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Degeneration of fungiform and circumvallate papillae following molar extraction in rats

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Abstract

Objective. Proper occlusion facilitates food intake and gustatory function is indispensable for the enjoyment of food. Although an interaction between dentoalveolar and gustatory afferent neurons has been suggested by previous studies, the relationship between occlusion and gustation remains unclear. This study investigated the effect of upper molar extraction which diminished occlusal support on peripheral gustatory receptors in rats. ***Materials and methods.*** Thirty-six 7-week-old male Wistar rats were randomly assigned to either the experimental or the control group. All maxillary molars were extracted from rats in the experimental group under anesthesia, while a sham operation was conducted in the control group. The rats were euthanized 7, 14 or 28 days after the procedure. The morphology of the circumvallate papillae and taste buds using immunohistochemical methods and the fungiform papillae were visualized with 1% methylene blue. ***Results.*** Defects in the gustatory epithelium were observed after maxillary molar extraction. Rats in the experimental group had significantly fewer fungiform papillae, narrower circumvallate papillae, shallower trench depth, smaller trench area, smaller taste bud area, lower ratios of taste bud area to trench area and fewer taste buds than those in the control group. ***Conclusions.*** The findings indicate that molar extraction would affect peripheral gustatory receptors. This is the first study to characterize changes in rat fungiform and circumvallate papillae after maxillary molar extraction. This study suggests a possible synergic relationship between dentoalveolar perception and gustatory function, which has clinical implications that occlusion is closely correlated with gustatory perception.

Key Words: *cytokeratin 8, immunohistochemistry, taste*

Introduction

Taste is the essential sensory modality that guides organisms to identify and consume nutrients while avoiding toxins and indigestible materials. Individual variation in taste tolerance may have important consequences for food selection and nutrition, which has a significant impact on our quality-of-life and health [1,2].

Gustatory signals originate from 'taste buds', sensory organs in the oral cavity triggered by water-soluble compounds contacting their apical cells. Taste bud stimulation initiates physiological reflexes that prepare the digestive system for nutrient absorption and other organs for metabolic adjustments. In addition to lingual papillae, taste buds are also located in the epithelium of the palate, pharynx and epiglottis. The distribution of taste buds varies by species and by type of papilla. There are four papilla types on the mammalian tongue: circumvallate, fungiform and foliate papillae containing taste buds, and filiform papillae, which do not contain taste buds but have the ability to detect food texture [3]. Mammalian taste buds are clusters of elongated neuron-like epithelial cells, many of which have synapse-like contacts with gustatory axons [4]. Innervation and specific neurotrophins play an important role in the development and maintenance of taste papillae and taste buds [5–7]. The gustatory system is unique in that taste bud innervation is crucial to taste bud cell turnover. Several studies have reported that fungiform taste buds and circumvallate papillae degenerate after

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nerve injury or depletion of neurotrophin-dependent innervation [8,9]. The dynamic state of tongue papillae and taste buds makes them an excellent model for research in neuroplasticity and taste.

Taste represents a multisensory interaction: not only gustation but also somatosensory sensation participate in the recognition of food. It has been shown that the brain regions associated with gustation and somatosensory sensations overlap and have close proximity. At the peripheral level, somatosensation of the tongue contributes to synergizing gustatory sensation [10,11]. The interaction between gustation and somatosensation of the tongue has been widely studied. However, the relationship between peripheral gustatory receptors and dentoalveolar sensation has not been investigated. The purpose of the study is to investigate the effect of molar extraction on peripheral gustation. In this study, we used a rat model to investigate the effect of molar extraction on gustatory function by observing changes in the gustatory papillae and taste buds.

Materials and methods

Animals

All animal use and experimental procedures were approved by the Institutional Animal Care and Use Committee and were performed in accordance with the Animal Care Standards of Tokyo Medical and Dental University (approval 0130060A).

Seven-week-old male Wistar rats (n = 36) were purchased from Sankyo Labo Service Corporation (Tokyo, Japan) and housed in groups of three rats per cage in a temperature- and humidity-controlled room with a 12:12 light/dark cycle. The rats were randomly divided into either the experimental or control group, with six rats in each group. In the experimental group, the first, second and third maxillary molars on both sides were extracted under general anesthesia with an intraperitoneal injection of chloral hydrate (0.4 mg/g body weight). The rats in the control group were anesthetized without tooth extraction. All rats were provided *ad libitum* access to a powdered chow diet (CE-2, Clea Japan, Shizuoka, Japan) and tap water. Body weights were recorded throughout the experimental period.

