STUDY OF CONCENTRATION AND MORPHOLOGY OF MECHANORECEPTORS IN THE MUCOSA OF UNCINATE PROCESS OF THE HUMAN NOSE

By

DR ADIL S. ABD ALRAZAQ

Dissertation Submitted In Partial
Fulfillment Of
The Requirement for the Degree Of
Master Of Medicine
(Otorhinolaryngology- Head and Neck Surgery)

UNIVERSITY SAINS MALAYSIA

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FESS	-	Functional Endoscopic Sinus Surgery
EDTA	-	Ethylenediaminetetraacetic Acid
TBS	-	Triss Buffer Saline
DAB	-	Diamino Benzide
HPF	-	High Power Field
HUSM	-	Hospital Universiti Sains Malaysia
cAMP	-	Cyclic Adenosine Monophosphate

ABSTRACT

BAHASA MALAYIA VERSION

TAJUK: Kajian mengnai kepekatan dan ciri-ciri reseptor mekanikal pada lapisan kulit "uncinate process" hidung.

TUJUAN: Untuk mengkaji mekanoreseptor dalam mukosa hidung manusia, dan membandingkan min kepekatan reseptor mekanikal dalam mukosa uncinate pada pesakit yang mempunyai polip hidung dan tenap polip hidung.

METADOLOGI: Jumlah 12 subjek oranng dewasa direkrut, yang mana enam peserta dalam kumpulan kajian (pesakit dengan polip hidung) dan enam peserta legi dalam kumpulan kawalan (pesakit tanpa polip hidung). Kedua-dua kumpulan menjalani pembedahan FESS untuk patologi hidung mereka. Semasa pembedahan / surgen, 1×1 cm tisu daripada mukosa uncinate dipotong dan dimasukkan ke dalam cecair formalin.Tisu tersebut dihantar ke makmal patologi untuk pewarnaan antibodi berlabel calretinin dan antibodi berlabel neurofilamen. Setelah pewarnaan sampel menggunakan teknik imunohistokimia, slaid diperiksa dengan mikroskop cahaya.

KEPUTUSAN: Tidak ada sel dikenalpasti yang diwarnai oleh antibodi calretinin pada 12 sampel.Tersebut Namun sampel yang diwarnai dengan antibodi neurofilamen menunjukkan adanya terminal saraf di mukosa di semua 12 sampel. Konsentrasi terminal saraf secara signifikan lebih besar pada pesakit tanpa polip hidung (20.67 ± 5.046) berbanding untuk pesakit dengan polip hidung (11.67 ± 7.257).

PERBINCANGAN: Keputusan menunjukkan bahawa tidak ada sel-sel khusus di mukosa hidung yang bertindak sebagai reseptor mekanikal. Namun kehadiran terminal saraf di mukosa hidung dan antara sel-sel epithelia menunjukkan bahawa mereka adalah "C-mechanoreceptors" yang dianggap sebagai terminal saraf polymodal. Selain itu, penurunan konsentrasi mereka pada pesakit dengan polip hidung boleh menjadi alasan ada atau tidak adanya rasa hidung tersumbat.

ABSTRACT

ENGLISH VERSION

TITLE: Study of concentration and morphology of mechanoreceptors in the mucosa of Uncinate Process of the human nose.

OBJECTIVE: To study the mechanoreceptors in the human nasal mucosa and to compare the mean concentration of mechanoreceptors in the Uncinate Process mucosa in patients with and without nasal polyp.

METHOD: Subjects were 12 adult patients; six participants in the study group (patient with nasal polyp) and six participants in control group (patients without nasal polyp). Both groups underwent functional endoscopic sinus surgery for their nasal pathology. During operation 1×1 cm from the uncinate process mucosa was excised then fixed with formalin and sent to the pathology laboratory for staining, each sample was stained for Calretinin-labeled antibody and Neurofilament- labeled antibody. After the staining process, the slides were examined by light microscope.

RESULT: There were no cells identified to be stained by Calretinin antibody in all 12 samples. However sample that stained with Neurofilament antibody showed the presence of the nerve terminals in the mucosa of all 12 samples. The mean concentration of nerve terminals was significantly higher in patients without nasal polyp (20.67±5.046) than for patients with nasal polyp (11.67±7.257).

