

REVIEW

Why is Periodontitis Painless?

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ABSTRACT:

Periodontitis is an infectious disease resulting in an often-painless destruction of tooth supporting tissues (the periodontium) and enhances the risk for various systemic diseases. Infection and inflammation of mucosal tissue may induce the production of neuropeptides. The biological effects of the neuropeptides substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and neuropeptide Y (NPY) are summarized. This review focuses on the recent research highlighting the role of the nervous system in suppressing pain and inflammation suggesting that neuropeptides have a pivotal role in the complex cascade of chemical activity associated with periodontal inflammation.

Key words: *Neuropeptides, SP, CGRP, VIP, NPY, periodontitis*

Introduction

Periodontal disease is a chronic inflammatory disease that affects the majority of adult humans. It is a multifactorial disease, principally associated with infection by specific pathogenic organisms. Despite the chronic inflammation seen in this condition, patients with this disease do not present with pain, nor do they self-medicate analgesic.¹

It is now generally accepted that the nervous system contributes to the pathophysiology of local inflammation. Stimulated sensory peripheral nerves (mainly C and A δ fibers) can release neuropeptides which are believed to play a crucial role in the evolution of inflammatory symptoms. Studies supporting the involvement of neuropeptides in the pathophysiology of neurogenic inflammation are

based on the proinflammatory effects of neuropeptides administration to a wide range of tissues including the oral mucosa.²

Inflammation represents the response of vascular tissues to insult or injury. It is usually protective but, if the causative agent persists, can become chronic with associate tissue damage. The magnitude of the inflammatory responses to plaque micro-organism, particularly their lipopolysaccharide component, is crucial in determining the effect and duration of gingivitis and periodontitis. The inflammatory response to LPS is the result of a complex series of interactions between soluble factors, and cells whose functions need to be precisely regulated to defend the body and promote healing. In recent years, the nervous system has been identified as a critical regulator of inflammation.³

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Neuropeptides

All nerve cells or neurons perform the same basic tasks. Every neuron generates an electric impulse in response to a chemical or mechanical stimulus, conducts the impulse through its elongated cell structure, and its terminal, and translates the electrical activity in to a chemical signal. The active chemical called a neurotransmitter crosses the synapse, to the membrane of the next neuron in the neuronal circuit.³

Various neuropeptides:

Substance P and Tachykinins:

The vasoactive material extracted into a powder by Von Euler and Gaddum in 1931 was named as substance P (SP), for powder.⁴ SP is an 11- amino-acid peptide believed to be identical in all mammalian species. SP is a member of the tachykanin family of neuropeptides, also known as the neurokinin. Two other tachykinin is known to exist, neurokinin A (NKA) and neurokinin B (NKB). Sp and NKA are derived from preprotachykinin A gene as a result of alternative splicing of a common transcription product.⁵ NKB is not expressed in detectable amounts in most peripheral tissues.³

SP causes vasodilatation by acting directly on smooth-muscle cells and indirectly by stimulating histamine release from mast cells in a concentration-dependent manner.⁶ The edema induced by SP is primarily due to increased vascular permeability mediated through its action on NK-1 receptors situated on Post-capillary venule endothelial cells.⁷ The SP- induced contraction of endothelial cells and subsequent plasma extravation allow substance, such as bradykinin and histamine, to gain access to the site of injury and to afferent nerve terminals.⁸

Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) was discovered by Amara and Colleagues in 1982.⁹ It is a 37-amino-acid peptide with slight difference in sequence homology between different mammalian species. CGRP is released simultaneously with SP and

is a potent vasodilator.¹⁰ It has immunosuppressive effect and may be considered to down regulate the inflammatory response. In contrast to SP, CGRP has been shown to suppress IL-2 production and the proliferation of murine T-cells.¹¹

Vasoactive intestinal polypeptide

Vasoactive intestinal polypeptide (VIP) is a 28-amino-acid peptide isolated from pig intestinal extracts by Said and Mutt in 1970.¹² These are one of the groups of regulatory molecules termed macrophage-deactivating factors that are believed to prevent the excessive production of pro-inflammatory cytokines.¹³ It inhibits LPS- induced TNF-alpha, IL-6, and IL-12 production in activated macrophages.¹⁴

