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Opinion

Pannexins In Dentistry: Hype, Hope or Both?

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Sensation of inflammatory tooth pain or dentinal hypersensitivityoccurs in response to a variety of innocuous stimuli and is therefore initiated via distinct mechanisms (thermo-, hydro- and/or mechanico-dynamic).With the increased consumption of acids in our diet (i.e. carbonated drinks), for example, approximately one out of four adults will experience/suffer from dentinal hypersensitivityduring the course of their life, causing discomfort; one of the main reasons for patients to consult the dental office. Furthermore, oro-dental pathologies that also result in dentin hypersensitivity can alter both the dentin structure and the function of the intra-dental nerves. This often complicates preventive oral hygiene procedures thereby jeopardizing periodontal therapy. If left untreated, dentinal hypersensitivity can lead to chronic inflammation of the dentin-pulp complex and/or surrounding periodontal and oral tissues, which could eventually lead to therapy failure and more complex perio-/endo-donticconditions.

On the other hand, the known healing processes whether within the tooth and/or post-application or use of de-sensitizing therapies can target both dentinal as well as nerve function - in order to alleviate or reduce the stimulus and its sequelae. Indeed, current *non-invasive* treatments are mainly based eitheron (a) ion saturation of the buccal cavity and saliva (strategy which impedes pain signal conduction through the pulp nerve) or (b) physical blocking of the exposed dental tubule with hydroxyapatite and/or arginine; yet, with major limitations in clinical self-reported efficacy, where no definitive solution to pain and inflammation is provided.

Hence, it has been suggested to approach this dilemma from the anatomic, physiological, and more importantly, perhaps, the molecular perspective; in order to facilitate the developmentof novel preventive and therapeutic strategies, effective in cases of dentinal hypersensitivity; an alternate offer topatients in need.

Several molecular mechanisms have been attributed in relation to pain conduction. However, to date, the physiological mechanisms responsible for these pain sensations are not fully understood. It is well-known today that extracellular ATP signaling *as a neurotransmitter* is involved in one of the pathways that could lead to the transmission of the nociceptive electrical stimuli. Actually, ATP signaling seems to participate in dentin hypersensitivity and dental pain. Taking this into consideration, Pannexin (Panx), a hemi-channel glycoprotein-discovered in the year 2000 as the second family of gap junction proteins, in vertebrates – has been shown to form mechano-sensitive ATP-permeable channels, in human dental pulp.

Briefly, the Panx family has 3 members - *Panx1, Panx 2 and Panx3*; which are involved in the (1) signaling of pain through ATP and calcium homeostasis; and (2) initiation of inflammation via enhancement of the production of inflammatory cytokines by neutrophils and other cells of the immune system. It has been recently reported that Panx channels play a role in external dentin stimulation-induced

ATP release. On the other hand, Panx expression has been demonstrated in tissues including the brain, heart/coronary arteries, skeletal muscle, skin, lung, liver, etc …

Thus, the blocking of Panx, a logical strategy, has been pre-clinically explored as a therapeutic approachto decreasepain in neuropathic diseases of the central nervous system, with promising results. Recently, Panx has been found to be expressed in the oral cavity, mainly via epithelial and fibroblast cells, in gingival soft tissue (*in vivo*) and odontoblasts (*in vitro*). This opens the door wide for investigating the potential of blocking Panx as a novel therapeutic target and strategy in the management of oral disease-associated acute and chronic pain and inflammation. In fact, Panx blockers, such as Probenecid or *Probalan* - a *Panx1* channel inhibitor used to treat gout and hyperuricemia, have already been developed targeting different diseases. However, no application in oral diseases, to the best of our knowledge, exists. This, in our opinion, will definitively not be the case soon, with the accumulating evidence-based knowledge (expression characterization and efficacy testing/evaluation) becoming available to the scientific community; regarding potential application in the management of oral pain and inflammation. Without doubt, Panx carries hype and hope to the future of dentistry.

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