Structure of Human Fetal and Adult Olfactory Neuroepithelium

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Human olfactory neuroepithelium and respiratory mucous membrane in fetal and adult human subjects were studied. In the fetus, the olfactory neuroepithelium extends from the roof of the nasal cavity to the midportion of the nasal septum and onto the superior turbinate in a continuous fashion. In the adult, the zonal distribution of supporting, sensory receptor, and basal cells is frequently disrupted, and the supporting and sensory receptor cells are often depleted or degenerate. The degree of the degeneration of the adult olfactory neuroepithelium varies from case to case. The most striking feature in the adult is the replacement of large areas of olfactory neuroepithelium with respiratory epithelium. The extensive replacement of olfactory neuroepithelium with respiratory epithelium points out the sampling problem related to small, random biopsy specimens of the olfactory area.

The fine structure of the olfactory neuroepithelium in several vertebrates has been studied with light and electron microscopy in conjunction with immunoenzymologic and autoradiographic techniques. The histopathologic changes in the cellular constituents of the olfactory neuroepithelium in experimentally induced anosmia in animals have been investigated, and neuron regeneration, neurogenesis, and continuous neuron renewal have been documented in the olfactory system in mammals.

Although studies with various animal models have added much to our understanding of the abnormalities of the olfactory system, knowledge of the acquired histopathologic findings of human olfactory neuroepithelium is limited. This situation has occurred in part because of the difficulty in obtaining human olfactory tissue in a well-preserved state. Obtaining the olfactory neuroepithelium from patients is difficult because of the restricted access to the superior portion of the nasal cavity and the danger of injury to the meninges and brain, which are separated from the olfactory neuroepithelium by the fragile cribriform plate.

In 1982, Lovell et al developed an instrument and technique to obtain small biopsy specimens of human olfactory neuroepithelium under local anesthesia. Fresh material suitable for electron microscopic examination obtained in this way has led to the discovery of a possible fourth cell type, the microvillar cell, in human olfactory neuroepithelium.

Douek et al have described the histopathologic changes in the olfactory neuroepithelium in several types of anosmia. Incorrect or incomplete contact of the olfactory receptor neurons with the CNS has been investigated, and neuron regeneration, neurogenesis, and continuous neuron renewal have been documented in the olfactory system in mammals.
Fig 1. — Left, Bone cuts made in floor of anterior cranial fossa. Right, Olfactory neuroepithelium and cribriform plate (CP). Arrows indicate filum of olfactory nerve penetrating CP.

Fig 2. — Left, Respiratory mucous membrane of inferior turbinate of 7-month-old fetus (hematoxylin-eosin [HE], X80). Center, Olfactory epithelium at roof of nasal cavity of the 7-month-old fetus. Note that olfactory epithelium is thicker than respiratory epithelium of inferior turbinate (Fig 2, left) (HE, X800). NS indicates nasal septum; SC, superior concha. Right, Olfactory neuroepithelium of 7-month-old fetus. Supporting cells (dark, elongated nuclei) and sensory cells (relatively clear, round nuclei) are evident (HE, X400).

mine the degree of degeneration of the olfactory neuroepithelium and distribution of olfactory and respiratory epithelia in adults who did not have a history of olfactory dysfunction.

MATERIALS AND METHODS

The olfactory region was removed from five fetuses and 21 human adults at autopsy. The fetus had the following gestational ages: 5 months (two specimens), 6, 7, and 9 months, as determined by estimating the postmenstrual age and by measuring the crown-to-heel length. The 11 male and ten female adults ranged in age from 20 to 91 years (Table). With only one exception (a 37-year-old man who died of trauma), the patients had been admitted to the hospital and had received medication. None of the patients received antineoplastic chemotherapeutic agents, drugs interfering with cell division, or radiation therapy to the head. None of the patients had a history of olfactory dysfunction.