Post-mortem analysis

The rats were euthanized at 7, 14 or 28 days after the surgical procedure. Tongue tissues were removed and fixed overnight with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) at 4°C.

The tongues were sectioned in front of the intermolar eminence and then divided into left and right side along the median sulcus with a surgical blade. The left side of the tongue was stained with 1% methylene blue tetrahydrate (Wako Pure Chemical Industries, Osaka, Japan) and the surface carefully removed for evaluation (Figure 1A). The number of fungiform papillae was counted using a light microscope (Microphoto-FXA, Nikon, Tokyo, Japan) equipped with a digital camera (DXm1200, Nikon, Tokyo, Japan).

Immunohistochemical staining and structural measurement of taste papillae and taste buds

Twenty-eight days after molar extraction, we evaluated the morphology of the circumvallate papillae and taste buds by immunohistochemistry.

The laryngeal portion of the tongue was embedded in paraffin according to a standard protocol using an automatic process machine (RH-12DM, Sakura Finetek Japan, Tokyo, Japan). Serial 5-μm-thick coronal sections were prepared using a microtome (Leica RM 2155, Leica, Nussloch, Germany). The continuous sections of whole circumvallate papillae were performed and numbered; the middle number of 10 sections were selected for histological evaluation, because the taste buds were generally less than 50 μm in diameter, most were encompassed in 10 5-μm sections.

To evaluate taste buds in the circumvallate papillae, immunostaining was performed using a streptavidin-biotin-peroxidase method. The sections were deparaffinized with xylene and rehydrated in a graded ethanol series. Endogenous peroxidase was blocked by incubation for 15 min at room temperature in peroxidase-blocking solution (DAKO, Carpinteria, CA). Then samples were washed for 3 min each in 0.1% Tween 20 in 0.1 M phosphate-buffered saline (PBS) and exposed to 1% bovine serum albumin at room temperature for 30 min, followed by overnight incubation at 4°C in 1:100 rabbit anti-rat polyclonal antibody against cytokeratin 8 (Abcam, Cambridge, MA) in 0.1 M PBS. The sections were then incubated with a secondary antibody, biotin-conjugated goat anti-rabbit polyclonal antibody (Histofine Simple Stain Rat MAX PO MULTI, Nichirei, Tokyo, Japan) for 30 min at room temperature. Three additional washes in PBS preceded incubation with 3,3-diaminobenzidine (Vector Laboratories Inc., Burlingame, CA) for 1 min. After incubation, the sections were rinsed in distilled water, counterstained in hematoxylin, rinsed for 30 min under running tap water and mounted with mounting reagent (Aqua Poly/Mount Coverslipping Medium, Polysciences Inc., Eppelheim, Germany).

Sections were examined using a light microscope (Microphoto-FXA, Nikon, Tokyo, Japan) equipped with a digital camera (DXm1200, Nikon, Tokyo, Japan). Length and area measurements were determined with the aid of digital imaging software (ImageJ 1.33, NIH, Bethesda, MD).

