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REVIEW ARTICLE

The human olfactory mucosa

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Abstract Studies of the tissues of the human olfactory mucosa have been performed to investigate olfactory dysfunction and, more recently, olfactory mucosa has attracted a novel interest of investigators because it can be used as an early marker of neurodegenerative conditions of the brain and as a source of multipotent neural stem cells, with applications in regenerative medicine. The olfactory mucosa is readily available to the otolaryngologist, but the harvesting of this tissue must be safe, effective, and reliable, obtaining as little tissue as necessary, while avoiding unnecessary harm to the remaining olfactory tissue and function. The purpose of this review is to summarize the results of the most important studies and knowledge with regard to the human olfactory mucosa and its applications, emphasizing the issue of the distribution of the olfactory mucosa in the nasal cavities.

Keywords Biopsy · Humans · Nasal cavity · Nerve regeneration · Nervous system diseases · Olfactory mucosa

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Introduction

The distribution of the human olfactory mucosa in the nasal cavities was insufficiently documented in the past, probably because olfaction has been a relatively neglected area of rhinology. Studies based on biopsy of the olfactory mucosa were solely of research value, intending primarily to correlate structural histopathological changes with the nature and degree of olfactory dysfunction, and had been performed only in a limited number of centers [1, 2].

There is a general agreement that olfactory mucosa is located in the dorsoposterior aspect of the nasal vault, septum, and lateral wall of the nasal cavity. However, the exact anatomical distribution and size covered by olfactory neuroepithelium is unknown [3], and although the olfactory epithelium in the human fetus has been reported to be uniform with distinct boundaries, the olfactory epithelium of adults is characterized by irregular boundaries and interspersed patches of respiratory epithelium [4–6].

The olfactory mucosa has attracted, in recent years, a renewed interest of investigators, because of the potential for studying the olfactory mucosa as an early marker of neurodegenerative conditions, such as schizophrenia, Alzheimer's disease, multiple sclerosis, and Parkinson's disease, among others diseases [7–11]. Because olfactory neural cells are the only surface neural cells of the body, olfactory mucosa could be considered, in this aspect, as a "window to the brain" [12], and biopsy studies of these cells can potentially help in the early diagnosis and in the introduction of medical or behavioral interventions to ameliorate the effects of these devastating diseases.

The other field, where olfactory mucosa has achieved a particular attention of neuroscientists, is its potential use in regenerative medicine: the olfactory system exhibits continual turnover of primary afferent neurons and their projections

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into the brain throughout life [13], and the human adult olfactory mucosa is a potential source of olfactory ensheathing cells and multipotent neural stem cells, which have been used in autologous transplantation therapies aimed at the treatment of degenerative or traumatic conditions of the central nervous system, such as spinal cord injury or Parkinson's disease [14–19].

As this newest importance attributed to the olfactory mucosa, the harvesting of this tissue with safe, effective, and reliable methods in humans is critical. It is important to preserve the ability to smell [20], but preservation of the olfactory tissue that can be used for diagnostic or therapeutic purposes is also an important ethical aspect [21–23]. In this pursuit, the obtaining of olfactory tissue in each tissue sample, collecting as little tissue as necessary and avoiding multiples biopsies or rebiopsy is important [24]. These concerns put the emphasis on the issue of the distribution of the human olfactory mucosa.

This review is an attempt to summarize some of the current knowledge regarding the human olfactory mucosa and its applications, emphasizing the issue of the distribution of the human olfactory mucosa in the nasal cavities.

Olfactory mucosa cellular composition

The human olfactory mucosa consists of a pseudostratified columnar epithelium resting on a highly cellular lamina propria. The epithelium has four cell types: ciliated bipolar olfactory receptors, sustentacular cells, microvillar cells, and basal cells [4, 7, 25, 26].

The ciliated bipolar olfactory receptor cell is a true bipolar neuron, projecting a single dendrite to the surface of the olfactory neuroepithelium and a single axon to the olfactory bulb. The dendrite has a thickened club-like ending known as the *olfactory vesicle* or *knob*, which extends to the epithelial surface and contains non-motile cilia with membrane receptors, where odor molecules bind. The single axons of the 10 to 20 million olfactory receptor neurons cross the basement membrane of the epithelium into the lamina propria, join together into fascicles and nerves, and pass through the 15 to 20 foramina of each cribriform plate to synapse within the olfactory bulb [27].

