IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 8 Ser.5 (August. 2022), PP 107-117
www.iosrjournals.org

Nociceptors and mechanoreceptors in the periodontal membrane: A Review.

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Abstract:
Introduction: *The periodontal membrane is the anatomical structure of loose connective tissue located between the cementum of the tooth and the alveolar bone of the maxilla and/or mandible which has defensive, formative, and protective functions in the stomatognathic system.* **Goals**: *Describe some anatomic components and nociceptive and proprioceptive functions of the periodontal ligament.* ***Methods:****The database Google Academics was used to search papers about nociception and proprioception in the periodontal membrane. Key Words including receptors, proprioceptors,nociceptors, andperiodontal ligament were entered into the database in order to search and assess papers relevant to the topic to be reviewed. Only papers written in the English language were searched and accepted****Outcome:****Sixty papers were found. However, using exclusion criteria, for instance, insufficient information and/or paperswritten in other languages, 19 papers were excluded and thus, forty-one papers were selectedand used to carry out the current study.****Conclusion:****The periodontal ligament is the loose connective tissue situated between the walls of two mineralized tissues (bone and cement). It is richly innervated and vascularized and is involved in many specialized functions of the masticatory system. The periodontal ligament is an extremely complex structure which serves numerous functions including repair, nourishment, sensory and defensive.Nociceptors and mechanoreceptors are profusely found in the periodontal ligament. Nociceptors project to the trigeminal ganglion whereas mechanoreceptors project and transmit sensory information to the mesencephalic nucleus.* ***Key Words:****Periodontal Ligament. Nociceptors. Mechanoreceptors. Pain. Proprioception. Receptors.*

Date of Submission: 01-08-2022 Date of Acceptance: 14-08-2022

I. Introduction

The periodontal ligament (PDL) is a unique specialized connective tissue interposed in the tooth root and alveolar bone occupying an anatomic area of approximately 0.5 to 0.5mm^{2}between the cementum covering the tooth root and the alveolar bone[1]. The PDL is constituted in part by a complicated connective tissue system, containing blood vessels, nerves and connecting the alveolar bone to the radix of the tooth[2]. The PDL is constituted by both soft and hard tissues supporting the teeth[2]. The most basic anatomic elements of the PDL are the cement covering the tooth, alveolar bone and the gums or gingival tissue that also protects both the teeth and the PDL[2,3]. The connective tissue of the PDL is very loose, richly innervated and vascularized, non-mineralized, with important peculiar localization that carries out a series of functions in the masticatory system[4].

Some researchers define the PDL in terms of “a group of connective tissue fibers that essentially joints a tooth to the alveolar bone within which it is located”[5]. The PDL is the only ligament in the human body that connects two distinct hard tissues (cement and bone) It can also be defined as a complex, fibrous, soft connective tissue that attaches the tooth root to the inner wall of the alveolar bone[5).. The PDL is richly innervated by nerve endings and receptors involved in the complex functions of nociception, proprioception and neuromuscular reflexes[6]as periodontal mechanoreceptors provide significant feedback for the jaw-closing muscles and thus, are responsible for those reflexes developed to protect both muscles and periodontal structures.

II. Origin and development of the Periodontal Ligament

The PDL is derived from the dental follicle region which originates from the cranial neural crests cells[7].The dental follicle is a condensation of the ectomesenchymal tissue[7] which is stimulated so that its cells differentiate into cementoblasts during their apical development and form the cementum that covers the external surface of the root[8]. The PDL is produced mainly by fibroblasts before dental eruption but initiates its differentiationduring the stage of root development of the tooth[9].

III. Anatomic and histologic components of the PDL.

Introduction:The PDL is an essential anatomic and functional component of the stomatognhatic system. Even though the PDL is considered a very small structure as compared to the dental pulp, muscles, tendons, and joint capsule, the PDL is an extremely complex structure which serves numerous functions including reparation, nourishment, sensory and defense. The complexity and multiple functions of the PDL can be demonstrated by the presence of a large amount of anatomic and histologic structures including:

Blood vessels: The periodontal ligament is provided with a large amount of blood vessels arriving from different directions and structures. Blood vessels are anatomically adapted to carry out functions of nourishment, response to inflammation, oxygen and energy supply, metabolic exchange between blood and the PDL and also to resist high and intermittent pressures during chewing. An inflammatory reaction in the periodontal ligament is facilitated by the presence ofmany blood vessels and also by bacterial infection and/or from direct trauma to the PDL. Nutritional requirements to the cells of the periodontium are provided by numerous blood vessels which contain substances required by all cells in the PDL[3] in order to survive and carry out their functions.

Nociceptors and mechanoreceptors:

Nociception is a general term used to describea set of complex interrelated phenomena and components including receptors and reception, transmission, interpretation, neurophysiological pathways, molecules, pain, neurotransmitters, inhibition and disinhibition and many other mechanisms related to pain. Nociceptor is the name used for a specialized pain receptor located in all tissues whose major function is to protectand inform the SNC aboutactual or potential damage to the tissues. Even though some researchers argue thatsome mechanoreceptors may also be nociceptors, most researchers assert that mechanoreceptors are those nerve terminal that serve the function of proprioception which is mostly a mechanical and neurophysiological function different from nociception.