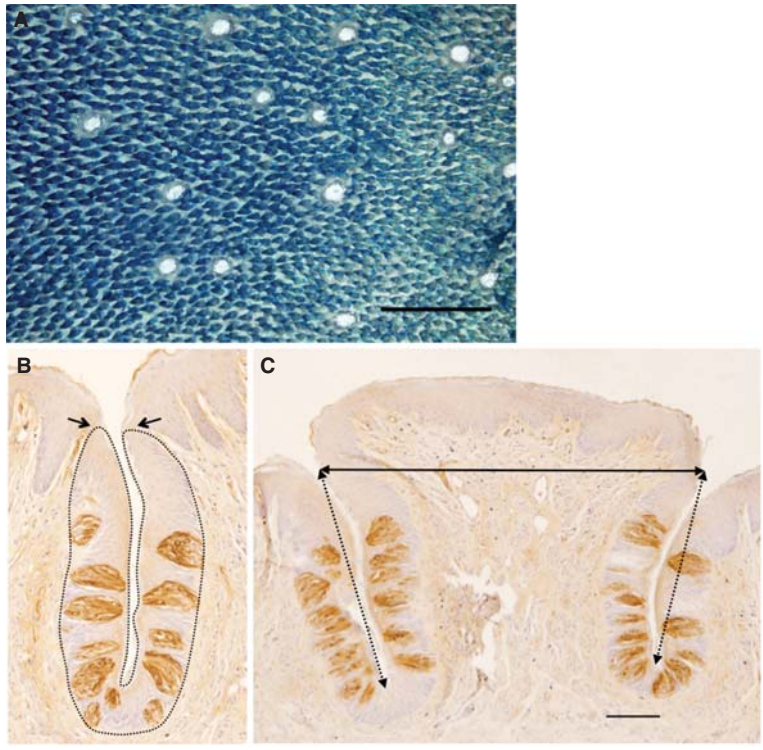

Figure 1. (A) Dorsal surface skin of tongue stained with 1% methylene blue under microscope observation. The white spot indicated the position of fungiform papillae while the small prominences are filiform papillae. The scale bar = 500 μm. (B) The figure illustrates method of measurement in circumvallate papillae. The black arrow indicated the 'opening the trench', by which papillary layer of lamina propria disappeared as a transition from the papillae to the trench. The area of trench was illustrated as dot outline, which contained the area beyond the basal membrane including taste bud and trench epithelium. (C) The black arrow showed the width of papilla, which was defined as the line from the opening of two inner trenches. The depth of trench was defined from the opening of inner trench to the bottom of trench as dot-line arrow indicated. The scale bar = 100 μm.

The width of the elevated portion of the circumvallate papillae and trench depth were measured. All trench depth measurements were obtained from cross-sections of uniformly mounted tongue tissue. The number of taste buds per trench, trench area, taste bud area and the ratio of taste bud area to trench area were determined (Figures 1B and C). The taste bud area is defined as taste bud sum per section, which was detected by immunohistochemical staining of cytokeratin 8. All parameters were measured three times independently and the average values were used for statistical analysis.

Statistical analysis

Statistical analysis of the independent samples was performed by Student's *t*-test using statistical analysis software (JMP, SAS Institute, Cary, NC). Data are reported as mean ± standard deviation and differences were considered significant when $p < 0.05$.

Results

Tongue lengths and numbers of fungiform papillae

Six rats from the control group and six from the experimental group were sacrificed on days 7, 14 and 28 after molar extraction. Tongue lengths were measured from the intermolar eminence to the point of transition from ventral smooth epithelium to rough dorsal surface. Tongue lengths are shown in Figure 2B. There were no significant tongue length differences between the control and experimental groups on days 7, 14 or 28 after molar extraction ($p < 0.05$).

The number of fungiform papillae on one half of the tongue from the tip to the intermolar eminence was counted. The mean number of fungiform papillae was significantly lower among the experimental rats compared with the control rats on days 7, 14 and 28 after molar extraction (Figure 2C), although there was no significant difference in tongue length between the experimental and control groups.

At 7 days after molar extraction, there were significantly fewer fungiform papillae on the tongues of animals in the experimental group (62.7 ± 1.2, $n = 6$, $p < 0.001$) compared with controls (48.8 ± 1.9, $n = 6$). At 14 days after molar extraction, we also observed a lower number of fungiform papillae in the experimental group (60.7 ± 1.9, $n = 6$, $p < 0.05$) compared with controls (55.0 ± 1.7, $n = 6$). At 28 days after molar extraction, the same trend of fewer fungiform papillae in the experimental group (65.7 ± 1.7, $n = 6$, $p < 0.05$) compared with controls (54.8 ± 2.8, $n = 6$) was

