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A biomimetic bioelectronic tongue: A switch for On- and Off- response of acid sensations

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ABSTRACT

The perception of sour taste in mammals is important for its basic modality properties and avoiding toxic substances. We explore a biomimetic bioelectronic tongue, which integrate MEA (microelectrode array) and taste receptor cell for acid detection as a switch. However, the acid-sensing mechanism and coding of the taste receptor cells in the periphery is not well understood, with long-standing debate. Therefore, we firstly construct a Hodgkin-Huxley type mathematical model of whole-cell acid-sensing taste receptor cells based on the electrophysiologic patch clamp recordings with different acid sensitive receptor expressing and different acidic stimulations. ASICs and PKDL channels are two most promising candidates for acidic sensation. ASICs channels contribute to the On response, and PKDL channels coding the Offset stimulations respectively, which function as a pair for switch. Therefore, with the advantage of effective and noninvasive detection for MEA, a sour taste biosensor based on MEA and taste receptor cells was designed and established to detect sour response from the elementary acid sensitive taste receptor cells during and after stimulus. From simulation and extracelluar potential recordings, we found the biomimetic bioelectronic tongue was acid-sensitive, as acid stimulation pH decrease, the firing frequency significantly increase. Furthermore, this reliable and effective MEA based bioelectronic tongue functioned as a switch for stimulation On and Off. This study provided a powerful platform to recognize sour stimulation and help elucidate the sour taste sensation and coding mechanism.

1. Introduction

Sour taste sensation is one of five basic chemosensory perceptions of taste modalities. In addition, sour sensation can help mammals avoid of toxic substances. Taste receptor cells are the fundamental element in taste sensing, due to the taste-sensitive receptors located on the microvilli. Taste information are detected by taste receptor cells, and then transmitted to gustatory nerve fibers, later to higher order neurons in the central nervous system and finally projected to gustatory cortex in brain. Therefore, taste receptor cells play a critical role in primary taste information integration and coding at periphery.

Several candidate molecules have been proposed to mediate the detection of sour, including acid-sensing ion channels (ASICs), two-pore domain K^+ channels, acid-sensitive potassium channels $Kir_{2.1}$ (Ye et al., 2016) and most recently the PKD2L1/PKD1L3 heterodimer, a member of the transient receptor channel family (Chen et al., 2015). Non-exclusive contributions from ASIC, TRPP or both are evidenced by the expression patterns in normal mammalian taste cells and in diseased taste cells from humans with sour ageusia (Lin et al., 2002; LopezJimenez et al., 2006; Huque et al., 2009). However, direct evidence linking any of these receptors to sour taste sensing, firing and coding is still lacking.

ASIC2a/2b (acid-sensing ionic channels) belongs to a family of proton-gated ion channels related to the superfamily of degenerins/epithelial sodium channels, which is permeable to Na^+(Fig. 1(a)). When acid stimulus applied, related inward current can be observed. *In situ hybridization*, immunostaining, PCR and patch clamp data revealed that ASICs have been localized to rat taste tissue with specific

