Effect of Experimental Periodontal Ligament Pain on Gingival Somatosensory Sensitivity

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Aims: To use a randomized, blinded, crossover design to evaluate the possible heterotopic effects of experimental periodontal ligament pain on adjacent gingival somatosensory sensitivity. **Methods:** A total of 12 healthy volunteers (8 female, 4 male; mean age ± standard error in means (SEM): 28 ± 1 years) participated in two randomized experimental quantitative sensory testing (QST) sessions, one in which capsaicin (experimental) was injected into the periodontal ligament and one in which isotonic saline (control) was injected. A total of 13 standardized QST measures were obtained on the buccal attached gingiva of a maxillary central incisor before, immediately after, and 30 minutes after injection of 30 µL of 5% capsaicin or isotonic saline into the periodontal ligament of the same incisor. The injection-evoked pain was evaluated on a 0–10 numeric rating scale (NRS). QST data were analyzed with two-way repeated measurement analysis of variance. **Results:** Capsaicin injected into the periodontal ligament evoked moderate levels of pain (mean peak NRS ± SEM: capsaicin: 5.5 ± .7; control: 0.6 ± 0.5 [$P < .001$]). Capsaicin injected into the periodontal ligament significantly modulated gingival somatosensory sensitivity: increased sensitivity to warmth and painful heat stimuli occurred immediately and 30 minutes after the injection ($P < .025$), whereas decreased sensitivity to both tactile and painful mechanical stimuli ($P < .011$) occurred immediately after the injection and to painful mechanical stimuli only after 30 minutes ($P = .016$). No somatosensory changes were detected following the injection of isotonic saline ($P > .050$). **Conclusion:** Capsaicin injected into the periodontal ligament caused gain of heterotopic somatosensory sensitivity toward warmth and painful heat stimuli as well as reduction in mechanical sensitivity of the gingiva adjacent to the injected tooth. These findings may have implications for interpretation of somatosensory functions in patients with chronic intraoral pain, where gingival somatosensory profiles similar to those detected after capsaicin injection in the present study may be interpreted as signs of nerve damage. *J Oral Facial Pain Headache 2017;31:72–79. doi: 10.11607/ofph.1765*

Keywords: *capsaicin, intraoral QST, pain mechanisms, periodontal ligament, somatosensory*

There are a number of enigmatic orofacial pain conditions that do not have well-established diagnostic criteria and have significant gaps in understanding of their underlying pathophysiology. One such condition is atypical odontalgia (AO),[1,2] for which the term persistent dentoalveolar pain (PDAP) has been suggested.[3] Furthermore, because a majority of AO patients appear to have localized disturbances in somatosensory function[4,5] consistent with the involvement of neuropathic pain mechanisms, it has been proposed that this subset of AO patients may represent painful traumatic trigeminal neuropathy (PTTN).[1,2,4,6–10] A concern in assessing AO or PTTN patients is the specificity of quantitative sensory testing (QST) to identify somatosensory abnormalities related to nerve damage or noxious stimulation of different intraoral tissues and structures.[11] Recently, it has been demonstrated that acute dental pain evoked by electrical tooth stimulation causes modest changes in adjacent gingival sensitivity.[12] This may suggest that conditions affecting intraoral afferents may lead to heterotopic gingival somatosensory changes.[12] Knowledge about the effect of

acute dental or periodontal pain on gingival somatosensory sensitivity is important for the interpretation of results from patients with chronic orofacial pain, for whom sensory testing is used for the evaluation of possible pain mechanisms and nerve damage. So far there have been no reports about the effects of noxious stimulation of the periodontal ligament on gingival somatosensory function.

QST can be used to examine intraoral somatosensory sensitivity.[4,11,13,14] The present guidelines for assessment of somatosensory sensitivity in the orofacial region are based on the standardized QST protocol proposed by the German Research Network for Neuropathic Pain (DFNS).[11,15] Currently, the DFNS battery of 13 QST tests is recommended, as it has not yet been possible to put forward a more simple and condensed protocol with adequate reliability and validity and sufficient assessment of the spectrum of nerve fibers.

