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Bioelectronic Noses Based on Olfactory Receptors

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1. Introduction

The discovery and characterization of the great multigene family encoding olfactory receptors has led the way to both fundamental and biotechnological investigations. Human and animal noses can perceive more than a hundreds of thousands of odorant molecules. Detection of different odors results from the association of the odorant molecules with olfactory receptors, carried by olfactory sensory neurons. Only a subtle difference in the molecular structure of an odorant can lead to pronounced modification in odor quality, due to the complex olfactory coding. These features have made the development of an artificial odor-sensing system, that is the bioelectronic nose challenging for research. Bioelectronic noses may have many potential applications in different fields of food and beverage, cosmetics and environmental monitoring, disease diagnostics...

Several biosensor concepts for odorant detection using different olfactory receptors have been published. Some of them are based on the direct immobilization of the olfactory mucus, or of various whole cells expressing olfactory receptors. Another type of sensors is based on immobilized cellular membrane fractions carrying olfactory receptors. The recognition of the odorant by such olfactory sensing elements can be detected by surface plasmon resonance, quartz crystal microbalance, or by direct electrochemical measurements. Here, a brief overview of different bioelectronic noses will be given.

2. Bioelectronic nose development

Odorant detections by terrestrial vertebrates have evolved to meet the numerical and physical challenges since olfactory systems operate over a dynamic range of several orders of stimulus magnitude and can recognize an enormous array of low to medium molecular weight organic molecules. Theoretically, there is no limit to the number and variety of compounds that can be considered odorant and that can be detected by some animal olfactory system. Humans, for example, are thought to be capable of distinguishing more than hundreds of thousands of distinct odor molecules. Subtle alternations in the molecular structure of an odorant can lead to pronounced changes in the perceptive odor. How are the diversity and specificity of olfactory perception accomplished? The detection and discrimination of chemically distinct odorants results from the association of odorous ligands with specific olfactory receptors expressed on the cilia of olfactory neurons that are located in a specialized epithelium in the nose. Olfactory receptors belong to the large super

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family of G protein coupled receptors (Mombaerts, 2004). The activated receptor interacts with the G protein which mediates the signaling cascade transmission to olfactory bulb, where olfactory signals are processed before reaching cortical structure in the brain (Firestein, 2001). Each olfactory receptor can recognize a range of odorants that share specific molecular characteristics. Their responses can vary along multiple odorant structural dimensions allowing discrimination of odorants with different molecular shapes and sizes, functional groups, charge, hydrophobicity, atomic composition and even concentration. The olfactory system utilizes an encoding mechanism in which a combination of activated olfactory receptors determines the odor quality. Functional analyses of structurally similar receptors that recognize overlapping sets of odorants with distinct ligand specificity and affinity have confirmed this combinatorial receptor code model (Firestein, 2001; Buck, 2004; Mombaerts, 2004).

Sensory evaluation is one of the important parameters for air quality monitoring, quality assessment for food, wine and beverages, as well as for control of many cosmetic and fermentation products. Furthermore, odors can constitute a signature of metabolic stress and diseases (tuberculosis, schizophrenia, diabetes, etc). Odors are associated with drugs and explosives or with domestic and environmental pollutants. Typically, sensory evaluation of odor is performed by a panel of well-trained professionals based upon their sense of smell, taste, experiences and mood. Likewise, trained dogs, rats or bees are employed to detect drugs or explosives. Within the clinical field, trained dogs and rats are also used for detection of some odors associated with different pathologies or with physiological states (Turner & Magan, 2004). Many efforts have been made to replace humans and animals by analytical instrumentations for odorant detection. Unfortunately, current electronic noses have significant limitations in odor detection concerning sensitivity, reliability and selectivity, among others. Typically, artificial electronic noses have as a recognition part metal oxide semiconductors, conduction organic polymers, porphyrins, or calixarenes (Harper, 2001). Their limitations are at the basis of persistent difficulty of this technology to reach essential applications in different areas. One possibility to overcome these limitations is replacing the physical and chemical sensitive elements of electronic noses with natural olfactory receptors. This results in bioelectronic noses. Due to the pharmacological profile of olfactory receptors, bioelectronic noses would provide detection and identification of specific odorants at even very tiny or trace amounts, large operational availability and fast and reliable detection. For instance, traditional electronic noses usually have concentration thresholds up to 0.1 ppb, while animal olfaction displays much lower detection limits down to 10^{-6} ppb, or even lower.