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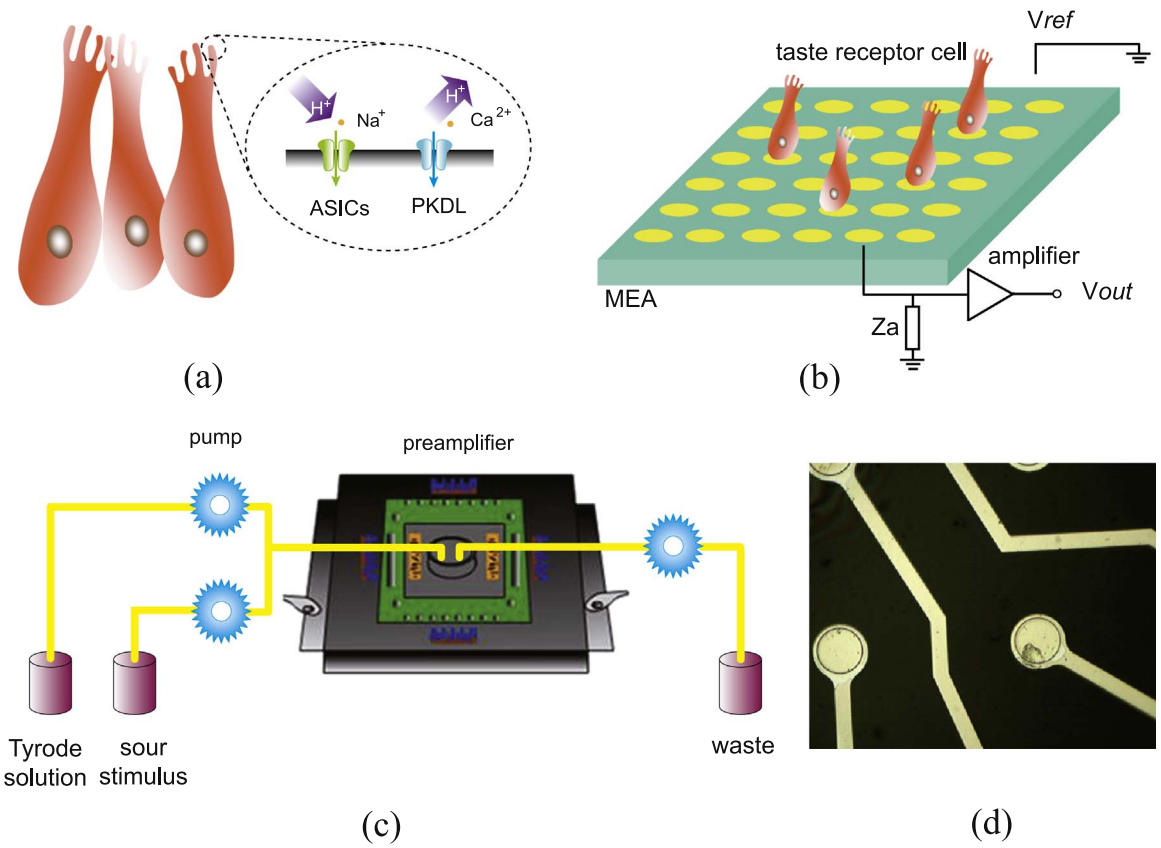

Fig. 1. Scheme of sour taste transduction and MEA based bioelectronic tongue measure system. (a) ASICs and PKDL channels are two candidates for sour taste sensation transduction; (b) Schematic diagram of the acid-sensing biosensor; (c) Bioelectronic tongue measure system for extracellular electrophysiological recordings of taste receptor cell; (d) Taste receptor cell cultured on the MEA chip.

and restricted region of the tongue (Ugawa et al., 1998, 2003; Shimada et al., 2006). ASIC channels play a central role in sour taste sensation and transduction with On response.

PKD2L1 (TRPP3) and PKD1L3 belong to the superfamily of nonselective cation channels transient receptor potential (TRP) channels, permeable to Ca^{2+} and involved in diverse physiological functions, notably playing essential roles in sensory transduction of physical or chemical stimuli (Ramsey et al., 2006; Venkatachalam and Montell, 2007). These two TRPP members, PKD2L1 and PKD1L3, are highly homologous to PKD2 (TRPP2) and PKD1, whose mutations cause autosomal dominant polycystic kidney disease (AKPKD) (Zhou, 2009). Studies indicated PKDL channel complex might code acid stimuli by its unique Off response (Inada et al., 2008; Chen et al., 2015; Hussein et al., 2015). PKDL channels facilitated at basic pH and inhibited at acidic pH, which indicated a novel role of PKDL in proton sensing and proton signaling.