Capsaicin is a transient receptor potential vanilloid 1 (TRPV1) agonist.[16] TRPV1 receptors are present in the gingiva as well as in the periodontal ligament.[17] When topically applied to human oral mucosa, capsaicin may induce a painful burning sensation and an axon reflex–like vasodilation, neurogenic inflammation, and somatosensory changes at the application site as well as in the surrounding tissues.[8,10,18–22] Thus, a positive feature of the use of capsaicin is that it may be useful to distinguish between somatosensory modulations at the application site (ie, the primary zone) and outside the application area (ie, the secondary zone),[23] as these modulations may reflect the involvement of different pain mechanisms. Somatosensory changes in the secondary zone are mostly attributed to mechanisms in the central nervous system (CNS).[21–23]

Sensory inputs from the tooth pulp and adjacent periodontal tissues converge in the CNS.[24] As mentioned above, a recent study indicated that electrical stimulation of the tooth pulp is associated with modest somatosensory changes in adjacent gingival tissue, thus suggesting the possibility of activation of axon reflex–like mechanisms in this area.[12] However, to the authors' knowledge, no studies have so far systematically investigated the effect of acute experimental periodontal ligament pain on the somatosensory sensitivity at the adjacent gingiva; ie, adjacent heterotopic sites. Knowledge about such possible somatosensory changes induced by acute pain is essential for guiding the correct interpretation of somatosensory abnormalities in orofacial pain patients.

Therefore, the aim of this human experimental study was to use a randomized, blinded, cross-over design to evaluate the possible heterotopic effects of experimental periodontal ligament pain on adjacent gingival somatosensory sensitivity.

Materials and Methods

Participants

A total of 12 healthy adult volunteers (8 female and 4 male) with a mean (± SEM) age of 28 ± 1 years were recruited by posting an advertisement on the website www.forsoegsperson.dk. Inclusion criteria were: healthy; at least one upper healthy central incisor without a filling/root canal treatment/crown. Exclusion criteria were: allergy to capsaicin/chili; pregnancy; mental disorders; orofacial pain; temporomandibular disorders (TMD); dental treatment within the previous month; and intake of medication within 48 hours of the investigation.[12] This study was performed in accordance with the Declaration of Helsinki II. The study was approved by the local ethics committee (Central Denmark Region) and all participants gave written informed consent before data collection. No bleeding after the injections was detected and no adverse events were registered.

Study Design

This study was performed in a double-blinded, controlled, crossover manner; ie, the participants each served as their own control. The full experiment included two QST experimental sessions, one with capsaicin (test) and one with isotonic saline (control), separated by 3 to 7 days to avoid possible carryover effects of pain or sensory alterations. The sequence of the two sessions was random. Randomization was performed by a research assistant who was not involved in data collection. Injection and test sites were identical between sessions.

A total of 13 standardized QST measures were obtained at the most cranial part of the buccal attached gingiva of a healthy upper central incisor (6 participants on the left side, 6 participants on the right side) before, immediately after, and 30 minutes after the periodontal capsaicin injection (duration of 7 minutes) at the same incisor.[12]

Periodontal Capsaicin Application

A lip retractor was used to keep the upper lip from touching the anterior tooth and gingival tissues. The same examiner injected either 30 µL of 5% capsaicin[18] (Aarhus University Hospital Pharmacy) or isotonic saline (0.9%) by using a pen-style intraligamental syringe (Paroject, Rønvig Dental) with a 30-gauge, 2-cm needle and with a controlled dosage that permitted a slow nontraumatic injection into the buccal aspect mid-portion of the periodontal ligament. The buccal and lingual aspects of the gingival margin were then immediately sealed with an oral bandage (Urihesive, ConvaTec Ltd), which was left in place for 7 minutes. In this way, it was possible to prevent the capsaicin from spreading to nearby regions.[25] After removal of the oral

bandage, the participants were instructed not to touch the application area with their tongue. The 7-minute application period was chosen based on an earlier study with another acute pain model (electrical tooth stimulation) and on the intent to elicit pain of a sufficient duration for induction of possible somatosensory changes in the surrounding tissues.[12]

The intensity of perceived pain was recorded by having the participants rate the intensity from immediately after the capsaicin or isotonic saline injection and then every 60 seconds throughout the duration of the session (0–7 minutes). Pain intensity was recorded on a 0–10 numeric rating scale (NRS), with 0 indicating no pain and 10 indicating the most pain imaginable. The total duration of the capsaicin-evoked pain was not recorded. In order to avoid movement of the jaw, the participants used their fingers to indicate the pain level (ie, a pain score of 2 on the NRS was indicated by showing two fingers to the examiner).[12]