3. Olfactory receptor preparations and their sensor integration

Despite intensive efforts to determine the pharmacological profile and odorant specificities of individual olfactory receptors, until now, response specificities to odorants have been examined in detail only for a few receptors. The main reason of such lack of knowledge is that these studies are difficult to be undertaken in the olfactory epithelium since individual sensory neurons mainly express a single type of olfactory receptor out of several hundreds of olfactory receptor genes in the genome (Mombaerts, 2004). Moreover, there are inherent difficulties associated with the expression of olfactory receptors in heterologous cell lines (Lu et al., 2003; McClintock & Sammeta, 2003), which have enabled the use of recombinant

receptors for pharmacological and biophysical studies. In consequence, until now, most bioelectronic noses have been developed for only a few olfactory receptors (rat receptor 17, human OR17-40, *C. elegans* ODR-10, human 2AG1). These receptors served as models to prove the feasibility of the bioelectronic nose concept since their preferential odorant ligand and working concentration ranges are known.

One of the major challenges for achieving the bioelectronic nose are sample preparation and immobilization onto a sensor solid surface. Since they are G protein coupled receptors, olfactory receptors need to stay in their membrane environment to be functional. So, the first bioelectronic nose was based on the direct immobilization of the olfactory cilia, or of various whole cells expressing olfactory receptors. A second type of sensor has been achieved using semi-purified receptor preparations such as membrane fractions carrying them. Such olfactory receptor preparations can be integrated into a sensor either by simple adsorption or by capturing via its specific antibody previously attached to the surface. By the adsorption method, olfactory receptors are bound to the sensor surface indirectly, through the interaction of their surrounding hydrophobic lipids with the substrate. In consequence, the receptor binding site is free and remains accessible for odorants. However, with adsorption, olfactory receptors are immobilized in a random orientation in relation to the sensor surface. In contrast, when the olfactory receptor is poorly expressed in the membrane fraction the second method is more adequate since specific receptor grafting increases receptor surface concentration and ensures its uniform surface orientation.

4. Bioelectronic noses based on whole cells expressing olfactory receptors

In 1999, Wu immobilized a crude bullfrog cilia preparation onto a piezoelectric electrode which served as a signal transducer. Using this biosensor he was able to detect trace levels of various odorants with concentrations fully correlated with the olfactory threshold values of human noses. Similarly, Liu et al., (2006) showed that the bionic designed hybrid system composed of olfactory receptor neurones and olfactory bulb neurones cultivated on the surface of a light-addressable potentiometric sensor can be used as a novel bioelectronic nose. Indeed, this device was sensitive to environmental odor changes.

Wu (1999), also partially fractioned olfactory receptors from the cilia preparation and coated them separately onto the crystal surface. A quartz crystal microbalance was used for detecting the binding of odorant molecules to the olfactory receptors. This method can be successfully applied for odorant detection, since odorant molecules binding to the receptors coated onto the crystal alters the resonance frequency of the crystal. An array made of six sensors consisting of five different cilia fractions was able to rapidly and stably detect responses to different volatile compounds. However, since olfactory receptors in these fractions were separated by gel filtration chromatography with respect only to their molecular weights it was inevitable that each fraction contained a mixture of various receptors.

To apply an olfactory whole-cell biosensor for checking ligand specificity of a particular olfactory receptor, heterologous cells expressing one type of receptor should be employed. For instance, mammalian HEK cells transfected to express rat receptor 17 were coated onto the crystal of a quartz microbalance (Sung et al., 2006). Their stimulation by one of the receptor 17 preferential ligands, octanal, produced strong and dose-dependent sensor responses. This device did not respond to several other odorant non-ligands. This work

suggested that bioelectronic noses can be applied for the quantitative measurements of odorants.

Similarly, the same authors heterologously expressed *C. elegans* olfactory receptor ODR-10 in HEK cells and applied the Surface Plasmon Resonance (SPR) technique to characterize molecular interactions (Lee et al., 2006). HEK cells were seeded on the sterilized bare gold sensorchip surface previously treated with poly-lysine to allow their good adherence to the gold substrate. The activation of the transfected cells by the receptor ligand diacetyl induced an increase in the intracellular calcium ions, which subsequently resulted in the SPR signal change. Moreover, the SPR signal increase was proportional to the diacetyl concentration. This cell-based SPR method was proposed to have a potential application in the identification of odorant ligands specific to each olfactory receptor in a real-time manner and without any labeling.

