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Evaluation of olfactory dysfunction in neurodegenerative diseases

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ABSTRACT

It is known that the olfactory dysfunction is involved in various neurological diseases, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, Huntington's disease and motor neuron disease. In particular, the ability to identify and discriminate the odors, as well as the odor threshold, can be altered in these disorders. These changes often occur as early manifestation of the pathology and they are not always diagnosed on time.
The aim of this review is to summarize the major neurological diseases which are preceded or accompanied by olfactory dysfunction.
In addition, new instrumental approaches, such as psychophysical testing, olfactory event-related potentials (OERPs) and functional magnetic resonance imaging (fMRI) measurements, supported by olfactometer for the stimuli delivery, and their combination in evaluation of olfactory function will be discussed. In particular, OERPs and fMRI might to be good candidates to become useful additional tools in clinical protocols for early diagnosis of neurological diseases.

Contents

1. Introduction

Many factors and pathological conditions can affect the normal olfactory function. In the recent years, the smell problems are generating considerable interest in the neurological field.

Olfactory disorders are often misjudged and rarely rated the clinical setting. Nevertheless, they are described in a wide range of neurological disorders and their evaluation can be useful for diagnosis. In particular, several neurodegenerative diseases are partially associated to disorders of smell [1–3]. Indeed, severe changes in olfactory tests have been observed in Parkinson's disease (PD), Alzheimer's disease (AD) and other neurological disorders, such as multiple sclerosis (MS), Huntington's disease (HD) and motor neuron disease (MND).

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According to Acebes et al., sensory perception changes, representing often subtle dysfunctions that precede the onset of a neurodegenerative disease, may be caused by synapse loss [4].

However, a cause–effect relationship between synapse loss and sensory perception deficits is very difficult to prove and quantify due to functional and structural adaptation of neural system.

In this brief manuscript, we have reviewed the anatomy and physiology of the olfactory system, the new instrumental approaches assessing its function, and the neurological disorders to which the olfactory dysfunction is intimately associated.

2. Anatomy of the olfactory system

The olfactory system is able to detect and discriminate a great variety of volatile molecules with high sensitivity and specificity. The human olfactory system can detect tens of thousands of chemicals, many at concentrations as low as a few parts per trillion [5,6]. This function is performed through molecular, anatomical and cellular trasductional pathways that amplify, encode and integrates an enormous array of incoming olfactory information. The olfactory epithelium is located inside the nasal cavity. It includes three basic cell types: olfactory receptor neurons (ORNs), supporting cells, and basal cells. Anatomical studies, explants cultures, and post mortem biopsies of olfactory neurons from different parts of the nasal cavity show that sensory epithelium extends from the olfactory cleft down to varying degrees into the superior aspect of the medial turbinate [7]. The turbinate structures are cartilaginous ridge covered with respiratory epithelium, a non-sensory ciliated columnar epithelial tissue also populated with mucus secreting goblet cells. This structure increases the surface area available for both warming and humidifying incoming air, as well as funneling volatile chemicals up into the sensory epithelium. Human ORNs have a generally similar morphology to those of other vertebrates, although there is variation among species. The receptor cell consists of a cell body with an apical dendrite terminating in a knob containing multiple non-motile cilia. The cilia project into the mucus overlying the nasal epithelium where they have direct contact with volatile chemicals in the air. Basally, an axon projects through the cribriform plate to synapse with the dendrites of mitral cells in the olfactory bulb. The mitral cells project via the olfactory nerve (cranial nerve I) to the entorhinal cortex, as well as regions involved in emotion and memory, such as the amygdala and hippocampus. Cortical input is relayed to the hippocampus through entorhinal cortex. Several types of interneurons modulate mitral cell activity, including periglomerular cells, tufted cells and granule cells. Granule cells are dopaminergic/GABAergic interneurons involved in signal processing and modulation [8,9]. About 1000 putative odorant receptors are believed to exist and each olfactory receptor is responsive to a determinate range of stimuli. The odorant-binding leads to a depolarizing current within the cilia of the bipolar receptor cells. These cells trigger the action potentials that collectively provide the neural code deciphered by higher brain centers [10]. An immunohistochemical study [11] has compared the molecular phenotype of olfactory epithelial cells of rodents and humans, allowing the correlation between the human histopathology and olfactory dysfunction. Using a comprehensive battery of proven antibodies, the authors identified two distinct types of basal cell progenitors in human olfactory epithelium similar to rodents. The similarities of human-rodent olfactory epithelium allowed to extend our knowledge of human olfactory pathophysiology provided useful information on the status of the epithelium and its connection with the olfactory bulb (OB) [11]. The OB, that plays an important role in the processing of olfactory information, collects the sensory afferents of the olfactory receptor cells located in the olfactory neuroepithelium. The OB ends with the olfactory tract and is closely related to the olfactory sulcus of the frontal lobe.