How sour taste stimulus detected and taste information coded in the periphery? Current data strongly suggest On (ASICs) and Off (PKDLs) receptors are functionally co-expressed in the same neurons, presumably type III taste receptors cells (Huang et al., 2006, 2008; Kataoka et al., 2008; Chang et al., 2010). They functioned as a switch for sour sensation. However, we still don't know what the functional roles of these paired receptors in acid sensing and coding.

Benefited from the MEMS (Micro Electro-Mechanical system) technology and advantages of reliable, effective and noninvasive detection for MEA (Micro-electrode array), the biomimetic bioelectronic tongue for sour taste sensation integrated with MEA and taste receptor cells can perform long-term and non-invasive recordings to recognize acid tastant. Meanwhile, this hybrid system provides a powerful and promising platform to investigate the taste sensations and coding mechanisms.

In this study, we develop a hybrid biomimetic bioelectronic tongue as a switch for On and Off acid sensation. For theoretically analyze this paired responses, we firstly construct a Hodgkin-Huxley type mathematical model of whole-cell acid-sensing taste receptor cells based on the electrophysiologic patch clamp recordings. The inward current from acid-sensing channels based on acid stimulus with various pH, the evoked action potentials firing during and after acid stimulus with different acid-sensing receptor expressing and firing frequency tendency based on acid pH were simulated and analyzed. Thereafter, the bioelectronic tongue based on MEA and taste receptor cells was explored to detected sour tastant from taste receptor cells during and after stimulus, which also functioned as a switch. This study provided a powerful and promising platform to recognize sour tastant and put forward an effective strategy to elucidate the sour taste sensation and coding mechanism.

2. Experiments and methods

2.1. Isolation and culture of taste receptor cells on chip

Primary taste cells were obtained from fungiform papillae in the frontal tongue of female adult Sprague Dawley rats, injecting 1–1.5 ml elastase/collagenase mixture under the epithelium. After 40 min incubation, lingual epithelium could be gently peeled off. Then the frontal epithelium was slightly pressed on a metal sieve with holes diameter of 75 μm. Thus was similar to the size of taste buds. And the taste bud could pass through the pore out of the fungiform papillas into tyrode solution. In this way, a larger amount of taste buds could be obtained than those in traditional polished pipette suction. Single receptor cells were dissociated from the buds and directly immobilized on to a microelectrode array (MEA) chip, as shown in Fig. 1(b). The

chip surface was pre-coated with poly-L-ornithine and laminin (PLOL) for a good coupling between taste cells and chip. Tyrode solution contained (in mM) 126 NaCl, 5 KCl, 2 $CaCl_2$, 2 $MgCl_2$, 5 HEPES, 1.25 NaH_2PO_4, 10 glucose, pH 7.5.

2.2. MEA chip and system

MEA chip was fabricated in standard CMOS-processing technology. Firstly a 30 nm Cr thin film was sputtered on Pyrex glass and then 300 nm Au was deposited. A 6×6 gold electrode array was fabricated using wet etching technique. The diameter of each electrode was 30 μm with the center to center distance of the electrodes 200 μm. Passivated layer silicon nitride (Si_3N_4) with thickness 1 μm was deposited above the metal layer by PECVD. A chamber was mounted on the chip for cell culture. The USB-ME16-FAI multichannel MEA system (MCS, Reutlingen, Germany) was employed in the extracellular electrophysiological measurement. A 16-channel data acquisition card was utilized in recordings with sampling frequency 20 kHz. Data were filtered with low-pass filter 2 kHz. Sour stimulation solutions, tyrode solution and waste solution were switched with pump as shown in Fig. 1(c).

2.3. Model and simulation of sour taste cells

Whole-cell Hodgkin-Huxley type mathematical model of taste cell was constructed based on Na^+, K^+, HCN ionic currents obtained from whole cell patch-clamp experiments (Chen et al., 2009). A nonlinear least-squares algorithm in Matlab was used to fit the recordings for parameter estimation. The models of individual ionic currents and the whole-cell sour taste receptor cell were created on the platform of NEURON software (http://www.neuron.yale.edu). The membrane potential of taste cells can be described by Eq. (1).

