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Review Article

Interneurons in the human olfactory system in Alzheimer's disease

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ABSTRACT

The principal olfactory structures display Alzheimer's disease (AD) related pathology at early stages of the disease. Consequently, olfactory deficits are among the earliest symptoms. Reliable olfactory tests for accurate clinical diagnosis are rarely made. In addition, neuropathological analysis postmortem of olfactory structures is often not made. Therefore, the relationship between the clinical features and the underlying pathology is poorly defined. Traditionally, research into Alzheimer's disease has focused on the degeneration of cortical temporal projection neurons and cholinergic neurons. Recent evidence has demonstrated the neurodegeneration of interneuron populations in AD. This review provides an updated overview of the pathological involvement of interneuron populations in the human olfactory system in Alzheimer's disease.

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1. Introduction

Aberrant protein accumulation in the cerebral cortex is a characteristic of Alzheimer's disease (AD). The microtubule associate protein (Tau) is hyper-phosphorylated and forms cytotoxic neurofibrillary tangles (NFTs) in the cytosol, which cause oxidative stress and cell death (Hernandez and Avila, 2008). The enzyme γ-secretase cleaves the amyloid precursor protein (APP) to form β-amyloid peptide fragments. Normal fragments from APP are related with neuroprotective, neurotrophic and cell adhesive functions, and are widely express in the human cortex (Hiltunen et al., 2009). In AD, incorrect cleavage of APP forms insoluble fragments of β-amyloid peptide (Aβ). These fragments form extracellular aggregates, which cause synaptic toxicity, hypoxia, inflammatory responses and increased apoptosis (Goedert and Spillantini, 2006). The characteristic senile plaques (SPs) in the cortex of AD patients are composed of spherical Aβ aggregates usually surrounded by NFTs. Henceforth, both Tau and Aβ are referred in this manuscript as the pathological forms of NFTs or SPs present in AD, respectively.

The pathological aggregation of Tau and Aβ progresses differently in AD and the causative relationship between the two has been discussed (Price and Morris, 2004). AD can be divided into six different neuropathological stages based on the presence of NFTs. AD pathology starts

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in the entorhinal cortex in the temporal lobe, extends to the hippocampus and continues to the basal forebrain (Braak and Braak, 1991). As a result, patients experience progressive impairment of cognitive functions including memory, language and decision-making. The severity of these symptoms determines the diagnosis of AD (Nestor et al., 2004), although a definite diagnosis is only possible by post-mortem analyses of the brain tissue.

The olfactory system is one of the first brain regions to be affected by AD (Attems et al., 2012b; Price et al., 1991). Therefore, hyposmia is an early diagnostic factor for AD, occurring even before cognitive impairment (Devanand et al., 2000; Doty, 2001). Recent evidence has emerged that pathological Tau and Aβ proteins can be propagated across synapses (Clavaguera et al., 2015; Nussbaum et al., 2013; Spillantini and Goedert, 2013). Multiple cortical regions are directly innervated by olfactory projection neurons; therefore, the olfactory system may contribute to the etiology of AD through the transmission of pathological proteins to cortical neurons.

Early loss of cholinergic and glutamatergic neurons (Davies and Maloney, 1976; Perry et al., 1977) is considered to be one of the main causes of Alzheimer-type dementia (Baker-Nigh et al., 2015; Hardy, 2006). However, interneuron function is disrupted by Aβ even before the loss of cholinergic and glutamatergic neurons (Palop and Mucke,

