Comparative Anatomy, Physiology, and Function of the Upper Respiratory Tract

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The anatomical characteristics of the upper respiratory tract of various experimental animals and man are described. There are a number of differences and similarities macroscopically and microscopically between the species. Perhaps one of the most obvious examples of anatomical differences is in the structure of the turbinates. Some of the differences could affect deposition and clearance of particles in the nasal cavities. Effects of compounds in the nasal cavity, larynx, and trachea can differ depending on the cellular composition of the mucosa.

Introduction

The upper respiratory tract, which includes the nose, larynx, and trachea, is complex. In addition to the obviously wide range of size and external shapes of the nose between humans and animals, there are also clear interspecies differences in the internal anatomy and physiology of the upper respiratory tract. The purpose of this article is to briefly review the comparative anatomy, physiology, and function of the upper airways, with special reference to laboratory animals used in toxicology studies.

Nasal Morphology

In man the nasal airway is characterized by a long, complex, and convoluted shape, quite in contrast to that of the trachea (1). The nostrils extend from ambient air to the nasal valve. The nasal valve lies between the nostrils and the main nasal passage. Just beyond the nasal valve the passage can be divided into three regions on the basis of their functional significance. The main nasal airway extends from the floor of the nose upward to the middle turbinate and from the nasal valve backward to the posterior termination of the turbinates. Above the main nasal airway is a space that we refer to as the olfactory airway; laterally are the meatuses, which are scroll-like passages formed by the turbinates. The nasopharynx is the space posterior to the termination of the nasal septum and the turbinates and extends downward to the inferior termination of the soft palate (2).

In the adult human, the nasal passage extends about 10 to 14 cm from nostrils to nasopharynx. The main turbinated portion of this passage is about 6 to 8 cm long and the surface area of its mucosa is about 120 cm² (sum of the two sides), about twice that of the trachea. Of this surface, some 40 cm² are accounted for by the olfactory airway. The air space is quite narrow everywhere, between 1 and 2 mm wide. The surface area as well as the cross-section is large. From a cross-section of only some 60 mm² (sum of the two sides) at the nasal valve the airway widens to some 260 mm² in the main nasal passage. This sum of the cross-sections of the two sides somewhat narrows as the double airway becomes one in the nasopharynx (3).

The folded shape of the airways assures intimate contact between the air and the surface wherever inspiratory air passes over it. But model studies indicate that most of the airflow passes over a relatively small percentage of the surface. Another complicating factor is the frequent and sometimes large change in the surface and the width of the airway associated with vascular congestion and decongestion. A point, which at this time remains unresolved, relates to the questions of when congestion leads to oronasal breathing and when decongestion might lead to an inefficient flow to surface relationship.

The total upper air passage begins, in upright man, by pointing upward from the nostrils, undergoes a sharp nearly right angle turn to pass backward through the main passage, and takes another right angle turn downward at the nasopharynx (4).

The nostrils are lined with skin and the nasal hairs project from it into the airway. Through the nasal valve there is squamous epithelium undergoing a gradual transition just beyond the anterior ends of the turbinates to

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ciliated secretory epithelium (5). Goblet cells are interspersed with ciliated cells through the main passage (6). The mucosa in the main passage contains a rich vasculature and a myriad of seromucous glands. Through the main passage, the surface is covered with airway secretions reaching at least some 10 to 12 μm above the cell surface. In the nasopharynx there is a transition, again, to squamous epithelium, although ciliated cells are found especially over the adenoids that project from the posterior nasopharyngeal wall.

Ancillary air spaces consist of the paranasal sinuses, the eustachian tubes, and the air spaces of the middle ears and temporal bones. The paranasal sinuses include the maxillary antra (the largest sinuses) the frontals, ethmoids, and sphenoids. These sinuses open through small ostia into the nasal passages and are normally in continual communication with the nasal air. The frontal sinuses communicate through long nasofrontal ducts opening into the anterior middle meatus. Just posterior to this duct lies the orifices of the maxillary antra. The ethmoid sinuses open along the middle meatus and, posteriorly, above the middle turbinate, while the sphenoid orifices lie just above the posterior termination of that turbinate (7). Airway secretions normally are consistently moving from the orifices onto the main nasal surfaces all along the lines of principal airflow. The sinuses are lined with ciliated secretory epithelium, but the mucosal vasculature is sparse, and both goblet cells and mucosal glands appear in smaller number there than in the main passage.

