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An overview of an artificial nose system

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ABSTRACT

The present review describes recent advances in the development of an artificial nose system based on olfactory receptors and various sensing platforms. The kind of artificial nose, the production of olfactory receptors, the sensor platform for signal conversion and the application of the artificial nose system based on olfactory receptors and various sensing platforms are presented. The associated transduction modes are also discussed. The paper presents a review of the latest achievements and a critical evaluation of the state of the art in the field of artificial nose systems.

1. Introduction

With thousands of years of evolution, humans can perceive and discriminate numerous odors through their olfactory systems [1]. This specific smell perception is triggered by a binding event between odorants and olfactory receptors expressed on the surface of olfactory neurons in the olfactory region [2,3]. Once certain odorants bind with specific odorant binding proteins, the olfactory signal cascade is activated and olfactory signals are subsequently generated. As is shown in Fig. 1, the olfactory receptor proteins are linked to guanine nucleotide-binding protein, G-protein. When the odorants bind to the olfactory receptors, this induces a change in the shape of the olfactory receptor. Thus, the modification in the structure of the receptor induces their binding to the G-protein. The G-proteins are comprised of three subunits: the alpha (α) subunit being the active subunit, beta(β) and gamma (γ). In the absence of a signal, the α subunit binds to guanine diphosphate (GDP). When activated by an odorant, the olfactory receptor couples with G-protein and GDP is replaced by guanine triphosphate (GTP). Once GTP is bound to the olfactory receptor, the α subunit protein dissociates from the β and γ subunits and attaches to the enzyme adenylyl cyclase (AC). AC converts adenosine triphosphate (ATP) into cyclic-3', 5'- Adenosyl monophosphate (cAMP). cAMP is a neurotransmitter. As the intracellular concentration of cAMP increases, it acts as a hormone and moves through the cell cytoplasm, activating the gated ion-protein channel (cyclic nucleotide-gated, CNG channel) which permits the entry of extracellular inorganic ions (Na+ and Ca2 +) and transmits the impulse. The result is the generation of an action potential in the receptor and the depolarization of the axon. Then, the generated signal is directed to the non-biological element where it is converted to an electrical signal. Finally, the signals are transmitted to the brain and humans become aware of the characteristics of odors such as quality and intensity [4–6]. Smell perception is basically derived from the odorant-discriminating ability of olfactory receptors [7]. In the case of humans, around 390 kinds of functional olfactory receptors exist and these receptors can recognize odorants with some specificity (although one receptor can be activated by different odorants, and one odorant can stimulate several receptors). Their responses combine following a combinatorial code. Investigations into odor perception at the gene and protein levels, published by Richard Axel and Linda Buck in 2004 [8], clearly explained the process of reading odor information by the brain. The results of those investigations have shown that the rhinencephalon is one site which is responsible for odor discrimination. Human genes coding particular receptor proteins are responsible for the interception of odorous substances. Differences in the structure of these proteins determine their interaction with different odorants. The aforementioned scientists, during independent investigations, revealed that in each cell there was only one type of chemoreceptor. Thousands of olfactory genes were discovered which belong to the rhodopsin-like family, each of them determining the formation of a particular olfactory receptor which reacts to a given chemical substance. The olfactory receptor gene superfamily is the largest in the human genome. A single odorant activates different types of receptor and at the same time a single receptor can be activated by several odorous substances. In this way numerous

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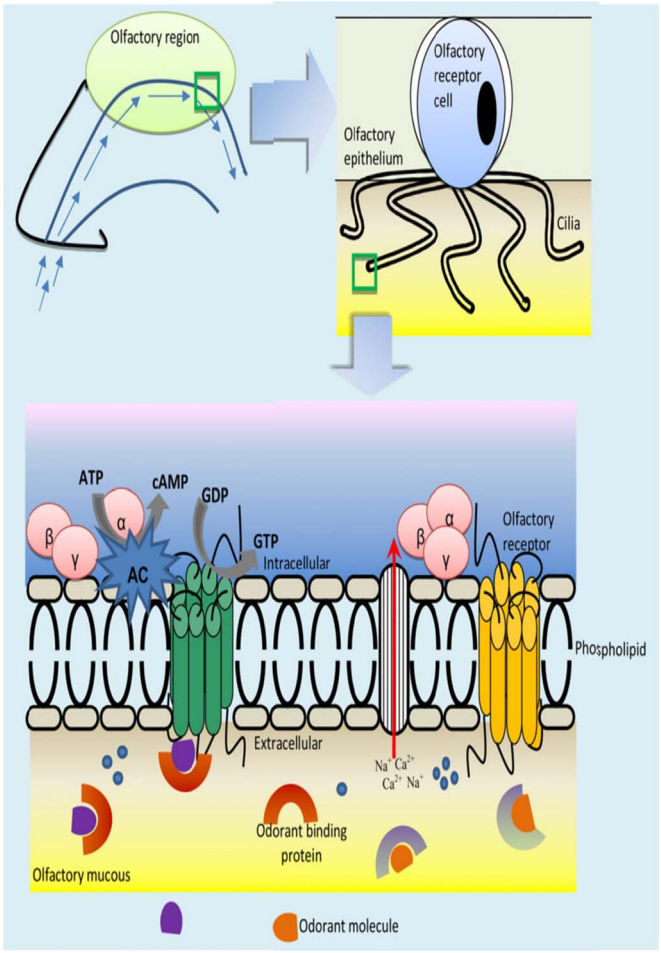

