

UNDERSTANDING PULPAL PAIN

AQEEL AL MOSAWI, BDS, MS

يعتبر الخوف من ألم الأسنان من أهم العوامل التي تمنع عامة الناس من مراجعة طبيب الأسنان بصورة دورية . وتبعاً لهذا فإن مجتمع أطباء الأسنان ملزمون بفهم أعمق وأوضح لعملية الألم وهذا لتقدم علاج متميز وسيطرة فعالة للآلام الناتجة عن علاج الأسنان . وهذا بدوره سيقبل من الخوف من زيارة طبيب الأسنان عند عامة الناس . لسنوات عديدة كان تصور الأطباء أن أعصاب الحس في الأسنان مسؤولة عن الإحساس بالألم فقط وأنها تؤدي هذه المهمة بعد إثارها من قبل منشطات الالتهاب . الدراسات الحديثة أثبتت أن الصورة أعقد بكثير مما كنا نتصور . أولاً الأعصاب المتأثرة تفرز مواد كيميائية معينة تسمى ملدة (ب . م . ب) وبروتين متعلق بمورثة الكالسوتونين (ب . م . م . ك) . هذه المواد تساعد بدورها في عملية الالتهاب عن طريق توسعة الأوعية الدموية المحيطة وتنشيط محفزات الالتهاب الأخرى . وقد أطلق على هذه العملية اسم الالتهاب العصبي . ثانياً الأعصاب المثارة بواسطة الالتهاب تعطي آلاماً مختلفة عن الآلام التي تصدر بغير الالتهاب وقد أسييت هذه الظاهرة بالتحسس العصبي المفرط ومن علاماتها الألم التلقائي وانخفاض حد التأثير للألم وزيادة مقدار الألم الحسوس . ثالثاً الأعصاب غير ساكنة أو مستقرة تجاه المؤثرات بل أنها تتفاعل مع المؤثرات عن طريق التفرع والتشعب ولتفسير ظاهرة صعوبة تخدير الأجزاء الملتهبة التهاباً حاداً يعتقد الآن أن السبب هو التفرع العصبي وزيادة معدل المواد (ب . م . ب) و(ب . م . م . ك) في أطراف وجذوع الأعصاب . وعقدة العصب مثلث التوائم، وصولاً إلى الجهاز العصبي المركزي . الجدير بالذكر أن المادة الأكثر استخداماً كمخدر موضعي وهي ليدوكين ٢% تؤدي إلى إحباط إفراز المواد الكيميائية من الأعصاب الملتهبة كما أن هرمون الأدرينالين والمستخدم بكثرة مع المخدر الموضعي له نفس الفعل الإحباطي على الأعصاب الملتهبة . ولهذا فإن فعالية الأدرينالين في التخدير الموضعي ليست بسبب التقلص الذي تحدثه على الأوعية الدموية فقط ولكن بسبب أيضا النشاط للأعصاب الملتهبة .

The understanding of the inflammatory, pain and healing processes is of great importance in the practice of dentistry. While bacterial byproducts or immunological agents arising from host inflammatory cells play a major role in pulpal pathosis, the release of neuropeptides from peripheral sensory nerve endings has also been suggested to contribute to pulpal inflammation and pain. The latter process has been termed neurogenic inflammation and has been suggested as an important component in the development of early periapical lesions. Pulpal pain has been widely researched yet there are a number of pain conditions not well understood. Examples are: 1) Symptomatic pulpitis, 2) Post-extirpation pain, 3) Individual variability of dental pain, and 4) Difficulty anesthetizing acutely inflamed pulp. This article reviews the current literature with more focus on neurogenic inflammation in an attempt to offer newer and clearer explanations for pulpal pain conditions.

Introduction

Dental nerve fibers are mainly sensory, but some sympathetic fibers have also been found along blood vessels in the central pulp. Most of the sensory nerve fibers pass through the apical foramen and then branch extensively in the coronal region before terminating in the peripheral pulp. An interesting and consistent finding is the extension of many nerve terminals into coronal dentin. The sensory nerve fibers in the dental pulp originate in the trigeminal ganglion and are categorized, from smallest to

Received 5.5.98; Accepted 9.30.98
Specialist Endodontist, Nairn Health Center, Ministry of Health, PO Box 2860, Manama, Bahrain
Paper was presented at the First Conference of Bahrain Dental Society, 21 - 23 April 1998.
Address reprint requests to: Dr. Aqeel Al Mosawi

largest diameter, into C-fibers, A-delta and some A-beta fibers. On the other hand, post-ganglionic sympathetic nerve fibers originate in the superior cervical ganglion. A-delta fibers are myelinated low-threshold mechanoreceptors and are responsible for the so-called "first pain signal". C-fibers are unmyelinated, high-threshold fibers. They are termed polymodal because they respond to several types of stimuli such as mechanical, chemical, or thermal stimulation of the pulp. C-fibers most likely mediate the sensation of "second pain."

