POTENTIAL PHARMACOLOGICAL TREATMENTS OF PROSTHETIC JOINT LOOSENING

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ABSTRACT


We are beginning to understand the biological events that lead to aseptic loosening of total joint prostheses. Particles of wear, mostly liberated from the articulating surfaces of implants, are phagocytosed by macrophages and induce the release of inflammatory mediators (such as interleukin-1, tumour necrosis factor, interleukin-6 and prostaglandin E2) or cause cell death. These biological responses are thought to cause the bone loss that leads to prosthetic loosening. Drugs that suppress inflammatory mediators are successfully used to treat inflammatory diseases. Certain drugs can also reduce the corrosion of metal wear particles inside macrophages which enhances mediator release or cell death. Here we consider the prospect that these pharmacological treatments may enhance the long-term survival of implants.

Keywords: anti-inflammatory drugs, prostheses, macrophages, wear particles, corrosion

INTRODUCTION

Aseptic loosening of total joint prostheses is a major problem, preventing the long-term success of arthroplasties. While mechanical factors and the material properties of the implants are important, biological and host factors may contribute significantly to aseptic loosening. There is substantial evidence that the tissue reaction to wear particles liberated from articulating surfaces leads to peri-articular osteolysis and loosening of the prosthesis. This reaction has many of the hallmarks of inflammatory responses. As we better understand the biological responses involved in this process, we can identify therapeutic strategies which may reduce these adverse biological responses and enhance the long-term survival of implants.

BENEFITS OF INCREASING THE TIME PROSTHETIC JOINTS REMAIN VIABLE

Artificial joints have now been used for over 3 decades, greatly enhancing the quality of life of the recipients. However, with time, several negative aspects of the long-term use of prosthetic joints have become apparent. All artificial joints will fail if implanted for long enough. Although these joints can usually be revised, the revised joints are more likely to fail sooner than an initial implant. Even though there have been great efforts to
improve the design, materials and implant procedures, the long-term viability of prosthetic joints has not dramatically improved. Studies have shown that 30–70% of patients show some radiological evidence of failure of fixation ten years after receiving total hip replacement with a majority of them failing by 10–15 years [1,2].

Improving the long-term viability of implants will not only enhance the quality of life of the recipients but will also be of great financial benefit to the community. As life expectancy in the developed and developing nations increases, more prosthetic implants will be required. The length of time that these implants need to remain viable will increase. Even adding 1–2 years to the average life expectancy of a total hip replacement would greatly reduce the need for revision and reduce the cost of health services.

THE PATHOLOGY OF PROSTHETIC JOINT FAILURE

Before ways of improving the longevity of prosthetic joints can be defined, there is a need to understand the major biological causes of implant failure. It has been recognized for some time that large amounts of small particles are associated with aseptic implant failure [3,4]. These particles can be made of prosthetic materials, cement (sometimes used to bond the implant to the bone) and bone itself. Most particles are produced by wearing of the articulating surface and also by cement and bone fragments becoming trapped between the articulating surfaces. Histopathological studies over the past twenty years have established that bone loss is associated with the invasion of macrophages and macrophage polykaryions (multinucleated giant cells) into the implant bed [3,4]. These macrophages have always been shown to contain particles of prosthetic material or cement. The larger the amount of prosthetic material present, the greater the degree of macrophage accumulation, and the presence of large amounts is often associated with death of the macrophages and nearby fibroblasts. Large numbers of macrophages containing particles are also found in the synovial tissues around the implant.

THE INFLAMMATORY RESPONSE TO WEAR PARTICLES

The pathological evidence is consistent with the hypothesis that wear particles are liberated from the bearing surfaces of the prosthesis and provoke a chronic inflammatory response dominated by macrophages but with sparse lymphocytes also present. This response leads to bone loss and loosening. The mechanism by which this occurs is now being understood. Figure 1 describes the pathological processes involved. Following phagocytosis of the particles, macrophages are stimulated to release mediators which, either alone or in combination, stimulate bone resorption by osteoclasts. The major factors involved are probably prostaglandin (PG)E₂, interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF). In-vitro [5] and immunohistological [6] studies of periprosthetic tissue obtained at revision show that macrophages containing wear particles produce these mediators of bone resorption. There is also the possibility that these activated macrophages may become transformed into high-grade bone-resorbing cells.