



Changes in the Excitability of Corticobulbar Projections Due to Intraoral Cooling with Ice

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Abstract

The aim of this study was to assess the effects of ice applied to the oral cavity on the excitability of corticobulbar projections to the swallowing muscles. The subjects were 8 healthy adult volunteers (mean age 29.0 ± 4.9 years). Motor-evoked potentials (MEPs) were recorded from the suprahyoid muscle complex using surface electrodes. Two blocks of 20 MEPs with a test stimulus intensity of 120% of the resting motor threshold were recorded at rest (baseline). Subjects then underwent 5-min thermal stimulation by either of 3 different types: (1) “ice-stick inside mouth,” (2) “ice-stick on neck,” and (3) “room temperature inside mouth.” Blocks of 20 MEPs were then recorded immediately and at 5-min intervals for the following 15 min. There was a significant difference in the effects of the 3 interventions on the amplitude of the MEPs following stimulation (two-way ANOVA: INTERVENTION \times TIME; $F_{8,84} = 3.76$, $p < 0.01$). One-way ANOVA was used to evaluate the changes over time for each intervention type. Only “ice-stick inside mouth” caused an increase in the MEPs (one-way ANOVA main effect of TIME: $F_{4,28} = 4.04$, $p = 0.010$) with significant differences between baseline and P10 (mean difference 0.050; confidence interval (CI) 95% 0.019–0.079; $p = 0.004$). There were no significant effects of either “ice-stick on neck” or “room temperature inside mouth” ($F_{4,28} = 1.13$, $p = 0.36$; $F_{4,28} = 1.36$, $p = 0.27$, respectively). Ice stimulation within the oral cavity increases the excitability of the cortical swallowing motor pathway.

Keywords Swallowing · Temperature · Reaction time task · Motor-evoked potential · Deglutition · Deglutition disorders

Introduction

It is known that swallowing is a complex sensorimotor activity involving hierarchical interactions between the cerebral cortex, the swallowing center in the brain stem, and cranial nerves V, IX, X, and XII [1]. Both volitional and reflexive factors play a role in swallowing, reflecting central pathways of the swallowing centers in the cortex and the brain stem, respectively [2]. Both of these factors are highly dependent on sensory feedback for the initiation and modulation of the

chronological pattern of neuromuscular events [3]. It is well known that sensory input is essential to initiate and modulate normal swallowing, and has been demonstrated by simulated dysphagia studies performed by superficial anesthesia of the oropharynx in healthy human subjects [4, 5].

Transcranial magnetic stimulation (TMS) has made it possible to map the normal pattern of motor cortex projections to various swallowing muscles in healthy adult humans using electromyography (EMG) to evoke and map responses in oral, pharyngeal, and esophageal muscles [6]. Several studies have demonstrated that altered sensory input to the swallowing system can change the excitability of the corticobulbar pathway. It has for example been shown that cranial nerve stimulation influences pharyngeal motor-evoked potentials (MEP) due to TMS of the human swallowing motor cortex [7]. Fraser and colleagues reported that the cortical excitability of swallowing is decreased after anesthesia [8]. Cortical swallowing pathways can also be modulated by sweet and bitter taste stimuli [9].

Temperature is a major sensory modality. Some studies have demonstrated a shorter time to trigger the pharyngeal

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phase of swallowing with cold [10, 11] and hot water [10] than with normal temperature water [10]. Logemann has proposed that thermal stimulation increases oral awareness by alerting a pharyngeal swallow stimulus resulting in increased speed to initiate swallowing at the level of the oral cavity [12]. Studies have also demonstrated that thermal stimulation shortened the pharyngeal phase of swallowing in health control subjects [13–15]. However, temperature-related factors affecting the central control and regulation of swallowing remain unexplored. We hypothesized that ice stimulation within the oral cavity increases the excitability of the cortical swallowing motor pathway. The aim of this study was to assess the effects of ice stimulation of the oral cavity on the excitability of the swallowing motor pathway.

Materials and Methods

Subjects

The subjects were 8 healthy adult volunteers (4 males, 4 females; mean age: 29.0 ± 4.9 years). All subjects met the inclusion criteria allowing magnetic stimulation studies, i.e., they had no history of previous brain or throat surgery, had no contraindications to magnetic stimulation like a cardiac pacemaker or history of epilepsy, were not using any central nervous system drugs like antidepressants, antiepileptics, or sleeping pills, and were not pregnant [16]. None of the volunteers had experienced previous or present swallowing difficulty. The UCL Research Ethics Committee approved the protocol, and all studies were conducted at the clinical laboratory of the Sobell Department of Motor Neuroscience and Movement Disorders at the UCL Institute of Neurology (London, UK).

