies have demonstrated that the cephalic phase of digestion includes the secretions of digestive juices and gastrointestinal hormones in the stomach, intestine, and
pancreas (1, 4, 5, 12, 18, 19, 29). Some studies have found that gastric motility changes and oxygen consumption increases during cephalic stimulation (2, 14, 25). Although these responses are evoked by the sight, smell, and even the thought of appetizing food, they are much smaller than those induced by the taste of food, suggesting that a gustatory factor is essential to the cephalic response phase (4). The gustatory component of food alters the autonomic nervous system via the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus nerve (DMN) (17). Thus, taste is a strong candidate factor for inducing early increases in the splanchnic BF.

Another candidate factor for increasing BF is chewing. This represents a moderate type of exercise, and hence might activate sympathetic nerve activity and induce a cardiovascular response through central and muscle-originated nervous pathways; that is, via central command and a muscle mechanoreflex (8, 13).

We therefore hypothesized that the chewing and taste are associated with meal-induced splanchnic hyperemia. The present study was designed to examine 1) whether the chewing and taste increase the splanchnic BF, 2) whether the chewing and taste affect the central and peripheral circulations to
other than the splanchnic region, and 3) whether chewing or taste stimulates the splanchnic BF the most. This was achieved by adopting the use of sham feeding (i.e., chewing and taste but not swallowing), which is the most frequently used method for studying responses related to the cephalic phase. We monitored the BF responses in the celiac artery (CA) and superior mesenteric artery (SMA), finger skin, and forearm during sham feeding with or without a food taste.

Methods

Subjects

Fifteen volunteers (5 males, 10 females; Age, 25 ± 2 years; height, 166 ± 9 cm; and weight, 56 ± 9 kg; mean ± SD) participated in the study. We measured the blood velocity in the CA and SMA in 12 subjects, with both vessels being measured in 9 subjects. The subjects were normotensive, nonsmokers, did not take any medication, and had no history of autonomic dysfunction or cardiovascular disease. The Ethics Committee of the Institute of Health Science, Kyushu University, approved the experimental protocols, and all subjects provided written informed consent. All protocols conformed to the Declaration of Helsinki.
Protocols

The subjects arrived at the laboratory after having abstained from eating, taking caffeinated beverages, and performing intensive exercise. The experiments were conducted in a quiet room with the subjects in a semirecumbent position and the legs extended approximately 130° relative to the trunk. Prior to measurements, the subjects were instructed to repeat the chewing and expectoration 12 times for 4 min (each chewing and expectoration period lasted for 10 s), and to be very careful not to swallow any food or saliva. The subjects first practiced this sham feeding procedure. After 5 min of baseline measurement, subjects performed sham feeding of 60 g of solid food with a chocolate taste containing 6.5 g of protein, 16.8 g of fat and 30.0 g of carbohydrate with a total caloric volume of 300 kcal (Calorie Mate, Otsuka Pharmaceutical, Tokyo, Japan) as the FOOD trial, and 15 g of paraffin wax without a food taste (dental base plate, medium stiffness, Yamahachi Dental, Aichi, Japan) as the WAX trial. Subjects then rinsed their mouths followed by 10 min of recovery-period measurement. Both the FOOD and WAX trials were performed on the same day in a randomized order.

Measurements
Heart rate (HR), mean arterial pressure (MAP), MBVs in the CA and SMA, BF in finger skin and the forearm, and masseteric electromyogram (EMG) were measured during the protocols. A standard electrocardiogram (ECG) was recorded continuously (MEG2100, Nihon-Kohden, Tokyo, Japan). The beat-by-beat blood pressure was monitored with an automatic sphygmomanometer on the right middle finger (Finometer, Finapres Medical Systems, Amsterdam, Netherlands).

Simultaneous pulsed and echo Doppler ultrasound flowmetry was used to measure the MBV in the CA and SMA as we described previously (22, 23). In brief, a curved-array Doppler-scan probe operating at a pulsed Doppler frequency of 3.3 MHz (LOGIQ3, GE Medical Systems, CT, USA) was used with the focal zone at the depth of the CA or SMA, and at the proximal segment of each artery. The Doppler-beam insonation angle was maintained at 60º or less relative to the blood vessel.