For years, sensory nerve fibers were thought of as static structures producing pain upon activation and stimulation by the inflammatory mediators. This is not the whole picture. Recent neurophysiological studies have shown that sensitized nerve fibers release

neuropeptides (NP), which in turn modulate the inflammatory process. This has been termed neurogenic inflammation. Sensitized nerve fibers also produce pain of special characteristics; a perceptual state termed hyperalgesia.¹ More interestingly, peripheral sensory nerve fibers show sprouting (branching) in the inflamed areas.² This sprouting is reversible and disappears as the inflammation subsides. The CNS is also not a static structure and seems to react to the continuous flow of pain impulses.³ The phenomenon is termed central sensitization.

These four processes: neurogenic inflammation, nerve sprouting, hyperalgesia and central sensitization will be reviewed in this paper. The literature is purposefully reviewed to offer explanations for a number of pain conditions that are not well understood.

Neurogenic Inflammation

Neuropeptides (NPs) are proteins synthesized in the cell body of the primary afferent nerve fibers, and then transported both to CNS and to the peripheral nerve endings.⁴ In the dental pulp, NPs are transported from the cell body in the trigeminal ganglion via the axons to the nerve endings and stored in vesicles. During pulpal inflammation, the peripheral inflammatory mediators stimulate and sensitize the sensory nerve fibers (nociceptors) to release the stored NPs. From a biologic point of view, most important NPs are calcitonin gene-related peptide (CGRP),⁵ substance P (SP),⁶ and neurokinin A (NKA).⁷

Pulpal sympathetic nerves release different class of neuropeptides such as neuropeptide Y (NPY).^{8,9} Vasoactive intestinal peptide (VIP) is another neuropeptide detected exclusively in parasympathetic neurons. Interestingly, VIP persists in the pulp even after injuring the inferior alveolar nerve and sympathectomy.¹⁰ Thus, it has been suggested that parasympathetic innervation does exist in pulp. Pulpal parasympathetic innervation has been a controversial issue. However, the neurophysiological investigations provided better classification of pulpal innervation than that of the histological studies.

As early as 1968, Kroeger found that when the inferior alveolar nerve was stimulated, the intrapulpal pressure increased.¹¹ The same finding was observed in dogs and rat's teeth following nerve stimulation.⁵ More specific studies showed that these changes were due to NP release.

Neuropeptides produce multiple biological effects and appear to have both circulatory and immuno-modulation modes of actions, injection of SP intradermally in rats produced plasma extravasation.¹² SP releases histamine from mast cells,⁶ which in turn stimulates the release of SP.¹³ Pre-treatment with anti-histamines reduces SP-induced extravasation.¹⁴ Thus, it has been suggested that SP-induced extravasation and edema is histamine-dependent.¹⁵ Edema induced by histamine and bradykinin is potentiated by CGRP and inhibited by pretreatment with anti-CGRP.¹⁶ This is because CGRP potentiates SP-induced extravasation through inhibition of SP degradation.¹⁷ Injection of CGRP in man induces a potent long-standing vascular response.¹⁸ Also, systemic administration of CGRP caused marked lowering of blood pressure in rats,⁴ hypotension and tachycardia in man.¹⁹ Consequently, CGRP is considered among the most potent endogenous vasodilators.

Local application of bradykinin in deep dentinal cavities in cats significantly increased pulpal blood flow in innervated but not denervated teeth.²⁰ This indicates that bradykinin is dependent as a vasodilator on NP. Plasma extravasation produced by SP, and vasodilatation produced by CGRP are integral components of the inflammatory reaction. It provides the area with plasma-borne precursors for the inflammatory mediators such as arachidonic acid and kininogen. Tissue enzymes convert an arachidonic acid to leukotriens and prostaglandins, and kininogen to bradykinin. The resulting inflammatory mediators will sensitize the nerve ending and the cycle goes on. Hargreaves et al proposed that CGRP and SP actions potentiate the vascular response and maintain the inflammatory reaction through a local positive feedback mechanism.²¹ By definition, neurogenic inflammation is the inflammatory response

mediated by neuropeptides, which are released from stimulated peripheral nociceptors.

