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

By

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LIST OF ABBREVIATIONS

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).

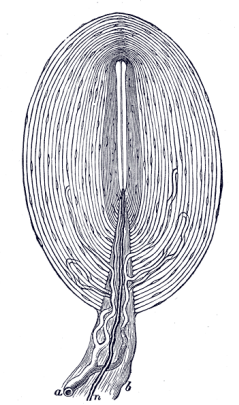

Figure1.1: Merkel corpuscle en.wikipedia.org

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).

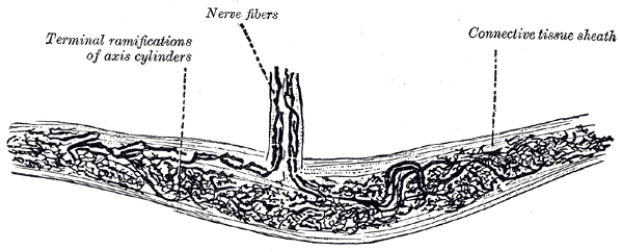

Figure 1.2: Ruffini corpuscle en.wikipedia.org

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).

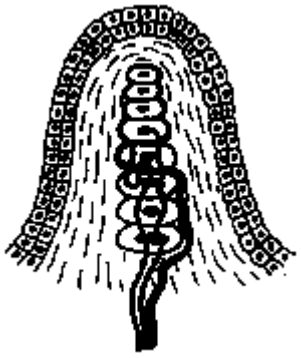

Figure 1.3: Meissner corpuscle. faculty.washington.edu

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).

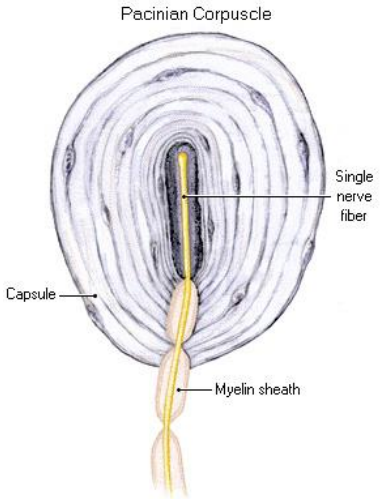

Figure 1.4: Pacinian corpuscles. www.medicalook.com

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

during negative pressure application leads to stretching and stimulation of these endings (Tsubone, 1990).

While in cats the mechanoreceptors stimulated by drive and/or pressure were found mostly in the posterior nasal and infraorbital nerve area. Only one receptor was found in the ethmoidal nerve area (Wallois, 1991).

In guinea pigs, 22 mechanoreceptors were identified by mechanical probing to the vestibule and the alae nasi. They were consisting of touch-responsive receptors and probably a smaller number of pressure and drive-responsive receptors. The touch–responsive receptors were silent until stimulated by probing and they are rapidly adapting receptors and none of these mechanoreceptors were stimulated by ammonia inhalation (Sekizawa and Tsubone, 1996).

In avian, 75 mechanoreceptors were identified and they were distributed throughout the nasal mucosa. Part of those receptors was slowly adapting receptors and others were rapidly adapting receptors. When the receptors were exposed to ammonia, 24 receptors shows response to chemical stimulation. These receptors are thought to be polymodal receptors responds to mechanical and chemical stimuli with different threshold (McKeegan, 2004).

All the above mentioned studies shared the same principles of identifying the numbers, distribution and the physiological properties of the mechanoreceptors in the animal nasal mucosa. The animal was anesthetized and tracheotomised. The infraorbital nerve, ethmoidal nerve and posterior nasal nerve were dissected and exposed and connected to electrodes. The nasal mucosa was then stimulated by different type of stimuli (probing,

negative and positive pressure, air jet stimulation and ammonia). The response to each stimulus was recorded from each nerve namely the latency, duration and frequency of discharge through the nerves.

However there are other animal studies which describe the morphological and histological properties of the mechanoreceptors in the nasal mucosa.