Comparative Morphology

The development of the nasal cavity in most mammals, excluding man and some higher apes (orangutan, chimpanzee, gorilla), is reflected by the demand for its primary function as olfaction. Carnivora including the dog and cat and other species such as rodents have complex nasal cavities with large areas for olfaction. On the other hand, the fact that optimum temperature and humidity are necessary for the detection of odor and normal function of the lower respiratory tract, plus the characteristic rapid movements and breathing patterns of these animals, triggered the development of a relatively large surface area for air conditioning. This air-conditioning mechanism is especially apparent in desert animals such as the camel and the cold-water diving mammals such as the seals.

Thus, from the comparative viewpoint, humans have relatively simple noses with primary function for breathing, while other mammals have more complex noses with primary function for olfaction. As a result of this distinction in primary function, the anatomy of the nasal cavity in relation to the oral cavity is arranged in such a manner that, while man (and some higher apes) can breathe both nasally and oronasally, other mammals are obligatory nose breathers, due to the close apposition of the epiglottis to the soft palate (1).

Despite the greater complexity and the variations in the shape and dimension of the nasal cavity and its turbinates, the nasal airways of most animals have characteristics similar to those in humans. From the nostrils, which are in line with the nasal fossae in most instances, air must pass the vestibule and through the nasal valve into the main chamber that is divided into two rather symmetrical compartments. Once inside the main chamber, air streams are divided to travel between the septum and the medial surface of the nasal-, maxillo-, and ethmoturbinates. The passage ventral to the maxillotubinate (equivalent to inferior turbinate in humans) between it and other turbinates, and dorsal to the nasoturbinate (middle turbinate) and ethmoturbinates are often referred to as the ventral (interior), middle, and dorsal (superior) meatuses, respectively. Posterior to the termination of the nasal septum, the air passages then merge into one and travel downward through the nasopharyngeal meatus into the nasopharynx. This airway, in general, is not as sharp-angled as compared to man, and a relatively straight course has been observed in fast-running animals such as horses, antelopes, and dogs.

The distance from the nostrils to the nasopharynx is usually proportional to the size of the head and particularly to the length of the snout, thus, the total length of the airway varies widely, as for instance between the elephant and the mouse. Also, because of differences in dimension and body size, the total surface area may range from about 3 cm^2 in a mouse to several thousand square centimeters in a camel. Of this total surface area, the fraction occupied by the olfactory or respiratory epithelium is further determined by the animal's olfactory sense. In the past, there has been great interest in the olfactory function of the nose; a larger olfactory to respiratory area ratio has been used to classify dogs, cats, rabbits, guinea pigs, and rats as macrosmatic. These contrast to the sheep, man, and monkey that are classified as microsmatic. But there have been only five published works on the surface area of various portions of the nasal cavity within a single species (1,8–11).

In a recent study by Gross et al. (12) the various surface areas of 7- and 16-week-old B6C3F$_1$ mice and F-344 rats were compared. It was found that the surface area of the mouse increased at a slower rate with body weight than in rats. But, within a given species, the percentage of the respiratory or olfactory area lining the cavity was the same at both ages, indicating that a definite area of respiratory epithelium is required to warm and humidify air for a given area of the olfactory epithelium. When compared between species, the mouse has more respiratory epithelium available for filtering air per unit volume of the nasal cavity than the rat. It is interesting to note that the total surface area for the B6C3F$_1$ mouse is not too much different from that of the vole or mouse peromyscus.

The surface area values are useful for calculating the theoretical dose of chemical or particulate that is likely

to be deposited upon the nasal surface, assuming uniform distribution and 100% retention. Unfortunately, it is, in reality, very difficult to derive the surface area of the nasal airway during exposure to chemicals that may affect the mucosal surface.

