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Long-term culture and morphological maturation of taste organoids enhance taste discrimination in a biomimetic biosensor

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Abstract

Taste is a multifaceted sensory experience that involves various human senses related to food and is a key indicator of food quality. A biomimetic taste-based biosensor, which utilizes taste bud organoids as sensitive elements, is able to simulate the real responses of taste transduction in vitro. Taste bud organoids are three-dimensional structures created from taste stem/progenitor cells, integrated with transducers to develop the biosensor. In this research, organoids derived from mouse taste epithelium were employed as the sensitive element, while a microelectrode array (MEA) device served as the transduction element to create the biosensor. Following exposure to sour, sweet, bitter, and salty stimuli, one specific channel was chosen, and the average discharge rates were calculated as 6.5 ± 2.29 Hz, 7.25 ± 3.77 Hz, 3.33 ± 2.62 Hz, and 4.6 ± 2.42 Hz, respectively. Statistical analysis indicated that, apart from the sour taste, the frequency and amplitude of the other three taste stimuli showed significant increases. Principal component analysis (PCA) demonstrated the ability to identify and differentiate various tastes during taste conduction monitoring. Additionally, it was observed that on day 14, the taste bud organoids exhibited aggregation and fusion, leading to the formation of typical taste bud structures, indicating their maturation. This research offers a theoretical foundation and a valuable tool for effective and objective taste detection in vitro.

Introduction

The evolution of food flavor analysis methods can be divided into four main phases: sensory analysis, instrumental analysis, a blend of both sensory and instrumental analysis, and automated analysis that incorporates machine learning (ML)¹. Food flavor analysis is based on the subjective experiences individuals have when tasting food. The introduction of instrumental analysis has allowed researchers to more accurately investigate the volatile and soluble components found in food and beverages. Traditional food analysis techniques generally depend on

laboratory methods such as Fourier-Transform Infrared Spectroscopy², Nuclear Magnetic Resonance Spectroscopy³, High-Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS)⁴, and Enzyme-Linked Immunosorbent Assay⁵. Although these techniques are very effective for identifying food safety issues, they often require specialized equipment, trained staff, and extensive sample preparation. Furthermore, they can be expensive and time-consuming, making them less ideal for on-site monitoring.

The organism's taste sensing system is highly effective at identifying taste substances due to its intricate biological design. Taste receptors or ion channels on the surface of taste bud cells engage with taste stimuli for transmission purposes⁶. Typically, taste buds are made up of 50 to 150 taste receptor cells, varying by species, and are found on different types of taste papillae⁷. The circumvallate papillae, located at the back of the tongue, contain

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hundreds to thousands of taste buds, depending on the species (mice versus humans). The foliate papillae, situated on the back sides of the tongue, house a dozen to several hundred taste buds. The fungiform papillae, found in the front two-thirds of the tongue, contain one or a few taste buds⁸. Taste receptor cells extend microvilli to the surface of the taste buds, creating “taste holes,” allowing the tongue to respond to the five fundamental taste qualities: bitter, sour, sweet, salty, and umami, across all regions of the tongue⁹.

Organoids are formed from pluripotent or adult stem cells and display fundamental characteristics specific to organs, including various cell types, organ functions, and organized tissue structures¹⁰. They have become a key research tool in many biomedical fields, including developmental and disease modeling¹¹, precision medicine¹², toxicology¹³, and regenerative medicine¹⁴. Progress in understanding biological taste has significantly advanced related research areas. For decades, scientists have been developing biomimetic taste-based biosensors that replicate the natural gustatory system’s functionality. However, previous biomimetic sensors faced challenges, such as the temporary nature of taste tissues and the limitations of two-dimensional taste cells or receptors. To address these issues, researchers created a taste organoids-on-a-chip system that integrates taste organoids with an array of extracellular potentiometric sensors, resulting in a new type of biomimetic taste sensor capable of detecting varying levels of sourness, sweetness, bitterness, and saltiness¹⁵. In our research, we not only combined taste bud organoids with sensors but also successfully recognized and differentiated various tastes based on changes in the internal structure of the taste bud organoids.

The processes involved in organogenesis are specific to each type of tissue and organ. Additionally, there is significant overlap in the research on organoids. A microfluidic device has been developed to capture and immobilize human intestinal organoids while applying fluid shear stress, which helps modify their surface structure and promotes the fusion of these organoids into larger ones¹⁶. In experiments with mouse tracheal epithelial organoids, researchers observed that these organoids fused more rapidly in a matrix-free, floating environment, resulting in a continuous inner lumen and a stable shape without the need for an external scaffold¹⁷. This ability to pattern and fuse multiple organoids facilitates large-scale organoid engineering, leading to the creation of integrated organoid devices and complex organoid lumens. In studies of chicken intestinal epithelial organoids, dynamic behaviors such as long-distance migration, fusion, and rotation were noted¹⁸. Therefore, the behaviors of these organoid types are essential for their complete functionality.