Nociceptors and mechanoreceptors are profusely found in the PDL constituting"terminal receptors" transported by the two lower divisions of the trigeminal nerve (V3 and V2). The functions of these receptors are to detect any noxious or destructive stimulus to the PDL and/or tooth, the perception of the position of the tooth and the control of the application of forces or tensions into the PDL, respectively. Both myelinated and unmyelinated nerve fibers can be encountered in the periodontal ligament. There are significant anatomic, histological and neurophysiological differences when these two receptor types are compared. Nociceptive fibers can be both myelinated (A delta fibers) and unmyelinated (C-fibers). Periodontal mechanoreceptors or proprioceptors constitute a special type of receptors directional and force sensitive that respond more to the direction of applied force but they are also temperature sensitive[6]. Input from these peripheral receptors is extremely important in reflex mechanisms used to protect the teeth and the PDL itself, from injury.

Collagen and other types of fibers: The periodontal ligament is rich in different types of collagen fibers that run in different directions from the cementum to the alveolar bone. The function of these fibers is to provide a strong connection of the tooth with the alveolar bone keeping proper position and stability of individual teeth. Some collagenous fibersrun from the cementum to the alveolar bone forming straight angles but others follow an oblique direction. It has been established that PDL fibroblasts produce collagen and ground substance. Large amounts of collagen – type fibers in the PDL are necessary to keep the shape or the normal and functional characteristics of the periodontium and to regenerate the periodontiumduring orthodontic tooth movement. Most common type of collagen within the PDL is collagen V, but others including collagen IV, VI and XII can also be found. Fibroblasts also contribute to the destruction of the non-functional collagen fibers. Because collagen and fibroblasts components are of upmost importance in the periodontal ligament, any disease that contributes to abnormal turnover or destruction of these components may lead to abnormal function or even tooth loss. For example, collagen fibers may be destroyed by the action of collagenase, a toxin elaborated by bacteriapresent in periodontal disease. Collagen isusually seen in the microscope as numerous cross-banded fibrils. However, small amounts of elastic–type fibers, including oxytalan and elastic fibers are also found.

The periodontal osteogenic component of the PDLis formed by collagen fibers inserted into the alveolar bone, by the alveolar bone, the proper, osteoblasts, osteoclasts and mesenchymal cells and local abundant blood supply. This "bone component" is closely related to some PDL functions including bone resorption, deposition and remodeling.The osteogenic zone is the area of the PDL in which osteoblasts, osteoclasts, Sharpey´s´ fibers and probably mesenchymal cells, predominate. Osteoblasts in the PDL maintain the bone volume in the socket by producing new bone following bone resorption and/or trauma to the PDL. Pressure to the PDL stimulates bone resorption whereas tension on the fibrous component of the PDL stimulate bone and cementum formation[3]. This clinical observation is used by orthodontists to facilitate tooth movement using orthodontic devices.

The periodontal cementogenic component is the part of the PDL located very close to the cementum where mesenchymal cells, cementoclasts andcementoblasts are more frequently found. Cementoblastsoriginate fromectomensenchymal cells of the dental follicle and are observed more frequently along the surface of the cementum[3]

Cellular components in the PDL: Because of the many functions carried out by the PDL, large amounts of different cells groups can be found in this structure of connective tissue. Most common cellular elements in the periodontal membrane include fibroblasts, mesenchymal cells, osteoclasts and osteoblasts, progenitor cells, epithelial rests of Malassez and cells of the connective tissue, cementoclasts,cementoblasts, monocytes, polymorphonuclear cells, macrophages and lymphocytes. Fibroblasts predominate in the PDL. They are interconnected by gap-junctions and adherence-type junctions. Further, they elaborate the collagen fibers and part of the ground substance, have micro-filaments and are able to contract, move and displace.Most fibroblasts can be found interspersed between the collagen fibers in the form of irregular discs with numerous branches and parallel to most collagen fibers. A large amount of undifferentiated mesenchymal cells can also be found. Further, defensive cells including macrophages, monocytes, neutrophils, esosinophils (small number) and mast cells can also be observed.

The ground substance of the PDL is very similar to that found in other areas of connective tissue. A large number of functional molecules or proteins can be found in the PDFlincluding alkaline phosphatase, hyaluronate, glycosaminoglycans (GAGS), proteoglycans, dermatan sulphate, fibronectin, tenascin[3] and many other molecules.

IV. Functions of the periodontal ligament

The PDL is functionally and histologically adapted to absorb forces or loading. Furthermore, this minute but sophisticated anatomic structure has the capacity to function as a sensory organ, and is able to comfortably adjust/and or align the dental arches during chewing[10],. The PDL has the ability to protect, provide support and to function as a sensory organ[3]. Proprioception in the PDL is more specialized and complex as compared to that of the dental pulp. Many functions have been attributed to PDL. This structure maintainsfixation of the tooth into the socket, participates in the absorption of the deciduous teeth, in the regeneration of both cementum and bone and regulates or controls masticatory movements[2].