Fig. 1. Structure and mechanism of human olfactory system (AC—adenylyl cyclase) .

combinations of the activated receptors are formed, which are believed to be a unique property of the brain [9]. Thus when biological signals from olfactory receptors are transduced into perceptible signals such as electrical or optical signals, the identification of specific odors is possible without the aid of the natural nose [10]. Olfactory receptors are produced from Escherichia coli, Saccharomyces cerevisiae, virus and mammalian cell systems. Then, they are used for the functionalization of nanotube-based field-effect transistors, optical and electrochemical platforms. Olfactory receptors can recognize target molecules with relatively good selectivity and generate biological primary responses. These responses are transduced and amplified in the secondary sensor parts. This strategy facilitates the development of a sensitive and selective artificial nose that mimics human olfaction. The devices developed can be effectively applied in many practical fields.

2. Artificial nose

2.1. Electronic nose

Various types of device called electronic noses have been and are still being developed [11–13]. These sensors are based on chemical adsorption methods rather than biological mechanisms [14,15]. Common electric noses are fabricated as arrays of several sensors providing physical or chemical responses. Such devices discriminate odors through analyzing the response pattern of the sensors [16]. However, they have critical limits [17] to their application in practical fields [18,19]. First, their sensitivity is insufficient. The human nose has been reported to detect odorants at concentrations lower than the ppt level in olfactory sensory tests, whereas electronic nose sensitivity was mainly in the ppm or ppb range [20]. Moreover, electronic noses could not specifically distinguish one odorant within a mixture of odorants. Overall, electronic noses cannot fundamentally mimic biological olfaction because olfactory receptors are not used [21].

2.2. Bioelectronic nose

A bioelectronic nose is based on olfactory receptor proteins or cells expressing olfactory receptors on their surface [22–26]. Olfactory receptors act as odorant-recognition elements, and combine with sensor devices to convert biological signals to electrical or optical signals. Because olfactory receptors provide the odorant-discriminating ability [27], the bioelectronic nose can closely mimic the animal olfactory system. The concept of odorant analysis using a bioelectronic nose is fundamentally different from the odor-discriminating strategy of electronic noses based exclusively on pattern recognition using sensor arrays [17]. Instead, when the olfactory receptors are utilized as a primary sensing material, the sensors benefit from their own selectivity towards the odorants [28,29] and can precisely distinguish a target molecule in a mixture, similarly to the human nose [30,31]. In addition, sensors based on olfactory receptors are more sensitive than electronic noses. The limit of detection reaches a femtomolar range in liquid conditions [32] and ppt range in gaseous conditions [33], a sensitivity similar to that of the animal nose [34]. By virtue of these excellent characteristics, such as precisely distinguishing a target molecule in a mixture, the low limit of detection in liquid conditions and so on, bioelectronics nose will be readily applied in different fields such as the disease diagnosis [35–37], the food safety assessment [38,39], and the environmental monitoring [40].

Differences and similarities in the structure of the human nose, electronic nose and bioelectronic nose are presented in Fig. 2 [17].

3. Production of olfactory receptors

3.1. Mammalian cells

The bottleneck in the development of an olfactory receptor-based artificial nose is the production of olfactory receptors. It is very difficult to culture olfactory sensory neurons [41]; moreover, the expression level of olfactory receptors in them is also very low. Thus, several attempts have been conducted to achieve functional expression in various heterologous systems [42–44]. Of these various systems, human embryonic kidney (HEK) − 293 cells [45] showed especially high expression levels [46,47]. Also, these cells contain all of the essential proteins for signal transduction such as G proteins [48,49], adenylyl cyclases [50], and ion channels [51]; hence, they have been broadly used for the expression of olfactory receptors. In addition, modification of HEK293 cells with 3 transmembrane proteins (RTP1, RTP2 and REEP1) promotes functional cell surface expression [52].

3.2. Escherichia coli

It is known that membrane proteins including olfactory receptors are difficult to express in bacterial cells due to their complicated structure and strong hydrophobicity. However, it has been proved that the mass production of olfactory receptors is possible when pDEST15 plasmid is used as a transformation vector. In addition, these proteins could be easily purified with surfactants such as Triton X-100 and sarcosyl sulfate [53–56].

3.3. Saccharomyces cerevisiae

It has been demonstrated that *S. cerevisiae* yeasts constitute an efficient means to heterologously express mammalian olfactory receptors (ORs). The advantage is that yeast cells withstand low temperature (15 °C), which probably improves OR folding and trafficking to the