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m} \tag{1}$$

V is the potential across the membrane and C_m is the membrane capacitance. I_{ion} is the total transmembrane currents which include the following ionic components in Table 1. In case of electrical stimulation, I_{stim} is the external current source added onto I_{ion}.

2.3.1. Current through acid sensing ion channels I_{ASIC}

$$I_{ASIC} = G_{ASIC} \cdot ASIC_a \cdot ASIC_i \cdot (V - E_{ASIC}) \tag{2}$$

$ASIC_a$ is the activation parameter of ASIC channels and $ASIC_i$ is the inactivation parameter. G_{ASIC} and E_{ASIC} denote the maximum conductance of ASIC channels and the reversal potential, respectively.

2.3.2. Currents through PKDL channels I_{PKD}

$$I_{PKD} = G_{PKD} \cdot PKD_a \cdot PKD_i \cdot (V - E_{PKD}) \tag{3}$$

PKD_a is the activation parameter and PKD_i is inactivation parameter of PKDL channels. G_{PKD} and E_{PKD} are the maximum conductance of PKDL channels and the reversal potential, respectively. Details see (Chen et al., 2015).

Table 1
Major components of the sour taste cell model.

Ion channels	E_{rev} (mV)	G_{max} (nS)
Na_V (Herness and Sun, 1995)	+60	18
K_V (Liu et al., 2005)	−75	15
HCN (Stevens et al., 2001)	−24	1.2
ASIC (Lin et al., 2002; Ugawa et al., 2003)	+45	6
PKDL (Chen et al., 2015)	0	21
Leakage (Chen and Herness, 1997)	−45	0.145
Nonspecific Current	−70	0.6

2.4. MEA recordings of taste signals from sour stimulation

In the experiment, we used pH 4 and pH 2 hydrochloric acid solutions in tyrode solution as sour stimulations. In single treatment assay, before sour stimulations, basic activities from taste receptor cells were recorded for 120 s. Then, pH 4 or pH 2 hydrochloric acid solutions were selected to treat the cells respectively. After 120 s stimulation, taste receptor cells were washed out with tyrode solution quickly and recorded for another 120 s. In consecutive treatment assay, sour stimulations were applied in consequence, also after stimulations washed out with tyrode solution. Both on-responses and off-responses of the cells were recorded. All recordings were performed at room temperature (20–23 °C).

2.5. Data analysis and statistics

Data were analyzed in igor and Origin software. Standard error of the mean (S.E.M.) and student t-test (two-tailed with criteria of significance $p < 0.05$) were calculated when applicable.

3. Results and discussion

3.1. Simulation results of firing from sour taste receptor cells

The molecular identity of acid transduction for sour taste has been debated, with ASIC and PKDL channels as representative candidates (Lingueglia, 2007; Ishimaru and Matsunami, 2009). The model of acid-sensing taste cells was created on the platform of NEURON software (Hines and Carnevale, 2001), which include the Na^+, K^+, HCN ionic currents, leak current, ASICs ionic current and PKDL current, as shown in Fig. 2(a). The general scheme of the model is summarized in Table 1. E_{rev} and G_{max} represent the reversal potential and the maximum conductance respectively.

For the ASICs ionic currents (On response) in respond to different levels of acidic stimuli were recorded when cells were held at −70 mV compared with the control conditions of pH=7.5 (Ugawa et al., 2003). Simulations (red, dash line) and experiment recordings (black, solid line) corresponding to sour stimuli were compared in the left panel of Fig. 2(b). Simulated current can well fit the experimental data. Overall, simulated and experimental responses followed similar trend of dose-dependency, as shown in the right panel of Fig. 2(b).