Thermal Stimulation

Thermal stimulation was performed using a 4-inch-long, 0.5-inch-diameter cotton-tipped stick that had been dipped into ice water (ice stick). [17] The stick was used after the cotton tip was dipped into ice water (ice stick) or room-temperature water. Stimulation consisted of thermal stimulation of the subject for 20 s followed by swallowing of saliva, a process that was repeated 15 times within 5 min. Three different types of stimulation were performed: (1) “ice-stick inside mouth,” (2) “ice-stick on neck,” (3) “room temperature inside mouth.” For “ice-stick inside mouth,” the ice stick was applied to the back of the tongue, the tongue base, velum, and posterior pharyngeal wall of the subject to provide stimulation. The cotton tip of the ice stick was dipped into the ice water between applications to maintain the ice-cold temperature. For the condition “ice-stick on neck,” the ice-stick was applied to the superficial skin covering the

sternocleidomastoideus muscle in the subject’s neck. The neck was stimulated on the same side as the stimulated hemisphere. For the condition “room temperature inside mouth,” the cotton tip of the stick was dipped into room-temperature water before stimulating the back of the tongue, the tongue base, velum, and posterior pharyngeal wall.

Cortical Stimulation

A magnetic stimulator (Magstim 200, The Magstim, Whitland, UK) connected to a figure-8 coil with an outer diameter of 70 mm placed on the scalp over the swallowing muscle representing M1 was used to perform cortical stimulation as previously described [6, 7]. The maximum magnetic field thus generated by the stimulator was 2.2 T. In summary, stimulation was performed as follows. The coil was positioned laterally over the scalp with the handle pointing backward at an approximate angle of 45° to the sagittal plane. The location over which maximal submental MEPs could be evoked consistently was marked on the scalp.

Submental Muscle Electromyographic Responses

In this study, the same procedures were followed as in the previously reported study [18]. A pair of bipolar surface electrodes were prepared, covered with conductive gel, and placed on the right and left suprahyoid muscle complexes, respectively, 1 cm lateral to the midline each. The inter-electrode distance for each pair of electrodes was 2 cm, as measured from the center of the electrodes. The subject was asked to maximally contract the muscles of interest (by pressing the tongue against the palate) while the investigator monitored the EMG activity online to verify correct placement.

Experimental Protocols

The volunteers were asked to sit comfortably in a chair. Electrodes were first positioned as mentioned above. The cranial vertex was identified using the international 10–20 system for electrode placement and marked on the scalp, and the optimum site for evoking MEPs in the suprahyoid muscle was then determined by discharging the coil over multiple scalp positions on both hemispheres using supra-threshold stimulus intensities. The site where the largest MEPs were evoked in each hemisphere was then marked on the scalp. A series of cortical stimulations was performed at these sites, starting with a sub-threshold intensity that was increased by 2% increments of stimulator output until the motor threshold (MT) intensity was found. MT was defined as the minimum intensity of stimulator output required to evoke an MEP of $20 \mu\text{V}$ in at least 5 of 10 consecutive trials. The hemisphere with the lower MT of each subject was chosen to be stimulated. After the MT and testing side were

determined, 2 blocks of 20 MEPs (B1, B2) at a test stimulus (TS) intensity of 120% of MT were recorded. The stimuli were delivered at 5-s intervals. After the intervention, further blocks of 20 MEPs were recorded immediately and then every 5 min for 15 min following thermal stimulation (P0, P5, P10, P15). All subjects underwent all 3 different thermal stimulations at separate sessions performed in a randomized order. Intersession intervals of at least 24 h were set.

Statistical Analyses

The 3 intervention conditions concerning resting motor threshold (RMT) and test MEP size at baseline were compared using the Kruskal–Wallis test. The Greenhouse–Geisser correction was used if necessary to correct for non-sphericity. Two-way repeated-measures ANOVA was performed using raw MEP values and the factors of INTERVENTION (“ice-stick inside mouth,” “ice-stick on neck,” and “room temperature inside mouth”) and TIME (P0, P5, P10, and P15). For each thermal stimulation condition, one-way repeated-measures ANOVA was performed using raw MEP values with the factor TIME (baseline, P0, P5, P10, and P15) to assess changes over time. Paired *t* tests were used for the *post hoc* analysis. Partial η^2 values are calculated as effect size in the ANOVA models. *P* value for TIME was set at $p = 0.005$ (0.05/10 for multiple comparisons applied) and *p* value for INTERVENTION was set at $p = 0.017$ (0.05/3 for multiple comparisons applied). Baseline measurement data were reported as the mean value \pm standard error. Data were analyzed using SPSS-software (SPSS ver. 23.0 for Windows; SPSS Inc.).