QST and Raw Data Processing

A standardized intraoral QST protocol was used in accordance with current guidelines and previous studies.[4,12,13,15] The protocol comprises 13 measures and tests the function of different afferent fiber types by testing 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 (ALL), wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT).[12–14] The room temperature was kept at around 20°C during the testing. Measurements were taken by the same trained investigator fully adhering to the test instructions and using standardized verbal instructions for the participants.[12] All 13 measures have been described in detail elsewhere.[4,12,14] All thermal tests were performed by using a Medoc Pathway (Medoc) with an intraoral probe 6 mm in diameter.[4,12,14] MDTs were measured by using a standardized set of modified von Frey filaments (OptiHair2, MARSTOCKnervtest) exerting forces between 0.25 mN and 512 mN.[4,12,14] MPT, MPS, and WUR were obtained using a set of custom-made weighted mechanical pinprick stimulators with forces ranging from 8 mN to 512 mN (Aarhus University).[4,12,14] Measures for ALL utilized a set of three tactile stimulators: a cotton wisp (~3 mN), a cotton wool Q-tip attached to a flexible handle (~100 mN), and a disposable toothbrush (Top Dent, Meda AB; ~200 mN).[4,12,14] VDT was estimated by using a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale), and PPT was measured with a digital pressure algometer (SOMEDIC Algometer, SOMEDIC Sales AB).[4,12,14]

All QST measures except for PHS, CPT, HPT, and VDT were transformed logarithmically before statistical analysis according to the DFNS instructions and to obtain a normal distribution of data.[15] To avoid a loss of 0 values, a small constant (0.1) was added to pain ratings in the WUR estimation.[4,14]

Due to the amount of time needed to complete the full QST battery (30 minutes)—which was speculated to outlast the hypothesized gingival somatosensory changes[12]—the full QST protocol was separated into approximate thirds: *(1)* thermal tests (CDT, WDT, TSL, PHS, CPT, HPT); *(2)* MDT, MPT, MPS, ALL; and *(3)* WUR, VDT, and PPT. The three sections of the QST protocol were applied in a randomized order to minimize possible sequence effects on the somatosensory assessment.[12]

Statistical Analyses

Data are presented as means ± SEM. NRS and QST data were analyzed with two-way repeated measurement (RM) analysis of variance (ANOVA) with session (two levels: capsaicin and saline) and time (NRS: eight levels: 0, 1, 2, 3, 4, 5, 6, and 7 minutes; QST: three levels: baseline, after injection, and 30 minutes after injection) as RM factors. When appropriate, Tukey honest significant difference (HSD) tests with correction for multiple comparisons were used for post hoc analyses. P values less than .05 were considered statistically significant.

Results

Experimental Periodontal Ligament Pain

For most participants (11/12), the injection of capsaicin into the periodontal ligament evoked moderate levels of pain (mean peak pain NRS ± SEM: 5.5 ± 0.7), which was significantly higher than that elicited by the injection of isotonic saline (mean peak pain NRS ± SEM: 0.6 ± 0.5, $P < .001$) (Fig 1). In one participant, none of the injections were perceived as painful. No adverse events were induced in any of the participants. There were significant main effects of session and time ($P < .001$) and there was a significant interaction between factors ($P = .032$). The pain in the capsaicin session was significantly higher than in the isotonic saline session ($P < .001$). Overall, the pain at the last time point was significantly lower than at the first four time points ($P < .047$); however, a separate analysis of the capsaicin session alone revealed that the pain was not statistically significantly different between time points ($P > .203$), indicating that the pain lasted throughout the 7-minute application period. Also, the capsaicin-evoked pain was significantly higher than the pain evoked by the isotonic saline injection at all time points ($P < .001$).

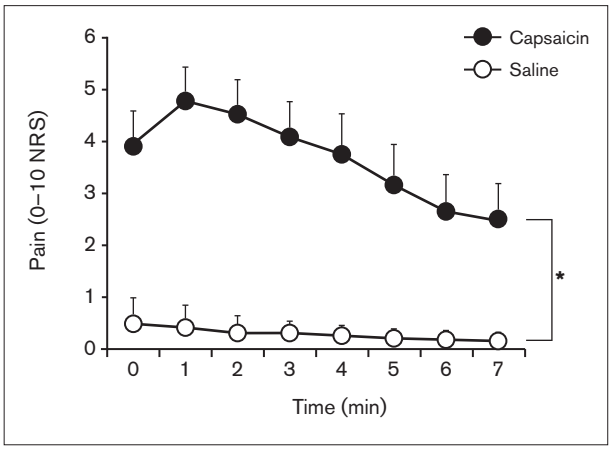

Fig 1 Subject-reported numeric rating scale (NRS) pain scores (mean values ± SEM) from the periodontal ligament injection of capsaicin *(black circles)* or isotonic saline *(white circles)*. The results represent NRS values (n = 12) obtained immediately after injection and every 60 seconds in the following 7 minutes. *Indicates significant difference between effects of capsaicin and isotonic saline ($P < .05$).