Peripheral Nerve Sprouting

CGRP-containing nerve fibers in the pulp are considered a major component of dental innervation.²² Therefore, the responses of these fibers have been studied extensively using different experimental injuries such as cavity preparation, pulpal exposures, occlusal trauma and replantation. Most of the fibers survive these injuries and continue to innervate dentin were found only in tubules occupied by viable odontoblasts. Dentinal cavities in rat molars caused depletion of CGRP and SP. However, by 1-2 days, those fibers have greater neuropeptide immunoreactivity than normal and have begun extensive sprouting reaction. Nerve sprouting eventually subsided when inflammation was reduced and when reparative dentin has covered the injury site.²³ Following tooth injury, Byers found that nerve growth factor synthesis proceeds the increased CGRP and SP nerve sprouting.²⁴ The author suggested that nerve sprouting is a vehicle to bring more neuropeptides to the inflamed area. Similar findings of nerve sprouting and increased levels of CGRP were also detected following tooth extraction,²⁵ induced occlusal trauma,²⁶ experimental replantation²⁷ and orthodontic tooth movement.²⁸

Pulpal exposures in rat molars produced pulpal CGRP nerve fiber sprouting along the abscess borders,² and two-fold increase in pulpal level of SP and CGRP with peak levels observed 7-14 days after the exposure.²⁹ Pulpal exposures also produced periapical nerve sprouting 5 days after the pulpal injury and persisted at later stages, with strong positive staining. Based on these results, it has been theorized that the ensuing neurogenic inflammation with the resultant release of NPs and apical nerve sprouting is responsible for the early appearance of the apical lesion.²

Hyperalgesia

Pain produced by inflammation produces a perception that is distinctly different from pain induced by transient non-inflammatory stimuli such as needle insertion. Inflammation causes

electrophysiologic changes in the peripheral nociceptors responses to produce a perceptual state of hyperalgesia. It results in a great dentinal responsiveness to stimuli such as heat, cold, and mechanical stimulation. Willis¹ defined hyperalgesia as the perceptual state which is characterized by spontaneous pain, decreased pain threshold, and an increased magnitude of perceived pain for a given stimulus.

Central Sensitization

Peripherally induced inflammation in experimental animals produces a number of central neural changes. These include increase in the CGRP-positive cells within L4 dorsal ganglion,³⁰ increased levels of SP and CGRP in the spinal cord,³¹ enhanced spontaneous firing,³² increased discharge response,³³ and expanded receptive fields in dorsal horn neurons.³⁴ Moreover, when injected intrathecally, CGRP altered the nociceptor behavior in mice.³⁵ Taken together, these findings suggest that the enhanced release of CGRP and SP in the dorsal horn may serve as a biochemical marker for the development of hyperalgesia.³ This hyperexcitability of the dorsal neurons at the level of spinal cord is termed central sensitization and is attributed, as a major mechanism, to produce hyperalgesia.³² Central hyperalgesia may contribute to acute as well as chronic pain states, and therefore, the CNS is no longer viewed as a static monolith that does not respond to peripheral nociceptive input.

Discussion

Pulpal pain has been widely researched, yet there are a number of pain conditions not well understood. Examples are: 1) Symptomatic pulpitis, 2) Post-extirpation pain, 3) Individual variability of dental pain, and 4) Difficulty anesthetizing acutely inflamed pulp. Putting in mind the literature reviewed earlier, a discussion will be made here in an attempt to provide further explanations to these clinical pain conditions.

Symptomatic Pulpitis

Symptomatic pulpitis is also known as acute irreversible pulpitis or acute pulpalgia. The

presence of hyperalgesia. It has been proposed that "hyperalgesic pulpitis" is a more accurate clinical term to describe the neurophysiology status of the inflamed pulp.²² Understanding signs of hyperalgesia offers a physiologic rationale for many of the symptoms of acute pulpitis. Spontaneous pain is produced by the spontaneous activity of the sensitized nerve endings. It is possible to speculate that the lingering pain following vitality testing is due, in part, to the local positive feedback cycle produced by secreted NPs. Central sensitization may as well contribute to the perception of such prolonged pain sensation. Nahri³⁶ suggested that throbbing pain may be due to the mechanical threshold reduced to the extent that arterial pressure wave of a heart beat is sufficient to activate sensitized pulpal nerve fibers.

