Somatosensory Profile Changes Evoked by Topical Application of Capsaicin to the Tongue in Healthy Individuals

Mika Honda, DDS
PhD Student
Department of Oral Function and Rehabilitation
Nihon University School of Dentistry
Matsudo, Japan
and Section of Orofacial Pain and Jaw Function
Department of Dentistry
Aarhus University, Aarhus, Denmark

Lene Baad-Hansen, DDS, PhD
Associate Professor
Section of Orofacial Pain and Jaw Function
Department of Dentistry
Aarhus University, Aarhus, Denmark
and Scandinavian Center for Orofacial Neurosciences (SCON)

Takashi Iida, DDS, PhD
Assistant Professor
Department of Oral Function and Rehabilitation
Nihon University School of Dentistry
Matsudo, Japan

Osamu Komiyama, DDS, PhD
Professor
Department of Oral Function and Rehabilitation
Nihon University School of Dentistry
Matsudo, Japan

Misao Kawara, DDS, PhD
Professor
Department of Oral Function and Rehabilitation
Nihon University School of Dentistry
Matsudo, Japan

Peter Svensson, DDS, PhD, Dr Odont
Professor and Head
Section of Orofacial Pain and Jaw Function
Department of Dentistry
Aarhus University, Aarhus, Denmark
and Department of Dental Medicine
Karolinska Institutet, Huddinge, Sweden
and Scandinavian Center for Orofacial Neurosciences (SCON)

Correspondence to:
Mika Honda
Department of Oral Function and Rehabilitation
Nihon University School of Dentistry
at Matsudo, 2-870-1, Sakaecho-nishi,
Matsudo Chiba 271-8587, Japan
Fax: 81-47-360-9615
Email: mika.honda49@gmail.com

Aims: To assess the effect of topical application of capsaicin to the tongue as a surrogate model of burning mouth syndrome (BMS) on somatosensory sensitivity by using a standardized battery of quantitative sensory testing (QST) in healthy volunteers. **Methods:** This study comprised two experimental sessions (experimental [capsaicin] and control [Vaseline]) with QST in 16 healthy women. The examiner applied capsaicin or Vaseline to the tongue tip for 5 minutes. Each participant kept their tongue tip in contact with the capsaicin/Vaseline at the bottom of a disposable cup for 5 minutes, during which time the participant rated the perceived intensity of the tongue pain every 30 seconds on an electronic 0 to 10 visual analog scale (VAS). QST was performed on the tongue tip before and immediately after application in each session. The QST data were analyzed by two-way analysis of variance (ANOVA). **Results:** Mean ± standard error of the mean (SEM) of VAS pain scores during the capsaicin and control sessions were 8.2 ± 0.5 and 1.9 ± 0.2, respectively. The peak of the perceived pain in the capsaicin session was significantly higher than in the control session ($P < .001$). In the capsaicin session, the postapplication heat pain threshold (HPT) was significantly higher than the preapplication HPT, and the postapplication cold detection threshold (CDT) and mechanical pain threshold (MPT) were significantly lower than before application ($P < .001$). The average *z* scores showed a significant somatosensory loss regarding CDT. In the control session, there were no differences between preapplication and postapplication values. **Conclusion:** Topical application of capsaicin to the tongue tip changed somatosensory sensitivity in healthy participants. *J Oral Facial Pain Headache 2017;31:139–146. doi: 10.11607/ofph.1728*

Keywords: *burning mouth syndrome, capsaicin, orofacial pain, quantitative sensory testing, tongue*

Burning mouth syndrome (BMS) is a chronic burning sensation confined to the oral mucosa that represents a great burden and suffering for the patient and a great diagnostic and therapeutic challenge for the clinician. BMS often affects the tip of the tongue, is more commonly observed in women,[1] and comprises complex clinical symptoms such as frequent physical and psychosocial comorbidities.[2] Moreover, BMS has been shown to be a chronic clinical entity that manifests as a burning type of pain or a burning sensation in the mouth without any accompanying abnormal clinical or laboratory results.[3] In addition, the International Association for the Study of Pain (IASP) identified BMS as a "distinctive nosological entity" characterized by "unremitting oral burning or similar pain in the absence of detectable oral mucosa changes."[3] In functional magnetic imaging studies, BMS patients show less activation throughout the entire brain compared to normal individuals.[4] Furthermore, Lauria et al showed that biopsies of tongue mucosa affected by BMS have a significantly lower density of epithelial and subepithelial nerve fibers than those of normal subjects.[5] Although BMS is considered to be a chronic pain disorder with significant impact on quality of life,[6] its pathophysiology remains unknown. So far, there is no conclusive evidence of the underlying pain mechanisms of BMS or recommendations for the most effective treatment therapies.

