Alterations in the gustatory papillae after anterior bite plate insertion in growing rats

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Abstract:
OBJECTIVES: To determine whether the modification of dental occlusion, without molar extraction, affected the gustatory papillae located in the tongue of growing rats.

MATERIALS AND METHODS: Five-week-old male Wistar rats were randomly divided into an anterior bite plate (ABP) group and a control group. Under general anesthesia, ABPs were placed on the occlusal surfaces of the maxillary incisors, while metal caps covered the mandibular incisal edges of the rats in the ABP group. The control group rats underwent a sham operation. The rats in both groups were euthanized 14 days after the procedure. The circumvallate papillae and taste buds were analyzed by immunohistochemical methods, and the fungiform papillae were observed and counted after immersion of the tongue in 1% methylene blue.

RESULTS: Two weeks after ABP insertion and mandibular incisal cap placement, the gustatory papillae exhibited morphological and structural changes. The rats in the ABP group had exhibited significantly fewer fungiform papillae, and narrower circumvallate papillae, with greater trench depths, larger trench profile areas, smaller taste bud profile areas, lower ratios of the taste bud profile area to the trench profile area, and more taste buds than those in the control group.

CONCLUSIONS: Our findings support the association between occlusal and taste functions and provide a basis for further studies on the gustatory function. In conclusion, loss of molar occlusion, resulting from the ABP and metal cap insertion, altered the peripheral gustatory receptors in the growing rats.

Keywords: Growing rat, gustatory papillae, occlusion, taste

Introduction

Oral function encompasses the ability to perceive and distinguish various categories of taste stimuli.[¹] The main purpose of the gustatory apparatus is to ensure the taste-sensing function. The sense of taste enables individuals to assess the nature of nutrients; thus, it contributes to the maintenance of healthy organisms. Gustatory information emerge from the interaction of aqueously dissolved substances with chemoreceptors located on the apical membrane of taste receptor cells (TRCs).[²] These chemosensitive cells complementarily contribute to the process of transduction for the five basic taste categories identified as sweet, salty, sour, bitter, and umami.[³] Clusters of TRCs form taste buds in the stratified epithelium of the lingual papillae, palate, epiglottis, oropharynx, larynx, and the superior portion of the esophagus in mammals.[⁴] The nomenclature classifies TRCs as types I, II, III, and basal or progenitor. Although constant innervation is primordial for the TRC maintenance and regeneration cycle, only few TRCs form synaptic contacts with the adjacent gustatory nerve axons.[⁵]

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Taste perception combines multisensory interactions. Several studies have demonstrated the proximity and interplay existing between gustatory and somatosensory pathways at not only the cortical but also the peripheral level, including the epithelium of the tongue and oral mucosa. Thus, various food features such as modality, intensity, temperature, texture, and pungency almost simultaneously generate gustatory and oral somatosensory signals that collectively inform the central nervous system and prepare the organism for meal ingestion.

Taste disturbances such as ageusia, hypogeusia, and dysgeusia have been reported in some patients who underwent root canal treatment in the anterior teeth, extraction of impacted third molars, and posterior periodontal surgeries with no records of gustatory nerve lesions. Other human subjects have reported taste impairments after undergoing orthognathic surgeries, despite preservation of the integrity of the greater superficial petrosal, palatine chorda tympani, and lingual nerve fibers. Taste disorders were also noticed after tonsillectomies associated with zinc deficiencies. Lesions of the chorda-lingual and glossopharyngeal nerves in rats reportedly have deleterious impacts on the taste buds in the fungiform and circumvallate papillae. Unilateral lesions involving either the lingual or the inferior alveolar nerve tangibly diminish the amount of taste-triggered reactions from neurons in the nucleus of the solitary tract (NTS) in rats. Moreover, electrical stimulations of the peripheral and central transected endings of the lingual and inferior alveolar nerves in rats buffer the activation of gustatory neurons in the NTS. However, other researchers have suggested a noticeable electrically induced excitation of the NTS neurons. These findings imply that oral somatosensations originating from the teeth and the periodontium during mastication provide additional sensory inputs converging with the taste-sensing function.

