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Impact of Oronasal Inflammation on Taste and Smell: an Introduction

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Introduction

Chronic inflammatory disorders of the nasal and oral cavities can result from a variety of external and internal causes such as infections, chemical exposures, traumatic injuries or surgery, cancer, medications or radiation therapy. The impact of these conditions on chemosensation has been characterized to varying degrees, and these chemosensory losses can be severe and long-lasting. In spite of the adverse impact on the patients, our understanding of the specific mechanisms underlying inflammation-associated chemosensory loss is limited, and therapeutic options are few and often are ineffective or only transiently effective. The lack of consistent diagnostic tools and criteria for defining these disorders has presented a challenge to researchers attempting to understand the chemosensory impact of inflammation. However, new insights into inflammatory pathways and tools to examine their activity in chemosensory tissues provide an opportunity for identifying targets for new therapeutic approaches. This symposium brought together researchers with diverse perspectives to present the current views, new findings and approaches, and highlight needs for further research in this area.

Pathophysiological studies of nasal and oral disorders

Welge-Lüssen reviewed the clinical cases of olfactory and taste disorders¹. The severity of olfactory disorders ranges from reduced olfactory functions to permanent anosmia. Most of these olfactory disorders are caused by nasal inflammation, particularly the sinonasal disorders (SND). Nasal infection, upper respiratory tract infection and allergic response can lead to different types of SND: acute rhinitis, hyposmia, anosmia or allergic rhinitis. It seems that these olfactory defects are not just due to nasal congestion but rather are attributable to the altered olfactory epithelium. Understanding how the alteration initiates and progresses will provide molecular and cellular bases for diagnosis and treatment of these nasal disorders.

The impact of chronic rhinosinusitis on the olfactory mucosa

By assessing morphological changes in the olfactory mucosa of patients with chronic rhinosinusitis, Yee et al found three histopathological patterns of the olfactory mucosa: 1) goblet cell hyperplasia, with excess goblet cells intermixed with olfactory receptor neurons in the apical layers; 2) squamous metaplasia, characteristic of abnormal olfactory neurons and the absence of supporting cells; and 3) erosion with loss of both the supporting cells and olfactory neurons as well as the infiltration of immune cells². These patterns may represent the distinct pathways of the disease incurred by different insults or specific stages of the olfactory mucosa remodeling and repair. The systemic classification of these histopathological patterns will shed light on the progression of chronic rhinosinusitis.

Transgenic mouse model for the study of chronic rhinosinusitis-associated olfactory dysfunction

Lane reported a transgenic mouse model of inducible olfactory inflammation wherein there was temporally-controlled expression of tumor necrosis factor α (TNF α) by sustentacular cells. Analysis of these mice revealed a progressive inflammatory infiltrate into the olfactory epithelium following the inflammatory induction, concomitant with the loss of olfactory sensory neurons and olfactory sensitivity. However, within two weeks after the discontinuation of TNF α expression, the epithelium was nearly reconstituted and the olfactory responsiveness recovered to the normal level. This study demonstrated the effectiveness of transgenic mouse models, which hold promise for improving current knowledge regarding inflammation-associated olfactory loss, and for developing novel treatment strategies³.

The neuroregulation of nasal mucosa

Nasal mucosa is innervated by nociceptive, parasympathetic and sympathetic nerves, which regulate the glandular secretion, vascular supply and immune responses in the olfactory mucosa. Baraniuk et al investigated a number of ion channels and G-protein coupled receptors that have been found in the olfactory mucosa, including TRPV1, CFTR, aquaporins, ASICs, and adrenergic, bradykinin, CGRP, substance P, histamine and endothelin receptors⁴. The activation of these ion channels and receptors by capsaicin and other irritants or by the mediators released from the nerve terminals or immune cells regulates the secretion of mucus and other antimicrobial agents, thus controlling the swelling and airflow in the nasal cavity, as well as the cell turnover and tissue remodeling in the nasal cavity. Identification of these molecular players in the regulation of nasal mucosa may provide a rationale for responses to a variety of stimuli such as air temperature change and inhaled irritants as well as new targets for therapeutic approaches.

Inflammation on taste disorders

A number of conditions can cause taste disorders, for example, oral surgery, medication, and bacterial or viral infection. However, little is known about the molecular mechanisms underlying the onset and development of taste dysfunctions. In an investigation of the possible contribution of immune responses to taste deficits, Wang et al revealed that a number of Toll-like receptors (TLRs) as well as receptors for interferons are selectively or more abundantly expressed in taste bud cells than in the surrounding non-gustatory lingual epithelium⁵. TLRs are part of the innate immune system that recognizes evolutionarily conserved pathogen-associated molecular patterns such as bacterial cell wall components or viral RNA molecules. Activation of TLRs triggers downstream signaling pathways, which can lead to the synthesis of interferons and other cytokines, or even apoptosis. The interferon signaling pathways are part of innate immunity as well, but they also interact with the adaptive immune system. The interferon receptors are localized to subsets of type II and

type III taste bud cells, and can be activated in an *ex vivo* system by recombinant interferons, resulting in the phosphorylation of some transcription factors and expression of IFN-inducible genes. With an animal model that mimics bacterial and viral infections, the systemic administration of lipopolysaccharide, polyinosinic: polycytidylic acid or synthetic interferons not only altered gene expression patterns but also increased the number of cells undergoing programmed cell death in taste buds. This study provides the first direct evidence that the immune system may affect taste bud function and cell turnover and suggests a molecular basis for understanding taste disorders⁶.

Future directions

While some diseases impact one chemosensory system exclusively or much more significantly than the other, many diseases and conditions, such as autoimmune diseases and upper respiratory tract infection, can cause both taste and olfactory disorders. It would be interesting to know whether there are common underlying mechanisms that could lead to an optimal strategy for diagnosing and treating dysfunctions of both taste and olfaction.

More clinical cases are to be investigated to determine there are correlations between the types of pathogens such as viral infection or medication and the histopathological patterns of the olfactory mucosa. Further studies are also needed to define the signaling networks that are mediated by multiple ion channels and receptors present in the olfactory mucosa. Transgenic animal models appear to be powerful tools to characterize the possible roles of each molecular player in the initiation and progression and inflammation and chemosensory dysfunctions. Quantitative evaluation of their contribution to the loss of olfactory receptor neurons and supporting cells, tissue remodeling and repair will enable us to establish a mathematical model that is capable of predicting the progression of the disorder and suggesting an appropriate treatment.

The expression of TLRs in taste buds but not in the surrounding lingual epithelium indicates that the end organs of taste retain innate immunity, which is consistent with the fact that taste bud cells are directly exposed to the external environment. A systematic survey seems to be needed to determine whether other immune response-related genes are expressed in taste buds. On the other hand, it would be interesting to know whether the activation of TLR receptors on taste bud cells elicits or interferes with taste perception since the immune system is known to be the “sixth” sense. Gustatory nerve recordings can be performed to examine the transmission of signals from taste buds to the afferent cranial nerves in response to signature molecules of microbial pathogens such as the aforementioned lipopolysaccharide, and polyinosinic: polycytidylic acid. By the same token, gustatory nerve recordings can be carried out to determine whether the amplitudes of the nerve responses to a variety of tastants have been changed following the interferon-mediated cell death in taste buds. Data from these studies will quantify the impact of inflammation on taste sensation.

In summary, these studies have laid a solid foundation for future studies, which will provide new insights into diagnoses, treatment and even cure of these disorders.

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