BACTERIAL BIOFILMS IN CHRONIC RHINOSINUSITIS

Essay

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البيوفيلم البكتيري ودوره في مرض الالتهاب المـزمن بالأنف والجـيـوب الأنفيـة

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OBPs	Odourant binding proteins.
IP3	Inositol phosphate.
cAMP	Cyclic adenosine monophosphate.
CRS	Chronic rhinosinusitis.
EPS	Extracellular polymeric substance.
ICU	Intensive care unit.
SEM	Scanning electron microscopy.
TEM	Transmission electron microscopy.
FISH	Fluorescent in situ hybridization.
CLSM	Confocal laser scanning microscopy.
MOXI	Moxifloxacin.
MIC	Minimal inhibitory concentration.
FESS	Functional endoscopic sinus surgery.
3-D	Three dimensional.
ESS	Endoscopic sinus surgery.
A.V	Arteriovenous.

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Introduction

Chronic rhinosinusitis (CRS) is a prevalent, debilitating condition, poorly controlled by antibiotics and a subpopulation of patients fails to respond to either medical or surgical intervention. Postulated etiologic factors leading to chronic rhinosinusitis include allergy, fungi, functional factors and biofilms. Evidences now suggest that bacterial biofilms may play an important role in chronic rhinosinusitis (Palmer, 2006) and would explain the refractoriness of chronic rhinosinusitis to antibiotic therapy (Ferguson and Stolz, 2005).

Bacterial biofilms are three dimensional aggregates of bacteria that are attached to a surface and encased in a matrix of exopolymeric material (Sanderson et al., 2006). The extracellular polymeric substance include exoplysaccharides, nucleic acids and proteins and it represents about 98% of the volume of the biofilm (Bendouah et al.,2006).

Bacterial biofilms are increasingly implicated in the pathogenesis of chronic diseases and have been established in several chronic ear, nose and throat conditions including chronic rhinosinusitis, chronic otitis media, cholesteatoma, chronic tonsillitis and chronic adenoiditis (Post et al.,2004).

Physiology of the nose and Paranasal sinuses

Nasal and paranasal mucosa :

The nasal lining has the same lining as the rest of the respiratory tract with pseudostratified ciliated columnar epithelium and there are up to 200 cilia per cell whose tips lie in the superficial gel layer (Jones, 2001). This pseudostratified columnar ciliated epithelium (respiratory epithelium) is composed of 4 major types of cells: ciliated, non ciliated, goblet, and basal cells (Cauwenberge et al ., 2004), with the proportion of goblet cells higher on the inferior turbinate and lower part of the nasal septum (Wagenmann and Naclerio, 1992). The nasal epithelium is separated from the lamina propria by a continous basement membrane. The supporting connective tissue is of loose type and its lymphoid layer is formed of lymphocytes and plasma cells (Watelet et al., 2006). A functional nasal mucosa can assume mucus production and transport, resorption of surface materials, and formation of new epithelial cells (Watelet and Cauwenberge, 1999).

The subepithelial region contains 2 layers of sero-mucous glands ; the superficial layer is situated just underneath the epithelium, and the deep layer under the vascular layer (Watelet et al., 2006). Besides resistant vessels, such as arteries, arterioles and capillaries, the vasculature of the nose is characterized by capacitance vessels, designated as “erectile tissue”. This vascular component is mainly

concentrated on the middle and inferior turbinates, the septum may extend posteriorly to the choanal orifices. These vascular specificities enable the nasal mucosa to regulate the air flow, adapt the nasal resistance, filter and condition the inspired air by producing nasal mucous, and help sustaining a mucociliary transport. Also, it serves as a support for immune response (Cauwenberge et al., 2004).

The mucosa isolated from sinuses is slightly different, mainly thinner and less specialized than nasal mucosa, the epithelium contains fewer cilia than nasal mucosa and the basal lamina is always easily identifiable. The glands are fewer and smaller and the venous erectile plexus is absent (Watelet et al., 2006). These differences could be explained by differences in flow of inspired air (Lindmann et al ., 2004) or in extent of mesodermisation during the formation of the midface and nasal cavities from 4-12 weeks of intrauterine (Watelet et al., 2006).

Olfactory mucosa:

The olfactory organ is unique in the central nervous system , being the only part in direct contact with the environment and also has the ability to regenerate damaged or lost neurones (Hadely et al., 2004). The olfactory epithelium covers an area of about 370 mm^2 lying partly on the nasal septum and partly on the superior and middle turbinate. Also, there is a vestigial olfactory organ “Jacobson’s organ” or “the vomero-nasal organ” which can be seen as a blind-ended pit on the side of the septum (Schiffman , 1993).