Sustentacular cells surround olfactory receptor neurons, presumably contributing to regulating and maintaining the appropriate ionic milieu around the receptor neurons for olfactory transduction to occur [28].

Microvillar cells were first described in 1982 and hypothesized as a second morphologically distinct class of chemoreceptor in the human olfactory mucosa, however, their putative role in the olfaction has not yet been definitively demonstrated [29, 30].

Basal cells, the only type of cells that do not project to the epithelial surface rest on the basement membrane. They are a well-recognized distinct population of stem cells of the olfactory epithelium, capable of continuously regenerating olfactory receptor neurons along the life span [13, 15, 31–33]. Self-renewal and multipotency characteristics of basal cells being able to give rise experimentally to other neural and non-neural cells have been documented [16, 34, 35].

The lamina propria contains axon fascicles, blood vessels, connective tissue, and Bowman's glands [36]. Axons of the olfactory neurons were supported, in their transition from the peripheral nervous system (olfactory epithelium) to the central nervous system (olfactory bulb), by a unique line of glial cells: the olfactory ensheathing cells [13, 37]. These cells were used in attempts to treat spinal cord injury in humans, and can be obtained via biopsy through the external *naris* under endoscopic visualization [17, 19]. Another characteristic component of the lamina propria is the Bowman gland, a serous-producing tubuloalveolar gland, composed of circular secretory acini secreting its exocrine products by a duct that passes through the olfactory epithelium [38]. The products secreted from the glands to the mucous layer of the olfactory region are probably essential for the olfactory transduction.

Evolutionary aspects

Olfactory epithelial surface or bulb volumes have been used to interpret differences in olfactory sensitivity between species and to designate them as "microsmatic" or "macrosmatic" [39]. Humans are considered microsmatic beings because the olfactory bulbs are proportionately smaller [40] and the regions of the nasal cavity that are covered with olfactory neuroepithelium have proportionately less surface areas in primates than in other mammals, particularly carnivores [41, 42]. Olfactory regression is an evolutionary process that may be exaggerated by the elaboration of other portions of the brain [43]. Humans and other primates have been considered microsmats with a concomitant increased emphasis on visual sense [44].

In reality, it is the number and capacity of neural olfactory receptors per unit area and not the size of the olfactory mucosa surface that determines the acuity of the sense of smell [45]. Anatomical particularities of the nasal cavities and other physical variables are also important in the olfactory response. For example, it was demonstrated that the anatomical configuration of the nasal cavities affects the olfactory airflow, and the fraction of the air stream entering the *naris* that reach in fact the olfactory cleft is only between 10 and 15% [46–48]. Other anatomical and physiological aspects of the olfactory system may reflect also evolutionary aspects. For example, ethmoidoturbinals (middle

and superior turbinates) and spaces within the *recessus cupularis* (olfactory cleft) are generally indicated as adaptations to increase the olfactory surface area [42, 49, 50].

Olfactory neural homeostasis

The bipolar neurons of the olfactory system are directly exposed to the external environment, optimizing olfactory transduction but rendering these neurons vulnerable to injury from inflammatory, infectious, and chemical agents [51].

As an adaptive mechanism, the olfactory epithelium of mammals maintains an impressive regenerative capacity into adult life. Basal progenitor cells (stem cells) give rise to immature neurons that further differentiate forming extensive dendritic cilia and extension axons through the foramina of the cribriform plate to synapse in the olfactory bulb [52–54]. The balance between olfactory neuron loss and regeneration has been termed *olfactory neuronal homeostasis*, and is responsible for the maintenance of an adequate number of olfactory receptor neurons necessary for olfactory sensation [55].

Cell death, which results primarily from apoptosis (or programmed cell death) can occur even in the absence of obvious disease, or can be influenced or triggered by a variety of factors including the nutritional status and hormonal changes, aging, viral or bacterial infection (sinusitis), various toxins, radiation, cytokines, and the withdrawal of trophic factors [51, 56–58]. Additional environmental hazards derived from human culture, including tobacco smoke exposure, industrial or occupational pollutants, air pollution or other volatile environmental agents can overwhelm the survival mechanisms of chemoreceptors and be damaging or destructive [59, 60].