Effects of Periodontal Capsaicin Injection on Gingival Somatosensory Sensitivity

Injection of capsaicin into the periodontal ligament significantly modulated gingival somatosensory sensitivity (Figs 2 and 3).

Thermal QST

There were no significant effects of session or time on CDT ($P > .163$). There were significant main effects of session and time on WDT ($P < .005$). A post hoc test revealed that immediately after and 30 minutes after the capsaicin injection, WDT was significantly reduced ($P < .004$), which was not the case after the isotonic saline injection ($P > .330$). There was no main effect of session ($P = .440$) but there was of time ($P = .046$) on TSL. Also, there was a significant session × time interaction ($P = .032$) on TSL, and the post hoc analysis indicated that the TSL was lower (indicating increased sensitivity) immediately after the capsaicin injection compared with immediately after the isotonic saline injection ($P = .047$). The CPT was not significantly influenced by session or time ($P > .210$); contrary to this, there were significant main effects of session and time on HPT ($P < .005$) as well as a significant interaction between factors ($P = .008$). The post hoc test revealed that HPT was significantly reduced (indicating increased sensitivity) immediately after and 30 minutes after the capsaicin injection compared with before the injection and compared with the isotonic saline session ($P < .025$) (Fig 2).

Mechanical QST

On MDT, there was no main effect of session ($P = .122$) but there was of time ($P < .001$), as well as an interaction between factors ($P = .019$) (Fig 3). The post hoc test demonstrated that MDT was increased (indicating decreased sensitivity) immediately after and 30 minutes after the capsaicin injection compared with before the injection ($P < .001$). In comparison with the isotonic saline session, MDT was reduced immediately after the capsaicin injection ($P = .011$), and there was a tendency in the same direction at 30 minutes after the injection ($P = .072$). There was a tendency toward a significant effect of time on MPT ($P = .056$). Also, there was a main effect of session ($P = .011$) and a significant interaction between factors ($P = .004$) for MDT. The post hoc test showed that MPT was increased (indicating reduced sensitivity) immediately after and 30 minutes after the capsaicin injection compared with before the injection ($P < .011$) and compared with the isotonic saline session ($P < .016$). A similar pattern was seen for MPS, where sensitivity was reduced at both time points after the capsaicin injection compared with before the injection ($P < .001$) and compared with the isotonic saline session ($P < .001$).

There was no main effect of session ($P = .175$) but there was of time ($P = .039$) on WUR, with no significant interaction between factors. A post hoc test revealed an increase in WUR at 30 minutes after both injections ($P = .035$). No main effects of session, time, or interactions between factors were found for PPT or VDT ($P > .016$) (Fig 3).

PHS and ALL were not registered in any participant in any of the sessions (data not shown since only 0 values were obtained).

Discussion

The main findings in this double-blinded experimental study were that an acute capsaicin-evoked pain in the periodontal ligament caused adjacent heterotopic gain of somatosensory sensitivity to warmth and painful heat stimuli, as well as loss of mechanical sensitivity, in the gingiva adjacent to the injected tooth, indicating a differential involvement of competing sensitizing and inhibitory mechanisms evoked by an acute adjacent nociceptive input.

