Role of Prostaglandins and Leukotrienes in Osteoarthritis. The good, the bad and the ugly

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Pharmacological interventions in osteoarthritis (OA) have primarily focused on treating pain using mainly NSAIDs, analgesics and more recently specific cyclooxygenase-2 (COX-2) inhibitors. The rationale was to inhibit COX, the key enzymes that metabolize arachidonic acid (AA) into prostaglandins (PG). It is well known that the PG and more specifically PGE_2 play a role in exacerbating joint inflammation and that many of the effects of pro-inflammatory cytokines are associated with PGE_2 production.

Although the possible contribution of PGE2 in the pathophysiology of OA has been explored extensively, the role of other by-products of AA metabolism has been relatively overlooked. Published findings on the effects of eicosanoid overproduction on the metabolism of joint tissues reveal a variety of both inflammatory and anti-inflammatory activities. The *in vivo* consequence of COX-2 over-expression in OA tissues may lead to the production of a variety of prostanoids, of which the net effect on the disease process may be difficult to assess *in vitro* (1). However, because of the widespread and prolonged use of COX inhibitors in clinical practice, this is an area that merits further investigation including the assessment of structural outcomes in the clinic.

COX converts AA into a series of final active products with different expressions in different cell types. Two COX isoforms, COX-1 and COX-2, have been identified. They are encoded by two different genes (2) and while COX-1 is expressed in mammalian cells particularly in endothelium, platelets, and kidneys under physiological conditions, COX-2 is inducible under pathological conditions by inflammatory stimulation (3, 4). It has, therefore, been hypothesized that constitutive COX-1 is involved in homeostatic processes, whereas COX-2 is the isoform that plays a major role in the inflammatory process and the related pain. Based on this assumption, selective COX-2 inhibitors were developed. Nevertheless, there is accumulating evidence that COX-1 and COX-2 have overlapping actions and that both isoforms are involved in homeostasis processes, just as both are modulators of inflammatory reactions.

With regard to joint tissue catabolic effects produced by eicosanoids, it is well known that the elevation of PGE2 via COX-2 plays a role in exacerbating joint inflammation. PGE_2 acts on the synovial membrane lining cells, macrophages, chondrocytes and bone resorption. It is also suggested that PGE_2 affects cartilage remodeling directly or functions indirectly as an autocrine regulatory factor. Moreover, in addition to exerting inflammatory effects on its own, PGE_2 can also potentiate the effects of other mediators of inflammation.

Other interesting eicosanoids found in articular tissues are the leukotrienes (LTs). LTs are also produced from the metabolism of AA but by the enzyme 5-lipoxygenase (5-LO) (Figure 1). LTA_4 is the first to be synthesized and it is then processed to LTB_4 or LTC_4, and subsequently to LTD_4 and LTE_4 (5), which are potent chemotactic and inflammatory factors. It has been shown that LTs themselves play a major role in the development and persistence of the inflammatory process. The level of LTB_4 was found to be elevated in the synovial fluid and membrane from patients with OA (6, 7). Recent studies from our laboratory showed that LTB_4 increased the production of the pro-inflammatory cytokines, IL-1β and TNF-α, in a dose-dependent manner in human OA synovial membrane (8).

It has been hypothesized that long-term COX inhibition likely results in a shunt of AA metabolism towards an excess production of LTs. Our recent data revealed that human OA osteoblasts from subchondral bone could be discriminated into two populations in regard to PGE_2 and LTB_4 levels. Indeed, one set of patients

demonstrated a low level of PGE_2 and a high level LTB4 while the opposite was found in another set (9). Moreover, we also demonstrated, *in vitro*, in these diseased cells that long-term inhibition with a specific COX-2 inhibitor up-regulated LTB_4. This was also true when human OA synovial membranes were studied (unpublished observations). Based on the shunt concept, it has been hypothesized that blocking both PGE_2 and LT production could have synergistic effects in achieving optimal anti-catabolic activities.

Taking into account the roles of LTs, against which neither selective nor non-selective NSAIDs are effective in the inflammatory process, it has been postulated that dual inhibition of COX and 5-LO pathways could produce a wider spectrum of anti-inflammatory effects. In the past few decades, several compounds were developed to block both COX and 5-LO, but their use was abandoned due to liver toxicity (10). However, liver toxicity was not related to the pharmacological mode of action of inhibition of COX and 5-LO but rather to a common molecular feature of these substances. All of these compounds are redox active and all have a di-tert-butyl moiety or are hydroxamid acids, which appear to be responsible for this side effect. Recently, a non-antioxidant compound, derivative of pyrrolizine, and an AA substrate analog has been described and named licofelone (formerly known as ML-3000). Docking calculations demonstrate that licofelone is a substrate analog of AA at the active site of 5-LO and acts as a dual COX/5-LO inhibitor. Because of this property, this compound did not show hepatotoxicity in either pre-clinical or clinical studies.