The anatomical distribution and size covered by olfactory neuroepithelium in each individual at a particular moment is strongly influenced by this *olfactory neuronal homeostasis*. Probably this process explains that the olfactory epithelium in the human fetus is uniformly distributed without interruption by respiratory epithelium and with distinct margins contrasting the olfactory epithelium of adults that is characterized by irregular boundaries and interspersed patches of respiratory epithelium [4–6].

It is often presumed that the presence of respiratory or non-neuronal epithelium in areas previously lined by olfactory epithelium represents a replacement or "invasion" of the olfactory area resulting from loss of neuronal and basal cell progenitors after some form of epithelial injury or related to the aging process [6, 8, 61–65]. However, the wide distribution of the olfactory epithelium within the nasal cavity of the adult also raises the possibility that the olfactory epithelium may invade, replace, or migrate into regions of respiratory epithelium [24].

Olfactory mucosa localization

The human olfactory mucosa constitutes probably 1.25% of the nasal mucosa, and occupies 2 cm^2 of the superior portion of the nasal vault, overlying the superior nasal septum, the cribriform plate and the superior aspect of the superior turbinate [1]. Other theoretical estimates are the number and density of bipolar olfactory neurons: 6×10^6 and 30,000/mm^2, respectively [25].

In 1892, von Brunn did measurements of the olfactory area in two post-mortem cases, revealing areas of 307 and 238 mm^2, respectively (Case 1: 133 mm^2 septum, 174 mm^2 lateral wall; Case 2: 99 mm^2 septum, 139 mm^2 lateral wall) [66]. The figure by Lang [67] based on von Brunn's measurements shows that the olfactory region extended inferiorly to the plane of the sphenoid sinus ostium and to portions of the middle turbinate, contradicting the assumption that in the lateral wall olfactory mucosa occupies only the superior turbinate.

Several studies acknowledged also that the olfactory mucosa is more anteriorly and inferiorly distributed than traditionally held [2, 3, 11, 12, 17, 21, 24, 36, 68–73]. In one of these studies, electro-olfactogram and anatomically located biopsy specimens were used by Leopold et al. to identify olfactory mucosa in the middle turbinate near the anterior insertion and anteriorly to this insertion, either in the medial or in the lateral wall of the nasal cavity [3]. Restrepo et al. obtained olfactory receptor neurons from biopsies taken from the septum opposite the high middle turbinate [71], and Féron et al. demonstrated olfactory epithelium distributed on portions of the middle turbinate in more than 50% of 71 biopsy specimens from healthy humans [24]. Similar results were demonstrated by Rawson et al. who obtained morphologically identifiable olfactory neurons taken from the septum opposite the superior portion of the middle turbinate and the middle turbinate itself [72]. Lima et al. [17] in a study involving several cadaveric dissections and histological studies of the nasal mucosa, removed from the septum opposite the superior and middle turbinates, confirm that olfactory mucosa was present in the chosen localization in individuals <35-years-old.

Rawson et al. [73] verified that biopsies obtained either from the superior half of the middle turbinate and apposed septum or from the inferior half of the middle turbinates produced odorant-responsive olfactory neurons in the majority of specimens. Immunohistochemical studies performed by Nibu et al. [74] also confirmed that olfactory mucosa extends over a broader area than was previously described, being present within the surface epithelium of the lower medial surface of the middle turbinates.

Biedlingmaier et al. [75] did not find olfactory tissue in the superficial tissue of partially resected middle turbinate removed in patients undergoing endoscopic sinus surgery;

however, the results may be explained by the pathologic changes of the olfactory mucosa induced by inflammatory disease [76].

Based on these studies, probably the most realistic assertion about the distribution of the olfactory mucosa in the nasal cavity is that it is located in the top of the nasal vault, the upper portion of the nasal septum, the medial surface of the upper turbinate, sectors of the medial surface of the middle turbinate, and the region of the cribriform plate [77]. However, we agree with Féron et al. [24], in assuming that the exact distribution of the olfactory mucosa within the nasal cavity of humans is unlikely to be resolved without a systematic mapping of the olfactory epithelium or tissues throughout the nasal cavity in individuals of different ages.