Surprisingly, in the OB, near astrocytes, there are so-called Olfactory Ensheathing Cells (OECs). OECs are unique glia found only in the peripheral olfactory system close to axon of the first cranial nerve. They are considered promising candidate for cell-based repair following a variety of CNS lesion [12–15].

In fact, they are able to remyelinate demyelinated axon [16] and to transform into Schwam cell-like cells in their remyelinating process [17].

In humans, the perception of nasal chemical stimuli is related to multiple sensations mediated by the olfactory and the trigeminal system [18]. The brain structures involved in odor processing mainly consist of the primary olfactory cortex, which comprises the anterior olfactory nucleus, tenia tecta, olfactory tubercole, piriform cortex (PC), anterior cortical amygdaloid nucleus, periamygdaloid and entorhinal cortices [19–21].

The piriform cortex is connected to thalamus, hypothalamus, and orbitofrontal cortex (OFC). The nuclei of the thalamus have further connections towards the OFC and the insular cortex. From the enthorhinal cortex fibers lead to the hippocampus (Fig. 1).

The olfactory processes are lateralized between the hemispheres. In particular, while areas located in the right hemisphere such as the OFC and PC are more involved in memory and familiarity ratings, those located in the left hemisphere, such as OFC, insula, piriform cortex, amygdala and superior frontal cortex participate more in the emotional response to odors [22].

3. Instrumental approaches assessing olfactory function

Olfactory function can be evaluated through the use of specific instrumental approaches, including psychophysical and electrophysiological methods and neuroimaging techniques. These approaches are described below (Fig. 2).

3.1. Psychophysical methods

For the clinical assessment of human olfaction, numerous validated psychophysical tests exist. The best-validated olfactory tests include the University of Pennsylvania Smell Identification Test (UPSIT or SIT), the Connecticut Chemosensory Clinical Research Center Test (CCCRC Test) and the Sniffin' Sticks Test [23–25]. The SIT, comprising 40 different odors, is a quick self-administered easily applied test to quantitatively assess human olfaction; it has also high test–retest reliability ($r = 0.94$) [26,27]. Its scores correlate strongly with the traditional olfaction threshold detection test which uses phenyl-ethyl-alcohol [3]. The performance is quite uniform when the SIT is administered in different laboratories using a standard method [1].

The CCCRC identification test is composed of 7 olfactory stimuli (baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, and soap). Three stimuli (ammonia, Vicks VapoRub [Procter & Gamble, Cincinnati, Ohio], and wintergreen) are also presented to test trigeminal nerve nasal sensation but are not included in calculating the olfactory function test score. Ten jars, each containing 1 of the 7 odor stimuli or 1 of the 3 trigeminal stimuli, are presented, and the subject is asked to select the stimulus name from a list of odors [28].

The Sniffin' Sticks test is frequently used in Europe and normative data have been established and obtained on a group of more than 3.000 subjects [25]. This test is based on pen-like odor dispensing devices. It consists of three tests namely for odor threshold, discrimination and identification, the sum of which is defined as "TDI score". This score can give an indication of patient's olfactory performance (normosmia: $TDI \geq 30.5$, hyposmia: $TDI \leq 30.5$, functional anosmia: $TDI \leq 16.5$). During these procedures the patient cooperation is necessary.

3.2. Olfactory event-related potentials

A useful addition for the clinical diagnosis of olfactory deficits is represented by olfactory event-related potentials (OERPs). It is an electrophysiological technique which allows to observe changes in olfactory function. OERPs are the result of the sequential activation of