Quantitative sensory testing (QST) is a useful tool for investigating somatosensory function and may aid in the study of pain mechanisms.[7–12] Past studies have found good reliability for QST on the face, the upper and lower limbs,[13] and the orofacial region.[11,14] Pigg et al further compared the sensitivity of the tongue, gingiva, and facial skin and demonstrated that the sensitivity to mechanical stimulation of the tongue was higher than that of the gingiva and the facial skin.[14] Moreover, these studies also reported that somatosensory sensitivity to thermal stimulation of the tongue was generally higher than for other intraoral sites but less than that of the facial skin. Although some studies have already investigated changes in somatosensory and neuropathic sensitivity in BMS patients, they did not apply a full QST.[15–17] In order to examine possible mechanisms underlying BMS, investigation of the somatosensory sensitivity of the tongue by using a standardized comprehensive QST battery is considered to be essential.[11,12,14]

Pain models that use an intraoral application of capsaicin on the tongue, mucosa, and gingiva have been demonstrated to show good reliability with regard to induction of somatosensory changes.[10,18,19] However, a complete battery of standardized intraoral QST has yet to be used to assess somatosensory changes after the application of capsaicin to the tongue. This study assessed the effect of topical application of capsaicin to the tongue as a surrogate model of BMS on somatosensory sensitivity by using a standardized battery of QST in healthy volunteers.

Materials and Methods

Participants

This study was carried out in 16 healthy women without any trauma, damage, or pain in the tongue (mean ± standard deviation [SD] age 25.5 ± 6.8 years). Informed consent was obtained from all participants before the experiment. This protocol was approved by the Local Ethics Committee in Central Denmark Region Denmark based on the guidelines set forth in the Declaration of Helsinki II. Participants were excluded if they were pregnant or if they had medical or psychological problems, allergy to capsaicin, or had taken analgesic, antidepressant, or hypnotic medications within 48 hours of the study.

Experimental Design

The study comprised two sessions (experimental [capsaicin] and control [Vaseline]), which were conducted on separate days in a randomized order. QST was performed on the tongue tip before and after application of the substances. The examiner applied capsaicin or Vaseline to the tongue tip for 5 minutes. The duration between the first and second experimental day was set to 3 to 5 days to avoid any possible carry-over effects. The same researcher examined all participants in a quiet room.

Topical Application

The method and time period of the application were based on the results of previous studies.[10,13] Syringes were used to apply 0.2 mL of 0.1% capsaicin and 0.2 mL of Vaseline into small disposable cups (23 × 32 mm, DMD01, Medenstar). The participants were asked to keep their tongue tip in contact with the capsaicin or Vaseline at the bottom of the cup for 5 minutes, and they rated the perceived intensity of tongue pain every 30 seconds during the 5-minute application period. An electronic visual analog scale (VAS) (Foresee-IMS Scale, Interacting Minds Centre) was used to rate the pain on a scale that ranged from 0 (no pain) to 10 (most intense pain imaginable). The participants indicated their current pain by clicking the appropriate number, shown on a computer.

QST

The standardized battery of QST on the tongue tip involved 13 thermal and mechanical tests.[14,20–22] These tests included cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT).

A thermal sensory testing device (Pathway; Medoc Inc) was used to perform the thermal tests.[11] A probe with a 6-mm diameter surface area was used for all of the tests.[11,12,14] The CDT and WDT were measured first using cold and warm stimuli, followed by the TSL. In the TSL, when the ramped stimulus reached a point where the participant first perceived the temperature as being warm, the participant pressed a button. Subsequently, the direction of the temperature ramp was reversed and the thermode cooled down until the participant perceived a temperature change and again pressed the button.[11,21] During this procedure, the number of occurrences of PHS was recorded, after which the CPT and HPT were determined.[21] Ramped stimuli of 1°C/second were used with the procedure ending when the participant pressed a button,[11,21] and the participant was not able to look at the computer screen during these measurements. The starting temperature on the tongue tip was 37°C, and the cut-off temperatures were set at 0°C for CPT and 50°C for HPT.[11,21] The interstimulus interval between each thermal measurement on the tongue tip

was 4 to 6 seconds. CDT, WDT, CPT, and HPT on the tongue tip were calculated as the mean of three measurements. Each measurement was repeated if the thermode slipped and provoked a mechanically induced pain sensation on the tongue tips.[11,21]