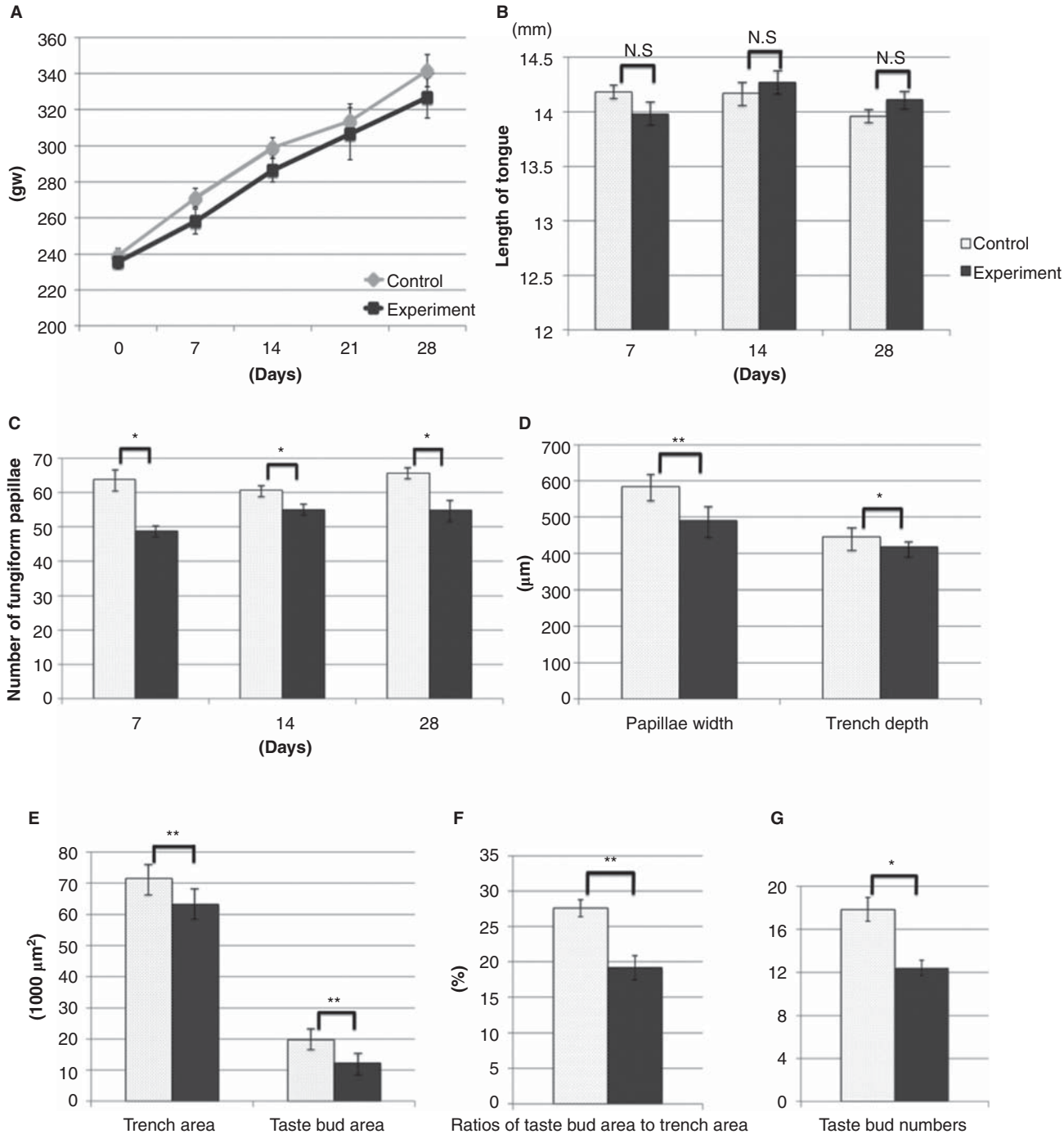

Figure 2. (A) The weight change throughout the experiment period, no significant weight change was noted between the control group and experimental group during the experiment period (N.S: not significant). (B) The length of tongue. (C) Numbers of fungiform papillae at 7, 14 and 28 days after molar extraction at 7 weeks of age. (D) Width of circumvallate papillae and trench length (means ± SD) at 28 days after molar extraction. (E) The trench wall area and total taste bud area (means ± SD) in a trench. (F) The ratios of taste bud area to the trench wall area (means ± SD). (G) Taste bud numbers in trench wall (means ± SD). Statistical significance of control and experiment group is given on top of the bars: $*p < 0.05$; $**p < 0.005$.

evident. The differences in number and percentage of papillae are summarized in Table I.

Morphological changes in circumvallate papillae

The posterior dorsal surface of the rat tongue contains a solitary circumvallate papilla, which is enclosed by two anteroposterior-directed trenches. The inner and outer walls of the right and left trenches are lined by the main gustatory epithelium of the circumvallate papilla and contain more than 90% of the circumvallate taste buds. The remaining taste buds are located on the dorsal surface of the circumvallate papilla in rats.

