Modulation of human cortical swallowing motor pathways after pleasant and aversive taste stimuli

Satish Mistry, John C. Rothwell, David G. Thompson, and Shaheen Hamdy

Department of Gastrointestinal Sciences, University of Manchester, Hope Hospital, Salford; and Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, United Kingdom

Submitted 20 December 2005; accepted in final form 17 May 2006

Mistry, Satish, John C. Rothwell, David G. Thompson, and Shaheen Hamdy. Modulation of human cortical swallowing motor pathways after pleasant and aversive taste stimuli. Am J Physiol Gastrointest Liver Physiol 291: G666–G671, 2006. First published May 25, 2006; doi:10.1152/ajpgi.00573.2005.—Human swallowing involves the integration of sensorimotor information with complexities such as taste; however, the interaction between the taste of food and its effects on swallowing control remains unknown. We assessed the effects of pleasant (sweet) and aversive (bitter) tastes on human cortical swallowing motor pathway excitability. Healthy adult male volunteers underwent a transcranial magnetic stimulation (TMS) mapping study (n = 9, mean age: 34 yr) to assess corticobulbar excitability before and up to 60 min after 10-min liquid infusions either 1) as swallowing tasks or 2) delivered directly into the stomach. Infusions were composed of sterile water (neutral), 10% glucose (sweet), and 0.5 mM quinine hydrochloride (bitter). The order of delivery was randomized, and each infusion was given on separate days. Pharyngeal motor-evoked potentials (PMEPs) were recorded from an intralu-inal catheter as a measure of corticobulbar excitability and compared using repeated-measures and one-way ANOVA. After the swallowing task (water, glucose, or quinine), repeated-measures ANOVA revealed a significant time interaction across tastants (P ≤ 0.01). One-way ANOVA for each tastant showed changes in PMEP amplitudes for both quinine (P ≤ 0.001) and glucose (P ≤ 0.009) solutions, but not for water (P = 0.1). Subsequent t-tests showed that glucose and quinine reduced PMEPs by 47% (SD 34) and 37% (SD 54), respectively, at 30 min (P ≤ 0.03). No changes were observed after the infusion of any solution directly into the stomach (P = 0.51). In conclusion, cortical swallowing pathways are similarly modulated by both sweet and bitter tasting stimuli. Changes likely reflect a close interaction between taste and swallowing activity mediated in the central nervous system.

THE ABILITY OF ORGANISMS to detect the nature of molecules and ions in the mouth is known as the sense of taste. Human taste can differentiate at least five primary qualities: sugars (sweet), sodium chloride and other salts (salty), acids (sour), alkaloids (bitter), and amino acids (umami, protein). In mammals, the different modalities of taste are detected by elongated neuro-epithelial cells named taste receptor cells, which are seques-tered into morphological structures known as taste buds. Hu-man taste buds are located throughout the oral cavity in both lingual and extralingual locations, two-thirds of which are located in the tongue with the remaining third being located on the epiglottis, soft palate, larynx, and oropharynx (1, 27).

Three cranial nerves (VII, IX, and X) carry gustatory information away from the taste buds to the cortical taste areas via the nucleus of the tractus solitarius (NTS) and thalamus. Some of this information is also transmitted to the hypothalamus, which is an integral component for regulating feeding behavior (1, 18, 27).

Swallowing is a dynamic sensorimotor activity with both volitional and reflexive components. Swallowing is learned during gestation, organized at birth (16), and remains essential for the continuation of life. The neural control of swallowing is complex, incorporating an integrated hierarchical sequence of neuromuscular events between the brainstem swallowing center, 5 cranial nerves, and 26 muscle pairs. Swallowing allows the safe and coordinated delivery of ingested food from the mouth to the esophagus while ensuring protection of the airway (19, 23). The cerebral cortex also plays an important role in the initiation and regulation of swallowing and is modulated by oropharyngeal sensation (12–14, 21), with activity being identified in the sensorimotor cortex, insula, cerebellum, and amygdala (13, 14, 36).

Human functional brain imaging studies (31, 35) have also indicated that taste modalities recruit multiple brain regions including the orbitofrontal cortex, insula, and amygdala. These regions are of significance to feeding because they are similar to the cortical areas activated in swallowing, thus implying an important overlap of function.

