

The mechanism of action of anti-inflammatory drugs

Conference Chairman, Professor Sir John VANE, FRS, Honorary President of the William Harvey Research Foundation, London, UK, outlined how understanding of the mechanism of action of non-steroidal anti-inflammatory drugs evolved.

'Clinically relevant anti-inflammatory activity of the NSAIDs is reached with 80% or more inhibition of COX-2; the different adverse effect profiles of NSAIDs are determined by the extent to which they inhibit COX-1 at these doses.'

Non-steroidal anti-inflammatory drugs (NSAIDs) have long been the most widely used treatments for pain, fever and chronic inflammatory disease. For example, in 1500 BC the Ebers papyrus recommended the dried leaves of myrtle to expel rheumatic pain of the womb and Hippocrates recorded the use of willow bark to relieve pain associated with childbirth in 400 BC. Both preparations contain salicylate. The modern NSAIDs era began with the introduction of aspirin (acetylsalicylic acid) in 1899. It became the mainstay of treatment for inflammatory disorders and it was not until the 1960s that new NSAIDs offering a superior safety profile became available. Ibuprofen, introduced in the United Kingdom in 1969, was the first of the propionic acids.

At the time, none of the proposals to explain the mechanism of action of NSAIDs gave a full explanation of the actions of this group of drugs. The newly discovered prostaglandins were found to cause fever and hyperalgesia, to promote inflammation, and to inhibit gastric acid secretion and increase renal blood flow. In 1971, Vane realised that aspirin blocked all these properties and that this action could be explained by inhibition of the enzyme cyclo-oxygenase (COX). His unifying hypothesis of the therapeutic and adverse effects of NSAIDs established the role of prostaglandins, and prostaglandin E₂ in particular, as one of several mediators of inflammatory disease.

Vane demonstrated that the NSAIDs caused dose-dependent inhibition of COX. However, it remained unclear why they were similarly effective in the treatment of inflammatory disease but differed in the degree to which they caused adverse gastrointestinal effects. In 1991, Dr Daniel L Simmons identified COX-2, an enzyme with 60% homology with COX-1 but encoded by a different gene. COX-1 was then considered to be a constitutive enzyme involved in protecting the gastric mucosa, maintaining renal blood flow and promoting platelet aggregation. COX-2 is induced by inflammatory stimuli and cytokines released by migratory and other cells and by shear stress on vascular endothelial cells.

Clinically relevant anti-inflammatory activity of the NSAIDs is reached with 80% or more inhibition of COX-2; the different adverse effect profiles of NSAIDs are determined by the extent to which they inhibit COX-1 at these doses. However, the risk-benefit ratio of NSAIDs is not determined solely by their effects on the gastrointestinal tract. Inhibition of COX-2 is also associated with a reduction in the synthesis of prostaglandins important for the preservation of renal function. Interestingly, in the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial, rofecoxib was associated with a 4-5-fold increased risk of myocardial infarction compared with the non-selective COX inhibitor naproxen. There is no adequate explanation for this increased risk.

More positively, the discovery that COX-2 is over-expressed in colorectal and prostate cancers, and appears to have a role in the pathogenesis of Alzheimer's disease, suggests that the future roles of NSAIDs may broaden to include the prophylaxis of these conditions.

'The future roles of NSAIDs may broaden to include the prophylaxis of colorectal and prostate cancers and Alzheimer's disease.'