Differential changes in human pharyngoesophageal motor excitability induced by swallowing, pharyngeal stimulation, and anesthesia

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Swallowing is a complex sensorimotor activity that depends on a hierarchical interaction between the cerebral cortex, the brain stem swallowing center, and cranial nerves V, IX, X, and XII (11). The process of swallowing has both volitional and reflexive components, reflecting central pathways within swallowing centers in the cortex and brain stem, respectively, but is highly dependent on sensory feedback for both its initiation and modulation during the pattern sequence of neuromuscular events (12).

Over the last decade, transcranial magnetic stimulation (TMS) has become a well-established noninvasive technique for interrogating human cortical physiology (5). TMS appears to have much of its effect due to intracortical influences on the excitability of interneurons within the motor cortex, resulting in indirect activation of corticospinal tracts through synaptic inputs (5). TMS has recently been used to map the normal pattern of motor cortex projections to a number of swallowing muscles in healthy adult humans by evoking and mapping responses in oral, pharyngeal, and esophageal musculature by electromyography (EMG) (9). This demonstrated that the swallowing muscles are somatotopically but asymmetrically represented in the motor and premotor cortices of both cerebral hemispheres. This asymmetry is independent of handedness and is greatest in the pharynx and esophagus.

More recently, TMS has been used to measure pharyngeal responses in patients with brain injury on admission and at 1 and 3 mo after dysphagic hemispheric stroke (8). The study found that return of swallowing was associated with increased pharyngeal representation in the unaffected hemisphere, suggesting first that compensatory adaptation in the intact hemisphere drives much of this recovery and second that these responses have physiological relevance to swallowing recovery in stroke.

The cranial nerves involved in swallowing convey much of this sensory input and display extensive brain stem convergence, with trigeminal (and vagal) afferent fibers terminating within the trigeminal spinal nuclei and nucleus of the solitary tract (NTS) of the dorsal region of the brain stem swallowing center (11, 15, 16). These afferent fibers are not only capable of influencing brain stem motoneuron and interneuron excitability but also that of higher circuitry in the cerebral cortex (12, 18, 19).

Indeed, previous TMS studies (6, 7) have shown that excitation (afferent) pathways in cranial nerves V and X, for example from the face or neck, produces a “reflex” response in the human pharynx and esophagus that is likely to be generated via neurons within the brain stem and possibly through the central pattern generator itself. Stimulation of these cranial nerve responses, when combined with cortical input, produce short-term (100–200 ms) facilitation of the cortically evoked pharyngeal and esophageal re-

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Alte\nnations in sensory input by peripheral stimulation also produce more persistent changes in motor cortical excitability (4, 10): 10 min of pharyngeal stimulation increases pharyngeal cortical excitability for at least 30 min after the input, without changes in bulbar excitability. The application of pharyngeal stimulation to dysphagic stroke patients produces similar corticobulbar changes, which crucially are associated with short-term improvements in swallowing performance, seen as a reduction in aspiration at videofluoroscopy. Whether such central changes can be driven by more natural stimuli such as that produced by volitional water swallowing remains uncertain. Moreover, little is known about the effects of oropharyngeal anesthesia on the central swallowing pathways. There is evidence that a reduction in oropharyngeal sensation by local anesthesia can disrupt the normal pattern of voluntarily initiated swallowing measured by manometry (13), with the speculation that there could be centrally mediated factors.

Despite these suggestions, the comparative effects of increased sensory input (e.g., the motor task of swallowing vs. direct pharyngeal stimulation) or decreased sensory input (anesthesia) on the excitability of human pharyngeal and esophageal projections from cortex to motoneuron have not been examined. This is of particular importance, because an appreciation of how interventions such as behavioral training, passive stimulation, and denervation can alter central neural swallowing physiology is likely to be of importance in guiding the future rehabilitation of swallowing problems after brain injury (4).

The aims of our study were therefore to compare and contrast the effects of volitional (water) swallowing, pharyngeal (electrical), and oropharyngeal (topical) anesthesia on corticobulbar and cranialbulbar pharyngoesophageal sensorimotor pathways in healthy human subjects.

METHODS

Participants
Participants were healthy adult (n = 8) volunteers (6 male, age range 24–36 yr, mean age 31 yr). None reported any swallowing problems, and all gave informed written consent before study, previously approved by the Salford and Trafford Health Authority Ethics Committee.