DISCUSSION: The results suggest that there are no specific cells in the nasal mucosa that act as mechanoreceptors. However the presence of the nerve terminals in the nasal mucosa and between the epithelial cells suggests that they are C-mechanoreceptors which are thought to be polymodal nerve terminals. In addition, reduction in the concentration of nerve terminals in patients with nasal polyp can be the reason for the reduction or absence of the feeling of nasal obstruction in some patients with nasal polyp.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

The human nose which is situated at the beginning of the respiratory tract plays an important role in the respiration and olfaction; it provides humidification and filtration for the inspired air and also has an important role in regulation of body temperature through vaporization of the water from its surface epithelium.

The nasal cavity is lined by respiratory epithelium which is composed of ciliated and non-ciliated pseudostratified columnar epithelium with basal stem cells and goblet cells, except for the superior part of nasal cavity which is lined by olfactory epithelium (Stammberger, 2008a).

The submucosa of the nasal cavity contains many seromucinous glands which is important in the production of mucus. The submucosa also contains the cavernous venous plexus and the arteriovenous anastomoses which are also present in the nasal mucosa. The nasal mucosa receives sensory nerve supply from the Maxillary division of the Trigeminal nerve (Stammberger, 2008a).

In case of inflammation of the mucosal lining of the nasal cavity caused by allergy or infection there will be release of inflammatory mediators like Histamine and Interleukins which leads to dilatation of the venous sinusoids in the submucosa with increase secretion of fluid and mucous from the glands with subsequent mucosal edema leading to nasal congestion. Those inflammatory mediators also can cause modulation in the sensory afferent of the nasal mucosa with subsequent feeling of nasal obstruction (Robert, 2010).

Those sensory afferents of the mucosa play an important role in the feeling of nasal congestion and nasal obstruction in patients with nasal polyp.

It seems to be that the nasal polyp exerts pressure on the nasal mucosa causing mechanical stimulation to the sensory afferents with subsequent feeling of nasal obstruction. However, there are some patients with nasal polyp do not have the feeling of congestion or nasal obstruction.

In addition to those functions of the sensory afferents, it is believed that they play an important role in the protective function of the nose by provoking many defensive reflexes in response to foreign body and mechanical stimulation ranging from sneezing, bronchospasm to cardiorespiratory arrest (Widdicombe J, 1988).

Such sensory functions of the nasal mucosa have been thought to be mediated by nasal Trigeminal afferents and several types of mechanoreceptors such as pressure, drive and touch (Sant'Ambrogio, 1995).

1.1 MECHANORECEPTORS

Mechanoreceptors are group of receptors that are stimulated by variety of external stimuli like touch, change in pressure and vibration. In addition to the important functions of these mechanoreceptors in controlling and regulation of many body functions, it is believed that they play a major role in the development of different body tissue such as the bones, skeletal system, blood vessels and cartilage. They also play an important role in maintaining the intracellular haemostasis (Wu *et al.*, 2009).

Mechanoreceptors are present in the skin (Johansson and Vallbo, 1983) and in other part of the body such as joint (Lee, 2009) and mucosal surface(Griffin, 2006). They are formed from the terminal ending of the sensory nerve fibers that innervate the skin and other part of the body (Scott, 2000). Some of the sensory nerve fibers in the skin and mucosal surface are ended by expanded terminals called the corpuscles which have a capsule and contain mitochondria and vesicles (Hamann, 1995). These corpuscular nerve terminals act as mechanoreceptors stimulated by mechanical force applied to the skin and mucosal surface.

Mechanoreceptors are classified into five types based on their morphology (Scott, 2000):

1- Merkel corpuscles

2- Ruffini corpuscles

3- Meissner corpuscle

4- Pacinian corpuscles

5- Free nerve ending (C-mechanoreceptor)

The first four corpuscles are encapsulated and the myelinated sensory nerve fibers that supply the skin or the mucosa lose its myelin sheath upon interring the capsule. While the fifth type are non-encapsulated and they are considered a simple non-expanded free nerve terminals of the sensory nerve fibers (Hamann, 1995).

The mechanoreceptors also classified into five types depending on their physiological properties in response to mechanical stimulation (Hamann, 1995).

