Bibliographic Update Work:

Dental Pulp Sensory Function. Pain.

E J E R

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Dental pulp is a highly vascularized and innervated tissue. The neural component of the pulp tissue consists of motor and sensory nerve fibers, the latter coming from the cranial nerve V; all stimuli that provoke these fibers will result in a painful sensation. Dental pulp tissue is not the only tissue with this characteristic. The eye cornea and the tympanic membrane of the ear are also sources of pure pain and like the pulp, of high neural density.

The sensitive type fibers, belongs according to its diameter, conduction velocity and function to two groups: las Aδ (myelinated) and C (unmyelinated). [Ingle J (2002).] Both act as nociceptors that contribute to the defensive function. The myelinated axons have fast conducted speed, low stimulation threshold, they convey a sharp and stabbing pain type and are superficial (they are located in the pulp and dentin junction). These characteristics make them as the first nerve fibers to react and transmit the pain impulse even when there is no irreversible tissue damage. The stimuli that excite them are mechanical, thermal (cold) and chemicals. Among the Aδ fibers population the arousal thresholds vary. Low threshold fibers respond to stimuli such as cooling and vibration, and they rarely participate in nociception, however, there is evidence that they may be involved in reflection or other functions related to perception. The higher threshold A fibers respond to a much stronger stimulus, such as mechanic and they can act as nociceptors. The A fibers diameter ranges from 1 a 4 μ with a conduction velocity of approximately 13 m/sec. C fibers are unmyelinated; they have low conduction velocity and higher excitation threshold. They are located deeper than the myelinated fibers and they are principally activated by heat, causing slow, diffuse and durable pain. . [Bergenholtz (2007).] If the pain stimulus intensity increases, the sensory C fibers are recruited and the pain becomes a burning sensation. The C fibers reaction shows that the pulp damage is irreversible. [Bircher ME, et al (2009).] C fiber diameter is less than 1 μ and it conduction velocity is of about 1 m/sec. C fibers also differ from A fibers in their ability to maintain its functional integrity when the tissue becomes hypoxic, this is because the oxygen consumption is higher in the thick A fibers than in the thin C ones. Thus, when an injury results in an interruption in the pulp microcirculation, the C fibers continue to function for more time than the A because the latter have been inactivated or infarcted by lack of oxygen. [Narhi MVO (1985); Bergenholtz.]

It is worth mentioning that several decades ago, in 1982, *Narhi M* has reported the presence of thicker fibers in rats pulp with a high conduction velocity (48 m/sec). They were classified as A-β˜ fibers. The function of these nerve fibers or their presence in human pulp, even thirty years later has not been clarified.

Sensory nerve fibers of the dental pulp are afferent endings of the Trigeminal cranial nerve V and reach the root canal through the apical foramen, going thru the root pulp in lumps. These lumps are often associated with blood vessels in a collagen sheath, forming the neurovascular bundle. Only few bifurcations occur in the root canal, but when these reach the cameral pulp, the nerve fibers begin to divide and send branches to the surrounding dentin. Approaching the subodontoblastic pulp region, the fibers form an intricate network known as Plexus of Rashkow. After this the myelinated fibers lose their myelin sheath and emerge as free nerve endings. In different studies performed by *Gunji* from 1982 to 1988 it has been shown that many nerve fibers end in the extracellular space of the rich cell zone or in the odontoblast layer, while others extend into the predentin or dentin tubules, being able to penetrate them from a few micrometers to 150 μ . These intratubular fibers are more numerous in the region of the cameral horns, where its presence has been estimated of around 25% of the tubules, while in another part of the dentin crowns they are the smallest number, of about 15%. In the root, only about 10% of the tubules contain nerve fibers, these tend to be smaller and do not extend above the predentin.

In *Trowbridge Henry O., et al (1986)* and Johnsen*, et al (1985)* works was found that the newly erupted teeth have non-myelinated axons longer than mature teeth and it was speculated that some of these fibers then acquire a myelin sheath. They have also shown that human pulp has a large number of non-myelinated axons (C fibers) during the early development of the tooth, but that posteruptive changes occur not only in the size of the fibers but also in the configuration of axons groups. In comparison immature teeth have fewer myelinated axons than older teeth, these fibers do not reach their maximum number until the root complete it apical development and even later than that.