Sensory receptors or nerve terminals profusely distributed into the PDL are able to react to touch, pressure sensation, and tooth position as well as tissue injury. The mechanical sensation in the PDL can evoke various oral reflexes which facilitate mastication[11].Sudden and/or strong stimulation of the PDL via sudden tap or biting on a hard object (for instance, a small stone), elicits fast activation of mechanoreceptors in the PDL and inhibitory responses from the jaw closing muscles. The reflex is induced to protect the involved tooth and the PDL preventingsudden damage or injury. This reflex evokes inhibition of the activity of the jaw closing muscle and/or sudden mouth opening. The inhibitory response evoked when the steady pressure on the tooth is removed in loading and unloading experiments is probably the result of disfacilitation resulting from the withdrawal of the tonic excitatory input from the receptors. This observation is in line with previous observations indicating that the periodontal proprioceptors contribute with both positive and inhibitory feedback to the jaw closing muscles via mesencephalic nucleus of the trigeminal nerve.

Reflex facilitation from the mechanoreceptors in the PDL to the jaw closing muscles is observed when pieces of food are maintained between opposing teeth[12] and the mastication process proceeds. However, when a foreign object is perceived unexpectedly between opposing teeth that presumably could cause damage to the tooth and PDL, an inhibitory reflex is immediately induced in which muscle activity is inhibited and the mouth is opened. This is clearly a protective reflex.

Chewing is basically the disintegration of food of greater size that is progressively transformed in food of minor particles so as to become ready to be swallowed. It seems plausible to argue that as food becomes progressively transformed into minor particles both the pattern of feedback from periodontal mechanoreceptors, the force, and the electrical activity of the jaw closing muscles decrease. During chewing, the mechanoreceptors around the teeth are strategically placed to record the force being applied to the teeth and are then analogous to the Golgi organs in the masticatory muscles[12].With the first bite on the food, PDL mechanoreceptors become activated and the pressure exerted on the tooth is the basic stimulus to the control of activity of the jaw closing and opening muscles. Thus, it is expected that this activity decreases during progressive chewing cycles. Even though, axial forces are preferred and are physiologically and esaily tolerated by the PDL mechanoreceptors, horizontal forces controlled bythe superficial masseter, contra-lateral medial pterygoids andlateral pterygoids, also occur. It has been found that most periodontal mechanoreceptors respond to both axial and horizontal forces.

During chewing, both facilitation and inhibition mechanismscontrolled by both PDL and muscle mechanoreceptors and jaw closing muscles operate and the basic mechanism for both activities is the information provided to muscles by PDL mechanoreceptors. Facilitation is basically a control mechanism used to attain physiological chewing whereas inhibition is protective in nature to automatically limit the powerful jaw closing muscles preventing damage to the teeth and components of the PDL. Thus, as Brodin and colleagues[12] described it: " both facilitation and inhibition depends heavily on the instantaneous information provided to muscles by the periodontal mechanoreceptors".

During orthodontic treatment, the PDL has a specific role compensating the resorption induced by the orthodontic device and facilitating the deposition of bone in the opposite or non pressure side of the PDL. Further, in man, stimulation of the teeth can induce the sensations of touch, pressure and pain and it is known that dentinal, pulpal and PDL receptors contribute producing these sensations. PDL mechanoreceptors are involved in the jaw opening and closing reflexes both in man and animals[13] .PDL mechanoreceptor can also be stimulated when the tooth is moved within the alveolar bone. This is so as mechanoreceptors are located interspersed in the large amount of collagen fibers. When these fibers are stretched duringorthodontic or non orthodontic tooth movement, mechanoreceptors are immediately stimulated (stretching) and their signals are initially sent to the mesencephalic nucleus of the trigeminal nerve in the brainstem.

V. Innervation and blood supply in the periodontal ligament

The innervation to the PDL comes from the trigeminal nerve through the second (maxillar) and third (mandibular) division of the trigeminal nerve. The nerve fibers within the PDL are usually found in the outer section of the ligament space, that is, in the proximities of the alveolar bone[3]. There is a rich plexus of nerve fibers arising in the apical region and other group of nerve fibers that perforate the lateral wall of the alveolus and thus, enter in the PDL[3]. Single myelinated and unmyelinated nerve fibers branch off from the main nerve bundles and run toward the cementum to supply the innermost part of the ligament[14].

The apical region of the ligament is abundantly supplied with nerve terminals including sympathetic nerve fibers whereas parasympathetic nerve fibers are usually notfound[3] The sensory nerves of the periodontium originate from the maxillary and mandibular division of the fifth cranial nerve. Nerves with origin in those sources are nociceptors (for pain) and mechanoreceptors[2] (for proprioception). Periodontal nerves react to touch, pressure sensation and tooth position as well as tissue injury. Additionally, mechanical sensations in the periodontal nerve structures are able to induce some oral reflexes that not only facilitate mastication [15] but prevent damage in the PDL as well. The Ruffini endings are extremely specialized mechanoreceptors capable of responding both to mechanoreception and to noxious stimuli.[16]. The PDL receives dense sensory innervations by nociceptive free-nerve-endings and mechanoreceptive specialized nerve endings whose cells bodies are located in the trigeminal ganglion and in the mesencephalic nucleus, respectively.

