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Environmental Factors Affecting Chemoreceptors: An Overview

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Vertebrate olfactory and gustatory receptors are necessarily exposed to the fluid which contains their relevant chemosensory environment. In terrestrial mammals, the nasal airways serve as protective accessory tissues for the olfactory receptors, but taste receptors in all vertebrates and olfactory receptors in fish are directly exposed to the liquids which bring chemosensory stimuli to them. The differentiated epithelial cells which form taste buds and the specialized neurons which are the vertebrate olfactory receptors are constantly replaced in normal adult animals, suggesting that chemosensory function per se is damaging to the receptors. Organic and sulfur-containing air pollutants may be among those which adversely affect olfactory receptors, but adequate data are not available. Surfactants and heavy metals can produce physiological and/or morphological damage in gustatory receptors. Some heavy metals are concentrated in saliva, a liquid which interacts closely with taste receptors. A failure to evaluate human chemosensory function in relation to potential chemosensory toxicants accounts for the present inability to specify the incidence or severity of the problem.

Introduction

Interaction with the chemical environment is the ultimate fulfillment for olfactory and taste receptors. As is often the case with such intimate and intense interaction, the results, while stimulating, can be damaging or destructive. Nonetheless, the continued presence and operation of these chemoreceptors indicate that mechanisms are available to cope with whatever morphological and/or physiological damage may be produced by common terrestrial and aquatic chemosensory environments. Additional environmental hazards derived from human culture (*1-3*) can, however, overwhelm the survival mechanisms of chemoreceptors (*4*, *5*).

Olfaction

For terrestrial vertebrates, the environmental challenges to taste and olfactory receptors are rather different. Chemicals in solution or suspension in air comprise the major chemosensory hazards for olfaction in terrestrial forms. Since solids and liquids need not arrive at the receptor sheet, olfactory receptors can be so located that "accessory tissues" of the nose permit access only to gases. In mammals, in particular in humans, the sharp bends, narrow passages and extensive ciliated mucosal surface of the turbinates and septum of the nasal airways cause almost all particles larger than 5 μm to be deposited before they reach the olfactory receptors (*6*), which are located on the most superior turbinate and associated septum. During normal breathing, little of each inspiration flows above the middle turbinate, although a more even flow occurs during expiration. The large mucosal surface extending from the anterior nares absorbs over 90% of water-soluble vapors present in inspired air. Considerable adsorption of water-insoluble gases also occurs. Thus, the air flow pattern and mucosal sorption tend to protect the olfactory receptors against exposures to high concentrations of chemicals (*6-9*). Finally, the mucus-containing surface liquid and the rich blood supply of the nasal airways modulate the temperature and control the relative humidity of inspired air such that air temperature at the superior turbinate is

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within ±5°C of 37°C, and the relative humidity is 100%, for a wide range of ambient temperatures (*6*). The resulting "constant temperature and humidity chamber" for the olfactory receptors, which are also well protected from most nonvapor input, might seem to be a benign if not extraordinarily safe environment.

If the olfactory receptors could interact with the chemosensory environment without incurring damage to themselves, we might expect these specialized neurons (*10, 11*) to be relatively static structures. However, many studies have found that the olfactory receptor cells are constantly being replaced (*10, 12, 13*), and that the entire receptor neuron can regenerate from basal cells in adult vertebrates, including birds and mammals. The regeneration produces not only morphological replacement but also functional recovery (*14*). These observations indicate that olfactory function is inherently damaging to the receptor. That is, the usual finding in healthy animals which have not been subjected to an intentionally polluted environment is constant replacement of the mucosal portion of the olfactory receptors. This receptor turnover, which must have a considerable metabolic cost, can provide an adaptive advantage only if it is necessary for satisfactory olfactory function.

Olfactory damage due to pollutants may result from an additional burden added to the challenge of normal olfaction. Structural and functional damage to the olfactory epithelium by ether or chloroform vapor was confirmed in the 1960s (*5*). Exposures to a sufficient concentration of either vapor for 6-10 min produced morphological damage, but the same concentrations for less than 4 min resulted in only a brief depression of function. However, ether and chloroform are not common environmental pollutants (*3*). Therefore, they may be useful research tools and possible model agents rather than problem chemosensory toxicants.

