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Taste Function in Patients with Oral Burning

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Abstract

Burning mouth syndrome (BMS) is an oral pain disorder occurring primarily in post-menopausal women and is frequently accompanied by taste complaints. This association of symptoms suggests an interaction between the mechanisms of nociception and gustation, two senses with strong hedonic components. Seventy-three patients of the Taste and Smell Clinic at the University of Connecticut Health Center who reported experiencing 'unexplained oral burning' were evaluated for taste function. Both intensity ratings and quality identifications were measured for a concentration series of sucrose ('sweet'), NaCl ('salty'), citric acid ('sour') and quinine–HCl ('bitter'). The 57 women with BMS gave lower intensity ratings to NaCl and sucrose than comparably aged, same sex controls. Concentrations of NaCl and sucrose >0.10 M were most affected; concentrations of sucrose and NaCl <0.10 M were rated similarly by BMS and control women. No intensity differences were found for citric acid or quinine–HCl at any concentration and no differences were evident between the 16 BMS men and the 14 control men for any stimulus. The BMS women also misidentified the quality of 19% of the stimuli that were detected whereas control women misidentified 8%. Both groups detected a similar proportion of stimuli and found lower stimulus concentrations more difficult to identify than higher concentrations. Identification of NaCl as 'salty' and citric acid as 'sour' was particularly difficult for BMS women. The present findings are consistent with the hypothesis that pain pathway activation may affect neural and behavioral taste function.

Introduction

Burning mouth syndrome (BMS) is an oral pain disorder that is believed to be a multi-factorial syndrome involving the interaction of biological and psychological systems. In addition to the primary oral burning symptom, BMS patients may report distorted taste perceptions or persisting dysgeusias (Grushka, 1987). BMS patients were also reported to have an increased threshold for sucrose relative to controls (Grushka *et al.*, 1986), however, no threshold differences were found for NaCl, citric acid or quinine–HCl (QHCl). We recently reported that topical anesthesia treatment blocks dysgeusia symptoms present at time of testing and concluded that dysgeusia in BMS might be due to altered peripheral gustatory function (Formaker *et al.*, 1998b). Peripheral gustatory function encompasses not only the taste buds, but also the peripheral nerves innervating those taste buds.

Peripheral gustatory information is transmitted from the taste buds to the central nervous system primarily by cranial nerve VII (facial) and cranial nerve IX (glossopharyngeal). The facial nerve innervates taste buds in the fungiform papillae on the anterior tongue via the chorda tympani (CT) (Miller, 1976) and taste buds on the palate via the greater superficial petrosal nerve. Lingual branches of the glossopharyngeal nerve innervate taste buds in the circumvallate and foliate papillae on the posterior tongue. In addition to gustatory innervation, taste papillae also receive extensive innervation from general sensory fibers (Farbman and Hellekant, 1978; Whitehead *et al.*, 1985). For example, in the rat three times as many trigeminal fibers (cranial nerve V) innervate fungiform papillae than CT fibers. Thus, trigeminal and gustatory afferents have overlapping receptive fields on the anterior tongue, a site of intense burning in BMS (Grushka and Epstein, 1997). In addition, substance P, a pain system neuromodulator, has been identified in trigeminal perigemmal fibers of the rat (Nishimoto *et al.*, 1982). Trigeminal innervation of hamster fungiform papillae is predominantly perigemmal while CT innervation is intragemmal (Whitehead *et al.*, 1985; Whitehead, 1988). However, the CT and the lingual branch of cranial nerve V have projections to the same gustatory relay nucleus in the brainstem (Whitehead and Frank, 1983). Furthermore, human psychophysical phenomena have been attributed to mutual activation of the taste and somatosensory systems of the oral cavity (Bartoshuk *et al.*, 1996).

The database of the Connecticut Chemosensory Clinical Research Center (CCCRC) contains information about

supra-threshold taste function in BMS patients seen at the University of Connecticut Taste and Smell Clinic (TASC). In order to determine how supra-threshold taste function may be altered in a BMS patient population, we compared whole-mouth taste data in a group of BMS patients with age- and sex-comparable controls. Given the receptive field overlap between the gustatory and trigeminal systems, the identification of substance P in trigeminal perigemmal fibers (Nishimoto *et al.*, 1982) and the overlapping anatomical juxtaposition of these systems in the central nervous system (Whitehead and Frank, 1983; Whitehead, 1988), we hypothesized that taste function in BMS might be altered in conjunction with chronic, trigeminal pain pathway activation.

