Introduction

Primary burning mouth syndrome (BMS) is chronic, idiopathic, burning pain in healthy mucosa of the tongue or other oral tissue. It is defined as “daily persistent pain in the mouth with normal oral mucosa after excluding local and systemic diseases” [1] and primarily affects perimenopausal and postmenopausal women [2-4]. BMS pain is usually described as moderate to severe, and BMS remains poorly treated [5] because of the lack of effective treatments.

BMS patients often complain of pain after eating hot or spicy foods [6,7] but not after eating bland food, which can sometimes alleviate pain [2,8]. Some BMS patients chew gum to decrease pain [7]. In contrast, pain in oral diseases such as neuralgia, oral lichen planus, recurrent aphthous ulceration, and herpes zoster is usually enhanced by mechanical stimulation of oral mucosa [9-12]. Thus, among oral diseases the analgesic effect of chewing gum is unique to BMS. Gum chewing relieves pain and reduces the need for analgesics for specific pains, such as pain caused by fixed orthodontic appliances, electrical stimulation of the sural nerve, and postoperative pain [13-17]. BMS is believed to be caused by a neuropathic mechanism resulting from atrophy of small nerve fibers in the tongue epithelium [18,19]. However, the role of Aδ fibers in the pathology of BMS is unclear. Moreover, the mechanisms underlying the analgesic effect of gum chewing have not been identified and remain controversial.

The present authors previously reported that plasma adrenaline level was significantly lower in BMS patients than in healthy controls, which suggests dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [20]. Previous studies reported that chronic stress-induced anxiety is associated with BMS, and with dysregulation of the sympathetic nervous system as well as dysregulation of the HPA axis [21-25]. These findings suggest that plasma adrenaline might play an essential role in BMS pathogenesis. Prolonged gum chewing changes plasma serotonin concentration in humans [13,26]. However, the functional mechanisms underlying this change are unknown, although serotonin is a known mediator of pain in peripheral tissues.

This study investigated the pathogenesis and potential treatment strategies for BMS by examining the analgesic effect of gum chewing and plasma levels of neurotransmitters, catecholamines, and serotonin in BMS patients and healthy controls after gum chewing and simulated chewing without gum.

Materials and Methods

Participants

The participants were 40 Japanese women, namely, 20 BMS patients with chronic tongue pain for longer than 3 months who were randomly recruited from the outpatient pain clinic of Nihon University Dental Hospital and 20 healthy volunteers, without systemic or local conditions that induced orofacial pain, who were randomly recruited to serve as controls. Controls were excluded if they had pain or discomfort, somatosensory changes, or a medical history of pain in their orofacial area, if they used any pain medication, or if intraoral or extraoral examination or blood screening revealed systemic or local disease.

Forty-eight participants initially enrolled in the study. Of these, 8 declined further participation and withdrew. The BMS patients underwent routine hematologic screening tests and intraoral and extraoral examinations to rule out secondary BMS and satisfied the inclusion and exclusion criteria for BMS, as specified in the International Classification of Headache Disorders 3 (ICHD 3rd edition) of the International Headache Society, and in previous studies [20,27]. BMS pain was defined as spontaneous superficial tongue pain; tongue pain while eating or during palpatation was excluded. All patients reported that burning pain occurred daily for longer than 2 hours and for a period longer than 3 months. Patients were excluded if they had endocrine gland dysfunction or systemic disease (including diabetes mellitus, anemia, multiple sclerosis, Sjögren syndrome, and Parkinson disease) or psychological disorders (including major depression, schizophrenia, cancer, and endocrine disease), if they were undergoing hormone replacement or steroid hormone therapy or taking analgesic medicines, or if they had local conditions such as allergy to metals or dental materials, oral candidiasis, or occult viral infection.

The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Bioethics Committee of the Nihon University School of Dentistry (EP16D024). Details of the study were explained to all participants, and all participants provided written informed consent before enrolling in the study and before collection of demographic data. The period of the study was from April 2016 through November 2019.

