A perspective from experimental studies of burning mouth syndrome

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Abstract: Burning mouth syndrome (BMS) is one of the most frequently seen idiopathic pain conditions in a dental setting. Peri- and postmenopausal women are most frequently affected, and patients who experience BMS complain of persistent burning pain mainly at the tip and the bilateral border of the tongue. Recent studies have assessed whether BMS is a neuropathic pain condition, based on morphologic changes in biopsied tongue specimens, and whether there are abnormal pain responses in patients with this disease. Somatosensory studies have reported some abnormal findings in sensory and pain detection thresholds with inconsistency; however, the most distinct finding was exaggerated responses to painful stimuli. Imaging and electrophysiologic studies have suggested the possibility of dysregulation of the pain-modulating system in the central nervous system, which may explain the enhanced pain responses despite the lack of typical responses toward quantitative sensory tests. Basic studies have suggested the possible involvement of neuroprotective steroids, although the underlying mechanisms of this condition have not been elucidated. Experimental studies are looking for preferable supportive therapies for BMS patients despite the obscure pathogenesis.

Keywords: altered somatosensory function, burning mouth syndrome, experimental model, functional MRI, nociplastic pain, pain modulation

Introduction

One of the top concerns in chronic orofacial pain may be burning mouth syndrome (BMS). It is a typical idiopathic pain condition in which no causative local and systemic pathologies are observed [1]. Interestingly, however, there is a consensus among clinical practitioners that BMS patients have some common characteristic features. Pain is limited to the oral mucosa mainly at the tip and bilateral borders of the tongue [2]. Women have a marked predilection, and peri- and postmenopausal women are more frequently affected [2]. BMS patients often experience psychologic distress, and stressful events aggravate their pain [3]. Some patients report pain alleviation after eating some spicy foods, although the burning pain usually ameliorates with daily meals (except for spicy foods) [4]. Historically, these common features have led to the hypothesis that BMS is a climacteric disorder, and hormonal dysregulation and mental stress are involved in its onset and exacerbation. Research groups from Italy [5] and Britain [6,7] have reported that there is small-fiber atrophy in the tongue showed a loss of sensation; however, mechanical pain sensitivity observed both decreased and increased warm or hot sensitivity in the affected area in BMS patients [11,12]. Other studies reported no differences in the cold and warm detection thresholds between BMS patients and controls [13-15]. When considering a patient’s responses to these stimuli, attention should be paid to these data. Researchers have used various types of stimulus sources: e.g. different sizes of the thermode for hot and cold stimulation (Table 1). A large thermode can generate intense energy and involves a large number of fibers at once. Using a large thermode, it may be easy for an examinee to recognize changes in thermal perception; however, it may be difficult to maintain steady contact of the thermode to the perioral mucosa and surrounding skin. After eliminating this methodologic bias, four studies investigated a patient’s responses to thermal stimuli at the perioral region utilizing small-sized thermodes (5 to 9 mm square). Only one reported cold pain allodynia and hypersensitivity in warm and cool detection in BMS patients [11]. The other three studies reported no significant differences in warm and cool detection thresholds and hot and cold pain thresholds between BMS patients and controls [13-15]. Jääskeläinen et al. noted an elevation in mechanical detection thresholds (MDTs) by observing provocation of the R1 component in the blink reflex [16]. A study using laser irradiation indicated that the hot pain threshold was significantly higher and the ratio of the pain threshold to the warm threshold was significantly lower in BMS patients than in controls, not only at the lower lip but also outside the trigeminal area [17]. Another study reported that BMS patients perceive significantly more intense and more long-lasting pain after mechanical stimulation than healthy people [18]. It has been reported that BMS patients show hyperalgesia with topographic changes in the trigeminal area [19]. These findings indicate that the problem in BMS patients involves pain tolerance rather than pain detection. Watanabe et al. investigated the association between disease duration in BMS patients and somatosensory dysfunction utilizing a standardized battery of QST and reported that the MDT at the tip of the tongue showed a loss of sensation; however, mechanical pain sensitivity showed a gain of sensation only in BMS patients experiencing burning pain for over 6 months and not in those experiencing pain for less than 6 months as compared with controls [15]. Taken together, despite the lack of strong evidence, the loss of function of large and small fibers has been suggested in BMS patients. These findings may suggest the underlying mechanism of chronic intraoral burning pain. First, the pain response is
enhanced when noxious stimulation is applied repeatedly, even though chronic BMS patients are less sensitive to innocuous stimuli Zone [15,16]. Second, the longer a BMS patient experiences burning pain, the more chronic BMS patients are less sensitive to innocuous stimuli-zone [15,16].

