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Review

Nanoparticles and the control of oral infections

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ABSTRACT

The potential of antimicrobial nanoparticles to control oral infections is reviewed. Such particles can be classified as having a size no greater than 100 nm and are produced using traditional or more novel techniques. Exploitation of the toxic properties of nanoparticles to bacteria, fungi and viruses, in particular metals and metal oxides, as well as their incorporation into polymeric materials have increased markedly over the past decade. The potential of nanoparticles to control the formation of biofilms within the oral cavity, as a function of their biocidal, anti-adhesive and delivery capabilities, is now receiving close attention. Latest insights into the application of nanoparticles within this field, including their use in photodynamic therapy, will be reviewed. Possible approaches to alter biocompatibility and desired function will also be covered.

1. Introduction

Nanotechnology represents the ability to image, manipulate and model functionalities on the nanometre scale. This discipline includes the study of nanoparticles, which can be classified as particles with a size no greater than 100 nm. Those particles with an antimicrobial function have received considerable attention within a range of diverse fields, including medicine and dentistry. These include spherical, cubic and needle-like nanoscaled particles (ca. 5–100 nm) and near-nanoscaled devices (up to micrometres) [1]. Properties of nanoparticles, e.g. their active surface area, chemical reactivity and biological activity, are often radically different from particles of a greater size [2]. For example, the antimicrobial effectiveness of metallic nanoparticles has been suggested to be due both to their size and high surface-to-volume ratio. In theory, these characteristics should allow them to interact closely with microbial membranes and thus elicit an antimicrobial effect that is not solely due to the release of metal ions [3]. Metallic and other nanoparticles are now being combined with polymers and other base materials as well as coated onto surfaces to provide a variety of potential antimicrobial and anti-adhesive applications within the oral cavity [4,5].

The oral cavity provides habitats for a wide diversity of microorganisms including bacteria, yeasts and viruses, with members of all groups being associated with oral infections. Bacteria are the predominant components of this resident microflora, and the diversity of species found in the oral cavity reflects the wide range of endogenously derived nutrients, the varied types of habitat for colonisation including surfaces on the teeth, mucosa and tongue, and the opportunity to survive as a biofilm [6,7]. However, the relationship between this microflora and the host can be disrupted in a number of ways, resulting in the development of disease of the oral structures. These are mainly localised and include dental caries, gingivitis, periodontitis, candidiasis, endodontic infections, orthodontic infections and peri-implantitis [6].

Most bacterial infections within the oral cavity are polymicrobial in nature and it is quite unusual to find any that are clearly due to a single species. The relative contribution of different bacterial components in such infections is thus difficult to determine. Oral infections may arise either from an endogenous source, i.e. one yielding micro-organisms normally found in the mouth, such as the main plaque-related diseases, namely dental caries and periodontal disease, or from an exogenous source yielding micro-organisms not normally found as part of the oral microflora. Dental caries and periodontal disease involve the adherence of bacteria and development of biofilms both on the natural and restored tooth surface.

Plaque-related diseases are probably the most common bacterial diseases occurring in man. Dental caries (dental decay) is a destructive condition of the dental hard tissues that, if unchecked, can progress to inflammation and death of vital pulp tissue, with eventual spread of infection to the periapical area of the tooth and beyond. The disease process involves acidogenic plaque bacteria, including *Streptococcus mutans*, *Streptococcus sobrinus* and *Lactobacillus* spp. [6]. Periodontal diseases can involve both the soft and hard tissues and are the most common inflammatory destructive conditions that affect man. They are initiated by components of the plaque that develops on the hard root surface adjacent to the soft tissues of the supporting periodontium and may be confined to the

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gingiva (gingivitis) or extend to the deeper supporting structures with destruction of the periodontal ligament and the alveolar bone that supports the teeth (periodontitis). Such loss of attachment, with associated periodontal pocket formation, may ultimately lead to loosening and loss of the affected teeth. *Porphyromonas gingivalis*, *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans* are regarded as the major pathogens in advancing periodontitis [8]. Furthermore, it has been recently suggested that there is an association between the oral microbiota and systemic diseases such as cardiovascular disease and complications during pregnancy [9,10].

Prevention of dental caries and the periodontal diseases is traditionally targeted at the mechanical or non-specific control of dental plaque, as this is the precipitating factor. However, the individual response of the host and other confounding factors can influence disease initiation and progression. Antimicrobial approaches, including the use of antimicrobial agents, represent a valuable complement to mechanical plaque control. Such strategies should ideally prevent plaque biofilm formation without affecting the biological equilibrium within the oral cavity, which is inhabited by up to 1000 different species of bacteria at 10^8–10^9 bacteria per millilitre of saliva or per milligram of dental plaque [11]. Use of nanotechnology offers the possibility to control the formation of these and other oral biofilms through the use of nanoparticles with biocidal, anti-adhesive and delivery capabilities.

