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BOOK REVIEW

COX-2 Inhibitors

(Pairet, M., and van Ryn, J., eds., 2004, in *Milestones in Drug Therapy*, Parnham, M. J., and Bruinvels, J., eds., Birkhauser Verlag, Basel-Boston-Berlin)

The key enzymes of arachidonic acid metabolism are cyclooxygenase (COX) and lipoxygenase (LOX). They catalyze the production of eicosanoid lipid products playing an important role in inflammatory responses. The COX pathway leads to prostanoids (prostaglandins, prostacyclin, and thromboxane), and the LOX pathway leads to leukotrienes. COX enzyme exists in two forms, COX-1 (constitutive) and COX-2 (inducible). Increased expression of COX-2 has been demonstrated in inflamed tissues and in carcinogenesis. Non-selective inhibition of COX-1 and COX-2 by established nonsteroidal anti-inflammatory drugs (NSAIDs) is regarded as the reason for the inevitable side-effect of gastrotoxicity. The establishment of the existence of the COX-2 isoform and selective COX-2 inhibitors has provided for refined treatment of inflammatory conditions and pain, and the issue of the book *COX-2 Inhibitors* reflects the importance of this field of research for pharmacology and medicine.

The first chapter (R. M. Botting and J. H. Botting) of the book gives introduction to the history of COX and the discovery of COX-2. The famous COX inhibitor aspirin (acetylsalicylate) was introduced into medicine over a hundred years ago, and for over 3000 years herbal medicines have been used with salicylate as the active constituent. In 1938, endoscopic studies demonstrated unequivocally that aspirin caused erosions and ulcers in the stomach. Aspirin inhibits the synthesis of prostaglandins (PGs) by both forms of COX. PGs are known to be pyrogenic and hyperalgesic and present at inflammatory foci. Recently it has been accepted that the COX-2 isoform is responsible for the synthesis of PGs at pathological foci and COX-1 for the synthesis of the beneficial, "housekeeping" PGs. The active sites of COX-1 and COX-2 are similar, of crucial significance being the difference in positions 523 and 513, which are sufficient to construct selective inhibitors of COX-2. Drugs specifically designed to inhibit COX-2, celecoxib and rofecoxib, were shown to be effective analgesics and produced minimal gastrotoxicity. There is less clinical experience with other COX-2 inhibitors.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used agents in the treatment of pain and inflammation. The first NSAID, aspirin, continues to be popular. The global production of aspirin is approximately 50,000 tons annually. The pharmacological effect of NSAIDs arises from the inhibition of the rate-limiting step in arachidonic acid cascade involving arachidonic acid conversion to prostaglandin H2, the common precursor to prostaglandins and thromboxane. For screening COX inhibitors and examination of their selectivity, the COX-2/COX-1 activity ratio is used. COX-2 is one of the most attractive and highly pursued targets in the history of the pharmaceutical industry. The clinical and commercial successes of celecoxib and rofecoxib validate the "COX-2 hypothesis" and guarantee that additional candidates will be advanced to the clinic. The structural diversity of selective COX-2 inhibitors is outlined in chapter 2 (L. J. Marnett and A. S. Kalgutkar). Research within diaryl-heterocyclic compounds resulted in approval and marketing of well-known celecoxib and rofecoxib. Alkylsulfonanilide derivatives such as nimesulide and flosulide have demonstrated COX-2 selectivity and anti-inflammatory properties. Modifying nonselective NSAIDs into selective COX-2 inhibitors is an interesting strategy. Certain di-*tret*-butylphenolic analogs were recently disclosed as a novel class of potent and selective COX-2 inhibitors. In addition to inhibiting COX-2, these compounds also possess 5-lipoxygenase inhibitory properties.

The molecular and biological basis for COX-2 selectivity is discussed in detail in chapter 3 (G. Trummlitz, J. van Ryn, and T. D. Warner). Before the development of the three-dimensional structure of COX, it was difficult to understand why very chemically diverse inhibitors acted via similar mechanism for this same enzyme. Molecular modeling approaches allowed visualizing the recognition process of substrates and inhibitors by COX isoenzymes. Aspirin is the only COX inhibitor that covalently modifies the enzyme. COX-1 and COX-2 are membrane bound enzymes with similar structure and catalytic activity. The mature COX-1 and COX-2 proteins contain 576 amino acids and 587 amino acids, respectively. The knowledge of COX-2 selectivity is based on X-ray structure analysis, assay of binding of COX mutants, enzyme kinetics, and molecular modeling of COX-2 inhibitors.