The MDT was measured by using a standardized set of modified von Frey filaments (OptiHair2, Marstock Nervtest Ltd).[11,12,14,22,23] The OptiHair2 set contains 12 monofilaments that exert different forces upon bending. Each monofilament increases the force by a factor of 2, ranging from 0.25 to 512 mN.[11,21] All monofilaments were applied perpendicular to the examination site, with contact times ranging from 1 to 2 seconds. The five threshold measurements were made by application of a series of ascending and descending stimulus intensities, and the threshold value was calculated using the geometric mean of these five measurements.[11,21] For the MPT measurements on the tongue tip, a custom-made set of seven weighted pinprick stimulators (The Pin Prick; Aarhus University) was used.[11,12,14,22,23] The pinprick stimulators had a flat contact surface of 0.2-mm diameter. The range of forces of pinprick stimulators was from 8 mN to 512 mN, and contact times on the tongue tip were approximately 2 seconds. All pinprick tests were made with the stimulators in a vertical position and perpendicular to the tongue tip. The method of limits technique, similar to the one used to determine the MDT, was also used to determine the MPT.[11,14,25] Similar to the MPT evaluation, the seven weighted pinprick stimulators were used for the MPS determinations.

The DMA was estimated by using three tactile stimulators including a cotton wisp, a cotton wool tip (Q-tip) attached to a flexible handle, and a disposable toothbrush (Top Dent®, Meda AB). For the DMA measurement, the three tactile stimulators were applied in a single stroke over a distance of 1 to 2 cm of the tongue tip. The MPS and DMA measurements consisted of five stimulations with each of the 10 stimulators (7 weighted pinprick stimulators and 3 tactile stimulators) in randomized order according to the German Research Network on Neuropathic Pain (DFNS) protocol.[14,21] In each of the total of 50 stimuli, the participant rated the pain on a 0 to 100 numeric rating scale (NRS) with the endpoints 0 indicating no pain and 100 indicating most intense pain imaginable. The MPS was calculated as the geometric mean of all the numeric ratings by using the seven weighted pinprick stimulators.[11,21] The DMA value was calculated as the geometric mean of all the numeric ratings using the three tactile stimulators.[11,21]

To measure the WUR, 10 pinprick stimuli were repeated at a rate of 1 Hz and the perceived magnitude on the 0–100 NRS for pain was determined. The 10 pinprick stimuli were kept constant through the use of a metronome (MA-30 Digital metronome, KORG) and the score from the 10 repeated stimuli was divided by the score from a single pinprick stimulus with the same force.[11,12,14,21–23] In the WUR assessment, the same custom-made pinprick stimulators as in the MPT determinations were used. A pinprick stimulator that delivered a force that the participant perceived as slightly painful was selected, and the 128-mN stimulator was tried first. If the response from participants to the 128-mN pinprick stimulus was 0 (not painful), the WUR assessment was performed using a greater force. If the participant perceived the stimulus as intolerable, less force was used.[11,21] If a participant did not perceive the 512-mN stimulator to be painful, the WUR assessment was abandoned. The WUR was calculated as the mean of three trials of the WUR assessment.

The VDT was assessed by using a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale).[11,12,14,21–23] In the VDT assessment, the participant was asked to raise their hands to indicate when the vibration could no longer be sensed. A 9-point scale (0–8) was used to measure the intensity of vibration, with all values recorded to an accuracy of 0.5 units. The VDT assessment consisted of three trials, and the means of the VDTs from three repetitions were calculated from all participants. The PPT was measured by using a digital pressure algometer (Somedic Algometer, Somedic Sales, Sweden) with a pinch handle and a probe with a surface area of 0.18 cm^2. During the PPT assessment, a rate of increase in pressure of 50 kPa/second was used. The participant pressed a button to interrupt the stimulation when the first painful sensation was felt. The PPT assessment consisted of three trials, and the mean of PPT from the three trials was used for analysis.

Statistical Analyses

The QST data were analyzed using two-way analysis of variance (ANOVA) with the different test substance sessions (capsaicin as experimental, and Vaseline as control) and time (pre- and postapplication) as the repeated measurement factors. Post hoc tests were performed by using Tukey honestly significant difference (HSD) test with correction for multiple comparisons. *P* values less than .05 were considered statistically significant.

With the exception of PHS and DMA, all the data were log transformed before the analyses and converted into *z* scores, with the means and SDs of the preapplication test data used as the reference.[11,14,21] A *z* score > 1.96 was regarded as a gain in somatosensory function while $z < -1.96$ was regarded as a loss of somatosensory function.[10,11,21] The area under the curve (AUC) and mean VAS pain scores during applications of capsaicin and Vaseline were calculated.