Electrophysiological Techniques

Cortical stimulation. Cortical stimulation was performed by using a magnetic stimulator (Magstim 200; Magstim, Whitland, Wales) connected to a 70-mm outer diameter figure-8 coil placed over the regions of interest on the scalp (9). In this configuration, the maximal magnetic field generated by the stimulator is 2.2 T.

Cranial nerve stimulation. Cranial nerve stimulation was performed by using the magnetic stimulator connected to a smaller, 50-mm-diameter figure-8 coil, placing the center of the coil over the supraorbital branch of the trigeminal nerve on the face, as previously described (6). In this configuration, the maximum magnetic field generated by the stimulator is 2.0 T.

EMG responses. EMG responses were detected from the pharynx and upper esophagus by using two pairs of bipolar platinum ring electrodes, 7 cm apart, built into a 3-mm-diameter intraluminal catheter (Gaeltec, Dunvegan, Scotland). Two single solid-state strain-gauge transducers (Gaeltec) also incorporated into the catheter, one between each electrode pair, enabled manometric positioning of the catheter within the lumen. Each electrode pair was connected to a preamplifier (CED 1902; Cambridge Electronic Design, Cambridge, England) with filter settings of 5 Hz–2 kHz. Response signals were then collected through a laboratory interface (CED 1401 plus) at a sampling rate of 4–8 kHz.

Electrical stimulation of the pharynx. Stimulation was performed by using the pharyngeal electrodes connected to an electrical stimulator (Model DS7; Digitimer, Welwyn-Garden City, UK) via a trigger generator (Neurolog System; Digitimer), which delivered stimuli (0.2-ms pulses, 280 V) at a frequency of 5 Hz, as previously determined (4), using a set intensity of 75% maximum tolerated sensation (see Pharyngeal sensory thresholds) and 10-min duration.

Volitional water swallowing. Sterile water was infused from a 1,000-ml-capacity fluid reservoir attached to a plastic infusion line, the ending of which was placed into the oral cavity in the midline 4 cm from the incisors. The base of the fluid reservoir was positioned 10 cm above the mastoid processes. The infusion line was connected to a peristaltic pump (H. R. Flow Inducer; Watson-Marlowe, Falmouth, England), allowing continuous water infusion at a rate of 60 ml/min, thus maintaining a constant bolus volume per swallow of 5 ml when subjects swallowed at a fixed frequency of 0.2 Hz.

Topical anesthesia of the pharynx. Twenty standard-dose aerosol puffs (equivalent to 200 mg) of lidocaine (Xylocaine spray; AstraZeneca, Kings Langley, England) were sprayed into the oropharynx of each subject, the applicator being placed 4 cm aboral to the incisors in the midline. At the end of the application, the subject was asked to swallow rapidly three times to ensure adequate dispersion of the local anesthetic.

Pharyngeal sensory thresholds. To quantify the level of electrical pharyngeal stimulation to be applied and to assess the effects of topical anesthesia, electrical pulses (0.2-ms pulses, 280 V) were delivered to the pharynx at 5 Hz by using the pharyngeal electrodes of the swallowed intraluminal catheter, and the mean of three (just perceived) sensory thresholds (ST_{min}) and maximum tolerated sensory thresholds (ST_{max}) were measured. The 75% maximum tolerated intensity was calculated as follows: ST_{min} + 0.75(ST_{max} - ST_{min}).

Experimental Protocols

For each study, the volunteer sat comfortably in a chair and the pharyngoesophageal EMG catheter was inserted transnasally or transorally depending on subject preference. The catheter was then adjusted manometrically so that the pharyngeal electrodes were 3 cm above and the esophageal electrodes were 4 cm below the upper esophageal sphincter.

The cranial vertex was then marked on the scalp, and the optimal sites for magnetic stimulation were determined for both the pharynx and esophagus by discharging the 70-mm figure-8 coil over multiple scalp positions by using suprathreshold stimulus intensities. The sites evoking the largest EMG responses for the pharynx and esophagus were then identified and marked on the scalp. A series of cortical stimulations over these positions was then performed, commenc-
Pharyngeal stimulation was well tolerated, being decreased at 15 min (P < 0.05) before returning to baseline. There was also a small reduction in response latencies at 15 min (P < 0.01; Table 1).

