EFFECT OF NSAIDs ON THE ULTRASTRUCTURE OF ARTICULAR CARTILAGE

Thesis

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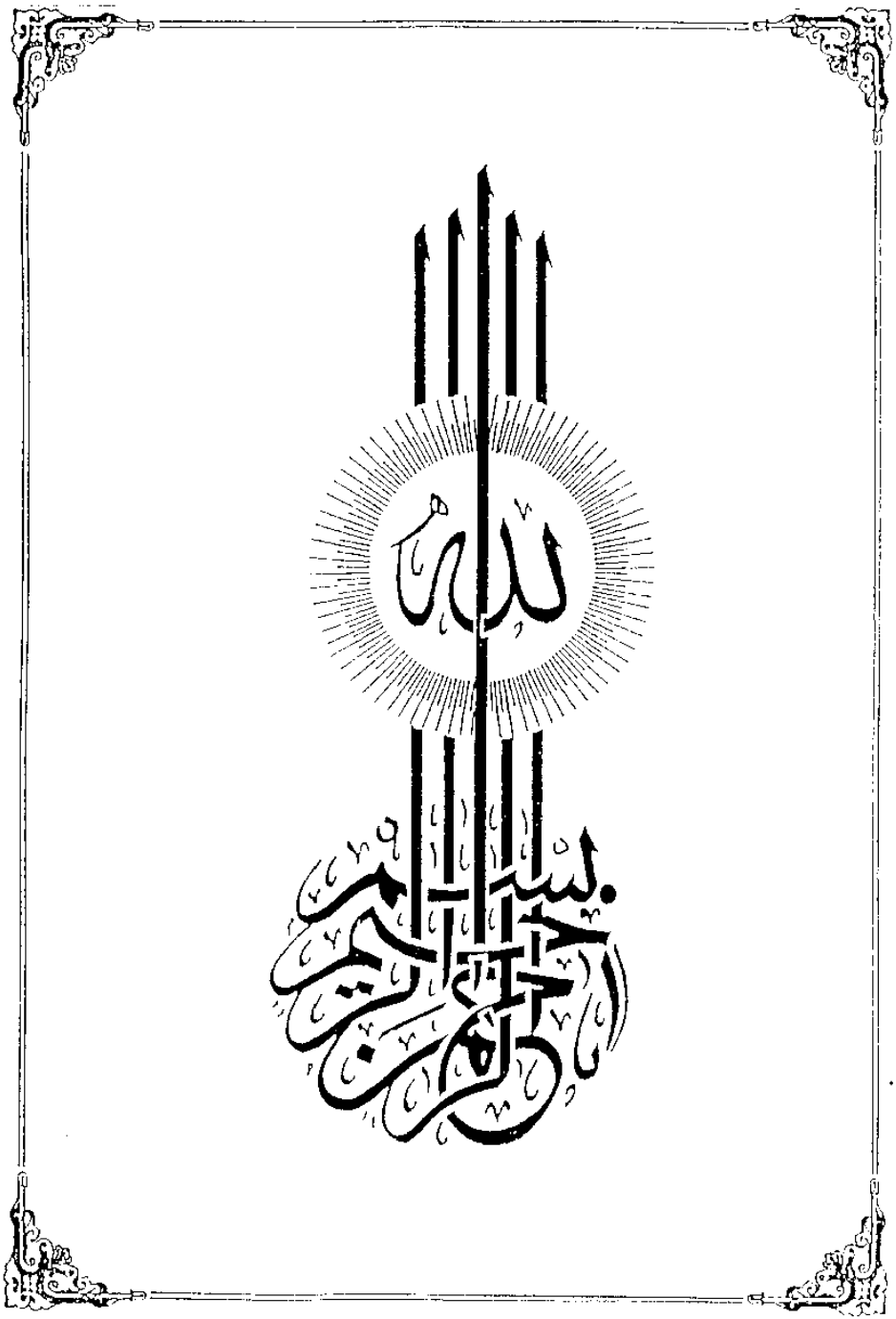
بسم الله الرحمن الرحيم

إقرأ بسم ربك الذى خلق ۞ خلق الإنسان من علق ۞
إقرأ وربك الأكرم ۞ الذى علم بالقلم ۞
علم الإنسان ما لم يعلم .