MEAs consist of numerous electrodes embedded in a substrate, typically made of glass. These microelectrodes are often made from various metal conductors such as titanium nitride, gold, platinum, aluminum, or stainless steel. Each electrode can detect changes in the electrical field around it, which result from the ionic flow of neurons¹⁹. Unlike the patch-clamp technique, MEAs allow for non-invasive recording of electrical activity in vitro. Similar to calcium imaging methods, they can capture the activity of multiple neurons at once, offering greater spatial resolution than the patch-clamp technique and delivering detailed insights into network dynamics for mapping purposes²⁰. MEAs can record local field potentials (LFPs) and extracellular action potentials (EAPs). LFPs are variations in the extracellular field caused by the collective ionic activities of neurons and surrounding cells²¹. The recorded potential is affected by several factors, including the distance from the electrode and the strength and polarity of the signals²². This project is centered on the investigation of EAPs, which can yield extensive information and can be analyzed in various ways depending on the specific parameters of interest.

In this research, organoids derived from mouse taste epithelium were utilized as a sensitive component, while MEAs served as the transduction element to create a biomimetic taste-based biosensor. The study examined spontaneous activity and post-stimulus electrical responses by analyzing the frequency and amplitude of the emitted EAPs. Additionally, the long-distance migration of taste bud organoids was observed. The merging of multiple organoids and the formation of internal structures highlighted specific stages in the maturation of the taste bud organoids. Consequently, a biomimetic taste-based biosensor was developed that integrates taste bud organoids with microelectrode array (MEA) technology, allowing for the identification and differentiation of various tastes. It is important to note that the taste bud organoids and MEA devices used in this research are primarily intended to demonstrate the technical viability of this innovative approach to biomimetic taste-based biosensors.

Methods

Preparation of taste bud organoids

Taste bud organoids were created following previously established methods²³. In summary, the tongue epithelium from 5 to 7 day old mice (sourced from the Laboratory Animal Center of Xi’an Jiaotong University, China) was carefully removed, cut, and digested with 0.25% trypsin for 20 min. The resulting single-cell solutions were filtered through a 40 µm filter and then placed in a 24-well ultra-low attachment culture plate. The culture medium (DMEM/F12, Gibco, 10565018, United States) was replenished every 3–4 days and consisted of a

modified Hans Clever intestinal organoid medium, which included R-spondin-1, Noggin, Jagged-1, Y27632, epidermal growth factor, N-2 supplement (a chemically-defined serum-free additive), and a B-27 serum-free supplement. After 10–15 days of cultivation, taste cell spheres were formed and utilized for subsequent experiments. The use of animals in this study was approved by the Medical Ethics Committee of Xi'an Jiaotong University.

Taste sensing system construction

An Intan RHS2000 stimulation and recording system (Intan RHS2000, Los Angeles, CA, USA) equipped with a 32-channel stim/record headstage was connected to a computer. Previously prepared 14-day taste bud organoids were utilized as the sensitive components for the differentiation of various target substances. Electrophysiological response signals were recorded from the taste bud organoids that were affixed to a MEA chip (Multichannel system, United States) which electrodes and the surrounding contact pads are composed of planar titanium nitride arrangement in the form of electrodes with a diameter of 30 μm and an electrode spacing (center to center) of 200 μm . The conductor material is titanium metal covered with 500 nm thick silicon nitride. Then the system was maintained in a cell incubator at 37 °C with 5% CO_2 . The amplifier's sampling rate was set to 30.0 kS/s (thousand samples per second), and the cutoff frequency for the elimination offset filter was established at 1.00 Hz. The amplifier's lower bandwidth limit was 0.1 Hz, while the upper limit was 1000 Hz. Electrical responses were displayed in real-time, which were then processed to distinguish between different taste substances.

Long-term monitoring of taste bud organoids

Utilizing the Cellaview Cell Intelligent Monitoring Assistant MN-100 (INVIEW, Yuyao, Zhejiang Province), position the culture plate beneath the camera, adjust the field of view, and focus accordingly. Set the duration and interval for recording, then click start to continuously display the status of the organoid culture. The video retrospective feature provides a comprehensive view of the dynamic changes in the organoids throughout the recorded timeframe.

Haematoxylin and eosin (H&E) staining

Taste bud organoids that were cultured for varying durations were centrifuged at 2000 rpm for 5 min, and the supernatant was discarded. The resulting pellet was washed twice with PBS, followed by the addition of paraformaldehyde fixative. After embedding in paraffin, the sections were deparaffinized, hydrated, and stained for nuclei and cytoplasm using hematoxylin and eosin

staining solutions. Finally, images were captured using a microscope (Carl Zeiss, Axio Scope A1, Germany).

Taste stimulation methods

The efficacy of a biomimetic taste-based biosensor was evaluated through the application of various taste substances, specifically: bitterness (10 mM Saccharin), saltiness (6 M NaCl), sourness (25 mg/mL Citric acid), sweetness (1 g/mL Sucrose) and umami (0.25 g/mL Glycine). Initial analyses focused on the peak potential signals generated by taste bud organoids in response to these taste substances. The organoids were subjected to stimulation with the five taste stimuli presented in a randomized sequence, with each taste being administered three times. Consequently, effective discharge signals were recorded from responsive channels for each stimulation.