Given the close relationship between taste and swallowing, it is perhaps surprising that the effects of taste on the central control and regulation of swallowing remain unexplored. The aim of this study was thus to describe the effects of taste modalities on corticobulbar pathway excitability as measured by transcranial magnetic stimulation (TMS). We hypothesized that changes in taste input would have modulatory effects on measured swallowing cortical excitability.

METHODS

Participants

Nine healthy (right handed) adult male volunteers (mean age: 34 ± 4 yr) participated in the study. All met previously established inclusion criteria for participation in magnetic stimulation studies (17, 34), i.e., no previous swallowing difficulty; no previous brain or throat surgery; no contraindications to magnetic stimulation, including a cardiac pacemaker in situ or history of epilepsy; no use of any drugs that influence the central nervous system (CNS) such as antidepressants, antiepileptics, or sleeping pills; and not pregnant. None of the volunteers reported any swallowing difficulty past or present. Ap-
The protocol was granted by the Salford and Trafford Local Research Ethics Committee, and all studies were conducted in the clinical laboratory of the Gastrointestinal Physiology department at Hope Hospital (Salford, UK).

### Taste Solutions

Three different solutions were used: sweet (10% glucose), bitter (0.5 mM quinine hydrochloride), and neutral (water). Two liters of these concentrations for each solution were made and then randomly labeled as solutions 1, 2, and 3 by a staff member not directly involved with conducting the experiment; therefore, the identity of the solutions in each bottle was unknown to the experimenter. Solutions were prepared before the start of the experiment, and all bottles were refrigerated at a temperature of 4°C both to stabilize and standardize the solutions.

Solution concentrations used in the experiments were chosen based on the results of a preliminary study in 10 healthy volunteers using a range of 1%, 3%, 5%, and 10% glucose solutions and 0.5, 1, 1.5, and 2 mM quinine solutions. Subjects were asked to rate solutions based on pleasantness and tolerability. Subjects chose the 10% glucose and 0.5 mM quinine solutions as those providing the greatest stimulus with acceptable tolerability.

### Visual Analog Scales

A visual analog scale (VAS) was presented to subjects after they had swallowed each solution. Subjects were asked to identify the taste of the solution and rate its pleasantness/unpleasantness using an 11-point VAS. Anchors were set on a scale ranging from 0 (extremely unpleasant) to 5 (neutral) to 10 (extremely pleasant). Subjects also wrote down additional comments concerning each solution.

### Cortical Stimulation

Cortical stimulation was performed using a magnetic stimulator (Magstim 200, The Magstim, Whitland, UK) connected to a figure-8 coil with an outer diameter of 70 mm placed over the regions of interest on the scalp as previously described (12). In this configuration, the maximum magnetic field generated by the stimulator was 2.2 T.

### Pharyngeal Electromyographic Responses

Pharyngeal electromyographic (EMG) responses to TMS, known as pharyngeal motor-evoked potentials (PMEPs), were detected using a pair of bipolar ring electrodes built into a 3-mm-diameter intraluminal catheter (Gaeltec, Dunvegan, UK) passed into the oropharynx either transnasally or transorally according to subject preference. This catheter also housed an infusion channel through which solutions could be delivered to the stomach. The recording electrodes were placed in the optimum position for recording PMEPs by adjusting the catheter position and direct inspection of raw EMGs.

The catheter was connected to a preamplifier (CED 1902, Cambridge Electronic Design, Cambridge, UK) with filter settings of 5 Hz to 2 kHz. Response signals were processed through a 50/60-Hz noise eliminator (HumBug, Quest Scientific, Vancouver, BC, Canada) to remove any unwanted electrical interference. Signals were then collected through a laboratory interface (CED micro 1401, Cambridge Electronic Design) at a sampling rate of 4–8 kHz. Responses were recorded using a Pentium III personal computer, which allowed both “on-line” visualization and archiving to file for later “off-line” analysis.