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The clinical relevance of COX-2 inhibitors depends on their pharmacology and toxicology, which is discussed in the next chapter (K. D. Rainsford). In this chapter, one finds a detailed analysis of the chemical transformation in animals and humans of a list of COX-2 inhibitors (etodolac, meloxicam, nimesulide, and coxibs—celecoxib, valdecoxib, parecoxib, rofecoxib, etoricoxib, lumiracoxib), as well as their pharmacological activities, basic (analgesic, anti-inflammatory, and antipyretic) and side-effects (gastrointestinal irritancy, renal syndrome, and hepatotoxicity). A review of various COX-2 selective inhibitors has revealed that there are important pharmacokinetic and pharmacodynamic differences among these drugs. The eventual safety and clinical significance of the known and newer COX-2 selective inhibitors has yet to be evaluated.

In the next chapter, F. Degner reviewed efficacy and gastrointestinal safety of selective COX-2 inhibitors. NSAIDs are among the most commonly prescribed drugs in the world. Their use is mainly limited by adverse side-effects. The efficacy of selective COX-2 inhibitors has been proved in the treatment of rheumatoid arthritis, osteoarthritis, and other rheumatological conditions. In the absence of evidence of significant differences in anti-inflammatory efficacy between the COX-2 selective drugs and standard NSAIDs, the avoidance of serious adverse effects, particularly on the gastrointestinal tract, becomes the most relevant factor when considering the use of COX-2 inhibitors. The role of COX-2 in ulcers and ulcer healing is described in the next chapter by J. van Ryn and M. Pairet.

The COX products, thromboxane and prostacyclin, play an important role in vascular homeostasis. The role of COX-2 in the cardiovascular system is outlined by R. Nayak and B. F. McAdam. Traditional NSAIDs do not discriminate between the COX isoforms and concomitantly suppress the formation of thromboxane and prostacyclin. Suppression of vascular prostacyclin by selective COX-2 inhibitors without coincident inhibition of platelet COX-1-dependent thromboxane formation may result in cardiovascular complications. There may be thrombotic risk.

The value of selective COX-2 inhibitors in terms of renal safety is reviewed by D. O. Stichtenoth. Risk factors for renal side-effects of NSAIDs, like edema and hypertensions, have been documented also for selective COX-2 inhibitors of the first generation, celecoxib and rofecoxib. Clinical experience with the renal safety of the second generation of COX-2 inhibitors (valdecoxib, parecoxib) is very limited.

The chapter written by R. S. Peebles, Jr., and K. Hashimoto outlines data regarding effects of COX-2 inhibitors on lung. To date, probably the greatest surprise in this field is the therapeutic benefit in the treatment of human lung cancer. Sepsis induces pulmonary inflammation with augmented production of COX products. COX-2 inhibition has profound effects on LPS-induced animal model sepsis. Pulmonary fibrosis is accompanied by reduced prostaglandin E2 production. Investigations *in vitro* strongly suggest that COX-2 is a critical regulator of this disease, but there have been no reports examining COX-2 specific inhibitors in models of pulmonary fibrosis. Though COX-2 inhibitor therapy of lung is just in its infancy, the ability of selective COX-2 inhibitors to reduce human lung cancer adds to the motivation to continued study in this field.

Prostaglandins play a key role in human reproduction. A. R. Mohan and P. R. Bennett have summarized the implication of COX-2 inhibitors for the treatment of various pathologies in reproductive function.

The last chapter added more data on COX-2 in cancer. Higher COX-2 levels were found in gastric and lung adenocarcinoma. K. Saukkonen with coauthors has analyzed many cases of adenocarcinoma but failed to give a universal protocol on COX-2 correction for different types of adenocarcinoma. Elevated COX-2 level is often associated with tumor size over 2 cm and lymph metastasis and thus can be a marker for poor prognosis in certain types of adenocarcinoma. The mechanism by which COX-2 is upregulated in human cancer is largely unknown, and detailed investigations should help to determine the mechanisms of COX-2 overexpression and the discovery of its role in tumor formation.

An advantage of this book is its detailed analysis of COX-2 inhibitors. The book will be interesting and useful for researchers in biochemistry, molecular biology, and pharmacology.

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