Taking into account the way in which matures the nerves network that enters the tooth through the apical foramen and in how these fibers change their structure and number, increasing with age in number of A fibers, with the results obtained in the pulp vitality electrical tests, it is possible to find a viable explanation for why this type of tests performed in immature teeth tends to give unreliable results.

PULP NOCICEPTION MOLECULAR BASIS

Pain is an unpleasant feeling, a complex phenomenon that involves not only the sensory but also the emotional response, the social representation, the valuation of previous experiences and the features related to behaviour and motivation. It is a very subjective sensation, therefore difficult to quantitatively investigate it in human beings.

Dental pain is caused by dental pulp nerve fibers stimulation. The trigger stimuli can be mechanical or thermal. . *Leffingwell et al* (2004), *Ricarte J. M. et al* (2007). A wide range of molecules and structures of different characteristics play a fundamental role in the onset of pain. The neural component is not the only one involved in this response, the vascular structures also play a role in this alert and tissue protection mechanism.

As a complex expression it involves multiple systems that contribute to its occurrence and regulation. From a coordinated intervention between the Central Nervous System and the Endocrine System, the hypothalamus and hypophysis gland may be related with some of the events that occur in the pulp during a symptomatic period. *Rutz J. Carson (2007)* establishes an interesting relationship between the endocrine system and the dental pulp. He describes the events that occur when the corticotrophin (CRF) releasing factor binds to its membrane receptor (CRF-Rs). Among the final actions of the activated receptor, the release of endorphin from immune cells increases the peripheral antinociception. If the dental pulp is considered to be a peripheral tissue, the above statement may be applied to the tooth. The physical and psychological stress enhances the release of CRF from the hypothalamus. *Houssay A* (2009), *Silverthorn D* (2009) When this binds to its receptor CRF-Rs in the anterior hypophysis, allows the release of the adrenocorticotropic (ACTH) hormone and the endorphin into the bloodstream. The ACTH acts on the suprarenal gland cortex to stimulate the secretion of cortisol, an anti-inflammatory glucocorticoid, while the endorphin produces a nociception decrease. The synthetic use of CRF stimulates immunocompetent cells to secrete the endorphins cell deposits and it interacts with the opioid receptors on the peripheral afferent nerves, causing a significant antinociception. CRF peripheral analgesic effects, as we think then, are due to the release of opioid peptides by immune cells as a result of the interaction of CRF and CRF-Rs of its membrane.

The first description of μ opioid receptors in humans was conducted by Gómez-Román JJ in 2002, who along with his colleagues found this receptor in the respiratory system cells. *Gómez-Román J.J., et al* (2002). The immunohistochemical localization of μ type opioid receptors in human tooth pulp was discovered by *L. Jaber, et al. (2003)* along the ramification of the nerve root and in the cameral pulp. Positive immunostaining was also detected along individual nerve fibers in the pulp chamber region. This demonstration of opiate receptors on pulpal nerve fibers suggests a peripheral site in the dental pulp where endogenous and exogenous opioids can interact with μ opioid receptors. Based on pharmacological studies, at least three classes of opioid receptors have been defined: μ; δ and κ. The hypothesis of this work refers to the μ opioid receptors may be associated with small-caliber nerve fibers (C fibers), although further studies are needed to clarify this possibility. However, there is evidence that a local morphine injection lessens the pulpitis pain. *Dionne RA (2001).* Recent studies show the δ opioid receptors ability to

regulate the homeostasis of the potassium ion (K $^{+)}$ [Chao D , et al (2007)], considering the importance of this ion for nerve conduction, further studies may be needed to place them in the pulp tissue and determine if they have implications in the odontogenic pain conduction.

Taking into account that the adrenal glands medulla is an important source of catecholamines (dopamine, adrenaline and noradrenaline) production and the pulp has receptors for these compounds located mainly in the blood vessels membrane and in some neurons membrane, it can be established another relationship in reference to the adrenal glands.