Cell viability assay

The viability of taste bud organoids was evaluated using the Animal Live and Dead Cell Viability/Cytotoxicity Assay Kit (Calcium Xanthophyll AM, PI method) from Proteintech (PF00007). To prepare the staining solution, bring the Calcein AM and PI stock solutions to room temperature. Combine 15 μL of 1.5 mM PI with 2.5 μL of 4 mM Calcein AM in 5 mL of PBS and mix thoroughly using a vortex. Wash the cells with 1 $\times$ PBS 2–3 times. Then, add an adequate amount of the Calcein AM/PI staining solution and incubate the cells at room temperature, protected from light, for 15–20 min. Finally, observe the stained cells using a fluorescence microscope (Carl Zeiss, Axio Scope A1, Germany).

Data analysis

The electrophysiological data collected were analyzed offline using custom programs developed in MATLAB (MathWorks, Inc.) and Spike 2 (Cambridge Electronic Design). The original signals underwent filtering with a third-order Butterworth bandpass filter to isolate the peak potential (Spike, 300–5000 Hz) signals. Spikes were then identified from these peak potential signals. The baseline noise level was defined as the standard deviation (SD) of the signals, with the spike detection threshold set at 5 times the SD. Each time a spike was detected, a timestamp was recorded for subsequent calculations of spike firing rates. Principal component analysis (PCA) was performed to identify taste response patterns from multichannel signals while minimizing information loss. During PCA, the key variables for each channel were determined by the differences in neuronal firing rates before and after taste stimuli. For m stimuli, n eigenvalues (where $n > 3$) were recorded for each stimulus, resulting in an $m \times n$ data matrix. The three principal components with the highest variance were derived through linear transformation and

orthogonalization of the data matrix, serving as the three feature values to replace the original n features, thus achieving data dimensionality reduction. GraphPad Prism (GraphPad Software) was utilized for one-way ANOVA and the Dunnett test, with statistical significance set at $p < 0.05$. A heat map of firing rates was generated using Excel.

Results and discussion

Characterization of taste bud organoids

To use taste bud organoids as sensitive components in a biomimetic taste-based biosensor, it is essential to create functional taste bud organoids that closely resemble the structure and function of natural taste buds. To achieve this, taste epithelium was extracted from mouse tongues and enzymatically separated into individual cells, which were then cultured to promote the development of taste bud organoids. During the cell culture process, it was observed that many non-taste cells were present in the initial generation of taste organoids (G0). Consequently, a passaging screen was implemented. The first step involved checking if the passaged organoids could grow normally. Results from various culture periods indicated that the first (G1) and second (G2) generations of taste bud organoids gradually increased in size over time, similar to organoids derived from progenitor cells (Fig. 1). The morphology transitioned slowly from single cells or multicellular aggregates (with red arrows indicating newly formed taste organoids), and there were very few other cells that failed to thrive in the culture system. This implies that a more uniform cell type, specifically gustatory stem/progenitor cells, was achieved after passaging.

It was observed that as the incubation period lengthened, the locations of the organoids shifted, and several organoids seemed to cluster and merge together. Consequently, the dynamic changes of the organoids over 8–10 days were captured through real-time monitoring. The results indicated that within the monitored area, as illustrated by the red, yellow, and white circles in Fig. 2, the positions of the taste bud organoids did change,

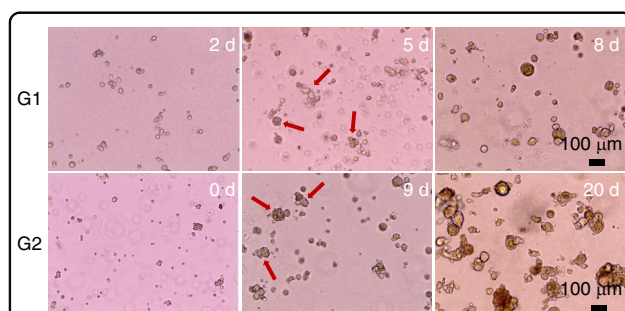


Fig. 1 Morphological results of different developmental stages of taste bud organoids

suggesting that multiple organoids were indeed aggregating and fusing.

The phenomenon of fusion among taste bud organoids raises important questions regarding its underlying mechanisms and the resultant alterations in the organoids' characteristics. To explore these inquiries, hematoxylin-eosin staining (HE staining) was conducted on 14 days of taste bud organoids at various stages of culture (refer to Fig. 3a). Notably, on day 14 of the G0 and G1 phases, taste bud organoids were observed to develop within the larger organoids, exhibiting structural and functional similarities to native taste bud tissues. In contrast, during the second generation of cultures (G2), there were no distinct taste bud structures identified with few fused organoids at the same time. Furthermore, a progressive reduction in the size of the organoids was noted with each subsequent generation (see Fig. 3b). Additionally, the fusion process appeared to result in the release of internal materials. These observations provide compelling evidence for assessing the maturation timeline of the taste bud organoids. The presence of taste bud structures is essential for the development of mature taste cells, which confer the organoids with the capacity to detect tastes. Consequently, for subsequent experiments, the 14-day-old taste bud organoids were selected as the focus of study, as they are deemed appropriate candidates for the development of biomimetic taste-based biosensors.

