Progress in Neurobiology 93 (2011) 270–296

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Mimicking nature's noses: From receptor deorphaning to olfactory biosensing

Richard Glatz [a,b,*], Kelly Bailey-Hill [a,b]

[a] South Australian Research and Development Institute (SARDI), Entomology, GPO Box 397, Adelaide, 5001, Australia
[b] Cooperative Research Centre for National Plant Biosecurity, Australia

ARTICLE INFO

Article history:
Received 18 August 2010
Received in revised form 9 November 2010
Accepted 22 November 2010
Available online 2 December 2010

Keywords:
Bioelectronic nose
Olfaction
Olfactory biosensing
Olfactory receptors
Pheromone receptors
Receptor deorphaning

ABSTRACT

The way in which organisms detect specific volatile compounds within their environment, and the associated neural processing which produces perception and subsequent behavioural responses, have been of interest to scientists for decades. Initially, most olfaction research was conducted using electrophysiological techniques on whole animals. However, the discovery of genes encoding the family of human olfactory receptors (ORs) paved the way for the development of a range of cellular assays, primarily used to deorphan ORs from mammals and insects. These assays have greatly advanced our knowledge of the molecular basis of olfaction, however, while there is currently good agreement on vertebrate and nematode olfactory signalling cascades, debate still surrounds the signalling mechanisms in insects. The inherent specificity and sensitivity of ORs makes them prime candidates as biological detectors of volatile ligands within biosensor devices, which have many potential applications. In the previous decade, researchers have investigated various technologies for transducing OR:ligand interactions into a readable format and thereby produce an olfactory biosensor (or bioelectronic nose) that maintains the discriminating power of the ORs *in vivo*. Here we review and compare the molecular mechanisms of olfaction in vertebrates and invertebrates, and also summarise the assay technologies utilising sub-tissue level sensing elements (cells and cell extracts), which have been applied to OR deorphanisation and biosensor research. Although there are currently no commercial, "field-ready" olfactory biosensors of the kind discussed here, there have been several technological proof-of-concept studies suggesting that we will see their emergence within the next decade.

Contents

Abbreviations: BAW, bulk acoustic wave; BRET, bioluminescence resonance energy transfer; cVA, 11-cis-vaccenyl acetate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CNG, cyclic nucleotide gated; EAG, electroantennagram; EOG, electroolfactogram; EIS, electrochemical impedence spectroscopy; EG, eugenol; EC_{50}, half maximal effective concentration; FET, field-effect transistor; FLIPR, fluorescence imaging plate reader; FRET, fluorescence resonance energy transfer; GC–MS, gas chromatography–mass spectrometry; G-protein, guanine nucleotide binding protein; GPCR, G-protein coupled receptor; Gα, the alpha subunit of the G-protein; Gβ, the beta subunit of the G-protein; Gγ, the gamma subunit of the G-protein; GDP, guanine diphosphate; GTP, guanine triphosphate; GTPγS, non-hydrolysable GTP; GFP, green fluorescent protein; IP_3, inositol triphosphate; LAPS, light-addressable potentiometric sensor; MEA, microelectrode array; OR, olfactory receptor; OSN, olfactory sensory neuron; OBP, olfactory binding protein; QCM, quartz crystal microbalance; SAM, self-assembled monolayer; SAW, surface acoustic waves; SNMP, sensory neuron membrane proteins; SPR, surface plasmon resonance; swCNT, single-walled carbon nanotube.

* Corresponding author at: South Australian Research and Development Institute (SARDI), Entomology, GPO Box 397, Adelaide, 5001, Australia. Tel.: +61 8 83039539; fax: +61 8 83039542.
E-mail address: Richard.Glatz@sa.gov.au (R. Glatz).

0301-0082/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2010.11.004

1. Introduction

One of the great success stories of biological research has been the discovery of important genes and the functional characterisation of their encoded proteins, which directly regulate the higher order biological processes that we witness daily. Olfaction is a prime example; the discovery of the gene family encoding vertebrate olfactory receptors (ORs) (Buck and Axel, 1991) has led to a relatively detailed understanding of the molecular and neurological bases for how organisms can "smell" volatile compounds. Since the first successful attempt to match an OR to a volatile ligand (Zhao et al., 1998), numerous ligand-binding assays have been developed and used to deorphan a range of ORs (see review by Touhara, 2007). These assays have generally utilised cells expressing recombinant ORs combined with a transduction (reporting) system that allows detection of OR:ligand binding, initially for the purpose of research into olfaction mechanisms. However, the ability to detect volatile ligands at biologically relevant concentrations (approximately nanomolar and below) is crucial for an enormous range of applications, a fact that has seen the expansion of a relatively new field of research, olfactory biosensing. This research has generally utilised characterised OR:ligand interactions to validate a range of sensor platforms and transduction approaches to produce an olfactory biosensor (Lee and Park, 2010). Biosensor research is therefore generally application-driven rather than being driven by pure biological research, with a focus on detection of important ligands in complex environments.

