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Role of enzymes in oral disease

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Abstract

Host responses to periodontal disease include the production of different enzymes that are released by stromal, epithelial or inflammatory cells. There are important enzymes associated with cell injury and cell death like: aspartate and alanine aminotransferase (AST, ALT), lactate dehydrogenase (LDH), creatine cines (CK), alkaline and acidic phosphatase (ALP, ACP), Gama glut amil transferase (GGT).

Biofilm-related infections of the oral cavity, including dental caries and periodontitis, represent the most prevalent health problems. For years, treatment was largely based on antibacterial chemical agents.

For the better anti-inflammatory or analgesics effects of drugs; enzymes have been widely used in the medical field either it may be arthritis or fracture of the bone or it may be oedema. Along with anti-inflammatory action these drugs have anti-oedema properties, healing properties and fibrinolytic properties as like trypsin-chymotrypsin. Recently, however, there has been growing interest in the application of more preventive and minimally invasive biotechnological methods.

This review focuses on the potential applications of enzymes in the treatment and prevention of oral diseases. In this article we are also going to discuss about the importance or applications of these enzymes either alone or in combination with other NSAIDS in the field of dental practice.

Keywords: Antimicrobial enzymes, Caries control, Dental plaque, Glucan hydrolases, Proteases.

Introduction

Three quarters of all microbial infections found in humans are associated with microbial biofilm, for instance oral diseases, dental caries, and periodontal diseases caused by oral biofilm known as dental plaque[1].

Dental caries is a health problem in a majority of developed countries (mainly due to cariogenic diet) and, as shown by a report of the World Health Organization, it affects people of all ages, i.e., 60 – 90% of school-age children and most adults[2].

In most countries, the periodontal disease burden also remains high, with approximately 15 – 20% of adults and 2% of young people affected by severe periodontitis.

These diseases have a significant effect on the quality of life and may deteriorate systemic health[3,4].

In recent years, increasing emphasis has been placed on more preventive and minimally invasive concepts of caries treatment based on anticariogenic diet, proper oral hygiene, and development of various kinds of new, human-friendly approaches to prevention of cariogenic biofilm formation such as replacement therapies and the use of probiotics and prebiotics, antimicrobial peptides, or natural substances such as plant-based extracts, essential oils, etc[5,6,7].

For some time now, the application of enzymes has been considered as an alternative strategy to fight with various kinds of biofilm e.g., that associated with medical devices or industrial biofilm[8,9,10].

This review focuses on the use of enzymes as an unconventional approach to control and treat oral diseases.

Enzymes as alternative anti-biofilm agents

Enzymes, mainly microbial, added to oral hygiene products such as mouth rinses, toothpastes, and chewing gums effectively support mechanical cleaning of teeth through different mechanisms.

Enzymes act gently and specifically and, therefore, they hardly affect the biological environment of the oral cavity. A great advantage of this type of strategy is that resistance of bacteria to enzymes, in contrast to chemicals, is rare[11].

Antimicrobial enzyme system

One of the important functions of saliva is to protect oral tissues from the harmful effect of microorganisms. Therefore, saliva contains a spectrum of proteins with antibacterial properties. Among the non-immunologic salivary protein components, there are peroxidases and lysozyme, i.e. part of the innate defense system[12].

Using a number of different mechanisms, these enzymes exhibit bactericidal or bacteriostatic activity against a broad spectrum of microorganisms.

They are found in almost all secreted body fluids and tissues of human and animal organisms, such as milk, tears, and saliva[13].

Human whole saliva contains a salivary peroxidase enzyme secreted by the salivary glands. It is a porphyrin-containing glycoprotein forming an antimicrobial peroxidase system with its cofactors. The active component of this system is, depending on the pH, a hypothiocyanite ion (OSCN–) or hypothiocyanous acid (HOSCN), which is formed by peroxidase-catalyzed oxidation of salivary thiocyanate (SCN–) using hydrogen peroxide derived from bacteria and host cells[14,15]

The antibacterial activity of the enzyme also includes aggregation of bacteria, activation of bacterial autolysins, and inhibition of bacterial adherence and glucose metabolism.

Lysozyme has higher antibacterial activity towards Gram-positive bacteria; however, the peptidoglycans of some of these bacteria are resistant to being hydrolysed by this enzyme

Bio tene products contained all the components of the peroxidase system, i.e., lactoperoxidase, KSCN, hydrogen peroxide-generating glucose oxidase (from added glucose), and additionally lysozyme and lactoferrin[16].