1.1.1 Slowly-adapting Type I receptor (e.g. Merkel corpuscles):

In this type of mechanoreceptor the response arises from a very small receptive field with sharp margins. Continuous low force mechanical stimulation applied to the receptor in vertical manner results in irregular slowly adapting response and the receptor have no spontaneous discharge (Johansson and Vallbo, 1983).

Merkel corpuscle

The Merkel corpuscle is flat to round shape corpuscle (Figure 1.1). The superficial part of the corpuscle embedded in the epidermis of the skin while its deep part embedded in the dermis. In human its maximum diameter is about 8.0 μm (Beira, 1987).

The sensory nerve fibers that entered the Merkel corpuscle lose its myelin sheath upon crossing the basement membrane forming a thin sheet with thickened edges to hold the dermal aspect of one Merkel corpuscle. The terminals contain a high concentration of mitochondria and vesicles. However the function of these vesicles is still unknown (Hamann, 1995).

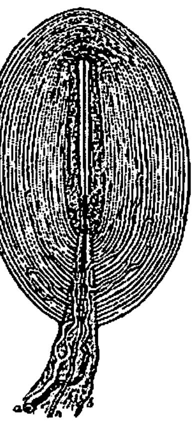

Figure1.1: Merkel corpuscle en.wikipedia.org

1.1.2 Slowly-adapting Type II receptor (e.g. Ruffini corpuscles):

In this type of receptor the response arises from a large receptive field with vague margins. In contrast to Type I slowly adapting receptor, this receptor shows regular slowly adapting response upon continuous low force vertical mechanical stimulation (Johannson, 1978).

Ruffini corpuscles

The Ruffini corpuscles is elongated in shape, encapsulated, located in the dermis and supplied by one axon which is bifurcated within the capsule to form a terminal arborisation (Figure 1.2). This terminal is rich in mitochondria, particles of glycogen, electron-opaque lipid material and numerous vesicles.

This Ruffini corpuscle carried a resting discharge and responded to vertical stimulation of the skin and they are sensitive to skin stretch. The response of the Ruffini corpuscles to vertical stimulation consisted of a static phase and dynamic phase with a period of adaptation in between (Chambers, 1972).

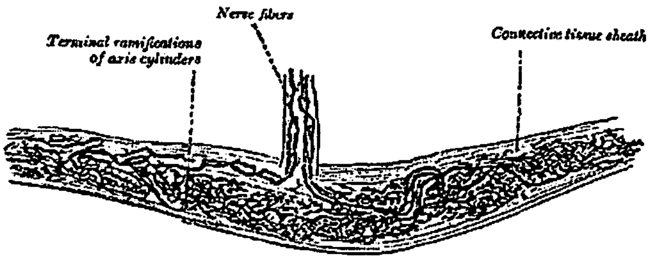

Figure 1.2: Ruffini corpuscle en.wikipedia.org

1.1.3 Rapidly-adapting Type I receptors (Meissner corpuscle):

The receptors shows rapidly adapting response to vertical low force mechanical stimulation with pointed receptive field (Lynn, 1982).

Meissner corpuscle

Meissner corpuscle consists of vertical column of flat cells which are supportive cells (laminar cells) surrounded by fibrous capsule consist of collagenous and elastic fibres (Figure 1.3). The myelinated sensory nerve fibres inter the capsule at the base of the corpuscle following the same arrangement of the laminar cells making synapses with them. Once inside the capsule they lost their myelin sheath and arborized inside the corpuscle without recommunications and ends by forming terminal expansion near the cell membrane (Cauna, 1966).

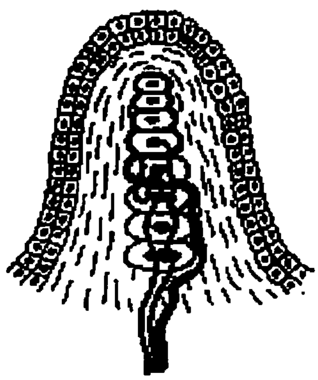

Figure 1.3: Meissner corpuscle. faculty.washington.edu

1.1.4 Rapidly adapting type II receptors (Pacinian corpuscles):

The response of these receptors evoked by vibration with vague margins of response from the stimulated surface.

Pacinian corpuscles

Pacinian corpuscles are oval and large in size. Each corpuscle supplied by only one myelinated afferent axon. The axon with its sheath passes through the capsule to the inner core. Before interring the core the axon lost their perineurial sheath and become tortuous forming internodes and terminates in a single node. In the core the terminals send hundreds of lateral process called spins which ends by club-like expansion (Figure 1.4) (Zelená, 1974).