For the PKDL ionic currents, pronounced inward currents associated with offset of the sour stimuli were observed as shown in the left panel of Fig. 2(c). PKDL currents (Off response) were elicited at pH_{off} after withdraw the acid and recorded with whole-cell voltage clamped at −60 mV. We employed the alkaline-activated model as discussed in our previous work (Chen et al., 2015). From the patch clamp experimental data and simulation results, we found the pH_{on} range is much smaller than pH_{on} range for ASIC channels. Actually, during the sour stimulation pH_{on}, the PKDL channels are in closed state. After withdraw of the acid, the PKDL channels open. Simulations (blue, dash line) and experiment recordings (black, solid line) corresponding to sour stimuli were compared. Also, as pH increase, the corresponding current decrease, as shown in the right panel of Fig. 2(c).

Among several potential mechanisms proposed to be responsible for On-response I_{on} upon acid stimuli, ASICs serve as one of the most plausible candidates, due to its pH sensitivity, kinetics, distributions and other properties (Shimada et al., 2006; Chang et al., 2010). Based on the recordings from recombinant ASICs and native acid sensing taste cells, we reconstructed the On responses of taste cells firing upon acid stimuli, as shown in Fig. 2(d). PKDL channels were scrutinized from multiple aspects to ensure its consistency with experimental data and underlying mechanisms (Fig. 2(c)). Upon acid stimuli, PKDL channels generated rather small onset current compared with On response mediated by ASICs channels, which are native expressed in HEK293 cells, thus exerting negligible effects on the onset firing. Upon