Post-extirpation Pain

Effective extirpation of acutely inflamed pulps does not always relieve patient symptoms completely. Central sensitization causes neural changes that may persist even after removal of inflamed pulpal tissues similar to phantom limb pain. Thus, it is possible that dental pain remains even when no peripheral (pulpal) input can be detected. Another explanation for post-extirpation pain is the presence of the early periapical nerve sprouting and inflammation that accompanies acute pulpitis. Such periapical inflammation is often noticed as widening of the periodontal ligament space, but sometimes is hard to detect radiographically. This reversible periapical sprouting will eventually disappear few days after the extirpation. It is not surprising then to recommend the prescription of mild-to-moderate analgesics following pulpal extirpation.

Individual Variability of Dental Pain

It appears that the vasodilatation and edema formation produced by sensory NPs is counteracted by vasoconstriction produced by the release of sympathetic NPs such as NPY. Like most of the sympathetic innervation, pulpal NPY-containing fibers are associated with blood vessels. Thus, it has been suggested that while sensory NPs potentiate inflammation through vasodilatation, sympathetic NPs represent an endogenous mechanism to control inflammation

control mechanisms is variable. Olgart et al³² attributed this variability to explain why symptoms of pain, and probably pain thresholds, are so unpredictable and individual.

Difficulty Anesthetizing A Cutely Inflamed Pulp

Establishing a profound anesthesia for an acutely inflamed tooth is sometimes a serious clinical challenge to the dentist. This is true whether the planned procedure is pulpectomy or tooth extraction. Two theories are widely accepted as possible explanations. The first theory states that the acidic pH of the inflamed area inhibits the dissociation of the local anesthetic, while the second theory stresses that the edematous inflamed tissues cause rapid transportation of the local anesthetic. In either case, failure to produce profound anesthesia will result.³⁸ These explanations sound logical when the local anesthetic is administered locally as in infiltration injections. However, it does not address the problem when the local anesthetic is administered in remote sites such as block injections. Research in the field of neurophysiology has offered a new explanation for the ill understood situation. Pulpal inflammation causes pulpal and periapical nerve sprouting,^{22,4} increased NPs staining in axonal nerves,² increased neuropeptide levels in trigeminal ganglion,³⁰ and CNS.³²⁻³⁷ Collectively, it has been suggested that these neural plasticity and cytochemical changes extending throughout the affected nerve fibers alter the nerve capacity for anesthesia.

The results of current pharmacological studies have shown that a number of drugs inhibit NPs release. For example, Lidocaine 2% blocks the evoked-release of CGRP from dental pulp.³⁰ Interestingly, adrenergic agents, such as epinephrine and norepinephrine, have potent actions for inhibiting the release of CGRP.⁴⁰ This hints to the possibility that the enhanced efficacy observed with the vasoconstrictor-containing local anesthetic drug may be due to not only vasoconstriction but also to an inhibitory action of adrenergic agonists on certain primary afferent fibers.

Conclusion

Pain represents a major stimulus for patients who seek emergency dental treatment. On the

other hand, fear of pain represents a significant barrier that discourages patients from seeking routine dental care. Research conducted in the last 20 years has probed our understanding of pulpal pain. Following the scientific attitude, we are obligated to reevaluate our classical assumptions and explanations of pain mechanisms and pain management. Better understanding of pulpal pain mechanism enables the clinician to diagnose and manage acute pain conditions effectively, thus, reducing public dental phobia.

Regulation of peripheral NPs release may provide a new therapeutic approach for managing pain and inflammation that accompanies injuries to the pulp and periapex. Future research is promising in providing drugs that inhibit NP. These drugs may be used in endodontic emergencies in the form of pulp capping agents, intracanal medicaments, infiltration injections, or incorporation with local anesthetics.

Despite the large body of literature of the pulpal neurophysiology, it is surprising to note that what is taught in the undergraduate dental programs is quite little. Academicians are urged to incorporate the new pain theories that challenge the known ones in the didactic courses.

