A short Review:
A perspective on the Role of Prostaglandins (PGE2) on Periodontium in Health and Disease
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INTRODUCTION
Prostaglandins (PGE2) are important lipid soluble signaling molecules produced essentially by all cells in the body. They have very short half-lives and have potent local effects in the inflammatory responses, regulation of blood pressure, blood clotting and in many physiological functions including induction of child birth.

Chronic periodontitis is a prevalent oral disease, which is characterized by destruction of the tooth supporting structures. The condition is initiated by pathogenic microbes in dental plaque. The microbial challenge posed by the sub gingival biofilm causes recruitment of immune cells into the periodontium that produce cytokines and inflammatory mediators.

Amongst the inflammatory mediators implicated in periodontal disease pathogenesis, prostaglandins are well known. PGE2 causes vasodilatation, increased vascular permeability and can regulate the production of osteoclast activating factor thereby mediating bone destruction. This paper reviews the various possible interactions between systemic disease and their periodontium in both health and disease with respect to the role of PGE2.

The role of prostaglandin E2 in human physiology:

Inflammation:
Prostaglandin E2 exhibits a broad range of proinflammatory effects. It contributes to the flare and wheal effects by inducing vasodilation and increasing capillary permeability and these effects are enhanced by synergism with other inflammatory mediators. Interleukins-1 (IL-1) and tumor necrosis factor-α (TNF-α) activate the arachidonic acid pathway and a number of their effects can be attributed to prostaglandin E2. Both PGE2 and PGI2 have been found in the synovial fluid from knee joints of arthritic patients1.

Pain:
Pain producing action of inflammatory mediators such as bradykinin or histamine were increased when prostaglandins sensitize chemical receptors on primary afferent nerve terminals. Prostaglandins are therefore hyperalgesic. To produce its hyperalgesic action, PGE$_2$ released during the inflammatory response or by other trauma, lowers the activation threshold of tetrodotoxin-resistant sodium channels on sensory neurons$^2$.

**Fever:**

Fever is caused by PGE$_2$ released by inflammatory mediators from endothelial cells lining the blood vessels of the hypothalamus$^3$. PGE$_2$ generated by PGE synthase diffuses out of the endothelial cells into the organum vasculosum lamina terminalis (OVLT) region of the hypothalamus, which is responsible for controlling body temperature.

**Immune system:**

Prostaglandin E$_2$ has been shown to have a clear role in the regulation of cellular and humoral immune responses. In cellular immune responses such as T cell proliferation, lymphokine production, and cytotoxicity, PGE usually acts as a feedback inhibitor of the response. This is also true of macrophage and natural killer cytotoxicity. In some instances PGE is responsible for cellular activation rather than inhibition. This is clearest in the control of humoral immunity, where PGE production is a necessary component in the generation of some type of T suppressor cells. Disturbances in immune function found in several human conditions and diseases have been linked to changes in PGE mediated immunoregulation. Either increased production of PGE or increased sensitivity to PGE results in depressed cellular immunity$^4$.

**Gastrointestinal tract:**

A physical barrier, mucus may act to create an unstimred layer of secreted bicarbonate on the epithelium, and hence help to neutralize hydrogen ions diffusing back from the lumen into the mucosa. In the stomach, EP1 mRNA was detected in gastric muscle layers, whereas EP3 and EP4 receptor gene expression was mainly present in the gastric mucosal layer. PGE$_2$ stimulates bicarbonate secretion via the EP$_3$ receptor and the acid secretion induces more severe damage to the stomach mucosa$^5$.

**Cardiovascular system:**

Various prostanoids are secreted by vascular cells, including PGI$_2$, PGE$_2$ and PGF$_2\alpha$. In addition, cells in the vascular wall respond to various prostanoids. The major prostanoid secreted by endothelial cells is PGI$_2$. This prostanoid binds to the Inositol phosphate receptors (IPR) on
vascular smooth muscle cells and inhibits vascular contraction.

