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Biomimetic sensors and biosensors for qualitative and quantitative analyses of five basic tastes

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ABSTRACT

The five basic tastes namely sweetness, bitterness, sourness, saltiness and umami have been qualitatively and quantitatively analyzed using biomimetic sensors and biosensors listed in this review. This review puts great emphasis on the sensing materials or elements used in these sensors. Biomimetic sensors consist of potentiometric, voltammetric and impedance spectrum sensors modified with specific and designated biomimetic materials. More importantly, biosensors based on taste cells, tissues, nerves and enzyme as the sensing elements have been developed, and nanotechnology and microfluidic chip have been utilized for the fabrication of biosensors. There are two main aspects of practical application for five basic tastes via biomimetic sensors and biosensors: one aspect is to clarify taste sensation and transduction mechanism; another aspect is to obtain taste sensing information of food and pharmaceutical. The future perspectives for improvement of biomimetic sensors or biosensors are discussed.

1. Introduction

The sense of taste, which is one indispensable perception of human sensory organ, incorporates two meanings. On the one hand, it refers to the five basic tastes of the tongue, namely sweetness, bitterness, sourness, saltiness and umami [1,2]. Sweetness, which is emerged from natural sugars or artificial sweeteners, exerts a great influence on prompting nutrient sources; bitterness, termed an unpleasant taste, prevents the ingestion of harmful substances; sourness is evoked by organic acids which contain ionized hydrogen ion; saltiness, which displays the status of electrolyte balance, is mainly produced by ionic materials; umami, called a savory, broth-like or meaty taste, is generally caused by some amino acids. On the other hand, the sense of taste plays an important role in recognizing chemicals or tastants, edible constituents offered prospective perceptions in tongue [3].

Sensory evaluation and chemical detection, as the methods of evaluating flavor quality, are commonly used in many products such as food stuffs, beverages and drugs. However, these methods have exposed their drawbacks. Sensory evaluation employing the panelists is susceptible to human physical and psychological conditions as well as individual preference, leading to high subjectivity but low objectivity and reproducibility. And chemical detection via high-performance liquid chromatography (HPLC), liquid chromatography mass spectrometry (LC–MS) and ion chromatography (IC) can acquire quantitative data of substances which cannot be linked to the taste sensing. In order to improve the situation, more effective methods or technologies for clarifying the sense of taste are expected.

Electronic tongue system, which consists of a number of poor-selective sensors and trusts in the pattern recognition or multivariate data analysis, shows high objectivity and less time-consuming in food analyses [4–8], but also reveals the weakness i.e. non-specificity for quantification of multiple components in solution. Biomimetic materials can be used or modified on electrodes so that the improved sensor can mimic the human tongue responding to the same tastant with global selectivity, possess some clearly defined units of information and clarify the interactions of taste substances.

The biological organ for human taste sensing is the tongue without any doubt. The tongue contains tens of thousands of taste buds (Fig. 1), which has microvilli that poke through taste pore to the top of the bud, consisting of approximately 50–100 taste receptor cells in each bud [9,10]. The taste sensation of human tongue, is elaborated that the specific signals generated on the buds stimulated by various substances or tastants were conveyed to the brain, which can interpret those signals based on neural network pattern recognition to differentiate, classify and analyze the

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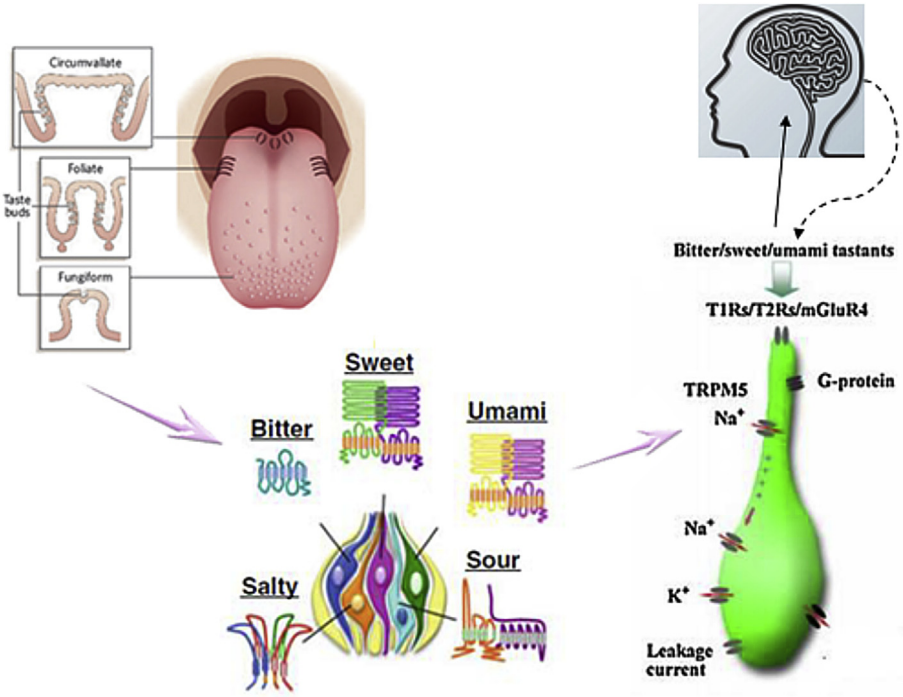


Fig. 1. Schematic diagram of biological taste sensing system.

concerned substances or tastants. It has been reported that sweetness, bitterness and umami receptors are expressed in not only taste buds, but also digestive organs and kidneys of which the perception mechanisms are not clarified yet [11]. With regard to the tongue, taste receptor cells play a vital role in taste perception, briefly referring to their responses to tastants which are initially coded in taste buds of the epitheliums or taste nerves. The coding of taste is the specific interaction of tastants with taste receptors or ion channels in cells, where a complex series of stimulation occurs and the potentials generated [12].

Taste cells and taste tissues can receive multiple taste signals evoked by different substances or tastants [13–16]. Furthermore, neurons in nerves also can exhibit the capability of perceiving the taste information by responding to multiple biochemical signals transmitted through neurotransmitters [17–19]. Therefore, cells, tissues and nerves are considered as promising candidates of sensing elements for the taste biosensors [20]. Biological taste sensors owning good sensitivity, accuracy and reliability, have unique and specific performances that are unmatched with any artificial devices so far [21]. The biosensors based on cells, tissues, and nerves have been developed to quantify the type of basic taste focusing on the fact that humans tongue discriminate the taste qualities of samples, in other words, samples can be discriminated in the case of five basic tastes can be identified [22].

This review summarizes the recent advances concerning biomimetic sensors with the utilization of various non-biological materials and biosensors with the utilization of biological functional elements for analyses of five basic tastes, combs the taste sensation and transduction mechanisms, and lists the applications for taste sensing information of food and pharmaceutical.

2. Biomimetic sensors

Biomimetic sensors consist of potentiometric sensor, voltammetric sensor and impedance spectrum sensor, which are modified with specific and designated biomimetic materials, simulating the function and performance of biological organs. Table 1 summarizes these three types of biomimetic sensor including biomimetic materials, stimuli and applications, which equates to the comparison of different types.

2.1. Potentiometric sensors based on biomimetic materials

Potentiometric sensors, as the earliest researched and developed sensors for biomimetic system, can measure the potential of the two end electrodes in the sensor and identify the properties of samples by analyzing the change of potential difference. The temperature dependence and the adsorption of solution components that affect the potential present the demerits of potentiometric sensors [23]. Biomimetic materials used in sensors including artificial lipid polymer membrane and chalcogenide glass with PVC film, can be beneficial for more accurate and objective determination of basic taste qualities.

2.1.1. Artificial lipid polymer membrane as the sensing material

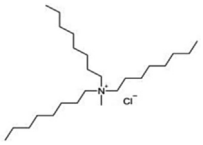
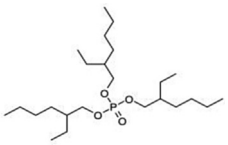
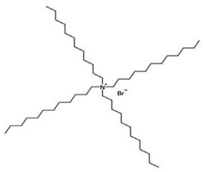
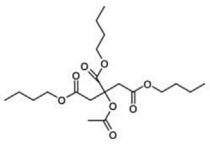
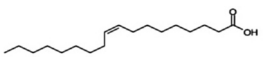
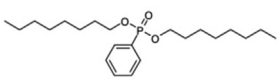
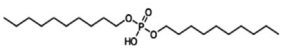
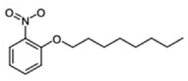
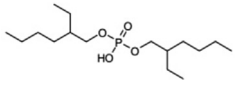
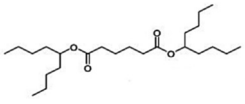
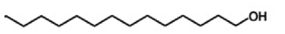
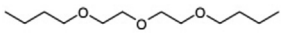
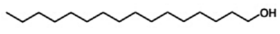
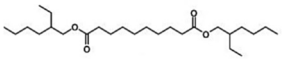
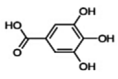
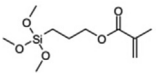
An artificial lipid/polymer membrane [2,24–27] consisting of a lipid, a plasticizer (Table 2) and poly vinyl chloride (PVC) is utilized as the sensing material mimicking biological cell membranes of the sensor which exports a change in the membrane potential caused by the interaction between the lipid/polymer membrane and taste substances in sample solution and reference solution. The lipid and plasticizer are responsible for controlling electrochemical properties of the membrane surface, and poly vinyl chloride contributes to encapsulate the lipid and change a mixing ratio with respect to plasticizer [28].

Sharma et al. [29] proposed a potentiometric sensor with artificial lipid membranes (TOMA-DOPP, TDAB-DOPP, TDAC-TC-DOPP, TOMA-OA-BP-DOPP) coated on printed electrode chip and gold electrode. The potentiometric responses to the membranes for sweetness, sourness, saltiness and bitterness were measured using corresponding tastants such as glucose, hydrogen chloride, sodium chloride and quinine, which displayed accuracy and reproducibility.

Table 1
Summary of biomimetic sensor including sensor type, biomimetic materials, tastants/stimuli and applications.

Sensor type	Biomimetic materials	Tastants/stimuli	Applications
Potentiometric sensor	Lipid polymer membranes (lipid, plasticizer, PVC) Chalcogenide glass with PVC film	Sucrose, glucose, hydrogen chloride, sodium chloride, quinine, amino acid, monosodium glutamate	Bitterness evaluation of non-steroidal anti-inflammatory drugs, herbal medicines; Umami taste intensity of green tea; Bitterness intensity of black and oolong tea; Distinguish types of soy sauce; Identification of alcohol, tea, other beverages
Voltammetric sensor	Polymers Metallic nanoparticles Phthalocyanines	Sucrose, saccharine, quinine	Bitterness detection of organic and ionic compounds; Differentiate the bitterness degree of olive oil; Discrimination of wine
Impedance spectrum sensor	Langmuir–Blodgett film Ultrathin film	Sweet, bitter, salt and acidic solutions	Assessment for orange juice; Classification of wine

Table 2
Names, abbreviations, chemical structures of artificial lipids and plasticizers.