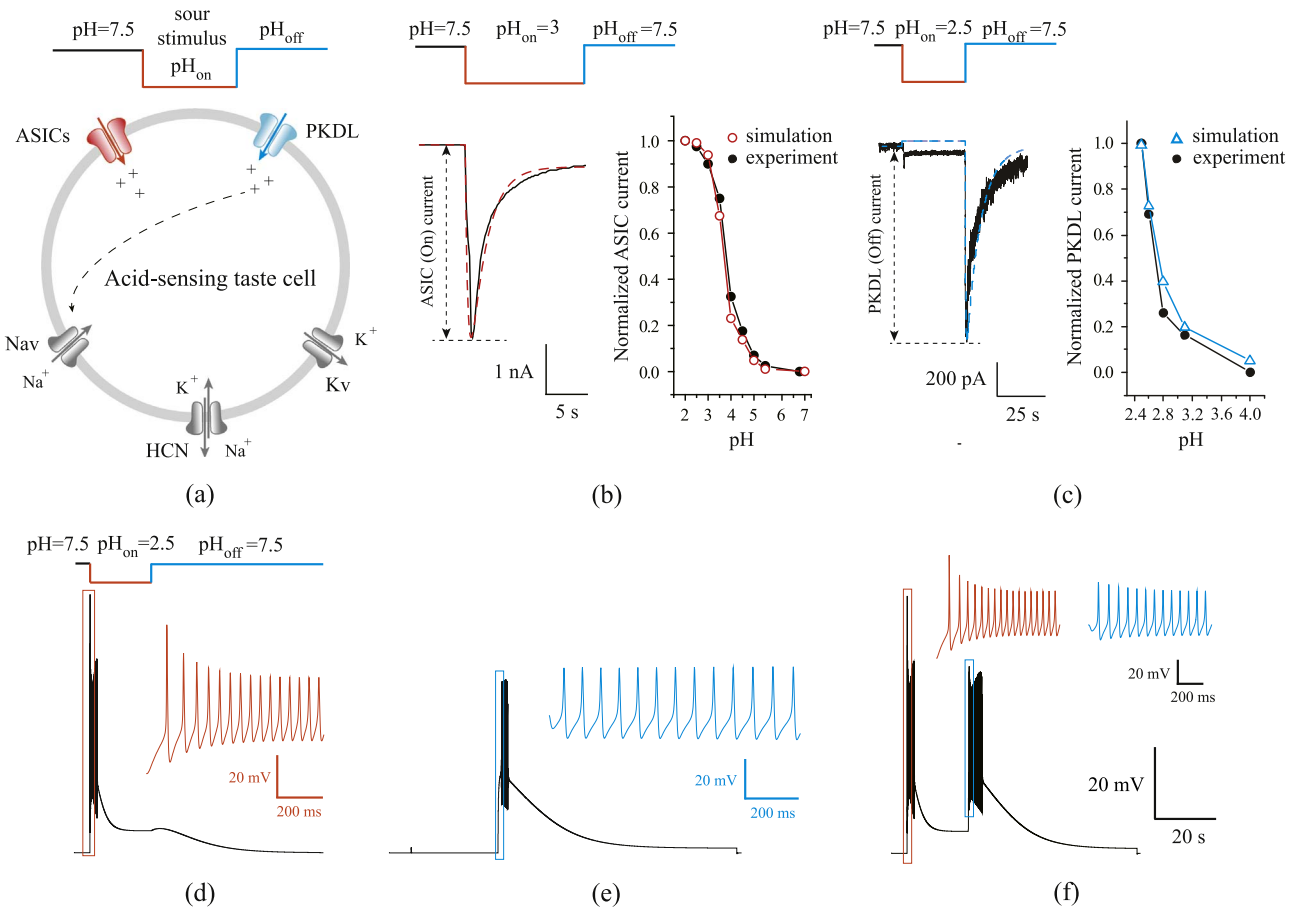

Fig. 2. Modeling and simulation of Onset and Offset Firing mediated by ASIC and PKDL Channels in Sour taste receptor cell Model. (a) The model of acid-sensing taste cells include the Na^+, K^+, HCN ionic currents, leak current, ASICs ionic current and PKDL current; (b) Inward current mediated by ASICs channels with acid stimulation. Left: experimental recordings (black, solid line) and simulation (red, dash line) upon sour stimuli (representative traces, pH_{on}=3). Right: the normalized peak current under various pH_{on} from simulations are plotted to compare with experimental results. Solid circle: recordings; open circle: the simulation results; (c) Inward current mediated by PKDL channels after withdraw of acid stimulation. Left: experimental recordings (black, solid line) and simulation (blue, dash line) upon sour stimuli (representative traces, pH_{on}=2.5). Right: the normalized peak current under various pH_{on} from simulations are plotted to compare with experimental results. Solid circle: recordings; open triangle: the simulation results; (d) Temporal firing mediated by ASIC channels with acid stimulation pH_{on}=2.5; (e) Temporal firing mediated by PKDL channels with acid stimulation pH_{on}=2.5; (f) Temporal firing mediated by both ASIC and PKDL channels with acid stimulation pH_{on}=2.5. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

removal of the acid, Off responses of taste cell firing mediated by PKDL channels was evoked, as shown in Fig. 2(e). Both onset APs (action potentials) and offset APs exhibited adaptive patterns, *i.e.*, firings were substantially attenuated after being initiated, in large part due to the inactivation or desensitization properties of the channels, data not shown. ASICs or PKDL channels could function in separate taste receptor cell as above, alternatively, the two mechanisms could coexist in the same taste receptor cell to encode complete temporal information (both onset and offset) of the acid stimulus (Fig. 2(f)). And as pH decrease, the firing frequency increase.

3.2. Extracellular potential recordings upon sour stimulations

Taste receptor cells with size about 15–20 μm, were cultured on MEA chips, as shown in Fig. 1(d), adhered and coupled to the microelectrode. The spontaneous and sour stimulus evoked activities from taste receptor cells were detected. The downward phase of the signals should be due to the influx of Na^+ ions. And the upward phase was mainly caused by the efflux of K^+ ions.

