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Unravel the Secret of Olfaction

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As a special sense, olfaction is an inherited biologic function to monitor our environment. This sense alerts us to dangerous situations such as gas leaks or fires, and provides cues to the freshness of food. Smell is tightly associated with flavor and taste, and therefore smell and taste loss frequently occur simultaneously. Olfactory stimuli evoke emotions and memories that are related to the neighbouring brain circuits of the amygdala and hypocampus [1,2]. Animals use this sense to avoid predators, while searching for food and evaluating potential sex-partners. Therefore, sense of smell is the primitive brain function and the first door to understand brain sciences.

The olfactory epithelium is located on the most superior structures of the nasal cavity at the cribriform plate, superior turbinate, and superior septum [3]. Olfactory epithelium consists of multiple functional cells such as 1) olfactory receptor cells (chemoreceptors and bipolar neuron cells) transmitting signal to the brain, 2) supporting cells (sustentacular cells) that provide metabolic and mechanical support, 3) basal cells which provide a stem cell niche for olfactory tract neurogenesis, and 4) microvillar brush cells that are part of the afferent trigeminal tract. In addition, the Bowman's glands that produce mucus which contains odorant-binding proteins [4,5]. This important sensing area is susceptible to inflammation, occupational toxins, and trauma, and therefore, various mechanisms are involved in the pathogenesis of olfactory dysfunction.

Humans have about 800 gene segments analogous for odorant receptor (OR) and about half of which seem to be non-coding pseudo-genes [6]. Genomic drift, the random process of gene duplications or deletions, plays a key role for olfactory evolution. The genomic drift shapes the OR repertories of different species and also accounts for part of the interpersonal differences of functioning OR in human. Therefore, interestingly, each person detects environmental odors in a unique fashion using a different set of OR.

Olfactory mechanisms have been largely a mystery until the recent discovery of G protein coupled receptors (GPCR) by Linda Buck and Richard Axel in 1991, a breakthrough for which the two researchers were awarded the 2004 Nobel Prize for Physiology and Medicine. Their discovery showed 1) the existence of a novel family of OR genes, 2) the organization of odorant receptors in the olfactory epithelium, 3) a topographic map of the olfactory bulb, 4) combinational receptor codes for odors, and 5) mechanisms of signal conveyance in the olfactory cortex (stereotypy, divergence, and convergence). Surprisingly, vision and taste also use G-protein in their signal transduction, and G-proteins play key roles in many biologic functions such as gene expression, immunity, metabolism, and sleep. Park will discuss the mechanism of olfactory signal transduction in detail [7].

Olfactory dysfunction is a relatively common disorder caused by three etiologies such as sinonasal diseases, upper respiratory infection, and head trauma. Quantitative (hyposmia and anosmia) and qualitative (parosmia and phantosmia) olfactory dysfunction significantly decrease patients' quality of life and may affect emotion and memory. A detailed history and appropriate physical examination will be helpful to identify the underlying causes of olfactory dysfunction. In addition, simple psychophysical test (olfactory test) are essential to quantify the residual function which is the most important factor for prognosis. Psychophysiologic tests such as electroencephalography and odorant-event related potentials, and imaging study such as functional MRI are sometimes

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used adjunctively in clinical practice but they are usually performed in research setting. At now, there has been a lack of well-designed randomized control study of treatments for olfactory dysfunction. Moreover, there are no specific proven modalities for the treatment of olfactory deficit except corticosteroids in conductive olfactory loss. Cho will discuss summarized and updated information on the clinical diagnosis and treatment of olfactory dysfunction [8].

Anosmia was first reported in idiopathic Parkinson's disease in 1975 [9]. After that, olfactory dysfunction has been recognized as a prodromal and early sign of many neurodegenerative disorders such as Parkinsonian syndrome, essential tremor, motor neuron disease, Alzheimer's disease, and Huntington's chorea. These disorders have routinely been diagnosed with imaging studies such as CT, MRI, and functional MRI but they are expensive, and therefore, have limited utility to be used as screening tools. Therefore, monitoring of olfactory function in especially high risk populations will be helpful to early diagnosis. There may be an unrecognized neuroprotective role of olfaction in the prevention and treatment of neurodegenerative disorders. The pathophysiological association between olfactory dysfunction and neurodegenerative disorders will discussed by Kim [10].

There has been significant progress in the clinical diagnosis of olfactory dysfunction with the development of psychophysical (UPSIT, CCCRC, and KVSS) and psychophysiological (olfactory-event related potentials, OERP) tests, and imaging studies (CT, MRI, and fMRI). Although psychophysical testing is simple and routinely used in clinical practice, it has some disadvantages such as subjective test and an inability to diagnose malingering. Moreover, it cannot be used in children or in un-cooperative older ages. Therefore, there is an unmet need for more direct and objective olfactory test. OERP-based olfactory test can provide direct evidence of residual olfactory function. Kim et al. will discuss the technical issues concerning the measurement of OERP signal in human [11].

In line with recent brilliant developments in IT and BT technology, physical and molecular methods for clinical diagnosis have rapidly matured in recent decades. Previously, the major human sources of materials for diagnosis have been focused on blood and urine but recently methods utilizing volatile organic compounds (VOC) are highlighted. Expired breath gas is a heterogeneous mixture of nitrogen, oxygen, CO_2, inert gases, and a small fraction of VOC [12]. Some of these VOCs have been reported as potentially sensitive markers for tumors and metabolic diseases. Therefore, appropriately arrayed bio-chips (an electric or "nano-nose") can detect targeted VOC originating from specific diseases. Byun et al. will discuss the updated concept and technology regarding the "electric nose" and its application for clinical diagnosis [13].

Taste is tightly associated with olfaction and brain recognition of taste is mostly dependent on flavors from food. That means that taste is sensed largely by way of olfactory system. Many patients with olfactory deficit complain of decreased taste sensation and most cases of taste loss are associated with and/or caused by concomitant olfactory loss. Similarly to smell, taste is also a primitive biologic function and all living organisms from bacteria to human have special chemoreceptors analogous to the human taste receptors. After the first discovery of gustatory receptors in Drosophila melanogaster (2000), there has been an explosion of research in the field of taste science [14]. Lee et al. will discuss the current state of knowledge about Drosophila taste and odor chemo-senses and give us some commentary on what insights they provide in our understanding of human taste [15].

Pheromone is derived from the Greek *pherein* (convey) and *hormone* (motion). Pheromones play an essential role in the mating of animals and their detection is mediated by the vomeronasal organ (Jacobson's organ). The vomeronasal organ of humans, in comparison with many other animals, is largely resorbed during human fetal development and a vestige is located in the anterior nasal septum. However, there a number of chemically similar pheromones candidates that have noted between human and animals. Interestingly, olfactory preferences concerning the choice of potential mates in humans may be influenced by variations in immune system genes (human leukocyte antigen, HLA) [16]. Females prefer the scent of males with dissimilar HLA to their own. Pervez et al. will discuss pheromone sensing in relation to ion channels and provide understanding of our currently limited knowledge concerning the possible actions of human pheromones [17].

We discussed here many important fields on smell and taste sciences including physiology (olfaction, taste and pheromone), diagnosis (conventional and OERP tests), neurodegenerative disease, and innovating device (electric nose). These big progress will be helpful to diagnose and monitor the olfactory dysfunction and its impact on brain functions. Deep understanding on biological nose will contribute the early and precise diagnosis of anosmia, the discovery of therapeutic candidates, and also be helpful to develop novel artificial nose to be used in medical and industrial fields.

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