In rat, the Ruffini corpuscle (slowly adapting mechanoreceptors type II) was identified as expanded axon terminals in the periodontal ligament by using the immunohistochemical staining(Ochi, 1997). Polyclonal anti-calretinin anti serum was used to identify those Ruffini corpuscle.

Calretinin is one of the intracellular calcium–binding proteins. There are two groups of calcium binding proteins inside the cell, the first group is the “trigger” group such as calmoduline which change their shape upon binding to calcium. The second group is the “buffering” group which simply binds to calcium without changing their shape. Calretinin and calbindin D-28K are considered from the last group (Andressen, 1993).

The role of these calcium-binding proteins is to regulate the intracellular calcium concentration which play very important role in the transduction of the mechanical stimuli to an electrical signal (Akoev, 1989).

When the cell is targeted by neurotransmitters, an intracellular second messenger like cAMP and intracellular calcium are activated. These messengers then targets another intracellular proteins such as protein kinase, G-protein and calcium binding proteins like calretinin (Andressen, 1993).

In mechanoreceptors, the mechanical stimuli results in deformation of the axon terminals of the receptors which leads to rapid influx of calcium into the terminals. One of the roles of calcium-binding proteins is to buffer the increase in the intracellular calcium concentration (Tachibana, 1992).

Recently the use of these calcium binding proteins as neuronal markers by using antibodies against them is increasing. This allows study of the anatomical and morphological properties of different cells of the nervous system. They can give very good cytoskeleton staining and allow visualization of cellular morphology (Andressen, 1993).

In dogs, the corpuscular nerve ending which thought to be pressure receptors and stretch receptors (Ruffini corpuscles) were identified in the nasal mucosa by immunohistochemical staining method. The shape of these corpuscles was complicated but in general three main shapes was identified, laminar, bulbous and varicose. Also a free nerve ending which is thought to be noiceceptors was identified. They were distributed on the dorsal part of nasal septum and dorsal part of nasal concha (Yamamoto, 1998).

In human, there is physiological evidence suggesting the presence of these mechanoreceptors in the nasal cavity. These studies show also the clinical importance and the role of these mechanoreceptors in maintaining the patency of the upper airway. Packing of the nasal cavity with gauze stimulates the mechanoreceptors in the mucosa resulting in change in the airway resistance which is measured by plethysmograph which shows either increasing or reducing in the value of the resistance. In some subjects the resistance value rose immediately or within five minutes then start to return

to its pre-packing level. In others, the resistance fell immediately or within 20 min after packing then return to its pre-packing level (Ishizuka and Usui, 1980).

Nasal intermittent positive pressure ventilation used for the treatment of patient with respiratory failure seems to cause significant increase in the upper airway resistance which is not seen when using oral positive pressure ventilation. These finding suggest the presence of nasal mechanoreceptors which evoked a nasopulmonary bronchoconstrictor reflex (Fontanari *et al.*, 1999).

Insertion of endotracheal tube through the nasal cavity results in unexplained bradycardia which is seems to be due to nasocardiac reflexes evoked by the mechanical stimulation of the nasal mucosa (Adrian, 2008).

So far there is significant lack in the histological information of the mechanoreceptors in the human nasal mucosa.

There is only one study done to explain the morphology of the sensory nerve fibres in the nasal mucosa in general. The study shows that the nasal respiratory epithelium is supplied by non-myelinated nerve axons devoid of nerve sheath. These nerve fibres inter the mucosa in fascicles containing 200 axons and ending in the lamina propria. These fibers contain mitochondria and granules and fine vesicles (Cauna, 1969).

Studies had shown the presence of these mechanoreceptors in other part of the body such as oral cavity, Meissner corpuscles and free nerve ending had been demonstrated in the oral cavity. By using the electron microscope, the Meissner corpuscle was located in the mucosa of soft palate, hard palate, gingiva and cheeks while the free nerve ending

was seen in the submucosa and extends into lamina propria just beneath the epithelium (Griffin, 2006).