Lipid			Plasticizer		
Name	Abbreviation	Chemical structure	Name	Abbreviation	Chemical structure
Trioctylmethylammonium chloride	TOMA		Phosphoric acid tris (2-ethylhexyl) ester	PTEH	
Tetradodecylammonium bromide	TDAB		Tributyl *O*-acetylcitrate	TBAC	
Oleic acid	OA		Dioctyl phenylphosphonate	DOPP	
Phosphoric acid di-*n*-decyl ester	PADE		2-Nitrophenyl octyl ether	NPOE	
Bis(2-ethylhexyl) phosphate	BP		Bis(1-butylpentyl) adipate	BBPA	
1-Tetradecanol	TC		Diethylene glycol dibutyl ether	DGDE	
1-Hexadecanol	HC		Bis(2-ethylhexyl) sebacate	BEHS	
Gallic acid	GA		3-(Trimethoxysilyl)propyl methacrylate	TMSPM	

Potentiometric sensors with specific sensing materials were set up to selectively evaluate the bitter, sweet and complex tastes of amino acids. A sensor with highly hydrophobic lipid/polymer membrane comprising phosphoric acid di-*n*-decyl ester as the negatively charged lipid, bis(1-butylpentyl) adipate and tributyl *O*-acetylcitrate as the plasticizers, was employed to measure the bitterness [30]. On the other hand, a sensor with positively charged lipid/polymer membrane comprising tetradodecylammonium bromide as the lipid, dioctyl phenylphosphonate as the plasticizer and trimellitic acid, was used to measure the sweetness. It was indicated that the bitterness, sweetness of amino acids could be quantified, and the bitterness suppression effect could be clarified. Besides, Habara et al. [31] improved the membrane for analysis of the sweetness using 1 M sucrose as tastant by means of the comparison of electric responses from seven conventional membranes and new one (phosphoric acid di-*n*-hexadecyl ester + tetradodecylammonium bromide). It was resulted that the responses from conventional membranes were commonly weak, however, the response from the newly developed membrane was greatly enhanced.

An improved bitterness sensor which has a membrane surface with high hydrophobicity, and a taste sensor based on sourness-responsive membrane were jointly employed to determine the bitterness and sourness intensities of acidic pharmaceutical active

ingredients using nine non-steroidal anti-inflammatory drugs (NSAIDs) for examples [32]. The bitterness intensities of some pharmaceutical ingredients such as etodolac, diclofenac sodium, both increased in a concentration-dependent manner although no changes of sourness intensities were revealed at any concentration. It was confirmed that these sensors were useful for predicting the taste intensity of pharmaceutical. In order to ensure the quality, safety and efficacy of herbal medicines [33], a specific sensor combined with proper methods must be utilized. In the recent study, a disposable screen-printed array sensor strip based on methacrylate–acrylate polymer blend with lipids was applied to quantify bioactive caffeic acid in Orthosiphon stamineus Benth through standard addition technique. The results showed that similar and low root mean square error of prediction (RMSEP) values were given via partial least square and principal component regression.

The umami taste also can be evaluated through potentiometric sensors with lipid polymer membrane. In a previous report, Iiyama et al. [27] employed Ag/AgCl electrode filled with 100 mM KCl and a reference electrode to detect electric potential across the membrane made by eight kinds of lipid analogs for measurement of umami taste which induced by monosodium glutamate (MSG). It was resulted that MSG increased the membrane potential at higher concentration, but the reverse happened at lower concentration due to the dissociation of phosphate group of the membrane lipid accelerated by the dissociated carboxyl group of MSG. A sensor with the lipids of methyltrioctylammonium chloride and di(2-ethylhexyl) phosphate was fabricated to detect the membrane potential changes in the sample and in the standard solution, respectively. A method for evaluating the umami taste intensity of green tea using the above taste sensor by removal of the catechins was successfully established [34]. Moreover, a high correlation of the sensor output concerning umami and the human gustatory sense was confirmed.

A sensor with trioctylmethylammonium chloride and dioctylphosphonate as the lipid membrane was used to determine iso-α-acid as an acidic bitter substance [28]. It was reported that the membranes were prepared with different lipid concentrations because the charge density and hydrophobicity of the membranes depend on the lipid concentration, which has an influence on the value of potential caused by adsorption and the amount of adsorbed bitter substances. Similarly, Hayashi et al. [35] continued to engage in the research on the sensor coupled with common techniques for both black and oolong teas. The sensor for measuring the bitter taste intensity, which was composed of tetradodecylammonium bromide, 2-nitrophenyl octyl ether and poly vinyl chloride, was calibrated with standard solutions prepared with ethyl gallate.

2.1.2. Chalcogenide glass with PVC film as the sensing material

A type of potentiometric sensor using chalcogenide glass with PVC film has been designed. Legin et al. proposed solid-state crystalline ion-selective electrodes based on chalcogenide glass with PVC film to realize the detection of the potential signal generated by the types and concentrations of ions in the solution. A disposable solid-state planar-type potentiometric sensor, composing of highly cross-sensitive solvent polymeric membranes based on different matrices such as aromatic polyurethane, polypyrrole and PVC which doped with specific electroactive components, was set up with the carbon paste electrode array screen-printed on a polymeric substrate [36]. Solid-state potentiometric sensors are likely to be a promising multisensors applied to analyze natural or artificial complex ingredients for the characterization and identification of alcohol, tea and other beverages [37–39].

2.2. Voltammetric sensors based on biomimetic materials

Voltammetric sensors are built on the basis of electrochemical principle, of which analysis systems are used for the measurement of the bare metal electrodes. A three-electrode cell including the working electrode, the auxiliary electrode and the reference electrode is usually applied. Voltammetric electrodes modified with various chemosensitive and biomimetic materials such as polymer, metallic nanoparticle [40–42], phthalocyanine [43–45] and other chemical, have been developed rapidly.

2.2.1. Polymer and metallic nanoparticle as the sensing material

Heterocyclic polymer such as polypyrrole, polyaniline and polythiophene can be conveniently prepared, and exhibited a great number of electrochemical properties which mainly depend on the synthesis conditions [46]. A voltammetric sensor system consisting of several modified epoxy-graphite electrodes [47] was employed for qualitative analysis, recognition and classification of food. The electrodes were modified with different components as nanoparticles of copper, platinum nanopowder or conducting polymer in powder, polyaniline and polypyrrole.

For measurement of the bitterness and sweetness, a piezoelectric quartz crystal (PQC) sensor array based on molecularly imprinted polymer (MIP) was developed with respect to quinine and saccharine as taste-causing compounds [48]. The MIP-PQC sensor was set up through fixing quartz crystal with silicone glue and coating with MIP which was allowed to make contact with the solution on one side of the crystal. This type of sensor produced a satisfactory repeatability (RSD < 5%), high sensitivity (2.04 mg/L for quinine and 32.8 mg/L for saccharine) and wide working range (10–1080 mg/L for quinine and 51–3420 mg/L for saccharine) to detect the change in bitterness of sample with much less suppressing effect in the presence of saccharine as compared to the human taste. In addition, there was no significant interference from most substances universally contained in samples except sucrose.

2.2.2. Phthalocyanine and other chemical as the sensing material

Phthalocyanines including monophthalocyanine and bisphthalocyanine, which have abundant electrochemical behaviors and properties to endow with sufficient stability and cross-selectivity, are also a reliable choice for modifying voltammetric sensors. As the complex, monophthalocyanine is coordinated with a phthalocyanine ring, whereas bisphthalocyanine coordinated with two phthalocyanine rings. A type of voltammetric sensor modified with electroactive compound like phthalocyanine has been reported by Apetrei and coworkers. The capability and the function of the sensors were estimated accurately and used to detect the bitterness of organic and ionic compounds. The development of voltammetric sensors based on the modification with phthalocyanines combined with various voltammetry methods including cyclic voltammetry, normal pulse voltammetry and so on has been carried on in order to determine and characterize different sample solutions [43,49]. Furthermore, more interesting electrochemical properties of phthalocyanine can be modulated and performed through changing the central metal atom or introducing substituents in the phthalocyanine rings [50,51].

As reported, the sensor employed carbon paste electrode (CPE) as the working electrode with olive oil as the electroactive binder material [52]. According to the report, the modified CPE electrodes prepared by mixing the graphite in a mortar with the corresponding olive oil in a proper weight ratio, were successfully fabricated to differentiate the degree of bitterness via the analysis for characteristic curves of cyclic voltammetry (CV) and square wave voltammetry (SWV).

2.3. Impedance spectrum sensors based on biomimetic materials

A type of sensor named impedance spectrum sensor, which has been developed to analyze samples by impedance spectroscopy measurement technology, employs precious metal electrodes modified with specific films like Langmuir–Blodgett film and ultrathin film.

A sensor with Langmuir–Blodgett film deposited onto interdigitated electrodes that coated with stearic acid, polyaniline oligomer and polypyrrole, performed over the frequency range from 20 to 10^5 Hz to distinguish sweet, bitter, salty and acidic solutions [53]. Analogously, the array comprising sensitive units made from Langmuir–Blodgett (LB) films of conducting polymers and lipids was deposited onto gold interdigitated electrodes [54]. It can be employed with impedance spectroscopy technology to differentiate taste substances. Besides, ultrathin film of polyaniline nanofibers deposited by self-assembly and casting onto interdigitated microelectrode was used as the efficient sensing element in taste sensor which was able to detect citric acid with concentration limit as low as 2 ppm [55].

3. Biosensors/biosensing methods

Biosensors namely the synergistic coupling of biotechnology and electronics are mainly focused on using the sensing elements such as taste cells, tissues and nerves. In addition, nanomaterial and microfluidic chip, as innovative materials, have been developed for the fabrication of biosensors which can be used to detect and analyze a wide spectrum of targets with a high degree of sensitivity and specificity. Table 3 summarizes six types of biosensors including biosensing element, transducer and target substances.

3.1. Taste receptor cell-based biosensors

Cells, especially taste receptor cells (TRCs), are popularly recognized to be biological functional elements for biosensors aimed to basic tastes. So far, there are two classes of cells available for the fabrication of biosensors, which are natural taste receptor cells and bioengineered taste receptor cells. Natural cells are isolated from biological taste systems, which keep natural structures and properties. On the other hand, bioengineered cells that are the category of functional cells treated specially to be used as effective and sensitive elements for biosensors can respond to the tastants or the specific chemicals.