### Experimental Protocols

For each study, the volunteer sat comfortably in a chair, and the catheter was then passed. The electrode pair was next positioned in the pharynx either 11–14 cm from the incisors or 13–17 cm from the external nose, with the tip of the infusion channel 48 cm distal to the electrodes. The cranial vertex was then identified according to the international 10–20 system for electrode placement and marked on the scalp. The optimum site for evoking PMEPs to TMS of the motor cortex was then determined by discharging the coil over multiple scalp positions on both hemispheres using suprathreshold stimulus intensities. The site evoking the largest PMEPs was subsequently marked on the scalp (see Fig. 1). A series of cortical stimulations over this site was then performed, commencing at subthreshold intensity and increasing by 5% increments of stimulator output until a motor threshold (MT) intensity was found. MT was defined as the minimum intensity of stimulator output required to evoke PMEPs of >20 μV on at least 5 of 10 consecutive trials. Repeated stimulations were then carried out at suprathreshold stimulus intensities (≥110% MT). Five stimuli were delivered with a 5-s interval between each stimulus.

After baseline PMEP data were recorded, the intervention was performed in a pseudorandomized manner on separate days (at least 24 h apart). This was composed of a 10-min liquid infusion of 5-ml boli delivered every 15 s using a hand-held syringe and connecting catheter. The liquid used was one of the three previously titrated solutions: sterile water, 10% glucose, or 0.5 mM quinine. During this period, volunteers were also asked to identify and rate the taste sensation based on the 11-point VAS.

**Protocol 1: oral infusion.** In this protocol, solutions were delivered into the mouth, and volunteers were instructed to taste the solutions for up to 10 s and then swallow. A total of 40 swallows were performed over the 10-min period.
Protocol 2: stomach infusion. In this protocol, solutions were delivered directly into the stomach via a fine-bore channel built into the intraluminal catheter without taste sensation (confirmed by volunteers) or swallowing activity.

After either of these interventions, cortical stimuli (identical to baseline) were repeated immediately after and 30 and 60 min postintervention. These times were chosen based on previous studies (6, 7) that have demonstrated that sensory stimulation of the pharynx can alter pharyngeal motor cortical excitability for at least 1 h.

Data Analysis

For each protocol, mean values of the peak-to-peak change in PMEPs were calculated for each time interval pre- and posttastant. The response amplitude was defined as the maximum peak-to-peak difference in the PMEP. The response latency was defined as the time taken between magnetic pulse discharge and the onset of the first deflection of the relevant PMEP. Because each subject acted as his own control, factors such as age and diet, which might conceivably alter these results, were thus equalized and so not considered for any additional analysis. PMEP amplitude data were not normally distributed and so were log transformed and analyzed using repeated-measures ANOVA (SPSS 13.0). One-way ANOVA was then performed on the transformed data to identify any taste-specific effects for each solution. Latency data were normally distributed and so were analyzed using repeated-measures ANOVA. A P value of ≤0.05 was used to indicate statistical significance. All data are presented as group means with SD unless stated otherwise.

RESULTS

Figure 1 illustrates the scalp sites where the center of the TMS coil was applied for stimulation during both oral and stomach infusions. This shows that the main site for stimulation was ~3–5 cm lateral and anterior to the cranial vertex. The mean intensity of cortical stimulation for both studies was 81% (SD 7) of stimulator output. During studies, swallowing or intragastric infusions of solutions were performed in all volunteers without any adverse effects.

Pleasantness/Unpleasantness Ratings

Figure 2 shows the mean ratings of pleasantness and unpleasantness on an 11-point VAS for each taste modality recorded during the oral infusions. Water was rated as neutral with a mean VAS score −0.1 (SD 0.26), Glucose was rated as pleasant with a mean VAS score of 2.1 (SD 0.38), Quinine was rated as unpleasant by all subjects with a mean VAS score of −3.6 (SD 0.57).

Protocol 1: Oral Infusion

Amplitude. PMEP traces to TMS from a single representative individual are shown in Fig. 3. PMEP amplitude data for each taste solution across time are shown after oral infusion in Table 1. Mean (%) changes in PMEP amplitude from baseline after infusion of the solutions directly into the stomach are shown in Fig. 5. As with the oral infusions, repeated-measures ANOVA of the log-transformed data were performed but showed no significant interactions between time and solution for response latencies [F(3,72) = 1.3, P = 0.25] or effect of time alone [F(3,72) = 0.2, P = 0.89].

Protocol 2: Stomach Infusion

Amplitude. PMEP amplitude data for each taste solution across time are shown after oral infusion in Table 1. Mean (%) changes in PMEP amplitude from baseline after infusion of the solutions directly into the stomach are shown in Fig. 5. As with the oral infusions, repeated-measures ANOVA showed no significant interactions between time and solution for response latencies [F(3,69) = 0.8, P = 0.51] or time × solution interaction [F(6,69) = 1.6, P = 0.15].