From the recorded signals in single treatment assay, the sour-sensitive taste receptor cells can be classified into three groups. We found 30.4% sour-sensitive taste cells (7 cells in 23 cells) with stimulation pH equals to 2 shown electrical activities during sour stimulation (On response) without Off response after washout (Fig. 3(a)). The amplitude of the spikes was 100–300 μV, with duration of 50–80 ms. From our taste receptor cell modeling and simulation, it seems ASICs channels should be responsible for the On response. No PKDL channels expressed in this group of taste cells. And 21.7% of the taste cells (5 cells in 23 cells) shown no On response during sour stimulation (pH 2), however, with Off response after washout (Fig. 3(b)), with magnitude of 100–450 μV and duration of 50–80 ms. PKDL channels might be located in this group of taste cells, not ASICs channels. In addition, 47.8% of the taste cells (11 cells in 23 cells) firing both during and after the sour stimulus, as shown in Fig. 3(c). The amplitude of the spikes was 100–200 μV, with duration of 50–80 ms. We thought in these taste cells, both PKDL and ASICs channels contribute to the electrical activities. When sour stimulus with pH 4 was applied, the proportion somehow changed, as summarized and shown in Fig. 3(d).

The statistics analysis indicated the frequency of On and Off response show similar pH dependency. With pH decrease, the firing frequency increase, which is consistent with the simulation results, as shown in Fig. 3(e). And the firing frequency of On response (5.18 ± 1.26 Hz) and Off response (5.72 ± 0.57 Hz) with pH 2 stimulation was significantly larger than On response (2.83 ± 0.19 Hz) and Off response (3.2 ± 0.28 Hz) at pH 4. And the spontaneous activity was 1.1 ± 0.49 Hz at pH 7.5.

In the consecutive treatment assay, sour stimulus with pH 4 was firstly applied, after washout more acidic solution with pH 2 was used as sour stimulation. The recordings from the same taste receptor cells

