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Role of Nitric oxide in the Pathogenesis of Periodontitis and Future Perspectives for the Treatment Needs – A comprehensive review

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Abstract

Nitric oxide is a short-lived bioactive molecule that serves as a messenger molecule for various physiological and pathological processes. It is synthesized from L-arginine by nitric oxide synthase (NOS), which is present in various tissues. NOS produced physiologically in endothelium, central and peripheral nerves are classified as endothelial NOS (eNOS) and neuronal NOS (nNOS), whereas inducible form of NOS (iNOS) is expressed in response to pro-inflammatory stimuli. NO is associated with a multitude of physiological functions. It has been demonstrated that human gingival fibroblast cells can produce NO when stimulated with inflammatory cytokines IL-1β, TNF-α and INF-γ. In recent years, a growing number of researchers have explored the role of NO in the pathophysiology of periodontal disease. Periodontal pathogens evade host defense cells, possibly by generation of reactive oxygen radicals, and induced production of pro-inflammatory cytokines. The iNOS enzyme is induced in response to cytokines and it, in turn, increases production of No. Animal experiments have shown that pharmacological inhibition of iNOS with mercaptoalkylguanidines is associated with decreased inflammation. Enhanced production of nitric oxide has been demonstrated in periodontal disease. The use of a selective iNOS inhibitor, mercaptoalkylguanidine, has been demonstrated to reduce periodontal attachment and bone loss in animal experimental periodontitis. The use of iNOS inhibitors in conjunction with anti-biofilm treatments may prove to be advantageous.

Keywords: iNOS, Nitric oxide, anti-biofilm.

Introduction

Nitric oxide is a short-lived bioactive molecule produced by immunocompetent cells, such as macrophages, and serves as a messenger molecule for various physiological and pathological processes (Moncada and Higgs, 1991)[1]. It is synthesized from L-arginine by nitric oxide synthase (NOS), which is present in various tissues (Nathan C, 1994)[2]. NOS produced physiologically in endothelium, central and peripheral nerves are classified as endothelial NOS (eNOS) and neuronal NOS (nNOS), whereas inducible form of NOS (iNOS) is expressed in response to pro-inflammatory stimuli. eNOS and nNOS are named as constitutive NOS (cNOS) and produce modest levels of NO for a short period. Conversely, iNOS is expressed upon stimulation by proinflammatory mediators, such as IL-1β, TNF-α, interferon-γ (Beasley D, 1991; Kilbourn RG, 1990)[3,4] and bacterial LPS in macrophages, lymphocytes, and PMNs, in the connective tissue, blood vessels, fibroblasts, basal layer of the epithelium and endothelial cells of the blood vessels following bacterial infection.

Effects of no

NO has been identified as the endothelium- derived relaxing factor (EDRF) which in normal physiological homeostasis, helps regulate blood pressure. NO is associated with a multitude of physiological functions. These functions included regulation of platelet aggregation (Radomski 1987)[5], neuro transmission, and strong oxidative activity that contribute to the killing of microorganism (Lyons CR, 1995)[6].

Immunohistological studies of human iNOS in periapical tissues indicated that iNOS was widely distributed in epithelial cells, endothelialo cells, fibroblasts, macrophages, and polymorphonuclear leukocytes. Inducible nitric oxide synthase, once expressed, can generate large amounts of nitric oxide for extended periods of time, which have been implicated in the control of host defense mechanism, as well as immunity. However, endogenous cytokines such as transforming growth factor β (TGF- β), IL-4 and IL-10 decreases iNOS expression in macrophages. Dag high et.al (2002)[7] demonstrated that human gingival fibroblast cells can produce NO when stimulated with inflammatory cytokines IL-1β, TNF-α and INF-γ.