The PDL is richly vascularized and innervated. Blood vessels to the PDL have their originin the subglingual artery, the superior alveolar artery, the maxillary artery, the descending palatine artery and from the facial artery[2]. The PDLis profusely irrigated with blood vessels and cells from the blood system. Blood vessels in the PDL are anatomically and physiologically adapted to resist high intermittent pressure during mastication. They also provide a substrate and metabolic exchange between blood and periodontal tissue including, the dentine[17]Non-myelinated terminals (C-fibers) are capable of providing information about nociception, whereas proprioceptors or mechanoreceptors are responsible for maintainingthe position of the tooth into the dental arches and the control of the spatial relationship between the upper and lower jaw during chewing[18].

VI. Classification of receptors in the PDL

Receptors in the PDL are classified in many different forms:

1.In Maeda and associates´ studies[11], receptors in the PDL are classified as free nerve endings and specialized nerve terminals. Free nerve endings are distributed abundantly in the PDL and supposedly represent mainly nociceptors whereas specialized nerve endings are considered to be mechanoreceptors[11].In the category of mechanoreceptors, the Ruffini endings occupy a special position as they are profusely distributed in the PDL and probably play multiple roles including their function as "stretch receptors" [11]

Periodontal Ruffini Endings

Periodontal Ruffini Endings are by far the most important mechanoreceptors found in the PDL, subcutaneous tissue, tendons, ligaments, the capsule of the TMJs, fascia and hair follicles. They are characterized (using a light microscope) by the presence of extensive arborizations with thick axon terminals[11].

2.Sanosyan and associates[19], classify receptors in the PDL in four types described as follows:

Free nerve endings (tree-like configuration)
Ruffini-like corpuscles (found mainly in the apical zone of the PDL)
Coiled endings (usually found in the middle area of the PDL)
Spindle – like endings. (those receptors found close to the root apex)

3.Cash and Linden[13]classified the population of periodontal mechanoreceptors in basically two distinct and well defined subgroups:Rapidly adapting mechanoreceptors and slowly adapting mechanoreceptors.

4.Based on Sakada´sinvestigations[20], "the sensory units" in the periodontal ligament can be classified as follows:
1.Fast-adapting units
2.Slow adapting units
3.Spontaneously discharging units.

Further, these units are capable of responding to mechanical stimulation applied to the teethfrom various directions and are characterized by specific threshold, latency and impulse frequency of individual fibers.Regarding Ruffini´s endings, it has been found that these receptors can be classified in two types: A slowly adapting mechanoreceptor and a rapidly adapting unit[11] On the other hand and based on ultrastructural studies, periodontal Ruffini´s endings have also been classified as follows:

Type 1 Ruffini´s endings is the one characterized by lamellar terminal Schwann´s cells, expanded axon terminals and axonal spines which penetrate surrounding tissues.Type 2 Ruffini´s mechanoreceptors are those terminal characterized by less branching, fewer axonal spines, less elaborated Schwann cells and less basal lamina[11]

2.Regarding nociceptors, these specialized free nerve endings are classified as mechanical,thermal and polymodal nociceptors
Nociceptors are also classified in two different types:
1.A delta fibers have been described as"thicker fibers protected by a thin myelinated sheath" and are capable of transmitting faster information about nociception. Such fibers transmit accurate and fast information about pricking or sharp sensations and also touch, warm and cold[21].
2.C–fibers arethough to be smaller nociceptive fibers, non protected with a myelin sheath and transmit nociceptive information at a slower velocity. Furthermore, C-fibers are thought to transmit information about diffuse, dull and aching pain which is reported by patients following an episode of acute sharp pain. C-fibers are capable of transmitting accurate information about itch, warm, burning and cold sensations[21].

VII. Definition of proprioception

Proprioception is the ability of some sensory receptors localized in the PDL, muscles, tendons, ligaments, capsules and temporomandibular joints (TMJs) to monitor and control amount of force, changes in velocity, position, angulation., distension, amount of tension, excessive stretching and pressure in all those anatomic structures in which they are located. Their role is to prevent any activity that can produce damage to the structures they monitor, protect or control. In this regard, proprioceptorsprotect some structures, for instance joint capsule and PDL from excessive stretching and or pressure than can produce damage to cells, fibers and the receptors themselves. Various types of mechanoreceptors in the PDLare extremely sensitive and capable of detecting forces of only a few miligramsin the order of 10-100[3] ug and at the same time, excessive forces or objects placed between the teeth are avoided to prevent damage to the periodontal structures.

PDLmechanoreceptors or proprioceptive sensors are very specialized.These sophisticated peripheral pressure receptors can be found in the connective tissue supporting the roots of the teeth in the upper or lower jaw. These receptors respond to forces applied to the crowns of the teeth and when activated they stimulate reflex changes in the activity of the jaw closing muscles[22]. These receptors provide automatic information as to how fast and hard to bite[3] as there is a close relationship between mastication speed and hardness of the food. Mechanoreceptors located in the PDLare extremely sensitive when pressure is exerted on the crown of the tooth. It has been established that information from these receptors is important to coordinate jaw movements. It has also been demonstrated that these receptors function together with receptors in the major masticatory muscles (muscle spindles). PDL mechanoreceptors and those from the gingival tissues have their cell bodies in the mesencephalic nucleus of the fifth cranial nerve[23]. They transmit afferent information to the SNC which is converted into efferent signals to the muscular motor units that coordinate jaw movements[24]. Afferent from other structures, for instance, muscles, tendons, ligaments and capsules, provide automatic information so as to enhance synchronization of information and produce elaborated and refined jaw movements with a minimum of trauma and expenditure of energy in the system.