Using the immunohistochemistry technique, the Merkel corpuscle was identified in the mucosa of the gingiva, palate and buccal mucosa together with free nerve ending which was located in the submucosa and some of them extend between the epithelial cells (Hilliges, 1996).

However the Ruffini corpuscles were identified as expanded nerve terminals in the anterior cruciate ligament of the human knee. Using immunohistochemistry with neurofilament antibody, it was able to identify eight Ruffini corpuscles in normal ligament and six corpuscles in ruptured ligament (Lee, 2009).

Neurofilaments are one type of the proteins that form the neural axons filaments. They are present almost exclusively in neural axons and consider as intermediate filament between the other filaments of the nerve axons namely the actin and microtubules filaments. They form a major component of the cytoskeleton support for the axonal cytoplasm (Tong *et al.*, 1999).

Labeled antibody against this neuronal protein is used for the identification of the nerve cells and axons in the central and peripheral nervous system using the immunohistochemistry technique.

The information about the distribution, concentration and morphology of the mechanoreceptors in the nasal mucosa seems to be very important in understanding of many symptoms and signs of patient with different nasal pathology such as the nasal polyp. The main complain of a patient with nasal polyp is nasal obstruction. However

some patient with the same degree nasal polyp does not have any symptoms of obstruction. It is seems to be that these mechanoreceptors in the nasal mucosa play an important role in the feeling of nasal obstruction.

In this study it is hoped that more information about the morphology and the concentration of these mechanoreceptors in the human nose can be brought about. So far there is only one study done by cauna in 1969. He examined the mucosa of middle turbinate, inferior turbinate and mucosa from the nasal septum and he only explain in general the morphology of the sensory nerve ending in the human nasal mucosa by using light and electron microscope.

In this study the mucosa of the uncinate process is taken after the process is excised as part of procedure during the operation of Functional Endoscopic Sinus Surgery for patient with and without nasal polyp. The mucosa then examined using the light microscope with tissue stained by immunohistochemical staining using anti-calretinin and anti-neurofilament antibodies to visualize these mechanoreceptors. By using electron microscope, to detect the cellular morphology of these mechanoreceptors.

By comparing the concentration of the mechanoreceptors in the uncinate process mucosa of patients without nasal polyp to their concentration in patients with nasal polyp, we are hoping to answer the question of why some patients with nasal polyp have the feeling of nasal obstruction while other patients do not.

1.3 ANATOMY OF NASAL CAVITY

The nasal cavity is extending from external nares anteriorly to the posterior choanae posteriorly where it joints the nasopharynx. It is divided into two cavities by nasal septum

1.3.1 Nasal septum

The septum composed of membranous part which is the most anterior portion, cartilaginous part (quadrilateral cartilage and small portion from upper and lower lateral cartilages) and the bony part (perpendicular plate of ethmoid bone which forms the anterior and superior portion, and the vomer bone which form the posterior and inferior part of the bony septum) (Figure 1.5) (Stammberger, 2008b).

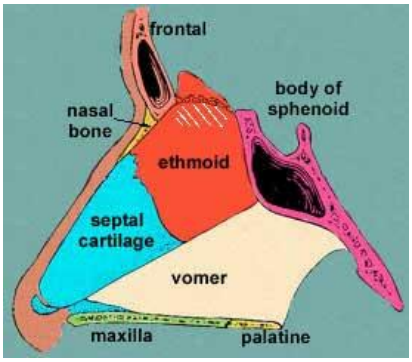

Figure 1.5: Anatomy of nasal septum

1.3.2 Lateral nasal wall

The lateral wall of the nasal cavity composed of three bony projections (inferior, middle and superior concha) covered by epithelium. Each of them overlies a corresponding meatus which is contains the sinuses ostium (Stammberger, 2008b).

There are also a number of structures in the lateral wall that are covered by middle turbinate forming an area called osteomeatal complex. These structures are the maxillary hiatus through which the secretion is drained from the maxillary sinus, the ethmoidal infandibulum which is a three dimensional space belong to anterior ethmoidal air cell, ethmoidal bulla which is the most anterior ethmoidal ear cells. Medial to the infandibulum and anterior to the ethmoidal bulla is the uncinate process (Figure 1.6) (Stammberger, 2008b).