Our team has shown the feasibility of a bioelectronic nose based on whole yeast cells expressing human receptor OR-1740 immobilized onto an interdigitated thin film microelectrode (Marrakchi et al., 2007). When yeast cells attached to the gold microelectrode surface pre-treated with poly-lysine solution were stimulated with the receptor ligand helional it was possible to detect conductometric changes due to the ionic exchanges resulting from the recognition of the ligand molecule by the olfactory receptor. *S. cerevisiae* yeasts are more convenient than mammalian cells for olfactory receptor expression since they are much cheaper and easier to cultivate. In addition, *S. cerevisiae* has been successfully used for functional expression of many G protein coupled receptors including olfactory receptors (Pausch, 1997, Minic et al., 2005a) which is one of the major difficulties in olfactory sensor development. In addition, yeasts provide a null background for mammalian G protein coupled receptors (Minic et al., 2005a), thus allowing the correct pharmacological characterisation of receptors. Indeed, specificity, selectivity and dose-response to helional obtained with immobilized yeast carrying OR1740 receptor suggested that this conductometric biosensor preserves the natural receptor characteristics of odorant recognition (Marrakchi et al., 2007).

It should also be noted that modified yeast cells in solution may serve as a biosensor. Functional similarities between the signal transduction cascade of olfactory receptors in mammalian neurons and the pheromonal response pathway in yeasts allows the development of the yeast cell-based biosensor for odorant screening. Such systems are easily adaptable for a high throughput format (Minic et al., 2005a). Upon stimulation of the olfactory receptor by its odorant ligands in yeasts engineered to co-express either rat I7 or human OR 17-40 receptor and the mammalian G α subunit, an activation of a MAP kinase signaling pathway takes place, which induces the synthesis of a functional reporter luciferase (Minic et al., 2005b). In that way bioluminescence responses are detected upon odorant binding to the receptor. This assay enables the quantitative measurement of receptor activity, or alternately the detection of its odorant ligands. In one previous study yeasts were modified to provide odorant-dependent yeast growth on histidine-deficient or hygromycin-containing medium, respectively (Pajot-Augy et al., 2003; Minic et al., 2005a). Such assays are commonly used by pharmacological laboratories for ligand screenings of non-olfactory G protein coupled receptors. However, luciferase is the more convenient reporter because of its sensitivity, rapidity and easy to perform enzymatic reaction.

Using whole cells as biological recognition elements in bioelectronic noses provides the opportunity to elicit full functional information since it necessarily involves the influence of

the cellular signaling cascade on sensor response. Whole cell systems have, thus, possible applications in the fields of pharmacology, cell biology, toxicology and environmental measurements (Keusgen, 2002; Bousse, 1996).

5. Bioelectronic noses based on partially purified olfactory receptors

When analytical information is needed instead of functional information, it is more adequate to use isolated biological molecules as recognition parts in biosensors. This second approach allows developing specific analytical devices for fast routine measurements in many fields of analysis. Moreover, using isolated olfactory receptors instead of whole-cells enables scaling down the biosensors and their convergence with micro- and nano-technologies.

The first requirement to develop such bioelectronic noses is the immobilization of receptors in a manner to preserve their function. As mentioned before, olfactory receptors are extremely hydrophobic and require a lipid or detergent environment to maintain their native conformation and function. Usually membrane receptors are expressed in heterologous cells, solubilized and purified in an adequate detergent before being reconstituted in proteoliposomes and immobilized onto the sensor (Minic et al., 2005c). However, olfactory receptors are poorly expressed in heterologous cells and, so, their purification before reconstitution typically cannot be considered. Consequently, producing lipid vesicles by disturbing the membrane of the cells where receptors have been expressed seems to be a better strategy. In this way, the receptor remains in its native membrane environment which obviates the risk of receptor alternation or activity loss, which may occur when G protein coupled receptors are reconstituted in proteoliposomes.