Cranial MOTOR. As with the cortical responses, swallowing facilitated both pharyngeal and esophageal cranial nerve-evoked response amplitudes. Again, the main effect occurred immediately after volitional swallowing (pharynx: Δ = 49 ± 9%, P < 0.01; esophagus: Δ = 45 ± 20%, P < 0.05) in Figs. 1 and 2 and Table 1.

Pharyngeal Stimulation on Corticobulbar and Cranial Motor Pathways

Pharyngeal stimulation was well tolerated, being described by subjects as a “sharp buzzing” or “acid” sensation felt in the throat. Mean stimulation intensity for pharyngeal stimulation was 13.7 ± 0.5 mA. The effects of pharyngeal stimulation on the cortical and cranial motor pathways are shown (Figs. 1 and 3, Table 1).

Protocol 3: effects of oropharyngeal anesthesia on corticobulbar and cranial motor pathways. As with protocol 2, following baseline measurements, and with the catheter in situ, the pharyngeal sensory threshold was measured. Two hundred milligrams of lidocaine was then sprayed into the oropharynx. The number of spontaneous swallows was then recorded over the next 10 min. Cortical and cranial nerve stimulations, using the identical intensities and experimental sequence to those used for the baseline measures followed by rechecking of pharyngeal sensory thresholds, were then performed immediately and at 15-min intervals for 1 h.

Data Analysis

For each protocol, the individual mean values of the cortically evoked early and cranial evoked late EMG responses were compared by using two-way ANOVA (Friedman test) across all intensities for each interval in both the pharynx and esophagus: 1) to determine the effect of time against prestimulation levels and 2) to determine the conditional effects of volitional swallowing, pharyngeal stimulation, and oropharyngeal anesthesia.

The response amplitude was defined as the peak-to-peak difference in the EMG potential, and the response latency was defined as the time taken between stimulus onset and the onset of the first deflection of the relevant EMG potential.

RESULTS

The mean intensity used for cortical stimulation across studies was 1.7 ± 0.1 T. In all subjects, cortical stimulation evoked reproducible early biphasic or triphasic pharyngeo-esophageal responses (Fig. 1), with preintervention mean amplitudes of 57 ± 9 and 47 ± 8 μV for pharynx and esophagus, respectively. The mean intensity used for trigeminal nerve stimulation was 1.1 ± 0.2 T. In all subjects, trigeminal nerve stimulation evoked early (~25 ms) and late (~60 ms) EMG pharyngeo-esophageal responses, which were usually polyphasic. Because these early reflex responses were small and inconsistent, only the late responses (preintervention mean amplitudes being 32 ± 4 and 28 ± 6 μV for pharynx and esophagus, respectively) are reported below. The number of swallows made during water swallowing, pharyngeal stimulation, and anesthesia were 120 ± 5, 23 ± 3, and 9 ± 1, respectively.

Effects of Volitional Swallowing on Corticobulbar and Cranial Motor Pathways

Volitional swallowing of water boli was well tolerated by all subjects. The effects of volitional swallowing on the cortical and cranial pathways are shown in Figs. 1 and 2 and Table 1.

Corticobulbar. Both pharyngeal and esophageal cortically evoked response amplitudes were facilitated immediately after volitional swallowing (pharynx: Δ = 59 ± 12%, P < 0.001; esophagus: Δ = 45 ± 20%, P < 0.05) in Figs. 1 and 2 and Table 1.

Pharyngeal Stimulation on Corticobulbar and Cranial Motor Pathways

Pharyngeal stimulation was well tolerated, being described by subjects as a “sharp buzzing” or “acid” sensation felt in the throat. Mean stimulation intensity for pharyngeal stimulation was 13.7 ± 0.5 mA. The effects of pharyngeal stimulation on the cortical and cranial motor pathways are shown (Figs. 1 and 3, Table 1).
Corticobulbar. Pharyngeal stimulation facilitated pharyngeal and esophageal cortically evoked response amplitudes. Compared with volitional swallowing, changes were greater both in magnitude and duration. Pharyngeal response amplitudes were more affected than the esophageal responses, the maximal effect being seen at 60 min (pharynx: $\Delta = 76 \pm 19\%$, $P < 0.001$; esophagus: $\Delta = 45 \pm 23\%$, $P = 0.05$). Response latencies were unaffected.

Craniobulbar. In contrast to cortical responses, pharyngeal and esophageal cranial nerve responses were unaffected by pharyngeal stimulation.