Materials and methods

Subjects

The 73 BMS patients (mean age ± SD, 57.62 ± 12.00 years; 57 women, 16 men) in the current analysis answered 'yes' to the CCCRC chemosensory interview question 'Do you ever experience unexplained oral burning?' The CCCRC multidisciplinary diagnostic team of physicians reviewed each case and found no clinical signs to explain the burning symptom (mean duration of complaint ± SD, 3.13 ± 4.12 years). We compared the data from BMS patients with data from 52 age- and sex-matched controls (mean age ± SD, 53.37 ± 10.40 years; 38 women, 14 men). Of the 52 controls, 38 were obtained in conjunction with the University of Connecticut Health Center (UCHC) General Clinical Research Center (GCRC). GCRC controls were compensated for their participation. The remaining 14 controls were volunteers who were selected from the UCHC faculty and staff. No statistically significant differences were found between the two control groups and, thus, data from compensated and non-compensated controls were pooled into one control group. Before chemosensory testing, all subjects were asked to read and sign an informed consent form that had been approved by the UCHC Internal Review Board. Subjects were also asked to complete a 24 question chemosensory interview. Interview data was unavailable for one BMS patient. Of the 72 BMS patients completing the chemosensory interview, 48 reported experiencing some type of persistent taste or dysgeusia within 6 months of chemosensory testing and 15 had active dysgeusia at the time of testing. Because individuals may construe the word 'taste' to mean 'any sensation that occurs in the mouth', patients were also asked about the quality of the reported dysgeusia. Of the 48 patients reporting dysgeusia, 26 identified it as 'sweet', 'sour', 'salty' or 'bitter', 15 identified it as 'foul', four identified it as 'smokey' or 'fecal' and three identified it as 'tactile'. Thus, the three patients identifying a 'tactile' sensation may have been describing oral burning, which they also reported experiencing at the time of testing.

Procedure

Subjects rated the intensity and quality of five concentrations (in half-log steps) of NaCl ('salty', 0.01–1.0 M), sucrose ('sweet', 0.01–1.0 M), citric acid ('sour', 0.00032–0.032 M) and QHCl ('bitter', 0.00001–0.001 M). Each stimulus was presented in 5 ml samples, sipped and expectorated. A deionized water rinse followed each taste stimulus presentation. Each concentration of each stimulus was presented randomly twice with the exception that 0.1 M NaCl was always presented once at the start of each session. In addition, the loudness of six 1000 Hz tones (38–98 dB, in 12 dB steps) presented through headphones was also rated (Bartoshuk *et al.*, 1983; Bartoshuk, 1989).

The method of cross-modal magnitude estimation was used to rate stimulus intensity. The intensity of each stimulus (gustatory or auditory) was rated on an open ended ratio scale. After every fourth or fifth taste stimulus, one of the tones was presented randomly. Intensity ratings given to the solutions were averaged over the two replicates and normalized relative to the five loudest tones. Thus, intensity data from the lowest tone was dropped from the analysis. Taste intensity data were normalized by averaging the intensity ratings to each of the five loudest tones over the two replicates and computing the geometric mean of those five averages. A tonal scaling factor was computed by dividing the geometric mean of the five tones into 20. The average intensity rating of each solution was then multiplied by the tonal scaling factor to obtain a normalized taste score. Normalized ratings were used in the statistical analysis of the data and in calculating concentration–response functions. Because of hearing difficulty, one 80-year-old BMS patient was excluded from the analysis.

Data analyses

Normalized intensity data were first analyzed as a four-way mixed factor ANOVA (sex × group × stimulus × concentration); throughout the manuscript, this four-way analysis is referred to as the Grand ANOVA. Sex (men versus women) and group (BMS versus control) were the between-subjects measures while stimulus (NaCl, sucrose, citric acid and QHCl) and concentration level (1–5) were the within-subjects measures. Because BMS is a disorder that primarily affects post-menopausal women, we also partitioned the data into separate ANOVAs for the men and women (group × stimulus × concentration). Where necessary, subsequent *post hoc* analyses were conducted with the Studentized Newman–Keuls test (SNK).

Quality identifications were tabulated and counted as 'correct', 'incorrect' or 'tasteless'. For each stimulus, the total number of misidentifications was summed over all concentrations and was expressed relative to the total number of stimulus detections for each subject. A stimulus was defined as detected if the subject gave the stimulus an intensity rating greater than 0. Intensity ratings equal to 0

were defined as 'tasteless'. The resulting misidentification ratios for each stimulus were converted to arc sines (to stabilize the variance) and analyzed with a two-way ANOVA, group × stimulus (Helms *et al.*, 1995). The results of these analyses are reported in the text as percentages. Appropriate frequency data were analyzed with the χ^2 statistic.