Table 1 Comparison of Quantitative Sensory Testing (QST) Results Between Pre- and Postapplication in Capsaicin and Control Sessions

Applications	CDT (°C)	WDT (°C)	TSL (°C)	PHS (/3)	CPT (°C)	HPT (°C)	MDT (mN)	MPT (mN)	MPS (NRS)	DMA (NRS)	WUR (ratio)	VDT (/8)	PPT (kPa)
Capsaicin													
Pre	29.6 (0.6)	42.0 (0.7)	11.9 (1.2)	0.0	12.9 (2.4)	46.0 (0.6)	0.2 (0.0)	97.4 (15.7)	5.2 (1.6)	0.0	3.1 (0.9)	6.3 (0.2)	75.5 (4.6)
Post	25.0 (1.2)	42.0 (0.6)	13.5 (1.2)	0.0	9.2 (1.9)	42.0 (0.6)	0.2 (0.0)	140.3 (26.0)	3.0 (1.0)	0.0	3.5 (0.6)	6.0 (0.1)	74.0 (6.1)
P value	0.002*	0.985	0.347		0.236	0.000*	0.663	0.014*	0.262		0.719	0.250	0.852
Control													
Pre	30.1 (0.5)	41.8 (0.4)	12.0 (0.8)	0.0	7.6 (1.4)	46.2 (0.5)	0.2 (0.0)	113.5 (14.8)	3.4 (1.1)	0.0	3.2 (0.5)	6.3 (0.1)	81.1 (7.1)
Post	30.1 (0.7)	41.6 (0.5)	12.7 (0.9)	0.0	8.8 (1.7)	46.0 (0.5)	0.2 (0.0)	115.3 (15.7)	2.9 (1.1)	0.0	2.8 (0.4)	6.1 (0.2)	77.2 (5.6)
P value	0.992	0.738	0.561		0.558	0.835	0.674	0.931	0.781		0.604	0.425	0.647

All data are presented as mean and standard error of the mean. CDT = cold detection threshold (°C); WDT = warm detection threshold (°C); TSL = thermal sensory limen (°C); PHS = paradoxical heat sensation (score/3); CPT = cold pain threshold (°C); HPT = heat pain threshold (°C); MPT = mechanical pain threshold (mN); MPS = mechanical pain sensitivity (mean pain rating, 0–100); DMA = dynamic mechanical allodynia (NRS); WUR = wind-up ratio; MDT = mechanical detection threshold (mN); VDT = vibration detection threshold (score/8); PPT = pressure pain threshold (kPa). $P < .05$.

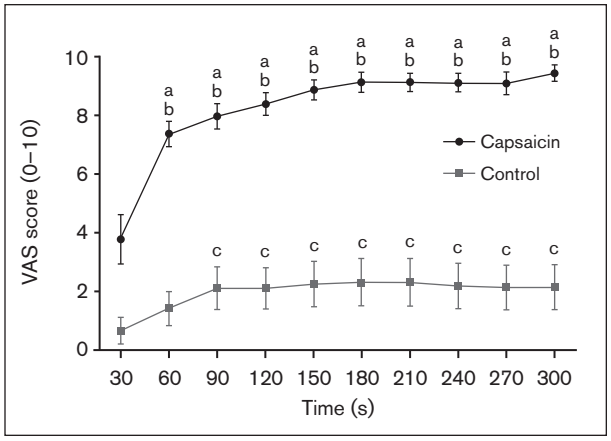

Fig 1 Self-reported visual analog scale (VAS) pain scores, which were calculated every 30 seconds for 5 minutes during the topical application of capsaicin and Vaseline on the tongue tip. Error bars indicate the standard error of the mean (SEM). [a]Indicates significant differences between capsaicin and control ($P < .05$). [b]Denotes significant differences from baseline in capsaicin session ($P < .05$). [c]Indicates significant differences from baseline in control session ($P < .05$).

The means of the VAS pain scores were compared between substances (capsaicin and control) and time points using a two-way ANOVA with Tukey tests for post hoc analysis.[17]

Results

Pain Intensity During Topical Application of Capsaicin

No participants withdrew during this experiment. Figure 1 shows the mean of self-reported VAS pain scores, which were calculated every 30 seconds for 5 minutes during the topical applications of capsaicin and Vaseline. The VAS pain scores during the application of capsaicin were significantly higher than those observed during the control condition ($P < .001$). The mean ± SEM peak of pain that occurred during the capsaicin application was 9.4 ± 0.3. The mean ± SEM of the AUC of VAS pain score in the capsaicin session (2,545.1 ± 90.2) was significantly greater than in the control session (474.3 ± 171.6; $P < .001$) (Fig 1). The overall mean ± SEM of the VAS pain scores for the 5-minute capsaicin application was 8.2 ± 0.5, while it was 1.9 ± 0.3 for the control session ($P < .001$) (Fig 1). Five participants reported VAS pain scores (0.8 to 7.1) during the control session. The capsaicin-evoked VAS pain scores from 60 seconds to 300 seconds were significantly higher than the VAS pain scores in the control session ($P < .05$; Fig 1). Interestingly, for the control condition, the VAS pain scores from 90 seconds to 300 seconds were significantly higher than those reported at baseline ($P < .05$; Fig 1).

