OXY RADICALS AND CONTROL OF INFLAMMATION

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INDEX

CHAPTER 2: CHEMILUMINESCENCE OF POLYMORPHONUCLEAR LEUCOCYTES FROM RHEUMATOID JOINTS

CHAPTER 3: PRODUCTION OF OXY RADICALS AND EFFECT OF METAL CHELATORS, ANTI-OXIDANTS AND ANTI-INFLAMMATORY AGENTS I: HYDROXYLATION OF SALICYLATE

CHAPTER 4: PRODUCTION OF OXY RADICALS AND EFFECT OF METAL CHELATORS, ANTI-OXIDANTS AND ANTI-INFLAMMATORY AGENTS II: DEGRADATION OF HYALURONATE

CHAPTER 5 GENTISATE: A SALICYLATE METABOLITE WITH ANTI-OXIDANT PROPERTIES

CHAPTER 6: MACROMOLECULAR CONJUGATES OF SUPEROXIDE DISMUTASE (SOD): STUDIES OF CLEARANCE ANTI-INFLAMMATORY EFFECT AND IMMUNOLOGICAL REACTIVITY

CHAPTER 7: CORTISOL PALMITATE LIPOSOMES FOR SYSTEMIC THERAPY OF INFLAMMATION

ABSTRACT

Inflammation is a response to injury mediatd through a complex of interacting systems. Clinical disorders may result when inflammation is persistent, uncontrolled or inappropriately triggered.

Oxy radicals are reactive oxygen-derived molecules. Their generation by activated polymorhonuclear (PMN) leucocytes and macrophages constitutes part of the normal defense against microbial invasion. The high reactivity of these molecules makes them likely to be (a) contributors to tissue damage occurring in chronic inflammatory disorders (e.g. damage to joints of patients with rheumatoid arthritis), and (b) a major influence on the metabolism of cells adjacent to their sites of production. Studies were undertaken in order to (i) obtain a better understanding of the ways in which oxy radicals may contribute to chronic inflammation and (ii) establish a basis for new approaches to treatment of inflammatory diseases.

Leucocytes obtained from inflamed joints of patients with rheumatoid arthritis were shown to produce a burst of chemiluminescence following appropriate stimulation, suggesting an intact mechanism for oxy radical production in these cells.

Studies of the mechanisms of production and inhibition of effects of oxyradicals were undertaken. Production of radicals was acheived (a) enzymatically and (b) non enzymatically. Oxy radical effects were monitored by (a) hydroxylation of salicylate measured spectrophotometrically and (b) degradation of hyaluronic acid measured viscometrically. The need for iron in a suitably chelated form for the production of the most potent oxy radical, hydroxyl radical, was established. The inhibitory activity on oxy radical effects of (i) anti-inflammatory agents, (ii) oxy radical eliminating enzymes (superoxide dismutase (SOD), catalase) and (iii) anti-oxidants was established in the above systems. Of particular interest was an observed enhancement of non-enzymatic hydoxyl radical production seen with some concentrations of penicillamine, a thiol containing anti-rheumatic agent.

SOD has been claimed to possess anti-inflammatory effect and this agent was studied. Intravenously administered SOD was rapidly cleared from plasma ($t_{1/2}$ 4-6 minutes) and lacked anti-inflammatory activity. Glutaraldehyde-crosslinked conjugates were formed comprising SOD and albumin or SOD alone. These conjugates retained 60-70% of enzymatic activity of constituent SOD. Plasma clearance of SOD activity following intravenous injection

of conjugates was greatly prolonged ($t_{1/2}$ up to 12 hours). SOD-homologous albumin and SOD-SOD conjugates injected intravenously had potent anti-inflammatory effects in rats. These effects may not necessarily be attributable to their SOD activity because an anti-inflammatory action was also seen with conjugates of albumin alone formed by the same method in absence of SOD.

Arachidonate metabolism, which leads to the production of oxylipids with potent pro-inflammatory properties, may be enhanced indirectly by oxy radical production. Arachidonate metabolism is most comprehensively inhibited by anti-inflammatory corticosteroids, but the use of these agents for therapy is limited by unacceptable unwanted effects. A drug carrier system comprising cortisol palmitate in liposomes, designed to enhance delivery of cortisol to phagocytic leucocytes, was found have 10-fold greater potency than a soluble cortisol preparation when given by intravenous injection.