Gum chewing task

All 40 participants (BMS patients and controls) were requested to refrain from activities such as eating or swallowing during the period 1 hour
before the experiment. During the experiment, participants were requested to rhythmically chew a tasteless, scentless chewing gum (CAT 21 chewing pellet, 1.0 g. Willdent, Osaka, Japan) at a comfortable rate for 20 min, to determine the analgesic effects of gum chewing, as described in previous studies [13,26], or to rhythmically perform simulated chewing without touching their teeth by pretending to chew gum at a comfortable rate for 20 min. There was a 1-week interval between the gum chewing task and simulated chewing task.

**Psychological testing and pain measurement**

All participants underwent psychological testing, including the Japanese version of the Profile of Mood States (POMS)-long form, which is used to evaluate tension-anxiety (T-A), depression-dejection (D-D), anger-hostility (A-H), vigor (V), fatigue (F) and confusion (C) [28]. Complaints of oral pain in BMS patients were assessed by using the visual analogue scale (VAS), which was rated from 0 (no pain at all) to 100 (the worst pain imaginable).

**Blood samples**

At around 10:00 am on the experimental day, to facilitate blood collection, intravenous (IV) access was obtained from the median antebrachial vein of the forearm by using a 22-gauge cannula (Terumo, Tokyo, Japan). IV fluid (Ringer’s solution, Otsuka, Naruto, Japan) was administered at a rate of 50 mL/h. All blood samples were obtained from the IV cannula, to avoid repeated needle insertion. A previously described procedure [20] was used for blood analysis. Briefly, blood collected in a tube containing a separating agent for plasma assay was separated by immediate centrifugation at 3,000 rpm for 10 min. Then, the plasma was frozen at −20°C until the catecholamine and serotonin assays were conducted. Adrenaline, noradrenaline, dopamine, and serotonin were measured by using high-performance liquid chromatography with a fluorescence detector (FP920, Jasco, Tokyo, Japan). The samples were partially assessed at a cooperating extramural laboratory (SRS, Tokyo, Japan) using commercially available reagents.

**Experimental protocol**

BMS patients and controls were randomly allocated to the initial interventions, ie, gum chewing or simulated chewing. The study designer (N.S.) gave instructions to each participant on the action required (gum chewing or simulated chewing). The evaluators (A.O. and Y. I.) were blinded to the intervention and collected VAS data on pain (BMS patients) and psychological test scores and blood samples (BMS patients and controls). The experiments were conducted between 10:00 and 12:00. Blood samples, psychological test scores, and VAS scores were collected from BMS patients and controls before the intervention and at 20 min after completion of gum chewing or simulated chewing. Gum chewing and simulated chewing were completed after collection of scores and samples.

**Statistical analysis**

All data are presented as mean ± standard error. The Student t-test was used to compare age in the BMS and control groups. Repeated-measures one-way and two-way ANOVAs were used to assess changes in VAS, plasma catecholamine and serotonin concentrations, and POMS scores, after checking for significant differences in variance with the Levene test for homogeneity of variances. If significance was reached on ANOVA, post-hoc comparisons were performed with the Tukey-Kramer test. Multiple regression analysis was used to examine the effects of blood factors, adrenaline, noradrenaline, dopamine, and serotonin on change in VAS score attributable to gum chewing. The relationship between percentage decrease in VAS and percentage decreases in adrenaline, noradrenaline, dopamine, and serotonin after gum chewing were analyzed. Pearson correlation coefficients were used to evaluate correlations between adrenaline concentration and VAS score and between percentage decrease in adrenaline and percentage decrease in VAS score, in linear regression analysis. Differences were considered significant when P was less than 0.05.

**Results**

**Participants**

The demographic characteristics of the BMS and control groups are shown in Table 1. Mean age was 58.65 ± 2.16 years in the BMS group and 60.85 ± 1.63 years in the control group. There was no significant difference between groups in age at baseline. Mean pain duration was 7.17 ± 2.92 months in BMS patients.

**Change in VAS after gum chewing**

Mean VAS scores for pain intensity in the BMS group were significantly lower after simulated chewing and gum chewing than at baseline. Moreover, VAS scores were significantly lower after gum chewing than after simulated chewing (Fig. 1).