References

1. Willis W. The pain system. Basal, Switzerland, 1985:1-345.
2. Kimberly CL and Byers MR. Inflammation of rat molar pulp and periostium causes increased calcitonin gene-related peptide and axonal sprouting. *The Anatomical Records* 1988; 222:289-300.
3. Garry MG and Hargreaves KM. Enhanced release of immunoreactive CGRP and substance P from spinal dorsal horn slices occurs during carrageenan inflammation. *Brain Res.* 1992; 582:1:139-142.
4. Rosenfeld MG, Mermoud JJ, Amara SG, et al. Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. *Nature* 1983;304:129-135.
5. Olgart L, Hokfelt T, Nilsson G and Pernow B. Localization of substance P-like immunoreactivity in nerves in the tooth pulps. *Pain.* 1977; 4:153-9.
6. Gazelius B, Brodin E, and Olgart L. Depletion of substance P-like immunoreactivity in the cat dental pulp by antidromic nerve stimulation *Acta Physiol Scand* 1981:111:319-327.
7. Wakisaka S, Nishimoto T, Ichikawa H, Matsuo S, Takano Y and Akai M. The distribution and origin of substance P-like immunoreactivity in rat molar pulp and periodontal tissues. *Arch Oral Biol* 1985; 30:813-818.
8. Uddman R, Grunditz T and Sundler F. Neuropeptide Y. Occurrence and distribution in dental pulps. *Acta Odontol Scand* 1984;42:361-365.
9. Wakisaka S, Akai M, Takano Y, Ichikawa H, Nishimoto T, Uchiyama T and Matsuo S. Distribution of peptidergic nerve fibers in the walls of blood vessels in the feline dental pulp. *Japanese J Oral Biol* 1985; 27:1202-1209.
10. Avery JK. Repair potential of the dental pulp. *J of Endod* 1981;7:205.
11. Krouger DC. Possible role of neurohormonal substances in the pulp, in biology of the dental pulp organ: A symposium (ed S.E. Finn.), 1968; University of Alabama Press, Birmingham, pp 333-346.
12. Marshall et al. Substance P-induced cutaneous plasma extravasation in rats is mediated by NKA tachykinin receptors. *Neuroscience* 1989; 103:203-208.
13. Saria A and Martling CR, Theodorsson-Norheim E, Gamse R, Hua XY and Lundberg JM. Coexisting peptides in capsiacin sensitive sensory neurons: release and actions in the respiratory tract of the guinea pig. *Acta Physiol Hungarica* 1987; 69(3-4):H21-4.
14. Gamse R, Posch M, Saria A, and Jancso G. Several mediators appear to interact in neurogenic inflammation. *Acta physiol Hungarica* 1987; 69(3-4):343-54.
15. Saria A, Martling CR, Theodorsson-Norheim E, Gamse R, and Lundberg JM. Release of multiple tachykinins from capsiacin-sensitive sensory nerves in the lung by bradykinin, histamine, dimethylphenyl piperazinium, and vagal nerve stimulation. *American Review of Respiratory Disease.* 1988; 137:6:1330-5.
16. Buckley TL, Brain SD, Jose PJ and Williams TJ. The partial inhibition of inflammatory responses induced by capsiacin using the fab fragment of a selective calcitonin gene-related peptide antiserum in rabbit skin. *Neuroscience* 1992; 48:4:963-968.
17. Le Greves P, Nygerg F, Terenuis L and Kokfelt T. CGRP is a potent inhibitor of SP degradation. *European J Pharmacol* 1985; 115: 309-311.
18. Brain SD, Williams TJ, Tippins JR, Morris HR and MacIntyre I. Calcitonin gene-related peptide is a potent dilator. *Nature* 1985; 313:54-56.
19. Struthers AD, Brown MJ, Beacham JL, Morris HR, MacIntyre I and Stevenson JC. The acute effect of human calcitonin gene-related peptide in man. *J Endocrinology* 1985; 104 (suppl.): 129.