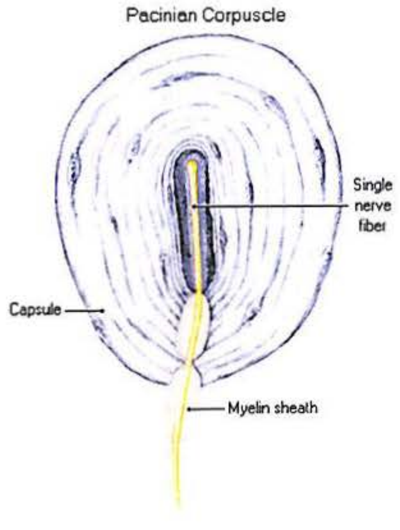

Figure 1.4: Pacinian corpuscles. www.medicalook.com

1.1.5 C-mechanoreceptor

They are non-encapsulated free nerve ending present in the epidermis of the skin and other part of the body. Their response is easily fatigued to low force mechanical stimulation of the skin and to bending of hair (Hamann, 1995). These free nerve ending are considered as a polymodal nerve terminals which are act as noiceceptors when stimulated by noxious event producing pain sensation and mechanoreceptors when stimulated by mechanical force (Scott, 2000).

1.2 MECHANORECEPTION

The process by which the mechanoreceptors transmit the mechanical stimuli into electrical signal that is transmitted through the sensory axons to the central nervous system is called mechanoreception.

Mechanoreception have three component : coupling, transduction and encoding (Loewenstein, 1959).

The stimulus is first coupled mechanically to the receptors membrane. Then it is transduced to receptors potential. When the cell is excited, the receptors potential is encoded into action potential which is then transmitted through the sensory axons.

1.2.1 Coupling

Process by which the mechanical stimuli are attached to the cell membrane of the mechanoreceptors. Most mechanoreceptors are not exposed to the external environment; they have some sort of tissue which separates the receptors from the origin of mechanical stimuli. These tissues are designed to change or modify the amplitude and properties of the signal in attempt to attenuate the stimulus so that the receptors membrane displaced to less extent than original movement.

1.2.2 Transduction

Transduction means conversion of the mechanical force into receptors potential across the cell membrane. These receptors potential depend on the presence and concentration of specific ion in the external environment (French, 1992).

The cell membrane of the mechanoreceptor contains an ion channel that is activated mechanically. However it cannot be sure that these ion channel are situated in the fine sensory ending in which the transduction mechanism take place.

In Pacinian corpuscles and stretch receptors for example, its seems to be that the mechanotransduction depend on the presence of sodium ion in the surrounding solution which are good indicators that these channel are permeable for sodium (Loewenstein, 1971).

Each type of receptor ending is surrounded by a solution with high sodium ion concentration. During the mechanical stimulation these mechanically active sodium ion channel are opened and the sodium ion pass in to the cell causing depolarization of the cell membrane (Höger, 1997).

1.2.3 Encoding

After the conversion of the mechanical stimulation into receptor potential, the depolarization of the cell membrane provokes a chain of action potentials.

In some receptors the depolarization results in the entry of calcium into the cell through a voltage–gated calcium channel, which causing an outward movement of potassium ion through the calcium–activated potassium channel and increase the potassium movement outward the cell and in turn reduce the depolarization (Lewis, 1982).

However in other receptors the receptors current can be activated by influx of sodium ion through voltage-gated channel causing depolarization which in turn leads to activation of sodium–potassium pump leading to outward movement of potassium and repolarisation (Sokolove, 1971).

These two repolarisation processes are strongly linked to the adaptation mechanism of the receptor.

Most information about the morphology and distribution of these mechanoreceptors in the nasal cavity are obtained from animal study and very little is known about human nasal mucosal mechanoreceptors.

In rats, pressure-responsive receptors had been identified in the nasal mucosa and they were distributed at the ethmoidal nerve area. However the majority of these receptors where stimulated by maintained negative pressure and they are in active in maintained positive pressure. The exact mechanism by which these mechanoreceptors are stimulated is unknown. However one explanation is that the distortion of the mucosa