Beyond the similarity in airway anatomy, there are major structural differences between man and other mammals in the nostrils, vestibules, nasal septum, and the turbinates that can modify the course of the air currents. The nostrils of some diving mammals and bats can be regulated to open and close, while those of bisons are comma-shaped so as to direct the airflow above the nasoturbinate and below down on the floor of the nasal fossa, simultaneously. The vestibule of rats, mice, and cats contains atrioturbinates that are effective baffle systems to deflect a large volume of air and impact particulates. In addition, the vestibule also functions as a reservoir for droplets of serous secretions produced by the serous or mucoserous lateral nasal glands. In man and higher primates, the lateral nasal glands are absent (13). Inside the main chamber, the air streams are further affected by the juxtaposition between the septum and the turbinates. Although the septum in most mammals effectively divides the chamber into two symmetrical compartments, the septum of rats, mice, hamsters, and guinea pigs contains the so-called "septal window" so that in some experiments, the two halves cannot be treated individually (14-17). On the ventral part of the septum of most macrosmatic species, including dogs, cats, rodents, and rabbits, there is a structural prominence formed by a number of vascular spaces beneath the epithelium called swell bodies. When these are collapsed they will allow the air to pass freely beneath the maxilloturbinate and directly towards the nasopharynx. When distended, they will cause the inspired air to pass over the maxilloturbinate (18).

The maxilloturbinate of humans is of the simplest type, being merely an unbranched lamellar projection with a coiled end (single scroll). This type of structure does not divert or obstruct the air stream as much as the maxilloturbinates of macrosmatic species. Ungulates, rodents, and some New World monkeys have a double scroll-like structure which resembles a "T" in section with the double ends coiled, whereas rabbits and most other carnivora (including dogs, cats, and ferrets) have the branched type. The structure reaches the highest complexity in seals and sometimes obstructs the nasal lumen completely.

Although the ethmoturbinates of macrosmatic species are also far more complex than in humans, this region generally lies so far back in the nasal fossa that it does not have a significant influence on air passage. The major inspiratory airflow generally only reaches the anterior end of the olfactory area (19), in some species this area is protected from the direct air streams by the presence of a subethmoidal shelf. This shelf is well-developed in cats and dogs, is small in ungulates and rodents, and is absent in primates, including the higher apes and man (18).

Histologically, the relative distribution of squamous, respiratory, and olfactory epithelium from the nostrils to the nasopharynx is rather similar between man and other mammals. But, whereas, the respiratory epithelium of the human nasal cavity is of the pseudostratified, ciliated columnar type, the nasal cavity of other mammals is partly covered by other nonciliated types of epithelium. From the keratinized, squamous epithelium-lined nostrils and vestibule to the mostly olfactory epithelium-lined ethmoturbinates, gradations of respiratory epithelium from the stratified cuboidal, simple cuboidal, ciliated low columnar, and ciliated pseudostratified columnar epithelial linings can be found over the septum, nasoturbinates, and maxilloturbinates. The percentage of these epithelia and their presence over the nasal surface cannot be generalized, and, is not always accompanied by the presence of goblet cells (14,18). In fact, Adams (8) showed that the ciliated epithelium and goblet cells are present only in a very small portion of the nasal cavity in hamsters. Thus, the nasal respiratory epithelium of man appears to be more evenly covered by the cilia and goblet cells and secretory acini than most animals.

Underneath the respiratory epithelium, the lamina propria is rich in venous plexes. When altered they can affect the thickness of the respiratory mucosa and thus the width of the airway. In general, there is very little difference between man and other mammals in the organization and the ultrastructure of the vascular system within the nose (20-22). The olfactory areas of both man and animals are not covered by ciliated cells and are devoid of goblet cells. The Bowman's gland that secretes onto the surface is generally considered as a serous or mucoserous gland. Finally, the nasopharyngeal meatus of most animals is covered by ciliated pseudostratified columnar cells with goblet cells (14,18,23,24).

The size, shape, number, and interconnection of the sinuses vary widely among mammals, in general, they can be divided into a lateral maxillary sinus and a dorsal frontal sinus, as well as sphenoidal and ethmoidal sinuses. The maxillary sinus is absent or relatively small in macrosmatic animals with large maxilloturbinates, in contrast to it being the largest sinus in humans. The ethmoidal sinuses, similarly, are present only in the higher apes and man (18). The Macacus rhesus monkey has only a maxillary sinus (1).

Among the laboratory rodents, guinea pigs have no equivalent sinuses present, but they do possess posterior and anterior lateral recesses (16), whereas mice, rats, and hamsters have only a maxillary sinus (14,15,17). Dogs, cats, and ferrets have a frontal sinus and a rather large maxillary sinus that is divided into an upper and lower chamber, despite the presence of a branched maxilloturbinate (13). Rabbits, in addition to the maxillary sinus, have a marsupium, which is an air space enclosed inside the nasoturbinate (25).