Somatosensory Sensitivity

The ANOVA of the CDT showed that there was a significant effect of the type of substance ($P < .001$, $F = 17.481$), time ($P < .001$, $F = 20.394$), and interaction between session and time ($P < .006$, $F = 10.451$). Post hoc analysis showed that the CDT after the application of capsaicin was significantly lower (decreased sensitivity) than after Vaseline application ($P < .001$). Moreover, the HPT after the application of capsaicin was also significantly lower (increased sensitivity) than that observed prior to the application ($P < .001$). The MPT after the application of capsaicin was also significantly higher (decreased sensitivity) than that observed prior to the application ($P < .05$) (Table 1).

There were no significant differences observed for the WDT, TSL, CPT, MDT, MPS, WUR, VDT, and PPT between pre- and postapplication in either session. PHS and DMA were not encountered in any of the sessions.

z Score Analysis

Figure 2 shows the *z* scores after application of capsaicin and for the control condition when the means and SDs of the preapplication data were used as the reference values. The individual *z* scores for 16 participants from the capsaicin session indicated a somatosensory loss regarding the CDT (in 8 out of 16 participants), CPT (4 out of 16), and MPT (4 out of 16). On average, the *z* score of 16 participants after capsaicin also showed a loss of function for CDT (Fig 2). With the exception of CDT, all the other QST measures were within the range between –1.96 and 1.96.

Discussion

Pain Intensity During Topical Application of Capsaicin and Vaseline

Past studies have demonstrated that topical application of capsaicin to the tongue, mucosa, and gingiva are effective surrogate models of intraoral pain conditions.[10,18,19,25] In the current study, topical application of capsaicin to the tongue tip caused pain in all participants, and the pain intensity for capsaicin was higher than that observed during the control conditions. These results indicate that use of capsaicin on the tongue tip is a safe and effective way to create pain and therefore may be a valuable surrogate in human models to mimic some of the clinical characteristics of BMS.[25,26] However, it should be noted that five participants unexpectedly felt mild pain during the application of Vaseline. This can perhaps be explained by the fact that the whole QST battery had been applied before the Vaseline application and this may have caused minor irritation of the oral mucosa,