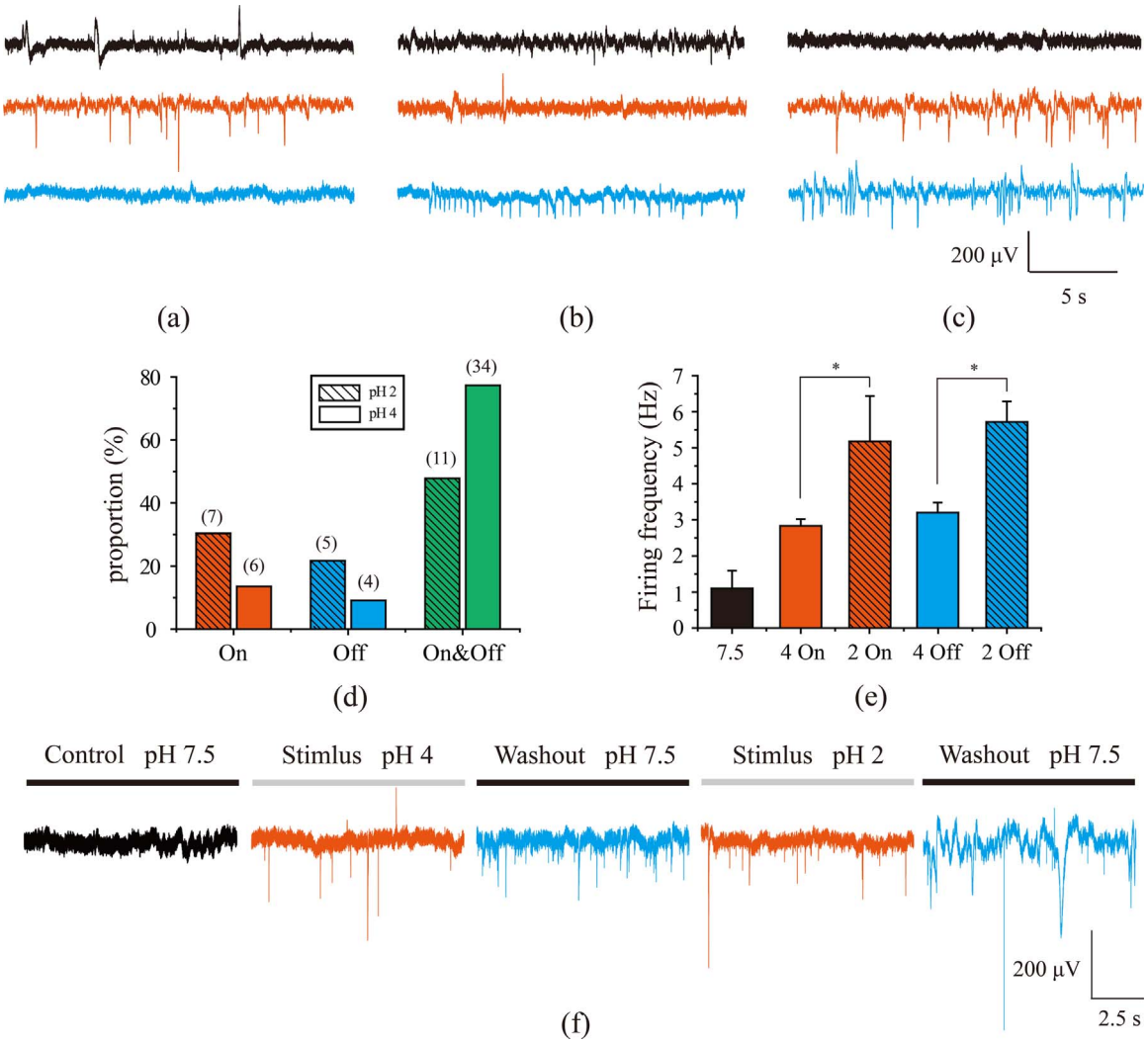

Fig. 3. MEA extracellular potential recordings before, during and after acid stimulation. (a) Evoked firing with only On responses; (b) Evoked firing with only Off responses; (c) Evoked firing with both On and Off responses; (d) Statistics of the proportion of three groups of cells with acid stimulation pH equals to 2 and 4; (e) The firing frequency with and after withdraw of different acid stimulation pH; (f) In the consecutive treatment assay, the extracelluar potentials are recorded from the same taste receptor cell.

were shown in Fig. 3(f). ASICs and PKDL channels should attribute to the On and Off responses. And the firing frequency from the latter acid (pH 2) stimulation was not significantly different from pH 4 stimulation. In another word, the response was attenuated after been already stimulated, might be due to the inactivation or desensitization properties of the channels.

From the experimental data and simulation results, we propose that On response might code the information of onset and long-lasting sour tastants, however, Off response infers to the offset of the sour response or the elevation of pH value. In addition, On response from ASIC channels code the sour taste, which parallel with other taste modalities, sweet, bitter and umami. Off response might provide a tag for sour taste in time sequence to separate it from the other three types of taste modalities.

4. Conclusions

Integration of the taste chemosensory and micro-chip, a biomimetic bioelectronic tongue for sour detection was designed as a switch for Onset and Offset for the acid stimulation. This hybrid taste sensor was explored for sour taste detection and sour signal coding. The spontaneous before sour tastant and evoked activities during and after sour stimulations were detected. Three groups of signals were divided with On, Off, and On & Off responses, separately. In order to elucidate the acid-sensing and sour taste information coding mechanism, a Hodgkin-Huxley type mathematical model of whole-cell acid-sensing taste receptor cells based on the electrophysiologic patch clamp recordings was constructed. From simulation, we propose that ASICs channels contribute to the On response, and PKDL channels coding the Offset stimulations respectively. In addition, response was attenuated after been already stimulated, which might be due to the inactivation or desensitization properties of the channels. This MEA and taste receptor cell based bioelectronic tongue provided a promising platform to recognize taste stimulations and help study taste chemosensory and coding mechanism in a noninvasive way.

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