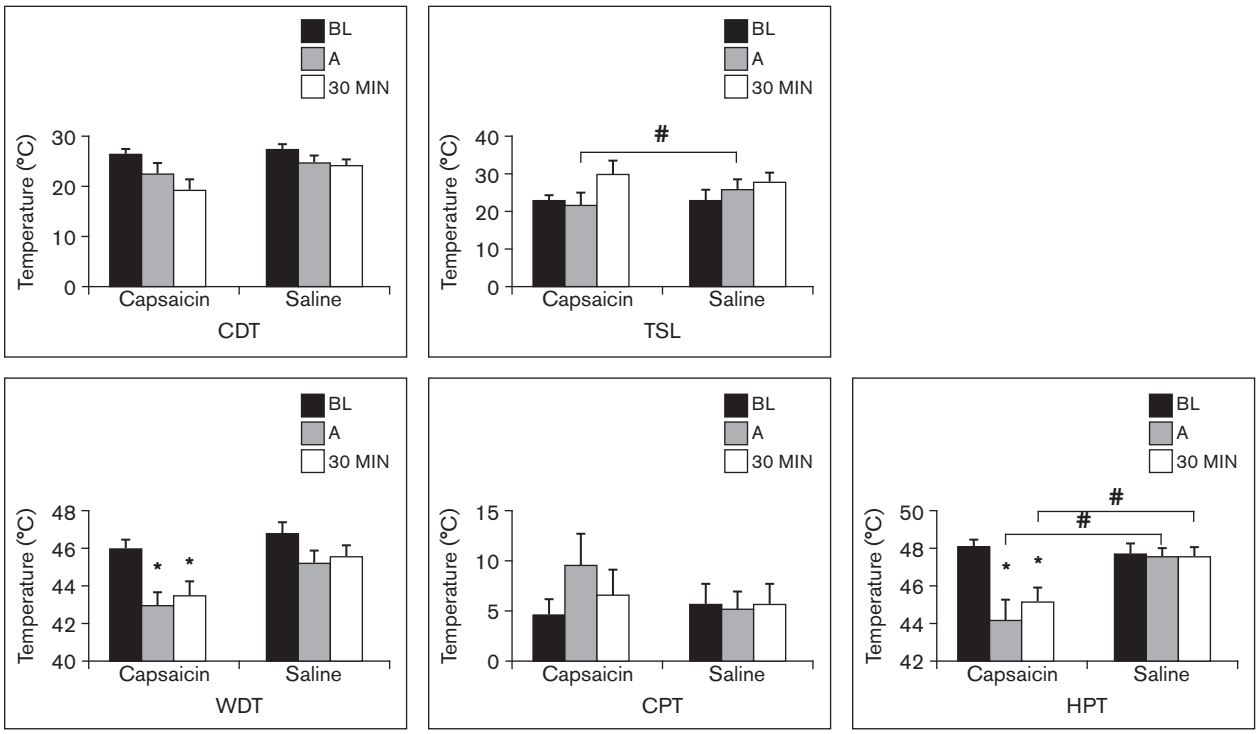

Fig 2 Mean ± SEM values of thermal thresholds at three time points (BL = baseline, black bars; A = immediately after injection, dark grey bars; 30 MIN = 30 minutes after injection, light grey bars) during two QST sessions with capsaicin or isotonic saline (control). CDT = cold detection threshold (°C); WDT = warmth detection threshold (°C); TSL = thermal sensory limen (°C); CPT = cold pain threshold (°C); HPT = heat pain threshold (°C). *Indicates significant difference from BL ($P < .05$). #Indicates significant difference between sessions ($P < .05$).

Experimental Pain Intensity

The pain models of topical application of capsaicin to the gingiva are well described,[18,21,26,27] while the injection of capsaicin into the human periodontal ligament has only been described once before.[25] In the present study, 5% capsaicin was chosen on the basis of the findings of earlier studies.[18,26–28] As a result, the injection of capsaicin into the periodontal ligament caused moderate levels of pain, except in one participant. The moderate levels of pain were similar to those reported in previous studies in which capsaicin was applied to the gingiva.[8,10,18,26–28] In addition, in the present study, no pain from other intraoral sites was reported by the subjects, indicating a successful avoidance of spreading of capsaicin outside the periodontal ligament.

Gingival Somatosensory Changes after Adjacent Heterotopic Painful Stimulation

In agreement with a previous study in which somatosensory gains for warmth and painful heat were induced by topical application of capsaicin to the gingiva,[18] the present study demonstrated gingival sensitization to warmth and to painful heat stimuli induced by the injection of capsaicin into the periodontal ligament. However, whereas previous studies found homotopic somatosensory changes in the primary and secondary zones induced by topically applied capsaicin on the gingiva,[18,21,28] the present study showed heterotopic somatosensory changes in the adjacent gingival tissue by capsaicin injected into the periodontal ligament. In a previous study with painful tooth stimulation, activation of the pulpal afferent nerve fibers induced similar but less pronounced heterotopic somatosensory changes in the gingival area, which in combination with earlier studies was explained by an axon reflex–like response.[12,20,29] Prolonged cold allodynia has been found in patients with AO,[7] whereas no changes in cold pain sensitivity have been detected in the present study with experimental acute pain. This possible difference in somatosensory changes between acute and chronic orofacial pain could be further explored in future studies.

