

# Role of Neuropeptides in Pulpal Pathosis-An Overview

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## Abstract

Neuropeptides are proteins generated from somatosensory and autonomic nerve fibers after tissue injury. Neuropeptides play an important role in hemodynamic changes and pain mechanisms in the pulp. Neuropeptides also play an active role in orthodontic tooth resorption, restorative procedures involving carious dentin and acid etching. They are responsible for difficult anaesthesia in inflamed teeth. This paper highlights the role of neuropeptides seen in the dental pulp.

## INTRODUCTION

The dental pulp is a soft tissue of mesenchymal origin which houses a number of tissue elements including nerves, vascular tissue, connective fibers, ground substance, interstitial fluid, odontoblasts, immunocompetent cells and other cellular components. (1) Sympathetic innervation of the dental pulp terminates as free nerve endings and innervates the arterioles. (2) An interaction between exogenous irritants and defensive host cells results in the release of neuropeptides such as Substance P (SP), Calcitonin Gene Related Peptide (CGRP), Vasoactive Intestinal Polypeptide (VIP), Neurokinin A (NKA), Neuropeptide Y (NPY). Neuropeptides are proteins generated from somatosensory and autonomic nerve fibers after tissue injury. (3)

Increased production and release of these neuropeptides play an important role in initiating and propagating pulpal inflammation. (4) During inflammation, sprouting of nerve fibers is associated with increased expression of neuropeptides such as SP or CGRP closely surrounding the areas of inflammation or abscess. (5) Denervation of the inferior alveolar nerve depletes the pulp of its content of SP and CGRP, but not of NPY, and also increases the magnitude of pulpal necrosis following experimental pulpal exposures. (5)

Neuropeptides contribute to inflammatory processes via number of mechanisms where SP, CGRP and VIP function as potent vasodilators and NPY as a vasoconstrictor. (6) Vasodilatation following infusion of SP or VIP in the pulp is

associated with a transient increase in pulpal blood flow that was followed by a substantial and prolonged reduction in pulpal blood flow. Neuropeptides also reduce the threshold of pain in the pulp, accounting for symptoms associated with certain cases of pulpitis in children. (7)

## VARIOUS NEUROPEPTIDES DETECTED IN PULP

### SUBSTANCE P (SP)

SP 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. (8)

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. (8)

### CALCITONIN GENE RELATED PEPTIDE (CGRP)

CGRP is expressed in small to medium diameter sensory ganglion neurons whose central terminals lie in the superficial spinal and medullary dorsal horn. When extensive pulpal exposures were made on rat molars, the teeth exhibited an irreversible pulpitis, with complete necrosis of the pulp by 3-5 weeks post-injury. (8) Analysis of those teeth at various times post-injury shows persistent sprouting of CGRP-nerve fibers in the surviving vital pulp, and deformed nerve fibers at the vital / non-vital interface. (8) Silent pulpitis occur when fibrotic changes in the pulp form a barrier between the lesion and the nerve fibers.

Coexistence of vital pulp and periapical lesions is caused by CGRP nerve sprouting and the effect of released neuropeptides on bone and periapical tissue.

Difficulty in acquiring anaesthesia in inflamed teeth is due to increased number of CGRP nerve fibers, which causes Ascending Neuritis. (9) CGRP due to its unique stimulatory effect on osteoblast proliferation inhibits bone resorption. (10)

### **VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)**

VIP is a stimulator of bone resorption. Hohmann et al (1986) have shown that VIP stimulates bone resorption via Prostaglandin (PG)-E<sub>2</sub>-independent pathway and by enhancing the activity of undifferentiated osteoclasts. VIP also stimulates bone resorption by affecting osteoblast formation. (10)

### **NEUROPEPTIDE (NPY)**

Synthetic NPY exerts vasoconstrictor actions in the pulp in the low nanomolar range and, this effect is resistant to  $\alpha$ -adrenoceptor blockade. Compared to the effect of Noradrenaline (NA), Neuropeptide Y causes a more sustained vasoconstriction that lasts for several minutes after the end of an intra-arterial infusion. It is therefore plausible that NA and NPY act in concert in initiating and maintaining an appropriate vascular tone in the pulp. (8)

Neuropeptides play a vital role in hemodynamic regulation, orthodontic tooth movement of traumatized teeth, restorative procedures and tooth injury.