Coupling of taste bud organoids with MEA chip

In the present study, an in-vitro biomimetic taste-based biosensor was developed, as illustrated in Fig. 4a. The growth state of the organoid on the chip is shown in Fig. 4b. The system operates as follows: Taste stimuli are introduced to taste bud organoids cultured on a MEA chip. The organoids, comprising functional taste receptor

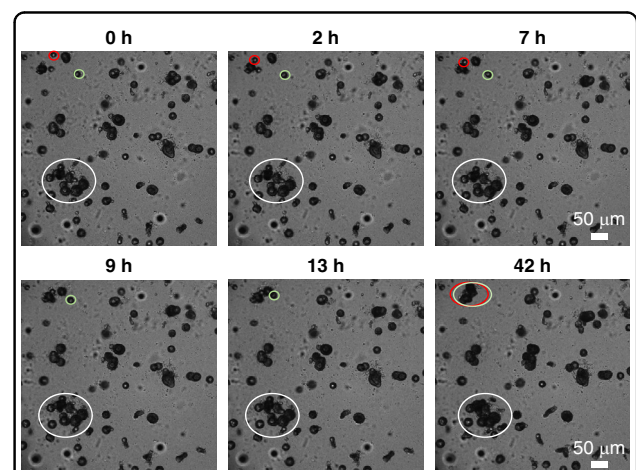
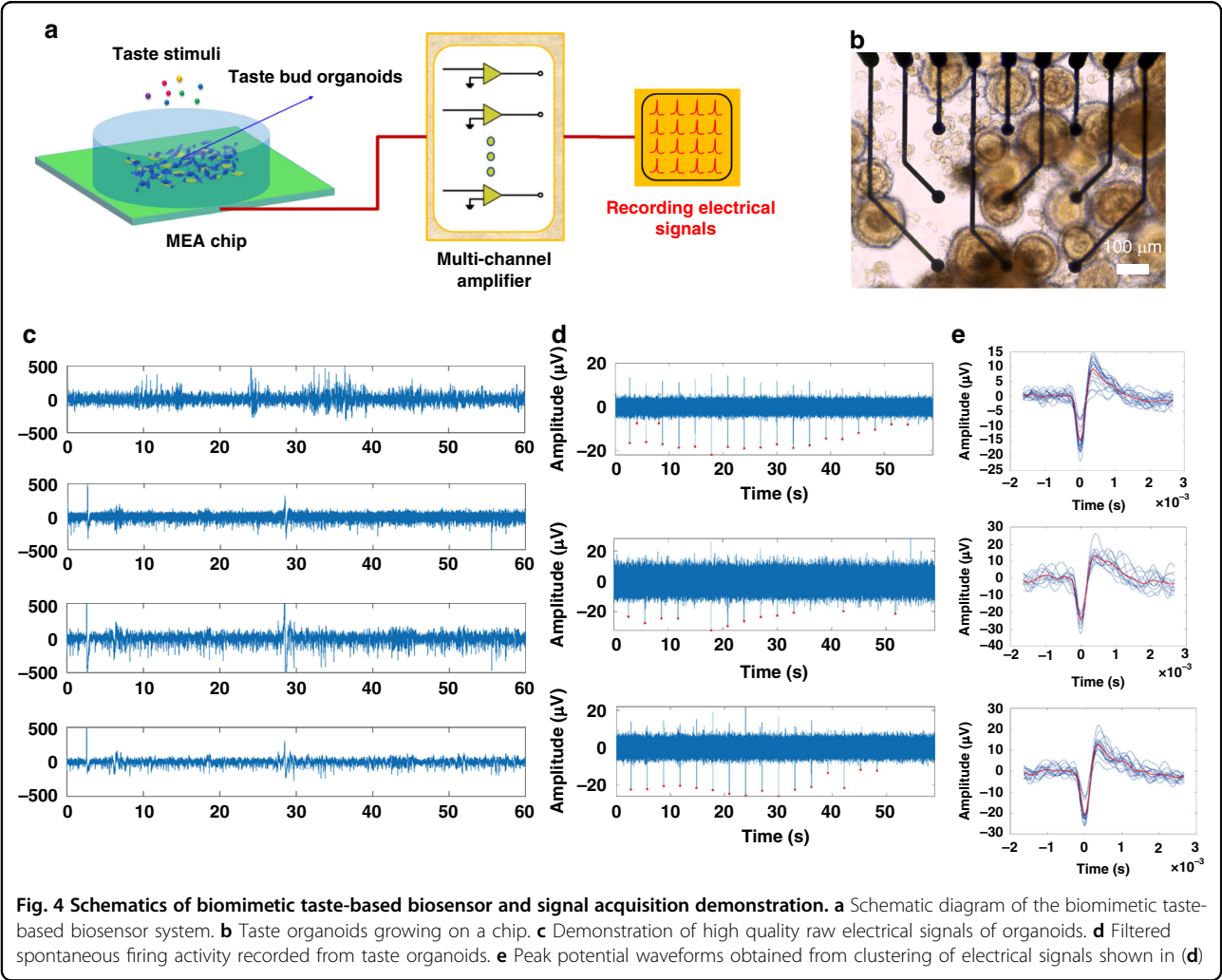
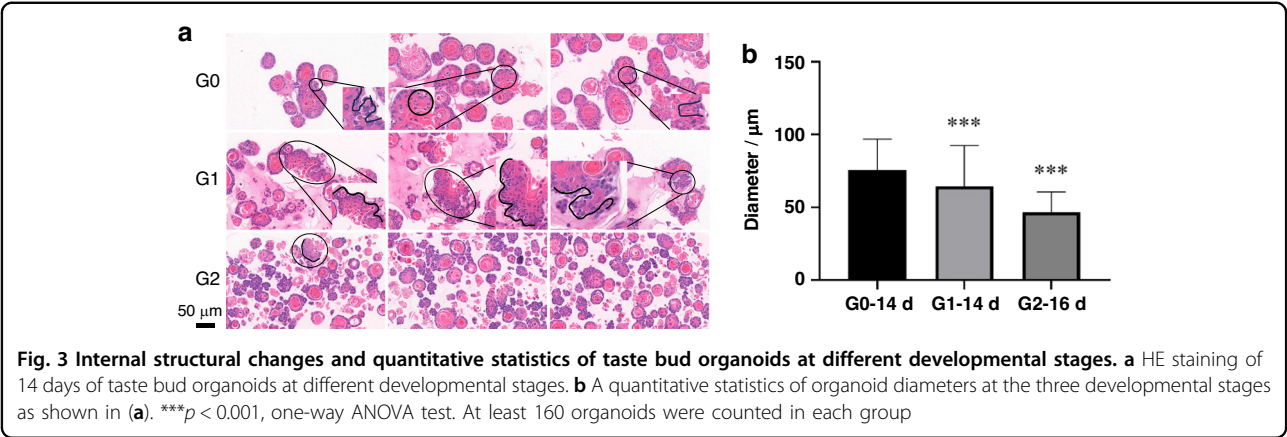


