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Salicylates, copper complexes, free radicals and arthritis

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I would like to suggest that salicylates and copper complexes with various ligands protect synovial fluid from degradation and leucocytes from premature death by biologically-generated hydroxyl radicals during the treatment of arthritis.

Quick (1974) has pointed out the efficacy of salicylates in the treatment of inflammatory arthritis. McCord (1974) has shown that superoxide radicals reacted with hydrogen peroxide to produce hydroxyl radicals which depolymerized purified hyaluronic acid and bovine synovial fluid. Since phagocytizing polymorphonuclear leucocytes present in the synovial fluid produce superoxide radicals with attendant generation of hydrogen peroxide and hydroxyl radicals, the above reaction was suggested as the *in vivo* mechanism of synovial fluid degradation in inflamed joints. Superoxide dismutase and catalase protected synovial fluid from degradation *in vitro*. In addition, mannitol, an effective hydroxyl radical scavenger, prevented the depolymerization of hyaluronic acid. These same reagents have been shown (Salin & McCord, 1975) to protect phagocytosing leucocytes from premature death and release of hydrolytic enzymes and chemotactic factors which play a role in perpetuating the inflammatory cycle. Fridovich (1975) has suggested that superoxide dismutase, injected into an inflammed area, might minimize the damage caused by superoxide anion secreted by the phagocytes.

Salicylate reacts very readily with hydroxyl radicals (Amplett, Adams & Michael, 1968). In fact, the *ortho*-hydroxy group of salicylate activates the molecule for reaction with hydroxyl radicals when compared with the reaction of hydroxyl radicals with benozate. It is suggested that salicylate acts as a scavenger for hydroxyl radicals generated from superoxide radical resulting from phagocytizing polymorphonuclear leucocytes in synovial fluid. Interestingly enough, cupric salicylate had a greater anti-oedemic effect than sodium or zinc salicylates when administered subcutaneously to rats (Rainsford & Whitehouse, 1976). Furthermore, Sorenson (1976) has demonstrated that cupric ion and copper complexes with a variety of ligands including amino acids and aspirin, administered subcutaneously to rats, were effective anti-inflammatory agents. In this regard, cupric ions and cupric amino acid chelates have been shown to catalyse the dismutation of superoxide anion, a reactant in the generation of hydroxyl radical (Brigelius, Spottl & others, 1974; Brigelius, Hartmann & others, 1975). In part, the mechanism of action of salicylates in the treatment of arthritis may be to protect the synovial fluid, leucocytes and other sensitive elements from attack by hydroxyl radicals. Also, the efficacy of cupric ion and copper complexes as anti-inflammatory agents may, in part, be due to dismutation of superoxide anion.

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