3.1.1. Natural taste receptor cells

Natural cells which can obtain messages of basic taste sensation by means of the corresponding tastants or stimuli, embrace the specific cells and taste receptors expressed in cells (Table 4). On the basis of morphological characters, taste cells on the taste buds can be classified into several types including Type II and Type III cells. Sweetness can be sensed via G-protein-coupled dimeric receptors (T1R2/T1R3) expressed in NCI-H716 cells and Type II cells, with the stimulation of sucrose or glucose. Bitter stimuli as $MgSO_4$ and quinine act through G-protein-coupled T2R receptors expressed in SCT-1 cells and Type II cells. Umami stimuli such as glumate and L-amino acid bind to mGluRs receptors [56–59] and G-protein-coupled dimeric receptors (T1R1/T1R3), which are expressed in Type II cells. Taste receptors of sourness and saltiness are expressed in Type III, HEK293T cells and general TRCs respectively via sensitive ion channels.

The sensitive and responsive features of human taste cells can be presented coupling with the suitable electrodes. A taste cell chip based on LAPS (light-addressable potentiometric sensor) treated with poly-*l*-ornithine and laminin mixture, on which taste receptor cells achieved from fungiform papillas of taste buds were cultured for a week, was employed to detect extracellular potential of taste cells stimulated by five taste substances (NaCl, HCl, $MgSO_4$, sucrose and glumate) [60]. As a non-invasive, real-time measurement technique, the biosensor with taste cell chip and LAPS was used to analyze cell responses to stimuli for studying taste transduction mechanism *in vitro*. The firing rate and temporal firing of taste receptor cells were investigated in another research [61]. Firing rate of cells depended on the concentration of stimulus. The temporal firing response proved that different taste receptor cells responded to stimuli in different ways.

For the measurement of the sweetness, NCI-H716 cells, the human colorectal carcinoma cell lines, expressing α-gustducin and sweet taste receptor T1R1/T1R3, were cultured on the surface of carbon screen-printed electrode (CSPE) coated with

Table 4
Taste receptors/channels and cells for taste sensation.

Taste	Taste receptors/channels	Cells
Sweetness	T1R2/T1R3	NCI-H716, Type II
Bitterness	T2Rs (T2R38)	STC-1, Type II
Umami	T1R1/T1R3, mGluRs	Type II
Sourness	ASIC, PKDL	HEK293T, Type III
Saltiness	ENaC, VR-1 variant	General TRCs

Table 3
Summary of biosensor including biomolecule type, biosensing element, transducer and target substances.

Biomolecule type	Biosensing element	Transducer	Target substances
Cell	Taste receptor cells (Type II, Type III cells)	LAPS	NaCl, HCl, $MgSO_4$, sucrose, glumate
	NCI-H716 cells	CSPE	Sweeteners, sucrose, quinine
	STC-1 cells, IMITD cells	CSPE	Quinine
	HEK293T cells	LAPS	Acidic stimuli
	Bioengineered HEK-293 cells	LAPS	Sweet and bitter substances
Tissue	Taste epithelium	MEA	Hydrochloride, sodium chloride, quinine, quinine hydrochloride, glucose, sodium glutamate, artificial sweeteners, denatonium, cycloheximide, amino acid
Enzyme	Naringinase	Fiber-optic sensor	Naringin
	Laccase, tyrosinase, peroxidase	Glassy carbon electrode	Bitter phenolic and polyphenolic compounds
	Glucose oxidase	Epoxy-graphite	Glucose
Nerve	Chorda tympani, glossopharyngeal, greater superficial petrosal	Sliver plate electrode	NaCl, HCl, sucrose, quinine hydrochloride, monosodium L-glutamate, 5′-inosine monophosphate
Nanotechnology	AuNP	Nanoprobe	DNA molecules
	SiO_2NP	Amplified probe	Micromolecular substance
	SWCNT	Field effect transistor	Bitter tastants
	CPNT	Field effect transistor	Bitter tastants
Microfluidic chip	Continuous flow chip	Capillary micro reactor	Glucose
	Fluorescein isothiocyanate	MCE	D-Tyrosine

poly-*l*-ornithine and laminin to form NCI-H716 cell-based sensor [62]. As a negative control, COLO-205 cells, mammalian cell lines without the expression of gustducin, T1R2 and T1R3, were selected and cultured on CSPE. NCI-H716 cell-based sensor was proposed to detect four basic tastants and sucrose solutions in seven concentrations using electrochemical impedance spectrum (EIS) measurement and bistable stochastic resonance (BSR) method. The results indicated that the NCI-H716 cell-based sensor made more intensive response to the sweetness than other tastes, and valid concentration discrimination for sucrose solutions. The CSPE with COLO-205 cells lacked the ability to detect tastants, which was circumstantial evidence for the availability and reliability of NCI-H716 cell-based sensor. In another report [63], NCI-H716 cell-based sensor was improved to distinguish sweetener mixtures and tastant mixtures through analyzing the EIS data process by stochastic resonance (SR). On the other hand, several glucose transporters (GLUTs), a sodium-glucose cotransporter (SGLT1), and sulfonylurea receptor (SUR) 1 of the ATP-gated K^+ (K_{ATP}) metabolic sensor [64] were selectively expressed in taste cells. Depending on electrophysiological recordings, functional K_{ATP} channels were present in taste cells. The signaling proteins may provide T1r-independent sweet taste mechanisms in the sweet-sensitive subset of taste cells.

For the measurement of the bitterness, the enteroendocrine STC-1 cells [65], expressing G-protein coupled receptors (GPCRs) and T2R, were cultured on CSPE coated with poly-*l*-ornithine and lamimin under standard conditions. The ICR mouse isolated taste bud (IMITD) cells were dissociated from the fungiform papillae and incubated in a medium. STC-1 cells and IMITD cells, as sensing elements, were used for bitter taste receptor cell-based sensors coupled with shift-frequency electrochemical impedance spectrum (SFEIS). STC-1 cell-based sensor and IMITD cell-based sensor selectively responded to bitter tastants at the optimal frequencies (9 kHz for STC-1 cells and 1.2 kHz for IMITD cells) due to the perceptions abilities of cells. Meanwhile, the results of negative control in which the HEK-293 cells and the dead IMITD cells were used, illuminated that cells with no taste receptor expression lacked the ability to discriminate tastants even if they were excited by different frequencies. STC-1 cell-based has been developed to quantify the bitter components, in virtue of the high positive correlation of the sensor response and quinine concentration [63]. And, the bitter receptor T2R38 as a potential sensing element [66], is expected to be applied for bitter-sensing biosensor. It has been reported that T2R38 can be found in peripheral blood neutrophils, monocytes, lymphocytes and epithelial cells in the lung.

As is well known, Type III cells contain synaptic specializations that are able to execute further signal transmission and taste information delivery, in capability of responding to sour or salty stimuli [67]. It has been reported that a hybrid biosensor based on cells including taste receptor cells and HEK (human embryonic kidney) 293T cells and LAPS integrated with an electrolyte-insulation-semiconductor structure was developed for electrophysiology recording [68]. Taste receptor cells dissociated from circumvallate papillae and HEK293T cells derived from human embryonic kidney, were cultured on LAPS under standard conditions of 37°C and humidified air with 5% carbon dioxide in Dulbecco's modified eagle medium. It was demonstrated that this kind of hybrid biosensor could realize acidic sensation by analyzing the characteristic features of temporal signals from LAPS recordings upon acidic stimuli (pH = 2, 4, 7.5). Generally, most receptor taste cells only react to one single taste, however, a majority of presynaptic taste cells can receive useful signals from labeled cells that respond to two or more different tastes [69]. The T1R1 + T1R3 receptor, as umami receptor, mainly responds to L-amino acids rather than sweet D-amino acids. The 'bitter partner' of a bitter-sweet pair used as a stimulus to umami receptor cells whose response signal is interpreted as bitter taste, owing to the signals from umami and bitter receptor cells on the same presynaptic cell that can be activated by more than one taste cell.

3.1.2. Bioengineered taste receptor cells

Bioengineered cells, reformed with special properties using the powerful biotechnology, are applied for biosensors as sensing elements. The advantage of bioengineered cells is to conquer the weakness namely the limited amount of cells and undefined sensing properties.

Some researchers have successfully restructured taste receptors and cells via genetic engineering technologies [9,70]. HEK293T cells as the original cells, were reformed and cultured to bioengineered taste receptor cells both for the sweet-sensing and the bitter-sensing biosensor [71]. For the sweet-sensing biosensor, original cells were cultured in a mixture of Dulbecco minimum essential medium and GlutaMAX-I media, adding 10% fetal bovine serum and 1% Pen/Strept 10 K/10 K stock. The target cell line was reproduced by expressing the chimeric G protein G15Gi1 alpha subunit and the two sweet receptor subunits T1R2 and T1R3 under the control of an inducible promoter. For the bitter-sensing biosensor, original cells were cultured in Dulbecco minimum essential medium containing high glucose and L-glutamine, adding 10% fetal bovine serum and 1% Pen/Strept 10 K/10 K stock. The target cell line was reproduced by constitutively expressing the chimeric G protein G15Gi1 alpha subunit and the cDNAs for the different T2Rs. Similarly, bioengineered HEK-293 cells were reformed by expressing with a taste receptor hT2R4 based on localized extracellular acidification measurement using LAPS chip [21]. It was concluded that this bioengineered cell-based biosensor responded to the target molecules in a dose-dependent manner, showed a potential to be a novel tool for the label-free functional assays of bionic chemical receptors as well as protein coupled receptors.

3.2. Tissue-based biosensors

In view of the simulation of the sensation process *in vivo*, taste tissues including taste buds and taste epitheliums are good candidates as the biological sensing elements for biosensors. In these biosensors, taste tissues do well job on sensation conduction and signal performance for evaluation and analysis of basic tastes. Biological tissues used in previous reports mainly refer to taste epitheliums or taste buds in tongue containing filiform, fungiform, foliate and circumvallate papillae.

As the technology of simultaneous determination, the fabricated microelectrode arrays (MEA) chip was deposited and prepared by Ti (30 nm), Au (300 nm) and Si_3N_4 layer (500 μm) [12]. The isolated epithelium excised from the rat tongue and then incubated in Ringer's solution, was fixed on MEA (Fig. 2A) as the sensing elements of the biosensor which was used to measure basic taste qualities upon taste stimuli (hydrochloride – sour, sodium chloride – salt, quinine hydrochloride – bitter, glucose – sweet, sodium glutamate – umami). The amplitudes ranging from about 100 μV to 500 μV of the multi-channel signals presented obvious differences, resulting from the position of the taste epithelium in MEA chip. Hence, this type of biosensor could simultaneously recognize multiple taste qualities via electrophysiological activities (Fig. 2B) of taste epitheliums.

