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EXPERIMENTALLY INDUCED DISEASE: REVIEW ARTICLE

A Review of the Comparative Anatomy, Histology, Physiology and Pathology of the Nasal Cavity of Rats, Mice, Dogs and Non-human Primates. Relevance to Inhalation Toxicology and Human Health Risk Assessment

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Summary

There are many significant differences in the structural and functional anatomy of the nasal cavity of man and laboratory animals. Some of the differences may be responsible for the species-specific nasal lesions that are often observed in response to inhaled toxicants. This paper reviews the comparative anatomy, physiology and pathology of the nasal cavity of the rat, mouse, dog, monkey and man, highlighting factors that may influence the distribution of nasal lesions. Gross anatomical variations such as turbinate structure, folds or grooves on nasal walls, or presence or absence of accessory structures, may influence nasal airflow and species-specific uptake and deposition of inhaled material. In addition, interspecies variations in the morphological and biochemical composition and distribution of the nasal epithelium may affect the local tissue susceptibility and play a role in the development of species-specific nasal lesions. It is concluded that, while the nasal cavity of the monkey might be more similar to that of man, each laboratory animal species provides a model that responds in a characteristic and species-specific manner. Therefore for human risk assessment, careful consideration must be given to the anatomical differences between a given animal model and man.

Keywords: experimental animals; human risk assessment; nasal cavity; toxicological pathology

Contents

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Introduction

The nose is a structurally and functionally complex organ with multiple functions that include olfaction, warming, humidifying and filtering of the inspired air (Negus, 1958; Proctor and Andersen, 1982; Proctor and Chang, 1983). Although its filtration functions are essential for the protection of the lower respiratory tract, the deposition of particulate material on the nasal epithelium also renders it vulnerable to injury (Harkema *et al*., 2006). This is particularly evident in inhalation toxicity studies in laboratory animals, where relatively high incidences of chemical-induced nasal lesions are often recorded (Renne *et al*., 2007). Some of the lesions show a characteristic distribution pattern that is both site- and species-specific (Monticello *et al*., 1989). This site- and species-specificity is thought to be due to the local tissue susceptibility and dose at the site of deposition, or a combination of the two (Morgan and Monticello, 1990; Kimbell, 2006). The local tissue susceptibility is influenced by the morphological, biochemical and physiological characteristics of the epithelium at the site of deposition (Morgan and Monticello, 1990; Harkema, 1991), while regional deposition and uptake are determined by nasal airflow patterns (Morgan and Monticello, 1990; Kimbell, 2006). Airflow is influenced by the nasal anatomy, such as the variations in the structure and complexity of the turbinates, folds or grooves on the nasal walls, or the presence or absence of accessory nasal structures (Mery *et al*., 1994; Kimbell, 2006). Therefore, for a proper evaluation of toxic effects in the nasal cavity, and extrapolation of data from animal studies to human risk assessment, a working knowledge of the comparative anatomy, histology and physiology of the nasal cavity of laboratory animals is required.

Some excellent reviews have been published on the comparative anatomy and physiology of the nasal cavity of laboratory animals (Reznik, 1990; Harkema, 1991; DeSesso, 1993; Harkema *et al*., 2006; Renne *et al*., 2007), but none have included detailed descriptions of the gross anatomy and histology of the nasal epithelium in the dog and the cynomolgus monkey and, to our knowledge, there are no published reviews on the spontaneously arising pathology of the nasal cavity in these two non-rodent species used in inhalation toxicology. This review describes the structural details of the nasal anatomy of the four most commonly used laboratory animals species, the rat, mouse, beagle dog and monkey, highlighting the main interspecies similarities and differences that are relevant to inhalation toxicology. The response of the various nasal epithelia to inhaled toxicants and environmental agents, the factors influencing lesion distribution and site specificity, and the issues related to the extrapolation of data from experimental animal studies to human risk assessment, are also discussed. The final section discusses the more commonly observed spontaneously arising and age-related non-neoplastic pathological findings that may be confused with treatment effects, in the various laboratory animals.

General Gross Anatomy

The general layout of the nose is similar among laboratory animals and between animals and man (Negus, 1958; Reznik, 1990). The nasal cavity extends from the nostrils to the nasopharynx, and is divided into two symmetrical passages by a partly cartilaginous and partly bony median septum. The cartilaginous septum is located rostrally and articulates with the cartilages of the nares (Lucas, 1932; Negus, 1958; Evans and de Lahunta, 2013), while the smaller bony part is located caudally and attaches to the vomer ventrally, the ethmoid bone caudally and the frontal and nasal bones dorsally (Nicholson and Kreel, 1979; Evans and de Lahunta, 2013).

From rostral to caudal, the nasal cavity is divided into the vestibule (Fig. 1), the nasal valve or ostium, the nasal chamber proper (Fig. 2) and the

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