The occlusion status, coherence, and masticatory performance influence the structure, dimension, function, morphology, and development of the maxillofacial complex including the stomatognathic system, in mammals. Using posterior bite blocks, some researchers have investigated the adjustments of maxillofacial bony and muscular structures to occlusal modifications in rats. Other investigators have used anterior bite plates (ABPs) to modify the relationship between the dental arches and analyze the subsequent effects on the mandibular position and condylar processes in rats. In addition, ABPs and incisor metal caps have been used to study how non-occluding antagonist molars affect the rat periodontium. Therefore, occlusion determines the health and proper function of the periodontal ligaments, alveolar bone processes, mandible, maxilla, masticatory muscles, and temporomandibular condyles.

Nevertheless, few studies have reported about the association between occlusion and gustation. Consequently, the interaction between the masticatory and gustatory systems remains poorly understood. Variations in occlusal function subsequent to occlusal modification, without tooth loss, may synchronize with observable changes in the taste apparatus. The aim of this study was to assess whether occlusal modifications achieved with ABP and metal cap insertion affected the gustatory papillae located in the tongue of growing rats. The findings describe the morphological and histological changes in the circumvallate and fungiform papillae after occlusal modifications.

**Materials and Methods**

**Animal husbandry and study design**

Five-week-old male Wistar rats (n = 10; weight 155–160 g) purchased from Sankyo Labo Service Corporation (Tokyo, Japan) served as subjects for this study and were randomly divided into an ABP group (n = 5) and a control group (n = 5). All animals were free of specific pathogens and maintained throughout the experiments in optimum conditions of a 12-hour day–night cycle, with a powdered chow diet (CE-2; Clea Japan, Shizuoka, Japan) provided ad libitum and unlimited access to tap water.

**Experimental procedures**

Animals and experimental procedures described below were approved by the Institutional Animal Care and Welfare Committee and implemented according to the Animal Care Standards of Tokyo Medical and Dental University (#0170398A). General anesthesia was achieved through inhalation of 4% isoflurane (Wako Pure Chemical Industries, Ltd., Osaka Japan) and intraperitoneal injections of pentobarbital sodium (30.0 mg/kg body weight; Tokyo Chemical Industry Co., Ltd., Tokyo, Japan).

ABPs made of band material (0.180 × 0.005 in; Rocky Mountain Morita Corp., Tokyo, Japan) were placed on the occlusal surface of the maxillary incisors of the rats in the ABP group. In addition, metal caps, also fabricated from band material, were fixed over the mandibular incisal edges of the rats in the ABP group, using photopolymerizing composite resin (Clearfil Liner Bond II; Kuraray, Okayama, Japan). The rats in the ABP and control groups were weighed daily, and their health condition was regularly checked. At the age of 7 weeks, all rats were euthanized by cervical dislocation under general anesthesia accomplished with 4% isoflurane.
Collections of tongue tissues and counting of fungiform papillae
Each rat tongue was resected from its intraoral root attachment at the level of the trachea and fixed overnight with 4% paraformaldehyde in 0.1 M phosphate buffer (pH, 7.4; Mildform; Wako Pure Chemical Industries) at 4°C. Tongue tissues were sectioned transversely and posteriorly to the intermolar eminence and divided into apical and laryngeal segments [Figure 1]. Immersions in 1% methylene blue tetrahydrate (Wako Pure Chemical Industries) completed the staining procedure for the apical tongue segments. The fungiform papillae on the right and left sides of the midline sulcus were counted from the median eminence to the apex using a dissecting stereo-microscope (SMZ1270; Nikon, Tokyo, Japan) equipped with a digital camera (DXm1200; Nikon).

Immunostaining procedures for the circumvallate papillae and taste buds
Morphological, dimensional, and anatomical assessments of the circumvallate papillae, including the taste buds, were conducted using immunohistochemistry for the tongue specimens obtained from the rats in both groups. Following a conventional standard protocol, the laryngeal tongue segments were synchronously embedded in paraffin using an automatic processor (RH-12DM; Sakura Finetek Japan, Tokyo, Japan). These specimens were consecutively sectioned into 5-µm-thick coronal slices using a microtome (Leica RM 2155; Leica, Nussloch, Germany). The circumvallate papillae were entirely sliced into successively numbered sections. Each taste bud exhibited an approximate diameter of 60 µm; therefore, the middle number of 12 consecutive slices with a 5-µm thickness was subjected to immunostaining and histological assessments, as described below.