VIII. Where mechanoreceptors can be found ?

Mechanoreceptors in the masticatory system are usually found in the PDL, muscles, tendons, joint capsule and ligaments and probably in other anatomic structures. Proprioceptors in the PDLhave similar functions to those in the capsule of the TMJs as they control position of the mandible, velocity of movement, shape and consistency of the food being chewed, amount of force, pressure and degrees of stretching in some structures of the PDL. It has been demonstrated that following anesthesia to the joint capsule and or PDL, there is a significant decrease in perception ability during chewing. Based on the studies carried out by Sanosyan and colleagues[19], Table 1 shows a brief description of the anatomic areas where PDL receptors can be found:

Table 1: Receptor types in the PDL and anatomic area where they can be found (Based on the studies carried out by Sanosyian and colleagues[19]:

Receptor type	Anatomic location within the PDL
Free nerve endings	Throughout the length of the root
Ruffini-like corpuscles	Mostly found in the apical portion of the root
Coiled nerve endings	Middle portion of the PDL
Spindle –like endings	Proximities of the root apex

Receptors from different tissues in the stomatognathic systemare involved in controlling the spatial position of the lower jaw[24] during different normal or abnormal functions of the masticatory system. In dentate individuals, mechanoreceptors in the mucosa, periosteum, muscles and tendons acting in concert with those in some structures of the TMJ and PDL[24] are involved in different activities of the masticatory system.

IX. Proprioceptors in the periodontal ligament

1.Introduction:

The physical control of the proper position of a tooth in the dental arches and/or in the alveolar bone and the pressure exerted on the tooth is controlled mainly by the set of different collagen fibers which maintain the tooth in position and also by a set of receptors called proprioreceptors which control position, movement, forces and displacement by informing the central nervous system about these biomechanical parameters. Proprioceptors in the PDLwork together with receptors in the pulp, muscle, capsule and ligaments of the TMJsto control parameters of proprioception in the PDL, that is, pressure, speed of movement, position and force applied to the teeth.

2.What is proprioception: Proprioception is a general term used to describe neurophysiological and biomechanical processes related with position, distension, movement, stretching, velocity and pressure. Information about these parameters is sensed by receptors called proprioceptors located in areas of movement, application of forces, stretching, pressure and/or distension. Thus, proprioreceptors are mainly found in the PDL, muscles, tendons, ligaments, capsules of the joints and other structures. Most important peripheral sensory inputthat significantly assist in the control of mastication comes from PDL mechanoreceptors around the teeth and from muscle spindles in the jaw muscles[25].

3.Control of forces or movement under loading

Force of pressure applied to the periodontal tissues is one of the most important parameters controlled by local mechanoreceptors as they are stimulated by the amount of force being applied to the teeth.When an external force, such as occlusal force, is applied to a tooth, a minor tooth displacement occurs[26]. Such displacement involves stretching and thus tension in some of the periodontal fibers and then the periodontal mechanoreceptors are stimulated changing the periodontal sensory threshold and at the same time, they send accurate and instantaneous information to the masticatory muscles through the mesencephalic nucleus in the brainstem.

When mastication or any activity involving tooth contact ceases, unloading of periodontal receptors occurs. For instance, in the final stage of mastication when the food has been broken to minor particles, the unloading reflex is set to function. Thus, informationconveyed from mechanoreceptors in the PDL to the mesencephalic nucleus of the trigeminal nerve, including to the motor nucleus, assists muscles to decrease the force applied to the teeth and PDL[22]. In other words, the muscles receives feedback from the PDLthrough information sent from the mesencephalic and motor nucleus of the trigeminal nerve. The mesencephalic trigeminal nucleus where a concentration of neurons cell bodies is located, is unique in the trigeminal nervous system. Cell bodies in this nucleus provide abundant afferents to the muscle spindles, to Ruffini´s endings in the PDL and to the dental pulp. Projections from the mesencephalic nucleus in the trigeminal complex indicates that the mesencephalic nucleus is pivotal in the control of jaw movements[27].

When teeth are extracted, the remnants of the PDL break down and disappear but it has been found recently that neurons in the area of extraction do not disappear completely and can be found around the site of extraction[10].Even the population of neurons and their cell bodies present in the mesencephalic nucleus of the trigeminal complex do not disappear and do not degenerate completely following tooth extraction[10].Based on the studies carried out by Sanctuary and associates[28] and from a structural point of view, it is apparent that there are three systems that control the dynamics of a tooth being subjected to loading: the fibrous component (a number of different collagen and elastic fibers, the ground substance and the blood vessels.

Biomechanics of loading in the PDL: Studies published by Sanctuary and associates[28] indicate that the set of collagen fibers broadly distributed in the PDL is extremely active during tension states. On the other hand, during a state of compression, the glycans in the ground substance in the PDL, dissipate the force or tension. Glycans are able to do so by forming a biomechanical medium with water that enables this biologic complex to dissipate such force or tension. This glycan-water environment is endowed with a set of properties including the capacity to swell, viscosity, and resistance to flow when the tooth is subjected to shear loading[28].

