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 findings were 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, nociceptive 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 epithelial layer of BMS patients. These histologic studies, based on the tongue biopsies of BMS patients, reported the overexpression of pronociceptive ion channels (transient receptor potential vanilloid 1: TRPV1) and purinergic receptors (P2X3) in the epithelium of the lingual mucosa [6-8]. TRPV1 and P2X3 are involved in hypersensitive reactions to some spices and hot foods. These findings have raised crucial questions about whether BMS is one of the neuropathic pain conditions and whether damaged fibers lead to typical sensory changes.

In this article, patients’ perceptional responses and their brain behavior to various stimuli will be discussed. Some interesting findings from animal studies that support these responses will also be discussed.

Unique somatosensory findings in patients with BMS

There is inconsistency in the reports of pain thresholds measured by quantitative sensory testing (QST) in BMS patients. For instance, some studies have observed a decreased sensitivity in cold detection on the tongue (cold hypoaesthesia) [9,10], whereas others have reported an increased cold pain sensitivity in BMS patients (cold hyperesthesia) [11]. Some studies 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 hyperalgiesia with topical capsaicin and a reduction in heat pain tolerance [12]. 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 stimulus[15,16]. Second, the longer a BMS patient experiences burning pain, the more intensively the pain response is affectedzone[16,19]. These exaggerated pain responses cannot be explained only with peripheral mechanisms, and there is a strong suggestion of involvement of the central nervous system in pain development in BMS.

Brain responses to chronic pain input
Melzack et al. classified the brain into three principal components: sensory-discriminative, affective-motivational, and cognitive-evaluative (Melzack and Casey. Sensory, motivational, and central control determinants of pain. CC Thomas, 1968). Pain has classically been thought to consist of only sensory-discriminative components. Talbot et al., however, suggested that not only somatosensory cortices but also several distant parts of the brain are involved in pain perception [20]. These sites are collectively referred to as the “pain matrix” [21], which includes the primary and secondary somatosensory cortices (S1 and S2), the insular cortex (IC), the anterior cingulate cortex (ACC), and the prefrontal cortex (PFC). These areas are reported to be activated during painful stimulation as compared with non-painful stimulation in imaging studies.

In chronic pain, a study utilizing positron emission tomography (PET) has shown that spontaneous pain in the extremities in chronic neuropathic pain patients led to a reduction of blood flow in the contralateral thalamus, and the authors of this study have hypothesized its mechanism where the activation of inhibitory gamma-aminobutyric acid (GABA)-ergic neurons against excessive nociceptive inputs from the lower level led to excessive suppression of the activity of the thalamus [22]. In a PET study using an experimental model of heat allodynia that was induced by subcutaneous capsaicin, it was found that pain-related blood flow was extremely increased in the pathway from the medial thalamus and the ACC to the PFC, which represents the medial pain system [23-25]. These imaging studies have reported specific brain responses that represent pain transmission and especially modulation in the central nervous system.

Historically, attention has been focused on changes in brain function rather than morphologic changes, because few researchers thought that the brain would indicate morphologic changes with chronic pain. Grachev et al. reported that chronic pain diseases mediate a sustained painful input from the periphery, which induces a significant reduction of glucose and N-acetylaspartate in the dorsolateral prefrontal cortex (dPFC) [24]. Together with this finding, magnetic resonance imaging (MRI) studies using voxel-based morphometry analysis have reported neocortical gray matter volume (GMV) changes under various chronic pain conditions [26-31]. In particular, it was found that the GMV in the PFC and the thalamus decreased under both trigeminal and low back pain conditions [27-30]. Further, atrophy of PFC is observed in proportion to pain duration [26]. Although the pathophysiologic significance of a decrease in the brain parenchyma has not been fully elucidated, it suggests that the brain shows not only functional but also plastic changes in response to chronic pain.

Brain activity in BMS
Sinding et al. found that a major part of the pain matrix included modifications of the gray matter concentration in patients with BMS. These regions included the cingulate gyrus, lobules of the cerebellum, IC, inferior temporal area, primary motor cortex (M1), and dPFC [31]. Tan et al. reported that BMS patients had smaller GMV in the bilateral mPFC as compared with controls, and there was increased connectivity between the mPFC and amygdala. Further, the intensity of the connectivity between these two areas showed a correlation with the suffering period in BMS patientszone [32]. Wada et al. reported a strengthened connectivity of the ACC and mPFC with the basal ganglia, thalamus, and brainstem. ACC and mPFC are the major components of the default mode network [33] and form the medial pain system with the basal ganglia, thalamus, and brainstem [34]. All these findings are consistent with those observed in previous studies with various chronic pain conditions and support the involvement of mood and affect in this condition [34]. Contrarily, there are some findings that appear to be specific to BMS. Shinozaki et al. have shown that habituation of pain perception after repetition of painful hot stimulation with an interval applied at the lower lip in healthy controls was not observed in BMS patients. Further, their functional MRI data revealed that ACC activation was decreased only in BMS patients as the stimulus was repeated [35]. Kohashi et al. used tonic noxious hot stimulation to study the brain responses in BMS patients. They reported that ongoing heat pain indicated a time-dependent facilitation of brain activation both in BMS patients and in controls, and this facilitation was more prominent in the PFC, the premotor cortex, the thalamus, and the secondary visual cortex (V2) in BMS patients during lower lip stimulation [36]. These two studies have suggested dysregulation of the pain-modulating system in the BMS brain, which may explain the specific somatosensory findings described in the early section of this manuscript in which BMS patients showed decreased pain tolerance but no significant abnormalities in pain thresholds.