Sulfur compounds (*2*) and formaldehyde vapor (*1*) are common air pollutants. Olfactory deficits are reported to occur in humans exposed for some hours to formaldehyde vapor (*15*), but satisfactory psychophysical documentation is lacking. If formaldehyde vapor were an occupational hazard only for plastic, wood and textile workers, as well as anatomists, formaldehyde olfactory toxicity would be a potential problem for only a small segment of the population (*1*). However, the development and commercial use of formalin-based synthetic polymers for phenolic and urea resins have brought the challenge of this possible chemosensory toxicant to the general population (*1*). The problem may be more serious in urban settings, since formaldehyde occurs in gasoline and diesel engine exhaust, and as a photodecomposition product in smog. Irritant actions on the eyes and pulmonary airways are observed at air concentrations of formaldehyde no more than two to three times that needed to recognize by smell the presence of formaldehyde. Indeed, it is recommended that if a formaldehyde odor is consistently recognized in one's environment, a problem is likely to exist (*1*). Of course, if formaldehyde damages olfactory receptors, the recommended bioassay would be of limited value. Thus, an adequate evaluation of the severity of the effects of formaldehyde on olfaction is needed, with reliable dose-response profiles.

Irritant properties of sulfur dioxide are widely recognized (*16*). Although the presence of such irritants does increase airway mucus secretion (*17*), sulfur dioxide concentrations of 1 ppm or more impair nasal mucous flow (*6*). Surprisingly, continuous exposure to sulfuric acid aerosols with concentrations from 150 to 502 mg/m^3 for 7 days produced no nasal septum (or pulmonary) damage in rats or rhesus monkeys (*18*). Lesions were seen in guinea pigs; in mice, somewhat longer exposures resulted in ulcerations in the larynx and upper trachea. Since the highest concentrations in this study were several times that found in industrial pollutant-induced smog, generalization of sulfur-induced nasal damage from rodents to primates may be contraindicated. No evaluation of olfactory effects was made.

The central nervous system target of the olfactory receptor neuron axons, the olfactory bulb, apparently shows structural alterations in the rat as a function of the chemicals in inspired air (*19*). Initial reports suggested that bulb damage due to overstimulation was being observed. However, replication of the changes using the original stimulus paradigm has been difficult. Some reports suggest that the anatomical changes are signs of normal function, with unchanged olfactory bulb regions reflecting a pathological state due to insufficient input from the olfactory receptors (*19*). Finally, some investigators, while finding transient behavioral changes, have observed no alterations in olfactory bulb morphology (*20*).

In general, olfactory systems of terrestrial animals respond to, and permit adaptive behavior in relation to, very low concentrations of a broad range of molecules in air (*21*). This high and differential sensitivity uses "accessory tissues," the nonolfactory portions of the nasal airways, to humidify, temperature control and desaturate inspired air. The olfactory receptor neurons undergo constant turnover, and the entire neuron can develop in adult mammals from basal cells. These protective and replacement mechanisms may be insufficient to

handle culturally produced air pollution. Formaldehyde vapor is potentially a serious olfactory receptor toxicant, but more data are needed. More broadly, any form of air pollution which adversely alters nasal mucosa, such as pH changes (*3*) or organic vapors (*1*), may also affect the nasal chemoreceptors.

The postsynaptic neurons of the olfactory bulb show histochemical changes following prolonged inspiration of air containing sufficient concentrations of a range of chemicals. Whether these changes, or their absence, are pathological is not understood.

Taste

Taste receptors of vertebrates occur in loci where contact with environmental chemicals in aqueous solution is a likely event (*22*). For fully aquatic forms such as fish, these loci include, in addition to the mouth, the exterior surface of the body, and sometimes appendages literally covered with taste buds (*4*, *23*). Other specialized "contact chemoreceptors," such as portions of the lateral line system and scattered chemoreceptors, are also found in fish and elasmobranchs. However, the receptor cells of these latter systems do not resemble those of taste buds, and the innervation may be either cranial or spinal nerves.

Since the fluid in which fish live is a liquid, olfaction and taste share the same stimulus solvent, and both can be affected by water pollution. For example, olfactory epithelium damage in fish due to exposure to petroleum in water has been reported (*24*).

Terrestrial vertebrates have taste receptors only within the mouth and pharynx. Adult humans and other mammals usually have taste buds on the tongue (generally on papillae located on the dorsal surface and sides of the tongue), the soft palate, and the epiglottis (*22*, *25*). Extensive protective and filtering accessory tissues comparable to the nasal airways are not found for vertebrate taste receptors. At best, a mucosal layer (*26*) [covering external taste buds in aquatic forms (*23*, *27*)] or a mixture of saliva and mucus (oral and pharyngeal taste buds) covers the receptor cell complex.