They were available in the form of toothpaste, mouth rinse, moisturizing gels (Oral Balance, without lysozyme and lactoferrin), and a denture adhesive (Denture Grip). The products were especially intended for patients who suffer from dry mouth but also for normal oral hygiene[16]

Glucan hydrolases

Mutans and dextran's are considered the most important dental plaque matrix polysaccharides.

Water-insoluble mutans produced by surface-adsorbed glucosyltransferases are essential to the assembly of the three-dimensional structure of the EPS matrix[17].

They easily adsorb to pellicle-coated enamel, promote bacterial co-aggregation, and substantially enhance the cohesive and adhesive properties of plaque.

Due to the presence of (1→3)-α-glucoside links, which are resistant to the action of enzymes present in the oral cavity, mutans provide dental plaque with stability and durability[18,19].

Water-soluble dextran's together with other matrix polysaccharides function as a reserve of carbohydrates and retain water to prevent desiccation of the biofilm. Therefore, both these glucans may be promising targets for anti-biofilm agents including exogenous glucan hydrolyzing enzymes such as mutanases and dextranases[20].

Dextran-degrading enzymes commonly called dextranases form a diverse group of different carbohydrase's and transferases. They specifically hydrolyze (1→6)-α-glycosidic linkages in dextran's, their derivatives, and is maltodextrins. Dextranases have often been classified as endo- and Exodextranases. Exodextranases, remove successively one or more glucose units from the non-reducing ends of the dextran chains[20].

Anti-plaque, anti-calculus, and whitening proteases

Generally, dental plaque is formed by

(i) Colonization of the acquired protein pellicle (composed of mucins, other glycoproteins, and proteins) that covers the surface of the teeth with early colonizers and

(ii) Extensive co-aggregations and co-adhesions mediated by different adhesion proteins synthesized by secondary colonizers.

Therefore, a promising anti-biofilm option seems to be to interfere with plaque accumulation by disruption of proteinaceous connections or weakening of the structure of the biofilm matrix by proteolytic enzymes[21].

Role of enzymes as drugs in oral diseases

Serratiopeptidases

Serratiopeptidase is a proteolytic enzyme that is produced by non-pathogenic enterobacterium Serratia sp. And this microbe was first isolated from silkworm's intestine to allow the dissolution of its own cocoon[22].

It has been used for years for reducing inflammation and pain due to surgery, trauma, and other inflammatory conditions.

Serratiopeptidase acts as an anti-inflammatory agent to pacify mild to moderate pain and inflammation.

Common conditions associated with pain and inflammation includes arthritis, trauma, surgical wounds and fibromyalgia and in many other diseases in general practice. Additionally, SP helps to reduce fluid retention in affected areas, which contributes to proper drainage and faster recovery[23].

SP has also been shown to increase the clinical activity of many antibiotics including the ampicillin, cephalexin, minocycline and it can also be useful in dental infections since the activity of antibiotics will get enhanced along with anti-inflammatory action of SP[24].

In dentistry it has also anti-inflammatory, anti-endemic and analgesic effects, it is widely used after removal of wisdom tooth, postoperatively after maxillofacial surgeries and in TMJ arthritis. Also, SP were found to improve trismus in a better way than corticosteroids[24].

The usual adult dose of SP ranges from 15 to 60 mg per day. The concomitant use of SP with aspirin should be avoided as anticoagulants interacts with SP and might reduce its effects and the general consideration that should be taken to take this medicine is to take with food to avoid the GI upset. Like other drugs, SP too have few adverse effects that may include anorexia, GI upset, skin rashes, epistaxis[25].

Trypsin- chymotrypsin

Both TC are a family of serine proteases, and these two types of proteases originally synthesized in the pancreas in the inactive form of zymogen precursors (trypsinogen and chymotrypsinogen) for the purpose of stopping unnecessary cellular activity and controlling when and where enzyme activity occurs.

These active forms of enzymes also aid in the digestion of food. TC give the body the extra boost it might need for smoother digestion of proteins as well as for reducing inflammation and fighting infection[26].

TC provides better resolution of inflammatory symptoms and promotes speedier recovery of acute tissue injury than several of the other existing enzyme preparations.

Thus, the clinical activities of TC include

- Fibrinolytic activity - TC breaks down the fibrin barrier thus improving and restoring circulation, resolving edema, hematoma and pain, promoting phagocytosis to remove the debris an accelerate recovery[27].
- Reduction in Plasmin Inhibitor levels within 3-5 days to post-surger
- Release of Intestinal Plasminogen activators - Studies have shown that TC brings about release of Plasminogen activators from the intestinal mucosa and those are absorbed into the systemic circulation along with TC thus, contribute further to bringing about fibrinolysis; thereby increasing tissue circulation and decreasing edema[27]. Due to these antioxidant, anti-inflammatory, antifibrinolytic, antiedema properties these can be indicated in dentistry in number of ways-
- Post-operative wounds
- Oedema and hematoma caused after LA injection,
- Prevention of inflammation of the surgical stitches,
- After tooth extraction especially in case of impacted teeth or wisdom tooth,
- Peri-apical abscess (where SP might have negative effects)[28],
- Maxillofacial surgery,
- Post-traumatic oedema,
- Soft tissue injury & maxillofacial fractures and dislocation after trauma,
- TMJ arthritis
- Oral ulcers – due to its antioxidant & healing properties by removing the dead tissues.