Neuropeptide Y

Neuropeptide Y (NPY), a 36- amino-acid peptide isolated from porcine brain by Tatemoto in 1982.¹⁵ It is a potent vasoconstrictor and amplifies the post-synaptic effects of other vasoconstrictors such as noradrenaline.¹⁶

Pain pathway of periodontal tissues

The periodontal tissues are innervated by sensory fibers of the maxillary and mandibular divisions of the trigeminal nerve. Sensory nerve fibers, which make up the great majority of periodontal innervations, originate in the trigeminal ganglion and range in size from C fibers to A α and A β fibers. At least 10% of the non-myelinated nerves comprise the autonomic supply made up of either sympathetic fibers derived from the superior cervical ganglion or parasympathetic fibers from either the sphenopalatine ganglion for the upper teeth or the otic ganglion for the lower teeth. Periodontal tissues are extensively innervated by myelinated nerve fibers, closely associated with blood vessels.¹⁷

Painless periodontitis

The periodontal ligament receives a rich sensory nerve supply. Periodontal afferents encode information about both the teeth stimulated and the

direction of forces applied to individual teeth. Ruffini endings, which are the primary mechanoreceptors, play a significant role in the specification of the level, duration, and point of attack of forces used to manipulate food between the teeth.¹⁸ Almost a century ago, Sherrington proposed the existence of the nociceptor, a primary sensory neuron which is activated by stimuli capable of causing tissue damage. The periodontal tissues also contain many nociceptors. Both A δ and C fibers are present in the periodontal ligament, and their response characteristics suggest that they have role in periodontal nociception.¹⁹ Fibers innervating the periodontal tissues in human are immunoreactive to a number of neuropeptides, including SP, CGRP, VIP, and NPY.²⁰

VIP can be considered an integrator of the effects of many noxious stimuli, including heat, extracellular acidification, and vanilloid ligands. It has been hypothesized that there are factors termed endovanilloids, produced under inflammatory conditions, which modulate the response of VRI. Factors such as leukotriene B₄, which favours the opening of these ion channels, facilitate pain. Less is known about factors which close VRI channels and therefore acts as exogenous analgesic agents.²¹ It is possible that such ion channel blockers may be involved in the lack of pain associated with periodontal inflammation

Recently, a gene named *painless* which is known to encode a novel member of the Transient Receptor Potential Vanilloid family has been identified in *Drosophila*.²² It is not known whether a mammalian homologue exists or whether this gene could have a role in nociceptive signaling in painless conditions such as periodontitis.

Mice with disruption of the preprotachykinin A gene, which encodes SP/NKA, had significantly reduced responses to moderate or intense pain, and neurogenic inflammation was virtually absent in these mutant mice.²³ Peripheral administration of SP may activate primary afferents, producing

nociceptive behaviors, which can be blocked by a SP antagonist.²⁴ An increase in the proportion of axons expressing NK-1 receptors has also been observed during inflammation.²⁵ Therefore, it is possible that there could be increased SP-induced activation of peripheral nociceptors in inflamed sites. Despite the increased levels of SP in periodontitis sites and the presence of the NK-1 receptors in gingival tissue, periodontitis is painless.²⁶

Undetectability of CGRP in GCF from periodontitis sites, α CGRP being critical for the production and possibly the transmission of somatic and visceral pain signals may partly explain the absence of pain as a major symptom in periodontitis.²⁷

Conclusion

The pathophysiology of the periodontal disease is more complex, and neuropeptides are not solely responsible for the initiation and progression of disease.

Until more information is gathered about the potential post-synaptic interaction of neuropeptides and the expression of receptors in periodontal tissue, the mechanisms underlying the painless nature of periodontitis remain to be determined. Further understanding of complex regulatory system, in particular those governing neuropeptides inactivation, should extend our knowledge of the inflammatory process and provide potentially novel therapeutic approaches to the management of inflammatory disorders such as periodontitis.

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