Astrid Reiter

Dopamine and Olfaction

Olfactory Functions in Patients with Parkinson's Disease

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1. Introduction

This thesis aims to investigate two main aspects of olfaction.

First, as lateralization of olfaction has not been homogenously described in previous literature (Kobal et al., 2000; Zatorre & Jones-Gotman, 1991), the present work integrated measures about laterality of olfaction in healthy subjects and in patients with Parkinson's disease (PD). Laterality of olfaction in patients with PD is interesting for two reasons. Primarily, there is good evidence that patients with PD show an olfactory impairment (Ansari & Johnson, 1975). In addition, PD related symptoms are usually lateralized to one body side at disease onset (Liberini et al., 2000). Therefore, it is interesting to consider whether olfaction of patients with PD is lateralized according to the motor symptoms of PD.

Second, as already mentioned above that there is good evidence that patients with PD show an olfactory impairment (Ansari & Johnson et al., 1975). The reasons for this olfactory deficit are still not fully understood. This work considered two possible explanatory approaches that could help to better understand the development of an olfactory impairment in PD.

The first approach was based on the finding that dopamine plays an outstanding role for the olfactory system (Liberini et al., 2000). Since PD is associated with a significant loss of dopamine cells in different structures of the brain, it is assumed that the olfactory impairment in PD is related to the PD specific dopaminergic cell loss in the olfactory system (Liberini et al., 2000). In order to collect more information about this assumption the influence of antiparkinsonian medication on olfaction of patients with PD was studied.

In addition, the consequences of an acute tyrosine and phenylalanine depletion (ATPD) on olfaction of healthy subjects were also measured and evaluated. Dietary manipulation can lower plasma concentrations of tyrosine and phenylalanine, the amino acid precursors of dopamine (Moja et al., 1996), and thereby diminish access of tyrosine and phenylalanine to the brain through competition with other large neutral amino acids for the transport site. Indirect evidence from endocrine and psychological paradigms suggests that plasma tyrosine and phenylalanine depletion lowers brain dopamine activity in healthy volunteers (Harmer et al., 2001). Thus far, only emotional (Leyton et al., 1999), cognitive (Harmer et al., 2001; Booij et al., 2003) and behavioral (Grevet et al., 2002) aspects have been studied in humans with acute tyrosine depletion, but the consequences of APTD on olfaction was neglected in previous literature. This manipulation can imitate a dopamine diminution in the striatum and other brain structures (During et al., 1988; Leyton et al., 2002; Tam et al., 1990) which is similar to the dopaminergic cell losses found in PD. Therefore, it is possible that an APTD can also provide some explanatory aspects for the development of the olfactory impairment in PD.

In addition to the possibility that the dopaminergic cell loss in patients with PD contribute to the olfactory impairment in PD, the present work also examined sniffing techniques of patients with PD. A recent study has indicated that both a sensory impairment and a sniffing impairment could contribute to the development of the olfactory impairment in PD. Therefore, a study about smelling and sniffing in patients with PD has been integrated into the investigation.

Taken together, the two major approaches of this thesis can be described as an attempt to clarify laterality of olfaction in healthy subjects and patients with PD as well as to offer some reasonable explanations for the olfactory impairment in PD.

1.1 The olfactory system

On the top of each nostril is a region called the nasal mucosa. This region contains the olfactory epithelium, which lines the medial and lateral walls of the roof of the nasal cavity and is covered by mucous (Doty & Snow, 1987). The olfactory epithelium contains olfactory receptor cells, as well as olfactory glands (Bowman's glands) and sustentacular cells, both of which contribute to the mucous secretion that coats the epithelial surface. The sustentacular cells also act as supporting cells for the olfactory receptors. The olfactory receptor cells are unique to the extent that they are capable of regeneration. Although it was long thought that the olfactory epithelium undergoes a complete cell turnover about every 30 days (Graziadei & Monti Graziadei, 1979), recent data have suggested that the situation is much more complex (Hinds et al., 1984; Mackay-Sim & Kittel, 1990). Thus, many receptor cells are relatively long-lived despite continuous neurogenesis within the olfactory epithelium (Hinds et al., 1984), and both endogenous and exogenous factors can lead to a receptor cell death or to a supplement through stem cells (Mackay-Sim & Kittel, 1990).

At the surface of the epithelium, the apical end of the receptor cell widens into an olfactory rod, which gives rise to 10 to 15 cilia that project into the mucous layer covering the epithelium. At the base, where the nucleus of the cell is located, the olfactory receptor cell narrows and gives rise to a fine unmyelinated axon. Large numbers of these axons converge to run together within a single Schwann cell sheath, eventually penetrating the cribiform plate to collectively form the olfactory nerve. In humans, this nerve contains on the order of 100 million axons.

The bundled axons, which penetrate the cribiform plate of the ethmoid bone, terminate in the olfactory bulbs in each nasal cavity. The axons make contact with glomeruli. In these glomeruli, dendrites from the principle neurons in the olfactory bulb, called mitral cells, receive input from around 25 000 axons of the olfactory receptor neurons. Each of the estimated 50 000 mitral cells sends its dendrite to only a single glomerulus. In addition to the large mitral cells there

are smaller cells of the olfactory bulb, known as tufted cells. These tufted cells similarly have a number of dendrites, one of which participates in the formation of the glomerulus. The olfactory receptor neurons that contribute axons to a particular glomerulus are receptive to a specific type of odor signal so that different odors, which excite a variety of receptor types, end up activating different subsets of glomeruli. Also present in the olfactory bulbs are a couple of different types of inhibitory interneurons, the periglomerular cells and the granule cells. The contacts between these interneurons and the mitral cells are an example of two-way synaptic feedback connections: mitral cells and efferent neurons from higher centers, which, in turn, inhibit the mitral cells, excite the interneurons. These synaptic arrangements result in series of local circuits, which form the basis for integrative processes within the olfactory bulb, so that there is a striking transformation in the response to odors from the glomeruli to the mitral cells.

Finally, axons of the mitral and tufted cells enter the olfactory tract as secondary fibers. The olfactory tract connects the olfactory bulb with the central olfactory pathways, which can be divided into three different systems (Martin, 1989). Independent of the central systems, the olfactory system is unique among the senses in that it does not use the thalamus as a primary relay center to the cortex, and pathways are predominantly ipsilateral (Doty, 1997; Pansky and Allen, 1980). The first central system, the medial system is associated with the most basic olfactory reflexes (Qureshy et al., 2000). The lateral olfactory system consists of the prepiriform and piriform cortices as well as the cortical portion of the amygdaloid nuclei. From here the signals are relayed to almost all portions of the limbic system that generate emotions (Nolte, 1993), including the anterior olfactory nucleus, prepiriform cortex, peri-amygdaloid complex, and the olfactory tubercle. A phylogenetically new pathway, into orbitofrontal cortex, is thought to be associated with conscious analysis of odor (Guyton & Hall, 1996). In addition to these connections, there are widespread interconnections with many other areas, including the dorsal medial nucleus of the thalamus, hypothalamus, dorsal lateral regions of the frontal lobes and temporal cortex (Eslinger et al., 1982; Doty & Snow, 1987; Price, 1990).

It must also be recognized that the olfactory epithelium contains another sensory system in the form of trigeminal nerve receptors. The trigeminal nerve mediates via both chemical and non-chemical stimuli, somatosensory sensations (e.g. irritation, burning, cooling, and tickling), and induces reflexive responses, such as secretion of mucus and halting of inhalation, that prevent or minimize chemically or thermally induced injury of the nasal and pulmonary passages (Doty, 2001).