Results

Taste intensity analyses

Although differences between the BMS and control groups were apparent for specific stimuli at certain concentrations, the overall main effects for group and sex were not significant in the Grand ANOVA. Simple effects analysis of the significant group by concentration interaction [$F(4,484) = 3.70$, $P < 0.006$] indicated that BMS patients gave significantly lower intensity ratings to higher stimulus concentrations than controls. In particular, analysis of the significant group × stimulus × concentration interaction [$F(12,1452) = 2.32$, $P < 0.006$] showed that BMS patients gave lower intensity ratings to higher concentrations of NaCl and sucrose than controls. Intensity ratings to QHCl and citric acid were similar for the two groups.

Partitioning the data into separate analyses for men and women illustrated that the differences described from the Grand ANOVA were driven primarily by group differences among the women. Gustatory function in BMS men did not differ significantly from their taste controls. Because of this result and the fact that the number of men in our BMS population was so small (BMS primarily affects postmenopausal women), we focused all subsequent analyses on gustatory function in BMS women.

As indicated by a significant group effect (Table 1), BMS women gave overall lower mean intensity ratings to all stimuli (mean ± SE 18.01 ± 0.82) than controls (20.57 ± 0.97). In addition, simple effects analysis of the significant group × concentration interaction (Table 1) indicated that BMS women gave lower intensity ratings to higher stimulus concentration levels than controls. However, the rate by which perceptual intensity grows as a function of concentration differs between these four stimuli (McBurney, 1978). Furthermore, effective concentration ranges of these four stimuli also differ (Pfaffmann, 1959) and, thus, between stimulus concentrations do not match for all stimuli in the TASC whole mouth taste test. This makes a comparison among the stimuli at different concentration levels difficult to interpret. Therefore, we partitioned the data into a separate analysis for each stimulus and found significant group effects for NaCl [$F(1,93) = 5.43$, $P < 0.05$] and sucrose [$F(1,93) = 8.45$, $P < 0.01$]. No significant group differences or group × concentration interactions occurred for citric acid or QHCl. The group × concentration interactions were significant for NaCl [$F(4,372) = 3.58$, $P < 0.01$] and sucrose [$F(4,372) = 9.52$, $P < 0.001$]. Simple effects analyses of the significant interactions showed that BMS women gave lower intensity ratings to higher concentrations of NaCl and sucrose than controls (Figure 1). These results mirror the results reported for the Grand ANOVA and demonstrate that the effects found in the Grand ANOVA were driven by group differences between BMS and control women.

Table 1 Taste intensity data for BMS and control women (ANOVA)

Effect	df	*F*	*P*
Group	1,93	4.02	<0.05
Stimulus	3,279	34.21	<0.0001
Concentration	4,372	553.36	<0.0001
Group × stimulus	3,279	0.40	<0.75
Group × concentration	4,372	5.12	<0.0005
Stimulus × concentration	12,1116	6.05	<0.0001
Group × stimulus × concentration	12,1116	1.21	<0.27

Taste quality analysis

Stimulus misidentification ratios were computed for each woman (see Materials and methods, Data analyses), one ratio for each taste stimulus, and used to analyze the effects of BMS on taste quality identification. Ratios ranged between 0 and 1. A misidentification ratio of 0 meant that all stimulus detections were correctly identified (i.e. no misidentifications) and a misidentification ratio of 1 meant that all stimulus detections were misidentified. One BMS patient was excluded from the misidentification analysis because all solutions were judged 'tasteless' by that individual.

The percent of stimulus detections by the two groups was equivalent, regardless of taste stimulus (Figure 2a). The χ^2 for sucrose failed to reach significance [$(1, n = 94) < 2.27$, $P < 0.14$]. However, a significant group main effect [$F(1,92) = 11.67$, $P < 0.001$] indicated that BMS women misidentified more detected stimuli (19 ± 2%) than controls (8 ± 1%). A significant group × stimulus interaction [$F(3,276) = 3.54$, $P < 0.05$] indicated that misidentification ratios between the groups varied as a function of test stimulus. Figure 2b shows that among detected stimuli, BMS women made proportionately more identification errors (15 ± 3%) than controls (5 ± 3%) for NaCl [$t(92) = 2.82$, $P < 0.01$] and citric acid (33 ± 4 versus 15 ± 3%, respectively) [$t(92) = 3.00$, $P < 0.01$].