**Change in catecholamines and serotonin after gum chewing**

Plasma adrenaline level at baseline was significantly lower in the BMS group than in the control group (P = 0.0483). In addition, adrenaline level in BMS patients was significantly lower after gum chewing than at baseline, which was not the case after simulated chewing (P = 0.000626). Adrenaline level in the controls was also significantly lower after simulated chewing and gum chewing than at baseline (P = 0.0252 and P = 0.00224, respectively; Fig. 2a). Noradrenaline, dopamine, and serotonin levels at rest did not significantly differ between the BMS and control groups (Fig. 2b).
Dopamine and serotonin levels were significantly lower after gum chewing than at baseline, which was not the case after simulated chewing ($P = 0.0196$ for dopamine, $P = 0.0364$ for serotonin; Fig. 2c and d). Moreover, as compared with baseline levels, there was no significant difference in noradrenaline level after gum chewing or simulated chewing (Fig. 2b).

Multiple regression analysis showed that adrenaline level was associated with VAS score ($P = 0.035$), whereas noradrenaline, dopamine, and serotonin levels were not. Moreover, on correlation analysis, plasma adrenaline concentration was positively correlated with VAS score of BMS patients at baseline (Fig. 3). However, neither plasma noradrenaline, dopamine, nor serotonin concentration was significantly correlated with VAS scores of BMS patients. In addition, multiple regression analysis showed that rate of decrease in adrenaline was associated with rate of decrease in VAS in persons who chewed gum ($P = 0.020$), which was not the case for noradrenaline, dopamine, and serotonin. Moreover, rate of decrease in adrenaline was positively correlated with rate of decrease in VAS scores of BMS patients who chewed gum (Fig. 4, $P = 0.040$). In contrast, there were no significant correlations in the rates of decrease in noradrenaline, dopamine, or serotonin with the rate of decrease in VAS score among BMS patients.

Change in POMS score after gum chewing

There was no significant difference between groups in any POMS score (T-A, D-D, A-H, V, F, or C) at baseline. The T-A score for the BMS group was lower after gum chewing than at baseline, which was not the case after simulated chewing ($P = 0.0196$ for dopamine, $P = 0.0364$ for serotonin; Fig. 2c and d). Moreover, as compared with baseline levels, there was no significant difference in noradrenaline level after gum chewing or simulated chewing (Fig. 2b).

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Discussion

The present results indicate that gum chewing alleviated the intractable pain experienced by BMS patients. Moreover, plasma adrenaline, dopamine, and serotonin levels were significantly lower after gum chewing. This finding was associated with pain reduction and was not observed after simulated chewing by BMS patients. Peripheral adrenaline, dopamine, and serotonin may thus be involved in the analgesic effects of gum chewing. However, multiple regression analysis and linear regression analysis indicated that VAS scores of BMS patients were significantly positively associated with adrenaline level but not with serotonin or dopamine levels. In addition, the decrease in VAS score after gum chewing in BMS patients was significantly positively associated with a decrease in adrenaline level but not with a decrease in serotonin or dopamine levels. Therefore, adrenaline could be involved in BMS and the mechanism responsible for alleviating BMS pain during gum chewing, whereas serotonin and dopamine levels might not be directly related to BMS pain.

Gum chewing includes the chewing motion, periodontal ligament (PDL) compression, and contact stimulation of the oral cavity. The chewing motion exercises the masticatory muscles, which might affect chronic pain in the orofacial area as a form of exercise therapy [29]. Such therapy is an effective treatment for various forms of chronic pain, such as osteoarthritis, headache, fibromyalgia, and chronic lower back pain [30,31]. Evidence suggests that exercise affects endogenous opioids and has an analgesic effect on chronic pain [30,32,33]. The present authors previously reported that mastication of hard food had an antinociceptive effect on chronic pain in a rat model of inflammation and that this effect might be derived from the opioid descending system [34]. Previous studies reported that stimulation of the motor cortex induces pain relief [35,36]. However, ablation of the somatosensory cortex in rats did not completely reverse Fos expression, which suggests that neuronal pathways other than somatosensory pathways are involved. Therefore, the analgesic mechanisms of exercise therapy remain unclear. Profitt et al. proposed that orthodontic pain was relieved after ischemia was decreased in the PDL by inducing compression/decompression cycles in the PDL during gum chewing [Profitt WR et al. Contemporary orthodontics, St Louis: Mosby Elsevier; 2007]. However, it is unclear whether this mechanism also applies to burning pain in the tongue. More studies of this possible relationship are thus needed [37].