As in humans, the lining of the paranasal sinuses tend to be thinner and glands are less numerous than in nasal

mucosa. However, while all the sinuses in humans are lined with ciliated respiratory epithelium, the frontal and sphenoidal sinuses of some carnivores are lined by an olfactory epithelium as a result of the extension of naso-turbinate and ethmoturbinates into these cavities (18).

Very limited information is available on the ultra-structure or the character of the cell types found in the rodent nasal mucosa (26,27). The rat nasal mucosa reveals six morphologically distinct cell types: goblet cells, basal cells, ciliated cells, nonciliated columnar cells, cuboidal cells, and brush cells (28). Cuboidal cells observed on the conchae and lateral wall have short apical microvilli that are less dense than the microvilli of the nonciliated columnar cells. Nonciliated columnar cells also identified on the conchae and lateral wall have short microvilli and an extensive network of smooth endoplasmic reticulum in the apical region. The brush cell has distinct ultrastructural features, being pear-shaped, with a broad base adjacent to the basement membrane and large microvilli on the surface. Brush cells occur singly on the conchae and lateral wall but they have not been identified in the respiratory epithelium of the nasal septum. The brush cell identified in the rat nasal respiratory epithelium has not been previously described in the nasal mucosa of any species (28).

The morphology of the goblet cell in the rat is similar to that of the previously described goblet cell in the nasal epithelium of the mouse (29), dog (30), and human (31). The nonciliated columnar cell has not been previously characterized by transmission electron microscopy in the rat but does have some similarities to a cell described in the mouse nasal mucosa (29).

Simple cuboidal cells have not been previously described in the rat, mouse, dog, or human respiratory epithelium. They are consistently found in the same region of the rat nose and are frequently found in areas containing few or no nonciliated columnar or goblet cells. It is unclear whether this cell is unique to the rat respiratory epithelium or whether it has not been described in other species because of the limited number and depth of previous studies (28).

Nasal Carcinogenesis

Although the incidence of tumors of the nasal and paranasal cavities in humans is relatively low, animal experiments with different rodent species (mice; rats; and Syrian golden, European, and Chinese hamsters) have shown that many nitrosamines, 1,4-dioxane, p-cresidine, phenacetin, procarbazine, thio tepa, vinyl chloride and other chemical substances (32–35) found in the environment have induced different types of neoplasms in the nasal cavity. In earlier carcinogenesis bioassays of chemicals, the protocol frequently required removing parts of the nasal bones to inspect the linings of the nasal interior. It is presently recommended that the skin of the nose be removed and the entire nasal cavity be fixed in situ. After decalcifying the skull, coronal sections should be prepared to include the nasopharynx. The procedures are discussed in detail in another article in this series (36).

Larynx

Bends and linear velocity in the airstream, turbulence in flow, the proximity of inspired air to surface, and factors influencing the passage of air nasally or oronasally are all important to the initial fate of inhaled materials (1,2). Their final fate is under the influence of mucociliary clearance and the permeability of secretions, as well as to blood flow. At the nasopharynx the air must make a 90° turn downward to reach the larynx of humans and some nonhuman primates; this is not the case for rodents.

The larynx is situated behind the root of the tongue and is ventral to the esophagus. It provides a sphincter valve at the entrance to the trachea. In rodents, the larynx is lined by stratified squamous epithelium and pseudostratified ciliated columnar epithelium in a highly specific regional distribution pattern. At the cranial base of the epiglottis, the uniform structure of this epithelium is interrupted by excretory ducts of some subepithelial glands, so that the epithelium sometimes takes on a mixed appearance (24). The dorsal part of the lateral walls of the vestibule of the larynx is covered with stratified squamous epithelium, whereas its ventral surface is lined by pseudostratified ciliated columnar epithelium. At the vestibular fold (plica vestibularis) this stratified columnar epithelium is also found, while the vocal folds (plicae vocales) are covered with stratified squamous epithelium. Between these two folds is situated the ventricle of the larynx, which is lined by a pseudostratified ciliated cylindrical epithelium with areas of stratified squamous epithelium.

In the normal rat, the floor and ventro-lateral curvatures of the cavity and the lateral and upper medial surface of the vocal cords are lined by pseudostratified, nonciliated, columnar epithelium that are lacking goblet cells. This epithelium merges with a stratified squamous epithelium that is usually thin around the dorso-lateral curvatures of the cavity and thicker over the lower medial aspects of the cords, but rarely keratinized. Occasional deviations from this pattern include an extension of squamous epithelium to invest either the lateral aspects of the cords or—where the section exposes the pharyngeal opening—their complete medial surface (37). Caudally, from the vocal folds begins a ciliated columnar epithelium, two-cell layers thick, which extends to the trachea.