We also examined the distribution of misidentification errors with respect to group and stimulus concentration without regard to stimulus compound. Since intensity differences between the groups were only apparent at the higher stimulus concentrations (Figure 1), we combined the two lowest and two highest concentration levels across all stimuli to test whether identification errors were also made at the higher stimulus levels. We examined the

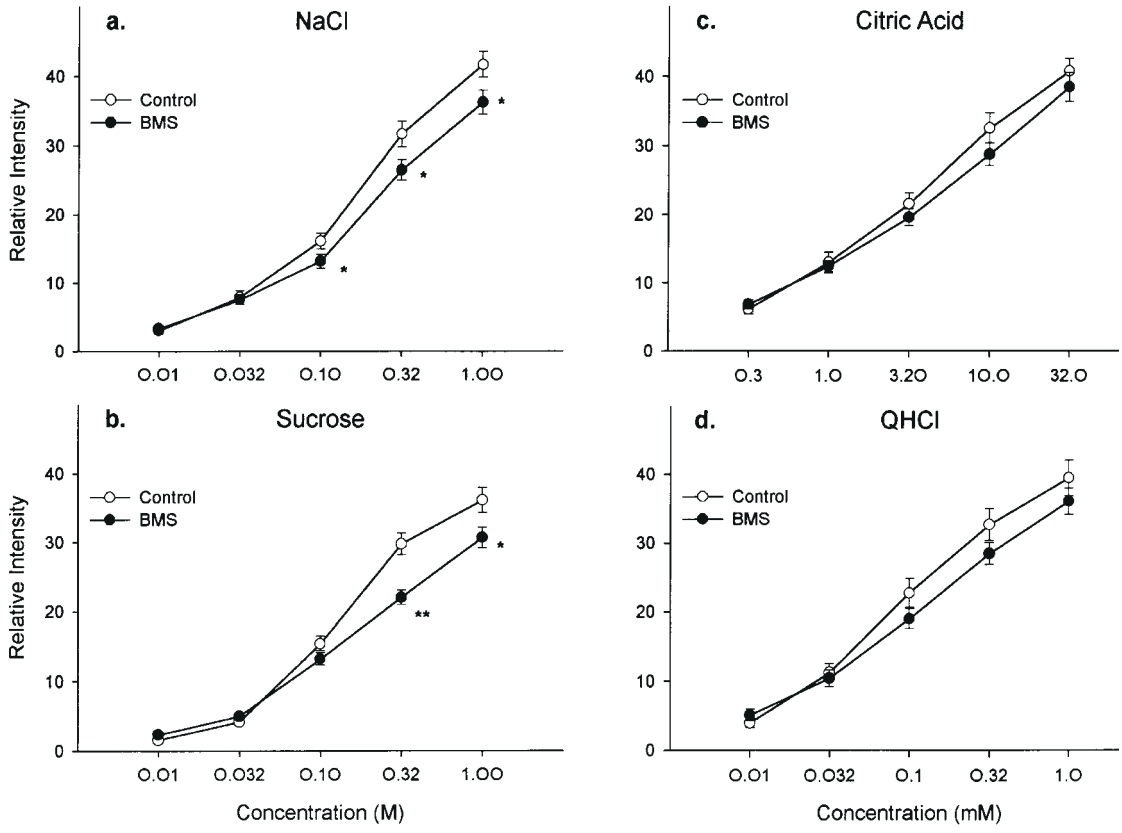

Figure 1 Mean relative perceptual intensity ratings for **(a)** NaCl, **(b)** sucrose, **(c)** citric acid and **(d)** QHCl in BMS (n = 57) and control (n = 38) women. BMS women gave significantly lower average intensity ratings for NaCl and sucrose compared to controls. No group differences occurred for citric acid or QHCl. NaCl and sucrose are shown in molar concentrations; citric acid and QHCl are shown in millimolar concentrations. *$P < 0.05$; **$P < 0.01$.

resulting misidentification ratios with a two-way ANOVA, group × concentration level (low versus high). Thus, stimulus was not a factor in this analysis. As with the previous analysis, the significant group effect [$F(1,351) = 21.56$, $P < 0.0001$] verified that BMS women made more identification errors than controls (28 ± 3 versus 12 ± 2%, respectively). A significant effect of concentration level [$F(1,351) = 50.38$, $P < 0.0001$] indicated that regardless of group, more errors were made at the low (31 ± 3%) versus the high (12 ± 2%) concentration levels. The group × concentration interaction was not significant [$F(1,351) = 1.98$, $P > 0.15$]. This analysis illustrates that as stimulus concentration level increased, identification errors decreased in all subjects, however, BMS patients made reliably more errors than controls.