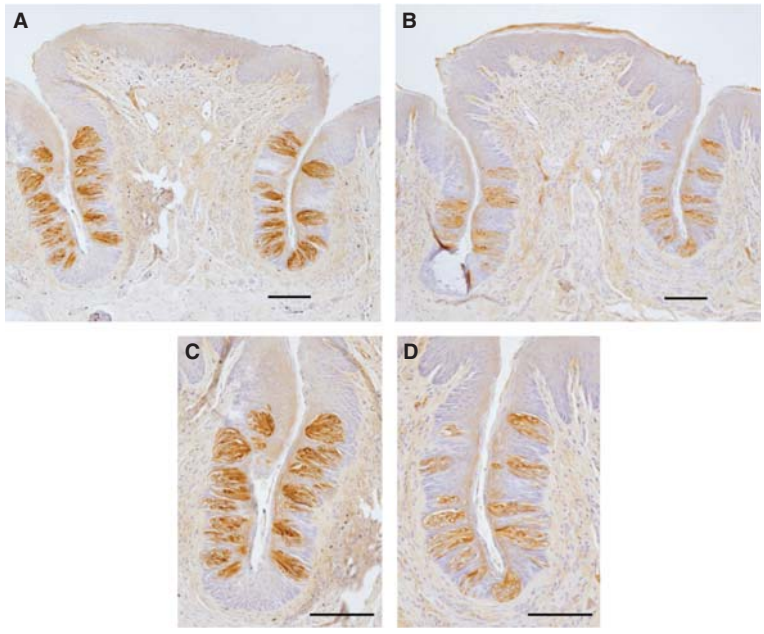

Figure 3. Two circumvallate papillae immunopositive for cytokeratin 8 (brown) and counterstained with hematoxylin. (A) Circumvallate papilla in the control group and (B) in the experimental group. Close-up view of taste buds in papilla trench in (C) the control group and in (D) the experimental group. In the experimental group (B, D), there were obviously dispersed taste buds in the trench and the shape of taste bud was shrunken, compared to the control group (A, C). The scale bars = 100 μm.

Cytokeratin 8 antibodies were used to identify taste buds in the circumvallate papillae in the study. Cytokeratins are the intermediate filament proteins characteristic of epithelial cells. Cytokeratin 8 is expressed only in taste buds and not in non-taste bud lingual epithelium on the tongue's surface, making it a useful marker in studies of taste bud development and expression [12,13].

At 28 days after molar extraction, the circumvallate papillae in the experimental group were stunted in both width and height, with statistical analysis demonstrating significantly narrower papilla width ($p = 0.0029$) and shorter trench depth ($p = 0.035$) compared with the control group.

In the circumvallate papillae, smaller trench wall area ($p = 0.004$), fewer taste buds per trench ($p = 0.0153$) and smaller total taste bud area ($p = 0.0078$) were also observed of experimental animals at 28 days after molar extraction (Figure 3). To determine whether smaller trenches were hindering the number of taste buds, the ratio of taste bud area to trench area was also investigated. The ratio of taste bud area to trench area was lower in the experimental group than in the control group ($p = 0.0008$; Figures 2D–G). The statistical results are summarized in Table II.

Body weight

The body weights of the rats are shown in Figure 2A. There were no significant weight differences between the control and experimental groups during the experimental period.

Discussion

In the present study, upper molar extraction was associated with degenerative changes in fungiform papillae and taste buds, a finding that illustrates the substantial co-ordination of the stomagnathic apparatus. In the absence of teeth, the discrimination of food particles using textual and gustatory perception might be impaired.

We chose to remove maxillary molars instead of mandibular molars to avoid damaging the lingual nerves [14]. Indeed, lingual nerve damage during

Table I. Fungiform papillae numbers (means ± SD) on 7, 14 and 28 days after molar extraction. Compared to the control group, the percentage of decreased papillae in the experiment group was calculated.

	Days after teeth extraction		
Number of fungiform papillae	7	14	28
Control	62.67 ± 1.17	60.67 ± 1.86	65.67 ± 1.69
Experiment	48.83 ± 1.89	55.00 ± 1.65	54.83 ± 2.77
Decreased percentage	22.1%	9.3%	16.5%

Table II. The summary of the measurement of circumvallate papillae in the control and experiment group.

	Control	Experiment	% Reduction	*p*
Papillae width (μm), $n = 6$	584.4 ± 23.2	490.6 ± 19.2	16	0.0029
Trench depth (μm), $n = 12$	446.1 ± 13.0	418.1 ± 8.0	6	0.035
Trench wall area (1000 μm^2), $n = 12$	71 443.1 ± 2 088.6	63 178.5 ± 1 893.4	12	0.004
Total taste bud area (1000 μm^2), $n = 12$	19 741.4 ± 1 159.3	12 295.3 ± 1 365.3	38	0.0078
Ratios of taste bud area to trench area (%), $n = 12$	27.6 ± 1.2	19.2 ± 1.7	31	0.0008
Number of taste buds in one trench, $n = 12$	17.8 ± 1.8	12.4 ± 0.8	30	0.0153

dental extraction procedures can elicit temporary gustatory deficiency [15].

