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Sensory receptors in the temporomandibular joint: A review

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Abstract:
Introduction: *The study of nociception and mechanoreception in the temporomandibular joints is a complex issue with significant clinical applications in the field of temporomandibular disorders and orofacial pain.* ***Goals:*** *To further elucidate the location and role of nociceptors and mechanoreceptors in the temporomandibular joints.* ***Methods:*** *The database Google Academics was used to search papers about sensory receptors in the temporomandibular joints. Key Words including receptors, temporomandibular joint, nociceptors, mechanoreceotprs and proprioceptions were entered in Google Academics in order to search paper of interest.. Only papers written in the English language were searched, retrieved, analyzed and summarized.* ***Outcome****: Eighty relevant papers were identified. However using the excluding criteria, for instance, insufficient data and or/only a summary was available, fifty-eight papers were considered "of interest" and were used to carry out the investigation.* ***Conclusions****: Pain receptors and mechanoreceptors are strategically located in the periphery of the joint disk, around the joint capsule, in the zone of interaction of the posterior band of the joint disk and the bilaminar zone, in other areas of the bilaminar zone and in the synovial membrane. Pain and mechanoreceptors can be found in the branches of the auriculotemporal, masseteric, lateral pterygoid and deep posterior temporal nerves. Nociceptors convey nociceptive information to the trigeminal ganglion, main sensory nucleus and subnucleuas caudalis whereas mechanoreceptors project directly to the mesencephalic nucleus to the supratrigeminal nucleus and cerebellum. Nociceptors in the temporomandibular joint are responsible for the control of nociceptive information in the TMJ whereas mechanoreceptors act in concert with mechanoreceptors in muscles, tendons, and periodontal ligament to control and modulate jaw reflexes and movements.*

Key Words*: Mechanoreceptors. Nociceptors. Sensory organs. Jaw Movements. Mesencephalic Nucleus. Trigeminal Ganglion.*

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I. Introduction

1.The temporomandibular joint

The temporomandibular joint (TMJ) is the articulation of the upper and posterior part of the mandible (joint condyle) with the lateral and inferior part of the temporal bone (mandibular fossa). The TMJ is classified as a diartrodial joint and is known to participate in different functions including neurophysiological control of jaw movements when assisted by mechanoreceptors in the jaw muscles and periodontal membrane, and in the dissipation of forces produced by muscles and teeth. Further, during childhood and adolescence, the TMJs serve as a growth center for the mandible and craniofacial complex. The TMJ is a synovial joint consisting of the mandibular head, mandibular fossa, articular tuberosity and disk, collateral ligaments, temporomandibular ligaments, synovial membrane, blood vessels, nociceptors and mechanoreceptors and a joint capsule reinforced by the accessory ligaments[1].

As any diarthrodial joint, the TMJs allow a relative motion of the articulating bones as a response to the forces produced by adjacent muscles[2]. Each TMJ is a pressure- bearing compound double synovial joint[3] As other articulations of the human body, the TMJ is subjected to friction and wear and is able to maintain the relative stability of their major components by the secretion of synovial fluid which contains some lubricating molecules, for instance hyaluronic acid and lubricin. Such molecules have some important biomechanical functions including decreasing the coefficient of wear and friction. The vascular supply to the TMJ comes from the superficial temporal, maxillary and masseteric arteries[4].

II. Anatomy of the Temporomandibular joint

The joint disc

The TMJ disc is a biconcave structure made up of fibrocartilage formed by the anterior band (thinner than the posterior band) the intermediate band (the thinnest of the three bands) and the posterior band (thicker). The posterior band is connected with the two posterior disk ligaments whereas the anterior band anatomically closely relates with the insertion of the lateral pterygoid muscle. The human TMJ disk is comprised chiefly of fibrous tissue containing variable amounts of rounded cartilage-like cells. The joint disk is made up mainly of fibrocartilage in which chondrocytes-like cells are present more frequently in the disk of older persons[5]. One investigation[6] used electron microscopic technology to better assess the microscopic anatomy of the joint disk in the monkey. Researchers reported that the surface of the joint disk consists of a dense network of delicate collagen fibrils that run both horizontally and vertically presenting as a wavy, winding structure[6]. The joint disk is able to move smoothly together with the mandibular condyle along the articular eminence while simultaneously rotates underneath. The TMJ disk is connected superiorly to the temporal bone and inferiorly to the head of the mandible by loose fibrous structures[2]

Ultrastructure of the TMJ disk

Structurally, both molecules of elastin and collagen can be found in the TMJ disc. Elastin provides resistance and elasticity and is responsible for maintaining shape after disk deformation. The elastic fibers are ECM components that run along and parallel to the collagen fibers and branch forming a network, thus providing additional resistance, mechanical resistance and elasticity to the joint disk[7,8]. Elastic fibers and many other extracellular matrix (ECM) molecules contribute to the biomechanical properties of the TMJ tissues. Elastic, oxytalan and elauinin fibers can be found in severely damaged TMJ disks and biomechanically reinforce some joint areas where for some reasons the presence of collagen fibers is scarce[8], thus improving compressive, shock absorption and stretching properties[8] in areas where the concentration of collagen is defective and or has been damaged by a pathological process. The joint disk is composed mainly of fibrocartilage rather than hyaline cartilage. The major component of the joint disc is collagen which increases stiffness, resistance, deformation capability and durability. In humans, elastin is found more densely in the posterior band of the joint disc and in the bilaminar zone. Elastic fibers located posteriorly in the joint have the function of pulling back the joint disk from an anterior to a posterior condylar position during opening[7]. Theoretically, the joint disc is devoid of blood supply and nerve fibers, except in the periphery.

ECM of the joint disc and cartilage: The cartilaginous tissue of the TMJ is histologically and functionally very complex and consists of a network of very dense collagenous tissue and chondrocytes embebbed in abundant ECM. Types I, II and X collagen can be found in the fibrocartilaginous tissue of the joint disk. Collagen provides sufficient tensile strength to the cartilage of the TMJs. The network of collagenous tissue is very condensed and a number of molecules are present within the disk to provide elasticity, plasticity and resistance. With these features, in normal physiologic and anatomic conditions, the joint disk protects the TMJ and maintains its integrity even when a number of functions are carried out by the TMJs including chewing, swallowing, speech and jaw posture. However, given the vulnerability of the TMJ disk in the presence of parafunctional behaviors and forces of certain intensity, we can say that the capability of the TMJ disk and joint to withstand functional and parafuncional loading, is to a certain extent limited.

The ECM of the TMJ is primarily made up of collagen, proteoglycans, and water. Many large molecules including proteoglycans, byglicans, decorin, and aggrecan can be found enmeshed in the network of collagen fibers. In the absence of pathological loading and parafunctional behaviors, chondrocytes within the joint disk maintain a balance between synthesis and degradation[9] preventing the development of osteoarthritis (OA). Pathological disruption of this balance, alters the local biological equilibrium stimulating degradation of the tissues in which the chondrocytes attempt to repair the damaged ECM[9]. Local degradation of the ECM has closely resembles the presence of a local inflammatory process. Cytokines, tumor necrosis factor alpha and IL-beta 1 and metalloproteinases are up-regulated and participate in the pathological process of gradually degrading the cartilage. These events result in local biochemical and structural disequilibrium in which degradation and gradual destruction of tissue including the ECM, are observed. Further, compressive forces on the joint disk cause inflammation, displacement and degradation and cartilage which further stimulate the development of OA signs and symptoms.