Implant systems are increasingly being used to replace missing teeth, and most integrate with bone without complications. Small amounts of plaque consisting mainly of *Streptococcus* and *Actinomyces* spp. will accumulate on successful implants. However, in peri-implantitis, anaerobic Gram-negative organisms predominate [12]. This infection is a major cause of dental implant failure whereby the induced inflammatory changes in the soft tissues surrounding the implant lead to progressive destruction of the supporting bone (classified as peri-implantitis and seen in up to 43% of implant-treated subjects) or soft tissues (classified as peri-implant mucositis and seen in up to 50% of implant-treated subjects) [13]. Current forms of treatment are often inadequate, with chronic infection often requiring implant removal and expensive resective and regenerative procedures in an attempt to restore and reshape the supporting tissue [13]. Nanoparticle-based implant coatings may well offer useful osteoconductive and antimicrobial functionalities to prevent dental implant failure.

2. Control of oral biofilms

Agents classified as 'antiplaque' generally function by removing or disrupting biofilms or prevent the formation of a new biofilm. However, such agents do not necessarily kill the micro-organisms within the biofilm, whereas agents classified as antimicrobial act by inhibiting the growth of or by killing micro-organisms, as defined by the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), respectively. Uptake and penetration of antimicrobial agents into biofilms are key considerations in the administration of therapeutics [14]. Biofilm mode of growth is clearly distinguished from planktonic growth by a number of features, including resistance to antimicrobial agents at concentrations that approach 1000 times greater than those required to kill planktonic micro-organisms [15,16]. This is of significance in the development of nano-antimicrobials and the extrapolation of in vitro findings. Uptake and penetration are of particular importance within the oral cavity when these agents have to reach less accessible stagnation sites or pass through plaque to the enamel. Development of plaque control measures that require a minimum of patient compliance and professional healthcare intervention are therefore of particular interest [17]. Within this context, antimicrobial nanoparticles may be of particular value if retained at approximal teeth surfaces and below the gum margin.

The anticaries potential of fluoride and other conventional antimicrobial/antiplaque agents, which are mostly deployed in mouthwashes and toothpastes, has been extensively tested [18]. The potential of nanoparticles as constituents of topical agents to control oral biofilms through either their biocidal or anti-adhesive capabilities has now emerged as an area worthy of serious consideration. Studies using the 'Leeds in situ model', a device that allows dental plaque to develop in situ on a removable human enamel surface, have helped in the assessment of novel antimicrobial agents and take into account the extremely complex microbial composition and architecture of plaque biofilms [19]. Use of such intact biofilms on natural tooth surfaces would be of particular value to a study of the penetration of nanoparticles and released ions. This model has indicated that plaque contains voids and channels, sometimes extending completely through the biomass to the underlying enamel [20], which may have considerable influence on the transfer of nanoparticles through biofilms. The main considerations are the physical and chemical characteristics of the particular nanoparticles used, including the surface charge and degree of hydrophobicity, the surface area-to-mass ratio of the plaque biofilm, and the ability of the particles to adsorb and penetrate at the biofilm surface. Nanoparticles are potentially useful within this context because it is possible to alter their surface charge, hydrophobicity, and other physical and chemical characteristics [21].

3. Antimicrobial nanoparticles and control of oral biofilms

3.1. Nanoparticulate metals as antimicrobial agents

Metals have been used for centuries as antimicrobial agents. Silver, copper, gold, titanium and zinc have attracted particular attention, each having different properties and spectra of activity. Some of the most fundamental breakthroughs in medicinal history can be attributed to the antimicrobial properties of metals. Use of mercury as a medicinal agent can be traced back to the 10th century in Europe and the 2nd century BC in China. Skin diseases and syphilis were treated with inorganic mercury compounds, and more recently organomercurial compounds have been used as antiseptics and disinfectants [22]. Copper and zinc salts have also been investigated with respect to their use as antiseptics and as antifungal agents in the treatment of tinea pedis (athlete's foot). Many oral products, including toothpastes, now incorporate powdered (micron-sized) zinc citrate or acetate to control the formation of dental plaque [23].

With respect to nanoparticulate metals, the antimicrobial properties of silver [24] and copper [25] have received the most attention. Both of these have been coated onto or incorporated into various test materials [26], including poly(methyl methacrylate) (PMMA) [27] and hydrogels [28]. An inverse relationship between the size of nanoparticles and antimicrobial activity has been clearly demonstrated, where particles in the size range of 1–10 nm have been shown to have the greatest killing activity against bacteria compared with larger particles [3,29]. Indeed, it has been shown that smaller silver nanoparticles are more toxic than larger particles, and even more so when oxidised [30]. At the nanoscale, Ag^+ ions are known to be released from the surface of base materials incorporating nanoparticles [31]. Sotiriou and Pratsinis proposed that the antimicrobial activity of small (<10 nm) nanosilver particles is dominated by Ag^+ ions, whilst for larger particles (>15 nm) the contributions of Ag^+ ions and particles to the antibacterial activity are comparable, with the Ag^+ ion release being proportional to the exposed nanosilver surface area [32].