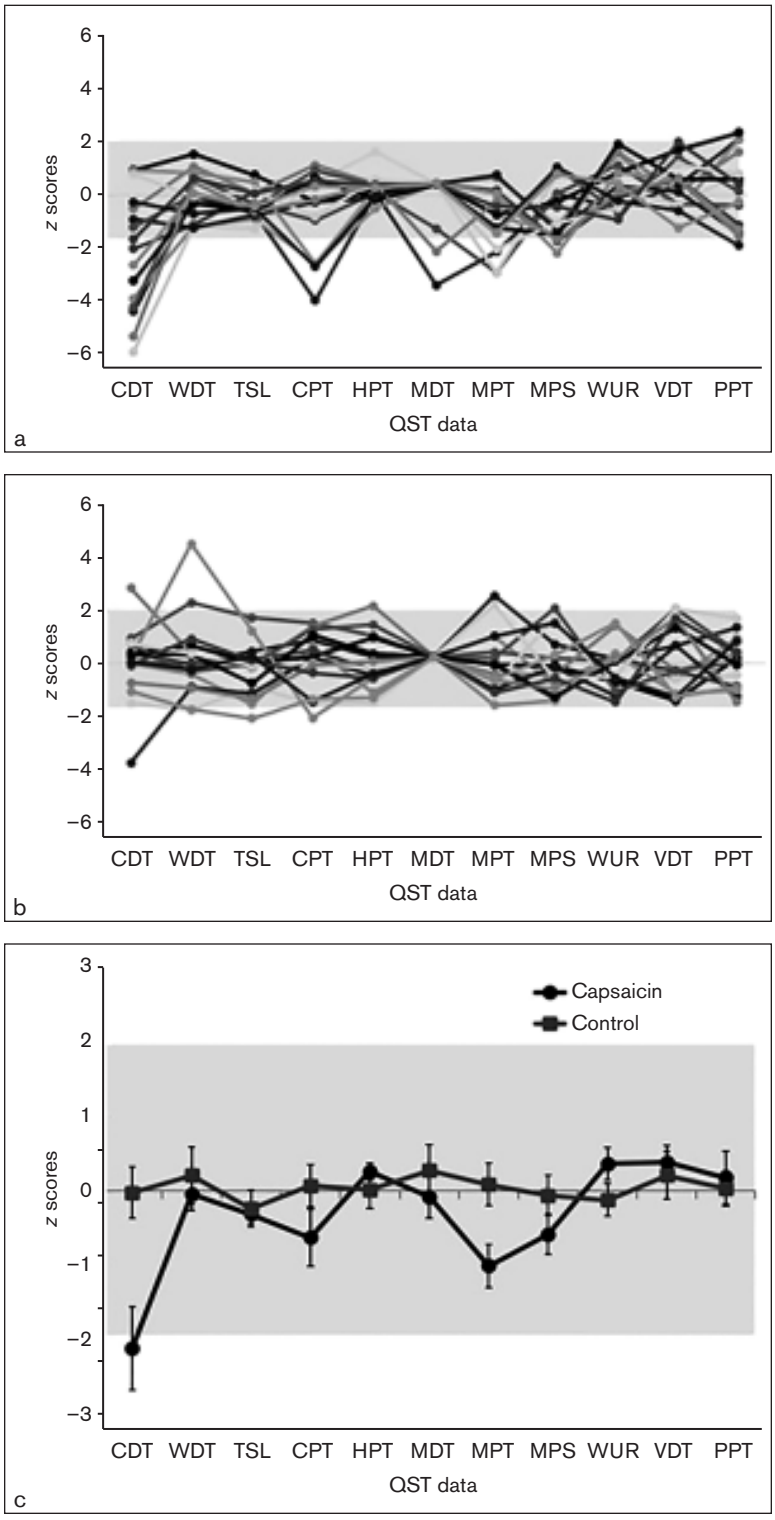

Fig 2 Individual *z* score profiles after application of capsaicin and Vaseline (control) with the use of means and standard deviations of preapplication data as the reference. Individual *z* score profiles based on QST data from the tongue tip at postapplication of **(a)** capsaicin and **(b)** Vaseline (control)**. (c)** The average *z* score (n = 16). Error bars indicate the standard error of the mean (SEM). CDT = cold detection threshold; WDT = warm detection threshold; TSL = thermal sensory limen; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; WUR = wind-up ratio; MDT = mechanical detection threshold; VDT = vibration detection threshold; PPT = pressure pain threshold. The gray zone (*z* score between –1.96 and 1.96) represents the 95% confidence interval of baseline values.

which led to low pain scores in some of participants. Moreover, the capsaicin-evoked pain on the tongue tip continued for about 1 hour. Since the duration of the QST for each session was 30 minutes, this ensured that there was enough time to document any changes in the somatosensory sensitivity that might have occurred.

Capsaicin-Evoked Changes in Somatosensory Function of the Tongue

Thermal tests in previous studies have demonstrated hypoalgesia to cold stimuli on the skin of the forearm after topical application of capsaicin.[27] In contrast, Lu et al showed that there were no changes to cold stimuli after the application of capsaicin to the gingiva.[10] The present study indicated that after application of capsaicin to the tongue tip, the CDT decreased and thereby pointed to a (relative) loss in somatosensory function related to cold stimuli. Differences in findings related to cold sensitivity between gingiva and the tongue may likely be explained by differences in afferent fiber populations between these tissues. Thermal tests have been reported to reflect the function of C- and A-delta fibers.[2,3,6] Microneurographic investigations in humans have also shown that the mechano–heat-sensitive parts of these fibers are sensitive to capsaicin.[28] The aim of the measurement of CDT on the tongue tip was to evaluate A-delta fiber function, and the observed cold hypoesthesia suggests a desensitization of these fibers. Interestingly, cold hypoesthesia has also been demonstrated in BMS patients,[15,17] indicating that application of capsaicin on the tongue tip is, indeed, a useful experimental surrogate model of aspects of BMS.

A previous study has reported gain in somatosensory functions related to WDT and HPT after an application of capsaicin to the gingiva.[18] In the present study, a gain in somatosensory function to painful heat stimuli on the tongue after the application of capsaicin was also found. Although another study suggested that sensitization of C-fibers of the gingiva can influence the HPT,[10] the present study found that there were no significant differences in the WDT between pre- and postapplication of capsaicin. The present results therefore suggest that sensitization/desensitization to nonpainful warm stimuli did not occur on the tongue tip after application of capsaicin. On the other hand, Mo et al showed that HPT and WDT of Chinese BMS patients were significantly higher (indicating sensory loss) than in normal participants.[15] However, Grushka et al reported that there were no significant differences in HPT between BMS patients and healthy participants.[16] Due to these seemingly conflicting results, further studies are needed to investigate the possible abnormalities in heat pain sensitivity in BMS patients.