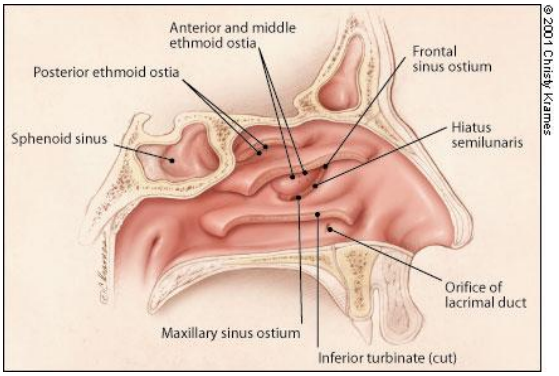

Figure 1.6: Anatomy of the lateral nasal wall

1.3.3 Uncinate Process

The uncinate process is a crescent shape bone in the lateral wall of the nasal cavity covered by the middle turbinate medially (Figure 1.7). It is attached laterally to the lateral wall of nasal cavity by three different attachments (Bayram, 2001).

Superiorly there are three variants in the attachment of the uncinate process. It is either turn laterally to attach to the lamina papyracea of the orbit, or it reaches the skull base or it turns medially to attach to the middle turbinate (Stammberger, 2008b).

Anteriorly it is attached to anterior bony part of the lateral nasal wall while inferiorly attached to ethmoidal process of the inferior concha (Bayram, 2001).

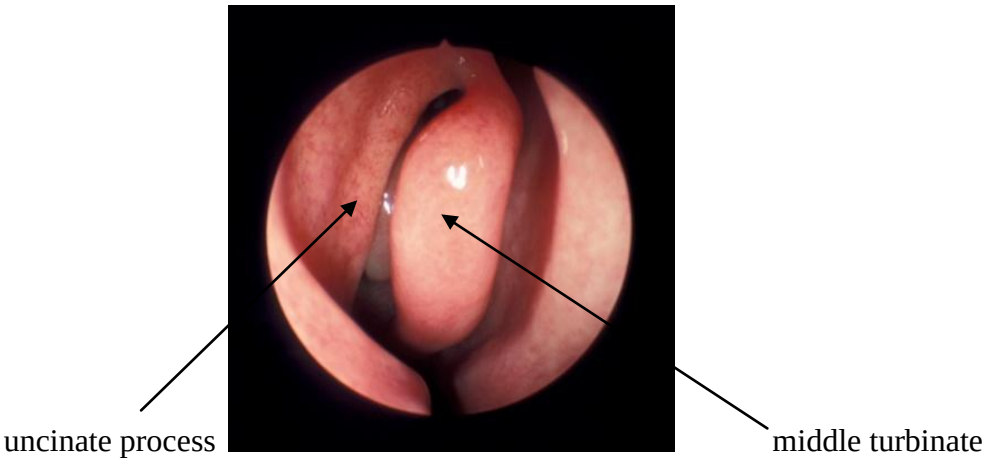

Figure 1.7: Right side uncinate process and middle turbinate as seen by nasal endoscopic examination

CHAPTER 2: OBJECTIVE

2.1 GENERAL OBJECTIVE:

To study the mechanoreceptors in the human nasal mucosa

2.2 SPECIFIC OBJECTIVES:

1- To determine the morphology of the mechanoreceptors in the mucosa of uncinate process.

2- To determine the mean concentration of mechanoreceptors in uncinate process mucosa without nasal polyp.

3- To determine the mean concentration of mechanoreceptors in uncinate process mucosa with nasal polyp.

4- To compare the mean concentration of mechanoreceptors in uncinate process mucosa with and without nasal polyp.

2.3 HYPOTHESIS

There will be reduction in the mean concentration of mechanoreceptors in uncinate process of patients with nasal polyp as compared to patient without nasal polyp duo to chronic compression of the polyp on the nasal mucosa results in degeneration of the receptors.