Our data showed that the effects of licofelone on experimentally induced OA cartilage lesions studied in a dog model (OA was induced by anterior cruciate ligament section), compared with placebo significantly reduced the severity of erosions and histological damage (11, 12). This appears to occur through the inhibitory effect of licofelone on the production of collagenase-1 in cartilage, IL-1β in synovial membrane, LTB_4 in synovium, and PGE_2 in synovial fluid. Licofelone was also shown in this model to be, *in vivo*, an effective treatment for reducing the level of chondrocyte death (12).

Another group of lipid mediators formed during AA metabolism are the lipoxins (lipoxygenase interaction products, LXs). They are considered stop-signal mediators, which possess anti-inflammatory effects. The most common LXs are the LXA_4 and LXB_4, and two others, 15-epi-LXA_4 and 15-epi-LXB_4, are formed following the administration of aspirin. Interestingly, 5-LO blockage does not impair the synthesis of LXs, as they are synthesized not only via the 5-LO pathway, but also by the action of two other enzymes, 12-LO and 15-LO (13, 14), and selective inhibition of 5-LO does not block the 12-LO and 15-LO pathways.

In the context of non-catabolic effects produced by eicosanoids on articular cells, it was recently shown that some PG are ligands to a group of nuclear transcription factors, the peroxisome proliferator-activated receptors (PPAR), which act as anti-inflammatory agents. One natural PPAR ligand is a PG derived from the activity of COX — the PGJ_2 (Figure 2). To date three different PPAR have been identified and cloned: PPARα, β, and γ. PPARγ appears to be the key factor involved as an anti-inflammatory agent. PPAR were first shown to play a critical role in lipid metabolism and cellular differentiation. Although the principal site of PPAR expression is the adipose tissue and liver cells, PPAR have been found expressed in other cells type. Recently, our laboratory showed the presence and activity of PPAR in human chondrocytes and synovial fibroblasts (15, 16). Very briefly, our results showed that PPARγ is expressed, produced and active upon stimulation in these human cells. The PPARγ natural ligand, 15d-PGJ_2, prevented the pro-inflammatory cytokine-induced production of catabolic factors (Figure 3) including nitric oxide, collagenase-3 (MMP-13), and the activity of the transcription factors NF-kB and AP-1 on chondrocytes and synovial fibroblasts. In view of the critical role of pro-inflammatory cytokines in arthritic diseases, our data strongly points to the fact that the PPARγ system may represent a therapeutic target for the treatment of these pathologies. A PPARγ ligand directed to arresting the pro-inflammatory effects of cytokines would be of immense value in the management of this debilitating disease.

In summary, the pharmacological properties (anti-inflammatory) of classic NSAIDs, aspirin-like products and selective COX-2 inhibitors which act via inhibition of COX activity, and the conversion of AA into biologically active PGE_2 have been well established. However, long-term COX inhibition likely shunts AA metabolism towards an excess production of LTs. The role of LTB_4 in the inflammatory process occurring during OA has been documented. Hence, the use of an inhibitor that will simultaneously inhibit COX and 5-LO could enhance their individual anti-inflammatory effects and reduce the undesirable side-effects associated with NSAIDs. Furthermore, eicosanoids act not only as catabolic mediators but some have also demonstrated anti-inflammatory effects. Based on data on two AA derivatives, LXs and PGJ_2, it is reasonable to presume that enhancing their production can counteract some of the inflammatory effects of other eicosanoids.

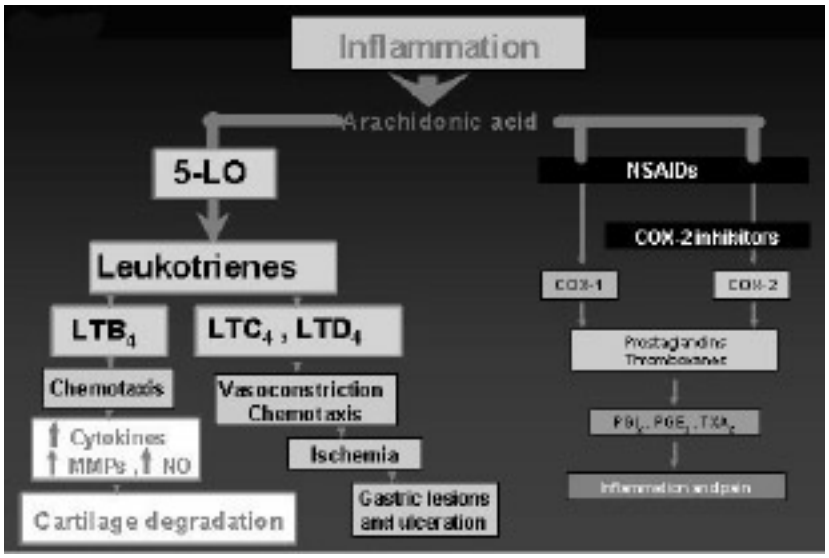

Figure 1.