In general, multi-channel MEA as the platform are also taken advantage for tissue-based biosensors to deliver the sensing of a single taste. The biosensor based on taste epithelium was developed to detect natural and artificial sweeteners. Tissue slice of an intact taste epithelium (about 5 mm × 5 mm) with the unit of survival Type II taste cells for sweet perception was prepared and

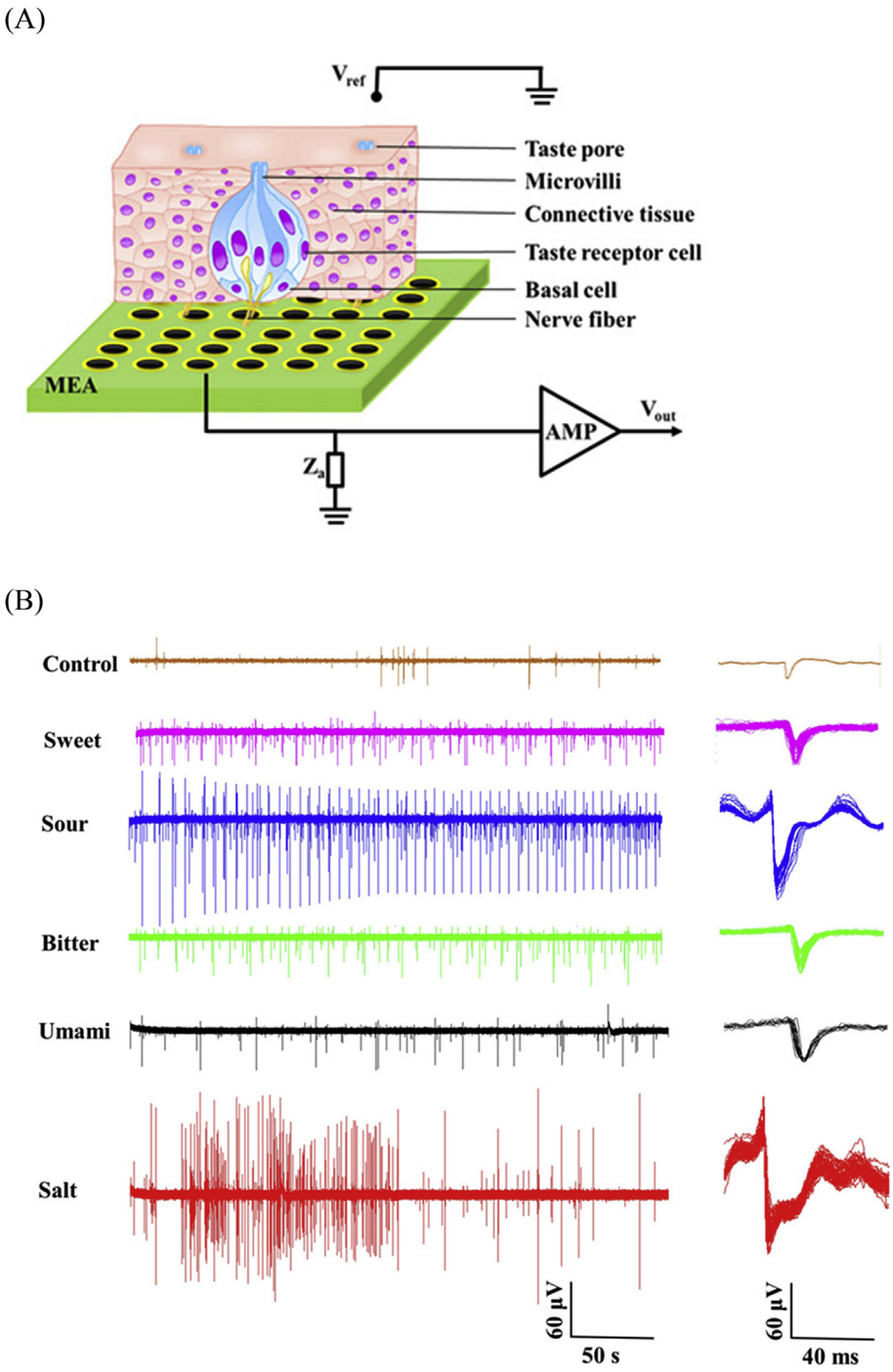


Fig. 2. The combination of microelectrodes and taste epithelium to record extracellular potentials of taste buds [12]. (A) Schematic diagram of tissue-based biosensor. (B) Electrophysiological activities under the stimulation of five basic tastes.

fixed on MEA chip [72]. It was drawn out that the electrophysiological activities of artificial sweeteners were quite different from those of natural in both time and frequency domains, that is, the signals induced by artificial sweeteners displayed large amplitude and short duration, but the signals of natural sugars showed small amplitude and long duration. According to the above results, the signal responses of taste epithelium with Type II taste cells were obtained to characterize different sweeteners. For the bitterness, a biosensor set up with 36-channel MEA as a recording platform and taste epithelium, was deemed to be a rapid and reliable biosensor for detecting and recognizing different bitter tastants such as quinine, denatonium and cycloheximide at the concentrations from 10 μM to 100 mM [73] through the analysis on electrophysiological activities of epithelium. As a biological sensing element, the epithelium was isolated from the tongue root on which there were plenty of circumvallate papillae, then rinsed with PBS and placed with taste pores side upon the surface of MEA. As mentioned, Type II cells of TRCs, participate in the signal processing of the bitterness. In that case, the intact tissues containing these cells can be considered as the sensing elements for the bitter-sensing biosensor.

Continuously, MEA composing of 60 electrodes coupled with taste epitheliums constituted a biosensing platform for detecting

umami tastants of amino acids (L-Glu and L-Asp) and sodium salt of amino acids (L-MSG and L-MSA) [56]. In this tissue-MEA biosensor, taste epitheliums fixed on the surface of MEA were isolated with a mixture of collagenase and proteolytic enzymes. Distinct differences between amino acids and their sodium salts, and the synergistic enhancement between umami compounds and purine nucleotides were found by the tissue-MEA biosensor with reasonable statistical methods.

As for saltiness, combining the taste buds with MEA, Liu et al. [9] fabricated a biosensor used to detect electrophysiological properties of the taste receptor cells, in which multi-channel MEA comprising an array of electrodes (a 6 × 6 array pattern) where intact taste buds including the filiform papillae and fungiform were fixed. In this biosensor, the taste buds whose native structures were preserved with the intact receptor cell populations, were stimulated by the salty stimuli i.e. NaCl solution with various concentrations to evoke the saltiness perception, and exhibited to be the predominance of sensing system.

3.3. Enzyme-based biosensors

Enzyme, molecular substance with biological catalysis function, has been utilized on sensors due to high specificity and efficiency. Enzymatic biosensors have been designed with enzyme modification and immobilization methodology.

In order to set up the bitter-sensing biosensor, the enzyme naringinase [74] was immobilized on the surface of silver coated core of the optical fiber in fiber-optic sensor using gel entrapment technique that is a popular enzyme-immobilization methodology. This biosensor was employed to determine the content of naringin as the bitter stimulus through a surface plasmon resonance (SPR) and signal to noise ratio (SNR) of the sensor. Results indicated that the SPR wavelength and the sensitivity increased but the SNR diminished, with an increase in the concentration of naringin. A series of biosensors based on the modified laccase, tyrosinase, peroxidase enzymes [75–77] have been developed, which can correctly measure the intensity of bitterness via the stimulation of bitter phenolic compounds. Glucose oxidase enzymes and epoxy-graphite biocomposites constituted one type of enzymatic biosensors [78] employed for the detection of glucose in different solutions.

3.4. Taste nerve methods

Neurophysiological properties of nerves in mammals have been progressively exploited for the development of taste sensing. Three major branches of nerves innervating taste buds, such as chorda tympani nerve (CT), glossopharyngeal nerve (GL) and greater superficial petrosal nerve (GSP), responded to umami stimuli including various mixtures of monosodium L-glutamate and 5′-inosine monophosphate in different concentrations [79]. These responses were performed through a silver plate electrode which was placed nearby the cut of nerve. The activities of nerves were amplified and recorded to achieve electrophysiological characteristic. The results showed that synergistic effects of multiple umami substances were significantly emerged in the CT and followed in the GSP, but not in the GL. Consequently, CT and GSP play major roles in mediating the umami taste sensation transduction, whereas GL as an ignorable role.

According to other studies [80,81], there are notable differences among taste responsiveness of these three nerves evoked by sweet, bitter, sour and salty stimuli. The CT is sensitive to sodium salts and sugars. The GL strongly responds to acids as well as quinine, but weakly to sodium salts and sugars. However, the GSP is particularly susceptible to sugars.

3.5. Nanotechnology-based biosensors

Nanotechnology can improve the detection performance of chemical and biological sensors, and promote the development of novel nanotechnology-based biosensors comprising nanomaterials and biological sensing elements. A great number of nanomaterials, such as nanoparticle (NP), carbon nanotube (CNT), conducting polymer nanotube (CPNT) and graphene, have been applied in virtue of unique chemical, physical and optical properties.

The biosensors based on nanoparticles that provide wide detection range, low detection limit and high selectivity have been developed rapidly. An ultrasensitive biosensor [82] with gold nanoparticle (AuNP)-enhanced fluorescence polarization for the detection of endonuclease was developed by using EcoRI as a model analyte, of which the principle shown in Fig. 3A. AuNPs were modified with capture DNA molecules, and then hybridized with fluorescently labeled DNA that sequences were partly complementary to capture DNA molecules, forming the duplex DNA—functionalized nanoprobes that contained the recognition sites of EcoRI. The EcoRI activity was quantified by monitoring the change in the fluorescence polarization value. In addition, a sensor based on aptarner structure-switching-triggered nanoparticle amplification for analyzing protein and biomolecule (Fig. 3B) was proposed by using adenosine triphosphate (ATP) as a model analyte. In that system, fluorescently labeled aptamer hairpin was used as recognition probe, and single-stranded DNA-functionalized silica nanoparticles (SiO_2NPs) was used as amplified probe. In the absence of ATP, fluorescently labeled aptamer hairpin was unable to bind with functionalized DNA, and showed low fluorescence polarization value of the system. Upon the addition of ATP, their hybridization happened, leading to a significant increase of the value, which provided the quantitative basis of the detection of ATP (40 pmol/L to 100 μmol/L).