Sung et al., (2006) coated the surface of a quartz crystal microbalance with crude insoluble membrane extract of *E. coli* expressing the ODR-10 receptor and examined its interactions with various odorant molecules. They showed linear dose-dependent responses of the piezoelectric biosensor upon the membrane extract stimulation with natural receptor ligand diacetyl. Using a similar set-up but with the rat olfactory receptor I7 specifically captured on a quartz microbalance transducer, Rodriguez Segui et al., (2006) explored the first step toward the production of a quartz microbalance olfactory sensor. For this, a self-assembled multilayer was grafted onto the sensor surface. It was composed of a mixed MHDA - Biotinyl PE self-assembled monolayer and a biotin-avidin bridge system which allows binding of biotinylated antibodies. In the final step, the receptor specific biotinylated antibody was used to bind a membrane fraction carrying receptor I7 to the quartz crystal.

In one recent study, the membrane fraction carrying human olfactory receptor 2AG1 was covalently integrated by amino-link to conducting polymer nanotubes functionalized with carboxylic acid (Yoon et al., 2009). Nanotubes were then attached to a microelectrode array to create a field-effect transistor, which generated changes in electrical signal when odorant molecules activated the receptor protein. Through the miniaturization of the sensor, the signal was efficiently transferred to the nanotubes due to the covalent attachment. The bound receptor detected a femtomolar concentration of its natural ligand amyl butyrate. Related esters that differ from the ligand molecule by a single carbon atom (butyl and hexyl butyrates), produced no response at a billion times higher concentration. This good selectivity suggests that the receptors remain in good conformational shape after being grafted which is very promising.

We developed a surface plasmon resonance bioelectronic nose in our laboratory in Jouy-en-Josas. Small membrane fragments (nanosomes), obtained from cells expressing a given olfactory receptor can be easily immobilized on commercial L1 Biacore sensorchips. We demonstrate that olfactory receptors maintain their activity in such membrane fragments (Vidic et al., 2006). Since the surface plasma resonance signal is proportional to the molecular weight of the analyte, low-molecular weight molecules, as the majority of odorants, cannot be detected directly by the Biacore3000 system. To overcome this problem, we took advantage of the presence of G protein in the nanosomes to monitor receptor activation by an odorant, through the departure of the G_{α} subunit from the preparation (Vidic et al., 2006). The same bell-shaped concentration-dependence responses were obtained as in a whole cells, in terms of threshold concentration and concentration at the maximum, which gives evidence that this receptor functional response in the living cell indeed arises from its own behavior upon odorant stimulation, with no artefactual contribution from the cellular transduction pathway. As assessed by surface plasmon, resonance responses monitoring olfactory receptors efficiently discriminate between odorant ligands and unrelated odorants.

This system can fruitfully serve to evaluate the comparative coupling efficiency of olfactory receptors to various G_{α} protein subunits, without the interference of cellular contribution (Vidic et al., 2006). Furthermore, this new bioelectronic nose can be applied for the fundamental investigation of molecular mechanisms of olfaction. Indeed, it is assumed that the first event in peripheral olfactory detection involves at least 3 partners: olfactory receptor, odorants and olfactory binding protein (OBP). Whole yeast cell expressing an olfactory receptor cannot be applied for investigation of receptor-OBP interaction because their cell wall impairs OBP penetration. However, a bioelectronic nose based on nanosome expression of a given olfactory receptor was successively applied for characterization of this three-partner reaction (Vidic et al., 2008). Interestingly, such a study showed that the presence of OBP enhanced odorant detection sensitivity of the device.

6. SPOT-NOSED prototype of olfactory nanobiosensor

In 2003, the European project SPOT-NOSED began with the aim to develop nanobiosensors based on single olfactory receptors anchored between nanoelectrodes, in order to mimic the performances of a natural olfactory system. The next step was to create arrays of nanobiosensors that could then increase odorant sensitivity and/or widen the odorant detection spectrum. For this, two model receptors, rat I7 and human OR 17-40, were expressed in *S. cerevisiae* yeast (Minic et al., 2005a). Then, lipidic nanosomes bearing the olfactory receptors were prepared from the yeast. Nanosomes are small vesicles (50-100 nm in diameter). They can be obtained by cell disruption, purification of membrane microsomes and then by size homogenization and miniaturization of microsomes by extensive sonication (Vidic et al., 2006; Casuso et al., 2008). Each of this nanometric vesicular structure was shown to contain one or few receptors of the given type (Casuso et al., 2008; Vidic et al., 2007). The maintenance of nanosome homogeneity in the solution suggested that they can be used as a recognition part in an elementary nanobioelectronic sensor (Casuso et al., 2008; Vidic et al., 2006; Gabriel et al., 2006).