A New York University Endodontics Department study established a base level of catecholamine (dopamine, epinephrine, or adrenaline, and norepinephrine or noradrenaline) in the human pulp not excited in virgins teeth, without pathology. Nerve stimulation is considered a vital factor in catecholamine synthesis. A mild stimulation increases the tyrosine hydroxylase enzyme activity, a catalyst in the catecholamine synthesis. When there is an exposition to extraordinary stimuli (childbirth, burns, cold, hypoxia, immobilization, or physical exercise), the catecholamine synthesis is markedly increased. Patients with pulp pain associated with inflammation can also produce increased amounts of catecholamine in the pulp. This presence in the human pulp has been demonstrated by histochemistry fluorescence.

Anneroth and Norberg in 1958 demonstrated the presence of the noradrenaline neurotransmitter in adrenergic nerve terminals of human dental pulp. Ten years later, Pohto and Antila confirmed this by demonstrating the presence of adrenergic nerve fibers closely connected with blood vessels in human dental pulp, suggesting a vasoconstrictor function. These data indicate that blood flow in human pulp is at least partly controlled by adrenergic innervation. In 1980 [Kim et al.] stated, continuing this line of research that the sensory nerves help to regulate the blood supply of the dental pulp. Catecholamines such as epinephrine or norepinephrine, exert their physiological effects on receptors (adrenoceptors) in the blood vessels. Pulp vessels contain both α and β-andrenoceptors. The α receptors are responsible for the contraction of the vascular muscle, producing vasoconstriction. Stimulation of β1 receptors causes a relaxation of the vascular musculature. These receptors influence the pulpal hemodynamic system variations. A few years later, in 1986, [Wakisaka et al]. were able to show the distribution of feline dental pulp adrenergic nerve fibers before and after cavity preparation. After cavity preparation an inflammatory process with alterations in morphology and biochemical content of nerve fibers occurs. These authors concluded that these changes do not occur as an acute response to noxious stimuli generated by the cavity preparation, although the alteration of biochemical substances such as substance P, VIP (vasoactive intestinal peptide) and catecholamine might have occurred. Higher levels of noradrenaline, adrenaline and dopamine were found in inflamed pulps. *Nup Caroline,* in 2001, managed to quantify catecholamine in inflamed pulp tissue and considered the possibility of using pharmacological agents that reduce their concentrations [Nup Caroline et al. (2001)].

INFLAMMATION AND PAIN

The two key components in pulp inflammation are the microcirculation and the sensory nerve fibers activity. The excitement of A-δ fibers seems to have a negligible effect on pulpal blood flow, whereas activation of C fibers causes an increase of it. This increase induced by C fibers is caused by neurokinins, especially P substance, which is released from C fibers nerve terminals. The alteration of pulpal blood flow has varying effects on sensory nerve activity. The pro-inflammatory neuropeptide Sustance P was first mentioned around the 30's and there was so much progress in relation to its study. *Harrison Selena (2001)*. Previous studies have shown that substance P is involved both in inflammation and in pain *Dionne RA (1998)*, and that extracellular levels of Substance P are increased in symptomatic pulp tissue diagnosed with irreversible pulpitis. Subsequent studies have found that it is involved in plasma extravasation and therefore in the edema formation (fluid accumulation in the interstitial space). Neurogenic inflammation which is the result of neuropeptide peripheral release causes changes in vascular permeability of the dental pulp. The SP evokes a vasodilatation and endothelial cell contraction, causing an increased leakage of plasma proteins. These effects are mediated by G protein associated with NK-1 receptor. Although its action is not as fast as ion channels, receptors associated with G protein have a wide impact because they involved second messengers such as AMPc, GMPc and IP3. *Bowles Walter R (2003)*. An 8 times increase in SP was noted in the pulp tissue diagnosed with irreversible pulpitis against clinically normal pulp tissue. Thus, irreversible pulpitis is associated with this significant activation of the peptidergic system. Odontogenic pain often involves pulpal tissue inflammation. Dental pulp is highly innervated with a subpopulation of sensory neurons containing neuropeptides. Substance P released from afferent fibers (eg nociceptors) is associated with the development of neurogenic inflammation. This SP extracellular increase can affect the complex interaction between pulp cells, immunocompetent cells, blood vessels and nerve fibers.