Fig. 2 Long-term monitoring of dynamic changes in the growth and development of taste bud organoids



cells, respond to the stimuli by the activation of taste receptors or ion channels, which then generate electrical signals. These signals are weak and require amplification. The MEA chip acts as a transducer array, converting the weak signals into measurable electrical signals at each

electrode. These signals are then transmitted to a multi-channel amplifier, which significantly increases their amplitude for accurate detection and minimizes noise. The amplified signals, representing the electrical activity of the taste bud organoids in response to specific taste

stimuli, are subsequently recorded and analyzed for the sake of taste sensing. The taste bud organoids were maintained in a controlled environment at 37 °C with 5% CO₂ at all times. The recording system was interfaced with the chip through two wires, and the alterations in raw electrical signals following the introduction of stimuli were visualized using computer software. The findings indicated that the system successfully captured electrical signals, and the spontaneous firing patterns, as well as the waveforms of the taste organoids, exhibited regularity and stability after filtering. Four representative spontaneous firing signals, as depicted in Fig. 4c, were recorded during one of the experimental trials. The cells demonstrated spontaneous activity characterized by varying firing states of high quality (Fig. 4d). Characteristic spikes with analogous shapes were extracted from the signals, as illustrated in Fig. 4e.

Performance testing of biomimetic taste-based biosensors

Figure 5a presents a heatmap that illustrates the average variations in discharge rates of peak potentials for each channel before and after the application of each stimulus. This analysis indicated that individual channels could demonstrate diverse response patterns—excitatory, inhibitory, or non-responsive—when exposed to different substances. Conversely, identical taste could elicit responses of varying characteristics and intensities across different channels. A further comparison of the alterations in firing frequency increased after the five taste stimulations. And amplitude revealed significant increases under salt and umami substances (refer to Fig. 5b, c).

By calculating the difference between the average discharge rates of the seven channels before and after stimulation with different substances, the radargrams of the front potential response of taste organoids under five