Discussion

The current results indicate that altered taste function in BMS extends beyond that previously reported for near-threshold concentrations of sucrose and citric acid (Grushka *et al.*, 1986). Relative to controls, BMS patients in the current study gave reliably lower intensity ratings to supra-threshold concentrations of NaCl and sucrose, particularly at higher stimulus concentrations. The differences found between BMS and control subjects were driven primarily by differences among the women. In addition to decreased intensity ratings, BMS patients made proportionately more errors identifying detected stimuli than did controls. All subjects detected a similar proportion of taste stimuli and made more identification errors at lower concentration levels. BMS patients made more identification errors than controls at both the low and high concentration levels, but rated stimulus intensities as weaker only at the higher concentrations.

Recent reports indicate that stimulus identification improves with increases in stimulus concentration and perceptual intensity in the general population (Gent *et al.*, 1999; Hettinger *et al.*, 1999). However, there appears to be a stimulus identification limit, beyond which further increases in stimulus intensity lead to no further improvements in stimulus identification. The perceptual intensities of the higher concentrations in the present study may have exceeded that stimulus identification limit for all subjects. This suggests that the identification deficit in BMS women is not likely a consequence of lower perceptual intensities.

Previous evidence of altered gustatory intensity function

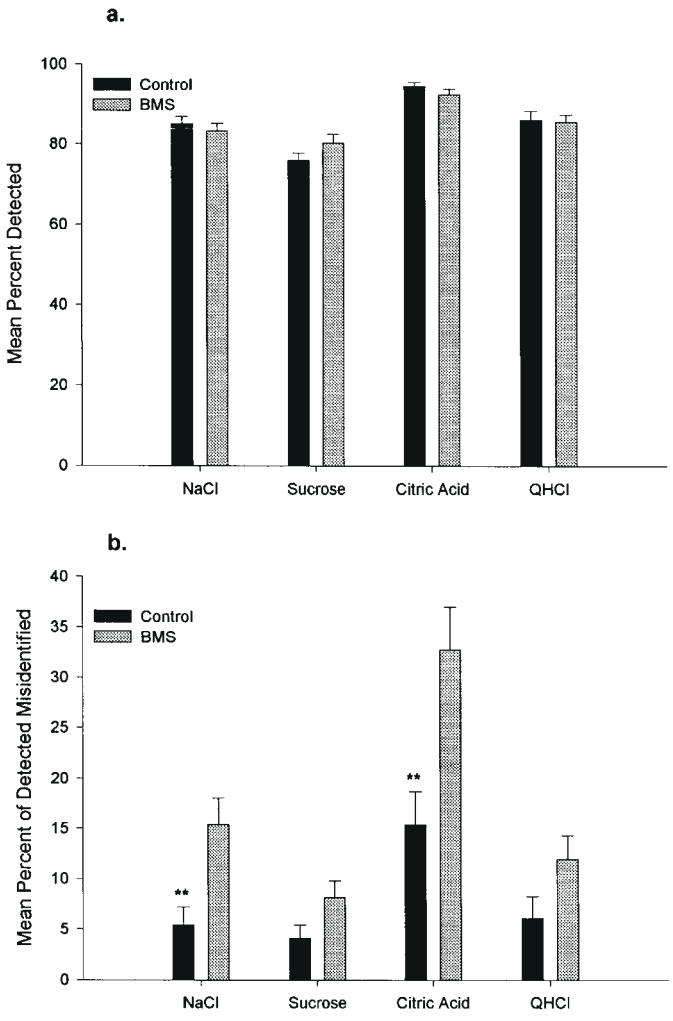

Figure 2 **(a)** Mean percentage of stimulus presentations detected for NaCl, sucrose, citric acid and QHCl in BMS and control women. Stimuli were defined as detected if the subject gave the stimulus an intensity rating greater than 0. The relative number of stimulus presentations detected across the four stimuli did not differ for the two groups. **(b)** Mean percent of detected stimuli misidentified by BMS and control women. As a group, BMS women misidentified detected stimuli more frequently than controls. $^{**}P < 0.01$.