In the case of the blood flow and the temperature of the tongue, Boudreau et al showed that both the blood flow and the temperature of the tongue increased after local application of capsaicin.[26] Heckmann et al showed that blood flow in the tongue in BMS patients was lower than in healthy participants.[29] However, this study also showed that vasoreactivity in BMS patients was higher than in healthy participants.[29] Further studies are needed to investigate the blood flow and the temperature of the tongue in BMS patients.

Previous studies on mechanical sensitivity have shown that cutaneous or intradermal application of capsaicin normally results in mechanical allodynia and hyperalgesia.[20,28–31] However, Lu et al applied mechanical test stimuli to the intraoral area and found that mechanical sensitivity decreased (ie, MPT increased and MPS decreased) after the topical application of capsaicin to the gingiva.[10] The present study also showed that mechanical sensitivity decreased (MPT increased) after the topical application of capsaicin to the tongue tip. These findings suggest that the change in mechanical sensitivity from the application of capsaicin to the intraoral area was different from the hairy skin of the hand or foot.[20,28] On the other hand, Mo et al showed that there were no significant differences in MDT and MPT between Chinese BMS patients and normal participants.[15]

Recent investigations have demonstrated that after the application of capsaicin to the gingiva, the mean *z* score reflects somatosensory gain of heat sensitivity on the gingiva.[10] The mean *z* score for capsaicin in all 16 participants in the current study showed somatosensory loss related to cold detection. Although there were significant differences for the HPT and MPT between pre- and postapplication of capsaicin to the tongue tip, the mean *z* score indicated that the HPT and MPT were within the normal range based on the preapplication data. Hence, the *z* score analysis may be considered more conservative than a simple comparison of mean values.[10]

The present study investigated the effect of topical application of capsaicin to the tongue tip on somatosensory sensitivity, and the results were different from studies using application of capsaicin to the gingiva. Abe et al demonstrated that the basement membrane of the epithelia of oral mucosa, gingiva, and tongue is morphologically the same not only by transmission but also by scanning electron microscopy.[32] However, transient receptor potential vanilloid type 1 (TRPV1) receptors have been found to be most abundant in the circumvallate, foliate, and fungiform papillae of the tongue.[33] In addition, some immunohistochemical studies of mucosal biopsies from clinical BMS cases have revealed significant increases in the expression of nerve growth factor

(NGF), TRPV1, ion channels, and P2X3 receptors within surviving subepithelial nerve fibers.[34,35] To further evaluate the pathologic mechanisms of BMS, additional studies are needed to investigate the relationship between somatosensory sensitivity by using QST and immunohistochemical information from mucosal biopsies of the tongue tip.

Notably, psychological factors were not investigated in the present study because only healthy women participated. However, previous studies have shown that BMS patients have a high occurrence of psychological comorbidities.[36,37] Further studies are therefore also needed to investigate the relationship between somatosensory sensitivity and psychological factors using QST.

Conclusions

Topical application of capsaicin to the tongue tip changed somatosensory sensitivity in healthy participants.

Acknowledgments

The authors report no conflicts of interest.