It was reported that the bitter taste receptor immobilized on a single-walled carbon nanotube (SWCNT) with lipid membrane was utilized for a biosensor to distinguish between bitter and non-bitter tastants [83]. In another study [84], a caboxy-lated polypyrrole nanotube modified with taste receptor hT2R38 could selectively and sensitively respond to bitter tastants at low concentration.

3.6. Microfluidic chip methods

Microfluidic chip which has a great advantage of little sample and reagent consumption, and high degree of automation, can offer a helpful method for the integration with biosensors. Microfluidic chip for continuous flow was established for glucose sensing using the technology of capillary micro reactor [85]. The capillary connected to the chip was injected by glucose oxidase or a mixture of glucose oxidase and chitosan after chemical treatment. The time ampere signal response curves of glucose at different concentrations presented equilibrium response within 30 s. The method based on microfluidic chip greatly improves the efficiency of electrochemical detection.

Microchip electrophoresis (MCE) is a primary part of the microfluidic chip technology, and is also one of the fastest growing separation techniques in recent years. Compared with conventional technique, MCE has several advantages of high separation efficiency, short analysis time, low sample and reagent consumption. A simple and sensitive MCE method based on laser induced fluorescence technology and fluorescein isothiocyanate as precolumn derivatization reagent has been developed for the detection of D-tyrosine (D-Tyr). In previous study [82], γ-Cyclodextrin was selected as chiral selector, and the mode of micellar electrokinetic chromatography was applied for the separation of D/L-Tyr within 150 s. Hence, the proposed method could quantify D-Tyr in biological elements.

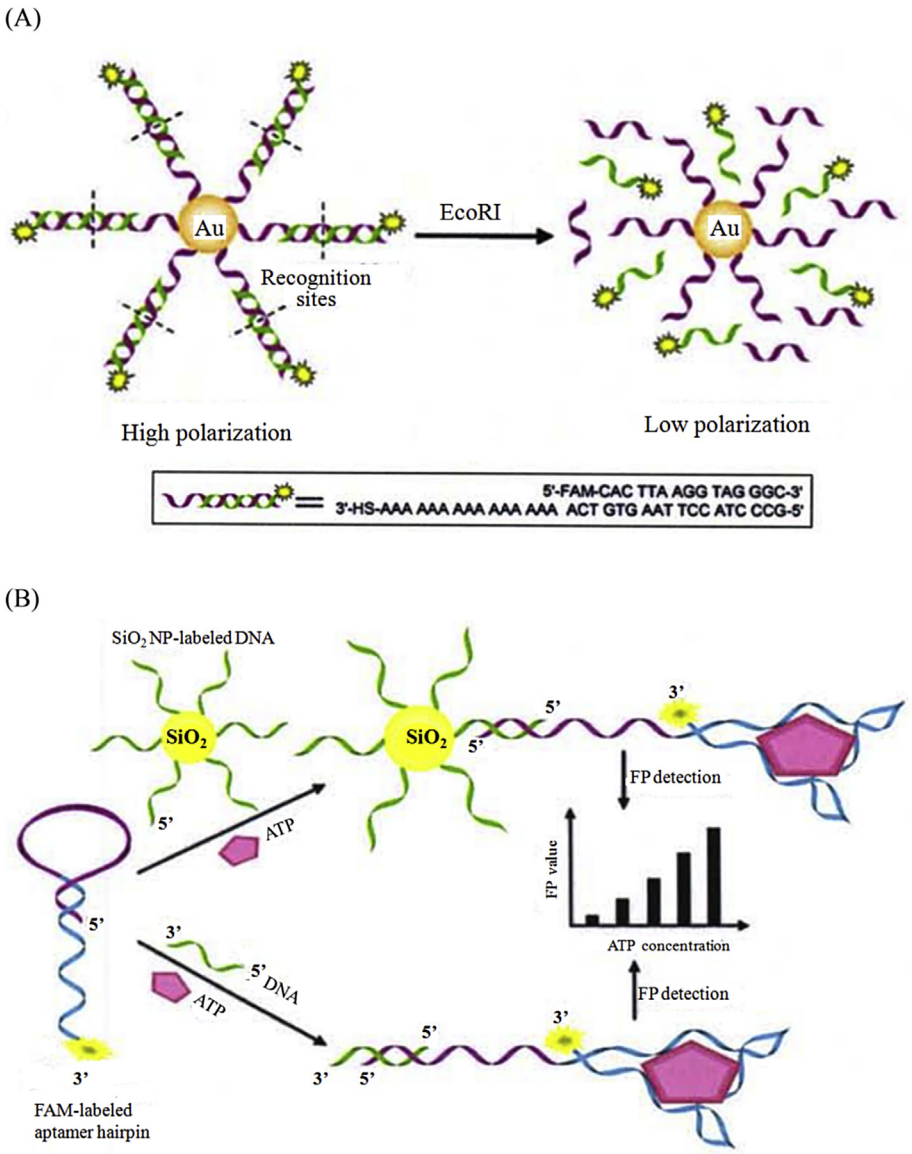


Fig. 3. (A) The principle of gold nanoparticle (AuNP)-enhanced fluorescence polarization for the detection of endonuclease. (B) The principle of aptarner structure-switching-triggered nanoparticle amplification for analyzing protein and biomolecule [82].

4. Applications for five basic tastes

4.1. Applications for taste sensation and transduction mechanism

Taste sensation and transduction mechanism, namely the process of taste mediated through taste stimuli binding to specific receptors on the membrane of the taste cell, can be clearly exposited in the case of biomimetic sensors or biosensors as useful tools.

For the sweet, bitter and umami sensation and transduction (Fig. 4), homologous G-protein-coupled receptors or transmembrane domain receptors interacting with intercellular G proteins are the principal participants. Sweet receptors i.e. G-protein-coupled dimeric receptors (T1R2/T1R3), activate the second messengers involving the closure of potassium channels [86]. Bitter receptors i.e. T2Rs [14,87] produce a depolarization and neurotransmitter release with the release of calcium ions. Umami receptors i.e. dimeric receptors T1R1/T1R3 or mGluRs receptors bring about the release of packets of neurotransmitters. Besides, the inositol triphosphate (IP3), phospholipase C-type β 2 (PLCβ2) and a transient receptor potential cation channel, subfamily M, member 5 (TRPM5) [88], are required in these modalities. TRPM5, activated by GPCR signaling, is a common transient receptor potential channel to sweet, bitter and umami-responsive cells. PLCβ2, one of the four PLCβ isoforms, has overlapping patterns of expression in sweet, bitter and umami receptor cells in comparison with TRPM5. However, sour and salty sensation and transduction pathways are conducted without presence of IP3, PLCβ2 and TRPM5.

For sour sensation and transduction, the protons, as the major stimuli, interact with ionic channels in taste receptor cells. Different species might have different transduction mechanisms of sour sensation. As shown in Fig. 4D, acid-sensing ionic channel (ASIC) [68,89] and polycystic kidney disease-like channel (PKDL) have been regarded as plausible mechanisms of sour taste encoding. The proton ($H+$) can permeate $H+$-activated sour receptor channels and voltage-gated sodium or potassium channels to enter the cell, and ultimately result to depolarize. And for salty sensation, $Na+$ ions enter the membrane of receptor cell through epithelial sodium channel (ENaC) and lead to the depolarization [2,90]. There

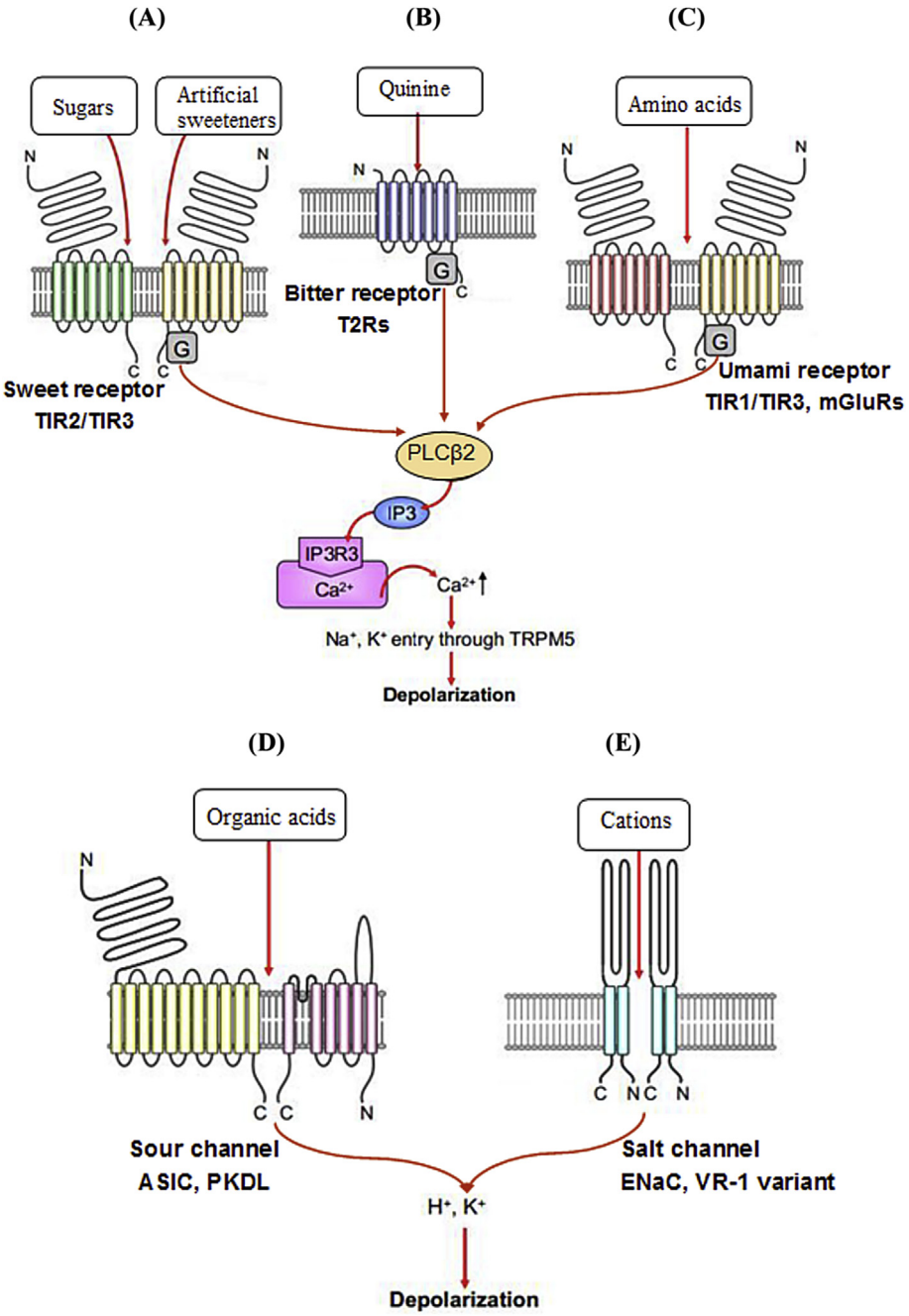


Fig. 4. The taste sensation and transduction mechanisms of five basic tastes: (A) sweetness; (B) bitterness; (C) umami; (D) sourness; (E) saltiness.

is another possibility of a non-selective positive ion channel with vanilloid receptor (VR)-1 variant [91,92].

