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REVIEW ARTICLE

Clinical importance of olfactory function in neurodegenerative diseases

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Abstract Impairments in olfactory function can be potential indicators of the onset or progression of neurological disorders. Nevertheless, olfaction is barely explored in routine clinical examination. This review provides a general idea of how olfaction is related to normal ageing and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and epilepsy, and an overview of recent studies in this field.

PALABRAS CLAVE
Olfato;
Envejecimiento;
Neurodegenerativo;
Epilepsia

Relevancia clínica de la función olfatoria en las enfermedades neurodegenerativas

Resumen Las alteraciones en la función olfatoria pueden ser indicadores potenciales del curso o inicio de enfermedades neurológicas. Sin embargo, no se le ha dado la importancia debida a la exploración de este sentido en la evaluación clínica cotidiana. Este artículo de revisión pretende proporcionar una idea general de la relevancia e impacto que tiene el olfato en las enfermedades neurodegenerativas más comunes como son la enfermedad de Alzheimer, la enfermedad de Parkinson y la epilepsia, así como investigaciones recientes en este campo.

Introduction

The sense of smell is of great importance in everyday life because it continuously informs us about our surroundings: it assesses and warns us about potential air hazards, thus

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making it a primary warning mechanism; it is the only sense that remains active during sleep; and, along with the sense of taste, it determines the taste and smell of food. There is a strong connection between smells and memory, with olfaction having a great influence on a person's emotional state.

Deterioration in olfactory function has a detrimental impact on quality of life. Impairments in olfaction have been described in preclinical stages in certain neurodegenerative diseases and may be correlated with disease progression. As a result, olfaction can be considered as a valid potential indicator of ageing brain.

Several hypotheses have been proposed to explain the relationship between olfactory function and neurodegenerative diseases, highlighting the olfactory vector hypothesis, among others.

Methodology

A review of the literature from October 2016 to February 2017 was carried out using the TRIP (Turning Research Into Practice) meta-search engine and databases such as the Cochrane Library, PubMed, Wiley Online Library and Medigraphic; sites like ScienceDirect and JoVE (Journal of Visualised Experiments) were also consulted. Search terms such as ''olfaction'', ''neurodegenerative diseases'', ''epilepsy'', ''ageing'' and ''olfactory dysfunction'' were used. Systematic reviews mainly from 2004 to 2016 were included, as were original articles, clinical trials and meta-analyses on the subject-matter, the methodology of which was clearly described from 1993 to 2016.

The olfactory system and its ageing

Olfaction is a chemical sense specialised in detecting odorous molecules that must be volatile so that when vaporised, they reach the nostrils and dissolve in the nasal mucosa, thus initiating the process of olfaction (Fig. 1).

(1) Odorous molecules activate specific receptors located in the cilia of bipolar neurons in the olfactory mucosa. Olfactory signal $\rightarrow$ Olfactory receptor $\rightarrow$ G protein activation$\alpha \rightarrow \uparrow$Adenylyl cyclase 3 $\rightarrow \uparrow$cyclic AMP $\rightarrow Ca^{++}$ entry $\rightarrow Cl^{-}$ exit $\rightarrow$ depolarisation.[7,16,28]
(2) The axons of receptor neurons form the cranial nerve I (olfactory), cross the lamina cribrosa and synapse with mitral or tufted cells in the olfactory bulb, forming a glomerulus.
(3) Each glomerulus receives stimuli from olfactory receptor neurons that express the same type of receptor for a specific scent[13]; however, there is no chemotropic map in the olfactory bulb.[68] Glomerular activity is crucial for detecting odorous stimuli.
(4) These axons also synapse with periglomerular cells, which are interneurons that establish a local reciprocal inhibition with other mitral cells and connect glomeruli with each other.
(5) Granular cells form dendrodendritic synapses with mitral cells to reinforce the response to a particular scent.
(6) The axons of mitral cells project to the ipsilateral olfactory cortex through the lateral olfactory tract. These axons project to primary olfactory areas: anterior olfactory nucleus, piriform cortex, anterior cortical amygdaloid nucleus, periamygdaloid cortex and entorhinal cortex.
(7) The piriform cortex connects directly and indirectly to the posterior orbitofrontal cortex via the dorsomedial nucleus of the thalamus, as well as to the entorhinal cortex and the amygdala. The entorhinal cortex sends information to the amygdala and hippocampus. The piriform cortex and the amygdala project to the hypothalamus, the nucleus accumbens and, via the ventral pallidum, the medial portion of the dorsomedial nucleus of the thalamus. The posterior orbital cortex and the adjacent anterior insula have reciprocal connections with all primary olfactory areas and interact with other cortical areas to integrate the information with other sensory stimuli.
(8) Both the olfactory bulb and the primary olfactory cortex receive afferents from the hypothalamus and brain stem. Cholinergic stimulation acts on M_2 receptors by reducing the release of gamma-amino butyric acid (GABA) in periglomerular and granular cells for modulation. Noradrenergic stimulation of the locus coeruleus acts on adrenergic receptors α_1 by increasing the mitral cell response to weak olfactory stimuli.

Outlining the olfactory processing,[7,26,59,68] which involves the detection, perception, discrimination and identification of scents, in a hierarchical way is not easy because several structures participate simultaneously. Surgical, neurophysiological and neuroimaging studies, particularly functional magnetic resonance imaging and positron emission tomography, have enabled the identification of the activation of regions at different olfactory processing stages[6,8,14,24,29,40,51,54,58,61,62] (Table 1).

The olfactory epithelium, which is located in the upper part of the nasal cavity and measures approximately 4–6 cm^2 in each nostril, is composed of 10–20 million olfactory receptor neurons,[21,44] basal cells, supporting cells and olfactory glands. Each bipolar neuron contains 3–50 stationary cilia that project to the mucus layer. The olfactory receptors are located on the cilia and are coded by about 1000 different genes[28]; there are about 400 types of receptor, and an olfactory neuron can respond to more than one type of smell.[7,68]

Olfactory receptor neurons are derived embryologically from the olfactory placode and neural crest cells. They have the ability to regenerate from basal cells,[42] but their number decreases with age,[45,48] particularly from the age of 65 years,[19] as a result of an increase in the death of receptor cells[36] and a decrease in neuronal proliferation.[15]

The olfactory bulb and the hippocampus are exceptional structures in terms of neurogenesis in the adult brain.[23] Subpopulations of interneurons in the olfactory bulb (periglomerular and granular cells) are constantly replaced by neurons derived from astrocytes originating in the subventricular zone of lateral ventricles and migrating via the rostral migratory stream to become part of the existing network. It is believed that the aim is to maintain adequate transduction of olfactory stimuli to the brain.

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