Effects of Oropharyngeal Anesthesia on Corticobulbar and Craniobulbar Motor Pathways

Oropharyngeal anesthesia was tolerated without difficulty. Sensory threshold increased from $4.7 \pm 1.0$ mA
Table 1. Table of corticobulbar and craniobulbar evoked response latencies for pharynx and esophagus after volitional (water) swallowing, pharyngeal stimulation, and oropharyngeal anesthesia after lidocaine

<table>
<thead>
<tr>
<th></th>
<th>Volitional Swallowing</th>
<th>Pharyngeal Stimulation</th>
<th>Oropharyngeal Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortex</td>
<td>Cranialobular</td>
<td>Cortex</td>
</tr>
<tr>
<td>Pharynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>8.6 ± 0.4</td>
<td>58.4 ± 1.5</td>
<td>7.8 ± 0.3</td>
</tr>
<tr>
<td>Immediate</td>
<td>7.8 ± 0.3</td>
<td>54.7 ± 2.1</td>
<td>6.9 ± 0.4</td>
</tr>
<tr>
<td>30 min</td>
<td>7.7 ± 0.4*</td>
<td>52.6 ± 1.4*</td>
<td>6.5 ± 0.5</td>
</tr>
<tr>
<td>60 min</td>
<td>8.1 ± 0.3</td>
<td>53.3 ± 1.3</td>
<td>6.4 ± 0.3</td>
</tr>
<tr>
<td>45 min</td>
<td>7.9 ± 0.3</td>
<td>54.9 ± 1.7</td>
<td>6.8 ± 0.4</td>
</tr>
<tr>
<td>60 min</td>
<td>8.0 ± 0.2</td>
<td>56.4 ± 1.6</td>
<td>6.7 ± 0.3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Pre</td>
<td>10.1 ± 0.4</td>
<td>61.4 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td>8.9 ± 0.4</td>
<td>57.9 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>8.7 ± 0.3*</td>
<td>56.6 ± 2.0*</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>9.1 ± 0.4</td>
<td>57.1 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>45 min</td>
<td>9.4 ± 0.4</td>
<td>58.2 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>60 min</td>
<td>9.3 ± 0.3</td>
<td>58.0 ± 2.5</td>
</tr>
</tbody>
</table>

Data are means ± SE (*P < 0.05 compared to baseline) given in milliseconds.

DISCUSSION

In previous studies we have demonstrated that short-term sensory stimulation of the pharynx can induce sustained changes in the corticobulbar pathway to pharynx and esophagus (4, 10), which we argued were indicative of “cross-system” effects in the cortical swallowing network. Our data now show that both the level and duration of motor excitability varies depending on the nature of the (sensorimotor) input.

With respect to volitional swallowing, we observed a transient early increase in corticobulbar excitability for pharynx and esophagus in the period immediately after swallowing, mirrored by the reflexes to cranial

Fig. 3. Effect of pharyngeal electrical stimulation on corticobulbar and craniobulbar motor excitability. A: after stimulation, pharyngeal and esophageal cortical response amplitudes are increased at 45 min, reaching significance at 60 min. B: craniobulbar reflexes remain unaffected.
nerve stimulation. One implication from these findings is that volitional swallowing could be altering brain stem circuitry, which in turn facilitates the changes in cortical excitability. Excitation of the brain stem would seem entirely reasonable, given that swallowing engages the entire deglutitive apparatus, so that input from multiple swallowing fibers arrives at the NTS before converging on brain stem swallowing interneurons and motoneurons (11, 12). Such continuous input to brain stem circuitry would probably provide more persistent (excitability) changes in the network that might be expected to last minutes rather than milliseconds, as normally seen after a single swallow. Whether volitional swallowing could have direct effects on cortical swallowing excitability remains less clear, since any brain stem changes would mask the former. Previous work assessing the effects of task training on cortical excitability has demonstrated that motor system organization can be modified by long periods of muscle use (3), an effect termed use-dependent plasticity. An example of this is seen after extensive (hours) use of the hand muscles in violin playing, where the motor cortical representation of the target hand muscle becomes enlarged without changes in spinal (motoneuron) excitability (3). Thus it is possible that a similar phenomenon might be occurring to repetitive swallowing, although in the absence of direct intracortical recordings this suggestion must remain speculative.