The pulp restoration also involves neuropeptides. These are defined as synthesized peptide neurotransmitters or neuromodulators and released from neurons that trigger biological effects by activating receptors on the plasma membrane of their white cells. *Azuero-Holguín M. M, et al (2008)*. They have an immunomodulatory role by recruiting immunocompetent cells, which can also express functional receptors for neuropeptides, suggesting an important role for neuropeptides in dental pulp, not only in pain and inflammation, but also in the protection and repair.

For thirty years, a variety of endogenous chemical mediators have been associated with inflammation and pain associated with inflammation. These mediators include histamine, bradykinin, 5-hydroxytryptamine, and prostaglandins.

Bradykinin (IBK) is a potent mediator of pain and inflammation. It can stimulate peripheral nociceptive terminals to cause pain and sensitize nerve fibers to thermal, chemical, and mechanical stimuli. It can also synergistically act in combination with other substances such as prostaglandins and 5-hydroxytryptamine to produce signs and symptoms of acute inflammation. Bradykinin Inflammatory responses include vasodilatation, plasma extravasation and recruitment of inflammatory cells. Also induce other side effects that can lead to the production of additional inflammatory mediators.

The extracellular levels of bradykinin are significantly elevated during irreversible pulpitis. The extracellular level of IBK is higher in patients who have reported historical pain, compared with patients who had pain at the collection of bradykinin time. This suggests plasticity in the IBK system that can largely contribute in the early stages of inflammation and pain.

Irritation of the dental pulp produced by bacteria, mechanical or chemical stimuli can cause inflammation. Besides the activation of other systems, such as the kinins, coagulation, and complement system, these stimuli may cause the enzymatic conversion of arachidonic acid in a biologically active group mediators. These are the hidroperoxieicosanoico, hidroxieicosanoico, leukotrienes, PGs, and thromboxane acid.

Prostaglandins have been implicated in many aspects of inflammation processes, including vasodilation, vascular permeability increased, bone resorption, chemotaxis, and pain. PGs are synthesized via COX enzyme. PG synthesis is initiated by the breakdown of arachidonic acid, by the phospholipase A2 action from the phospholipids membrane cell. The arachidonic acid via COX metabolism causes the PG production. COX is the rate limiting enzyme in PG production.

Within the PG family, PGE 2 has been documented in pulp disease. [Chan Yu-Chao et al (2003)]. PGE2 is a potent stimulator of bone resorption. PGE2 synthesis is regulated by multiple metabolic steps involving several different enzymes. COX is one of the enzymes responsible for converting arachidonic acid to PGE2. [Chang MC et al (2006)]. COX-2 is an inducible enzyme believed to be responsible for PG synthesis at the site of inflammation because it occurs in low or undetectable levels in healthy tissues and in increased levels in inflamed tissue; inflammatory mediators such as IL-1, TNF-α, growth factors, LPS, and tumor cells are stimulators of the of COX-2 expression. The PG E2 and F2 can be identified in inflamed and non-inflamed pulp tissue. In pulps with asymptomatic chronic inflammation, significantly higher values of PGE2 were found, but not of PGF2-α. The pulp tissue that had pain, showed higher concentrations of both PGs than those without pain, this can occur as a result of significant tissue damage and cell lysis that is observed in painful pulps exposed to dental caries and also by the addition of polymorphonuclear leukocytes to inflamed tissue. PGE2 may be able to produce pulp pain in two different ways. First, it presents hyperalgesic qualities, which sensitizes the nociceptive nerve endings. Second, it can increase the pain response to other pain mediators, such as bradykinin, histamine and 5-hydroxytryptamine.

The PGF2-α may have a modulating effect on the tissue response to PGE2.