Latency. Pharyngeal response latencies at baseline and each time point for the three solutions are shown in Table 2. Repeated-measures ANOVA showed no significant interactions between time and solution for response latencies [F(3,72) = 0.6, P = 0.73] or effect of time alone [F(3,72) = 0.2, P = 0.92].

DISCUSSION

This study examined the effects of different tasting solutions on corticobulbar swallowing excitability. We specifically chose sweet and bitter tastes because they represent the two extremes of the gustatory experience: one pleasant and the other aversive. We hypothesised that these tastes would influence swallowing pathway excitability, thus providing new data on how taste interacts with human swallowing neurophysiology.

The results of our experiments indicate that bitter and sweet tastes appear to alter swallow-related CNS function in a similar manner. Specifically, both glucose and quinine solutions produced reductions in PMEP amplitudes after a volitional swal-
lowing task. By contrast, when the solutions were infused directly into the stomach (thus bypassing the effects of taste and swallowing), no changes were observed. These observations are likely to have a neurophysiological basis and thus merit further discussion.

Electrophysiological data from animal studies (4, 15, 20) have suggested that taste information undergoes significant modification during the early stages of synaptic processing in brainstem taste nuclei before being transmitted to higher centers. In fact, gustatory cells in the rat NTS are subject to several modulatory influences including changes in physiological states such as gastric distension (10), blood glucose (8) and insulin levels (9), and conditioned taste aversion learning (2), all factors that may be relevant to this study. Indeed, a study by Scott et al. (29) on the monkey brainstem has shown that the macaque taste system has a dynamic sensitivity range equivalent to that of humans with recognition thresholds for glucose being higher than quinine. Moreover, there appears to be a progressive increase in responses to quinine when moving posterior to anterior through the NTS, suggesting that bitter sensitivity (unlike that of sweetness) is more evenly distributed throughout the NTS.

Table 1. Pharyngeal motor-evoked potentials for solutions across time points for oral and stomach infusions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Oral infusion</th>
<th>Stomach infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>0 min</td>
</tr>
<tr>
<td>Water</td>
<td>135 (SD 77)</td>
<td>159 (SD 53)</td>
</tr>
<tr>
<td>Glucose</td>
<td>117 (SD 39)</td>
<td>146 (SD 80)</td>
</tr>
<tr>
<td>Quinine</td>
<td>150 (SD 49)</td>
<td>167 (SD 57)</td>
</tr>
<tr>
<td>Water</td>
<td>114 (SD 33)</td>
<td>94 (SD 29)</td>
</tr>
<tr>
<td>Glucose</td>
<td>100 (SD 32)</td>
<td>87 (SD 37)</td>
</tr>
<tr>
<td>Quinine</td>
<td>93 (SD 39)</td>
<td>91 (SD 27)</td>
</tr>
</tbody>
</table>

Values are means with SD (in μV) for each taste solution across each time point for oral and stomach infusions.
Of relevance, when considering the factors that trigger swallowing, it has previously been proposed that stimuli must excite multiple peripheral sensory receptors in a dynamic fashion while activating neurons in the NTS (22, 30). By comparison, taste perception requires only chemical stimulation of taste buds while activating neurons and interneurons in the NTS (26). This sharing of brainstem circuitry suggests that taste could be an important facilitator of swallowing by providing additional sensory input to the NTS. Moreover, the cranial nerves involved with swallowing (that relay sensory signals) display considerable brainstem convergence with trigeminal (and vagal) afferent fibers terminating within the trigeminal spinal nuclei and NTS. These afferent fibers are capable of influencing brainstem motoneuron and interneuron circuitry as well as circuitry higher in the cerebral cortex (11). Interestingly, interneurons in the NTS can be excited or inhibited by different taste stimuli (32). For example, responses from the hamster NTS have demonstrated a significant reduction in spontaneous firing rates when exposed to quinine (33).