6.What are the proprioceptors in the PDL?:Because some biomechanical phenomena including pressure, application of force, stretching and distension have to be dissipated in some way by all components of the masticatory system, the PDL is endowed with numerous mechanoreceptors or proprioreceptors located in strategic anatomic areas (for instance, apex of the root) in order to dissipate forces and control pressure, distension and loading.Such proprioreceptors facilitate/control most parameters during mastication. Mastication is a very complex phenomenon usually controlled by mechanoreceptors located in different areas of the masticatory system including muscles, tendons, ligaments, capsule of the TMJs, PDL and probably tongue and mucosa. Afferents to the jaw-closing muscles have their origin in the cell bodies of neurons in the mesencephalic trigeminal nucleus, butthose cell bodies also send their axons or collaterals to supratrigeminal and intertrigeminal regions, to the motor trigeminal nucleus, lateral part of the medullary reticular formation, lamina VI of C1-C3 cord segments and cerebellum[29]. In experimental studies in the cat, periodontal receptor afferents were found to be located mainly in the caudal part of the mesencephalic trigeminal nucleus[29].

The sensors within the PDL called mechanoreceptors, send constant information to the brain so as to properly control mastication and prevent trauma to the system. Thus, most researchers in this field, regard the sensory input from this set of organs as fundamental to control the complex masticatory function.

Maeda and associates[11] believe that PDL proprioceptors are those receptors that react to touch, pressure sensation, distension, stretching and changes in minor tooth movement during function. Free nerve endings are those receptors found abundantly in the PDLand represent nociceptors whereas specialized nerve endings or mechanoreceptors can also be found abundantly in the PDL. Ruffini´ sending, a low-threshold stretch mechanoreceptor is the primary PDL mechanoreceptor and its properties have been described in numerous investigations.A typical Ruffini proprioceptor can be found in the fascia, hair follicles, joint ligaments, joint capsule, internal ligaments of a joint, and tendons[11]. These receptors have been anatomically characterized in numerous investigations as having two basic characteristics[11]: The receptor is more frequently concentrated in regions where components of PDL are stretched and is provided with numerous peripheral arborizationsto increase its sensory “field” or “the anatomic area to be sensed”.

Many researchers defend the notion that sensory receptors in the PDLconstitute both a mechanical and neurophysiological protective mechanism as they prevent excessive overload on the jaws and supporting apparatus and at the same time monitor and modulate masticatory force and work in concert with both muscle and joint proprioceptors[30,31]. Because receptors in the PDL, those in the masticatory muscles including tendons, receptors from capsules and ligaments in the TMJs, function as a unit, receptors in the PDL provide feedback to muscles and joints and this constitute the most important mechanism to maintain the stability of the PDL and TMJs. Thus, the neurophysiological protective mechanism present in the jaw muscles and their first control center in the mesencephalic and motor nucleus of the trigeminal nerve, is similar when compared to PDL receptors.Short or small ligaments in the TMJ are recognized as strategically located sensory organs capable of monitoring and supplying relevant kinesthetic and proprioceptive data to other adjacent anatomic structures[32].

The PDL provides unconscious sensory feedback during mastication and its receptors are able to detect minute particles between the occlusal surfaces of teeth. Further, proprioceptors in the PDL, provide sensory information as to how fast and hard to bite and this ability of the PDL mechanoreceptors is lost temporarily when the teeth are anesthetized[3]. Morphologic investigations have reported the presence of Ruffini endings in the PDL, a low-threshold stretch receptor which has the ability to respond both to noxious stimuli (nociception) and also to mechanoreception[33]. There are at least two types of mechanoreceptos in the PDL: Slowly adapting mechanoreceptors and rapidly adapting units[11].In experimental animals, the stimulus threshold and response magnitude of individual PDL mechanoreceptors depend on the direction of steady force applied to an intact tooth, for instance, the canine[34].

X. Forces and Ruffini endings in the periodontal ligament

The PDL is located between hard tissues such as the cementum and alveolar bone where it functions as a shock absorber or “dissipator of forces or tension” applied to the teeth. PDL mechanoreceptors are stimulated by jaw movements, application of forces, presence of foreign objects, voluntary or involuntary tooth contact, orthodontic treatment and jaw movements during bruxing activity. In experimental studies[33], it has been demonstrated in vitro that the application of forces to the PDL stimulates the production and expression of some inflammatory mediators including prostaglandins, interleukin 1-beta and COX-2. When PDL cells are experimentally subjected to mechanical stress, oteoclastogenesismay be induced through the up-regulation of RANKL expression via PGE_2 synthesis during orthodontic tooth movement[33].

Typically, a periodontal Ruffini ending is described based on light microscopy studies as a receptor characterized by many arborizations and thickaxon terminals. The receptor is usually found in a number of anatomic locations including the subcutaneous tissue, joint capsule, tendons, ligaments of a joint, fascia and hair follicles[11]. . Histological studies have been used to define some unique characteristics of Ruffini endings including its high concentration in the region of the periodontal fibers subjected to higher levels of stretch or tensionduring tooth functions, presence of extensive arborizations, the absence of a fibrous capsule.The periodontal Ruffini endings form a very complex three-dimensional structure within the PDL[11].