The introduction of PGE2 in tissue caused an accumulation of AMPc or the activation of adenylate Cyclase (AC). The PGF2-α has no effect on the AMPc except in very high concentrations. However, the PGF2-α has shown that it can increase the GMPc levels in various tissues. The AMPc and GMPc seem to be responsible for a number of contrary effects. The AMPc dilates vascular smooth muscle while GMPc constrict it. The GMPc enhances the chemotaxis while the AMPc retarded it. The GMPc induces the selective release of lysosomal enzymes whereas AMPc inhibits such release. The AMPc increases cause a hyperpolarization, which reduces the nerve impulses transmission. On the contrary, the GMPc, which apparently increases in

chronic inflammation, causes depolarization of some cholinergic neurons. The pain may be then, controlled by the predominance of a cyclic nucleotide over another during the different phases of the inflammatory response. The actions of at least five neurotransmitters are mediated by the AMPc. The GMPc mediates the activities of other four. The neurotransmitters histamine, acetylcholine, noradrenaline and dopamine have been found in animals and human dental pulps. All of these neurotransmitters have been implicated in the production of pain.

Thus, these second intracellular messengers (AMPc and GMPc) which act from the activation of plasma membrane receptors coupled to G proteins, also play an important role during the inflammatory response and Odontogenic pain.

IL-1 and TNF–α regulate the COX-2 expression in human pulp cells. The kinetics of this response showed that COX-2 was detectable in cells lysates as early as 2 hours post proinflammatory cytokines challenge and remained elevated throroughtout the 24 hours incubation period. This suggests that one of the pathogenic mechanisms of pulpal inflammation in vivo may be the synthesis of COX-2 by resident cells in response to a proinflammatory cytokines challenge. Thus, COX-2 may play an important role in the regulation of prostanoid formation in the pathogenesis of pulpal inflammation.

In 1995, [Tani-Ishii N et al] have shown that increased amounts of proinflammatory cytokines such as (IL)-1 and tumor necrosis-α TNF can induce pulpitis in rats. Besides, studies have shown that IL-1 and TNF-α regulate matrix metalloproteinase and the tissue plasminogen activator of human dental pulp cells. These conclusions highlight the importance of proinflammatory cytokines in the pulp injury. In the same year, [Sundqvist G et al] mentioned that the pulp cells have demonstrated the ability to secrete PGE2 and therefore, as it is believed, they are involved in tissue destruction of pulpal disease. Increased production of PGE2 has been demonstrated in periradicular lesions, which partly explains bone resorbing activity. [Coon David (2007)]. PGE2 levels in root canals periradicular exudates are associated with clinical symptoms of Endodontic pathology, especially with the onset of pain.

Recent data from the medical literature indicates that COX-2 plays a key role in production of vascular endothelial growth factor (VEGF), a glycoprotein that has the ability to increase the permeability of blood vessels and induce angiogenesis. [Güven Günseli (2007)]. This study investigates the inmunohistological co-expression of COX-2 and VEGF in inflamed human pulp, in conjunction with the expression of CD34, a transmembrane glycoprotein expressed in endothelial cells.

Human dental pulp, surrounded by inextensible structure of dentin and enamel is susceptible to tissue damage when there is an interstitial pressure increase in an inflammatory process. The vascular endothelial growth factor (VEGF), also known as vascular permeability factor is a glycoprotein that has the ability of increasing the blood vessels permeability, a major vascular disruption observed during inflammatory processes. VEGF also plays a critical role in angiogenesis and neovascularization, which may, actually increase and broaden the severity of inflammatory processes due to the increased transport of inflammatory cells,

nutrients and oxygen to the inflammation site. Recently, VEGF has been found at increased levels in inflamed pulp tissue and periapical lesions.

Healthy pulps have a normal morphology and regular distribution of stromal vessels and cells. Only some of the vessels show a moderate VEGF expression, as physiological angiogenic processes indicator. COX-2 expression was not observed in healthy pulps, while all inflamed pulps showed expressed COX-2 cells. Furthermore, VEGF, generally was not expressed in normal pulp tissue, but was strongly positive in inflamed pulps. CD34 was expressed in the endothelium of both normal and inflamed pulps tissues. Co-expression of COX-2 and VEGF in all inflamed pulps could be an suggestive of a possible release of VEGF via COX2 dependent pathway.