BF in finger skin was measured by laser-Doppler flowmetry (Flo-C1BV, Omegawave, Tokyo, Japan). The probe was attached to glabrous skin at the fingertip of the right index finger. BF in the forearm was measured by venous occlusion plethysmography using a mercury-in-Silastic strain gauge (EC-6,
Hokanson, WA, USA) placed around the left forearm at its largest girth. The left forearm was positioned slightly above the level of the heart and a venous occlusion pressure of 40 mmHg was used. Two measurements were made every minute.

The EMG was recorded from the right masseter muscle using skin electrodes. The positions of electrodes were determined by palpation while subjects clenched their teeth. Electrodes with conductive paste were placed on the largest area in the muscle separated by 1 cm and parallel to the muscle fiber. A body earth electrode was attached to the skin of the right earlobe.

The signals for antegrade and retrograde blood-cell velocities, as well as the ECG signal, were digitally sampled at 20 kHz using an A/D converter (PowerLab 8s, ADInstruments, CO, USA). The spectra of the signals were analyzes offline using our own Doppler signal processing software, and beat-by-beat MBV values were calculated. The sphygmomanometer, forearm plethysmography, finger skin BF and masseteric EMG signals were sampled at 1 kHz using an A/D converter (PowerLab 8/30, ADInstruments).

Data analysis

Minute-by-minute HR and MAP were calculated from ECG and blood
pressure recordings. To obtain minute-by-minute MBV data during baseline and recovery measurements, the ten largest values of the beat-by-beat MBV were averaged every minute because lower values are mainly artifacts caused by respiration. We obtained reliable velocity data using this method and data reduction (22). During the sham feeding, the two largest values of the beat-by-beat MBV during each 10-s chewing period were taken and six data points were averaged every minute. The magnitude of the peak response in the MBV and the time of its occurrence were determined for each subject.

Minute-by-minute finger skin BF was calculated and expressed in arbitrary units (a.u.). The forearm BF was calculated from the rate of increase of the forearm girth during venous occlusion and expressed in milliliters per minute per 100 ml of the forearm volume. The mean of two measurements was taken as the value at each minute.

On a minute-by-minute basis, MAP was divided by the MBV in the CA and SMA, and BF in finger skin and the forearm to assess the vascular resistance indexes (RI). We did not record the diameter of splanchnic arteries and or calculate the BF because the diameter of these vessels did not change and the change in the MBV reflected the change in BF induced by meal.
Ingestion (23).

Full-wave-rectification EMG signals were integrated over 2 min of the chewing period. The baseline resting EMG during the corresponding period was subtracted to assess the activity of the masseter muscle (iEMG).

Because the same protocols were repeated twice to obtain the MBV data from the CA and SMA in nine subjects, the data of minute-by-minute MAP, HR, BF and RI in the forearm and skin, and iEMG in each subject were averaged to obtain the values in the individuals (n = 15). Minute-by-minute data of each variable before and after sham feeding were averaged every 5 min.

Statistics

Paired t-tests were used to compare the baseline values between the FOOD and WAX trials, and to compare the iEMGs between trials. The main effects of time and trial were examined by repeated-measures ANOVA. When a significant F value was detected, this was further examined by Dunnett’s post-hoc test to assess the effect of time and by the paired t-test to compare the values at each time point between trials. Statistical significance was accepted at
These statistical analyses were performed with SAS (ver. 8.2, SAS Institute, NC, USA) at the Computing and Communications Center, Kyushu University.
Results

The baseline values did not differ significantly between the FOOD and WAX trials (Table 1), and there was also no significant difference in masseteric iEMG (0.31 ± 0.07 and 0.36 ± 0.07 a.u., respectively).

Central circulation (Figure 1)

The HR significantly increased during sham feeding in both trials. The HR was higher in the FOOD trial than in the WAX trial. The MAP increased at the 1st min of sham feeding in the FOOD trial, but did not change in the WAX trial.

Splanchnic circulation (Figure 2)

The MBV decreased and the RI increased in the CA at the 1st min of sham feeding in both trials. The CA MBV in the FOOD trial increased at the 3rd min of sham feeding. Significant differences between trials were observed in the CA MBV and RI. The peak increase in the CA MBV response of 13 ± 2 % relative to the baseline occurred at 7 ± 1 min (individual peak time ranged 1–14 min) after the start of sham feeding in the FOOD trial. In contrast, the SMA MBV and RI did not change significantly in either trial.
Peripheral circulation in the forearm and skin (Figure 3)

The skin BF decreased at the 1st min of sham feeding in both trials. The skin RI did not change significantly in either trial. The BF decreased and the RI increased in the forearm at the 1st min of sham feeding in the FOOD trial. The BF and RI in the forearm did not change significantly in the WAX trial.