It is known that NO is involved in acute and chronic inflammation (Nathan C, 1994)[2]. Accumulating evidence from basic and clinical research suggests that NO may play a key role in mediating tissue and bone damage in inflammatory conditions associated with cytokine activation (Dag high et.al, 2002)[7]. It was suggested that NO functions as a second messenger mediating the effects of the pro-inflammatory cytokine IL-1β. NOS inhibitors reduced the IL-1β stimulating mRNA levels of collagenase, and NO producing agents further induced these mRNA levels. It has been shown that NO activates matrix metalloproteins (MMPs) (Murrel et al 1995)[8], and down-regulates synthesis of tissue inhibitors of matrix metal proteinases.

Several studies suggest that tissue injury in inflammation involves induction of iNOS by certain cytokines or endotoxin, which leads to production of large quantities of NO (Dag high et.al, 2002)[7]. Excessive levels of NO production can promote tissue injury and contribute to progression of inflammatory diseases. Local concentration of NOS is an essential determinant of cytotoxicity. Micromolar concentrations generated by high output iNOS are microbicidal as well as pro-inflammatory and damaging to the surrounding cells and tissues.

In recent years, a growing number of researchers have explored the role of NO in the pathophysiology of periodontal disease. Periodontal pathogens evade host defense cells, possibly by generation of reactive oxygen radicals, and induced production of pro-inflammatory cytokines. The iNOS enzyme is induced in response to cytokines and it, in turn, increases production of NO.

It is well documented that NO production, particularly iNOS derived, increases in periodontal disease, indicating involvement in the pathogenesis of periodontal inflammation (Lappin et. al, 2000)[9]. On the other hand, the expression of eNOS in gingiva and its elevation in the gingival tissues following the application of orthodontic forces have been demonstrated. Despite the fact that eNOS is produced constitutively, there is current evidence that it could also be activated and released with certain cytokines before iNOS is upregulated (Rubin et al, 2003)[10]. eNOS mediated NO production is also involved in critical processes relevant to periodontal disease pathogenesis including inhibition of cyclooxygenase, regulation of osteoblast activity, prevention of the leukocyte adhesion and superoxide anion release from leukocytes (Berdeli et.al, 2006)[11], and suppressing T-cell proliferation. Therefore, eNOS may be a modifier molecule in the pathogenesis of periodontal diseases.

Matejka et.al (1998)[12] have shown increased NO synthesis in inflamed gingival tissues of patients with periodontal disease. There is also evidence for iNOS inhibition in gingival tissue. The protective effect of MEG, a selective inhibitor of iNOS was investigated by Lohinai et. al (1998)[13] in a rat model of periodontal disease. Results from this study demonstrated that NO production is increased in ligature induced periodontal disease and that MEG treatment protected against the associated bone destruction. Similar to the experimental study of Lohinai (1998)[13], iNOS expression in gingival tissue obtained from chronic periodontitis patients has been reported to be higher than in clinically healthy tissue samples (Lappin et.al, 2000)[9].

Gullu et.al (2005)[14] examined the correlation between the arginase, and NOS activity in patients with chronic periodontitis and compared the effects of scaling and root planning and modified Widman flap procedure on enzyme activity. The authors showed that the level of iNOS expression was greater in biopsies where abundant inflammatory cells were present. The intensity of iNOS expression was decreased after periodontal therapy, and flap procedures seemed to be more effective in reducing the number of iNOS expressed cells compared to scaling and root planning alone. Similarly, Lappin et.al (2000)[9] reported that iNOS presence was dependent on the extent of inflammation in the tissue and iNOS positive cells in connective tissue were observed predominantly macrophages. Hirose et.al (2001)[15] have found that NO production by macrophages and polymorphonuclear leukocyts via the iNOS pathway was enhanced in periodontal lesions and resulted in progression of periodontitis. This might also be valid as macrophage infiltration and activation are known to be characteristics of chronic inflammation such as periodontitis provoked by pathogenic bacteria.

Modulation of nitric oxide synthase (Nos) activity

Inhibitors of NO (MEG, PARP)

Animal experiments have shown that pharmacological inhibition of iNOS with mercaptoalkylguanidines was associated with decreased inflammation, hemorrhagic shock and arthritis scores (Zingarelli et al. 1997)[16]. This may be explained by the fact that this class of drugs (e.g. mercaptoethylguanidines (MEGs)) is able to (i) inhibit

COX, (ii) scavenge peroxin trite (i.e. the product of NO and superoxide) and (iii) block iNOS.