At first, COX-2 was identified as an inducible enzyme expressed at inflammation site, while recent evidence shows that the COX-2 prostanoids production promotes the VEGF expression and a subsequent angiogenesis. However, there is not much known about how the expression and synthesis of angiogenic factors are regulated. It has been shown *in vitro,* the VEGF induction in infected human fibroblasts pulp, and with this, the possibility that the COX-2 could be involved in pathological angiogenesis, which may have strong implications for the study of pulpal disease and also for future pharmacological strategies for the inflamed dental pulp treatment.

Since the COX-2 enzyme discovery, pharmaceutical companies have funded many researches searching for more potent and effective anti-inflammatory drugs with a selective criteria toward this enzyme. As there is COX-2 induction at inflammation sites, it is believed that the NSAIDs therapeutic properties are primary for the COX-2 inhibition. ^{Holt Claudia I. (2005)}.

As quoted above, within the cytokine family, the interleukin-1 (IL-1) can be placed within the proinflammatory properties molecules The IL-6 and IL-8, modulate the white series of immune cell response. Ultimately, that is why they facilitate the inflammatory process. The IL-6 is a cytokine that can be produced by various cells as T and B lymphocytes, monocytes / macrophages, fibroblasts endothelial cells and osteoblasts. Since excessive IL-6 and prostaglandins levels have been linked to several inflammatory diseases pathogenesis, this study results suggests the fibroblast involvement in the development of pulpitis via production of IL-6 and COX-2. ^{Lin Sze- Kwan (2002).}

However, these reactions tend to become uncontrolled or overexpressed during the majority of inflammatory processes and eventually leaded to tissue destruction. Therefore, high levels of IL-6 have been related with the pathogenesis of several inflammatory diseases such as periodontitis. Some recent studies also report that the Gram-positive Lactobacillus bacteria, cause of carious lesions can stimulate IL-6 production in human dental pulp. ^{Matsushima K (1998)}. Expanding this Barkhordar RA found that inflamed pulp tissue contains significantly higher levels High IL-6 than healthy pulps.

Besides the modulation of the immune response, IL-6, stimulates the plasminogen activator activity in pulpal cells, which then can activate collagenase enzymes and lead to tissue injury in inflamed sites.

Recently high amounts of IL-6 have been discovered in the dental pulp of patients with acute pulpitis. Fibroblasts from human dental pulp participate in the development and progression of pulpits via IL-6 synthesis, which is regulated by cytokines via prostaglandin. *Rie Miyamoto (2005)*

Several authors have also been described a number of enzymes involved in inflammatory and pain processes. Two of the most important are: the one involved in the beginning of the process and the other in final tissue repair, they are the aspartate aminotransferase (AST) and alkaline phosphatase. The first one is a cytoplasmic enzyme, and its extracellular presence is a sign of cell necrosis. AST is increased considerably in the early stages of the inflammatory process, and this could be related to early cell necrosis of the pulp, while its decrease observe in irreversible pulpits could be related to a depletion or destruction of this enzyme. *Spoto Giuseppe et al. (2001).*

Alkaline phosphatase (ALP) is an enzyme present in the vesicles of mineralized tissues matrix and seems to have a significant importance in their initial formation. It has been long regarded that ALP was involved in the process of early mineral deposition and calcification of these tissues. Matrix vesicles play an important role in the mineralization of the tissue extracellular matrix. High levels of ALP activity has been demonstrated in dental pulp cells because the fibroblasts from the isolated pulp showed high levels of ALP activity.

The decrease in ALP activity in irreversible pulpitis could be related to a massive release of inflammatory mediators from immune cells, these mediators have been shown to have an inhibitory effect on ALP synthesis. *Spoto Giuseppe et al . (2001)*

For the inflammation to occur blood vessel walls should allow the production of the extravasation of those essential substances for that purpose. The relaxation of the vascular endothelium is mediated by nitric oxide (NO), with a consequent increase in the release of intracellular GMPc. Recently it has been demonstrated in different vascular systems that to ensure that vasodilation the SP, GMPc and NO must be involved. Many inflammatory mediators in the dental pulp as histamine, 5-hydroxytryptamine, prostaglandins, bradykinin, calcitonin and P substance (SP) are liberated by cells and sensory nerves in response to different stimuli, whether pathological, pharmacological, and physiological. The release of these mediators leads to dilation of the arteriole and vascular leakage to promote the restoration in the injury site. However, vasodilation in dental pulp may be harmful to the tissue due to be hosted in an environment that does not allow much expansion.