In contrast to volitional swallowing, pharyngeal stimulation produced a sustained, albeit delayed, increase in corticobulbar excitability without altering craniobulbar excitability, a pattern seen in our previous studies. This effect occurred well beyond the period of input, being maximal at 60 min after stimulation. As with the findings from our previous experiments (4), it seems that pharyngeal stimulation can affect cortical excitability by activating direct and/or indirect ascending pathways to pharyngeal motor cortex. Nonetheless, an important question raised by our data is why pharyngeal stimulation does not induce the same sustained excitation in craniobulbar circuitry as with volitional swallowing. To answer this question, it is relevant to consider the sensory innervation of the pharynx and its processing within the brain. Input from the pharynx projects to NTS via the glossopharyngeal nerve and the superior laryngeal branch of the vagus. From this relay input is conveyed to interneurons of the central pattern generator, and via a relay in the pons input is conveyed to cortical centers (12). During volitional swallowing, the entire sensorimotor sequence (involving trigeminal, glossopharyngeal, and vagal cranial nerves) is activated, whereas during pharyngeal stimulation the input is from a small area of pharynx alone. Pharyngeal stimulation applied by our

Fig. 4. Lidocaine and pharyngeal sensory thresholds. Change in sensory threshold for the pharynx up to 1 h after the application of oropharyngeal anesthesia is shown. The maximal increase in sensory threshold occurs immediately after topical lidocaine, with a return to baseline level by 30 min.

Fig. 5. Effect of oropharyngeal anesthesia on corticobulbar and craniobulbar motor excitability. A: pharyngeal and esophageal cortical response amplitudes are maximally reduced 45 min after lidocaine. B: craniobulbar reflexes for pharynx are similarly affected over a similar time interval.
methodology may not, therefore, provide enough direct sensory input to produce long-term alterations in lower-level circuitry, even though it seems adequate for cortical excitation.

A further possible explanation is that with volitional swallowing there are likely to be strong descending cortical inputs to the brain stem associated with each task. Cortical input has been shown in animals to directly excite swallowing circuitry within the brain stem and can initiate swallowing movements (2, 20). In contrast, the cortical drive to the brain stem swallowing centers with pharyngeal stimulation alone may actually be reduced as subjects try to suppress the urge to swallow. Indeed, in our study, pharyngeal stimulation produced <1/5th of the number of swallows produced by the active volitional swallowing task. The result may be that pharyngeal stimulation produces much less cortically derived excitatory drive to the brain stem swallowing centers and that the latter may be important for inducing more sustained excitatory changes in brain stem swallowing circuitry when measured by craniobulbar stimulation.

A final explanation relates to the nature of the reflex responses evoked to cranial nerve stimulation. In previous studies (6, 7) we argued that the early and late pharyngo-esophageal reflexes evoked to both vagal and trigeminal nerve stimulation were likely to be of brain stem origin. The reason for this contention was that 1) the morphology and latency of the responses were similar to the R1 and R2 reflexes seen in the blink reflex, which has been well characterized and recognized to be brain stem mediated (1); 2) the properties of these reflexes to differing inputs (e.g., pharyngeal stimulation) were dissimilar to responses evoked to cortical stimulation; in the case of the latter, the cortical response is facilitated when the reflex response is not.

Nonetheless, it is conceivable that the late reflex response may be trans-cortical in nature, multisynaptic, and impinge on cortical networks outside of those utilized by the corticopharyngeal pathways evoked to TMS. If this were the case, then volitional swallowing, which likely activates all cortical swallowing networks, would activate both pathways. However, pharyngeal stimulation, being more direct, might only activate the corticopharyngeal pathway without altering excitability in other cortical swallowing networks and hence not affect the “reflex” response. Against this notion is the fact that following volitional swallowing (and with anesthesia) there were latency shifts in both pathways, which are more typically seen when motoneurons in the bulbar nuclei and/or muscle are depolarized (7). At present, our data cannot fully resolve the issue of the nature of the reflex pathway, and consequently this remains open to further study.

Following oropharyngeal anesthesia, both cortical and craniobulbar excitability was reduced, the effect maximizing at 45 min, when sensory thresholds were returning to normal. Given our observations, it could be argued that the change in excitability was secondary to changes in the muscle or motoneuron. Locally applied anesthesia such as lidocaine will preferentially block Aδ- and C-fibers involved in sensory transmis-

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