Thus, when considering the effects of both bitter and sweet tastes on swallowing, it is conceivable that these stimuli directly reduced activity in the NTS, which may have led to a reduction in the activity of cortical swallowing centers and hence the reduced PMEPs observed with TMS. Consistent with this suggestion, Zald et al. (35) using PET demonstrated strong activation of the amygdala while volunteers tasted concentrated quinine (0.02 M) and modest activations while volunteers tasted sucrose (30% solution). O’Doherty et al. (25) also observed moderate amygdala activations in five of seven subjects in an fMRI study comparing glucose (1 M) with artificial saliva. Electrophysiological studies (24, 28) in animals have also clearly indicated that an equal proportion of cells within the amygdala, if not more, respond to sweet tastes than bitter tastes. Although the concentrations used in the present study were considerably lower, amygdala activation in combination with a reduction in NTS firing rate may have resulted in inhibition of the cortical swallowing network and thus a reduction in swallowing motor cortex excitability.

With respect to the measured corticobulbar excitability changes we observed with both tastants, it could also be speculated that such inhibitory effects, although subtle, may have occurred as a behavioral consequence of its strong flavor. For example, it is known that quinine and glucose have effects on swallowing physiology, primarily decreasing swallow speed (3). In our swallowing task, volunteers were required to continually taste and swallow the solution every 15 s in a highly regimental manner, so constraining any natural compensatory swallowing behavior that may have been anticipated. In combination with any inhibitory inputs to the NTS and cortex, this “controlled” delivery of fluid without compensation may have been a factor in the delayed reduction in the excitability in the swallowing motor cortex.

The delay (30 min) in the inhibitory effect after the taste tasks may have been because of the more-immediate effects of repeated multiple swallowing on corticobulbar excitability (5, 7). For example, an early excitatory effect after repetitive swallowing has previously been demonstrated by Fraser et al. (7). Thus, the immediate, albeit transient, rise in corticobulbar pathway excitability produced in our study may have simply been a function of volitionally swallowing 5-ml water boli every 5 s for 10 min. The relatively modest rise in PMEP

Table 2. Corticopharyngeal latencies for solutions across time points for oral and stomach infusions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Baseline</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>8.5 (SD 0.6)</td>
<td>8.8 (SD 1.0)</td>
<td>8.8 (SD 0.8)</td>
<td>8.5 (SD 0.8)</td>
</tr>
<tr>
<td>Glucose</td>
<td>8.7 (SD 0.7)</td>
<td>8.6 (SD 0.8)</td>
<td>8.5 (SD 0.6)</td>
<td>8.5 (SD 0.9)</td>
</tr>
<tr>
<td>Quinine</td>
<td>8.3 (SD 0.8)</td>
<td>8.4 (SD 0.7)</td>
<td>8.5 (SD 0.7)</td>
<td>8.8 (SD 1.4)</td>
</tr>
<tr>
<td>Stomach infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>8.8 (SD 1.2)</td>
<td>8.7 (SD 0.8)</td>
<td>8.6 (SD 0.9)</td>
<td>8.7 (SD 1.2)</td>
</tr>
<tr>
<td>Glucose</td>
<td>8.4 (SD 0.8)</td>
<td>8.6 (SD 0.9)</td>
<td>8.6 (SD 0.7)</td>
<td>8.6 (SD 1.0)</td>
</tr>
<tr>
<td>Quinine</td>
<td>8.7 (SD 1.3)</td>
<td>8.7 (SD 1.3)</td>
<td>8.7 (SD 1.2)</td>
<td>8.8 (SD 1.2)</td>
</tr>
</tbody>
</table>

Values are means with SD (in ms) for each taste solution across each time point for oral and stomach infusions.
amplitude after all three volitional swallowing tasks could perhaps be explained by the slower volitional swallowing task used in our study (5-ml boli every 15 s) compared with that used by Fraser et al. (5-ml boli every 5 s). In this circumstance, it is conceivable that the reduction in PMEP amplitude from baseline (30 min posttaste infusion) may have begun immediately but was simply masked by the effects of the swallowing task itself. A future study looking at the excitability effects of tastsants on the tongue (without swallowing) may help to clarify this effect in more detail. Reassuringly, however, the lack of any effect after the gastric infusion of liquids does imply that this effect in more detail. Reassuringly, however, the lack of tastants on the tongue (without swallowing) may help to clarify it immediately but was simply masked by the effects of the swallowing motor pathways. Am J Physiol Gastrointest Liver Physiol 272: G802–G808, 1997.