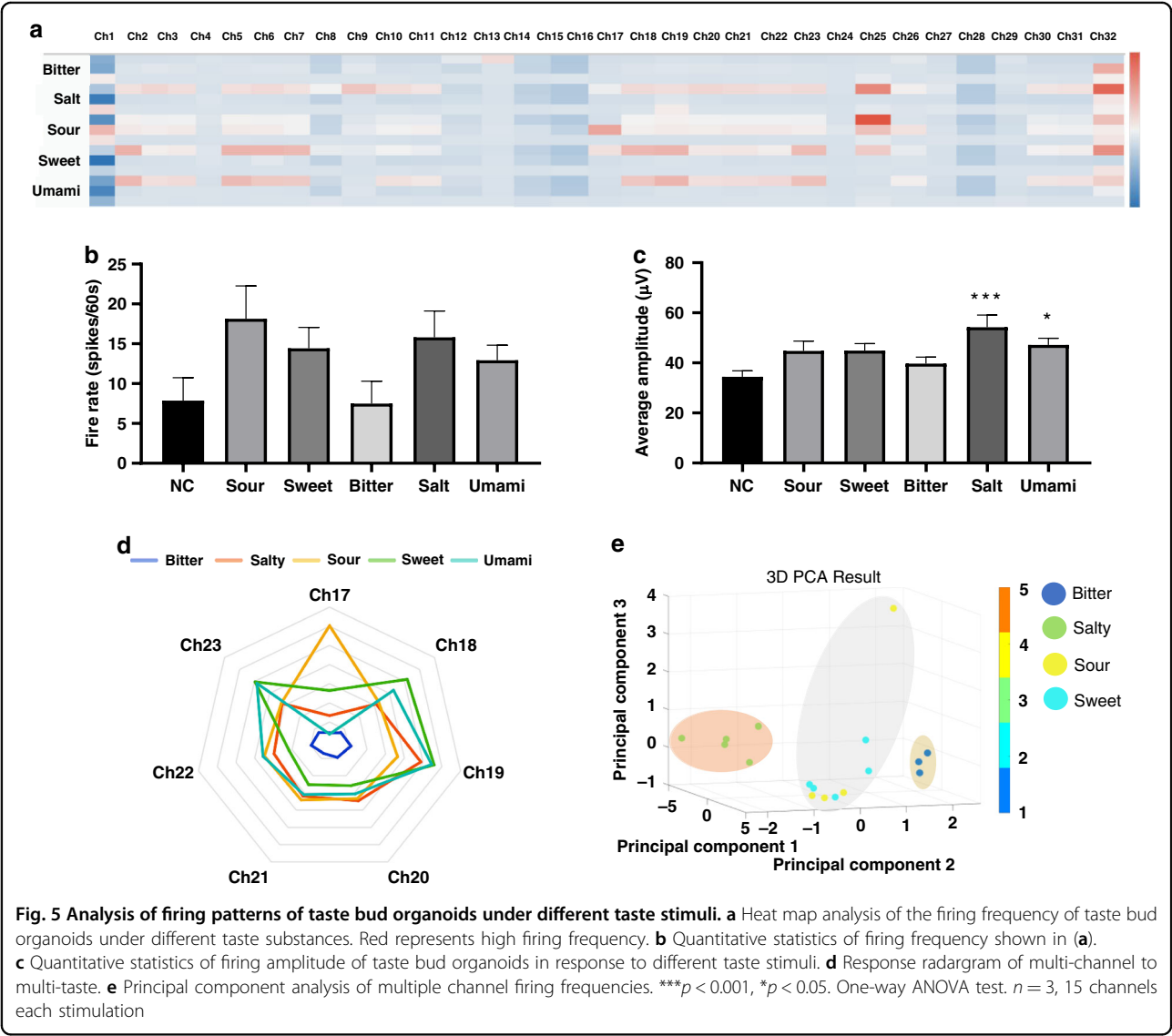
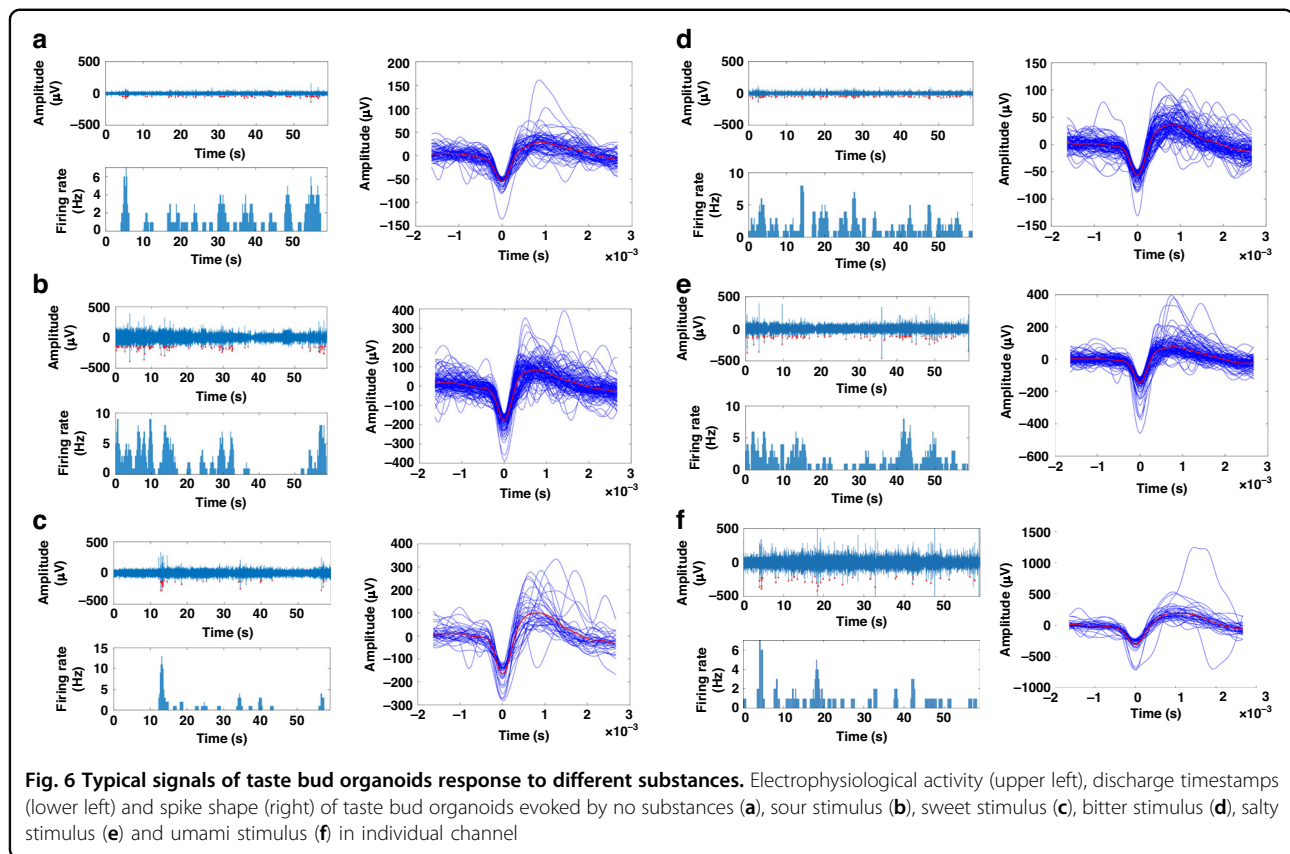