Results

The baseline physiological measurements are shown in Table 1 and were not significantly different between the intervention types. The intensity used for cortical stimulation were 68.9 ± 11.2 , 66.9 ± 11.6 and $69.0 \pm 12.8\%$ MSO, respectively.

Figure 1 shows MEP before and after thermal stimulation in a representative subject.

Figure 2 shows the time course of the different intervention types. There was significant INTERVENTION \times TIME interaction ($F_{8,84} = 3.76$, $p = 0.003$, Partial $\eta^2 = 0.33$;

two-way repeated-measures ANOVA), indicating that there is a difference between the effect of the 3 types of intervention on the corticobulbar excitability. One-way ANOVA showed that only the “ice-stick inside mouth” intervention produced a significant effect on the time course of corticobulbar excitability ($F_{4,28} = 4.04$, $p = 0.010$, Partial $\eta^2 = 0.37$). Post hoc paired *t* tests showed that there were significant differences between excitability at baseline and at P10 (mean difference 0.050; confidence interval (CI) 95% 0.019–0.079; $p = 0.004$). In contrast, “ice-stick on neck” and “room temperature inside mouth” failed to influence MEPs ($F_{4,28} = 1.13$, $p = 0.36$; $F_{4,28} = 1.36$, $p = 0.27$, respectively). When the raw data were adjusted to baseline to allow comparison between the post-session effects, the *post hoc* paired *t* tests showed that the main differences between “ice-stick inside mouth” and “room temperature inside mouth” at P0 (mean difference 0.050; CI 95% 0.026–0.114, $p = 0.007$) and P5 (mean difference 0.078; CI 95% 0.030–0.126, $p = 0.006$).

Discussion

This is a first study conducted to report the after-effects of ice stimulation of the oral cavity on the excitability of the human cortical swallowing motor pathway. “Ice-stick inside mouth, i.e., oral thermal stimulation” increased the excitability of the corticobulbar projection to the mylohyoid muscles for at least 10 min after application, but “ice-stick on neck” and “room temperature inside mouth” did not have any effects. This result was not inconsistent with Magara’s study demonstrated that cold oral stimulation was able to induce significant changes in pharyngeal cortical excitability. [19]

Several previous studies have reported that cold stimulation causes shortening of the trigger for the pharyngeal phase of swallowing in nondisabled and dysphagic patients [20–22]. Swallowing afferent input is mediated via the V, IX and X cranial nerves and terminates in the brainstem in the tractus solitarius and the spinal trigeminal nucleus. These fibres then converge on the nucleus of the tractus solitaries (NTS) with a proportion ascending directly and indirectly via a pontine relay to the cortex [23]. Thermal stimulation in this study could produce cortical excitability modulation and the sensorimotor interaction between oral and pharyngeal cortical areas, which were measured as increased amplitude of MEPs in the suprahyoid muscle after thermal stimulation,

Table 1 Baseline physiological measurements

	Ice-stick inside mouth	Ice-stick on neck	Room temperature inside mouth	<i>P</i> value
RMT (%MSO)	57.4 (9.4)	55.8 (9.7)	57.5 (10.7)	0.85
Test MEP (mV)	0.12 (0.05)	0.12 (0.06)	0.13 (0.06)	0.65

