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Oxidative Stress and Periodontal Disease

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Abstract

The concept of Free radicals and the damage they cause in the biological systems has been getting a lot of attention over the past few years. They have been recently known to be the fore bringer of many inflammatory diseases. Periodontal disease is no exception the accumulation of these various toxic free radicals that are a byproduct of inflammatory change in the different structural components of the periodontium lead to a condition known as oxidative stress, which predispose a positive environment for the aggravation of periodontal disease. Of late there are various therapeutic modalities used for neutralizing this harmful process and can be used as a preventive mechanism for progression of disease. This article is a humble attempt to give an insight to this process and how this knowledge can be applicable for future therapeutic modalities.

Keywords: Free radicals; Oxidative stress; Periodontitis; Inflammation

Abbreviations: NADPH: Nicotinamide adenine dinucleotide phosphate; DNA: deoxyribonucleic acid; ROS: Reactive Oxygen Species; PUFA: polyunsaturated fatty acid; PMN: Polymorphonuclear Neutrophils

Introduction

Periodontal disease is considered as an inflammatory disease but many aspects of its pathogenesis still remain unknown [1]. Inflammation represents the response of the host to a noxious stimulus, whether mechanical, chemical or infectious. It is a localised protective response elicited by injury or destruction of tissues, which serves to destroy [2], dilute or wall off both the injurious agent and the injured tissue. Acute or chronic inflammation is dependent upon the regulated humoral and cellular responses. However an event characteristic of mammalian inflammation is tissue infiltration by polymorphonuclear leukocytes and monocytes and subsequent phagocytosis, which features a "respiratory burst" phenomenon. This is a burst of non-mitochondrial oxygen consumption which may be several folds higher than that of the normal resting consumption of the cells.

Oxygen uptake in neutrophils and macrophages is due to the action of a plasma membrane bound flavoprotein cytochrome b_{245} NADPH oxidase system that increases NADPH production through the hexose monophosphate shunt and generates certain potentially harmful radical species [3]. A variety of these molecules appears in the inflamed tissues and is all capable of damaging either cell membranes or associated biomolecules. As a consequence the body has evolved certain defence systems and repair systems inherently to prevent the accumulation of oxidatively damaged molecules which are toxic. In health a judicious balance exists within the pro-oxidant and anti-oxidant mechanism but in disease it is tipped in favour of the former which is due to oxidative stress [4]. This has also been recently seen in the case of periodontal inflammatory diseases. A better knowledge about this

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mechanism can pave the way for future pharmacological interventions and therapeutic strategies to cure periodontal disease [5].

Free Radicals and Reactive Oxygen Species

A free radical may be defined as an atomic or molecular species with one or more unpaired electrons in its structure. There are three possible means of free radical formation [6].

- The covalent bonds are cleaved and there is an imbalance of electrons and each fragment retains an unpaired electron.
- Loss of a single electron from a normal molecule.
- "Electron transfer" occurs where there is addition of a single electron to a normal molecule: it is very common in biological systems.

Reactive Oxygen Species

The nature of the oxygen molecule is such that it loses one electron at a time and this result in the formation of a reactive unstable molecule known as the reactive oxygen species.

Radicals		Non-radicals	
Superoxide	O_2	Singlet oxygen	O_2
Hydroxyl	OH	Ozone	O_3
Hydroperoxyl	HOO	Hypochlorous acid	HOCl
Alkoxyl	RO	Hydrogen peroxide	H_2O_2
Aryl oxyl	ArO		
Aryl peroxyl	ArOO		
Peroxyl	ROO^-		
Acyloxyl	RCOO		
Acylperoxyl	RCOOO		

Superoxide: When one electron is reduced from oxygen it would result in the production of a superoxide anion.

$$O_2 + e^- \longrightarrow O_2^-$$

4.3.1. Hydrogen Peroxide:

An electron is added to the superoxide radical resulting in the peroxyl anion which can react with hydrogen ions to form hydrogen peroxide

$$O_2^- + e^- \longrightarrow O_2^{2-}$$
$$O_2^{2-} + 2H^+ \longrightarrow H_2O_2$$

Hydrogen peroxide is naturally produced in biological systems through superoxide synthesis mechanisms.

$$2O_2^{2-} + 2H^+ \longrightarrow H_2O_2 + O_2$$

Hydroperoxyl: A proton when added to superoxide results in the formation of hydroperoxyl radical.

$$O_2^- + H^+ \longrightarrow HCOO^-$$

Hydroxyl Radical: One of the most reactive and damaging of the reactive oxygen species.

Hydrogen peroxide can be reduced to water by adding two electrons generated from the hydroxyl radical.

1) Superoxide driven fenton reaction
2) Metal catalysed – Haber Weiss reaction

In these reactions electrons are supplied by the oxidative ferrous (Fe^{2+}) or cuprous (Cu^+) ions to ferric ions (Fe^{3+}) or cupric ions (Cu^{2+}) respectively.

Sources of reactive oxygen species:

These reactive oxygen species can be produced

- Endogenously – intracellularly or within the body
- Exogenously – from external resources e.g.