« صدق الله العظيم »

سورة العلق . الآيات (١-٥) الجزء (٣٠)



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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

One of the many challenges facing today's clinician is the treatment of rheumatic pain. The non steroidal anti-inflammatory drugs (NSAIDs) are one group of drugs which have been developed to relieve mild pain of diverse causes (non narcotic analgesic). Their effects on pain, swelling, heat, erythema, and loss of function begin promptly after their absorption into the blood and become fully evident within few weeks. Regarding their analgesics , antipyretic and anti prostaglandin effects, they are the most widely used drugs in the history of medicine.

According to Butler and co-workers (1983) the NSAIDs include aspirin and the non acetylated salicylate, phenylbutazone, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, tolmetin, sunlindac, meclofenate, deflunisal and piroxicam. They are used extensively in the management of rheumatoid arthritis (RA), osteoarthritis (OA), and allied disorders. While the useful role these agents may play in controlling the inflammation and pain associated with articular disease is well documented, the effect they may also have on joint connective tissue, particularly cartilage ,has received less attention.

Over the last twenty years the in vitro and in vivo studies have shown that many of the commonly used NSAIDs display marked inhibitory actions on the biosynthesis by chondrocytes of the principle components of the extra cellular matrix. This is in addition to its known adverse reactions on other body systems, such as gastrointestinal damage , which is now known to extend to some degree from the oesophagus to the rectum, although the acid contact areas of the stomach and duodenum are the most important; Renal syndromes, of which functional renal impairment is the most important; Respiratory effects, in particular acute bronchospasm in subjects with a history of aspirin sensitivity; Other uncommon serious reactions include hepatocellular damage, acute interstitial nephritis, agranulocytosis and aplastic anaemia, Stevens-Johnson syndrome and toxic epidermal necrolysis. These are unpredictable reactions which generally need not be considered before prescribing (Henry , 1988).

Tons of NSAIDs are used in the treatment of osteoarthritic disorders, the "target organ" is articular cartilage. It is therefor of great importance to determine the direct effect of such compounds on articular cartilage. It is essential that compounds used to treat joint degeneration do not impair the ability of chondrocyte to

ARTICULAR CARTILAGE

STRUCTURE and FUNCTIONAL ASPECTS

Because joint affections probably represent the single most common cause of disability seen by physicians, medical researchers should make every effort to become thoroughly familiar with all relevant aspects of joint structure and function. The most common joint problems encountered in medical practice involve the synovial joints which is the issue in this work.

The synovial joints comprise most of the body's articulations and are characterized by wide ranges of almost frictionless movement. Free movement between the bones that meet at a synovial joint is facilitated because the gliding surfaces are efficiently lubricated. Because the lubricant in such a joint is viscous and clear like the white of an egg, it is called synovial fluid, hence the term synovial joint. Furthermore, to minimize friction, the gliding surfaces are quite smooth and shiny because the articulating ends are capped with hyaline cartilage. This cartilage is not covered by a perichondrium. Hence the surfaces that glide over each other consist of naked uncalcified matrix of articular cartilage. At the boundary of the joint, there is a tough joint capsule that merges with the periosteum of the

bones meeting at the joint. The capsule is lined by a more delicate connective tissue layer called the synovial membrane that produces and resorbs synovial fluid (Cormeck, 1990).

Dissection studies have shown that each joint has a dual **nerve supply** (1) specific articular nerves that penetrate the capsule as independent branches of adjacent peripheral nerves, and (2) articular branches that arise from related muscle nerves. The definition of joint position and the detection of joint motion are monitored separately and by a combination of multiple inputs from different receptors in varied systems (Griff et al., 1973).

There is evidence that the nerve endings in muscle as well as in the joint capsule are involved in articular kinesthetic sensation (Cross and McCloskey, 1973).

As regards the **joint blood supply**, the synovial joint has a relatively rich blood supply. The arterial branches approaching a joint commonly supply three structures: one branch goes to the epiphysis, another to the joint capsule, and the third to the synovial membrane. Arteriovenous anastomoses are also present in joints, but their significance is uncertain (Liew and Dick, 1981).

Normal function of any joint requires that all its structures act in combination to allow smooth steady motion while still maintaining stability. The articular cartilage which is one of these structures is a specialized connective tissue. It is an aneural, a vascular tissue which covers the ends of long bones and measure less than 5mm in thickness in human joints. It dissipates mechanical stresses imposed during normal activities. Its surface characteristics are such that in conjunction with joint synovial fluid it provides an almost frictionless surface for articulation (Simon, 1970).