Discussion

The main finding in the present study was that solid-food sham feeding increased the CA MBV. The CA supplies blood to the stomach, liver, and spleen, and it can be concluded that the BF to these organs starts increasing before chyme reaches the stomach.

The CA MBV was higher in the FOOD trial than in the WAX trial during and after sham feeding, which suggests that the gustatory component of food is effective at increasing the splanchnic BF. The present study was able to detect rapid BF responses during the cephalic phase due to the use of 1-min time bins. The results are similar to those obtained in previous studies that used longer time bins (e.g., >5 min), and revealed gastrointestinal responses to cephalic stimulation other than the BF response. Macdonald and Spurrell (15) observed the cephalic secretions of gastric juice induced by a pectin meal and a favorite meal in a subject with a gastrostomy, and reported that the pectin meal did not induce any gastric secretion, whereas the favorite meal induced a marked response. Richardson et al. (18) reported that gastric acid secretion increased during sham feeding of an appetizing food but not when chewing a plastic tube. Moreover, Stern et al. (25) demonstrated that the gastric myoelectric activity is
activated during sham feeding of appetizing food but not during sham feeding of unappetizing food. Together these results indicate that the taste and palatability of food play a significant role in cephalic responses in the gastrointestinal system, including in the rapid BF increase in the CA.

The peak increase in the CA MBV response to sham feeding was 13 % from the baseline at 7 min after the start of sham feeding. In our previous study (23), the peak increase in the CA MBV response to the actual ingestion of the same food was 60 % at 5 min after the start of ingestion. These observations suggest that chewing and taste accounts for approximately 20 % of the BF increase in the CA.

The mechanisms underlying the increased splanchnic BF during sham feeding with food taste are unknown, but there are several possible candidates. Gustatory afferent nerves input into the NTS, and gustatory neurons in the NTS establish synaptic contact with the DMN (17). Vagal efferent fibers from the DMN are activated during sham feeding, and evoked numerous responses in the gastrointestinal tract, such as the secretion of gastrin, which has a vasoactive property (5, 19). Moreover, an oxygen deficit in smooth muscle induced by motility can increase intestinal BF (6). These processes could increase the CA
In contrast to the CA, the MBV did not increase and the RI did not decrease in the SMA during and after sham feeding. This result is consistent with Sieber et al. (21) reporting that sham feeding did not affect the SMA BF. However, they measured the BF at 15-min intervals, which might have prevented the detection of BF responses during the early phase of sham feeding. The present result supports their findings and suggests that the increase in the SMA BF requires at least stimulation to the esophageal and/or gastrointestinal sensory systems.

Sham feeding increased the HR in the FOOD and WAX trials, and the MAP in the FOOD trial. These responses could be due to the activation of cardiac sympathetic nerve activity at the beginning of eating caused by a descending input from the central nervous system (16). The response in the central circulation was higher in the FOOD trial than in the WAX trial, which is consistent with Harthoorn and Dransfield (7) finding that the HR increased during sham feeding but not when chewing Parafilm. Both results suggest that the taste of food is important to inducing the cardiac sympathetic nervous activity. Gustatory and cardiovascular sensory information is both transmitted to the NTS,
which is relevant to autonomic control of cardiovascular system (17, 24). However, the effect of chewing on sympathetic nerve activity remains, with WAX chewing increasing HR in the present study. Mastication might play a role in enhanced sympathetic nerves activity (20).

The MBV in the CA and the BF in finger skin and forearm decreased at the 1st min of sham feeding, due to the increase in the RI. These vasoconstrictions could be related to the activation of regional sympathetic nerve activity at the beginning of eating, as well as cardiac sympathetic nerve activity as mentioned above. These findings also have potential implications for certain disease conditions where sympathetic nervous activity is enhanced. That is, chewing in these conditions, unlike in the healthy subjects, may cause exaggerated sympathetic activity, which may prolong vasoconstriction in vasculatures in some areas. The SMA MBV, however, did not decrease during the initial phase of sham feeding, which is due to the differential BF response to sympathetic activation as shown during a moderate cycling exercise and a mental task in human visceral organs (3, 9).