### Table 1 Somatosensory profile in patients with burning mouth syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Pain duration</th>
<th>Thermode size (mm)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forsell H et al.</td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>Sensory dysfunction in burning mouth syndrome</td>
</tr>
<tr>
<td>Iso M et al.</td>
<td>2002</td>
<td>36 m</td>
<td>NA</td>
<td>Pain threshold and pain recovery after experimental stimulation in patients with burning mouth syndrome</td>
</tr>
<tr>
<td>Grémeau-Richard C et al.</td>
<td>2010</td>
<td>&gt;4 m</td>
<td>9 × 9</td>
<td>Effect of lingual nerve block on burning mouth syndrome</td>
</tr>
<tr>
<td>Kaplan I et al.</td>
<td>2014</td>
<td>NA</td>
<td>20 × 20</td>
<td>Thermal sensory and pain thresholds in the tongue and chin are changed with age, but are not altered in burning mouth syndrome</td>
</tr>
<tr>
<td>Mo X et al.</td>
<td>2015</td>
<td>NA</td>
<td>6 × 6</td>
<td>Thermal and mechanical quantitative sensory testing in Chinese patients with burning mouth syndrome</td>
</tr>
<tr>
<td>Yilmaz Z et al.</td>
<td>2016</td>
<td>NA</td>
<td>5 × 5</td>
<td>Detection of small-fiber neuropathies in burning mouth syndrome and iatrogenic lingual nerve injuries</td>
</tr>
<tr>
<td>Hartmann A et al.</td>
<td>2017</td>
<td>NA</td>
<td>9 × 9</td>
<td>Profiling introral neuropathic disturbances following lingual nerve injury and in burning mouth syndrome</td>
</tr>
<tr>
<td>Watanabe K et al.</td>
<td>2019</td>
<td>Subchronic (&lt;6 m), Chronic (&gt;6 m)</td>
<td>16 × 16</td>
<td>Association of somatosensory dysfunction with symptom duration in burning mouth syndrome</td>
</tr>
</tbody>
</table>

NA, not applicable; m, month.
Historically, there are two types of BMS: primary and secondary [44]. Secondary BMS is a condition that manifests oral burning pain in association with various systemic or local diseases, and primary BMS is a condition that also manifests oral burning pain but without any known etiologies (i.e. an idiopathic oral burning pain condition). BMS now represents primary BMS, and its pathogenesis remains unknown [1]. In this context, there are currently no accepted animal models of BMS, because an experimental animal model should have an etiology that mimics BMS manifestations. A multifactorial etiology, such as psychogenic factors, hormone disorders, neuropathic alterations, oral phantom pain, neuroplasticity, and neuroinflammation, has been proposed for BMS [46], and the complex association of biologic and psychologic factors makes it difficult to establish an animal model of BMS.