Olfactory mucosa biopsy

Other than aiming at understanding the pathology of olfaction, according to the Virchow principle of correlating macroscopic and microscopic findings with clinical manifestations of disease [78], biopsy is essential in obtaining olfactory tissues for research, and olfactory mucosa specimens are being investigated as a tool to examine certain central nervous system disorders [79] or as a source of neuronal precursors to encourage regeneration of the diseased central nervous system [14–19, 70].

The first study based on biopsies of the human olfactory mucosa was published in 1975 by Douek et al. [80], who attempted to correlate clinical manifestations with the light and electron microscopic pathologic findings of the olfactory epithelium in selected patients with disorders causing smell abnormalities. The authors did the biopsies in the most upper septal surface, using a long thin pair of toothed dissecting forceps, a self-retaining speculum and the operating microscope, but recognized the limitations of the procedure, resulting from the indistinct margins and variable size of the olfactory epithelium. Polyzonis, in 1979, tried to study the light and electron microscopic features of the normal human olfactory mucosa taking two biopsies of himself, however, it was verified later that he probably missed the olfactory region and depicted respiratory epithelium in his specimens [81].

In 1982, Lovell et al. [82] developed and described a technique and instrument for the "safe biopsy" of the olfactory epithelium. The instrument, termed olfactory biopsy instrument (OBI), was designed to avoid crushing artifacts caused by biopsy forceps, and worked by cutting through the lamina propria and leaving the epithelial surface undistorted. It had a 1-mm diameter, 120-mm long shaft ending in a 1-mm long U-shaped trough, designed to collect 3 mm^3 specimens. The procedure was performed under local anesthesia and vasoconstriction, and the septum was the preferred biopsy site because of its vertical orientation and smooth surface.

In 1993, Lanza et al. proposed a new technique for the biopsy of the olfactory mucosa, using a more widely available instrument, the 3-mm, 70-degree upturned, vertical opening cupped giraffe forceps. The procedure was performed under endoscopic guidance, as opposed to the biopsy performed with the OBI, which was a "blind" technique [83]. The biopsy success rate was improved when performed under endoscopic guidance (2:3.5 as opposed to the success rate of 1:4 to 1:6 with the OBI [84], and no adverse effect was detected in the sense of smell after olfactory biopsy with this technique [20].

Other researchers have described the use of cupped [8] or other special forceps (Nakano's forceps) [85] to obtain olfactory tissue. Regardless of the design, forceps can obtain a larger specimen and also circumvent the occasional loss of the tissue that can occur with the OBI, but can induce a "crush artifact" to the specimens [2].

Biopsies of the olfactory mucosa were also performed using medial or superior turbinate tissue resected as part of the "standard medical care" in patients undergoing transnasal endoscopic approaches to the ethmoid or sphenoid sinus [75, 76, 86], or using the submucosal approach to the septal mucosa in patients undergoing a transeptal-sphenoidal pituitary surgery [70].

Biopsy of the olfactory region carries some inherent theoretical risks, including a leak of cerebrospinal fluid, however, there have been no instances of severe complications related to olfactory biopsy reported in the literature [86].

Conclusions

The olfactory mucosa is a dynamic structure with features reflecting innate and environmental as well as developmental influences. As a consequence, it can be assumed that the precise location of the borders and the overall dimension of the neuroepithelium may be different among individuals and change over time.

Many anatomical studies modified the previously established assumption that the area of distribution of the olfactory mucosa is restricted to the dorsoposterior aspects of the nasal vault, overlying the cribriform plate, the superior aspect of the superior turbinate and the opposite superior nasal septum. Recent studies demonstrated that the olfactory mucosa extends over a broader area than was previously described, being present within the medial surface of the middle turbinate and anterior to its anterior insertion, either in the lateral or in the medial wall of the nasal cavity.

Future research should help to clarify the exact distribution of the olfactory mucosa within the nasal cavity of humans. When performed, the collection of tissue

specimens must be conservative and safe, given the need to preserve olfaction as well as the potential usefulness of this tissue in the diagnosis and treatment of several conditions of the central nervous system.

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