Combination of TC enzyme may consist of purified proteolytic enzyme concentrate providing 50,000/1,00,000/2,00,000 arm our units of Trypsin and Chymotrypsin in the ratio 6:1. And it is possibly safe up to the dosage of 800,000 units per day of this combination up to 7-10 days[29].

Adverse effects include

- Gastric upset
- Corneal edema
- Allergy or anaphylaxis with symptoms include itching, shortness of breath.
- swelling of the lips or throat, shock, loss of consciousness, and death (rare)[29]

The contraindication of this combination includes – hypersensitivity, congenital cataracts, peptic ulcers, patients below 20 years as lens vitreous adhesion may

not be responsive to chymotrypsin lysis, severe hepatic & renal impairment[28].

Bromelain

Bromelain is a proteolytic enzyme present in the plant of pineapple (Ananas comosus). It has been used for a long time in traditional medicine in South-east Asia, Kenya, India, and China because of its anti-inflammatory, anti-fibrinolytic, anti-thrombotic, and antiedema properties.[30]

BR is used as an adjunct in the treatment of soft tissue inflammation and oedema associated with trauma and surgery, and also as an anti-inflammatory and analgesic agent in treating the symptoms of arthritis, thus, it can be used in TMJ arthritis, after 3rd molar extraction with combination with rutins, trypsin or with NSAIDs[30].

The analgesic and anti-inflammatory effects are reportedly due to inhibition of the arachidonic acid pathway of inflammation by selectively decreasing thromboxane generation, changing the ratio of thromboxane/prostacyclin (in favor of prostacyclin), and inhibiting PGE2 in addition to the direct effects on the nociceptors. Other reported anti-inflammatory mechanisms of action of bromelain include inhibition of bradykinin at the site of inflammation via depletion of the plasma kallikrein system, and limiting the formation of fibrin by reduction of clotting cascade intermediates[31].

Bromelain has also demonstrated anti-inflammatory action by inhibiting COX-2 expression and PGE2 production in murine microglial cells and human monocytic leukemia cell lines[31].

The efficacy of BR was studied in oral cancer cell line Ca9-22 and SCC25 cells to develop safer and superior anticarcinogenic agents and the treatment with BR inhibited the growth and proliferation of oral cancer cells, and induced apoptosis in Ca9-22 and SCC25 cells via various pathways and G1 cell cycle arrest[32].

Thus, it can be hoped that BR will be developed as an anticarcinogenic medicine in future. BR may cause nausea, vomiting, and diarrhea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma[32].

Limitations

However, like other treatments, the application of enzymes has some limitations. Enzymes are characterized by sensitivity to proteolysis and a limited possibility of penetration.

The low activity of wild-type enzymes and their insufficient stability in oral hygiene products limit their efficiency. Due to their specific mode of action, formulations containing several different enzymes may be necessary to be successful, for instance, in degradation or inhibition of formation of the complex and heterogeneous dental plaque matrix.

Another problem is the low availability and high cost of production of the enzymes, particularly in contrast to chemical antimicrobial agents.

Therefore, before the full potential of the enzymes may be realized, it is necessary to improve their efficiency and cost-effectiveness[31-32].

Conclusion

From the overall discussion it can be concluded that the use of enzyme therapy through oral route has good results in the anti-inflammatory, analgesics role specially more with tissue healing has been observed in studies as well as in our clinical experience with the use TC especially with NSAIDs.

But we can’t ignore the role of other drugs too since BR have also been found to have an anticarcinogenic properties especially in case of oral cancer.

Also, clinically it has been found that different people respond well to different combinations of these enzymes either it may be diclofenac + SP or TC + Diclofenac or BR + Rutins + trypsin.

And the most important in prescribing these enzymes with other medicine is mainly dependent upon patient selection in dental or medical practice.

Abbreviations

- SP = Serratiopeptidases,
- LOX = lipo-oxygenase,
- COX = cyclo-oxygenase,
- TC = trypsin-chymotrypsin,
- SPM = specialized pro-resolving mediators,
- BR = bromelain,
- NSAID = nonsteroidal anti-inflammatory drugs.

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