A combination of cartilage, a network of collagenous fibers and the presence of molecules of proteoglycans improve binding and enhance absorption of the interstitial fluid providing the TMJ disk and cartilage with strong viscoelastic properties and resistance to compression[2]. Other molecules forming part of the ECM of the joint disk includes versican, decorin and aggrecan which can be found in different zones of the articular cartilage of the mandibular head[2].

The TMJ capsule: The TMJ fibrous capsule attaches to the squamous portion of the temporal bone and inferiorly posteriorly and anteriorly to the neck of the condyle. Anteriorly and laterally the joint capsule attaches

also to the articular tubercle[10]. The joint capsule is surrounded medially by the synovial membrane from which receives abundant blood supply and nutrition. Histologically, the TMJ capsule is made up of dense collagen tissue located around the mandibular head which provides protection, biomechanical and neurophysiological control of mandibular movements. The capsule has fibroelastic properties, is very resistant and can be stretched to a certain limit. The joint capsule is also very rich in both nociceptors and proprioceptors, the latter contributing in part to the control of mandibular movements.

The joint capsule is vascularized and neurophysiologically protected from damage or injury by branches of the auriculotemporal, masseteric and lateral pterygoid nerves. The adjacent synovial membrane provides nourishment and nutrients to the joint capsule. Movements that stretch the capsule produces damage, inflammation and pain (capsulitis) which may initiate a cascade of inflammatory events which ultimately result in the presence of TMJ internal derangements. The fibrous joint capsule of the TMJ has strong biomechanical properties in the limitation of mandibular movements. For this reason, the joint capsule is provided with abundant mechanoreceptors located in different areas of this structure as shown many decades ago by the studies carried out by Klineberg[11].

The retrodiskal or bilaminar zone

Sicher´s bilaminar zone or retrodiskal pad is a complex set of anatomical TMJ structures located posteriorly to the posterior band of the joint disc. The bilaminar zone consist of an upper layer with the posterior superior ligament of the joint disk and the lower layer with the lower and posterior disk ligament. The upper layer of the bilaminar zone is attached to the back of the posterior wall of the mandibular fossa and on the squamo-tympanic suture whereas the lower layer is attached to the neck of the mandibular head or condyle[1]. The bilaminar zone has a number of functions including serving as a cushion during jaw movements, providing abundant blood supply and thus, nourishment to the joint tissues and is also a source of abundant sensory innervation to the joint. This zone is extremely vulnerable to mechanical trauma from jaw movements, external accidents and parafunctional behaviors. It has been observed that posterior and superior displacement of the mandibular head, causes trauma, pain inflammationand dysfunction of the bilaminar zone. The upper layer of the bilaminar zone is rich in elastic fibers and adipose tissue whereas the lower layer has only a few elastic fibers but is richer in collagen fibers[1]. The bilaminar zone is also a reservoir for synovial fluid which is pushed to that area during jaw movements.

Internal ligaments of the TMJ: The TMJs are protected externally by strong ligaments and internally by delicate, minute yet strong structures called "collateral ligaments". They are located posteriorly (upper and lower posterior ligaments), laterally (medial and lateral ligaments) and anteriorly (anterior superior and anterior inferior ligaments). These delicate structures are endowed with proprioceptive capacities and provide protection during jaw movements and fine control of movements of the joint disk. Disk displacement with or without reduction may be associated with pain and inflammation and with abnormal function, damage and even collapse of these minute ligaments.

Synovial membrane and synovial fluid:

The synovial membrane lining the joint capsule covers all of the articular surfaces except the pressure-bearing fibrocartilage. During jaw movements, the synovial membrane becomes more flexible[12], increases its production of lubricant molecules which are released in the joint spaces around the joint disk. Thus, the synovium is an important component of the TMJ contributing with to the normal joint physiology providing abundant blood supply, nutrition and joint fluid to adjacent anatomic structures (for instance the joint disk). The synovium is also a source of anti-inflammatory or pro-inflammatory cells. The synovial fluid has bactericidal properties and the subintimal tissue of the synovial membrane contains fibroblasts, macrophages, mast cells, blood vessels and lymphatic structures[13].

The synovial tissue is highly innervated and vascularized. This tissue is the source of a set of pro-inflammatory and phagocytic cells including macrophages, monocytes and neutrophils. The synovial fluid secreted by some cells in the synovial membrane including the synoviocytes , provides abundant lubricating fluid and nutrition for the articular disc, thus resulting in normal or friction-free condylar movements. The two most important molecules produced in the synovial membrane are hyaluronic acid and lubricin.

The TMJ cartilage:

The so called diarthrodial joints like the TMJ are those joints protected by a deformable layer of articulating and deformable cartilage which is considered by some as a subtype of connective tissue. In normal physiologic conditions, this cartilage facilitates some tribological characteristics of the joint, for instance, the capacity of support friction, the ability to lubricate some surfaces with molecules from the synovial fluid and the characteristic of undergoing wear with time and aging[2]. With aging and the presence of excessive and

prolonged loading from parafunctional habits, the surfaces protected with articular cartilage may be eroded, worn, destroyed and deformed[2] facilitating the development of osteoarthritic changes. It is known that parts of the mandibular head are anatomically and functionally different. Thus, the fibrous zone is one that serves as a transition and protection between the joint disk and the cartilage of the condyle and thus, is similar to the fibrous layer covering the lamina dura in the periodontal ligament. The other zones are the proliferative, mature and hypertrophic ones. The latter functioning as a transition area between the cartilage and adjacent bone.

The condylar cartilage has an important function in the TMJ as it facilitates articulation with the TMJ disc, reduces excessive loading on the underlying bone[14] and in the presence of certain levels of parafunctional habits it has the ability to undergo physiologic remodeling rather than pathologic one. The articular cartilage contains chondrocytes, a large amount of surrounding matrix molecules including glycosaminoglycans, type II, IX and XII collagens. OCnsequently, the cartilage is w endowed with some biomechanical qualities including flexibility, deformation and plasticity.

Fiber types in the TMJ : As mentioned before, a dense network of collagenous fibers predominate in the articular disk. Collagenous and elastic fibers can be seen in the posterior or bilaminar zone of the TMJ. Elastic fibers have more important properties in the posterior and superior zone of the TMJ as they have to pull back the joint disk in the final stage of mouth opening. Elastic fibers in the disk ECM along with other important ECM molecules, contribute to the mechanical properties of TMJ tissues[8]. Recent investigations[8] have demonstrated that oxytalamic fibers found in severely damaged discs appear to ensure biomechanical properties by reinforcing TMJ regions devoid of collagen bundles and thus, functioning as shock absorber and as a barrier during stretching and compression[8]. The molecule elastin is known to provide elasticity, resistance to deformation, flexibility and the maintenance of shape after deformation in the TMJ[7]. Recent investigations[7] using optic, scanning electronic microscopy and immunofluorescence have demonstrated the presence of both collagen and elastic fibers of the intermediate zone of the joint disc.