Next, surface plasmon resonance was performed on nanosomes for quantitative evaluation of olfactory receptor responses to odorant stimulation. These tests strongly suggested that

olfactory receptors in nanosomes retain their full activity (Vidic et al., 2006) since they discriminated between odorant ligand and unrelated odorants, as previously shown in whole yeast cells with a reporter gene (Vidic et al., 2006; Vidic et al., 2008). This finding led to the use of nanosomes in nanobiosensor fabrication.

Nanoelectrodes were fabricated using conventional photolithography and focused ion beam milling, with sizes in adequation with the nanosomes. In order to optimize nanosome functional immobilization on them, several immobilization methods were checked on milli- and micrometric scale. Functional responses were observed when nanosomes were simply adsorbed on the hydrophobic surface (Hou et al., 2006; Vidic et al., 2006; Benilova et al., 2008; Vidic et al., 2007) or when the receptor was captured by its specific antibody previously grafted to the sensor surface (Hou et al., 2006; Benilova et al., 2008). To further determinate optimal surface orientation of the receptor, various tagged OR17-40 were produced in yeast. The intensity of the specific response was particularly enhanced when nanosomes were captured via an antibody to the tag attached to the receptor C-terminal (Vidic et al., 2007). Strikingly, capturing the OR 1740 receptor via its tag attached to the N-terminus abolished functional responses upon odorant ligand stimulation. This probably originates from steric hindrances to the odorant binding due to the immobilization of the receptor N-terminus.

Thus, in the final device configuration, nanosomes bearing olfactory receptors tagged on their C-terminal were specifically immobilized onto conducting substrates via a self assembled monolayer containing biotinyl groups. Biotinyl groups were used to attach neutravidin and specific anti-tag antibodies to allow receptor specific grafting (Hou et al., 2006; Vidic et al., 2007; Benilova et al., 2008). The process was optimized by microcontact printing, and the anchored nanovesicles were visualized by Atomic Force Microscopy (Vidic et al., 2007, Casuso et al., 2008). Positive and negative elastomeric polydimethylsiloxane stamps were replicated from silicon-based molds elaborated using deep reactive ion etching. Patterning was performed by inking procedures of the stamps after hydrophilization with oxygen plasma in order to ensure correct surface coverage.

Finally a direct electrochemical impedancemetric spectroscopy method can be employed to directly detect electrical changes produced by olfactory receptor conformational change induced by odorant binding (Hou et al., 2006; Benilova et al., 2008; Minic et al., 2006a, Gomila et al., 2006). The same method was successfully employed to characterize each step of electrode functionalization and nanosome grafting. For nano-scale measurements a transimpedance preamplifier suited for low-noise wide-bandwidth measurements was designed and fabricated to be directly connected to the nanoelectrodes. Also, a friendly interface with a specific odorant identification algorithm was developed.

The bioelectronic nose prototype developed during the Spot-Nosed project has shown the feasibility of an olfactory nanobioelectrical sensor. Miniaturization of structures allows integration of many sensors into arrays that may mime the animal nose and may be suitable for the screening of natural and chemical odorants as well as their combinatorial libraries.

7. Perspectives

Until now, no commercially available bioelectronic nose based on olfactory receptors has existed but they can be expected in the future thanks to the strong demand and a constant

progress made in the field. Feasibility of bioelectronic noses based on olfactory receptors has been demonstrated. The next step is to assemble devices with an autosampler, electronic data acquisition and an odorant identification algorithm. Significant advances in bioelectronic nose fabrication are constantly being made. The development of sensor technology incorporating natural olfactory receptors provides the basis for a bioelectronic nose mimicking the animal olfactory system. Such devices can be used for qualitative and quantitative identification and monitoring of a spectrum of odorants with much higher selectivity and sensibility than the present electronic devices. Thanks to the natural combinatorial olfactory code these new bioelectronic noses should provide a platform for fingerprinting of complex mixture of odorants. I am currently involved in a research project that is developing an olfactory nanobiosensor array based on immobilized nanosomes carrying olfactory receptors in order to mimic the animal nose (BOND, European project).

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