1. Heat
2. Trauma
3. Ultrasound
4. Infection
5. Radiation
6. Hyperoxia
7. Exercise to excess

Tissue Damage or Biological Targets for Reactive Oxygen Species

There are five principal targets for reactive oxygen species in living systems

- Small organic biomolecules
- Proteins
- Nucleic acids
- Gene activation
- Unsaturated fatty acids

Small Organic Molecules: Vitamins, carbohydrates, amino acids, uric acid, cholesterol, and small soluble peptides like glutathione comprise this group.

The chain reactions usually are terminated when the Reactive oxygen species react with vitamins (A, C or E), quinines, glutathione and uric acid.

Carbohydrates: break down due to oxidation and this may have an impact on the DNA structure leading to strand breakage.

Proteoglycans such as hyaluronic acid can be depolymerised by ROS and they are one of the major components in the matrix of connective tissues thus having a negative effect on the integrity of tissues.

Amino acids: undergo direct oxidative modification which may affect their physiological role. The modifications can be reversible e.g. oxidation reduction of

thiol groups as well as irreversible e.g. the ring cleavage of histidine.

Cholesterol: when oxidised yields cholesterol hydroperoxide and a family of oxysterols which are further oxidised in the sterol B ring structure. These molecules are present at relevantly high concentration in human breast fluid and may act as cancer promoting agents.

They have also got other drastic outcomes since they augment the pathogenesis of atherosclerosis and cardiovascular diseases.

Proteins

The cell architecture on the whole may be in jeopardy by the oxidative process since proteins are the building blocks of any organ whose basic unit is the cell. The sensitivity of the proteins depends on its amino acid composition. The result of the oxidative stress is the conversion of the amino acid derivatives / residues to carboxyl derivatives that are related to protein damage.

Nucleic Acids

The DNA infrastructure comprising both the polyribonucleotides and polydeoxyribonuleotides (RNA and DNA) are highly susceptible targets to Reactive oxygen species. The frequency of base modifications per cell per day is around 10000. Certain products of modified pyridine and purine bases presumably proceeding from DNA excision and repair have been detected.
Thus indicating ROS may lead to mutagenesis and carcinogenesis of major significance.

Gene Activation

The reactive oxygen species have the ability to activate transcription which is a process by which transcription factors are encoded and they modulate cell growth differentiation and development and can activate apoptosis a “programmed” form of cell death.
Certain factors regulated by the Reactive oxygen species are the mammalian transcription factors such as nuclear factor (NF) –KB and activator protein -1 (AP-1) and also the “heat shock” (or stress protein) transcription factors (HSTF).

Unsaturated Fatty Acids

Polyunsaturated fatty acids are converted to lipid peroxides. The chain reactor consists of three essential steps.
1. Initiation
2. Propagation
3. termination

Hence a single initiation event can result in the conversion of several PUFA side chains in to lipid hydroperoxides. This process continues until oxygen and unsaturated PUFA chains are available.
Lipid peroxidation may give rise to several products which are biologically active and cytotoxic which may be divided in to three main categories.
1. Chain cleavage products i.e.
   - Alkanals
   - Alkenals
   - Alkanes
2. Products formed by rearrangement and consecutive oxidation
3. Higher molecular oxidation products resulting from polymerization reactions.

Reactive Oxygen Species Mediated Damage in Periodontitis

The physiological activity of phagocytosing leukocytes can result in mild oxidative damage wherein they release free radicals or reactive oxygen species [7]. But if this release is in an uncontrolled manner it contributes to the destruction of the surrounding tissues. Local factors like plaque microorganisms promoting periodontitis can also unbalance this equilibrium thus causing havoc. But there are certain inherent defence mechanisms that nullify this effect and they are the ‘antioxidant enzymes’.

Gingival epithelial cells are highly susceptible to attack by PMN-derived oxidants. It was observed that the activated neutrophils cause a non-lytic detachment injury to the gingival epithelial cells and the myeloperoxidase enzyme which released reactive oxygen species brought about lysis of the gingival epithelial cells. Free radical release in to the micro environment between PMN and adherent fibroblasts leads to cell damage.

An implication which stated that the general etiologic factors responsible for the disruption of the physiological system of lipid peroxidation inhibition created a low-level antioxidant protection of the periodontium and local factors promoted the breakouts of lipid peroxidation which was induced by the reactive oxygen species thus substantiating a role for this process in the pathogenesis of periodontitis [8]. Iron levels are higher in gingival fluid of human subjects affected by periodontitis. This could have unfavourable consequences due to the ability of iron to catalyse ROS reactions thus enhancing growth of periodontal pathogens.

Nutritional imbalances can provoke a deterioration of the periodontium by depleting the key antioxidant nutrients this leads to an impaired response to infections and thus increasing the susceptibility of periodontitis. A pathological status that induces periodontitis is Diabetes and the irreversible products of non-enzymatic glycation and oxidation of proteins and lipids which accumulate in the diabetic plasma and tissue are the Advanced Glycation End-products, a possible relationship between periodontitis and these products is responsible for inducing oxidative stress in tissues of diabetics.

Conclusion

Reactive oxygen species are products of normal cellular metabolism. However excessive production of ROS oxidises DNA, lipids and proteins inducing tissue damage. The reactive oxygen species is a major breakthrough in the etiopathogenesis of periodontal disease [9]. The dramatic elevation in ROS formation increases the oxidative stress in the periodontium favouring the progression of inflammation, bone resorption and possibly tooth loss contributes to periodontitis [10].

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