Two consecutive immersions in xylene achieved deparaffinization of the sliced specimens and preceded their rehydration in ethanol bath sequences of decreasing concentrations. Simultaneous application of peroxidase-blocking solution (Dako, Carpinteria, CA, USA) at room temperature for 15 min on each section blocked endogenous peroxidase activity. Three serial 3-min sessions of washing with 0.1% Tween 20 in 0.1 M phosphate-Tris-buffered saline (TBST) preceded the exposure of the sliced samples to 1% bovine serum albumin at room temperature for 30 min to prevent nonspecific antibody binding. Following three successive rinses in TBST for 3 min, all selected sample slices were incubated with 1:150 polyclonal rabbit anti-rat cytokeratin 8 (Abcam, Cambridge, MA, USA) primary antibody (Ab 59400) in 0.1 M phosphate buffered saline at 4°C. Then, biotin-conjugated goat anti-rabbit polyclonal antibody (Histofine Simple Stain Rat MAX PO MULTI; Nichirei, Tokyo, Japan) was applied as a secondary antibody for 30 min at room temperature. Three additional washing phases in TBST preceded the exposure of the samples to 3,3-diaminobenzidine (Vector Laboratories Inc., Burlingame, CA, USA) for 30 s. After a quick dip in distilled water, all specimens were counterstained by simultaneous immersion in hematoxylin, rinsed for 15 min under running tap water, and mounted with a mounting reagent (Aqua Poly/Mount Coverslipping Medium, Polysciences Inc., Eppelheim, Germany).

Dimensional analyses of immunostained circumvallate papillae and taste buds
Cross sections of uniformly mounted tongue tissues served as the basis for the dimensional and anatomical assessments of the circumvallate papillae. The separation between the two trenches at their anteroposterior midpoint determined the width of the elevated portion of the circumvallate papillae. The distance between the upper entrance and lower end of a papilla trench demarcated its depth. The surface of the fringing epithelium of the circumvallate papillae corresponded with the area of the inner and outer trench walls and indicated the trench profile area. Cytokeratin 8 immunostainings differentiated the taste buds from other papillary structures and facilitated the assessment of the number and area of taste bud profiles. The ratio of the taste bud profile area to the trench profile area determined the proportion of taste bud shapes per µm² of papilla trench outline. The thickness of the keratinized epithelium located on top of the elevated portion of the circumvallate papilla was also measured [Figure 2]. With the aid of digital software (ImageJ 1.33; NIH, Bethesda, MD, USA), six different measurements were performed for each of the above-mentioned parameters and independently repeated in triplicate, and the average values were used for statistical analysis.
Statistical analysis
Student’s t-test was performed for the assessment of the data collected separately for the fungiform and circumvallate papillae from the ABP and control groups. All statistical analyses were performed using software (R Studio, Version 1.0.153© 2009–2017). All values are reported as means ± standard deviations. P value < 0.05 was considered statistically significant.

Results
Differences in body weights
Throughout the experimental period, the differences in the body weight of rats between the ABP and control groups were significant between the ABP and the control groups. Although the increase in the body weight followed a similar trend in all groups, the rats in the ABP group showed noticeably lesser weight gain than did those in the control group [Figure 3a].

Variations in the number of fungiform papillae
After 14 days of occlusal alteration with the ABP and metal caps, the total number of fungiform papillae on the tongue surface was significantly lesser in specimens from the ABP group than in specimens from the control group. The number of apical fungiform papillae on the left side of the tongue was significantly greater in specimens from the control group than in specimens from the ABP group, whereas that on the right side of the tongue was similar in specimens from both groups [Figure 3b]. The surfaces of tongue specimens from the control group showed more fungiform papillae than did those from the ABP group [Figure 4]. Data are summarized in Table 1.