The quantity of chewed FOOD was not the same as WAX, because we balanced the intensity of mastication, not the amount of food. In a preliminary
trial, we found that 15 g of paraffin wax induced similar iEMG to 60 g of food. The absence of a difference in masseteric iEMG between the trials indicates that the intensity of mastication was similar. Thus, the differences between the cardiovascular responses in the FOOD and WAX trials cannot be attributed to the degree of masseter muscle activity.

We have not examined the influence of gender because of small number of subjects. The response patterns of MBV in both CA and SMA during and after sham feeding were similar between female and male, though the absolute values tend to be higher in female than male. These were similar to a previous study reporting that the blood velocity in SMA is higher in female than male at resting, whereas the responses to the food ingestion were similar (27). Although two third of the studied population is female, observed responses would not be influenced by the gender related factors.

In conclusion, the present study has demonstrated that 1) sham feeding (i.e., chewing and taste, but not ingestion) increases the CA MBV without the arrival of chyme at the stomach, 2) the central and peripheral circulations are also affected by sham feeding, and 3) the gustatory component of food could be
a trigger for an increase in splanchnic BF, suggesting that the cardiovascular response to sensory system stimulation at the oral cavity contributes to preparing the digestive system for food reception.

**Perspectives and Significance**

The data obtained in this study could be useful for future investigations of the neural control of cardiovascular system during and after food intake from both physiological and clinical standpoints. In particular, investigating the cephalic phase of response is clinically relevant to artificial nutrition.
Grants

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References

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Table 1. Baseline values

<table>
<thead>
<tr>
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<th>FOOD trial</th>
<th>WAX trial</th>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>62 ± 2</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>85 ± 2</td>
<td>85 ± 2</td>
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<tr>
<td>CA MBV, m/s</td>
<td>0.41 ± 0.02</td>
<td>0.40 ± 0.02</td>
</tr>
<tr>
<td>SMA MBV, m/s</td>
<td>0.31 ± 0.02</td>
<td>0.32 ± 0.02</td>
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<tr>
<td>Forearm BF, ml/min/100 ml tissue</td>
<td>4.5 ± 0.7</td>
<td>3.8 ± 0.6</td>
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<tr>
<td>Skin BF, a.u.</td>
<td>0.39 ± 0.06</td>
<td>0.38 ± 0.06</td>
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Data are the mean ± SE values. HR, heart rate; MAP, mean arterial pressure; CA, celiac artery; SMA, superior mesenteric artery; MBV, mean blood velocity; BF, blood flow. Baseline values did not differ between trials (p > 0.05).
Figure legends

Figure 1. Central circulation in the FOOD (●) and WAX (○) trials. The subjects performed sham feeding for 4 min after the baseline measurement. The heart rate (HR) increased during sham feeding in both trials, and was higher in the FOOD trial than in the WAX trial. The mean arterial pressure (MAP) increased at the 1st min of sham feeding in the FOOD trial. *Significant difference from baseline values. #Significant difference between trials (p < 0.05; (#)p = 0.05). Error bars show SE values.

Figure 2. Splanchnic circulation in the FOOD (●) and WAX (○) trials. The subjects performed sham feeding for 4 min after the baseline measurement. The mean blood velocity (MBV) in the celiac artery (CA) decreased at the 1st min of sham feeding in both trials, and increased at the 3rd min of sham feeding in the FOOD trial. The resistance index (RI) in the CA increased at the 1st min of sham feeding in both trials. Significant differences between trials were observed in the CA MBV and RI. The MBV and RI in the superior mesenteric artery (SMA) did not change significantly in either trial. *Significant difference from baseline
values. *Significant difference between trials ($p < 0.05$); (#)$p = 0.06$). Error bars show SE values.

**Figure 3.** Blood flow (BF) responses in finger skin and the forearm in the FOOD (●) and WAX (○) trials. The subjects performed sham feeding for 4 min after the baseline measurement. The skin BF decreased at the 1st min of sham feeding in both trials. The BF decreased and RI increased in the forearm at the 1st min of sham feeding in the FOOD trial. *Significant difference from baseline values. (#)Significant difference between trials ($p < 0.05$). Error bars show SE values.
Figure 1.
Figure 2.
Figure 3.