Lohinai et.al, (1998)[13] investigated the potential protective effect of mercaptoethylguanidines (MEG) on the bone loss associated with periodontitis in ligature induced periodontitis in 30 Wistar rats. Animals were divided into two groups (15 rats each): one group of rats was treated with MEG 30 mg/ kg, i.e., 4 times per day for 8 days, animals in the other group received vehicle. At day 8, the gingivobuccal tissue encircling the mandibular 1st molars was removed on both sides from ligated and sham operated animals for inducible nitric oxide synthase (iNOS) activity assay and for immunocytochemistry with anti-iNOS serum. Ligation caused a significant; more than 3-fold increase in the gingival iNOS activity, whereas it did not affect iNOS activity on the contralateral side, when compared to sham-operated animals. Immunohistochemical analysis revealed iNOS-positive macrophages, lymphocytes and PMNs in the connective tissue and immunoreactive basal layers of epithelium on side of the ligature, and only a few iNOS-negative connective tissue cells on the contralateral side. Ligation significantly increased Evans blue extravasation in gingivomucosal tissue and alveolar bone destruction compared to the contralateral side. MEG treatment significantly reduced the plasma extravasation and bone destruction[13]. The authors reported that ligature-induced periodontitis showed increase in local NO production and that MEG treatment protects against the associated extravasation and bone destruction.

Recently, the role of activation and pharmacological inhibition of nuclear poly (ADP-ribose) polymerase (PARP) enzyme, a mediator of downstream NO toxicity, was investigated using the ligature- induced periodontitis model in rats and mice. Lohinai et al. (2003)[17] investigated the role of the activation of nuclear poly (ADP-ribose) polymerase (PARP) enzyme, a mediator of downstream nitric oxide toxicity, using a combined approach of pharmacological inhibition and genetic disruption in a ligature-induced-periodontitis model in rats and mice. After ligature placement around the neck of the first left mandibular molar, the rats were administered a potent PARP inhibitor (e.g. PJ34) or vehicle by intraperitoneal injection. Non-ligated right first mandibular molars served as controls. Immunohistochemical analysis revealed significantly increased poly (ADP-ribose) nuclear staining (indicative of PARP activation) in the subepithelial connective tissue of the ligated side compared with the non-ligated side. Ligation-induced periodontitis resulted in marked plasma extravasation in the gingivomucosal tissue and led to alveolar bone destruction compared with the non-ligated side, as measured by the Evans blue technique and by video microscopy, respectively. PARP inhibition with PJ34, as well as genetic PARP-1 deficiency, significantly reduced the extravasation and the alveolar bone resorption of the ligated side compared with controls. Thus, PARP activation contributes to the development of periodontal injury. Inhibition of PARP may represent a novel host response modulatory approach for the therapy of periodontitis.

Conclusion

The primary causative agents of periodontal disease are particular gram-negative anaerobic bacteria that accumulate in gingival sulcus. The lipopolysaccharide from gram-negative anaerobic bacteria have been demonstrated to induce significant production of nitric oxide in macrophages (Sosroseno W, 2002)[18]. Nitric oxide is thought to have an important role in the pathogenesis of inflammatory periodontal disease as it

does in other inflammatory diseases. Enhanced production of nitric oxide has been demonstrated in periodontal disease.

The use of a selective iNOS inhibitor, mercaptoalkylguanidine, has been demonstrated to reduce periodontal attachment and bone loss in animal experimental periodontitis. However, further studies are necessary to determine the applicability of these agents as therapeutic drugs. The use of iNOS inhibitors in conjunction with anti-biofilm treatments may prove to be advantageous. However, this concept needs to be validated in controlled clinical trials. As methods that modulate the host response, they may be useful as adjunctive therapies for a variety of clinical situations.

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