Cellular components of the TMJ

For the sake of clarity, cells present in the TMJ should be classified in those found in the synovial membrane, capsular ligament and in/or around the joint disk. Cells present in the synovial membrane include synoviocytes, macrophages, monocytes and neutrophyls. Two types of cells can be found in the synovial membrane: fibroblast-like cells are those which produce subintimal collagen, proteoglycans and the glycoproteins of the synovial fluid (type B cells) whereas macrophage – like or type M cells are those whose major functions is phagocytosis of debris and other material[15].

Cells present in or around the joint disk includes fibroblasts, chondrocyte-like round cells and chondrocytes[15]. Cells in the TMJ disk constitute a heterogeneous population distributed in different areas in which fibroblasts predominate over fibrochondrocytes[16]. Traumatic events to the joint capsule, joint disk and synovial membrane increase the production of prostaglandin E_2 and other pro- inflammatory products. Such events induce the proliferation of pro-inflammatory cells in the synovial membrane and/or in the proximities of the joint disk. The articular cartilage is rich in chondrocytes. A large amount of molecules including glycosaminoglycans and type II, IX and XI collagens can be found in the joint disk. The fibrous zone of the joint condylar cartilage is rich in fibroblast –like cells which have a flat shape[2]. Fibrocartilage cells which receives nourishment from the intra-articular synovial fluid can be found in the fibrocartilage in the TMJ condyle and articular eminence[17]. The proliferative zone of the mandibular head or condyle is rich in mesenchymal cells which serve as chondrocyte precursors. Furthermore, differentiated chondrocytes are found in the mature and hypertrophic zonea whereas the fibrous zone is composed of fibroblast-like cells which have a flat shape[17].

It has been demonstrated in rats that mast cells and nerves containing SP can be found abundantly around blood vessels in the superficial synovial membrane[13]. In the human TMJ, the subintimal tissue of the synovial membrane is rich in fibroblasts, macrophages and mast cells[18]. In some areas of the TMJ, mast cells contribute with local inflammation by degranulating and releasing pro-inflammatory molecules including serotonin (5-HT)[13]. The synovial membrane lines the inner surface of the joint capsule and contains specialized cell types (type B synovial cells) with phagocytic and immune properties and produces the synovial fluid that provides nourishment to the avascular surfaces of the condyle, articular eminence and joint disk[17]. A complex set of cellular components including synoviocytes, chondrocytes, and osteoblasts work in concert to produce hyaluronic acid[17] and decrease the coefficient of friction in the articulating joint surfaces. As a whole, these observations demonstrate the complex variety of cellular components which can be found in many anatomic components of the TMJ. Mast cells and nerves that contain and release SP can also be found in the proximities of the blood vessels in the bilaminar zone of the TMJ.[13]. The subintimal layer of the TMJ synovial membrane is rich in fibroblasts, macrophages mast cells, blood vessels and lymphatics[18]. Because some of these cells are capable of releasing inflammatory mediators, it makes sense to find in inflammatory conditions of the TMJs, large amounts of such mediators including serotonine, prostaglandins E_2 and bradykinin.

Innervation and blood supply to the most important TMJ components

The TMJ is innervated by thinly myelinated and unmyelinated afferent fibers with non-specialized endings. Some of these afferent fibers release neurotransmitters and neuropeptides such as CGRP and SP from their terminal endings. These small diameter fibers project first to the gasserian ganglion and then to the trigeminal subnuclei interpolaris and caudalis[19] . Knowledge about the precise innervation of the TMJ has enormous practical and clinical importance. In cases of severe and acute pain, the TMJ can be anesthetized and pain abolished immediately. Thus, local anesthesia to the TMJ constitutes an additional mode of diagnosis or treatment. Supporting this point of view. Danzig and associates[20] injected an anesthetic solution in 23 adult female patients presenting with severe TMJ pain. Some minutes following injection, patients were interviewed and a patient profile pain was obtained. Twenty of the 23 patients demonstrated a significant decrease in pain located in facial, head and neck regions. Furthermore, do Nascimento and associates[21], used local anesthesia of the auriculotemporal nerve in 10 subjects presenting with signs and symptoms of TMDs. They concluded that nerve block of the auriculotemporal nerve may be used in acute cases in patients presenting with severe TMJ pain.

Innervation and blood supply to the joint capsule

Ishibashi[22] evaluated the sensory innervation in 27 human temporomandibular joints and reported that nerve endings in the TMJ capsule include Vater Paccini, Golgi-Mazzoni, and Ruffini corpuscles, noncapsular complex endings and free nerve endings. The nociceptive innervation to the TMJs is mainly provided by ramifications of the auriculotemporal nerve. A delta and C fibers whose cell bodies are found in the trigeminal ganglion project distally and terminate as non-encapsulated free nerve endings dispersed throughout the posterior and lateral part of the TMJ capsule, in the posterior band of the meniscus and in the posterior insertion of the collateral ligaments Small diameter nociceptive terminals from the orofacial structures project mainly to the subnucleus caudalis[23, 24] Klineberg and associates[25] evaluated the innervation of the TMJ in fresh cat cadavers in order to identify the individual articular nerve branches of the peripheral nerves of the jaw region. They reported the presence of posterior and lateral nerves in corresponding areas of the TMJ capsule derived from the auriculotemporal nerve. They also indicated that the auriculotemporal nerve provides a number of posterior nerve branches to the posterior and medial capsule and more lateral terminations to the posterior and posterior-lateral capsule.

Ishibashi[22] also found that anterior articular nerves arising from the masseteric nerve provide several terminals that fan out over the anterior and anterior lateral capsule. These nerves are branches of the masseteric nerve. Articular branches of the deep temporal muscles were found to innervate the temporal muscle and the anterior, lateral and medial aspects of the joint capsule. Klineberg and colleagues[25] also found that branches of the lateral pterygoid nerve arising from the mandibular nerve provide fine filaments to innervate the anterior and medial region of the joint capsule. These observations indicate that different parts of the joint capsule are innervated by branches of the masseteric nerve, auriculotemporal nerve, deep temporal nerve and lateral pterygoid nerve. This complex neural network provides support for the idea of the capsule is a sophisticated anatomic structure directly involved in the control of condylar movements.

Klineberg and colleagues[25] used electrophysiological methods to examine the mechanoreceptors in the anterior, lateral and posterior regions of the joint capsule in the TMJ in cats during graduated passive movements of isolated joints. They reported the presence of two varieties of mechanoreceptors in the joint capsule and concluded that these varieties of articular mechanoreceptors correlated well with the presence of corpuscular endorgans type I and type II in the TMJ capsule. They reported that the lowest threshold receptors were activated by capsular tension when the jaw was kept closed while higher threshold receptors were activated sequentially as normal jaw movements caused a progressive increase in local capsular tension.