4.2. Applications for taste sensing information of food and pharmaceutical

All sorts of biomimetic sensors and biosensors have been applied for qualitative and quantitative analyses of taste-causing components in food and pharmaceutical, strongly revealing their practical ability. In respect of food analysis, the flavors of food stuffs including soy sauce, alcohol, tea and other beverages have been discriminated and quantified.

Several kinds of soy sauce [93] were distinguished and classified using the sensor with a multichannel electrode based on various lipids by determining amino acids as a key to affect the quality. It was found that similarity of soy sauces in the same manufacturer was effectively confirmed by the sensor. Wang et al. [94] found that low molecular weight acidic peptides produced during the fermentation of soybeans resulted to the umami taste.

Matcha, a kind of green powdered tea, was evaluated its astringent and umami tastes using a potentiometric sensor fitted with an astringent and umami probe with standard substances [95], (−)-epigallocatechin-3-*O*-gallate for astringent taste and monosodium glutamate for umami taste. The results had the potential to characterize commercial matcha products. As mentioned in Section 3.3, the biosensor based on the enzyme naringinase can test the bitter substance or factor in citrus fruit juices. Towards wines [96,97] and beers, the enzymatic biosensors for determining phenolic

compounds have already been applied. For instance, a biosensor based on graphite-epoxy electrodes modified by enzyme was developed for component detection of beer, in which there were three major phenolic compounds namely ferulic, gallic and sinapic acid found [98]. Voltammetric sensors with different modifiers as polymers and metallic nanoparticles [47], were developed to perform the capability of discriminating and classifying different wine types as well as recognition of the oxygenation effect.

More interestingly, the biosensors combined with enzyme and nanotechnology have been designed and used for fruits and vegetables. Grapes were analyzed via a multi-sensing system constructed with nanostructured biosensor based on phenol oxidases [99]. A biosensor based on carbon nanotube and conducting polymer nanotube was fabricated to test antithyroid toxin in vegetables.

In most pharmaceuticals, the bitterness termed an unpleasant taste is particularly prominent. To alleviate this problem, the taste-masking technique has been developed. Generally, sourness can limit bitterness [100]. It was demonstrated that there were no changes in bitterness intensity of aspirin at any concentration while its sourness intensity increased in a concentration-dependent manner. The theory of aspirin decreased bitterness intensity because of its sourness was conjectured. In order to find out the inhibitory effects of food stuffs on the bitterness of topiramate, the sensor with tetradodecylammonium bromide which was a kind of bitterness-responsive membrane was utilized to test topiramate solutions added with yoghurt, pudding, ice cream, tea, orange juice, lactic drink, acidic sports drink and cocoa [101]. At certain concentration, some tea, pudding and ice cream suppressed the bitterness output of taste sensor in topiramate. More importantly, yoghurt was proved to be the most capable of limiting the bitterness of topiramate due to its lactic acid, orotic acid components and the viscosity. The bitterness intensity of an improved formulation of the enteral nutrient was determined by the bitter-sensing sensor, showing that it was significantly lower than that of the old product in accordance with human gustatory test [102]. This bitterness suppression mainly stemmed from the larger particle sizes of branched-chain amino acids in the improved formulation leading to slower release rate. Besides, the sourness and sweetness of the substances were proved to be responsible for the bitterness suppression.

For another pharmaceutical analysis, the simultaneous quantification of thiol pharmaceuticals in human plasma can be conducted using an integrated microfluidic device with online labeling and chemiluminescence detection [82]. In this device, the online labeling, electrophoresis separation and chemiluminescence detection were compactly integrated onto a hybrid microchip, which showed high integration and automatization. Using *N*-(4-aminobutyl)-*N*-ethylisolu-minol and *o*-phthalaldehyde as online labeling reagents, four thiol pharmaceuticals including captopril, 6-thioguanine, 6-mercaptopurine, and 2-mercaptopropionylglycine as model compounds were separated and simultaneously detected within 80 s. The detection limits of thiol drugs were in the range of 8.9–13.5 nmol/L.

5. Conclusion and future perspective

The sensations of five basic tastes are important branches of biological perception, requiring the development of reasonable and effective bionic technology or biotechnology. Basically, biomimetic sensors of which output signals are analyzed by pattern recognition techniques consist of an array of semiselective recognition elements have common merits of being operated easily and owning definite sensitivity. Comparatively, potentiometric sensor has wide pertinency, whereas voltammetric sensor can obtain enormous output data, and impedance spectrum sensor has high specificity. However, these sensors still cannot perfectly imitate the biological features of human tongue with regards to identifying elusive components in complicated mixtures. The temperature dependence and the adsorption of solution components that affect the potential present the demerits of potentiometric sensors. The chief objections to voltammetric sensor are poor selectivity, limit applicability to redox-active substances, and large surface alteration leading to sensor response drifts. It is difficult to modify impedance spectrum sensor which has poor reproducibility. In this case, biosensor can provide taste signals triggered by the binding activities between selective taste receptors and tastants, making it possible to develop artificial taste sensor that can mimic human taste system. To be considered as a biosensor, its recognition element should be biological origin namely taste cell, tissue, nerve and enzyme, and even other new type like nanomaterial and microfluidic chip. Natural taste cells can be convenient to obtain, but limited amount of identical cells and their unclear sensing properties lead to the difficulty of fabricating taste cell-based biosensors. Bioengineered cells require special treatments on the cells in order to make them possess suitable recognition and sensing capabilities as sensing elements for sensors. Compared to the cultured cells, the intact tissues can be gained easily with the taste-coding network structure well preserved. The use of bioengineered cells, tissues and nerves can enable greater flexibility with respect to analyte recognition and signal transduction. With the development of enzyme modification and immobilization methodology, the specificity and efficiency of detection using enzyme-based biosensors have been enhanced. Due to nanotechnology, these biosensors have high detection sensitivity and short detection time for biological molecules or cells in taste sensing, and can realize high-throughput analysis. The sensor with microfluidic chip has a great advantage of little sample and reagent consumption, and high degree of automation. A variety of biomimetic sensors and biosensors have been applied to clarify taste sensation and transduction mechanism of five basic tastes. These sensors also have been applied for food stuffs and pharmaceuticals through determining the inner ingredients that trigger the taste.

For future perspective, (i) Firstly, more and more biomimetic materials possessing high efficiency, sensitivity and easy-to-operate should be discovered for the modification of sensors. (ii) One of the future researches should place great emphasis on restructuring more selective and efficient bioengineered cells even receptors to promote greater development of taste-sensing biosensors. Generally, the preparation of bioengineered cells is time-consuming and high-cost. So how to obtain bioengineered cells in an easier and cheaper way becomes the pressing concern. (iii) The utilization of enzyme, nanomaterial and microfluidic chip should be expanded in the fabrication of biosensors. New types of enzymes, nanomaterials and microfluidic chips which own stable properties need to be found or made for the taste-sensing. Furthermore, the coupling between these sensing elements and transducers has decisive influence on the sensor performance. The selection of transducer and the utilization of coupling technology may contribute to the improvement of coupling efficiency. (iv) There is further need to develop more multiplexed and reliable biomimetic sensors or biosensors for rapider measurement of five basic tastes.

References

[1] L.M. Bartoshuk, Taste mixtures: is mixture suppression related to compression, Physiol. Behav. 14 (1975) 643–649.
[2] Y. Kobayashi, M. Habara, H. Ikezazki, R.G. Chen, Y. Naito, K. Toko, Advanced taste sensors based on artificial lipids with global selectivity to basic taste qualities and high correlation to sensory scores, Sensors 10 (2010) 3411–3443.
[3] D. Ha, Q.Y. Sun, K.Q. Su, H. Wan, H.B. Li, N. Xu, et al., Recent achievements in electronic tongue and bioelectronic tongue as taste sensors, Sens. Actuators B Chem. 207 (2015) 1136–1146.

