Substance p and pain in orthodontics: A brief review

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Introduction

Pain management in orthodontics is a key factor in order to guarantee a comfortable treatment to patients. Dental pain perception is related to an inflammatory reaction that involves different molecular mechanisms. Similarities have been observed between odontogenic pain mechanisms and mechanisms observed in all other body parts [1].

Anatomically the pain signal is conducted via two different structures thin fibers containing unmyelinated C-fibers and myelinated A-δ fibers of primary sensory neurons to secondary order neurons in the spinal cord and finally leading to the cortex through the thalamus [2].

Pain is perceived by the neural system through nociceptors that are excitatory neurons capable to release glutamate as their primary neurotransmitter as well as other components including peptides such as substance P (SP), somatostatin and calcitonin gene-related peptide [CGRP] [3].

These neurotransmitters are capable to act on specific receptors expressed in nociceptive sensory neuron thus resulting in the production of second messengers and eventually activating the downstream pathway of protein kinase and phospholipases [4].

Peripheral nociceptors are detectors of specific biochemical compounds and are also constituted by ion channels. Both type of receptors are involved in the inflammatory response and in the mediation of the pain signal to the central nervous system [5]. A broad range of neuropeptides are involved both in inflammatory response and pain. In particular, substance P is a neuropeptide produced in a capsaicin sensitive sensory peripheral neuron cell bodies that are localized in dorsal root and trigeminal ganglia [6]. This neuropeptide plays a key role in the transmission of noxious stimuli in the spinal cord [4, 6].

The aim of this brief review was to describe the role of substance P in pain transmission.

Structure, Receptors and Function

Substance P is a neuropeptide belonging to a family of structurally related peptides called tachykinins [7]. This family of neuropeptides has the same carboxyl terminal sequence Phe-X-Gly-Leu-Met-NH2. This terminal sequence is fundamental for receptor activities such as interaction and activation. SP is encoded by the preprotachykinin-A gene in the perikaryon of primary afferent neurons in the dorsal root and trigeminal ganglia and eventually is released both to central and peripheral processes of these anatomical structures [4, 7].
Three receptors have been characterized: neurokinin-1 (NK1), NK2 and NK3. NK1 receptors are expressed by neurons and glia in the Central Nervous System (CNS). NK2 is expressed in peripheral tissue such as smooth muscle while NK3 is primarily found in the CNS [8].

Substance P primary action is on NK1 receptors that are able to induce several second messengers systems, such as phospholipase C intracellular inositol 1,4,5-trisphosphate (IP3) turnover that subsequently elevates the intracellular calcium concentration. These receptors are highly found and represented in dental tissues [9].

Furthermore has been demonstrated that SP is able to activate ERK 2 and P38 mitogen-activated protein and also to activate an inflammatory response increasing the production of prostaglandin E2 and the expression of COX2 [10]. SP interaction with its receptors induces vasodilatation that eventually leads to an increased blood vessel permeability. This process allows plasma extravasation and mastocyte degranulation [9-10].

The mastocyte granules have the capacity to release histamine, which in turn further amplifies vascular processes and eventually activates nociceptors [44].

Substance p and Orthodontics

The mechanical force applied to the teeth due to orthodontic treatment induces an inflammatory reaction which leads to the remodeling of periodontal tissues thus resulting in tooth movement [11]. Since the periodontal ligament (PDL) and the dental pulp are well innervated and contain numerous receptors for noxious stimuli it is assumed that neurotransmitters such as substance P could be able to mediate the biological response to mechanical stress applied to the teeth during orthodontic treatment [12, 13].

After the placement of braces or other orthodontic devices patients often report discomfort feelings such as pressure, tension, and teeth pain [14].

We recently conducted a preliminary study investigating the changes of substance P in patients undergoing orthodontic treatment with the Invisalign® appliance (Align Technology, Santa Clara, California) [14]. Interestingly, this preliminary study showed that the stimulation of periodontal nerve fibers by means of mechanical forces may be capable to induce peripheral release of SP in dental structures such as pulp and PDL. The SP could be the primum movens for a biochemical cascade that leads to the activation of target cells in the periodontium. SP can either act directly on the target cells or enhance the release of other messengers as prostaglandins and cytokines leading to an increase of intracellular second messengers.

Several studies demonstrated high level of SP in patients with oral pathological conditions such as periodontitis and dental caries [15-16]. Furthermore it has been demonstrated that patients with chronic inflammatory disease such as periodontal disease a higher level of SP can be found in gingival sites not affected by this condition [17-18].

A correlation between inflammatory disorders such as periodontal disease and substance P is supported by a wide range of scientific articles. Regarding the correlation between substance P and teeth movement further studies are needed in order to fully elucidate the role of this neurotransmitter during orthodontic treatments. The presence of increased SP levels may represent a possibility for treating inflammation and pain in relation to the mechanical forces applied to the teeth during orthodontic treatments.

Author contributions

AM: wrote the article and was involved in the study design. GMA: revised the article and was involved in the acquisition of data. LL: revised the article and was involved in the study design.

References