Innervation and blood supply to the joint disk

The central region of the articular disk is not vascularized and no nerve terminal can be found there. This is so, as this region is constantly subjected to loading, pressure and functional movements. Its survival depends largely on the secretion of synovial fluid. On the other hand, Asaki, Sekikawa and Kim[26], used optical microscope, scanning microscope and silver impregnation to study the innervation of the human TMJ disk in 20 cadavers. They reported the presence of free nerve endings in the disk parenchyma in all 20 joints. Nerve endings in the disk parenchyma were observed in the anterior and posterior bands and around the synovial transitional region of the posterior band. They also reported that Golgi Mazzoni corpuscles were observed in 7 joints , Ruffini corpuscles in 4 and articular corpuscles as sensory organs in 3 joints. When they used SEM in only two cadavers they observed myelinated and nonmyelinated nerve fibers in the disk parenchyma of one joint.

Free nerve endings and sensory nerve end organs located around the disk parenchyma act as a receptors for proprioceptive sensation. They are associated with joint pain in TMJ arthrosis and disk disorders.

Myelinated and nonmyelinated nerve fibers can also be found in this parenchyma[26]. In this investigation, articular corpuscles with axon divisions into many branches to form reticulated ramifications were observed in the posterior band of the joint disk[26] . In another study, researchers reported that Golgi-Mazzoni corpuscles, Ruffini endings, myelinated and nonmyelinated nerve fibers can be found in the parenchyma of the articular disk[27]. Wink and colleagues[28], evaluated the presence of neural elements in six articular human disc obtained from three adult human subjects at the time of necropsy. Their findings are described as follows:

1.Nerve fibers were observed penetrating the disc from the pericapsular connective tissue;

2.Anatomic structures similar to Ruffini endings, Pacinian corpuscles and Golgi tendon organs were identified in the pericapsular connective tissue and within the disc.

3.The population density of neural elements was the greatest at the periphery of the disc and progressively decreased towards the center of the disc, in which no neural elements were identified.

4.The concentration of neural elements appeared to be greater at the anterior and posterior margins of the joint disc and greater concentration was observed posteriorly.

Innervation and blood supply to the synovial membrane

Kido and coworkers[29] used optical, electron microscopy , and the anterograde transport method injecting horseradish peroxidase (HRP) into the trigeminal ganglion of the rat to evaluate the TMJ innervation. They reported that no nerves were found in the central portion of the **disk**, that the anterior portion of the disc was densely innervated, and finally that HRP reaction products were found in the thinly myelinated and unmyelinated C axons in the anterior portion of the **joint capsule**. In the subsynovial layer of the synovial membrane, the majority of labeled axons were found located near blood vessels[29]. Neuropeptides including SP, CGRP, NPY and VIP have been identified in TMJ synovial tissues and synovial fluid obtained from patients with TMJ signs and symptoms[30]. Because these molecules are synthesized by neurons, it follows that nerve terminals in the synovial tissues produce such chemicals.

Innervation and blood supply to the retrodiskal zone

The retrodiskal zone is abundantly innervated and vascularized. This zone is innervated by sensory terminations of the auriculotemporal nerve which sends terminal to the area from a medial and posterior direction. Arterial blood supply to this region comes from the superficial temporal, tympanic, and deep auricular arteries[1]. Regarding the sympathetic and parasympathetic innervation to the TMJ, one investigation[31] evaluated the cells of origin of sensory and sympathetic innervation to the TMJ using the intraaxonal transport method in the rat. Researchers reported that labeled cells were observed ipsilaterally in the superior cervical and stellate sympathetic ganglia, in the sensory trigeminal ganglion and in the second to fifth dorsal root ganglia. Further, using the retrograde labeling technique some researchers[32] have found evidence that in cats the TMJs also receives innervations from neurons located in C2-C5 dorsal root ganglia as well as from the superior, cervical, stellate, sphenopalatine and otic ganglia.

Innervation to the discal ligaments of the TMJ: Studies on the innervations of the six internal ligaments (collateral ligaments) of the TMJs have not been published and thus the information about such receptors is scarce or absent. However, one investigation[33] indicates that free nerve endings immunohistochemically positive for neurofilaments NSE and S100 protein, have been detected only in periarticular soft tissues of the TMJ, higher density in muscles and in the vascular venous plexus in the posterior part of the discal ligaments and in the trilaminar zone of the TMJ. To a certain extent, discal ligaments subtly control the disk position and provide stability when jaw movements occur. Because, in one way or another, disk position involves stretching, we may assume that discal ligaments are richly innervated with mechanoreceptive and nociceptive terminals. One investigation[15] indicated that the medial and lateral internal ligaments of the TMJ (collateral ligaments) are collagenous and attach firmly to the lateral and medial poles of the condyle. They are vascularized and highly innervated.

III. Nociception and nociceptors in the TMJ

As explained previously, only some structures of the TMJs are provided with pain receptors. The reasons being that only some structures are not subjected to loading during function, thus, they cannot be loaded. In this regard, it is known that most part of the disk is neither innervated nor provided with blood supply. The TMJs receives abundant nociceptive and mechanoreceptive supply in the bilaminar zone, all areas of the joint capsule, collateral or discal ligaments, the synovium and the TMJ ligament. The current literature on this subject indicates that most nociceptive information from the TMJ comes from receptors or branches of the auriculotemporal, masseteric, deep temporal and lateral pterygoid muscle nerves.

Nociceptive fibers consist mainly of A-delta and C-fibers whose cell bodies are located in the trigeminal ganglion. Axons from these cell bodies, project distally and terminate as non-encapsulated free nerve endings

dispersed in the posterior and lateral part of the joint capsule, in the posterior band of the joint disk and in the posterior attachment[24,25]. These structures are involved in the protection of the joint, receive abundant blood supply (joint capsule), connects with the two posterior discal ligaments (posterior part of the joint disk), are profusely innervated, vascularized and have proprioceptive functions (joint capsule, posterior band of the disk and posterior attachment).

These nociceptive peripheral fibers have their cell bodies in the trigeminal ganglion, but project to other structures of the trigeminal complex including the subnucleus caudalis and supratrigeminal structures. It has been established in experimental studies that small nociceptive afferents (A-delta and C-fibers) originating from orofacial structures terminate in the superficial lamina of the medullary dorsal horn[23] where they synapse with second order neurons to further process ascending nociceptive information. The TMJ capsule receives both nociceptive and mechanoreceptive branches so as to convey information about pain and stretching to different anatomic areas in the CNS. A –delta fibers are larger, myelinated and conduct nociceptive information faster. C-fibers are thinner, have no myelin and transmit nociceptive information at a slower velocity. Even though both fiber types encode nociceptive information, neurophysiologically and functionally both types of fibers are completely different regarding quality of nociceptive information. Centrally, most nociceptive fibers are conveyed first to the trigeminal ganglion and then to the main trigeminal sensory nucleus in the brain stem.