Fig. 5 Analysis of firing patterns of taste bud organoids under different taste stimuli. a Heat map analysis of the firing frequency of taste bud organoids under different taste substances. Red represents high firing frequency. **b** Quantitative statistics of firing frequency shown in (a). **c** Quantitative statistics of firing amplitude of taste bud organoids in response to different taste stimuli. **d** Response radargram of multi-channel to multi-taste. **e** Principal component analysis of multiple channel firing frequencies. *** $p < 0.001$, * $p < 0.05$. One-way ANOVA test. $n = 3$, 15 channels each stimulation



stimuli were plotted. The results are shown in Fig. 5d, where the seven channels are numbered as Ch17–Ch23. It can be clearly observed that there were similar patterns under sweet and savory stimuli, but different from the unique patterns of each of the other three, which suggests that different tastes are able to stimulate the sense of taste organoids with specific electrical activities on different channels. When considering all signals elicited by a taste stimulus as a sample set, the number of response channels corresponds to the number of dimensions. The response of a channel is defined as the difference in discharge rates prior to and following the stimulus. Since it was not possible to distinguish between the five taste stimuli, this result only shows the results of the PCA for the sweet, sour, bitter and salty stimuli. Figure 5e shows the projection of the sample set according to the three principal components of the four tastes. The responses were categorized into three relatively independent clusters. The first three principal components accounted for 79.72% of the total variance observed in the assay, with 44.81%, 22.13%, and 12.77% of the variance attributed to PC1, PC2, and PC3, respectively. Therefore, it can be anticipated that the biomimetic taste-based biosensor system will exhibit a high degree of discrimination accuracy. It revealed the specific recognition ability of taste organoids for different tastes.

To assess the taste perception capabilities of taste bud organoids, membrane potentials were measured during taste stimulation using MEA devices. The investigation revealed elicited responses from taste organoids without stimulation (Fig. 6a) and with five fundamental taste modalities—sour (Fig. 6b), sweet (Fig. 6c), bitter (Fig. 6d), salty (Fig. 6e) and umami (Fig. 6f). Notable variations were observed in the peak potential response signals (upper left), response time stamps (lower left), and peak potential signal waveforms (right) corresponding to different tastes. Following the application of sour, sweet, bitter, salty and umami stimuli, response channels were identified, yielding mean discharge rate differences of 8.3, 4.59, −2.31, 5.99, and 3.12 Hz, respectively. These findings substantiate the capacity of taste organoids to encode information pertaining to five taste stimuli.

In light of the cellular damage associated with extended exposure to applied stimuli, the viability of the organoids was assessed at the conclusion of the experiment (see Fig. 7). The results indicated that the ratio of viable cells significantly exceeded that of non-viable cells, thereby demonstrating that the experimental procedures employed in this study did not jeopardize the survival of the organoids.