In humans and many other mammals, the tongue has a relatively thick and nonpermeable keratin layer (*28*). However, the keratin becomes very thin or disappears entirely in the vicinity of taste buds (*25*). An opening in the epithelium forms a pore (*28-31*) through which liquids, pastes and particles less than 5 μm can approach the microvilli which are the terminations of the receptor cells (*32*). These microvilli, and the distal ends of the taste bud receptor cells from which they project, are embedded in a matrix which may be a polysaccharide-protein mixture (*26*, *31*). The function of this pore chamber matrix is unknown, but it does not seem to present a substantial diffusion barrier (*28*, *33*). However, movement of chemicals from the pore chamber into either the taste buds cells or deeper into the taste buds does not readily occur (*28*), at least in living mammals (*31*). With prolonged contact, radiolabeled glycine, at least, can appear deep in the taste bud (*34*).

The relatively unprotected nature of taste receptors seems unavoidable if rapid but differential responses are to occur for a wide range of molecules and ions solvated in aqueous medium. One would expect that such exposure, which also can include a temperature range from 0°C to almost 40°C (potential terrestrial environment ambient range for drinking water sources) and small particle abrasion, would quickly damage the receptors. This seems to be the case, since the taste bud receptor cells of vertebrates undergo constant replacement (*28*). These cells continuously develop from epithelial cells, enter the taste bud, follow a sequence of differentiation, and disappear. In poikilotherms, the rate of cell turnover can be relatively slow (*12*) and is temperature-dependent. For mammals, a typical taste bud receptor cell has a life span of 10 days (*28*).

Water pollution damages taste receptors in fish. Surface active substances such as detergents appear to be one important factor (*4*, *35*); heavy metals, another (*36*). Mercurials reduce taste stimulus binding at relatively low concentrations, e.g., 100 μM $HgCl_2$. It may be that human taste receptors are also adversely affected by surfactants to which they are exposed. Situations such as detergents in water represent a pollution problem and are recognized as such. However, the surfactant sodium lauryl sulfate (dodecyl sodium sulfate), which is added to toothpaste (*37*), has been demonstrated to modify human taste perception (*38*), as does direct application of dentifrice to the tongue (*39*).

Saliva is a major component of the environment of mammalian taste receptors (*40*). Sufficient variations in its composition or quantity alter taste function. Thus, the ionic composition of saliva affects human taste judgments (*29*); a reduced supply modifies taste-dependent behavior (*40*), leads to altered neural responses and is associated with structural changes in taste bud cells (*32*).

A number of metals and other elements are concentrated in saliva (*41*). This phenomenon includes the heavy metals mercury and copper, and perhaps lead, as well as the halogen fluorine. It has given rise to the suggestion that saliva samples be used to

monitor exposure to metal pollution in humans (*41*, *42*). Heavy metals have a variety of effects on living organisms (*16*). With reference to gustation, salivary heavy metal levels may be significant because taste receptors are sensitive to topical application of heavy metals (*34*). For example, 100 μM $CuCl_2$ depresses mammalian gustatory neural responses to sugars and amino acids. Since water supplies can be contaminated with heavy metals (*43*), human ingestion and subsequent salivary concentration is possible.

In general, the differentiated epithelial cells which make up vertebrate taste buds have little protection from the liquid-borne chemical and thermal events which are their stimuli. The constant and relatively rapid replacement of taste bud cells suggests a high likelihood of damage. Most gustatory stimuli probably do not penetrate farther than the taste bud's pore chamber. Surfactants are known to affect and sometimes damage taste buds, can occur as pollutants in water supplies, and are used as additives in oral hygiene products. Saliva has an important but not fully understood interaction with taste receptors. Since many heavy metals tend to concentrate in saliva, and taste responses can be altered or blocked by topical application of heavy metal solutions, exposure to heavy metal pollution may lead to gustatory damage.

Overview

Many potential environmental hazards exist for olfaction and taste. There has been a general failure to consider or evaluate chemosensory deficits as potential toxicological problems. The importance of human chemosensory function, and the many difficulties which result from chemosensory dysfunction, have been recognized (*44*), but the incidence of chemosensory toxicants in the environment is largely unknown. Adequate testing of chemosensory function as part of industrial medical screening, and as a component of more general examinations, is needed. Our present ignorance may be obscuring a sizeable array of preventable or correctable chemosensory disorders. An active and aggressive program is needed to clarify the nature of environmental factors affecting chemoreceptors.

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