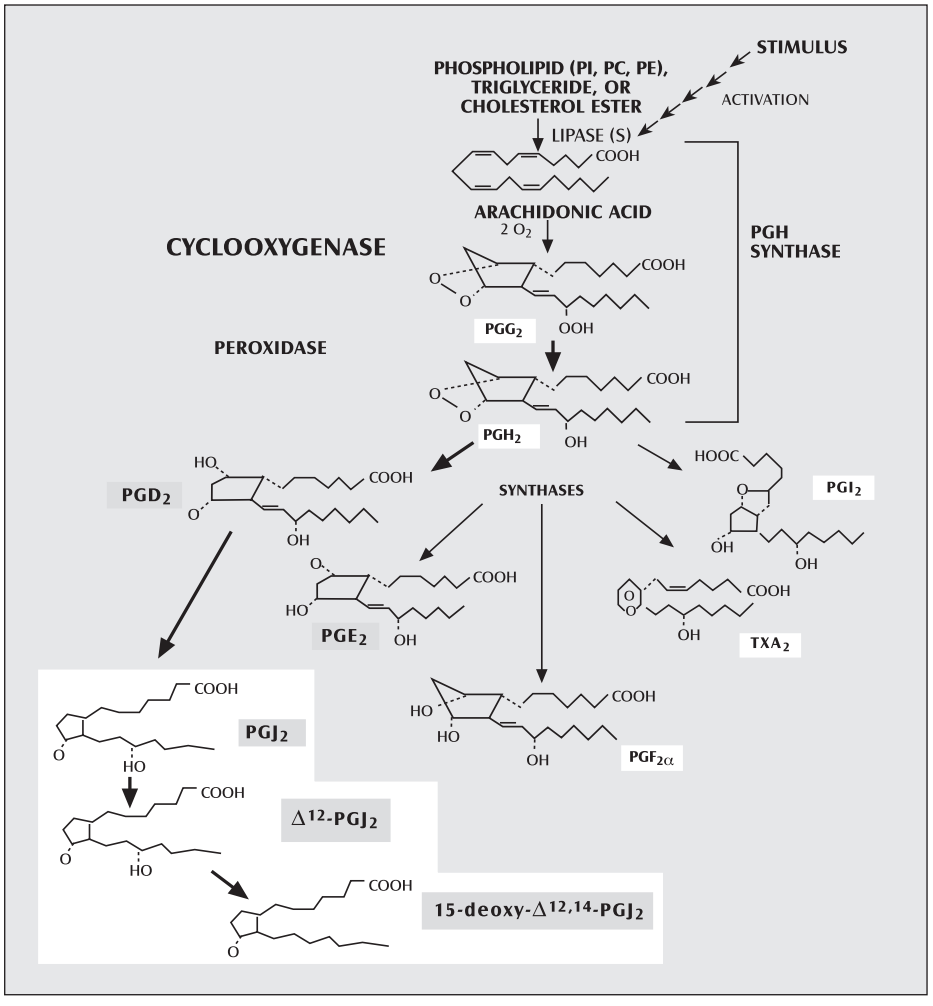

Figure 2.

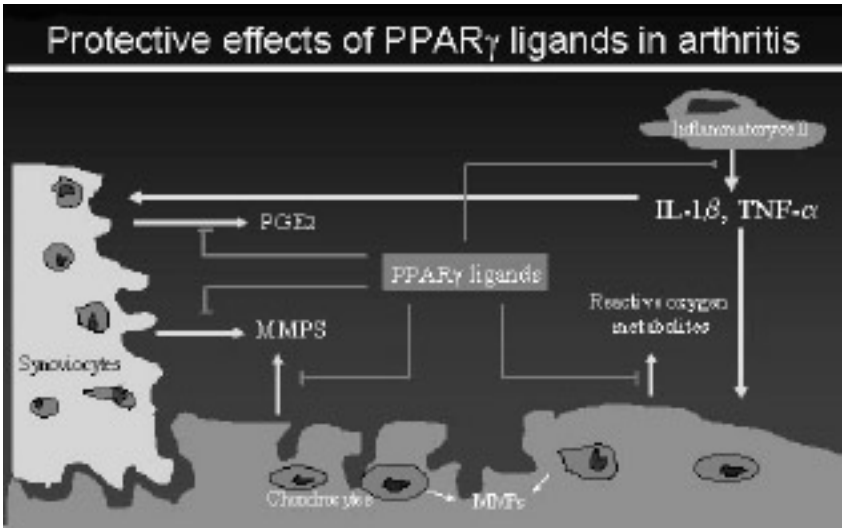

Figure 3.

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