References

1. Jimson S, Rajesh E, Krupaa RJ, Kasthuri M. Burning mouth syndrome. J Pharm Bioallied Sci 2015;7(suppl 1):S194–S196.
2. Coculescu EC, Tovaru S, Coculescu BI. Epidemiological and etiological aspects of burning mouth syndrome. J Med Life 2014;7:305–309.
3. Merskey H, Bogduk N. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Seattle: International Association for the Study of Pain, 1994.
4. Albuquerque RJ, de Leeuw R, Carlson CR, Okeson JP, Miller CS, Andersen AH. Cerebral activation during thermal stimulation of patients who have burning mouth disorder: An fMRI study. Pain 2006;122:223–234.
5. Lauria G, Majorana A, Borgna M, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332–337.
6. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sánchez-Siles M, Gómez-Garcia F. Burning mouth syndrome: An update. Med Oral Patol Oral Cir Bucal 2010;15:e562–e568.
7. Ishida Y, Ugawa S, Ueda T, Murakami S, Shimada S. Vanilloid receptor subtype-1 (VR1) is specifically localized to taste papillae. Brain Res Mol Brain Res 2002;107:17–22.
8. Komiyama O, De Laat A. Tactile and pain thresholds in the intra- and extra-oral regions of symptom-free subjects. Pain 2005;115:308–315.
9. Komiyama O, Kawara M, De Laat A. Ethnic differences regarding tactile and pain thresholds in the trigeminal region. J Pain 2007;8:363–369.
10. Lu S, Baad-Hansen L, List T, Zhang Z, Svensson P. Somatosensory profiling of intra-oral capsaicin and menthol in healthy subjects. Eur J Oral Sci 2013;121:29–35.
11. Baad-Hansen L, Pigg M, Ivanovic SE, et al. Intraoral somatosensory abnormalities in patients with atypical odontalgia—a controlled multicenter quantitative sensory testing study. Pain 2013;154:1287–1294.
12. Svensson P, Baad-Hansen L, Pigg M, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions--a taskforce report. J Oral Rehabil 2011;38:366–394.
13. Geber C, Klein T, Azad S, et al. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): A multi-centre study. Pain 2011;152:548–556.
14. Pigg M, Baad-Hansen L, Svensson P, Drangsholt M, List T. Reliability of intraoral quantitative sensory testing (QST). Pain 2010;148:220–226.
15. Mo X, Zhang J, Fan Y, Svensson P, Wang K. Thermal and mechanical quantitative sensory testing in Chinese patients with burning mouth syndrome—A probable neuropathic pain condition? J Headache Pain 2015;16:84.
16. Grushka M, Sessle BJ, Howley TP. Psychophysical assessment of tactile, pain and thermal sensory functions in burning mouth syndrome. Pain 1987;28:169–184.
17. Forssell H, Jääskeläinen S, Tenovuo O, Hinkka S. Sensory dysfunction in burning mouth syndrome. Pain 2002;99:41–47.
18. Baad-Hansen L, Jensen TS, Svensson P. A human model of intraoral pain and heat hyperalgesia. J Orofac Pain 2003;17:333–340.
19. Naganawa T, Baad-Hansen L, Ando T, Svensson P. Influence of topical application of capsaicin, menthol and local anesthetics on intraoral somatosensory sensitivity in healthy subjects: Temporal and spatial aspects. Exp Brain Res 2015;233:1189–1199.
20. Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. Brain 2001;124(Pt 9):1754–1764.
21. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
22. Krumova EK, Westermann A, Maier C. Quantitative sensory testing: A diagnostic tool for painful neuropathy. Future Neurol 2010;5:721–733.
23. Maier C, Baron R, Tölle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150:439–450.
24. Baumgärtner U, Magerl W, Klein T, Hopf HC, Treede RD. Neurogenic hyperalgesia versus painful hypoalgesia: Two distinct mechanisms of neuropathic pain. Pain 2002;96:141–151.
25. Ngom PI, Dubray C, Woda A, Dallel R. A human oral capsaicin pain model to assess topical anesthetic-analgesic drugs. Neurosci Lett 2001;316:149–152.
26. Boudreau SA, Wang K, Svensson P, Sessle BJ, Arendt-Nielsen L. Vascular and psychophysical effects of topical capsaicin application to orofacial tissues. J Orofac Pain 2009;23:253–264.
27. Callsen MG, Moller AT, Sorensen K, Jensen TS, Finnerup NB. Cold hyposensitivity after topical application of capsaicin in humans. Exp Brain Res 2008;191:447–452.
28. Liu M, Max MB, Robinovitz E, Gracely RH, Bennett GJ. The human capsaicin model of allodynia and hyperalgesia: Sources of variability and methods for reduction. J Pain Symptom Manage 1998;16:10–20.
29. Heckmann SM, Heckmann JG, Hilz MJ, et al. Oral mucosal blood flow in patients with burning mouth syndrome. Pain 2001;90:281–286.

30. Fuchs PN, Campbell JN, Meyer RA. Secondary hyperalgesia persists in capsaicin desensitized skin. Pain 2000;84: 141–149.
31. Chen J, Chen HS. Pivotal role of capsaicin-sensitive primary afferents in development of both heat and mechanical hyperalgesia induced by intraplantar bee venom injection. Pain 2001;91:367–376.
32. Abe M, Osawa T. The structure of the interstitial surfaces of the epithelial basement membranes of mouse oral mucosa, gingiva and tongue. Arch Oral Biol 1999;44:587–594.
33. Ishida Y, Ugawa S, Ueda T, Murakami S, Shimada S. Vanilloid receptor subtype-1 (VR1) is specifically localized to taste papillae. Brain Res Mol Brain Res 2002;107:17–22.
34. Yilmaz Z, Renton T, Yiangou Y, et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: Increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. J Clin Neurosci 2007;14:864–871.
35. Beneng K, Yilmaz Z, Yiangou Y, McParland H, Anand P, Renton T. Sensory purinergic receptor P2X3 is elevated in burning mouth syndrome. Int J Oral Maxillofac Surg 2010;39:815–819.
36. Komiyama O, Nishimura H, Makiyama Y, et al. Group cognitive-behavioral intervention for patients with burning mouth syndrome. J Oral Sci 2013;55:17–22.
37. Honda M, Iida T, Komiyama O, et al. Characteristics of middle-aged and older patients with temporomandibular disorders and burning mouth syndrome. J Oral Sci 2015;57:355–360.