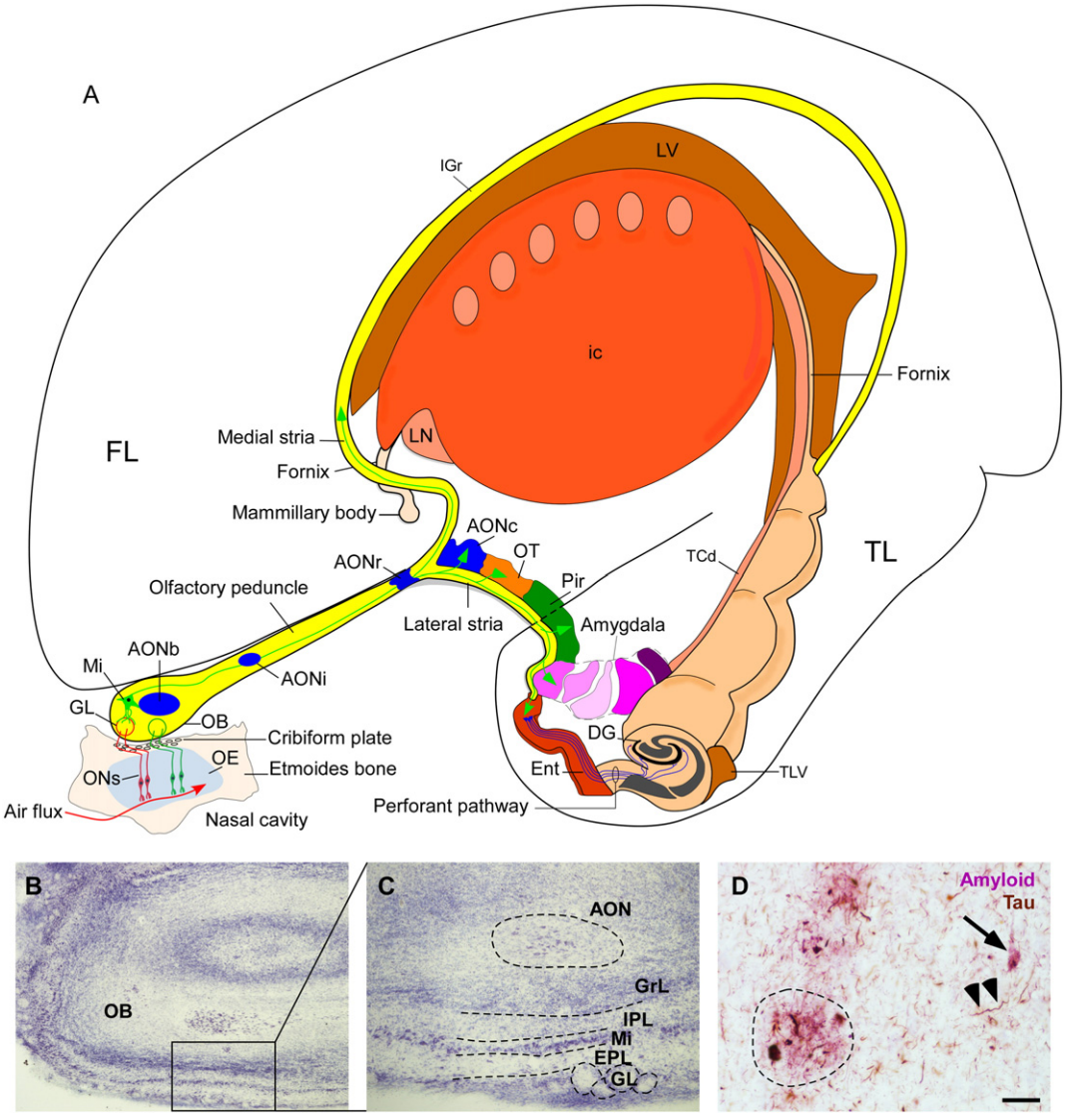

Fig. 1. Schematic representation of the human olfactory system. A; anterolateral view of the principal olfactory areas in the human brain. The olfactory sensory neurons detect odors after inhalation of air in the nasal cavity. This primary information is processed in the olfactory bulb and the mitral and tufted cells send their axons to the olfactory cortex (green projections). Anterior olfactory nucleus is distributed in different parts during the course of the olfactory bulb, olfactory peduncle and olfactory cortex and constitutes the first relay of the olfactory information. In the frontal lobe is located the olfactory tubercle which constitutes part of the ventral striatum and contains the Calleja's islands (with unknown function; not represented). The principal olfactory area is the piriform cortex. It is divided into two parts (dash line) regarding the anterior location in the frontal lobe and the posterior part in the temporal lobe. Inside the temporal lobe resides the amygdala, which is divided into different nuclei. The cortical and medial nuclei are primary involved in processing olfactory information. The last olfactory inputs from the olfactory bulb reach the rostral part of the entorhinal cortex, which in turn forms the main connection with the limbic system via the perforant pathway (blue lines). Please, note the hippocampus has been separated laterally from the amygdala and the relationships with the entorhinal cortex are topologically modified for clarity. B and C; Nissl stain of the olfactory bulb with a high magnification image detailing different olfactory bulb layers. D; double immunohistochemistry of amyloid-beta (purple) and Tau protein (brown) in the olfactory cortex showing typical senile plaque with central accumulation of amyloid-beta surrounded by Tau (circle). A detail of neuron with amyloid-beta affectation (arrow) and dystrophic neurite filled by Tau (arrowheads). Scale bar = B, 400 μm; C, 200 μm and D, 80 μm. Abbreviations: AONb, anterior olfactory nucleus (pars bulbar); AONc anterior olfactory nucleus (pars cortical), AONi, anterior olfactory nucleus (pars intrapeduncular); AONr, anterior olfactory nucleus (pars retrobulbar); DG, dentate gyrus; Ent, entorhinal cortex; FL, frontal lobe; GL, glomerular layer; ic, internal capsule; IGr, indiseum griseum; LN, lenticular nucleus; LV, lateral ventricle; Mi, mitral cell; OB, olfactory bulb; OE, olfactory epithelium; ONs, olfactory sensory neurons; OT, olfactory tubercle; Pir, piriform cortex; TCd, tail of caudate nucleus; TL, temporal lobe; TLV, temporal lateral ventricle.