Proprioceptive (mechanoreceptive) receptors in the TMJ: Proprioception is a complicated term. Sometimes is defined as "perception of parts of the body", but its significance is more complex. For the sake of clarity we shall define proprioception as the capacity to perceive and transmit information associated with forces, movement, velocity, distension and stretching of components of some anatomic system, for instance, joint and muscles. Proprioception may also be defined as the information transmitted by special neural units located in joints, periodontal ligament, skeletal muscles, tendons, ligaments usually associated with movements of the parts (for instance, during chewing and parafunctional jaw movements) and developed to control movement and prevent damage to the structures involved in proprioception, for instance, tendons, muscles and ligaments. The term "proprioception" was first used by Sherrington (a famous neurophysiologist) to denote the sensory information contributing to a sense of self-position and movement and also to describe a different type of sensory receptors, most frequently, those found in muscles and associated deep tissues in relation to unconscious or more automatic functions[34].

Proprioceptors or mechanoreceptors in the TMJ are strategically located peripherically and posteriorly in the joint disk, articular capsule, in the posterior, anterior and lateral collateral ligaments, TMJs ligaments and probably in other structures. The proprioceptors or mechanoreceptors transmit automatic information to the mesencephalic nucleus of the brainstem in the trigeminal complex about position of the condyle, tension in the collateral ligaments, pressure, distension and usually function in concert with periodontal ligament and muscle receptors. One investigation[35] indicated that peripheral receptors responsible for the modulation of masticatory movements are broadly distributed in the periodontal ligament, lips, oral mucosa, jaw muscles, and TMJs, playing a major role in regulating or controlling jaw movements.

The reflex proprioceptive control of jaw movements is essential in some activities of the masticatory system including swallowing, mastication, respiration, speech, and even in the maintenance of the rest position of the mandible. Supporting this point of view, one investigation[34] asserts that for the normal mandibular posture to be maintained, absolute positional peripheral information is needed, requiring absolute calibration of the muscle – spindle afferent information with the exact time of tooth contact. During mastication and biting, the masticatory muscles generate forces that are responsible for the movements and deformations. These forces are also transmitted to the teeth and TMJs[34]. Jaw movements are controlled by the peripheral information from proprioceptors in the TMJ, masticatory muscles, tendons, ligaments, periodontal ligament. The information is then transmitted to some parts of the trigeminal system, motor cortex, central pattern generator and cerebellum

Projection of sensory information from the TMJs: Sensory information from the TMJ structures is basically conveyed to two anatomic structures: Nociceptive information is projected to the trigeminal ganglion, then to the sensory trigeminal nucleus and then to portions of the descending subnucleus caudalis. On the other hand, sensory mechanoreceptive or proprioceptive information from the TMJs is conveyed to parts of the mesencephalic nucleus from which the information may also be projected to the supratrigeminal nucleus, motor nucleus and to a trigemino-cerebellar pathways to the cerebellum, in which jaw movements may be corrected and modified.

Sensory information from mechanoreceptors in the TMJs is probably coupled with periodontal and muscle feedback so as to correct or maintain ongoing and or intended movements of the jaw and/or forces applied to teeth, periodontal membrane and TMJs. These considerations are in line with one study[34] on neurological influences of the TMJs indicating that oral sensations especially from periodontal afferents are

necessary for the control of jaw movements during mastication. Further, sensory input itself induces neural plasticity in both cortical and subcortical structures[34].

Previous studies[36] using the "retrograde technique" with horseradish peroxidase, reported that the central processes of afferent fibers form the TMJs reach the rostral portion of the trigeminal sensory nuclei as well as the subnucleus caudalis. Further, some afferent nerve fibers in the sensory root of the trigeminal nerve bifurcate into ascending and descending branches at the level of the caudal pons and project to the main sensory nucleus and the trigeminal spinal nucleus, respectively. Noteworthy of mention is that information conveyed to the mesencephalic nucleus is also relied in thalamic neurons and conveyed to the motor cortex. However, the cerebellum receives a copy of intended and ongoing movements so as to maintain or modify such movements. It is well known that a major role of the cerebellum is the correction of movements.

TMJ pain and neurochemistry: The synovial membrane and synovial fluid constitute the most plausible elements from which reliable information about the neurochemical processes that occur in the painful chronic TMJ, can be obtained. It is well known that a number of inflammatory mediators related with TMJ pain can be obtained from the synovial TMJ fluid and evaluated in the laboratory. Disk disorders and trauma to the joints are usually associated with the production of inflammatory and pain mediators including prostaglandin E_2 (PGE_2) and leukotriene B_4[37]. Herb and associates[4] defend the notion that PGE_2 is a powerful vasodilator whereas leukotriene B_4 attracts inflammatory cells including macrophages, monocytes and neutrophils. By phagociting and destroying cells and residues, some byproducts are formed stimulating phagocytosis from cells in the synovial membrane, which in turn stimulates the development of pain and inflammation.

Some cells of the living tissues release nociceptive substances. For instance, mastocytes, platelets and basophils release serotonine (serotonine 5-HT). During inflammatory conditions and painful states, Serotonine 5-HT is found abundantly in the synovial fluid of the TMJs[37,38]. Serotonine contributes to pain in the region of the TMJ by the activation of B1 and B2 receptors for adrenaline located in the TMJ region and by the local release of sympathetic amines and prostaglandins. Histamine and bradykinin released by injured tissue cells stimulate pain receptors in the TMJ, thus, transmitting information to the subnucleus caudalis in the dorsal horn of the spinal cord[23] Many neuropeptides including SP, calcitonin-gene-related peptide (CGRP), neuropeptide Y (NPY), and vasoactive intestinal polypeptide (VIP) have been identified in the TMJ synovial tissues and synovial fluid obtained from individuals presenting with painful disorders and inflammation in the TMJs[30]. These findings indicate that the richness of pain associated chemicals is paralleled by a richness of nociceptive and proprioceptive innervation to the TMJs.