The olfactory neuroepithelium is composed of olfactory sensory neurons, sustentacular or supporting cells which ensheath the receptor neurones and maintain the normal extracellular potassium levels needed for neuronal activity. Also, there are basal cells which replace the neuroepithelium approximately every 40 days (Christensen et al., 1996). The olfactory neurone is a bipolar cell with round cell body and has 10 - 23 cilia on its surface, which are up to 200 m long and may overlap with the cilia of adjacent neurones. The cilia have a nine plus two pattern of microtubules characteristic of motile cilia but towards the tip there is only a central pair. The olfactory sensory neurone tapers into an unmyelinated axon and synapses in the olfactory bulb. Basal cells are small polygonal cells in contact with the underlying basement membrane and are the stem cells for receptor and sustentacular cells. The underlying lamina propria contains olfactory nerve fascicles and mucus-secreting tubuloalveolar Bowman`s glands (Jones, 2001).

When neuronal axons penetrate the cribriform plate, they become covered by schwan cells. One schwan cell usually contains 5 - 10 fibres , but occasionally it contains up to 100 fibres. About 15.000 olfactory receptor cells converge on one mitral cell or tufted cell in the olfactory bulb which is about 12.2 (6-16) mm long. Both mitral and tufted cells project a single primary dendrite to a single glomerulus and emit several dendrites within the external plexiform layer (Jones, 2001). Periglomerular cells, granule cells and short axon cells are interneurones connecting glomeruli. From the olfactory bulb tract, the main axons originate in the mitral or tufted cells and give off striae

which pass to the olfactory tubercle and then projections go to the amygdale, the prepyriform cortex, the anterior olfactory nucleus and the entorhinal cortex as well as the hippocampus, hypothalamus and thalamus. The olfactory axons have both convergent and divergent projections and are not point to point like the visual or somatosensory system (Christensen et al., 1996).

Functions of the nose and paranasal sinuses:-

We breath in about 12 to 24 times a minute, inhaling approximately 10.000 litres of air a day with different temperature, humidity and which contains dust and organisms (Jones , 2001) .

The nose and paranasal sinuses has the following functions that are often taken for granted until they are lost: (Jones, 2001):-

1- Olfaction. 2- Sensation. 3- Immunology.

4- Mucociliary clearance. 5- Filtration.

6- Warm and Humidify. 7- Nasal cycle and Airflow dynamics.

1- Olfaction:

Humans can detect more than 10.000 different odours and discriminate between 5.000 odours (Jones,2001). The olfactory sensory epithelium has several million olfactory sensory neurons (Rog and Jones, 1998). Odourant binding proteins (OBPs) bind and solubilise hydrophobic molecules, increasing their concentration up to 10.000 times than in ambient air (Ronnett and Moon, 2002). Also, they remove the odourant molecules after transduction, which occurs after specific interactions between the odourant molecules and

receptor proteins on the surface of the olfactory cilia (Christensen et al., 1996). Olfactory transduction is probably then mediated via a unique olfactory epithelium G_{olf} -protein coupled cascade, with cAMP and / or IP_3 (phosphoinositide specific phosphodiesterase C) as an intracellular 2nd messenger, exciting an ion channel in the cilia, which depolarises the olfactory neurone (Hadley et al., 2004). Yet, some odourants have been found to activate cAMP specificlly and others to activate IP_3 and it is not known if these odourants affect the same or different membrane ion channels (Rog and Jones, 1998).

The precise mechanism by which the vast number of smells is recognized and discriminated is unknown, but possible theories include; specific odourants exciting specific receptors which are randomly grouped or aggregated (Hadley et al., 2004), the differing solubility´s of odourant allowing a temporospatial distribution of the odourant across the olfactory mucosa (Ronnet and Moon, 2002), or a response to the molecules' vibration spectra within an inelastic electron tunnel formed by olfactory receptors and their associated G-protein (Jones, 2001). The structure based theories, on their own, can not explain differences in smell between identical substances,such as acetophenone, and its analogue acetophenone-d8. Thus, the vibration theory has received media prominence recently. It proposes that it is the vibration frequency of a molecule which is detected by receptors. When a molecule attaches to a receptor, it detects that vibrational mode and allows electrons to jump across the receptor and then trigger

the neurone (Christensen et al., 1996), and according to Lund (1996), it might be possible for one receptor to detect a range of vibrational energies.

Adaptation is a characteristic of olfaction and in the past, it has been thought to be due to receptor phosphorylation which modulates the normal signal transduction and activation of the adenyl cyclase /cyclic AMP second messenger system (Ronnett and Moon, 2002). More recent work suggests that the effect is downstream and a modulation of the cAMP-gated channel from ca^{2+} feedback (Barrody, 2007).

There are other effects caused by smell such as pheromones having a strong psychosexual influences. Moreover, odourants have biological meaning, a child preferring mothers' smell after only 6 to 10 days (Hadley et al, 2004). Established odour associations can last at least one year, three times as long as for visual stimuli (Schiffman, 1993).

2- Sensation:

The common chemical sense in the nose which originate from free nerve endings scattered throughout its lining is different from olfaction and provides the sensation of irritation or burning when stimulated by substances such as ammonia and chilli peppers. This is mediated by branches of the trigeminal nucleus, thalamus and somatosensory cortex (Christensen et al., 1996). Both sensations have