was reported for BMS patients, but only in those patients reporting dysgeusia (Grushka *et al.*, 1986). BMS patients with dysgeusia gave higher intensity ratings to sucrose and citric acid than BMS patients without dysgeusia. However, this effect occurred primarily at concentrations that are near the perceptual threshold (Pfaffmann, 1959) and lower than those we used. We found no differences in gustatory function among BMS patients experiencing dysgeusia at time of testing relative to those that did not experience dysgeusia at all (data not reported). Thus, while dysgeusia may elevate gustatory thresholds for some stimuli (Grushka *et al.*, 1986), it does not appear to affect supra-threshold perceptions at the concentrations reported here. However, methodological differences between the present analysis and the previous report (Grushka *et al.*, 1986), both in the concentrations tested and in the psychophysical measurements taken, make it difficult to directly compare the results of the two studies.

Interestingly, normal subjects treated with chemical irritants may also report decreased taste intensity judgements to supra-threshold concentrations of chemical stimuli (Lawless and Stevens, 1984; Cowart, 1987; Yau and McDaniel, 1992; Prescott *et al.*, 1993; Karrer and Bartoshuk, 1995; Prescott and Stevenson, 1995). To the degree that the oral pain of BMS can be modeled by chemical irritants, piperine (found in black pepper) and capsaicin (found in chili peppers) may both affect taste intensity judgements. Following treatment with capsaicin, taste intensities of sucrose, citric acid and quinine decreased; treatment with piperine decreased taste intensities of the same three stimuli and of NaCl (Lawless and Stevens, 1984). These effects were seen for stimulus concentrations similar to those we used. However, such effects are dependent on procedural variables (Cowart, 1987) as well as the irritant used (Yau and McDaniel, 1992). Sweetness intensity perceptions were reduced for sucrose solutions (Prescott and Stevenson, 1995) and tomato soup mixed with capsaicin (Prescott *et al.*, 1993), but mixing capsaicin with NaCl or citric acid had little effect on their saltiness or sourness. As with the work on chemical irritants, not all tastes in the present analyses were affected equally and a general response bias due to attentional effects cannot be used to account for the results. In the current analysis, of the 43 BMS women who were asked, 32 (74%) reported experiencing oral burning at the time of testing and 11 (26%) did not. However, we previously noted that active oral burning had no effect on taste intensity ratings (data not shown) (Formaker *et al.*, 1998a). If the patients were simply paying more attention to the oral burn than the chemical stimulus, then all tested stimuli would likely have been affected equally. These results also suggest that attentional variables were not at play.

A recent investigation indicates that capsaicin can decrease functional taste responses to NaCl in sodium-best CT fibers of the rat (Osada *et al.*, 1999). Furthermore, electrical stimulation of the lingual nerve also decreases CT taste responses to NaCl in the rat (Wang *et al.*, 1995). To the degree that electrical stimulation of the lingual nerve mimics chemical stimulation by capsaicin, these results suggest a peripheral physiological interaction between the trigeminal and gustatory systems of the rat. Similar interactions between oral chemosensory mechanisms of the trigeminal system and gustatory mechanisms of the taste system may occur for humans (Lawless and Stevens, 1984; Bartoshuk *et al.*, 1996).

We previously reported that topical anesthesia decreased dysgeusia in BMS patients and concluded that peripheral gustatory mechanisms mediate dysgeusia in BMS, however, the results of anesthesia on oral burning varied (Formaker *et al.*, 1998b). Topical anesthesia reduced oral burning in

one-third of the patients studied, indicating a role for peripheral mechanisms and raising the possibility for physiological interactions like those reported for the rat (Wang *et al.*, 1995; Osada *et al.*, 1999). However, the remaining two-thirds of the BMS patients experienced no relief from oral burn symptoms. Moreover, the intensity of oral burning actually increased in some patients following anesthesia application. These results raise the possibility of a central origin for oral burning in many patients. Thus, central as well as peripheral interactions between the nociceptive and gustatory systems may play a role in explaining the current results.

Although the current study did not examine effects of endogenous steroids on taste function, estrogen may affect sucrose consumption in rodents and humans (Than *et al.*, 1994; Hrupka *et al.*, 1997). Fluctuations in sensory sensitivity as a function of ovarian hormones have been reported for olfaction, taste (NaCl and sucrose) and touch (Wright and Crow, 1973; Henkin, 1974; Than *et al.*, 1994). Because menopausal oral pain can be alleviated with hormone replacement therapy, it is tempting to postulate a relationship between altered hormone levels in post-menopausal women, BMS and taste sensitivity.

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