In the osteoarthritic TMJ, metabolic or mechanical factors contribute to early damage to the cartilage which in turn initiates a cascade of mechanical and biomechemical events characterized by increased amount of inflammatory cells and release of biochemical substances thus, . triggering a subsequent immune response in the hard and soft TMJ tissues. Consequently, various inflammatory mediators such as cytokines and chemokines are released. Furthermore, some cartilage degrading factors including metalloproteinases and prostaglandins are released resulting in further damage to the joint surfaces[38] It has been demonstrated[13] that not only the classical mediators of inflammation (prostaglandins, serotonin, bradykinin…), but neuropeptides from activated nerve terminals can be released in the surrounding tissues initiating a neurogenic inflammation. It has also been demonstrated[29] that nerve terminals containing SP and CGRP can be released in the TMJs of various animals. Nerve terminals containing SP and CGRP are widely distributed in the joint capsule, peripheral articular disk synovial membrane and periosteum of the rat TMJ.[29]

TMJ osteoarthritis: Structures constituting the TMJ are critical to perform and control jaw movements during mastication, speech, occlusion and maintenance of jaw posture. One weakness of the human TMJ is the incapacity to tolerate long-term sustained loading, for instance, the forces applied during parafunctional behaviors, abnormal jaw posture and occupational habits. This weakness may be reinforced by the absence of structures that normally protect the joint, for example, some teeth. Tooth loss combined with severe parafunctional behaviors may progressively cause the destruction of articular surfaces paving the way for the development of osteoarthritic disorders. A combination of a systemic disease, loss of posterior dental support and or open bite, a mild traumatic event and presence of parafunctional habits may be sufficient to trigger pathological events that ultimately result in OA signs and symptoms. Supporting in part these considerations, one investigation[39] defends the notion that the TMJs are synovial joints that undergo repeated physiological loading and, in some cases, are subjected to pathologic overloading. Although TMDs, often have a complex multifactorial etiology, OA is the most common disorder affecting the TMJs. OA is very often associated with parafuncional habits, such as jaw clenching that increase mechanical loading on the mandible facilitating abrasion, remodeling and low-grade inflammation of the joint[39].

IV. Discussion

1.Distribution of sensory receptors in the TMJs

Two types of sensory receptors are frequently found in the TMJs: nociceptors and mechanoreceptors. Nociceptors are specialized protective terminal organs which convey information about real or potential damage to the tissues[40,41]. Two types of nociceptors can be found in the TMJs: A-delta and C-fibers. These two types of fibers are anatomically and functionally different. In line with these observations, two investigation[40,41] indicate that large diameter myelinated nerve fibers encode and transmit nociceptive signals which can be interpreted as being either dynamic or static. A delta fibers in the TMJ tissues conduct nociceptive information at a faster speed whereas C-fibers are nonmyelinated and conduct nociceptive information at a slower velocity. Marchand[42] asserts that nociceptive fibers originating in the periphery of the tissues fall into three groups: A beta fibers, A delta fibers and C fibers. A-beta fibers are large myelinated fibers that conduct nociceptive information at high speed. Usually they transmit non-nociceptive signals but participate in pain modulation.

Nociceptors are widely distributed in different areas of the TMJ. Experimental studies have demonstrated the presence of such terminals in the subchondral bone, periosteum, periphery of the joint disk, ligaments and joint capsule[40] The network of articular primary afferent terminals project to the dorsal horn of the spinal cord and to the brainstem complex and have an active role in acute articular pain, hyperalgesia, spread and referral of pain to other anatomic zones[42]. Mechanical, chemical and/or thermal nociceptive stimulation are common types of factors that induce the recruitment of peripheral nociceptors in the TMJs tissues and conduct the nociceptive signals in the primary somatosensory neurons to the trigeminal ganglion, main sensory nucleus and subnucleus caudalis[41] where the information is processed further to upper areas in the SNC.

In regard to proprioceptors or mechanoreceptors in the TMJs, they are involved in parameters related with movement, pressure, distension, stretching, forces and displacement[42,43]. Worthy of mentioning is the fact that mechanoreceptors are strategically located in areas where they can sense force, distension and stretching. For instance, they can be profusely observed in the capsular ligament, in the interaction zone of the posterior band of the disk and posterior discal ligaments, in the collateral ligaments and in the retrodiskal lamina. It is apparent based on the review of the literature, that "stretching" is a powerful stimuli that triggers the activity of most mechanoreceptors in the TMJs.

Regarding the joint capsule, the review carried out by Kawamura and Abe[44], reported some studies in which articular branches of the auriculotemporal, superficial masseter and deep temporal nerves were seen piercing the joint capsule where they divided in small branches and extended into the periphery of the articular disk. Because of the anatomic position of the auriculotemporal (more posterior) and masseteric nerve (more anterior), those researchers found that the auriculotemporal nerve was observed innervating the most posterior part of the capsule, whereas the masseteric innervated the most anterior region. These observations are in part in line with a similar investigation[45] in the cat reporting the presence of Golgi-Mazzoni nerve terminals in the TMJ capsule. Kawamura and Abe[44] reported that "because there are different types of receptors in the joint capsule, different kinds of information are conveyed by such receptors". In experimental studies in the cat[43] it was found that afferent discharges from the proprioceptors in the TMJ capsule make a significant contribution to the coordination of the masticatory muscle activities and jaw movements. Ishibashi[22], reported that nerve terminals to the TMJ capsule include Vater-Paccini corpuscles, Golgi-Mazzoni corpuscles, Ruffini endings, and free nerve endings. Very likely the topographic distribution of different types of mechanoreceptors do no change significantly in different joints of the human body. In the knee joint for instance, 4 types of receptors can be found: Type I or Ruffini endings, type II or Pacinian corpuscles, type III or Golgi tendon organs and type IV or free nerve endings. Ruffini endings, Pacinian corpuscles and free nerve endings are most frequently found in the fibrous joint capsule whereas Golgi tendons organs are more frequently observed in the meniscus[46].

Joint disc

Kido and associates[29] used the method of anterograde transport, horseradish peroxidase injected into the trigeminal ganglion and light and electron microscopic methods and reported that nerve fibers conducting information to the trigeminal ganglion were observed in the anterior and posterior portion of the joint disc whereas no nerve fibers were observed in the central portion of the disk. Nerve terminals were also observed in the anterior portion of the joint capsule and in the subsynovial layer of the synovial membrane. These observations are in part in line with the studies of Kyrkanides[23] reporting the presence of nociceptive receptors dispersed in the posterior band of the TMJ meniscus. Because Kido and associates reported that no nerve terminals were found in the central portion of the joint disk, their findings are in part in line with another investigation[1] indicating that "the central portion of the articular disk is not vascularized and metabolism in this area is regulated lymphatically and by the synovial fluid". Wink and associates[28] used microscopic

techniques to evaluate six articular human discs from three adult subjects. Such study reported that no nerve terminals were found in the center of the joint disc. Findings reported by Kido and associates are also consonant with another study[47], reporting that in the TMJ disk, "the mechanoreceptor density is greatest at the periphery and progressively decreases toward the center of the disk".

Receptors in the TMJ have their cell bodies in the trigeminal ganglion but project to many other areas of the trigeminal complex on the brain stem. Findings in the study of Kido and associates are in agreement with those of Asaki and associates[26] who evaluated the innervations of the joint disk in 22 human TMJ disks of 11 cadavers. Using the silver stain technique and light microscopy, researchers[26] reported the presence of free nerve endings in the anterior and posterior band of the disk parenchyma. Further, researchers identified the presence of Golgi Mazzoni corpuscles in 7 joints, Ruffini corpuscles in 4 joints and articular corpuscles in 3 joints.