NO plays an important role in maintaining the flow and blood pressure. The nitric oxide-synthase enzyme (NOS) is responsible for producing the endogenous NO; amino acid L-arginine is a precursor in this synthesis. The NO is activated by calcium ion, which is available for cell stimulation mediated by acetylcholine, SP and BKI. *Karabucak Bekir (2005).*

NERVOUS EXCITEMENT

POTASSIUM CHANNELS (Kv)

A ion channel subunit of voltage-gated (Kv 1.4), plays an important role in regulating neuronal excitability. *Wells Jason E (2007)* Kv1.4 subunits are found in myelinated sensory fibers and it is also the main determinant of C fibers excitability. There is a significant decrease in Kv1.4 expression in symptomatic human pulp axons compared with asymptomatic healthy pulp axons. This provides evidence that Kv1.4 may contribute to hyperalgesia and allodynia pulp generation.

SODIUM CHANNELS

The generation and propagation of action potentials in sensory neurons depends on the activity of sodium ion channels (Na $^{+)}$ regulated by voltage-gated. Na $^{+}$ channels increase neuronal excitability. Pulp inflammation induces alterations in primary afferent neurons, causing an increase in excitability and therefore participating in the generation of allodynia and hyperalgesia.

Painful pulp inflammation is associated with an increase of approximately 6 times the subtype of Na + NaV1.8 channels. *Warren Curt Aet al* (2008). This NaV1.8 increase should leave the pulp tissue relatively insensitive to local anesthetics, which could contribute to decrease the effectiveness of these drugs observed in different studies.

CONCLUSIONS

Human physiology as it is known and interpreted nowadays, arises from man's need to explain the adaptations that suffers his body against the constant changes in the surrounding environment, from the possibility of being born, grown, multiplied and died, from the ingenious way to survive despite having a terrible disadvantage since birth. From a philosophical point of view, it could take a long time discussion about the engine that drives him to investigate, learn and know. It could be corroborated in each methodology, in each new study, that the human body must have been created by something or someone who really knew what he was doing, something or someone who knows the complete piece of work in the most intimate and unimaginable way. Since the discovery of the microscope scientific knowledge has grown exponentially and has broken all barriers when the human genome could be mapped. It changes from a macroscopically relate structure-function as if the body were a machine that can be reproduced with just having the right parts to understand that obviously there are components that are much smaller than a cell, and that their lack or excess produces an imbalance that sometimes becomes the cessation of vital metabolic functions. These microscopic elements are critical to make every organ, every tissue, every cell fulfill their specific function, and all functions, more or less pronounced, contributed to a common purpose that is homeostasis, that is to say, precisely this desire to preserve the living man with the integrity that characterizes him. Getting to know all events that simultaneously occur throughout the economy, to shred each molecule involved in each process, to list the factors involved in each of the body functions, unfortunately is for the wise men, simply impossible. Despite the fact of knowing in advance that sooner o later is going to emerge something that will complete the knowledge so far considered by the discoverer to be total. It is always about moving forward and facing new challenges, because that is to be a grown up. It is all because the legend debunkers, who every day discourage the wise men, trying to convince them that everything they do is just smoke, that nowadays it was possible to advance so far in describing the intricate plot that allows the human tissue to react; that it is possible to talk about cytokines, neuromodulators, membrane receptors or ion channels. If the thirst for knowledge would have been satisfied just to discover that the odontogenic pain comes from the stimulation of nerve fibers that can be "thick" and superficial or "thin" and deep, today we had not known that prostaglandin E2 may be related to the onset of the pain, much less we had not known that it comes from an enzymatic reaction mediated by COX 2, and no one would have thought that in addition to this COX, there are the 1 and 3.

For all this, this updating bibliographic work seeks not only to approach the readers to the latest knowledge on a topic, in this case the sensory function of the dental pulp, but also proposes and encourages them to go on, within ones possibilities, in the pursuit of scientific knowledge, to accept that the fast daily pace has reach science and there is still much to discover and learn and that Learning not a weight on the back but a first step to takeoff.

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