[4] E.A. Baldwin, J.H. Bai, A. Plotto, S. Dea, Electronic noses and tongues: applications for the food and pharmaceutical industries, Sensors 11 (2011) 4744–4766.
[5] M. Peris, L. Escuder-Gilabert, On-line monitoring of food fermentation processes using electronic noses and electronic tongues: a review, Anal. Chim. Acta 804 (2013) 29–36.
[6] M. Sliwinska, P. Wisniewska, T. Dymerski, J. Namiesnik, W. Wardencki, Food analysis using artificial senses, J. Agric. Food Chem. 62 (2014) 1423–1448.
[7] Y.S. Kim, Y.S. Kim, Biometrics analysis and evaluation on Korean Makgeolli using brainwaves and taste biological sensor system, Biomed. Res. Int. (2015) 1–12, 918631.
[8] F. Winquist, S. Holmin, C. Krantz-Rülcker, P. Wide, I. Lundström, A hybrid electronic tongue, Anal. Chim. Acta 406 (2000) 147–157.
[9] Q.J. Liu, F.N. Zhang, D.M. Zhang, N. Hu, H. Wang, K.J. Hsia, et al., Bioelectronic tongue of taste buds on microelectrode array for salt sensing, Biosens. Bioelectron. 40 (2013) 115–120.
[10] A.K. Deisingh, D.C. Stone, M. Thompson, Applications of electronic noses and tongues in food analysis, Int. J. Food Sci. Tech. 39 (2004) 587–604.
[11] R.F. Margolskee, J. Dyer, Z. Kokrashvili, K.S.H. Salmon, E. Ilegems, K. Daly, et al., T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 15075–15080.
[12] Q.J. Liu, F.N. Zhang, D.M. Zhang, N. Hu, K.J. Hsia, P. Wang, Extracellular potentials recording in intact taste epithelium by microelectrode array for a taste sensor, Biosens. Bioelectron. 43 (2013) 186–192.
[13] R.A. DeFazio, G. Dvoryanchikov, Y. Maruyama, J.W. Kim, E. Pereira, S.D. Roper, et al., Separate populations of receptor cells and presynaptic cells in mouse taste buds, J. Neurosci. 26 (2006) 3971–3980.
[14] H. Matsunami, J.P. Montmayeur, L.B. Buck, A family of candidate taste receptors in human and mouse, Nature 404 (2000) 601–604.
[15] J. Chandrashekar, M.A. Hoon, N.J. Ryba, C.S. Zuker, The receptors and cells for mammalian taste, Nature 444 (2006) 288–294.
[16] T.A. Gilbertson, J.D. Boughter, H. Zhang, D.V. Smith, Distribution of gustatory sensitivities in rat taste cells: whole-cell responses to apical chemical stimulation, J. Neurosci. 21 (2001) 4931–4941.
[17] A.K. Engel, P. Fries, W. Singer, Dynamic predictions: oscillations and synchrony in top-down processing, Nat. Rev. Neurosci. 2 (2001) 704–716.
[18] G. Buzsaki, Large-scale recording of neuronal ensembles, Nat. Neurosci. 7 (2004) 446–451.
[19] G. Buzsáki, C.A. Anastassiou, C. Koch, The origin of extracellular fields and currents – EEG, ECoG, LFP and spikes, Nat. Rev. Neurosci. 13 (2012) 407–420.
[20] C.S. Wu, P.B. Lillehoj, P. Wang, Bioanalytical and chemical sensors using living taste, olfactory, and neural cells and tissues: a short review, Analyst 140 (2015) 7048–7061.
[21] L.P. Du, L. Zou, L.H. Zhao, P. Wang, C.S. Wu, Biomimetic chemical sensors using bioengineered olfactory and taste cells, Bioengineered 5 (2014) 326–330.
[22] Y. Tahara, K. Toko, Electronic tongues – a review, IEEE Sens. J. 13 (2013) 3001–3011.
[23] L. Escuder-Gilabert, M. Peris, Review: highlights in recent applications of electronic tongues in food analysis, Anal. Chim. Acta 665 (2010) 15–25.
[24] R. Chen, I. Hidekazu, K. Toko, Development of sensor with high selectivity for saltiness and its application in taste evaluation of table salt, Sens. Mater 22 (2010) 313–325.
[25] Y. Kobayashi, H. Hamada, Y. Yamaguchi, H. Ikezaki, K. Toko, Development of an artificial lipid-based membrane sensor with high selectivity and sensitivity to the bitterness of drugs and with high correlation with sensory score, IEEJ T. Electr. Electr. 4 (2009) 710–719.
[26] K. Toyota, H. Cui, K. Abe, M. Habara, K. Toko, H. Ikezaki, Sweetness sensor with lipid/polymer membranes: sweet-responsive substances, Sens. Mater. 23 (2011) 465–474.
[27] S. Iiyama, H. Kuga, S. Ezaki, K. Hayashi, K. Toko, Peculiar change in membrane potential of taste sensor caused by umami substances, Sens. Actuators B Chem. 91 (2003) 191–194.
[28] K. Toko, D. Hara, Y. Tahara, M. Yasuura, H. Ikezaki, Relationship between the amount of bitter substances adsorbed onto lipid/polymer membrane and the electric response of taste sensors, Sensors 14 (2014) 16274–16286.
[29] G. Sharma, S. Kumar, A. Kumar, A. Sharma, R. Kumar, R. Kaur, et al., Development of lipid membrane based taste sensors for electronic tongue, Procedia Comput. Sci. 70 (2015) 146–152.
[30] H. Akitomi, Y. Tahara, M. Yasuura, Y. Kobayashi, H. Ikezaki, K. Toko, Quantification of tastes of amino acids using taste sensors, Sens. Actuators B Chem. 179 (2013) 276–281.
[31] M. Habara, H. Ikezaki, K. Toko, Study of sweet taste evaluation using taste sensor with lipid/polymer membranes, Biosens. Bioelectron. 19 (2004) 1559–1563.
[32] M. Yoshida, T. Haraguchi, T. Uchida, Bitterness evaluation of acidic pharmaceutical substances (NSAIDs) using a taste sensor, Chem. Pharm. Bull. 62 (2014) 1252–1258.
[33] A.S. Islam, M.N. Ahmad, M.Y.M. Sim, Z. Ismail, A.M. Noor, Quantification of bioactive caffeic acid in Orthosiphon stamineus Benth using a disposable taste sensor, Int. J. Electrochem. Sci. 11 (2016) 322–332.
[34] N. Hayashi, R.G. Chen, H. Ikezaki, T. Ujihara, Evaluation of the umami taste intensity of green tea by a taste sensor, J. Agric. Food Chem. 56 (2008) 7384–7387.
[35] N. Hayashi, T. Ujihara, R.G. Chen, K. Irie, H. Ikezaki, Objective evaluation methods for the bitter and astringent taste intensities of black and oolong teas by a taste sensor, Food Res. Int. 53 (2013) 816–821.
[36] L. Lvova, S.S. Kim, A. Legin, Y. Vlasov, J.S. Yang, G.S. Cha, et al., All-solid-state electronic tongue and its application for beverage analysis, Anal. Chim. Acta 468 (2002) 303–314.
[37] A. Legin, A. Rudnitskaya, L. Lvova, Y. Vlasov, C. Di Natale, A. D'Amico, Evaluation of Italian wine by the electronic tongue: recognition, quantitative analysis and correlation with human sensory perception, Anal. Chim. Acta 484 (2003) 33–44.
[38] A. Legin, D. Kirsanov, A. Rudnitskaya, J.J.L. Iversen, B. Seleznev, K.H. Esbensen, et al., Multicomponent analysis of fermentation growth media using the electronic tongue (ET), Talanta 64 (2004) 766–772.
[39] L. Lvova, A. Legin, Y. Vlasov, G.S. Cha, H. Nam, Multicomponent analysis of Korean green tea by means of disposable all-solid-state potentiometric electronic tongue microsystem, Sens. Actuators B Chem. 95 (2003) 391–399.
[40] V. Martina, K. Ionescu, L. Pigani, F. Terzi, A. Ulrici, C. Zanardi, et al., Development of an electronic tongue based on a PEDOT-modified voltammetric sensor, Anal. Bioanal. Chem. 387 (2007) 2101–2112.
[41] L. Pigani, G. Foca, K. Ionescu, V. Martina, A. Ulrici, F. Terzi, et al., Amperometric sensors based on poly(3,4-ethylenedioxythiophene)-modified electrodes: discrimination of white wines, Anal. Chim. Acta 614 (2008) 213–222.
[42] J. Wu, J. Liu, M. Fu, G. Li, Z. Lou, Classification of Chinese yellow wines by chemometric analysis of cyclic voltammogram of copper electrodes, Sensors 5 (2005) 529–536.
[43] V. Parra, T. Hernando, M.L. Rodriguez-Mendez, J.A. De Saja, Electrochemical sensor array made from bisphthalocyanine modified carbon paste electrodes for discrimination of red wines, Electrochim. Acta 49 (2004) 5177–5185.
[44] C. Apetrei, I.M. Apetrei, I. Nevares, M. del Alamo, V. Parra, M.L. Rodriguez-Mendez, et al., Using an e-tongue based on voltammetric electrodes to discriminate among red wines aged in oak barrels or aged using alternative methods: correlation between electrochemical signals and analytical parameters, Electrochim. Acta 52 (2007) 2588–2594.
[45] M.L. Rodríguez-Méndez, V. Parra, C. Apetrei, S. Villanueva, M. Gay, N. Prieto, et al., Electronic tongue based on voltammetric electrodes modified with materials showing complementary electroactive properties, applications, Microchim. Acta 163 (2008) 23–31.
[46] C. Apetrei, M.L. Rodríguez-Méndez, V. Parra, F. Gutierrez, J.A. de Saja, Array of voltammetric sensors for the discrimination of bitter solutions, Sens. Actuators B Chem. 103 (2004) 145–152.
[47] J.M. Gutiérrez, L. Moreno-Barón, M.I. Pividori, S. Alegret, M. del Valle, A voltammetric electronic tongue made of modified epoxy-graphite electrodes for the qualitative analysis of wine, Microchim. Acta 169 (2010) 261–268.
[48] H. Sun, Z.H. Mo, J.T.S. Choy, D.R. Zhu, Y.S. Fung, Piezoelectric quartz crystal sensor for sensing taste-causing compounds in food, Sens. Actuators B Chem. 131 (2008) 148–158.
[49] S. Casillia, M. De Luca, C. Apetrei, V. Parra, A.A. Arrieta, L. Valli, et al., Langmuir-Blodgett and Langmuir-Schaefer films of homoleptic and heteroleptic phthalocyanine complexes as voltammetric sensors: applications to the study of antioxidants, Appl. Surf. Sci. 246 (2005) 304–312.
[50] H. Konami, M. Hatano, N. Kobayasi, T. Osa, Redox potentials of a series of lanthanide-bisphthalocyanine sandwich complex, Chem. Phys. Lett. 165 (1990) 397–400.
[51] M.L. Rodríguez-Méndez, R. Aroca, J.A. de Saja, Electrochromic properties of Langmuir–Blodgett films of bisphthalocyanine complex of rare earth elements, Chem. Mater. 4 (1992) 1017–1020.
[52] C. Apetrei, F. Gutierrez, M.L. Rodríguez-Méndez, J.A. de Saja, Novel method based on carbon paste electrodes for the evaluation of bitterness in extra virgin olive oils, Sens. Actuators B Chem. 121 (2007) 567–575.
[53] A. Riul, A.M.G. Soto, S.V. Mello, S. Bone, D.M.M. Taylor, L.H.C. Mattoso, An electronic tongue using polypyrrole and polyaniline, Synth. Met. 132 (2003) 109–116.
[54] A. Riul, H.C. De Sousa, R.R. Malmegrim, D.S. dos Santos Jr., A.C.P.L.F. Carvalho, F.J. Fonseca, Wine classification by taste sensors made from ultra-thin films and using neural networks, Sens. Actuators B Chem. 98 (2004) 77–82.
[55] E.S. Medeiros, R.J.R. Gregorio, R.A. Martinez, L.H.C. Mattoso, A taste sensor array based on polyaniline nanofibers for orange juice quality assessment, Sens. Lett. 7 (2009) 24–30.
[56] D.M. Zhang, F.N. Zhang, Q. Zhang, Y.L. Lu, Q.J. Liu, P. Wang, Umami evaluation in taste epithelium on microelectrode array by extracellular electrophysiological recording, Biochem. Biophys. Res. Commun. 438 (2013) 334–339.
[57] G. Nelson, J. Chandrashekar, M.A. Hoon, L. Feng, G. Zhao, N.J.P. Ryba, et al., An amino-acid taste receptor, Nature 416 (2002) 199–202.
[58] N. Chaudhari, A.M. Landin, S.D. Roper, A metabotropic glutamate receptor variant functions as a taste receptor, Nat. Neurosci. 3 (2000) 113–119.
[59] N. Chaudhari, E. Pereira, S.D. Roper, Taste receptors for umami: the case for multiple receptors, Am. J. Clin. Nutr. 90 (2009) 738–742.
[60] W. Zhang, Y. Li, Q.J. Liu, Y. Xu, H. Cai, P. Wang, A novel experimental research based on taste cell chips for taste transduction mechanism, Sens. Actuators B Chem. 131 (2008) 24–28.