Anatomical and dimensional alterations in the circumvallate papillae
After 2 weeks of occlusal alteration in the ABP group, the elevated portion of the circumvallate papillae became narrower. The width reductions recorded in the elevated portions were significantly different between the ABP and control group specimens. The circumvallate papilla trenches were significantly deeper, the circumvallate papillae were taller, and the keratinized epithelium coating the top of the elevated portion of the circumvallate papillae was significantly thicker in the ABP group specimens than in the control group specimens [Figure 3c].

The trench profile areas in the circumvallate papillae were significantly larger in the ABP group specimens than in the control specimens. On the other hand, the taste bud profile areas were significantly larger in the control group specimens than in the ABP group specimens [Figure 3d].

The ratios of the taste bud profile area to the trench profile area were significantly greater in the circumvallate papillae from the control group than in those from the ABP group. Therefore, the proportion of taste bud shapes per µm² of the papilla trench outlines was smaller in the ABP than in the control group specimens [Figure 3e]. On an average, the circumvallate papillae from the ABP group exposed significantly more taste bud profiles per trench wall than did those from the control group [Figure 3f]. Data summarized in Table 1 and Figure 5 show the changes in the circumvallate papillae after 2 weeks of occlusal alteration with the ABP and metal caps.

Discussion
This study unveiled the quantitative and morphological changes in the fungiform and circumvallate papillae of the tongue subsequent to occlusal alterations achieved by ABP and metal caps in the growing rats. The findings illustrate the conceivable interrelationships among the components of the stomatognathic system and provide evidence of the influence of occlusal function on the gustatory apparatus. The occlusal alterations induced by ABP and metal cap placement were associated with simultaneous diminutions and augmentations in different structural parameters for the gustatory papillae.
Previous studies have described how dentoalveolar stimuli contribute to taste sensations. Trigeminal and gustatory afferents are interconnected on the rostocaudal region of NTS. Oral somatosensation contributes to the taste-sensing mechanism by modulating the activity of taste neurons in NTS. Moreover, the trigeminal ganglion hosts both dental and lingual nerve afferents. As a result, functional interactions between taste and occlusal stimuli during meal consumption may exist in neural pathways at both the central and peripheral levels.

First, the significant decrease in the number of fungiform papillae and dimension of taste buds observed in our study is in line with the findings in a previous study also conducted in rats. In that study, all the maxillary molars of the animals were extracted to induce occlusal alterations, whereas in this study, ABPs and metal caps were used for the same purpose. In both models, the lack of contact between the occlusal surfaces of the molars impeded the function of the periodontal ligament and subsequently altered its neural structures, including the free peripheral nerves and Ruffini endings. Moreover, dentoalveolar mechanoreceptive and nociceptive

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**Figure 3:** Changes after anterior bite plate insertion in rats. (a) Body weight trend. (b) Fungiform papillae numbers after anterior bite plate insertion. (c-f) Circumvallate papilla width, trench depth, and keratinized epithelium thickness (c), trench and taste bud areas (d), taste bud area to trench area ratios (e), taste bud numbers per trench (f).

*P < 0.05, **P < 0.01, NS: Not significant.
influxes originating from the dental pulp, periodontium, and oral mucosa became unable to converge toward the gustatory afferent system and NTS located in the brainstem. In addition, masticatory deficiencies correspond with diminished activities and deteriorations in the insular cortex, thalamus, and hypothalamus, where the gustatory cortex is located, as well as the hippocampus of humans and other mammals. Therefore, a decrease in somatosensory inputs from the oral cavity into the taste system may partly explain the degeneration of the peripheral gustatory receptors in our experiment.