A biosensor can be described as a biological detector or recognition element (e.g. an OR for olfactory biosensing) linked to a physical transduction system (e.g. optical, electrochemical). This definition, however, is rather broad and for olfactory biosensors (also known as bioelectronic noses), could include the use of whole animals or tissues as the biological recognition element. As an example, the use of canaries to detect carbon dioxide in mining applications is legendary (Schmidt, 2009). Dogs have also been widely utilised for detecting people, narcotics or explosives (Furton and Myers, 2001) and it is known that they utilise at least 2-ethyl-1-hexanol and 2,4-dinitrotoluene as cues to detect the latter (Harper et al., 2005). Yale University School of Medicine maintains a website related to use of whole animals as sentinels for human diseases and toxins (http://canarydatabase.org).

Tissue-specific olfactory biosensors have also been produced. Such approaches, such as the electroolfactogram (EOG, for vertebrates) and electroantennogram (EAG, for invertebrates) have been utilised for decades and did not require any knowledge of molecular biology for their implementation (Scott and Scott-Johnson, 2002; Sevonkaev and Katz, 2008). While whole animal and tissue-based recognition elements both utilise ORs for detection at the molecular level, the ability to isolate cells expressing specific ORs or partially purified ORs themselves, has altered the perception of a biosensor to mainly encompass sub-tissue level recognition elements. The use of cells, cell extracts or purified ORs as recognition elements, has a range of advantages such as the level of miniaturisation (and potential transportability) that can be achieved, and the ability to design and control recognition elements to perform specific reporting functions or provide multiplexing. Here we will mainly discuss in detail those olfactory biosensors based on sub-tissue level recognition elements as this is where the main research efforts are directed and where the key advances are being made. In addition, we cover both biosensors used purely for research (e.g. OR deorphaning) and those developed for specific field-based applications or to refine transduction systems using characterised receptors. Both utilise similar technology, albeit for potentially different applications.

This paper reviews the history and developments in the specific area of olfactory biosensors (detecting volatile compounds), however, researchers are developing a much broader range of biosensors that utilise different biological recognition elements. For those interested in biosensing more generally, there are a good number of books and reviews covering the field (Borisov and Wolfbeis, 2008; Cooper and Cass, 2004; Cooper and Singleton, 2007; Knopf and Bassi, 2007; Leifert et al., 2009; Luong et al., 2008; Malhotra et al., 2005; Nakamura and Karube, 2003; Rasooly, 2005; Singh, 2007). While we do deal with some aspects of the detailed mechanisms underlying olfaction, we do not cover this exhaustively, and for further reference a number of detailed reviews have been published on the topic (Chesler and Firestein, 2008; Kaupp, 2010; Nakamura, 2000; Nakagawa and Vosshall, 2009; Silberling and Benton, 2010; Song et al., 2008; Su et al., 2009; Tall et al., 2003; Touhara and Vosshall, 2009; Wicher, 2010). This review aims to provide a glimpse of where these two general areas intersect as olfactory biosensing, with key concepts and techniques discussed.

1.1. Why biosensors?

There is speculation with regard to the worth of biosensor research (Kissinger, 2005), in particular, the applications of the research and the accessibility of alternatives to a "bio"-based sensor. The area of volatile detection is potentially a highly valuable area of biosensor research primarily because the ORs used as biological detectors are orders of magnitude more sensitive in detecting their respective ligands than the most advanced physical approaches such as chemical "noses" or gas-chromatography/mass spectrometry (GC–MS). There is also an extremely diverse range of applications to which a sensitive and specific olfactory sensor could be applied; a few examples include non-invasive disease diagnostics, process monitoring and quality assurance in the food and wine industries, agricultural and environmental monitoring, and detection of biowarfare agents and explosives for security purposes.

Alternative real-time methods to sense volatiles come in the form of electronic/chemical "e-noses", which include conducting polymers and electrochemical sensors (Wilson and Baietto, 2009). As mentioned, a key benefit of bio-based sensors, as opposed to these e-noses, mainly lie in sensitivity and also specificity, however, they are currently limited by the relative lack of stability of the biorecognition element under "field" conditions and lack of transportability. Other alternatives involve the use of a whole organism, however, this approach is not practical or applicable in many targeted applications; the shortcomings of these approaches has driven research towards development of small, tuneable, accurate and fast biosensing devices that maintain the sensitivity inherent in whole organisms, and is worthy of the commercial