One of the possible reasons for the deterioration of taste papillae and taste buds after molar extraction might be peripheral or central neuroplastic changes induced by dental deafferentation. After molar extraction, inflammatory cells infiltrate the surrounding tissue, damaging peripheral nerves [16]. Some studies have indicated that trigeminal afferent signals synergize with gustatory afferents. For instance, the mandibular nerve, which is responsible for oral somatosensation, has been found to contribute to the taste response [17]. Dental afferent neurons have been shown to project to the nucleus of the solitary tract in the midbrain of the rat [18]. Also, a recent study indicates convergence from dental afferents and lingual afferents in the trigeminal ganglion [19]. These studies suggest a close relationship between trigeminal function and gustatory function at both the central and peripheral level. Another possible reason for the deterioration of taste papillae and taste buds after molar extraction might be reduced periodontal, pulpal and mucosal mechanoreception.

Alterations of occlusion after molar extraction in rats have been shown to affect the mechanical stress distribution, morphology and structure of the temporomandibular joints [20], possibly resulting in alteration of jaw movement. Several studies have found that chewing increases salivary secretion and that diminished periodontal mechanoreception is associated with reduced salivary secretion [21,22]. Alteration of jaw movement and elimination of periodontal afferent activity after molar extraction may affect the secretion of saliva. Saliva is crucial in tasting and in protecting the oral mucosa [23]. In a study of desalivation, taste buds in the circumvallate papillae appeared shrunken and disorganized [24,25]. The removal of submandibular and sublingual salivary glands was found to result in loss of fungiform taste buds and normal fungiform papilla morphology because of insufficient epidermal growth factor [26]. In another study, molar extraction was found to affect water transport in rat submandibular glands [27]. Alterations in saliva production and composition after tooth extraction may also contribute to degeneration of the peripheral gustatory receptors.

Experimental animals were sacrificed on days 7, 14 and 28 after surgery and differences in taste papillae numbers were seen as early as day 7. The continuous formation of new connections between nerve fibers and receptor cells necessitates turnover of taste receptor cells. According to previous research, the turnover time of taste cells in the fungiform papillae of rats is ~10 days [28]. In rat circumvallate papillae, the turnover time of dark cells is ~7 days [29]. Another study found that loss of taste buds in the fungiform papillae of rats was evident 5 days after section of the chorda tympani nerve, with numbers reaching their minimum 20 days after surgery [8]. In an experiment involving neurectomy of the glossopharyngeal nerve, the taste buds of circumvallate papillae were diminished 3 weeks after surgery [30].

The decreased numbers of fungiform papillae in experimental rats throughout the study period showed that fungiform papillae numbers did not proportionally decrease by the time elapsed after molar extraction. Adaptive or compensatory mechanisms might exist to support gustatory function after molar extraction. A longer duration of observation or a recovery model would help to clarify any adaptive mechanisms.

In humans, the supertasting phenomenon, which results in a stronger sense of bitter, sweet and irritant compounds, is correlated with the number of fungiform taste receptors in the anterior portion of the tongue [31]. In this study, less abundant fungiform papillae were found on the rat tongue. Although the result did not identify the actual taste discrimination behaviors of the rats; however, the phenomenon of decreased fungiform papillae suggests that taste deficits may be a possible consequence of molar extraction.

Morphological changes in circumvallate papillae and taste buds have been investigated by measuring papilla width, trench length and trench area to provide quantitative indices of papilla stunting [32,33]. The narrow papilla width and shorter trench depth of papillae in the experimental animals in this study indicated that the normal morphogenesis of keratinized lingual gustatory epithelium was affected after molar extraction. The effects of molar extraction might be extensive, affecting not only the peripheral gustatory receptors, but also the gustatory epithelium.

This is the first study of the effects of upper molar extraction on the peripheral gustatory receptors of the

tongue. The neurologic basis for the diminished taste papillae and taste buds after tooth extraction remains to be clarified. However, our findings have clinical implications and support the idea that tooth loss is closely correlated with taste perception, providing impetus for further study in gustatory function.

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***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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