

# Adenosine A<sub>2A</sub> Receptor Stimulation: A New Strategy for the Treatment of Periodontitis



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## Abstract

Periodontitis is an unpleasant clinical condition in which an exaggerated inflammatory reaction occurs in the extravascular gingival tissue. Inflammatory cells release cytokines that amplify tissue inflammation and create the condition for periodontal tissue damage. Adenosine is a mediator that is released under several pathological conditions including ischemia and inflammation and participates in the regulation of inflammatory reaction. Among the several adenosine receptors, the adenosine A<sub>2A</sub> subtype plays a key role in resolving gingival inflammation and in protecting the periodontal tissues from damage. PDRN (polydeoxyribonucleotide) binds selectively the A<sub>2A</sub> subtype and exerts curative effect, suggesting that adenosine A<sub>2A</sub> receptor stimulation might be an innovative strategy for the treatment of periodontitis.

**Keywords:** Adenosine A<sub>2A</sub> Receptor; Periodontitis; PDRN

## Introduction

Periodontitis is common diseases of the oral cavity [1]. It is a devastating inflammatory condition that takes place at the level of the soft and hard tissues surrounding the teeth [2] and it is one of the leading cause of teeth loss worldwide [3]. Modifiable and diffuse risk factors (e.g., elevated blood pressure, increased blood cholesterol, metabolic syndrome) and unhealthy behaviors (poor physical activity, smoking and consumption of high fat rich food) may significantly influence the development of the disease [4]. An exaggerated inflammatory reaction represents the hallmark of the periodontitis pathogenesis. Bacteria overloading in the gingival sulcus induces accumulation of Polymorphonuclear Neutrophils (PMNs) and monocytes. PMNs and monocytes work in concert with epithelial cells of gingivae to cause the production of Interleukin (IL)-1 $\beta$ , Tumour Necrosis Factor  $\alpha$  (TNF- $\alpha$ ), IL-6 and High Mobility Group Box 1 protein (HMGB-1). These pro-inflammatory cytokines trigger the expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) that favors the adhesion and accumulation of the inflammatory leukocytes (PMNs and monocytes) to the endothelium and augment the cross-talk between the several cell types leading to the leakage of leukocytes into the infected tissues [5].

This cascade of events causes macrophages, that have been recruited in the inflammatory zone, to release Prostaglandin 2 (PGE<sub>2</sub>). This prostanoid and the inflammatory cytokine IL-1 $\beta$  prompt the accumulation of PMNs and monocytes to endothelial

cells, thus amplifying and empowering inflammation; finally, these two mediators together with IL-6 and TNF- $\alpha$ , cause osteoclasts to stimulate and reabsorb the alveolar bone [6,7]. Besides inflammation, apoptosis has been also shown to have a role in periodontitis: infact the pro-apoptotic protein BAX-1 is enhanced while the anti-apoptotic protein Bcl-2 is reduced, thus leading to an enhanced destruction of the alveolar bone.

Adenosine is a mediator that is released under several pathological conditions including ischemia and inflammation and participates in the regulation of inflammatory reaction [8]. Interestingly it has been proposed that adenosine may have an anti-inflammatory role. Adenosine is produced both in the intracellular and extracellular compartments through dephosphorylation of Adenosine Monophosphate (AMP) by ecto-5'-nucleotidases; then it is transformed to inosine via the activity of adenosine deaminase and finally degraded to uric acid [8]. Adenosine engages on cell membrane G protein coupled adenosine receptors that are localized in almost all mammalian cells. Four types of adenosine receptors have been identified and indicated as A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub>. These receptors differ in affinity for adenosine and have a different level of expression in the several cell types.

It has been previously reported that adenosine receptors are present in both human gingival cells and fibroblasts and that their up-regulation or down-regulation may serve as signal mechanisms to orchestrate the production of other inflammatory mediators [9].

Indeed, previous experimental work has suggested that the expression of  $A_{2A}$  and  $A_{2B}$  receptors are enhanced in periodontitis while  $A_3$  expression is reduced and  $A_1$  expression is unchanged. Regarding the finalistic meaning of these changes, it is generally accepted that over-expression of the  $A_{2A}$  and  $A_{2B}$  receptors may serve as a brake to halt the inflammatory cascade [9]. This leads to hypothesize that activation of one or both of these two types of Adenosine Receptors ( $A_{2A}$  and  $A_{2B}$ ) may represent a rational strategy to design new drugs for the treatment of periodontitis.

PDRN (polydeoxyribonucleotide) is prepared from DNA and it is made by fragments of deoxyribonucleotides [10]. It binds selectively the  $A_{2A}$  subtype that has a key role in down-regulating and resolving inflammation [10]. Theoretically PDRN might be beneficial in periodontitis where an inflammation cascade develops in soft tissues close to the bone. In experimental animals (e.g., rats and mice), the "pathology" may be induced and transferred by ligating the lower first molar cervix. This experimental procedure provides a valuable and reproducible "experimental paradigm" that can be used to test the preclinical efficacy of investigational drugs. A gel solution of 0.74% PDRN was studied in a rat model of periodontitis. The gel was topically administered for seven consecutive days alone or together with an  $A_{2A}$  subtype receptor antagonist. A control "arm" of rats with periodontitis received the vehicle gel. At the end of the experimental period, animals were sacrificed and the periodontium and surrounding gingival tissue were harvested to perform histological studies and molecular evaluation of inflammatory (TNF- $\alpha$ , IL-6) and apoptotic proteins (BAX and Bcl-2).

The administration of PDRN succeeded in blunting the severe histological damage, reduced in the inflamed tissue the expression of the several pro-inflammatory protein and rebalanced the apoptotic system towards augmenting the expression of Bcl-2 [11]. To confirm the PDRN mode of action, concomitant treatment with an adenosine  $A_{2A}$  subtype antagonist abolished all these protective effects. Indeed, topical application of the PDRN gel significantly preserved bone resorption and improved alveolar bone quality. This strongly points out that PDRN may also cause bone formation and regeneration.

Recently the Wnt/ $\beta$ -catenin signaling has been suggested to stimulate formation of alveolar bone. Wnt can be activated by  $A_{2A}$  receptor through an increase in intracellular cAMP, which is a well-known intracellular second messenger that boosts Wnt signaling [12]. Once triggered, the intracytoplasmic Wnt cascade causes  $\beta$ -catenin to translocate to the nucleus, where it binds to genes that codify for bone forming proteins. Unpublished findings from our

laboratory suggest that PDRN activates Wnt/ $\beta$ -catenin signaling in alveolar bone, thus offering a valid explanation for the positive effects of PDRN on alveolar bone during periodontitis.

In conclusion, the available data so far produced suggest that  $A_{2A}$  receptor stimulation might be an innovative strategy for the treatment of periodontitis. However, this experimental evidence deserves to be validated and confirmed in patients suffering from periodontitis. Since PDRN is available in the market in Europe and South Korea with different therapeutic indication, the design of a clinical trial aiming at confirming the pre-clinical evidence could be easily designed and performed.

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