In addition, in terms of the mechanical stimuli, the present study demonstrated gingival desensitization to both mechanical tactile stimuli (increased MDT) and painful pinprick stimuli (increased MPT and

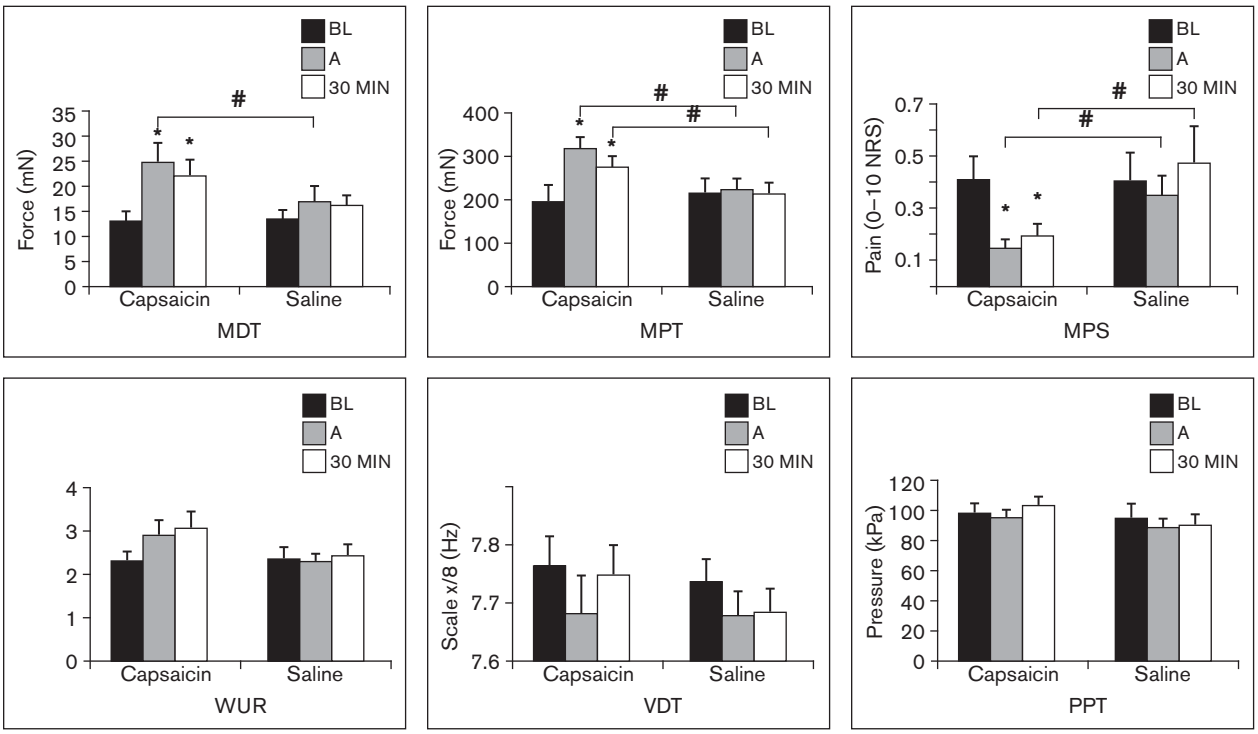

Fig 3 Mean ± SEM values of mechanical thresholds at three time points (BL = baseline, black bars; A = immediately after injection, dark gray bars; 30 MIN = 30 minutes after injection, light gray bars) during the two QST sessions with capsaicin and isotonic saline (control). MDT = mechanical detection threshold (mN); MPT = mechanical pain threshold (mN); MPS = mechanical pain sensitivity (geometric mean of 0–100 numeric rating scale [NRS] measures); WUR = wind-up ratio (ratio between NRS scores); VDT = vibration detection threshold (x/8 scale); PPT = pressure pain threshold (kPa). *Indicates significant difference from BL ($P < .05$). #Indicates significant difference between sessions ($P < .05$).

decreased MPS) after periodontal capsaicin injection. This finding is also in line with a previous study on intraoral topical application of capsaicin,[18,28] in which the effects on mechanical sensitivity were explained by a desensitizing effect of capsaicin.[28,30] However, other mechanisms may be responsible for the sensory loss, and it can be speculated that the reduced sensitivity to mechanical tactile and noxious stimuli may be the result of centrally mediated modulatory influences acting on both nociceptive and non-nociceptive pathways.[31–39] Importantly, such mechanical desensitization was not induced in the control condition with periodontal injection of isotonic saline, suggesting that the mechanical desensitization is specific to and dependent on the noxious input evoked by capsaicin.