The cadavers were placed in a cold room at 4 °C until the time of autopsy. The autopsy was performed within 24 hours of death. The skull was opened, and the brain was removed. There was no evidence of
neoplastic or inflammatory disease of the olfactory bulbs or anterior base of the skull. A rectangular piece of bone was cut from the floor of the anterior cranial fossa with an electric saw (Fig 1, left). The specimen included the cribriform plates and mucous membrane and bone of the nasal cavities superior to the middle turbinate.

The specimens were placed in Bouin’s solution at 4 °C for one hour and in 10% buffered formaldehyde or 95% alcohol at 4 °C for one day. After fixation, the bone was carefully removed from the olfactory epithelium and nerve fibers using a stereoscopic microscope (Fig 1, right). The fixation was continued at 4 °C for several days. The fixed tissues were sequentially dehydrated in 70% to absolute alcohol and embedded in paraffin. Serial sections were cut at 4 to 6 μm, deparaffinized, stained with hematoxylin-eosin or PAS, and studied with light or phase-contrast microscopy.12

RESULTS

The nasal cavities of the 5-month-old and older fetuses are lined with respiratory and olfactory epithelia. Ciliated and nonciliated respiratory epithelium covers the inferior turbinate and part of the middle turbinate and the inferior part of the nasal septum. The density of glands in the loose connective tissue of the lamina propria of the respiratory mucous membrane is low. Compared with the low cuboidal respiratory epithelium, the olfactory epithelium in the fetus is thick and highly cellular (Fig 2). The olfactory neuroepithelium of the fetus has a zonal distribution of supporting, sensory receptor, and basal cells. Generally, the round nuclei of the sensory receptor cells are arranged in multiple layers between the oval nuclei of the supporting cells near the surface and the single layer of nuclei of the basal cells adjacent to the basement membrane. Mitotic figures were observed in some areas of the basal cell layer.

Beneath the olfactory epithelium, the lamina propria is densely cellular and contains nerve fibers and stroma cells that extend to the uncalcified cartilage. Bowman’s glands are sparse. The olfactory neuroepithelium of the fetus extends from the roof of the nasal cavity to the midportion of the nasal septum and onto the superi-
or turbinate in a continuous fashion. The junction of the respiratory epithelium and olfactory neuroepithelium is definite.

A distinctive feature of the fetal nose is the vomeronasal organ of Jacobson. The vomeronasal organs are tubular structures that lie on both sides of the anterior part of the nasal septum (Fig 3, left). In the 7-month-old fetus, the vomeronasal organs are completely separate from the respiratory epithelium except at their opening into the nasal cavity anteriorly. The vomeronasal organ has an oval lumen (Fig 3, left). The cellular distribution of the vomeronasal epithelium is similar to that of the olfactory neuroepithelium (Fig 3, right). The vomeronasal nerves are located on the dorsal aspect of the vomeronasal organs.

The olfactory neuroepithelium is generally thinner than the respiratory epithelium in the adult (Fig 4, top left). The thin adult olfactory neuroepithelium is composed mainly of a layer of basal cells and degenerated supporting cells and sensory receptor cells with dark, irregularly shaped nuclei. The supporting cell nuclei have frequently lost their oval or elongated shape.

The adult olfactory neuroepithelium usually does not have the zonal distribution of supporting, sensory receptor, and basal cells characteristic of fetal olfactory neuroepithelium (Fig 4, top right). Although the configuration characteristic of fetal olfactory neuroepithelium was recognized in some areas, the zonal distribution of the cells is frequently disturbed. The degree of degeneration of the adult olfactory neuroepithelium varies greatly from case to case. In some areas, there is complete depletion of the sensory receptor cells (Fig 4, bottom left). The surface of the olfactory neuroepithelium is frequently irregular in severely degenerated areas. Numerous serous-type Bowman's glands and olfactory nerve bundles or fila are visible beneath the olfactory epithelium in the thick lamina propria. In degenerated areas, the lumina of Bowman's glands are distended and the glandular epithelium is atrophic (Fig 4, bottom left). The
openings of the ducts of Bowman’s glands are enlarged (Fig 4, bottom right).

The respiratory epithelium in the adult is easily distinguished from the olfactory neuroepithelium by its ciliated surface and the presence of goblet cells. Serous and mucous glands are evident in the lamina propria of the respiratory mucus membrane. The junction of olfactory and respiratory epithelia is distinct.