PGE$_2$ can also potently relax vascular smooth muscle contributing to the characteristic vasodilatation (via the EP$_2$ receptor) leading to the erythema seen in acute inflammation$.^6$ This increases blood flow through inflamed tissues and thus augments the extravasation of fluid, facilitating edema formation. EP$_2$ receptors generally mediate arterial dilatation and are also involved in salt sensitive hypertension.

**Parturition:**

Human seminal fluid contains high concentrations of several prostaglandins including PGE$_2$, PGE$_1$, PGE$_3$, and PGF$_2$, which perhaps function to relax corporeal smooth muscle. These prostaglandins may also facilitate conception by stimulating contractions of the cervix, fallopian tubes, and uterus$.^7$

**Role of prostaglandin E$_2$ in systemic disease:**

Prostaglandin E$_2$ plays an important role in progression of various systemic diseases such as rheumatoid arthritis, preterm low birth weight and osteoporosis.

**Rheumatoid arthritis:**

Rheumatoid arthritis (RA) is characterized by the accumulation and persistence of an inflammatory infiltrate in the synovial membrane, which leads to synovitis and destruction of the joint architecture resulting in impaired function. A substantial body of evidence suggests that prostaglandin E$_2$ contributes to the pathogenesis of Rheumatoid arthritis. PGE$_2$ has been associated with the edema and the erosion of cartilage and juxta-articular bone commonly found in Rheumatoid arthritis$.^8$

**Preterm Low Birth Weight:**

During normal pregnancy, maternal hormones and locally acting cytokines play a key role in regulating the onset of labor, cervical ripening, uterine contraction and delivery. Maternal infections during pregnancy have been demonstrated to perturb this normal cytokine and hormone-regulated gestation, sometimes resulting in preterm labor, preterm premature rupture of membrane, and preterm low birth weight, i.e., <2,500 g and <37 weeks of gestation. Prostaglandins appear to play a crucial role, and prostaglandin E$_2$ can be used to induce human labor. The women with preterm labor and intraamniotic infection had significantly higher amniotic fluid concentrations of PGE$_2$ and PGF2α than women with preterm labor without infection$.^9$

**Diabetes mellitus:**
It is a complex metabolic disorder characterized by chronic hyperglycemia. Diminished insulin production, impaired insulin action, or a combination of both result in the inability of glucose to be transported from the bloodstream into the tissues which in turn results in high blood glucose levels and excretion of sugar in the urine. Alterations in the host immunoinflammatory response to potential pathogens may play a predominant role. Diabetes may result in impairment of neutrophil adherence, chemotaxis and phagocytosis, which may facilitate bacterial persistence in the periodontal pocket and significantly increase periodontal destruction. The strong evidence suggesting that dysregulation of COX-1 coupled to prostaglandin contributes to diabetes-impaired wound healing.

**Osteoporosis:**

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro architectural deterioration with a consequent increase in bone fragility and susceptibility to fracture. The conjugates of bisphosphonates which is potential bone resorption inhibitors and prostaglandin E\textsubscript{2} enhanced bone formation and they were effective as a bone growth stimulant.

**Role of Prostaglandins E\textsubscript{2} in periodontal disease:**

Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both.” Microbial organisms in dental plaque are considered as primary pathogens of periodontal disease. However, the response of the host to the pathogens, which induces the production of inflammatory molecules including cytokines and prostanoids, is involved in the initiation and progression of periodontal disease.