[61] P.H. Chen, B.Q. Wang, G. Cheng, P. Wang, Taste receptor cell-based biosensor for taste specific recognition based on temporal firing, Biosens. Bioelectron. 25 (2009) 228–233.
[62] T.H. Wang, G.H. Hui, S.P. Deng, A novel sweet taste cell-based sensor, Biosens. Bioelectron 26 (2010) 929–934.
[63] G.H. Hui, S.S. Mi, Q.Q. Chen, X. Chen, Sweet and bitter tastant discrimination from complex chemical mixtures using taste cell-based sensor, Sens. Actuators B Chem. 192 (2014) 361–368.
[64] K.K. Yee, S.K. Sukumaran, R. Kotha, T.A. Gilbertson, R.F. Margolskee, Glucose transporters and ATP-gated K^+(K_{ATP}) metabolic sensors are present in type 1 taste receptor 3 (T1r3)-expressing taste cells, PNAS 108 (2011) 5431–5436.
[65] G.H. Hui, P. Ji, S.S. Mi, S.P. Deng, Electrochemical impedance spectrum frequency optimization of bitter taste cell-based sensors, Biosens. Bioelectron. 47 (2013) 164–170.
[66] S. Maurer, G.H. Wabnitz, N.A. Kahle, S. Stegmaier, B. Prior, T. Giese, et al., Tasting Pseudomonas aeruginosa biofilms: human neutrophils express the bitter receptor T2R38 as sensor for the quorum sensing molecule N-(3-oxododecanoyl)-L-homoserine lactone, Front. Immunol. 6 (2015) 1–9.
[67] P.A. Temussi, Sweet, bitter and umami receptors: a complex relationship, Trends Biochem. Sci. 34 (2009) 296–302.
[68] P.H. Chen, X.D. Liu, B.Q. Wang, G. Cheng, P. Wang, A biomimetic taste receptor cell-based biosensor for electrophysiology recording and acidic sensation, Sens. Actuators B Chem. 139 (2009) 576–583.
[69] S.M. Tomchik, Breadth of tuning and taste coding in mammalian taste buds, J. Neurosci. 27 (2007) 10840–10848.
[70] Q. Liu, W. Ye, L. Xiao, L. Du, N. Hu, P. Wang, Extracellular potentials recording in intact olfactory epithelium by microelectrode array for a bioelectronic nose, Biosens. Bioelectron. 25 (2010) 2212–2217.
[71] A. Bassoli, G. Borgonovo, F. Caremoli, G. Mancuso, The taste of D- and L-amino acids: in vitro binding assays with cloned human bitter (TAS2Rs) and sweet (TAS1R2/TAS1R3) receptors, Food Chem. 150 (2014) 27–33.
[72] F.N. Zhang, Q. Zhang, D.M. Zhang, Y.L. Lu, Q.J. Liu, P. Wang, Biosensor analysis of natural and artificial sweeteners in intact taste epithelium, Biosens. Bioelectron. 54 (2014) 385–392.
[73] Q.J. Liu, D.M. Zhang, F.N. Zhang, Y. Zhao, K.J. Hsia, P. Wang, Biosensor recording of extracellular potentials in the taste epithelium for bitter detection, Sens. Actuators B Chem. 176 (2013) 497–504.
[74] S. Rajan Chand, B.D. Gupta, Fabrication and characterization of a surface plasmon resonance based fiber-optic sensor for bittering component—naringin, Sens. Actuators B Chem. 115 (2006) 344–348.
[75] D.M. Gil, M.J. Rebelo, Evaluating the antioxidant capacity of wines: a laccase-based biosensor approach, Eur. Food Res. Technol. 231 (2010) 303–308.
[76] V. Carralero Sanz, M.L. Mena, A. González-Cortés, P. Yanez-Sedeno, J. Pingarrón, Development of a tyrosinase biosensor based on gold nanoparticles-modified glassy carbon electrodes: application to the measurement of a bioelectrochemical polyphenols index in wines, Anal. Chim. Acta 528 (2005) 1–8.
[77] R. Solná, P. Skládal, Amperometric flow-injection determination of phenolic compounds using a biosensor with immobilized laccase, peroxidase and tyrosinase, Electroanalysis 17 (2005) 2137–2146.
[78] A. Gutés, A. Ibanez, M. Del Valle, F. Céspedes, S.I.A. Automated, E-tongue employing a voltammetric biosensor array for the simultaneous determination of glucose and ascorbic acid, Electroanalysis 18 (2006) 82–88.
[79] N. Sako, S. Harada, T. Yamamoto, Gustatory information of umami substances in three major taste nerves, Physiol. Behav. 71 (2000) 193–198.
[80] S. Harada, D.V. Smith, Gustatory sensitivities of the hamster's soft palate, Chem. Senses 17 (1992) 31–51.
[81] S. Harada, T. Yamamoto, K. Yamaguchi, Y. Kasahara, Different characteristics of gustatory responses between the greater superficial petrosal and chorda tympani nerves in the rat, Chem. Senses 22 (1997) 133–140.
[82] Y. Huang, Study of Novel Bioassay Methods Based on Functionalized Nanomaterials and Microfluidic Chip, Central South University, Hunan, 2012.
[83] T.H. Kim, H.S. Song, H.J. Jin, S.H. Lee, S. Namgung, U.K. Kim, et al., Bioelectronic super-taster device based on taste receptor-carbon nanotube hybrid structures, Lab. Chip 11 (2011) 2262–2267.
[84] H.S. Song, O.S. Kwon, S.H. Lee, S.J. Park, U.K. Kim, J. Jang, et al., Human taste receptor-functionalized field effect transistor as a human-like nanobioelectronic tongue, Nano Lett. 13 (2012) 172–178.
[85] Y.Y. Wen, X.L. Bai, F. Fang, Z.Y. Wu, Electrochemical biosensor based on microfluidic chip continuous flow, Prog. Microfluid. Lab. 1 (2007) 125–126.
[86] G.H. Hui, S.S. Mi, S.P. Deng, Sweet and bitter tastants specific detection by the taste cell-based sensor, Biosens. Bioelectron. 35 (2012) 429–438.
[87] E. Adle, M.A. Hoon, K.L. Mueller, J. Chandrashekar, N.J.P. Ryba, C.S. Zuker, A novel family of mammalian taste receptors, Cell 100 (2000) 693–702.
[88] Y.F. Zhang, M.A. Hoon, J. Chandrashekar, K.L. Mueller, B. Cook, D.Q. Wu, et al., Coding of sweet, bitter, and umami tastes: different receptor cells sharing similar signaling pathways, Cell 112 (2003) 293–301.
[89] S. Ugawa, T. Yamamoto, T. Ueda, Y. Ishida, A. Inagaki, M. Nishigaki, et al., Amiloride-insensitive currents of the acid-sensing ion channel-2a (ASIC2a)/ASIC2b heteromeric sour-taste receptor channel, J. Neurosci. 23 (2003) 3616–3622.
[90] J. Chandrashekar, C. Kuhn, Y. Oka, D.A. Yarmolinsky, The cells and peripheral representation of sodium taste in mice, Nature 464 (2010) 297–301.
[91] S. Kellenberger, L. Schild, Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure, Physiol. Rev. 82 (2002) 735–767.
[92] V. Lyall, G.L. Heck, A.K. Vinnikova, S. Ghosh, T.H. Phan, R.I. Alam, et al., The mammalian amiloride-insensitive non-specific salt taste receptor is a vanilloid receptor-1 variant, J. Physiol. 558 (2004) 147–159.
[93] S. Iiyama, M. Yahiro, K. Toko, Measurements of soy sauce using taste sensor, Sens. Actuators B Chem. 66 (2000) 205–206.
[94] K. Wang, J.A. Maga, P.J. Bechtel, Taste properties and synergisms of beefy meaty peptide, J. Food Sci. 61 (1996) 837–839.
[95] T. Ujihara, N. Hayashi, H. Ikezaki, Objective evaluation of astringent and umami taste intensities of matcha using a taste sensor system, Food Sci. Technol. Res. 19 (2013) 1099–1105.
[96] J. Zeravik, A. Hlavacek, K. Lacina, P. Skládal, State of the art in the field of electronic and bioelectronic tongues—towards the analysis of wines, Electroanalysis 21 (2009) 2509–2520.
[97] X. Cetó, F. Céspedes, M. del Valle, Bioelectronic tongue for the quantification of total polyphenol content in wine, Talanta 99 (2012) 544–551.
[98] X. Cetó, F. Céspedes, M. del Valle, Assessment of individual polyphenol content in beer by means of a voltammetric bioelectronic tongue, Electroanalysis 25 (2013) 68–76.
[99] C. Medina-Plaza, J.A. de Saja, M. Rodriguez-Mendez, Bioelectronic tongue based on lipidic nanostructured layers containing phenol oxidases and lutetium bisphthalocyanine for the analysis of grapes, Biosens. Bioelectron. 57 (2014) 276–283.
[100] K. Kurihara, Y. Katsuragi, I. Matsuoka, M. Kashiwayanagi, T. Kumazawa, T. Shoji, Receptor mechanisms of bitter substances, Physiol. Behav. 56 (1994) 1125–1132.
[101] T. Haraguchi, T. Uchida, M. Hazekawa, M. Yoshida, M. Nakashima, H. Sanda, et al., Ability of food/drink to reduce the bitterness intensity of topiramate as determined by taste sensor analysis, Chem. Pharm. Bull. 64 (2016) 14–20.
[102] Y. Miyanaga, J. Mukai, T. Mukai, M. Odomi, T. Uchida, Suppression of the bitterness of enteral nutrients using increased particle sizes of branched-chain amino acids (BCAAs) and various flavours: a taste sensor study, Chem. Pharm. Bull. 52 (2004) 490–493.