Ruffini-like receptors are found primarily in the apical segment of the periodontal ligament. They have a dendritic appearace and are ensheated in Schwann cells. This receptor has finger-like processes that are anchored in nearby collagen bundles that serve to increase the receptive field of the nerve terminals. Biomechanically, the Ruffini mechanoreceptor is endowed with the capacity to detect deformation from the neighboring collagen fibers thus, stimulating opening of the ion channels in the receptor membrane, causing depolarization of the receptor[19]. Any sensory mechanoreceptor including the Ruffini´s corpuscle has been developed to prevent overload and damage or injury to teeth and periodontal ligament by regulating masticatory forces[19] and inducing some reflexes to prevent or stop tooth contact during function or dysfunction. Furthermore, Ruffini´s endings and other PDL receptors operate in concert with proprioreceptors in muscles, tendons, and capsule of the TMJs. In experimental studies in the cat, it was found that mechanoreceptors in the PDL respond when the area of the ligament in which they lie is in a state of tension not compression[13].

The cell bodies of the Ruffini receptors are found in both the trigeminal ganglion and in the mesencephalic nucleus of the trigeminal complex. It has been demonstrated experimentally that the Ruffini´s ending has a special ability to respond to noxious (nociceptive) and non–noxious (proprioceptive) stimulation. This duplicity of function likely explains the fact that this receptor has its cell bodies in both the trigeminal ganglion and the mesencephalic nucleus.Stimulation of the PDL mechanoreceptors stimulates a feedback mechanism on the closing muscles that results in inhibitory responses, for instance, inhibition of jaw closing and/or a decreased biting force. This is essentially a reflex protective mechanism which probably serves to reduce the activity of the jaw closing muscles when one bites unexpectedly[12] or as the result of a foreign and undesirable body that is suddenly detected between the teeth.

XI. PDL adaptation to forces or loading

The PDL is subjected to small or large amount of force during most activities of the masticatorysystem. Larger amounts of forces are transmitted to the PDL during nonfunctional activities, for instance, diurnal and nocturnal bruxing behavior. Such forces constitute a powerful stimulus for the development of compensatory mechanisms (resorption and deposition) in the PDL. Because the PDL is endowed with a diversity of local mechanisms to protect, support and provide sensory input to the CNS, the PDL is also able to maintain homeostasis and initiate repair of tissue destruction caused by local periodontal disease and by intense mechanical trauma like that observed in sleep bruxing behavior[35]

Force modulation is a mechanism that depends largelyon proprioceptors in the PDL as theycontrol the masticatory force and support the sensory feedback role within the ligament by providing constant information to other centers in the trigeminal system, for instance, to the trigeminal ganglion and/or to the mesencephalic nucleus. The PDL provides the means by which the forces exerted on the tooth are immediately transmitted to the collagen fibers and then to the bone[36] where a mechanism operates in order to dissipate force, tension and pressure. This ability of the PDL is lost when the teeth are extracted or when the individuals wear full dentures. In this cases and in order to protect the system (mucosa, bone, muscles and TMJs), the maximum bite force is reduced to five or six times less[36].

It has been demonstrated that mechanical stress or tension induces biomechanical and structural responses in a variety of cell types in vivo and in vitro. The mechanisms involved in the dissipation or transformation of physical stress is far from being completely understood but probably involves the role of receptors, periodontal fibers, periodontal fluid, the fibers that protect the bone, alveolar bone and cellular responses as it occurs during orthodontic tooth movement. The PDL functions as a cushion to withstand mechanical forces applied to the teeth. There are also complementary mechanisms that participate in the maintenance and remodeling of the ligament itself and the metabolism of cells, fluid and bone[33]. The mechanoreceptors in the PDL allow a continuous transfer of information about the direction and magnitude of the forces being applied to each tooth. Evidence for this mechanism comes from studies[30] in which anesthetized teeth loose their sensorymotor function as long as the teeth are kept dormant during local anesthesia.

XII. Nociception and nociceptors in the PD

Nociception is defined as a set of central and peripheral phenomena and mechanisms including the presence of nociceptive receptors, the mechanisms used by receptors, transmission, synapsis, modulation, facilitation, inhibition and disinhibition of nociceptive information and interpretation of information that occurs in the CNS and that ultimately results in pain. Nociception is the neural process of encoding noxious stimulus, whereas pain is defined as an unpleasant sensory and emotional experience associated with actual or potential damage on the body tissues, or described in terms of such damage[37].Plastic changes including allodynia and hypoeralgesia frequently observed in chronic pain states are also included in the concept of nociception.

Nociceptive nerve fibers supplying the PDL, pass through foraminae in the alveolar bone to occupy some spaces in the PDL close to the tooth apex. Other fibers though, enter through the lateral aspect of the alveolar wall and spread into the PDL[19].Nociceptors are endowed with many neurophysiological properties and functions including the transmission of informationabout local pain and inflammation[2].Some cells including mastocytes and basophils are able to release nociceptive substances including serotonin, histamine and cytokines which stimulate pain receptors and lower the threshold of the nociceptors for pain and nociception. If such receptors are sensitized, they discharge andrelyinformation to the trigeminal ganglion.

