Leader

Synovial fluid phospholipase A₂s and inflammation

SUMMARY The activation of phospholipase A₂ is believed to have an important role in the inflammatory process owing to its induction of eicosanoids, platelet activating factor, and other mediators. Soluble phospholipase A₂ has been associated with exudates in different inflammatory conditions. In this review the general physiology and control of this enzyme and, in particular, the most recent findings on human synovial fluid phospholipase A₂s are discussed.

The phospholipases are a group of enzymes widely distributed throughout nature, whose generic name indicates their common property of catalysing the hydrolysis of phospholipids.¹ Figure 1 shows the classification of phospholipases based on their site of attack. The phospholipases A are classified according to their hydrolysis of the 1-acyl ester (phospholipase A₁) or the 2-acyl ester (phospholipase A₂). Phospholipase B hydrolyses both acyl groups, phospholipase C cleaves the glycerol phosphate bond, and phospholipase D removes the base group.¹ Phospholipase A₂ was the first of the phospholipases to be recognised over a century ago when Bokay found that phosphatidylcholine was degraded by a component of pancreatic juice²; which is now known to be the pancreatic phospholipase A₂. In mammalian cells phospholipase A₂ can be found as membrane associated and extracellular (soluble), thought to be released from lysosomal stores upon

Fig. 1 Classification of phospholipases according to site of hydrolysis. AA=arachidonic acid.

cell stimulation.³ Phospholipase A₂ has received much attention because of its putative involvement in the signal transduction process that enables leucocytes to effect a repertoire of responses crucial to the development of inflammation.¹ Therefore it may be implicated in tissue injury associated with various diseases, such as rheumatoid arthritis,⁴⁻⁷ psoriasis,⁸ and adult respiratory distress syndrome.⁹ Under normal conditions the cellular content of free arachidonic acid is low. It is stored within the cell membrane in sterified form almost exclusively at the 2 position of phospholipids. The liberation of arachidonic acid during the process of cell activation is widely believed to be the rate controlling step in the production of biologically potent eicosanoids by inflammatory cells.¹⁰ Free arachidonic acid is rapidly metabolised by cyclooxygenase to form prostaglandins and thromboxanes or by lipoxygenase to form hydroxy fatty acids (hydroxyeicosatetraenoic acids) and leucotrienes.¹⁰⁻¹² Prostaglandin E₂ is a potent vasodilator and hyperalgesic agent that may cause erythema, oedema, and pain.¹³ It has also been implicated in bone resorption in rheumatoid arthritis.¹⁴ Leucotriene B₄, 12-hydroxyeicosatetraenoic acid, and 5-hydroxyeicosatetraenoic acid act as chemotactic agents for neutrophils and eosinophils and may contribute to the cellular migration into the rheumatic joint.^{15 16} Phospholipase A₂ itself may also have a role in inflammation; in rabbits purified exogenous phospholipase A₂ induces profound inflammatory lesions following intratracheal,¹⁷ intradermal,¹⁸ or intra-articular injection.¹⁹

Synovial fluid aspirated from inflamed arthritic joints has been found to contain a very high concentration of phospholipase A₂. Vadas *et al* characterised an extracellular phospholipase A₂ from rheumatoid synovial fluid.⁵ This phospholipase

A₂ was a calcium requiring protein of molecular weight 11 000 with a neutral pH optimum. More recently, Gonzalez-Buritica and coworkers presented evidence for the presence of at least two phospholipase A₂s in rheumatoid synovial fluid, one soluble or extracellular, present in the cell free fraction of synovial fluid and another, cell associated in mononuclear cells and neutrophils from synovial fluid.²⁰ Further studies by the same group, based on different substrate specificity, showed that soluble phospholipase A₂ from rheumatoid synovial fluid is quite different from the phospholipase A₂ reported in synovial fluid from patients with osteoarthritis.²¹ They suggested that a proinflammatory phospholipase A₂ must be able to release arachidonic acid rather than other fatty acids from the labelled substrate.²² Another known mediator of inflammation, interleukin 1, which has been identified in rheumatoid synovial fluid, has the unique ability among interleukins to increase phospholipase A₂ activity in chondrocytes and synovial cells.²³⁻²⁵ Therefore phospholipase A₂ may act as a mediator of the inflammatory actions of interleukin 1. It has been reported that rheumatoid arthritis peripheral blood leucocytes contain more phospholipase A₂ than those from healthy controls,⁶ and that serum concentrations of phospholipase A₂ correlate with disease activity.²⁶ It has not been shown, however, whether the leucocyte related phospholipase A₂ belongs to the membrane bound or to the soluble variety.

The anti-inflammatory efficacy of certain steroidal and non-steroidal drugs may partially reside in their ability to inactivate extracellular phospholipase A₂. The anti-inflammatory effect of corticosteroids has been explained by the induction of lipocortin synthesis, and lipocortin has been claimed to be a specific, non-competitive inhibitor of phospholipase A₂.²⁷⁻²⁸ It has recently been reported that some patients with systemic lupus erythematosus and rheumatoid arthritis have antibodies against lipocortin.²⁷⁻²⁹ The possibility that inhibition of lipocortin leads to an increase of phospholipase A₂ activity in arthritic patients should thus be considered. There is no conclusive evidence that aspirin and related non-steroidal anti-inflammatory drugs have effects on phospholipase A₂, though indomethacin has been reported to inhibit phospholipase A₂ through inhibition of calcium transport.³⁰ On the other hand, hydroxychloroquine and mepracrine, two antimalarials used with some success in the treatment of systemic lupus erythematosus and rheumatoid arthritis, among other actions, inhibit phospholipase A₂ activity and perhaps that explains part of their anti-inflammatory actions.³¹ In the search for the physiological control of phospholipase

A₂ two new developments seem to have relevance—namely, the calpactins or calcium dependent phospholipid and actin binding protein and, secondly, the phospholipase A₂ activating protein. The calpactins inhibit phospholipase A₂ by sequestering the phospholipid substrate,³² whereas the phospholipase A₂ activating protein activates phospholipase A₂ through an unknown mechanism.³³ Free arachidonic acid also inhibits phospholipase A₂, acting as a negative feedback.³⁴

Our knowledge of the mechanisms of inflammation and the treatment of inflammatory diseases is likely to increase substantially in the next few years. New insights into the biochemistry and the pharmacological modulation of the process should open new avenues and a promising future in the prevention and treatment of the so called autoimmune diseases.

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