Collateral ligaments

Kyrkanides and assocaites[23] reviewed the literature on the proprioceptive and nociceptive innervation to the TMJ and reported the presence of nociceptive terminals from the trigeminal ganglion projected in the posterior attachment of the TMJs. However those researchers did not specify if such terminals were present in the loose connective tissue and/or in the posterior inferior and superior discal ligaments. Favia and associates[32] evaluated tissue samples from 10 healthy individuals and from 7 subjects presenting with severe TMJ arthritis and arthrosis. They reported that free nerve endings positive for neurofilaments NSE and S100 protein were detected in the posterior part of the discal ligaments of the TMJ, in the trilaminar zone and but no free nerve endings were found in the cartilaginous disk.

Bilaminar zone: Nociceptive innervation from the TMJ is provided by an extensive neural network including the auriculotemporal, the masseteric, the deep and posterior temporal and the nerve to the lateral pterygoid muscle. Nociceptive branches from the auriculotemporal nerve terminate dispersed in a wide anatomic area including the posterior and lateral part of the joint capsule and the posterior attachment[23]. Thus, findings in the investigation of Kyrkanides and associates[23], are in agreement with the investigations carried out by Thilander[48] and Dixon[49], reporting that the retrodiscal zone is innervated by sensory terminations of the auriculotemporal nerve.

Synovial tissues: Milam[30] reviewed the literature on the pathophysiology and epidemiology of TMJ pain and reported that neuropeptides including vasointestinal polypeptide, neuropeptide Y, SP, and CGRP were identified in the TMJ synovial tissues. Because most of these molecules are synthesized and expressed by some neurons in the joint tissues, it is implicit that nociceptors and mechanoreceptors terminals are present in the synovial membrane of the TMJs. Asaki and associates[26] used the technique of silver impregnation and light microscopy in 22 joint of 11 human cadavers and reported the presence of free nerve endings in the synovial transitional region of the posterior capsule.

2.Proprioceptive mechanisms in the TMJs

Even though mechanoreceptors can be found in the TMJs (discal ligaments, joint capsule), masticatory muscles, tendons, and periodontal membrane, jaw movements and proprioceptive mechanisms that have been developed to protect the joint, muscles and periodontal ligament, are not independent events. Rather, they are involved in extremely coordinated functions controlled by brainstem and cortical centers. Thus, different mechanoreceptors in different anatomic zones function in concert to provide "finesse" to jaw movements and coordination. In line with these observations, Fujii and coworkers[50] assert that peripheral receptors responsible for the regulation of masticatory rhythm are distributed in the periodontium, lips, oral mucosa, jaw muscles and TMJs. Signals from periodontal receptors are used in the fine motor control of jaw activities associated with biting, intraoral manipulation and food chewing[51].

Regarding proprioceptive activity in the masticatory system, there is a functional integration between the TMJ mechanoreceptors, those in muscles, periodontal membrane, tendons a ligaments and probably those located in the cervical structures[33]. Klineberg, Greenfield and Wyke[25], evaluated the role of the mechanoreceptors in the anterior, lateral and posterior regions of the TMJ capsule in the cat. Analysis of the afferent potential discharges in the articular nerves indicated the presence of two varieties of mechanoreceptors (Type I and type II) in the joint capsule. Based on their studies, it seems apparent that type I receptors are important in the reflex regulation of the motor activity in the mandibular musculature. Type I mechanoreceptors contribute to the reflex regulation of the tonicity of the jaw muscles during posture and with a coordinated muscle activity during jaw movements and position of the mandible. This coordination is reinforced by type II mechanoreceptors[25].

Interesting to note is that studies carried out by Wink and associates[28] to assess the location of neural elements in the human TMJ disc reported that "structures resembling Ruffin endings, Paccinian

corpuscles and Golgi tendon organs were identified in the connective tissue **around** the joint capsule and within the joint disc".

Worthy of mentioning is that the topographic and strategic anatomic location of TMJ mechanoreceptors in the most posterior part of the disk, in the posterior diskal ligaments, and around the joint capsule, allows these mechanoreceptors to sense "any degree of tension, strain of stretching" which may be self-protective for such structures. Congruent with these observations, one investigation[47] indicates that "the concentration of mechanoreceptors appears greater in areas related to the extremes of movement and probably represents the first line of defense in sensing these extremes". The kind of input from these mechanoreceptors alerts the central nervous system of impending injury which can be prevented through reflex mechanisms[47].

Information from these mechanoreceptors is conveyed to the mesencephalic nucleus to modulate jaw movements and/or to prevent injury or lesion to the components of the masticatory system. Congruent with these observations, one investigation[39] asserts that "the magnitude of capsular stretch has been identified as a key factor modulating the onset and maintenance of pain". This means that in conditions of chronic pain in the TMJs, "painful and inflamed structures should not undergo stretching". However, in the presence of severe or extreme parafunctional behaviors, the discal ligaments, the bilaminar zone and even the joint capsule are subjected frequently to period of "stretching" which result in pain. Further, the local mechanical environment of joints rich in anatomic structures which "should not be stretched", can be significantly altered after injury implicating mechanical damage to the ligaments in pain production[39] . The joint capsule and adjacent internal and external ligaments function to limit the movements of the mandible. It follows that border jaw movements observed most frequently during nocturnal parafunctional habits cause damage or injury associated with higher frequency and greater intensity of loading . This assumption is supported by the clinical observation that severe or extreme sleep bruxers wake up with morning pain in many anatomic sites in the masticatory system with the protection of reflexes to unload the joints during sleep.

Clark and Wyke[52] evaluated some of the mechanisms of reflex control of the mandibular muscles. Their EMG experiments demonstrated that the articular mechanoreceptors located in the capsular ligament of the TMJ make a significant contribution to the reflex control of both static and dynamic motor unit activity in the jaw muscles. Further, pathological alterations in the muscular and articular system (for instance, by trauma), might result in changes in the normal patterns of mandibular muscle activity. Free nerve endings, Ruffini endings, Golgi organs and Vater Paccini corpuscles have been observed innervating the periphery of the joint capsule[52). Some researchers[53,54] defend the notion that the Ruffini endings and the Golgi organs located in the articular capsule function as static mechanoreceptors, the Vater-Pacini endings as dynamic mechanoreceptors and the free nerve endings as pain receptors.

The posterior zone of the TMJ or bilaminar zone is well innervated by ramifications of the auriculotemporal nerve[48]. This area is also profusely vascularized by branches of the superficial temporal, tympanic and deep auricular arteries[55]. Even though mechanoreceptors can be found in the posterior region of the joint capsule, in the posterior zone of the joint disk and probably in the superior and inferior posterior discal ligaments, given the high frequency of retrodiscal pain, protective mechanism in the bilaminar zone are not so effective protecting the joint from pain and dysfunction. This is so, when the joint disk is displaced anteriorly or medially and the joint condyle is frequently displaced posteriorly, thus compressing blood vessels and nerves in the bilaminar zone, resulting in pain and dysfunction. In line with these observations, one investigation[4] indicates that the posterior attachment of the joint disc is both highly vascularized and innervated, and thus, is very susceptible to pain and inflammation.