Second, adequate salivation depends on effective occlusal function and appropriate periodontal afferent activity during mastication. The salivary flow lubricates and preserves the oral mucosa in addition to ensuring the solubility of the initially ingested nutrients, thus contributing to taste detection by the TRCs. Saliva contains the epidermal growth factor, which is crucial for the maintenance and morphogenesis of the fungiform papillae and their taste buds. Prolonged hyposalivation after sialoadenectomy has been associated with hyperkeratinization of the gustatory epithelium, deterioration of the taste buds in the circumvallate papillae, and distortion of the circumvallate papillae in addition to taste preference alterations in rats. Another study demonstrated impaired water transportation in the submandibular glands of rats following molar extraction. The salivary volumes and flow rates from the parotid and submandibular glands of rats importantly rely on their masticatory performances. The insertion of ABPs and metal caps in this study may have impeded mastication and reduced periodontal mechanoreception in the molar region in addition to affecting the secretion of saliva. Consequently, the changes in the amount and content of saliva may have contributed to the decrease in the number of fungiform papillae. Conversely, the smaller taste bud profile area in the circumvallate papillae, narrower elevated portion on the circumvallate papillae, larger trench profile area in the circumvallate papillae, and thickening of the keratinized gustatory epithelium may have resulted from variations in the salivary flow induced by occlusal hypofunction.

In this study, less abundant fungiform papillae were found on the rat tongue after 2 weeks of ABP insertion. Although the results did not identify the actual taste discrimination behaviors of the rats, the phenomenon

![Figure 4: Methylene-blue-stained dorsal surfaces of the rat tongue obtained from control (a) and experimental rats (b). The black arrowheads indicate the fungiform papillae. Scale bar: 1 mm](image)

![Figure 5: Rat circumvallate papillae immunoreactive for cytokeratin 8 and counterstained with hematoxylin in the control (a) and experimental groups (b). An atypical ectopic taste bud (black arrowhead in b). Scale bar: 100 µm](image)

| Table 1: Summary of fungiform papillae numbers and circumvallate papillae measurements in ABP and control group |
|--------------------------------------------------|--------|-----|-----|
| Total number of fungiform papillae               | C     | BP  | % Decrease |
| Number of fungiform papillae on the right apical tongue portion | 123±4.9 | 117±4.7 | 5 | 0.014 |
| Number of fungiform papillae on the left apical tongue portion | 62.1±3.8 | 59.7±4.9 | 4 | 0.145 |
| Circumvallate papillae width (µm)               | 61.1±5.8 | 57.3±4.3 | 6 | 0.048 |
| Circumvallate papillae taste bud profile area (µm²) | 517±85.3 | 499±83.7 | 9 | 0.048 |
| Circumvallate papillae keratinized epithelium thickness (µm) | 120±2.1 | 138±7.2 | 2 | 0.041 |
| Ratios of circumvallate papillae taste bud profile area to trench profile area (%) | 9.0 | 8.0 | 11 | 0.035 |
| Number of taste bud profiles per circumvallate papillae trench wall | 14.0±0.7 | 16.2±1.8 | 14 | 0.034 |

| Circumvallate papillae trench depth (µm)          | C  | BP  | % Increase |
|--------------------------------------------------|----|-----|------------|
| Circumvallate papillae keratinized epithelium thickness (µm) | 497±23.6 | 547±12.9 | 9 | 0.003 |
| Circumvallate papillae trench profile area (µm²) | 71.6±7.3 | 95.1±21.5 | 25 | 0.049 |
| Circumvallate papillae trench profile area (µm²) | 166±17.8 | 178±42.7 | 7 | 0.015 |
| Number of taste bud profiles per circumvallate papillae trench wall | 14.0±0.7 | 16.2±1.8 | 14 | 0.034 |
of decreased fungiform papillae suggests that taste deficits may be a possible consequence of inserting ABPs to alter the occlusal relationship. However, this hypothesis should be verified through further investigations.

**Conclusion**

A narrow elevated portion, deeper trenches, enlarged trench areas, decreased taste bud profile areas, and an increased number of taste bud profiles per trench wall were observed in the circumvallate papillae of growing rats that received ABP and metal caps over their mandibular incisal edges. These results indicated that the normal morphology of the keratinized lingual gustatory epithelium, including the gustatory receptors, was affected after occlusal alterations induced by ABPs and metal caps. Our findings support the association between occlusal and gustatory functions and provide a basis for further studies on gustatory function. Any functional or postural changes in any one of the components of the masticatory system may involve one or more of the associated structures that ensure other oral functions. In summary, the occlusal modifications, resulting from the ABP and metal caps insertions, affected the fungiform and circumvallate papillae of the growing rats’ tongue.

**Data availability**

The quantitative datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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**Conflicts of interest**

There are no conflicts of interest.

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