The contact stimulus of gum is associated with stimulation of Aβ fibers in the oral cavity. Burning pain might be inhibited by the touch sensation of the gum on the tongue. This could be explained by the gate control theory [38], which posits that non-painful inputs inhibit pain signals conducted by C fibers through Aβ fibers. However, this theory has been a matter of controversy for several decades [39]. Recently, with the development of genetically engineered mice, the gate control theory has again attracted attention [40-42]. The present findings indicate that reduction of BMS pain was much faster after gum chewing than after simulated chewing. This suggests that the possible analgesic effect of gum chewing is induced not only by the chewing motion but also by other factors, such as stimulation of the periodontal membrane and the contact stimulus of gum on the oral cavity.

Adrenaline is released from the adrenal medulla through mediation of the sympathetic nervous system, which stimulates nociceptors to induce pain [43,44]. Circulating adrenaline from the adrenal medulla contributes to hyperalgesia in animals [45,46] and a decrease in plasma adrenaline level might alter pain sensitivity in the periphery. Consequently, the analgesic effect of gum chewing might be related to peripheral adrenaline. Moreover, psychosocial stressors trigger or worsen BMS pain [47,48]. Stress activates the SAM (sympathetic-adrenal-medullary) axis [49,50], and adrenaline is released from the adrenal medulla via hypothalamic activation [51]. Activation of the autonomic nervous system by psychological stress is attenuated by chewing or biting of wooden sticks in animals [52]. In addition, animal studies reported that serum adrenaline level is higher during mastication of powdered food and liquid feeding than during mastication of food with adequate hardness, which is associated with stimulation of periodontal ligaments [53,54]. Mastication during stressful conditions suppresses activation of the autonomic nervous system and local release of adrenaline, because of stress reduction [55-57]. Furthermore, nitric oxide levels are increased by restraint stress, and biting suppresses the increase in nitric oxide level in the rat hypothalamus [58]. NOS activates β-adrenergic receptors and contributes to the adrenal effect [59,60]. In the present study, decrease in tension-anxiety score was significantly positively correlated with decrease in adrenaline level after gum chewing in BMS patients. Although psychosocial stressors were not investigated in this study, anxiety could be part of the stress response and could also be a component of a potential stressor [Donald W et al. Hormones, Brain and Behavior, Third edition, Elsevier, 2017]. Therefore, a reduction in stress-induced anxiety might have decreased adrenaline release during gum chewing in this study. However, adrenaline level also significantly decreased after gum chewing in controls. Therefore, the mechanism responsible for the reduction in adrenaline was not specific to BMS. Interestingly, the present findings showed that, at baseline, plasma adrenaline level was significantly lower in BMS patients than in healthy controls, although adrenaline level correlated positively with BMS pain intensity. This result is consistent with previous finding that BMS dysregulated the HPA axis, which induced a decrease in the adreno-medullary response and lowered plasma adrenaline level [20]. Koszewicz et al. [25] conducted an electrophysiological evaluation of autonomic nervous system functions and reported significant impairment of sympathetic and parasympathetic nervous system activity in BMS patients. Therefore, dysfunction of the autonomic nervous system, and the HPA axis, might explain the paradoxical responses observed in the present study. Moreover, adrenaline level decreased after simulated chewing in controls but not in BMS patients and was correlated with VAS score. The analgesic effect of gum chewing might require the motion of gum chewing, as well as factors such as PDL compression and contact stimulus on the oral cavity, because of dysfunction in the autonomic nervous system and the HPA axis in BMS.

Dopamine has been studied as a biomarker of chronic orofacial pain, including BMS and myofascial TMD [61]. Persons with Parkinson disease sometimes have pain and a burning sensation in the oral cavity [62,63]. Koszewicz et al. [64] suggested that the pathogeneses of BMS and Parkinson disease are very similar in relation to the incidence and intensity of autonomic nervous system dysfunction. Parkinson disease is caused by a decrease in dopamine in the substantia nigra in the midbrain. The current results indicate a reduction in plasma dopamine after gum chewing. However, there was no significant difference in plasma dopamine level between BMS patients and healthy controls and no significant correlation between VAS score and dopamine level in BMS patients.