20. Olgart L, Edwall L and Gazelius B. Involvement of afferent nerves in pulpal blood-flow reactions in response to clinical and experimental procedures in the cat. *Archives Oral Biology* 1991; 36:8:575-81.
21. Hargreaves KM, Bowles W and Garry MG. Evaluation of the release of immunoreactive CGRP from peripheral tissue using an in vitro superfusion method. *Abstract. Soc Neuroscience* 1991,171371.
22. Akai K. and Wakisaka S. Distribution of peptidergic nerves. In: Reizo Inokai, Teruo Kudo and Leif M. Olgart: *Dynamic aspects of dental pulp*. 1990, Chapman and Hall.
23. Taylor PE, Byers MR and Redd PE. Sprouting of CGRP nerve fibers in response to dentin injury in rat molars. *Brain Res* 1988; 461:371-376.
24. Byers MR. Segregation of NGF receptor in sensory receptors, nerves and local cells of teeth and periodontium demonstrated by EM-immunocytochemistry. *J Neurocyt* 1990; 19:763-775.
25. Roszkowski M, Swift JQ and Hargreaves KM. Effects of ibuprofen on iPGE2, iLTB4, ibradynin, and substance P in surgery patients [abstract] *J Dent Res* 1994; 73:190.
26. Kvinnsland I, Heyraas KJ and Byers MR. Regeneration of calcitonin gene-related peptide immunoreactive nerves in replanted rat molars and their supporting tissues. *Arch Oral Biology* 1991 ; 36:11:815-26.
27. Byers MR, Wheeler EF and Bothwell M. Altered expression of NGF and P75 NGF-receptor by fibroblasts of injured teeth proceeds sensory nerve sprouting. *Growth Factors* 1992; 6:1:41-52.
28. Si, Ishii K, Hanada K, Sato O and Meada T. Responses of calcitonin gene-related peptide-immunopositive nerve fibers in the periodontal ligament of rat molars to experimental tooth movement. *Arch Oral Biology* 1991; 36:9:689-692.
29. Buck S, Reese K and Hargreaves KM. Pulpal exposure induces changes in the level of peripheral neuropeptides, [abstract] *J Dent Res* 1994; 73:314.
30. Nahin RL and Byers MR. Adjuvant-induced inflammation of rat paw is associated with altered calcitonin gene related peptide immunoreactivity within the cell bodies and peripheral endings of primary afferent neurons. *J Comparative neurology* 1994; 349:3:478-85. Schiabl H-G, Schmidt RF, Willis WD. Enhancement of the responses of ascending tract cells in the cat spinal cord by acute inflammation of the knee joint. *Exp Brain Res* 1987;66:489-499.
31. Garry MG, Richardson JD and Hargreaves KM. Sodium nitropruside evokes the release of immuno-reactive calcitonin gene-related peptide and substance P from the dorsal horn slices via nitric oxide-dependent and nitric oxide-independent mechanisms. *Neuroscience* 1994; 14:4329-4337.
32. Menetray D and Besson J-M. Electrophysiological characteristics of dorsal horn cells in rats with cutaneous inflammation resulting from chronic arthritis. *Pain* 1982; 13:343-364.
33. Schiabl H-G, Schmidt RF and Willis WD. Enhancement of the responses of ascending tract cells in the cat spinal cord by acute inflammation of the knee joint. *Exp Brain Res* 1987;66:489-499.
34. Hylden JLK, Nahin RL, Traub RJ and Dubner R. Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation : the contribution of dorsal horn mechanisms. *Pain* 1989;37:229-243.
35. Gamse R and Saria A. Nociceptive behavior after intrathecal injections of substance P, neurokinin A and calcitonin gene - related peptide in mice. *Neuroscience* 1986;70:1:143-147.
36. Nahri MVO. The characteristics of intradental sensory units and their responses to stimulation. *J Dent Res* 1985;64(special issue):564-571.
37. Olgart L, Matsuo M, Lindskog S and Edwall L. Enhanced formation of secondary dentin in the absence of nerve supply to feline teeth. *European J Oral Sciences* 1995; 103:3:160-5.
38. Trowbridge HO. Intradental sensory units: Physiological and clinical aspects. *J endod* 1985;11:489-498.
39. Hargreaves KM, Bowles W and Garry MG. Evaluation of the release of immunoreactive CGRP from peripheral tissue using an in vitro superfusion method. *Abstract. Soc Neuroscience* 1991, 17:137-1.
40. Engelstad M, Garry M, Jackson D and Geier H, Hargreaves KM. Adrenergic inhibition of iCGRP release from capsiacin-sensitive fibers in dental pulp. *Abstract. Soc neuroscience* 1992; 18:690