Temporal Aspects

The full QST assessment protocol as suggested by the DFNS at an intraoral test site takes approximately 30 minutes.[11,15] In the present study, the pain lasted throughout the 7-minute capsaicin injection period, and there was no significant decrease within the 7 minutes. The 7-minute injection period was chosen in order to closely mimic the design of a previous study, which used 7 minutes of electrical tooth stimulation.[12] Also, it was not found ethically acceptable to keep the capsaicin in place for the 30 minutes it took to complete the full QST protocol. Therefore, in order to minimize a possible sequence effect on the QST evaluations, the QST protocol was separated into three sections and the sequence of sections was randomized. The somatosensory changes detected in the present study were still present during performance of the third section of QST, which was initiated 30 minutes after the capsaicin injection. This indicates that the somatosensory changes clearly outlasted the presence of pain. The total duration of capsaicin-evoked pain was not recorded in the present study, but earlier studies with a similar amount and concentration of capsaicin have shown a significant reduction in capsaicin-evoked pain over time, even within a 15-minute application period.[18,26,27]

Study Limitations

In the present study, oral bandages were used to avoid spreading of capsaicin to the oral cavity. However, when they were removed after 7 minutes of

application, a small amount of capsaicin may have remained even though cotton rolls were used to gently remove any residual capsaicin. However, the participants, who were carefully instructed not to touch the application site with the tongue after removal, gave no reports of spreading to other areas in the oral cavity. The capsaicin may have activated the marginal gingiva through diffusion of capsaicin into the periodontal pocket, but the QST test site was clearly separated from the marginal gingiva.

No tests of the success of the blind design of the study were performed, and it can be expected that the participants could guess the order of the sessions (at least during the second session) due to the clear difference in pain intensity between sessions. However, the participants were not informed about the study hypothesis before testing, and so the authors believe that a possible hampered blinding process did not systematically influence the results.

Another study limitation was the relatively small sample size. However, the paired study design in which each participant served as his/her own control allowed for detection of significant differences between sessions; this argues that the sample was sufficient for evaluation of the outcome parameters. The present sample size, however, was insufficient for evaluation of possible gender effects, which was therefore not attempted.

Clinical Implications

The possible clinical implications of the present findings are that the neuroanatomy and nociceptive processing of the afferent inputs from the tooth pulp, periodontal ligament, and marginal/attached gingiva need to be taken into account when interpreting findings from somatosensory testing of these tissues, as studies in animal orofacial pain models have shown that the afferent inputs may influence each other.[12,37–42] Hence, as specific somatosensory changes in the gingiva have now been demonstrated to occur after minutes of adjacent painful stimulation, caution should be taken when interpreting somatosensory findings in chronic orofacial pain patients. AO/PTTN patients may have suffered deafferentation of the afferent fibers of the tooth pulp and/or the periodontal ligament in the painful region if the tooth has been endodontically treated or extracted, and therefore their pain may be neuropathic in origin, and somatosensory testing is often used in the diagnostic process. However, performance of somatosensory testing in the gingival region of the painful area may offer useful information about the nociceptive processing and pain mechanisms in such patients, although extrapolation to site and/or tissue-specific mechanisms of action may be difficult.[12]

Conclusions

In the present study, acute capsaicin-evoked pain in the periodontal ligament caused adjacent heterotopic gain of somatosensory sensitivity to warmth and painful heat stimuli, as well as loss of mechanical sensitivity, in the gingiva adjacent to the injected tooth. This indicates involvement of competing sensitizing and inhibitory mechanisms evoked by an acute adjacent nociceptive input. These findings may have implications for interpretation of somatosensory findings in patients with chronic intraoral pain, where gingival somatosensory profiles similar to those detected after capsaicin injection in the present study may be interpreted as signs of nerve damage.

Acknowledgments

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