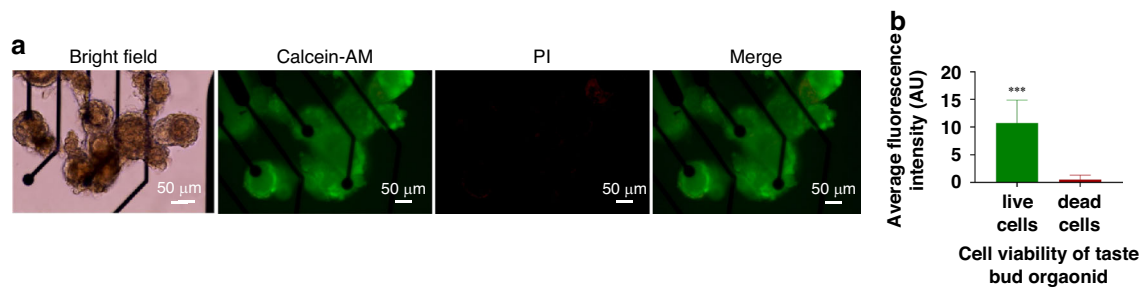


Fig. 7 Vitality testing of taste bud organoids after recording of electrophysiological activity. *** $p < 0.001$. Unpaired t test. The mean and SEM of 3 experiments are indicated. **a** Bright-field and fluorescence photographs of taste bud organoids at the end of the assay. Calcein-AM is for live cell staining (green). PI is for dead cell staining (red). **b** Quantitative statistics of green and red fluorescence in this figure (**a**)

Conclusions

Utilizing gustatory epithelial-derived taste bud organoids, real-time responses to various taste stimuli were assessed through a MEA device. In our previous work²³, the same method was used to record the electrical discharge signals of taste organoids. However, this was limited to the initial detection of sour and salty flavors and did not allow for clustering of waveforms or quantitative analysis of the data, much less differentiation of different tastes. Then, Wu et al.¹⁵ detected and differentiated between different concentrations of sour, sweet, bitter, and salty, but did not emphasize the dynamic changes in morphology, and only demonstrated that the organoid could survive stably on the chip for 7 days. In this study, migration, fusion, and internal structure formation of organoids were observed, suggesting 14 days as a critical time point for functional maturation. The self-assembly and fusion phenomena of taste organoids were reported for the first time, emphasizing the impact of structural maturation of organoids on function. The spontaneous discharge activity exhibited stability and regularity, with variations in firing rate and discharge amplitude observed following the application of taste stimuli. PCA was subsequently employed to evaluate the recorded responsive signals from the MEA devices. The findings suggest that taste bud organoids possess the capability to differentiate between distinct taste substances, categorizing them into specific clusters. This advancement enhances the understanding of the functional dynamics of taste bud organoids and their role in food taste detection. However, further research is necessary to achieve precise differentiation in real-world contexts, particularly in detecting the mixed responses of multiple taste substances to better simulate the complexities of actual environments.

In subsequent investigations, multi-culture protocols for organoids have been established. Research involving brain organoids has demonstrated that co-culturing organoids derived from cortical and subcortical regions facilitates the migration of subcortical intermediate

neurons into cortical organoids, resulting in the formation of fused cortico-subcortical organoids characterized by distinct neural activity²⁴. Furthermore, the fusion of vascular and brain organoids has led to the development of vascularized brain organoids, which display robust vascular networks and an increased presence of neural progenitor cells, indicating the influence of blood vessels on neural development. These fused organoids also incorporate functional blood-brain barrier structures and microglia²⁵. Such innovative studies pave the way for the in vitro simulation of taste buds and the living environment of the tongue, potentially advancing the development of biosensors and various applications through integration with artificial intelligence. Additionally, the possibility of combining multiple types of sensors or devices to facilitate multi-parameter measurements on a single chip is being explored. Recent research has employed three-dimensional (3D) microelectrode arrays and resistive-based skin sensors to investigate the acute cardiotoxic effects of adriamycin in heart organoids²⁶. In this study, 3D microneedle electrode arrays were utilized to probe from beneath the organoid, establishing bite-like contacts via a micromanipulator, while resistive skin sensors were accurately positioned atop the cardiac organoid to enable simultaneous electromechanical measurements. The 3D electrodes are well-suited to the three-dimensional architecture of organoids and demonstrate greater efficiency than two-dimensional electrodes in capturing changes in organoid activity. Future research may also consider the integration of sensors for measuring temperature or osmotic pressure alongside 3D electrophysiological sensors to expand the possibilities for taste analysis.

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Author contributions

Shuge Liu: writing—original draft, conceptualization, methodology, experimental manipulation, data curation. Yating Chen: software, methodology, hardware. Yuqi Chen: experimental manipulation, methodology, data curation. Yuxuan Yuan: writing—reviewing and editing, methodology, data curation. Minggao Liu: experimental manipulation, writing—reviewing and editing. Zhiyao Wang: experimental manipulation, methodology, writing—reviewing and editing. Wei Chen: supervision, data curation. Liping Du: conceptualization, methodology, supervision. Chunsheng Wu: conceptualization, supervision, funding acquisition.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics

All experiments and protocols outlined above were approved by the Biomedical Ethics Committee of Health Science Center of Xi'an Jiaotong University.

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