The prostaglandin E\textsubscript{2} levels in gingival crevicular fluid of patients exhibiting periodontal diseases are significantly higher than those in periodontally healthy subjects and furthermore that prostaglandin E\textsubscript{2} concentration in gingival crevicular fluid are effective for predicting periodontitis progression i.e. attachment loss, with a high degree of sensitivity and specificity. The endogenous PGE\textsubscript{2} production by host cells stimulated by plaque-associated bacterial endotoxin may be an important pathogenic factor in periodontal disease.
Effects of prostaglandin E\textsubscript{2} on immune and inflammatory responses in the periodontium:

The presence of bacteria adjacent to gingival crevice and the intimate contact of bacterial lipopolysaccharide with host cells trigger monocytes, polymorphonuclear leukocytes, macrophages and other cells to release inflammatory mediators such as IL-1, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and prostaglandin E\textsubscript{2}. IL-1 and TNF-\(\alpha\) have an important role in periodontal tissue destruction and PGE\textsubscript{2} appears to be partly responsible for bone loss associated with periodontal diseases. The endogenous PGE\textsubscript{2} induced by IL-1\(\beta\) plays an important regulatory role in IL-6 production by human gingival fibroblast\textsuperscript{17}. Studies have also shown that elevated levels of PGE\textsubscript{2} associated with inflammation will attenuate the IgG response and local humoral response tend to rebound\textsuperscript{18}.

PGE\textsubscript{2} down-regulates interleukin-1\(\beta\), TNF-\(\alpha\) and lipopolysaccharide-induced intracellular adhesion molecule-1 expression via EP\textsubscript{2}/EP\textsubscript{4} receptors in human gingival fibroblasts\textsuperscript{19}. PGE\textsubscript{2} and PGI\textsubscript{2} generated simultaneously with cytokines by macrophages treated with zymosan may influence the cytokine production through IP, EP2, and EP4 receptors\textsuperscript{20}.

Synopsis of findings from Studies investigating association between levels of PGE\textsubscript{2} in tissue biopsies or crevicular fluid and severity of periodontal infection:

Elevated PGE\textsubscript{2} levels are detected in gingiva and GCF of patients with periodontal disease, compared to periodontally healthy subjects and furthermore that PGE\textsubscript{2} concentration in GCF is effective for predicting periodontitis progression.

PGE\textsubscript{2} levels in human periodontal disease using Radioimmunoassay was found a 10-fold elevation of PGE\textsubscript{2} in diseased as compared to healthy tissue\textsuperscript{21}.

Gingival samples analyzed from 27 chronic periodontitis patients. They found that mean concentration of PGE was 42.2 ± 4.9 pmol/g (range 9 to 105 pmol/g). The author concluded that proinflammatory effects of PGE may be modulated by anti-inflammatory actions of PGF\textsuperscript{22}.

PGE\textsubscript{2} levels analyzed in 3 healthy, 8 superficial and 22 deep biopsies from
advanced periodontitis patients. They concluded that PGE$_2$ was not detected in the healthy samples, 73% of deep sites had measurable PGE$_2$ levels. Only 50% of superficial biopsies had detectable PGE$_2$ levels$^{23}$.

PGE$_2$ levels are low in health and non-detectable at many sites. In naturally occurring gingivitis there is a modest rise in GCF-PGE$_2$ levels to about 32ng/ml, and a higher rise (about 53 ng/ml) in experimental gingivitis$^{24}$.

**Effect of prostaglandin E$_2$ on bone metabolism and periodontal tissue regeneration:**

A number of arachidonic acid metabolites act as modulators of bone cell function. Immune, marrow and bone cells produce these factors. Prostaglandins of the E series are slow acting but powerful mediators of bone resorption and affect both active mature osteoclasts as well as osteoclast precursors. PGE$_2$ produced by osteoblasts have effects not just on bone resorption but on bone formation as well. Currently, studies with cell and organ cultures have indicated that forms of PGE$_2$ have a stimulatory effect on not only bone resorption but also bone formation.

The effect of systemic and local administration of prostaglandin E$_1$ in animals and humans was found that prostaglandin E$_2$ causes substantial bone formation$^{25}$. PGE receptor EP$_4$ was actually associated with lipopolysaccharide induced bone resorption in vivo. They showed that EP$_4$ subtype of the PGE receptor is involved in LPS-induced bone resorption$^{26}$. The activation of EP$_4$ induces bone remodeling in vivo and that EP$_4$ selective drugs may be beneficial in humans with osteoporosis$^{27}$.