However, several studies have aimed to investigate the pathogenesis of BMS using animal models that mimic the clinical manifestations of BMS. Table 2 shows studies that have investigated the mechanism of burning pain in the oral cavity using experimental models. A fundamental lingual pain model of rats induced by an inflammatory substance was used to study pathologic tongue pain [47]. This model showed mechanical and heat hypersensitivity of the tongue after an injection of complete Freund’s adjuvant (CFA), and mGluR5-pERK signaling in the trigeminal spinal subnucleus caudalis (Vc) had a key role in the neuronal mechanism. However, inflammatory conditions, such as lichen planus and herpes zoster, are classified into secondary BMS and regarded as a condition different from primary BMS. Shinoda et al. reported an experimental mouse model with peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam might have some etiologic factor in the peripheral nervous system.
to bind to GABA<sub> receptors in the mucosa of the tongue and increase the effect of the inhibitory neurotransmitter GABA. Tan et al. [72] supported the local effect of clonazepam using female rats. They found that numerous GABA<sub> receptors are present on the tongue afferent fibers in female rats, and the mechanical thresholds of the tongue are increased when the GABA<sub> receptor selective agonist muscimol was bath-applied. Grémeau-Richard et al. [69] classified BMS patients into three groups according to the pain-relieving effect of clonazepam, and Grushka et al. [73] reported the lack of the pain-relieving effect of clonazepam in patients experiencing burning tongue pain for a long time. It is hypothesized that in persistent pain with BMS, the GABA<sub> receptor subunit configuration changes, and those subunits with a high affinity to benzodiazepines decrease [57]. TRPV1 may be involved not only in pain but also in abnormal taste sensation [74]. Local capsaicin seems to provide good pain relief for burning pain in BMS [75], although it paradoxically increases the burning sensations and dysgeusia for a short period [76,77]. As already stated, the expression of TRPV1 and TRPA1 increased in a trigeminal ganglion of a BMS model mouse [50,51]. These results suggest that capsaicin and mustard oil have a potential effect on reducing the symptoms of BMS. Systemic SSRIs, zinc replacement therapy, alpha-lipoic acid and aloe vera, hormone replacement treatment, cognitive behavior therapy, and acupuncture may also be effective in reducing BMS symptoms in the short term [78-83]. Unfortunately, there is no solid evidence based on basic research to explore the mechanisms of these therapies for BMS. Further basic research is required to more precisely elucidate the pathogenesis of primary BMS and effective treatment for it.

Recent clinical studies have reported that superficial brain stimulation, e.g., transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), showed an analgesic effect by altering the pain-modulating system [84,85]. TMS is believed to mediate a neurostimulatory and neuromodulatory effect, whereas tDCS supplies a solely neuromodulatory effect [85]. A human study on tRMS applied at the PFC showed an increase in pain tolerance [84]. An animal study suggested that this increase in pain tolerance may be due to the modulation of brain activity between the dIPFC and ACC [86]. A clinical report documented that TMS at the PFC indicated significant pain reduction in BMS patients [87]. It is interesting to note that rTMS dysregulated the pain-modulating system in BMS. It is indeed a favorable therapy; however, further information about its therapeutic mechanism (e.g., lasting changes in blood flow and brain activity) is needed.

There are numerous patients seeking effective treatment for burning oral pain that is resistant to conventional treatment procedures. Supportive measures are sometimes effective, but the effect is usually case-specific. Therefore, etiologic and universal treatment procedures are expected. A clue in elucidating the etiology of BMS may lie in hormonal dysregulation and in hormonal replacement therapy, cognitive behavior therapy, and acupuncture may also be effective in reducing BMS symptoms in the short term [78-83]. Unfortunately, there is no solid evidence based on basic research to explore the mechanisms of these therapies for BMS. Further basic research is required to more precisely elucidate the pathogenesis of primary BMS and effective treatment for it.

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Conflict of interest
None of the authors has any conflict of interest related to the conduct of this study.

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Other measures are sometimes effective, but the effect is usually case-specific. Therefore, etiologic and universal treatment procedures are expected. A clue in elucidating the etiology of BMS may lie in hormonal dysregulation that leads to disorders in neuronal activity and connectivity in the brain network. Correction of the pain-modulating system and the distorted brain network could be a short-cut in ameliorating BMS symptoms, although it may not be an etiologic therapy. There is still a lack of evidence, and future basic and clinical studies are expected.

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