Articular cartilage is dense and white on gross inspection but tends to become somewhat yellow with age. It feels semisolid. Contrary to expectations. The surface is not smooth (Redler and Zimny, 1970).

Morphological, physiological, and pathological studies have confirmed that there are three mechanisms for nutrient transfer within cartilage matrix:-

[1] **Diffusion**, as the molecular weight of solutes needed for cellular metabolism is small enough to permit

adequate diffusion within the cartilage of mobilized healthy joint (Marondas, 1974).

[2] Intermittent compression of cartilage matrix serves as a pump mechanism for solute exchange in cartilage is a concept that has arisen from observations that joint interfere with normal movement of one articular surface upon its counter part lead to degenerative changes in cartilage. Exercise, in contrast, increases solute penetration into cartilage in experimental studies (McCutchen,1975).

[3] Active transport by chondrocytes as short cell processes are seen on all chondrocytes which is believed to play a role in pinocytotic function (Clement, 1989).

Regeneration in cartilage is generally poor. In the hyaline cartilage of joint surfaces small defects are made good by regeneration with larger injuries which damage the underlying vascular bone, a hematoma is formed which becomes vascularized and converted either into fibrous tissue or bone (Walter and Israel, 1987).

Organization of Articular Cartilage:

Articular cartilage is the unique structure of joints; it is highly differentiated and has physical properties that no other tissue or synthetic product of bioengineering laboratories can equal. Articular cartilage must provide a smooth, resilient surface for joint motion under conditions of intense pressure or high velocity, or both. At the same time, the cartilage must retain capacity for maintenance without morphologic change and, in the absence of any blood vessels, for transport of nutrients and removal of products of chondrocyte metabolism and matrix turnover. Even though endorsed with a capacity for maintenance, articular cartilage cannot effectively regenerate itself, and this imposes a limitation on the organism - a need to protect articular cartilage from destruction (Sledge, 1993).

Histologic and ultrastructural examination of the cartilage demonstrates a vast preponderance of extracellular matrix and only sparse cellularity (Stockwell and Meachim, 1973).

The articular cartilage is formed of three zones. The superficial, middle and deep zones. The superficial zone consists only 5 to 10% of the total thickness. As a rule, the chondrocytes and collagen fibers have the same

distribution in any zone. In other words, the arrangement of the cell nests in articular cartilage is determined by the predominant orientation of its collagen fibers (Salter, 1982). In the superficial layer the chondrocytes and the collagen fibers run parallel with the surface. Deeper down in the cartilage, the chondrocytes and collagen fibers are arranged longitudinally, perpendicular to the surface. The chondrocytes, in most parts, are longitudinally disposed in cell nests.

The proliferation that is responsible for generating such cell nests during growth of this cartilage is limited to the superficial zones near the articular surface. Further down the columns, the chondrocytes undergo hypertrophy. The deepest part of an articular cartilage is calcified and darkly stained. During postnatal growth, this part of the cartilage becomes progressively replaced by bone as the diaphysial side of an epiphyseal plate does. However, in this case, replacement is less regular. Compared with the calcified cartilage to which it is attached, the underlying bone tissue is somewhat lighter staining. Interlocking with the undersurface of the calcified cartilage. It constitutes a plate of subchondral bone that supports the articular cartilage. The superficial zones of the subchondral bone is

fairly compact, but some of the canals and soft tissue spaces remain rather wide (Cormack,1990).

Studies using the scanning electron microscope have demonstrated gentle undulations and irregular depression that appear to correspond to the location and shape of cells lying just beneath the surface. These depressions average 20 to 40 u in diameter (Clark, 1971). It is not known whether the depressions are present in vivo or whether they represents artifacts produced by desiccation and shrinkage during preparation for microscopy. Surface irregularity of some magnitude is essential for the full development of hypothesis of squeeze film lubrication which, during weight bearing, interstitial fluid from cartilage matrix would be trapped in surface depressions and prevent direct cartilage-cartilage contact (Chadially, 1976).

The articular cartilage like any connective tissue is composed of cells (chondrocytes) and extracellular matrix (proteoglycans, collagen and water up to 80% of the weight of the cartilage).

It is important to notice that the biomechanical aspects of the matrix are of particular importance at macroscopic levels of bones, joints, skin and at cellular