Kawamura and Abe[44] writing about the role of sensory information from the TMJs argue that "since different kinds of sensory receptors can be found in the TMJs, they may convey different types of sensory information and thus be responsible for different reflex mechanisms and coordination with jaw muscles and periodontal mechanoreceptors". Both nociceptors and proprioreceptors are involved in different mechanisms including the transmission of nociceptive information, neurophysiological and mechanical control of condyle and jaw position and in the coordination of information with adjacent receptors in muscles, tendons, ligaments and periodontal membrane.

Reflex mechanisms controlled by receptors in the TMJs may be both facilitatory and inhibitory. For instance, join receptors may facilitate and or reinforce mechanoreceptive information from muscles and periodontal ligament, thus modulating and/or maintaining jaw movements. In other occasions, information and reflex mechanisms in the TMJ may be inhibitory. For instance pain and inflammation may inhibit border jaw movements and the activity of muscle spindles so as to prevent jaw closure and/or full mouth opening thus preventing further damage to the joints. These mechanisms operate in the presence of disk-attachment pain and or disk displacement without reduction. Supporting this point of view, one investigation[43], indicates that some sensory information from the TMJ capsule acts to inhibit the activities of the masseter muscle and thus, contributes to prevent full mouth opening.

3.Nociception and Inflammatory mediators in the TMJ

Most researchers agree that nociceptive responses are mediated by the information transmitted by A delta and C-fibers (myelinated and nonmyelinated, respectively) which can be found in most TMJ tissues. Most of these fibers are capable of releasing both nociceptive and inflammatory neutransmitters including the neuropeptides SP, VIP, CGRP, somatostatin and serotonin. Inflammatory and nociceptive neuropetides can be released from activated peripheral nerve terminals in some regions of the TMJs and induce an inflammatory response. Further, nerve terminals containing SP and CGRP have been demonstrated in the TMJs of many experimental animals[13].

Regarding the association between pain, inflammation and serotonin, one investigation[37] evaluated levels of serotonine in the synovial fluid of painful TMJs of dysfunctional patients and reported higher levels of such mediator in the synovial fluid of the affected joints implicating the participation of serotonin in painful inflammatory states in the TMJs. Experimental studies in rats found that serotonin induces nociception in the TMJ region by the activation[38] of B1 and B2 adrenergic receptors located in the TMJ region combined with the local release of sympathetic amines and prostaglandins.

Pain and inflammation in the TMJs and other tissues may be induced by the release of inflammatory mediators including serotonin, SP, prostaglandins, leukotrienes, histamine and bradykinin. Nerves that produce and release neuropeptides have been identified using sophisticated methods in the human TMJ capsule.[13]. Further, microorganisms, and some neuropetides including SP can stimulate mast cells to degranulate and release serotonin, a powerful vasodilator. Henry and associates[13] reported that mast cells can be identified within the posterior bilaminar tissue of the human TMJ in patients with TMJ internal derangements. This observation probably explains the clinical observation of increased susceptibility of this region to present posterior capsulitis, retrodiskal and disk-attachment pain. Inflammation in the joint capsule, discal ligaments and the bilaminar zone is one of the main mechanism responsible for pain and discomfort in the TMJs and adjacent musculature. TMJ disorders can be associated with neural inflammation in the peripheral nervous system and with elevated levels of cytokine expression and microglia activation. Neural inflammation is reduced when the site of injury or lesion is appropriately treated.[56]

Henry and associates[13] used sophisticated histological methods to evaluate the presence of mast cells and SP in the posterior bilaminar tissue from 9 patients with TMJ internal derangements. Researchers reported the presence of SP-containing nerves and mast cells within the posterior bilaminar tissue associated with the local blood vessels. The synovial membrane of the TMJ functions as a reservoir for both nutrients and waste products from the local metabolism. It has also defensive functions as elements of the immune system including molecules and cells can reach the membrane through the blood supply to the TMJ. Debris from the local metabolism, from phagocytic activity and even from cartilage degradation can be deposited and or reabsorbed within the synovial membrane. Congruent with this point of view, one investigation[57] asserts that the synovial membrane is rich in synoviocytes, macrophages and fibroblasts. Synoviocytes in the synovial membrane are specialized in the production, secretion and resorption of components of the synovial fluid whereas macrophages phagocytes debris and other products.

Chemical breakdown of degenerative byproducts may accumulate within the synovial membrane and stimulate the production of inflammatory and pain mediators including PG_2 and leukotrienes[4] which can not only attract inflammatory cells including neutrophils and monocytes but stimulate the cascade of the arachidonic acid, thus resulting in local inflammation and pain. Excessive production of inflammatory molecules is a primary event mediating both acute and chronic TMJ inflammation and tissue destruction in most pathologic conditions[57], more specifically in advanced stages of TMJ-ID, for instance, disk-attachment pain, disk displacement without reduction, arthralgia and OA. Alstergren, Kopp and Theodorsson[58] used samples of the synovial fluid of 12 healthy individuals and 59 patients presenting with TMJ signs and symptoms to evaluate the levels of Il-1 beta and serotonin from aspirates of the synovial fluid. Their investigation indicated that Il-1 beta and serotonin are undetectable in samples of healthy individuals. They also reported that higher concentration of IL-beta and serotonin may have clinical and diagnostic relevance as the synovial fluid may be used to evaluate concentrations of such elements in individuals with internal derangements of the TMJ. Thus, a correlation between levels of suchmediators and degree of inflammation and pain can be established.

Conclusions

Based on the literature review used to carry out the current investigations, with certain limitations, various conclusions can be drawn:

1.Sensory innervations of the TMJs, is provided by branches of the auriculotemporal, masseteric, deep anterior and posterior temporal nerves, and nerve to the lateral pterygoid muscle. These anatomical structures convey information about nociception and mechanoreception.

2.Mechanoreceptors in the TMJs are strategically located in the parenchyma (periphery) of the joint disk, intersection of the posterior band of the joint disk and bilaminar zone, periphery of the joint capsule, synovial membrane and diskal ligaments. The central zone of the joint disk is devoid of sensory receptors.
3.TMJ mechanoreceptors act in concert with sensory receptors in muscles, tendons and periodontal ligament to modulate, control, facilitate, inhibit and/or modify jaw movements.
4.The fact that mechanoreceptors are located in the transition zone of the posterior band of the joint disk and bilaminar zone, in the periphery of the joint capsule and in the diskal ligaments, clearly suggest that a major role of mechanoreceptors is to provide proprioceptive information about stretching, thus preventing injury or damage to some anatomic structures.
5.There are two types of nociceptors: A-delta fibers and C-fibers and both have well defined neurophysiologic characteristics, for example, different velocities to conduct nociceptive stimulus, different thickness and detect pain of different qualities.
6. Some nerve fibers in the TMJ can synthesize and release SP and CGRP, two powerful nociceptive molecules that can sensitize local nociceptors. The synovial membrane is rich in synoviocytes, but macrophages, mast cells, monocytes and neutrophils which phagocyte and digest debris and cartilages residues, can also be found. A number of molecules including prostaglandins, leukotrienes, serotonine, bradykinin, histamine, SP and CGRP can be released by cells and induce inflammation and pain in the joint tissues.

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