Previous reports [13,26] suggested that plasma serotonin would increase after prolonged gum chewing, through mediation of the descending inhibitory pathway, which would result in lower pain scores. However, the results showed that plasma serotonin level decreased in association with the analgesic effect. Differences in the pain status of the participants could account for the discrepancy between present and past findings. The pain modulation theory suggests that serotonin mediates the descending inhibitory pathway and induces analgesia. However, the action of serotonin in peripheral tissue differs from that in central action [65]. Serotonin is an inflammatory mediator of pain, is released from platelets, mast cells, and endothelial cells in peripheral tissues after tissue injury, and directly influences C fibers [65,66]. Serotonin is also present in the masseter muscles of persons with fibromyalgia. A study of intramuscular microdialysis reported that plasma serotonin level was higher in patients with myofascial pain than in healthy controls and that the increase in serotonin was associated with pain and allodynia [67,68]. In addition, administration of serotonin through intradermal microdialysis produced burning pain [69]. Serotonin essentially has both inhibitory and facilitatory roles of nociception. Which works seems to depend on the type of pain model and the subtype of 5-hydroxytryptamine (5HT) receptors (5HT1A, 5HT2) [70]. 5-HT1A agonists excitate and 5-HT1D antagonist mediates inhibitory transmission in the peripheral nerve terminals and dorsal root ganglia [71,72].

Therefore, the effect of peripheral serotonin, whether antinociceptive or nociceptive, seems to depend on the type of 5HT receptor and the pain condition.

Central and peripheral relationships between serotonin and adrenaline levels have been reported. Sugimoto et al. reported that peripheral administration of 5-HT increased plasma adrenaline levels of rats [73]. Serotonin appears to enhance the nociceptive function of other mediators rather than induce pain by itself [65]. Injection of serotonin prolonged hyperalgesia after carrageenan injections into the hind paw of rats [74]. As compared
with 5-HT2A antagonist alone, 5-HT2A agonist greatly enhanced the algic function of PGE2 and NA in rats, which contributed to chronic pain states [75]. In healthy humans, 5-HT injected into muscle did not induce pain or hyperalgesia by itself but enhanced the effect of Bradykinin on producing muscle hyperalgesia [76]. In the present study, gum chewing similarly decreased plasma adrenaline, dopamine, and serotonin levels, an effect that was accompanied by analgesia, although serotonin might have an auxiliary effect on adrenaline in causing analgesia.

Gum chewing reduces pain, stress, and anxiety [77-79]. BMS patients have considerable anxiety and depression, as well as pain [80-82]. Therefore, in this study, the POMS questionnaire, which includes assessments of anxiety and depression, was used to examine the psychological characteristics of BMS patients. The decrease in total POMS score was not correlated with the decrease in VAS score, although the decrease in tension-anxiety psychological positive factors. Moreover, with the decrease in adrenaline therefore, the analgesic effect of gum chewing in BMS patients might have been caused by a reduction in adrenaline caused by a decrease in anxiety. However, there were no significant differences in T-A, D-D, A-H, V, F, or C scores between persons with and without BMS. These elements did not change after the gum chewing task, although tension-anxiety in BMS patients decreased slightly after gum chewing. The association of BMS with psychological symptoms has been investigated for nearly 30 years but remains unclear [83]. Many studies have reported higher levels of anxiety and depression in BMS patients [80-82]. However, some studies found no significant differences in psychological test scores between BMS patients and controls [84-86]. This discrepancy might be attributable to different factors, including pain duration and severity, sample size, and the type of psychological tests used. Moreover, any decrease in depression might lead to an increase in anxiety in some patients. Some studies reported that BMS symptoms tended to become chronic, which increases anxiety and depression, as does chronic pain in general [88,89]. In the present study, mean duration of BMS pain was 7.17 ± 2.92 months, which is shorter than values in previous reports (2-4 years) [90-92]. Therefore, future longitudinal studies should assess the association between pain duration and the psychological characteristics of BMS patients.

In summary, gum chewing was effective for relieving BMS pain, and blood adrenaline might have a crucial role in the analgesic effect of gum chewing. Anxiety is potentially associated with the effect of adrenaline. Moreover, blood serotonin might have an auxiliary effect on adrenaline in pain relief. Future studies should investigate if adrenaline can be used as a biomarker and valuable tool in BMS diagnosis and treatment.

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Conflict of interest

The authors declare no conflict of interest.

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