Trachea

In contrast to the nasal valve that offers, by far, the smallest cross-section through which the total respiratory air must pass, the diameter of the rodent trachea is approximately 60 mm^2 (sum of the two sides). This should be compared to a cross-section of about 2.5 cm^2 in the trachea of humans.

In spite of a relatively similar tracheal length, the number of tracheal rings differs greatly between animal species. In the three hamster species (European, Syrian golden, and Chinese), the European hamster with a mean number of 14.5, has the fewest tracheal rings; 16.6 tracheal rings were averaged for the Syrian golden hamster, and 18.2 for the Chinese hamster. No differences were found between the two sexes. In all hamsters examined, the diameters of the trachea were largest in the upper portion and smallest in the lower portion; however, the thickness of the tracheal cartilage remained constant (0.5 mm in the European hamster, 0.1 mm in the Syrian golden hamster, and 0.12 mm in the Chinese hamster). In the European hamster, the lumen of the trachea was, in all areas, more than twice as large as in the Syrian golden and Chinese hamsters.

The cervical and thoracic trachea of hamsters is a nearly cylindrical tube extending from the larynx at the level of the cervical vertebra to the sixth rib where it divides into a smaller left and larger right main bronchus. In the European hamster, for example, the trachea *in situ* is 34 mm long, the isolated organ has an average length of 23 mm and weighs about 86 mg in adult males and 68 mg in adult females (*38,39*). In adult rats the trachea is approximately 30 mm long with a diameter of 2 to 3 mm.

The cellular composition of the respiratory epithelium that covers the airways is basically similar in all mammals. However, pronounced differences among the species exist in the distribution pattern of cell types within the epithelium at the various levels of the airways. A pseudostratified respiratory epithelium composed of ciliated, goblet, and basal cells lines the upper parts of the rat airway from the trachea to the segmental bronchi, whereas in man these cell types are still found in the more peripheral subsegmental bronchi as well. As a peculiarity, the mucous cells in this portion of the rat respiratory tract are the goblet cell type, as are most of the mucous cells found in the human lungs, while the majority of the other rodents have small mucous granule cells instead. Occasionally, an individual brush or APUD-type cell may also be found in this upper part of the airways (*33*).

In Syrian hamsters subepithelial mucous glands are mainly concentrated in the upper third of the trachea. They are sparse in the lower third of this organ and disappear completely at the level of the main bronchi. In European hamsters prominent subepithelial mucous glands are found in all parts of the trachea. They decrease in number in the main and lobar bronchi. The respiratory epithelium of the trachea and main and lobar bronchi is pseudostratified and consists of ciliated, mucous, and basal cells. The mucous cells are the goblet cell type in the trachea and main bronchi. In the mouse, sparse subepithelial glands may be found in the upper part of the trachea. The epithelium is pseudostratified with ciliated, mucous, and basal cells in the trachea only. Brush cells and APUD cells are extremely rare.

The trachea of the guinea pig is 40 to 45 mm long and is made up of 35 to 40 cartilaginous rings. The trachea is lined by a pseudostratified respiratory epithelium that consists of ciliated, mucous, and basal cells. The mucous cells at this level are the goblet cell type featuring numerous, often confluent, mucous granules in their cytoplasm (*33*). In the wall of the human trachea and bronchi the mucosa consists of a pseudostratified ciliated epithelium with goblet cells and a lamina propria containing interwoven collagen and elastic fibers.

In the trachea of all species, the free ends of the dorsally open cartilages are connected by transversely oriented bundles of smooth muscle cells. In humans, the tracheobronchial glands are mainly located in the submucosa. In the dorsal region of the trachea where these glands are markedly developed, they even extend into the adventitia; in these cases, their ducts penetrate between the bundles of the tracheal muscle. The endpieces are composed of mucous tubules and carry short, terminally or laterally arising serous tubules, which often appear as crescents (*40*). The segment near the surface of the glandular duct, measuring about 350 μm in length, is lined by a ciliated epithelium that changes abruptly to the collecting duct epithelium, represented by eosinophilic, mitochondria-rich cells.

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