Volume : 4 | Issue : 6 | June 2015 • ISSN No 2277 - 8179

Research Paper

Medical Science

KEYWORDS :

# Substance P : Pulpal Pain

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## ABSTRACT

*Current evidence supports the central role of neuropeptides in the molecular mechanisms underlying dental pain. In particular, substance P, a neuropeptide produced in neuron cell bodies localised in dorsal root and trigeminal ganglia, contributes to the transmission and maintenance of noxious stimuli and inflammatory processes. The major role of substance P in the onset of dental pain and inflammation is increasingly being recognised. Well-grounded experimental and clinical observations have documented an increase in substance P concentration in patients affected by caries, pulpitis, or granulomas and in those undergoing standard orthodontic or orthodontic/dental care procedures. On this basis, SP can be considered a major mediator of neurogenic inflammation and associated hyperalgesia and represents a promising target for therapies aimed at controlling pain and minimising deleterious consequences of tissue injury.*

## INTRODUCTION

Toothache is one of the most common and unpleasant pain sensations experienced by man. Unfortunately, it is also fairly resistant to normal analgesics, and affected individuals can suffer severe symptoms and disturbed sleep. Tooth decay (caries) is the main cause of pulpal inflammation, which, in turn, may cause dental sensitivity or spontaneous pain. On occasions, the management of advanced tooth decay and pulp inflammation regrettably necessitates root canal therapy (removal of the dental pulp) or an extraction.

Substance P was the first neuropeptide to be detected in dental pulp. SP, CGRP and NKA coexist in the same nerve fibers in the pulp and originate from the trigeminal ganglion.

Pulpal vasodilatation is markedly reduced after systemic administration of a specific SP antagonist or Somatostatin. Thus, Somatostatin, present in trigeminal nerve, inhibits the release of SP and reduces the concomitant vasodilation in the pulp following inferior alveolar nerve stimulation.

Substance P is a neuropeptide produced in a subset of capsaicin sensitive sensory peripheral neuron cell bodies localised in dorsal root and trigeminal ganglia, which plays a pivotal role in the transmission of noxious stimuli in the spinal cord . Moreover, the stimulation of capsaicin-sensitive sensory peripheral terminal of the neurons results in the peripheral release of several neuropeptides, including SP.

## DENTAL PULP INNERVATION

The tooth pulp is a soft connective tissue that is densely innervated and highly vascularised. It is enclosed by rigid mineralised dentin, which strongly limits the ability of the tissue to increase in volume during inflammation and decreases the level of immune defence. Nerve fibers in the pulp include afferent (sensory) fibers originating from the trigeminal ganglia and sympathetic fibers originating from the cervical sympathetic ganglia. Parasympathetic innervation is also present.

The number of trigeminal sensory fibers in dental pulp is very high, and several types of sensory fibers are present in this tissue; therefore, the stimulation of pulpal nerves results mainly in pain sensations . For instance, one single human premolar contains 2300 axons at the apex, 87% of which are unmyelinated . Recent findings indicate that the regulation of innervation density is a dynamic process, and the number of nerve fibers can increase in the presence of caries or following orthodontal procedures.

SP is abundantly contained in the fibers that innervate the dental pulp and dentin . The production and release of this molecule are highly increased upon noxious, thermal, mechanical, and chemical stimulation of the dental pulp as well as in periodontal ligament. The amount of SP released by each sensory fiber is further increased during inflammatory processes, which sustains the vicious circle that underlies inflammation . A number of studies have measured SP concentrations in the human dental pulp, reporting an increase up to 100-fold in inflamed teeth and up to 1000-fold in irreversible pulpitis.

## STRUCTURE AND MECHANISM

SP is an undecapeptide (H-Arg1-Pro2-Lys3-Pro4-Gln5-Gln6-Phe7-Phe8-Gly9-Leu10-Met11-NH2) and belongs to the same neuropeptide family as neurokinin (NK) A and NK B , all of which share the same carboxyl terminal sequence, Phe-X-Gly-Leu-Met-NH2. SP is encoded by the preprotachykinin-A gene in the perikaryon of primary afferent neurons in the dorsal root and trigeminal ganglia and then is transported to both central and peripheral processes of these elements . Interestingly, most (around 80%) of the Substance P synthesised in dorsal root ganglia is exported towards the terminal regions of their peripheral branches rather than centrally . A number of enzymes are involved in the metabolism of substance P, due to their specific cellular localization it is probably Neutral endopeptidase and angiotensin converting enzymes (EP and/or ACE) which are most commonly involved.

The biological effects of released SP are induced following its binding to specific G protein-coupled NK receptors . There are three types of tachykinin receptors, NK1, NK2, and NK3 exhibiting preferences for substance P, neurokinin A, and neurokinin B, respectively. However, endogenous tachykinins are not highly selective for any given receptor, and all can act on all three receptors under certain conditions such as receptor availability or at high peptide concentrations.Substance P primarily acts on NK1 receptors and simulation of the NK1 receptor induces several second messengers systems, such as phospholipase C intracellular inositol 1,4,5-trisphophate (IP3) turnover with subsequent elevation of intracellular calcium.

These receptors are present in high concentrations in dental tissues .

Moreover SP has been shown to activate ERK 2 and P38 mitogen-activated protein and to increase the production of prostaglandin E2 and the expression of COX2 .

The interaction of SP with its receptors directly induces vasodilatation with increased blood vessel permeability and allows plasma extravasation and mastocyte degranulation. The mastocyte granules release histamine, which in turn further amplifies vascular processes and activates nociceptors [18]. Lymphocytes,

Volume : 4 | Issue : 6 | June 2015 • ISSN No 2277 - 8179

granulocytes, and macrophages have receptors for SP and these cells can be stimulated to produce cytokines. Macrophages stimulated by SP produce the inflammatory mediators PGE2, thromboxane, as well as the proinflammatory cytokines IL-1, IL-6, and TNF [11]. All these molecular events ultimately sustain the synthesis and release of new SP, therefore perpetrating the vicious circle (Figure 1). Moreover, these mechanisms do not involve only fibers at the site of tissue damage but are extended also to surrounding undamaged tissues, where they cause secondary hyperalgesia

**Conclusion**

In response to injury to the pulpodentin complex, numerous neuronal responses are produced leading to the local release of neuropeptides, which play an important role in initiating and propagating pulpal inflammation. SP, CGRP and VIP are potent vasodilators, whereas NPY is a vasoconstrictor. Peripheral release of neuropeptides modulates pulpal circulatory and immune system responses. Resorption during orthodontic tooth movement is less in endodontically treated teeth due to the absence of neuropeptides when compared to non-endodontically treated tooth. CGRP increases the in-vitro expression of bone morphogenetic protein (BMP) – 2 transcripts in human pulpal cells, which lowers dentin permeability. During dental injury, there is an initial depletion of neuropeptides that are released into the pulp tissue, followed by increased neuropeptide content and sprouting of the terminal fibres within 1 day after injury. SP was the first neuropeptide to be detected in dental pulp. CGRP is a strong inhibitor of bone resorption, which is due to the stimulatory effect of CGRP on osteoblast proliferation. VIP is a stimulator of bone resorption. VIP stimulates bone resorption by enhancing the activity of undifferentiated osteoclasts. VIP also stimulates bone resorption by affecting osteoblast formation.

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