Another characteristic feature of the adult olfactory region is the intercalation of respiratory epithelium. Although this admixture of the olfactory and respiratory epithelia is distributed randomly, the junction of the two types of epithelia is sharp. Furthermore, the junction of the two epithelia is often accompanied by glandlike invagination of the respiratory epithelium (Fig 5). Invasion by respiratory epithelium is more prominent in the roof of the nasal cavity (Fig 6, left). In some specimens, numerous glandlike ductules with ciliated respiratory epithelium occupy the roof of the nasal cavity and only islands of olfactory neuroepithelium persist (Fig 6, right).

**COMMENT**

The olfactory receptor cells are the most exposed neurons in the body. For this reason, this phylogenetically old system is considered to be one of the most primitive systems in the CNS. In 1979, observations of the olfactory

Fig 6.—Respiratory epithelium at roof of nasal cavity in adult. Left, Ciliated epithelium is surrounded by thin, degenerated olfactory neuroepithelium. Note invagination of epithelium-containing goblet cells (0). Arrowheads indicate junction of respiratory (RE) and olfactory (OE) epithelia (hematoxylin-eosin [HE], ×64). Right, Numerous glandlike invaginations at roof of nasal cavity. Arrowheads indicate junction of RE and OE (HE, ×32).
system in mammals demonstrated the capacity for continuous renewal of olfactory receptor neurons. It has been suggested that replacement of olfactory neuroepithelium occurs in response to environmental injuries. It is not known whether systematic turnover of the olfactory sensory neurons occurs in humans. The present study focuses attention on the study of the cellular distribution and topography of the human olfactory neuroepithelium.

Degeneration of the neuroepithelium appears to be characteristic of this sensory system in adult humans. This degeneration is particularly evident in comparing the cellular arrangement and topographic distribution of the olfactory neuroepithelium of the adult with those of the fetus. In contrast to the zonal distribution of fetal olfactory receptor cells between the layers of supporting cells and basal cells, there is extensive disturbance of cellular organization in the adult epithelium. This degeneration was not unexpected, since Naessen observed morphologic alteration of olfactory neuroepithelium in humans who did not have any intranasal or intracranial diseases. He also demonstrated that the cellular pattern and zonal distribution consistently detected in the fetal period are lost with age. Total degeneration with complete depletion of olfactory receptor cells was detected predominantly in elderly humans.

Pathologic changes of the olfactory neuroepithelium have been documented in patients suffering from diseases involving the olfactory region. Douek et al have reported severe destruction of the olfactory neuroepithelium due to infection with the influenza virus. Twomey et al have described severe damage to the olfactory neuroepithelium in patients in whom herpes simplex encephalitis via invasion through the olfactory neuroepithelium developed. It is conceivable, therefore, that environmental factors such as viruses and toxic chemicals may have caused the damage to the olfactory neuroepithelium found in this study. The possibility exists that some of these changes may be due to natural aging, as suggested by Naessen. Degeneration of the olfactory neuroepithelium in the younger adults in this study suggests the possibility that degeneration of the olfactory neuroepithelium is a usual phenomenon in humans and it may occur with or without exposure to infection or toxic substances. It seems more likely that repeated viral and perhaps bacterial upper respiratory tract infections account for much of the degeneration of the olfactory neuroepithelium demonstrated in this study. Furthermore, it appears that this degeneration of the olfactory neuroepithelium is asymptomatic and does not result in olfactory dysfunction such as anosmia, hyposmia, or parosmia. It may correlate with the known diminution in olfactory sensitivity that occurs with aging.

The presence of varying amounts of respiratory epithelium in the olfactory region is characteristic of adult humans. Since respiratory epithelium replaced olfactory neuroepithelium in the roof of the nasal cavity as well as on the nasal septum and superior turbinate, a random biopsy of the olfactory region does not guarantee acquisition of olfactory neuroepithelium. These findings raise serious questions regarding the efficacy of random biopsy specimens from the olfactory region.

References