CHAPTER 3: METHODOLOGY

The study was conducted in Otorhinolaryngology clinic in the Hospital Universiti Sains Malaysia in Kubang Kerian, Kota Bharu, Kelantan. Each patient going for Functional Endoscopic Sinus Surgery for nasal polyp or other nasal pathology had been examined in the clinic prior to the operation.

In addition to general medical history including any history of diabetes mellitus or hypertension, any history of previous nasal surgery and for which side and any history of recent upper respiratory tract infection had been taken.

The nose then was examined by zero degree endoscope to exclude any infection or inflammation of the nasal mucosa or any anatomical abnormalities in the uncinate process and to determine the nasal pathology. The study then explained to the patient including benefits of the study and any harmful effect to the patient and the consent had been taken.

During the operation, the Uncinate Process consisting of bone and its covering mucosa was removed from both sides as part of the Functional Endoscopic Sinus Surgery. One centimeter (10 ×10×3 mm) tissue from the removed uncinate process mucosa was taken for the study. However sometime it was difficult to excise the uncinate process in one piece so it was removed in many pieces which in that case all the mucosa was taken for study.

3.1 INCLUSION CRITERIA

1- Age from 18-50 years.

Its believed that here is reduction in the sensory function due to reduction in the density of myelinated and unmyelinated peripheral nerve fibers and changing in the morphology of the nerve fiber in elderly patient of more than 60 years old (Ochoa, 1969)

2- Patient with nasal polyp (ethmoidal polyp or antrochoanal polyp) grade 2 or grade 3.

3- Patient with grade 1 nasal polyp or any nasal pathology other than nasal polyp that is not exerting compression on the uncinate process mucosa.

3.2 EXCLUSION CRITERIA

1- Patient with nasal pathology other than nasal polyp that compressing the uncinate process mucosa.

2- Diabetes mellitus

One of the complications of diabetes mellitus is peripheral neuropathy which is thought to be due to increase intracellular glucose in the peripheral nerve leading to increase formation of sarbitol and fructose which affect the Na^+/K^+ -ATPase activity and reduced axonal transport and finally destruction of the nerve cells (Greene *et al.*, 1999).

3- Previous history of nasal surgery in which the uncinate process had been removed or the anatomy of nasal cavity is distorted. However septal surgery and inferior turbinate surgery is not considered exclusion criteria.

3.3 STUDY DESIGN:

The study design was prospective case control study.

3.4 SAMPLE SIZE

There is significant lack of data about mechanoreceptors in human nasal mucosa and almost all the information available about nasal mechanoreceptors were obtained from animal studies. For that reason the sample size calculation is not applicable. In addition patients with nasal polyp undergoing Functional Endoscopic Sinus Surgery in HUSM is rare because most of patient with nasal polyp can be treated medically or the patient refuses surgery. However the largest sample size seen in the previous studies was only 6 patients. Based on that 12 patients managed to be collected over an 18 months period. They were divided into two groups each group consists of six patients.

Group 1 (control group): patient underwent FESS in HUSM for nasal polyp grade 1 or patient with any nasal pathology other than nasal polyp not compressing the uncinate process mucosa.

Group 2 (study group): patient underwent FESS in HUSM for nasal polyp grade 2 or grade 3.

The study consists of four parts / objectives:

Part 1 is to determine the morphology of the mechanoreceptors in the uncinate process mucosa.

Part 2 is to determine the mean concentration of mechanoreceptors in uncinate process mucosa in patient without nasal polyp.

Part 3 is to determine the mean concentration of mechanoreceptors in uncinate process mucosa in patient with nasal polyp.

In part 1, 2 and 3 of this study, the tissue was stained by Haematoxylin and Eosin and immunohistochemical staining, and examined by light microscope and electron microscope.

Part 4 is to compare the mean concentration of the mechanoreceptors in uncinate process mucosa with and without nasal polyp.