Can BMS be classified into nociceplastic pain?
The IASP classification of chronic pain has defined chronic primary pain [37]. In this classification, chronic widespread pain, including fibromyalgia, requires features of nociceplastic pain, which consists of spontaneous or evoked pain in the symptomatic areas, and may be accompanied by sensitized pain perception (allodynia or hyperalgesia) and identified psychosocial contributors. These conditions are usually associated with sleep disturbance and pronounced fatigue [38]. Nociceplastic pain requires “altered nociceptive function” with “altered descending pain inhibition” [39], despite lacking clear evidence of tissue damage or diseases/lesions in somatosensory systems that lead to the activation of peripheral nociceptors [40]. Chronic primary headache or orofacial pain is another classification of chronic primary pain, and BMS should be classified into chronic primary orofacial pain[37]. BMS has a number of similarities to other chronic primary pain conditions with respect to features of nociceplastic pain. As stated above, altered nociceptive function with altered descending inhibition has been reported [16,34-36]. There are a number of studies that have reported an association between BMS and sleep disturbance [41-43] and fatigue [41,44,45]. Although the underlying mechanism of small-fiber atrophy in the tongue epithelium is unclear, there are no systemic or local diseases or lesions that explain this morphologic change.

A challenge in elucidating the etiology of BMS
There is a challenge in developing and implementing animal models of BMS to study its etiology. Nevertheless, a number of researchers are aiming to elucidate the basic mechanisms of the pathogenesis of BMS and develop management strategies by replicating the clinical symptoms of BMS in animals.
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 biological 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 hyperalgesia of the tongue after an injection of complete Freund’s adjuvant (CFA), and mGluR5-pERK signaling in the trigeminal spinal nucleus 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. [48] reported that local application of clonazepam to the tongue in BMS patients, but there were no significant differences in the stimulated flow rate between BMS patients and healthy controls [65,66]. It has been hypothesized that thin fibers specifically innervating the epithelial layer are damaged [5], and minor salivary glands (but not major glands that are located in the superficial layer of the oral mucosa) are involved [57]. These minor salivary glands are entirely innervated by the chorda tympani nerve and are characterized by a lack of sympathetic innervation. Nakaya et al. [67] created a dry mouth rat model by drying the tongue without damaging the major salivary gland function and investigated the central neuronal mechanism. The model showed that the tongue mechanical hyperalgesia was associated with tongue drying. The pERK-pGluR1 cascade was involved in the central neuronal mechanism of drying tongue pain in the trigeminal spinal nucleus caudalis (Vc). Chen et al. [68] studied the peripheral neuronal mechanism in dry mouth model rats and suggested that activation of TRPV4 via p38 in trigeminal ganglion neurons is involved in mechanical hyperalgesia.

### Development of treatment for primary BMS

There is no causal therapy for primary BMS, which is ruled out from other curable problems (i.e. secondary BMS inducing tongue pain). Basically, the treatment of primary BMS is supportive and focuses on the relief of symptoms. Topical and systemic application of clonazepam is one of the most widely accepted treatment options for BMS [69,70]. Woda et al. [71] reported that local application of clonazepam to the tongue in BMS patients induced a 50% reduction on the pain scale. They suggested that this local effect of clonazepam might have some etiologic factor in the peripheral nervous system. The neuronal mechanism for the local effect of clonazepam remains unclear; however, clonazepam has been presumed

### Table 2. Summary table of the animal models and therapeutic development for the study of the primary BMS

| Animal model | Year | Treatment | Animal | Main finding |
|--------------|------|-----------|--------|--------------|
| Liu et al.   | 2012 | CFA injection to tongue | Rat    | Mechanical and heat hypersensitivity of tongue |
| Shinoda M et al. | 2015 | Application of TNBS on tongue | Mice  | Heat hypersensitivity of tongue |
| Elliott CM et al. | 2008 | Transgenic mice of artemin gene | Mice  | Oral sensitivity to capsaicin and mustard oil |
| Boucher Y et al. | 2014 | Ovariectomy and transection of the chorda tympani | Rat   | No effect on pain after chorda tympani |
| Nakaya et al. | 2016 | Drying tongue | Rat    | Mechanical hypersensitivity of tongue |
| Chen JY et al. | 2019 | Drying tongue | Rat    | Mechanical hypersensitivity of tongue |

| Therapeutic development | Year | Treatment | Animal | Main finding |
|-------------------------|------|-----------|--------|--------------|
| Tan SN et al. | 2013 | Application of GABA<sub>A</sub> receptor selective agonist muscimol | Rat | Existence of y subunit of GABA<sub>A</sub> receptor in tongue nerve fiber |
| Cho et al. | 2010 | Zinc replacement therapy | Rat | Hyperkeratinization and increased mitosis on the dorsum of the tongue |

CFA, complete Freund’s adjuvant; mGluR5-pERK, metabotropic glutamate receptor 5 and phosphorylated extracellular signal regulated kinase; TRPV1, transient receptor potential vanillioid; TG, trigeminal ganglion; GFR, glial cell line-derived neurotrophic factor receptor; TRPA, transient receptor potential cation channel subfamily A; p38, phosphor-p38 mitogen activated protein kinase; GABA<sub>A</sub>, gamma aminobutyric acid A.

The neuronal mechanism for the local effect of clonazepam is involved in mechanical hyperalgesia.
to bind to GABA<sub>A</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>A</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>A</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>A</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 sensation 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. repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), showed an analgesic effect by altering the pain-modulating system [84,85]. rTMS is believed to mediate a neurostimulatory and neuromodulatory effect, whereas tDCS supplies a solely neuromodulatory effect [85]. A human study on rTMS 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 rTMS 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. outlasting 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 [88]. There is still a lack of evidence, and future studies are required to more precisely elucidate the pathogenesis of primary BMS and effective treatment for it.

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

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