### **ROLE OF NEUROPEPTIDES IN PULP HEMODYNAMIC REGULATION**

Dental Pulp is innervated by sensory neurons originating from the trigeminal ganglion (of which 80% of the nerves as C-fibers and the remaining are A-delta fibers). (11)

Although these neurons are classified as sensory (i.e., afferent) they have major efferent functions because of their release of neuropeptides (about 80% of SP) from their peripheral terminals. (12)

Activation of trigeminal sensory neurons induces pulpal vasodilation and increases pulpal blood flow, which produces plasma extravasation in the pulp. (8)

The association of calcitonin gene-related peptide and substance P with inflammation has been demonstrated via effects on blood flow (Brain et al., 1985; Kim et al., 1988),

histamine release (Piotrowski and Foreman, 1986), and immune cell function (Payan et al., 1987; Lotz et al., 1988). Both substance P and calcitonin gene-related peptide, which are released from peripheral neurons in response to injury, contribute to the inflammatory response and also stimulate proliferation of surrounding connective tissue cells and thus initiate the early stages of healing in the pulp. (13)

### **ORTHODONTIC TOOTH MOVEMENT**

Orthodontic tooth movement can cause degenerative and/or inflammatory responses in the dental pulp of teeth with completed apical formation. The impact of the tooth movement on the pulp is focused primarily on the neurovascular system in which the release of neuropeptides can influence both blood flow and cellular metabolism. (14) During tooth movement, release of Substance P (SP) causes pain perception and cellular recruitment in the pulp and alveolar bone remodeling in PDL. Studies have shown increased number of CGRP IR nerves in the pulp and periradicular tissues during tooth movement. Both A-delta and C fibers release various peptides by means of intra-axonal transport at the terminal nerve endings. When released, they act as neurogenic vasodilators and vasoconstrictors. Therefore these neuropeptides play an important role in the regulation of the blood flow to the pulp and the periodontium. The resultant increase in the blood flow to these tissues during tooth movement stimulates the osteoclast precursors to differentiate into osteoclasts and influence the resorptive remodeling process of the teeth. Thus, in endodontically treated teeth, due to the absence of neuropeptides the chances of resorption are less during orthodontic tooth movement, when compared to non-endodontically treated tooth as inferred by Bender in his extensive study. (15)

### **RESTORATIVE PROCEDURES**

Situations like traumatic cavity preparation and exposed cervical dentin are invariably associated with rapid dentinogenesis, (16) which may be due to hydrodynamic activation, which release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) in the pulp, where CGRP, increases the expression of bone morphogenetic protein (BMP). When this expression leads to more dentin formation, it also tends to lower dentin permeability by making the tubules longer. (17)

### **TOOTH INJURY**

Injury to the pulpodentin complex produces numerous neuronal responses. The nerve fibers not only send rapid

signals to the ganglion and central pain pathways, but they also release neuropeptides from the peripheral terminals. (18) Thus, if the sensory innervation has been removed prior to injury, the defense potential of the pulp to promote neurogenic inflammation or healing after pulpal exposure is considerably reduced. (19)

Injury can cause anatomic and cytochemical changes in the nerve endings. There is initial depletion of neuropeptides, followed by an increase in neuropeptide content and sprouting of terminal fibres within 1 day after injury. These responses differ in intensity and duration depending on the severity of the injury. (20)

### 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. Synthetic NPY exerts vasoconstrictor actions in the pulp in the low nanomolar range and, this effect is resistant to  $\alpha$ -adrenoceptor blockade.

Better understanding of the various roles of neuropeptides in dental pulp will help the clinician to preserve the pulp vitality during conservative procedures. Neuropeptides alerts the clinician in the difficulty of anaesthesia of inflamed teeth. Knowledge of neuropeptides will have a significant decrease in the orthodontic resorption of traumatized teeth.

By virtue of its hemodynamic regulation in the pulp, neuropeptides plays an important role in maintaining pulpal homeostasis.

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