When pain receptors in the PDL are activated, they can cause local inflammation and pain called “periodontal pain”. The most common cause of periodontal pain is the spread of inflammation and the release of toxins by bacteria that previously colonized and multiplied in the PDL. Trauma to the periodontal tissues (occlusal traumatism) is also a common cause of periodontal pain. It causes the release of many inflammatory mediators which in turn sensitize the local nociceptive receptors initiating a cascade of sensitization, transmission, reception in the CNS and finally pain. Periapical receptors become sensitized by the same factors or mechanisms as in pulp inflammation, for example, infection, trauma and inflammation that spreads from the pulpal tissues to the PDL. The nerves of the PDLare mainly sensory branches of the trigeminal nerve and can be classified as nociceptors when they send to the CNS information about tissue damage, potential pain and inflammation.

In the PDL, periodontal pockets may induce the release of pro – inflammatory mediators which then act on nociceptors to lower their pain threshold[21].Each nociceptive sensory receptor in the PDL is attached to a first order or primary afferent neuron whose cell body is found in the trigeminal ganglion (TG) of the trigeminal sensory complex. Once impulses reach the TG, they travel to a second order neuron in the trigeminocervical complex where the information is relied and transmitted to higher centers in the CNS..

Pain receptors in the PDL are also called nociceptors. There are two types of nociceptors in the PDL: A-delta and C- fibers. Such receptors are usually sensitized by many types of pro inflammatory molecules. During the first stages of inflammation in the PDL,sensory receptors can release SP, a powerful sensory neuropeptide. The PDL has the capacity to induce the secretion of many pro-inflammatory cytokines including IL-1, IL-1beta, TNF-alpha. These molecules can also be found in inflammatory conditions in the synovial membrane of the TMJs. Other nociceptive molecules including CGRP can also be released in the PDL. Nociceptors in the PDL are mainly free nerve endings classified as A delta and C fibers based on their anatomical and physiological characteristics, for instance, both transmit information about potential or actual tissue damage. However, A delta fibers are thicker, myelinated and transmit faster information to the CNS whereas C-fibers are thinner, non-myelinated and transmit nociceptive information at a lower speed.

XIII. Inflammatory mediators

Pain mediators are those molecules involved in the initial stages of pain usually releasedby many cells of human and animal tissues. A large amount of pain mediators is released by body cells immediately following tissue damage. Such pain mediators cause pain and body reflexes, including withdrawal of the affected body part but other reflexes and behaviors may also be present. A number of pain mediators has been described in the literature about pain, including histamine, serotonine, prostaglandin, leukotrienes, SP, CGRP, VIP, somatostatin, just to name a few.

Once a specific mediator (for instance histamine) is released, it acts on the specific receptor for that molecule expressed in nociceptive sensory organs resulting in the release of second messengers and the downstream activation of protein kinase and phospholipase[38]. One of the most known and investigated molecules in the field of physiology and neurophysiology is SP. SP is a neuropeptide produced in a set of capsaicin sensitive sensory peripheral neuron cell bodies located in the dorsal root and trigeminal ganglia of the fifth cranial nerve. SP has a prominent role in the transmission of noxious stimuli in the spinal cord[39].

XIV. Periodontal pain

Pain is one of the cardinal signs of inflammation being inevitable for any human being. Pain is the most common response when certain nociceptive substances, for instance, prostaglandin E_2, histamine and certain cytokines and serotonine, are released by some cells, for instance, mastocytes and platelets. Periodontal pain is defined as “pain caused by a lesion or disorder involving the PDL and/or adjacent alveolar (peri-radicular) bone tissue[40}. Thus, periodontal pain is caused by many factors including those related to infection and inflammation and others related to occlusal trauma.Local inflammation causes progressive tissue destruction and pain which is well localized due to the numerous nociceptors found in the PDL tissues. Periapical nociceptors become sensitized by the same mechanisms present in other inflammatory states including the release of pro-inflammatory substances like histamine, serotonin, prostaglandins and cytokines. For the sake of diagnosis, periodontal pain is usually described as constant, dull and aching[40]. However, pain may increase in intensity due to compression or pressure on (exerting vertical pressure on the crown of the tooth) the inflamed tissues of the periodontal fibers in which nociceptive fibers have a lower threshold for pain. Periodontal pain is relatively well localized and thus, extends less than the pain originating in the tooth pulp. In periodontal structures, pain may be manifested in two different ways: pain of periapical origin which is a deep somatic pain, or pain in the gingival tissue, which is superficial somatic pain[41].

Conclusion

The PDL is the anatomic structure located between the wall of the alveolar bone and the cementum of the teeth. It is formed by loose connective tissue rich incollagen fibers. Two types of sensory receptors are found in the PDL: nociceptors or receptors for pain and mechanoreceptors or receptors for proprioception. Various types of mechanoreceptors can be found in the PDL and they are classified according to their function and electrophysiological characteristics. Mechanoreceptors form part of a complex sensing apparatus found abundantly in the PDL, muscle, tendons, joint. These and probably other receptors, work in concert to control jaw movements and protect most components of the masticatory system. Nociceptors are extensions or branches of cell bodies located in the trigeminal ganglion whereas mechanoreceptors are mainly projections of cell bodies located in the mesencephalic nucleus of the trigeminal complex.

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