RMT resting motor threshold, MEP motor-evoked potential

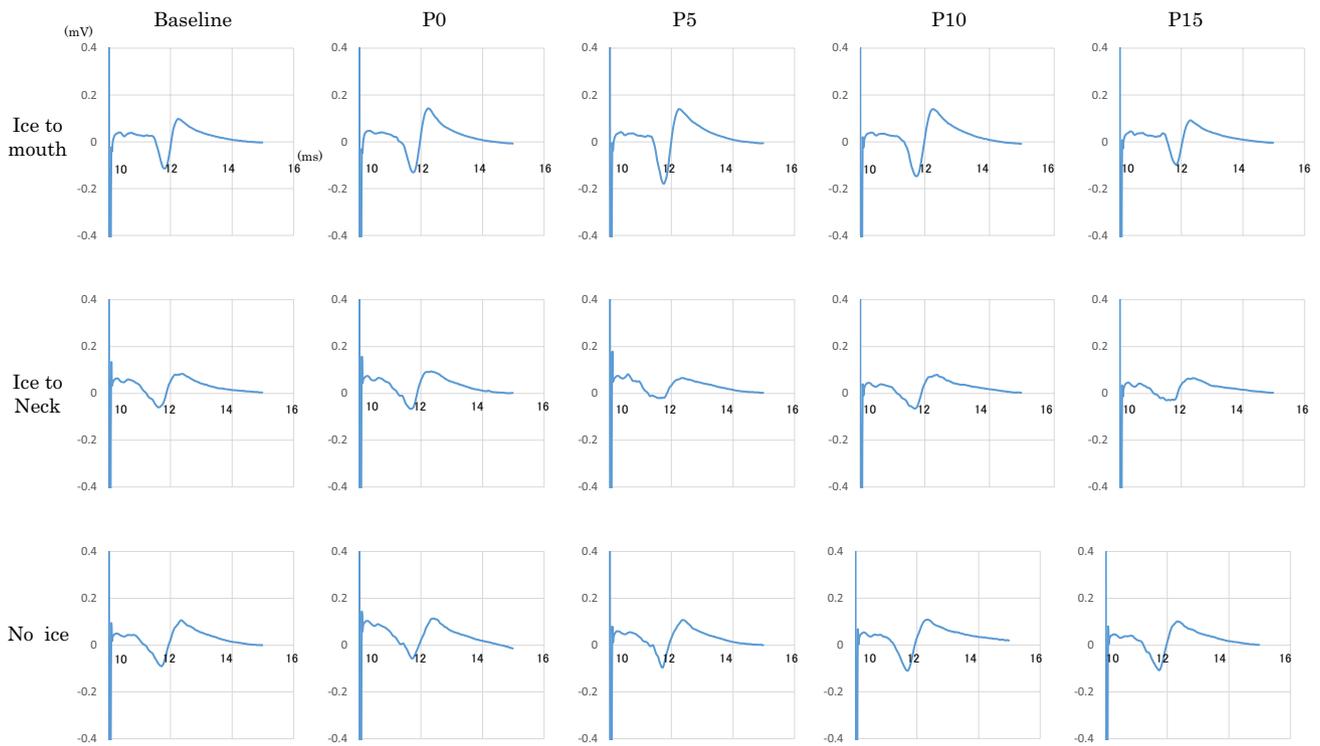


Fig. 1 Comparison of the MEP wave forms before and after thermal stimulation in a typical subject. These waves show the averaging of 20 times in each condition. *MEP* motor-evoked potential

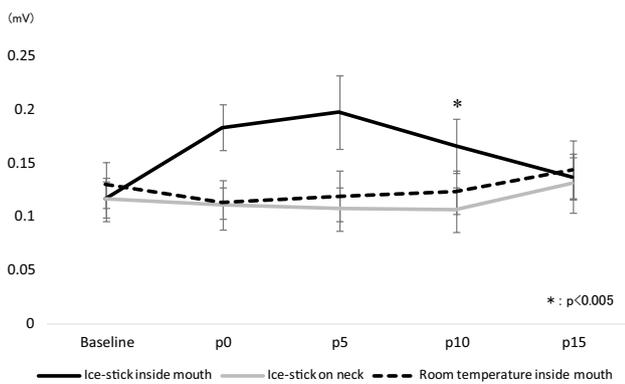


Fig. 2 Group data showing effects of each intervention on mean MEP amplitude and there was a significant effect of time on raw MEP only for “ice-stick inside mouth,” ($F_{8,84} = 3.76, p = 0.003$; two-way repeated-measures ANOVA). Post hoc paired *t* tests showed that there were significant differences between excitability at baseline and P10 ($p = 0.004$) after “ice-stick inside mouth.” *MEP* motor-evoked potential

although it can not be concluded how cortical excitability was regulated.

This reasoning is consistent with the fact that ice stimulation on the neck and room temperature stimulation inside the mouth had no effects. Note that all 3 types of stimulation involved repeated volitional swallowing. We can thus

conclude that such swallowing alone has no effect on corticobulbar excitability. Similarly, Al-Toubi and colleagues reported that repetitive volitional swallowing has no significant effect on MEPs [24].

Our study has some limitations. First, the small sample size is a limitation. Second, we did not explore MEP onset latencies. Future studies should investigate in larger samples and examine the parameters of MEP in more detail.

Overall, previous studies have mainly focused on the effect of ice on triggering of swallowing and shortening of the duration of the pharyngeal phase, but few studies have focused on changes in the cortical swallowing motor pathway excitability. Our results suggest that, in addition to the immediate effects on swallowing excitability, ice in the oral cavity leads to lasting changes in the corticobulbar excitability that persist for at least 10 min. Thus, ice stimulation has the potential for use as a pre-conditioning method for swallowing rehabilitation.

Conclusions

We found that ice stimulation of the oral cavity increases the excitability of the human cortical swallowing pathway. Further studies of swallowing patterns in patients with

dysphagia should incorporate similar forms of stimulation into the current training protocols.

Author Contribution MK and JCR contributed to the conception and study design, data acquisition, analysis and interpretation, and drafting of the manuscript. SS and RH contributed to data acquisition and analysis. ST and TF contributed to data acquisition, analysis and drafting of the manuscript. All authors revised the article critically and approved the final version for publication.

Compliance with Ethical Standards

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Informed Consent Informed consent was obtained from all participants.

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