**SMOKING AND PERIODONTAL DISEASE:**

Periodontal disease is a multifactorial disease, which is influenced by subject characteristics, social and behavioral factors, systemic factors, tooth level factors, microbial factors. Commonly recognized risk factors for periodontitis are diabetes, age, genetic factors, and environmental factor such as smoking. Smoking is well recognized as a modifiable risk factor for periodontitis.

**Influence of smoking on PGE$_2$ production in pathogenesis of chronic periodontitis:**

Among the factors that regulate PGE$_2$ production in periodontal disease the role of tobacco smoking is well known. Tobacco smoke can induce COX-2 expression and PGE$_2$ production in gingival cells in vitro. Studies have shown exposure to nicotine causing PGE$_2$ release
by monocytes, stimulated by lipopolysaccharide. The elevated IL-1 production by keratinocytes may have implications in tobacco-induced lesions, given the central role IL-1 plays in tissue response to injury.

The nicotine and LPS stimulate the formation of osteoclast-like cells via an increase in M-CSF and PGE2 production and that the stimulation is greater than with nicotine treatment alone. The lipopolysaccharide enhances the production of nicotine induced PGE2 with decreasing alkaline phosphatase activity and increased macrophage colony stimulating factor expression. It also increased cyclooxygenase-2 expression by osteoblasts.

**Influence of elevated PGE2 levels observed in chronic periodontitis on systemic conditions:**

**Preterm low birth weight and periodontal disease:**

PGE2 not only has local effects in the periodontium but when produced can also spill over into systemic circulation. This circulating PGE2 can also travel to distant sites and target organs causing damage. In this context, the role of PGE2 produced in periodontitis, in initiating preterm low birth weight and adverse pregnancy outcomes is well-understood. GCF- PGE2 levels are significantly higher in preterm low birth weight mothers, as compared with normal birth weight controls.

**Insulin-Dependent Diabetes Mellitus (IDDM) & periodontal disease:**

The high GCF and monocytic secretion of PGE2 and IL-1β in IDDM patients may be a consequence of a systemic response trait and further the presence of gram-negative infections such as periodontal diseases may interact synergistically to yield high local levels of these mediators and a more severe periodontal condition.

**Rheumatoid arthritis and periodontal disease:**

Rheumatoid arthritis (RA) is a chronic inflammatory condition affecting various joints in the body and is characterized by inflammation of the synovial membrane and destruction of joint architecture. PGE2 in particular has been implicated in inducing bone resorption and cartilage destruction observed in patients with rheumatoid arthritis.

**Conclusion:**

Prostaglandin E2 a vasoactive eicosanoid produced by monocytes and fibroblasts, plays an important role in health as well as in periodontal disease.
These inflammatory mediators cause periodontal tissue breakdown. The raised serum PGE₂ levels have possible implications in the pathogenesis of systemic condition such as diabetes mellitus, rheumatoid arthritis and preterm low birth weight.

There has been a very rapid growth in knowledge and understanding of tissue destruction. Nevertheless, research aimed at elucidation of pathways of tissue destruction at molecular level is only in its infancy. The role played by PGE₂ remains enigmatic. In vitro evidence documents that PGE₂ is a potent inducer of alveolar bone resorption on the other hand, PGE₂ has capacity to suppress cytokines like IL-1, TNFα produce and MMP release. Further experimental study is needed to understand the basics of periodontal ligament tissue destruction at molecular level. Thus having an understanding of the role of PGE₂ in health and periodontal disease becomes very important in treatment planning. By treating the patients as a whole instead of a mouth we can have a positive impact on our patient’s health.

References:


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Journal of Basic Medical and Allied Sciences 2012:1
Accepted on 5th Sep, 2012


