

Summary

R. M. Botting and J. H. Botting

The discovery of COX-2

The manifest efficacy of herbal preparations of salicylate-containing plants, and of aspirin and other synthetic analogues (NSAIDs) resulted in their widespread use. It soon became apparent that these antipyretic, analgesic and anti-inflammatory agents also shared common side actions, primarily gastrotoxicity. The establishment of prevention of synthesis of prostaglandins, through inhibition of cyclooxygenase (COX), as the mode of action of NSAIDs, implied that the common toxic actions of these drugs could not be divorced from their therapeutic effects. However, clinical experience indicated that with some NSAIDs, gastrotoxic actions were less severe at effective anti-inflammatory doses.

The demonstration that the beneficial action of NSAIDs was due to inhibition of an inducible COX, and the subsequent discovery that the inducible COX was a structurally distinct protein (COX-2) formed by a separate gene, paved the way for the synthesis of newer, less toxic NSAIDs that selectively inhibited COX-2, rather than the constitutive, housekeeping enzyme COX-1. Such COX-2-selective drugs manifest reduced toxic effects and are at present under clinical evaluation for inflammatory conditions and for other indications such as cancer, Alzheimer's disease and premature labour.

Key Words: Cyclooxygenase, prostaglandins, analgesia, antipyresis, aspirin, non-steroid anti-inflammatory drugs, gastrotoxicity.

Summary

Lawrence J. Marnett and Amit S. Kalgutkar

Structural Diversity of Selective Cyclooxygenase-2 (COX-2) Inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective pain relievers, but they are also associated with a high incidence of gastrointestinal ulcerogenicity. Both the beneficial and adverse effects of NSAIDs result from inhibition of the cyclooxygenase (COX) enzymes. Recognition of the two distinct COX isozymes prompted development of anti-inflammatory agents that selectively inhibit the inducible COX-2 enzyme, thus providing pain relief and reducing inflammation while sparing the constitutively expressed COX-1 enzyme. The COX-2 hypothesis has been validated in animal models of inflammation and in human clinical trials by inhibitors such as celecoxib, rofecoxib, valdecoxib, etoricoxib and lumiracoxib that are selective COX-2 inhibitors. This review highlights structure-activity relationship (SAR) studies on key structural classes of selective COX-2 inhibitors and novel candidate structures that have recently emerged due to a better understanding of the active site differences between the two isozymes with a special emphasis on the modification of the well-established NSAID scaffold.

Key Words: Inflammation, COX-2 inhibitor, NSAID, aspirin, indomethacin, diclofenac, diarylheterocycle, aspirin, celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib.

Summary

Guenter Trummlitz, Joanne van Ryn and Timothy D. Warner

The molecular and biological basis for COX-2 selectivity

X-ray structure data, results from site-directed mutagenesis experiments and molecular modelling approaches have been successfully used to gain insight into molecular mechanisms

of selective COX-2 inhibition. This has allowed key differences in structure to be studied that may confer differential sensitivity to inhibitors. As a consequence of different binding interactions, the kinetics of COX inhibition is also an important consideration in COX-2 selectivity.

Numerous *in vitro* assays have been developed, from recombinant enzyme assays important for screening programs to *in vitro* whole blood assays to predict potential clinical selectivity. Clinical pharmacological studies using the whole blood assay *ex vivo*, have also been important for helping to predict the selectivity of these compounds in the clinic.

Key Words: COX-2 inhibitor, cyclooxygenase, molecular modelling, NSAID, COX-2 selectivity, whole blood assay, COX-2 structure, X-ray, mutagenesis, enzyme kinetics.

Summary

Kim Rainsford

Pharmacology and toxicology of COX-2 inhibitors

The pharmacology and toxicology of established and newly-available COX-2 selective drugs has been considered in relation to their pharmacokinetics. This has highlighted important developments and with some drugs significant safety limitations that would not have been predicted in early stage developments of these drugs.

Key Words: Meloxicam, nimesulide, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, gastro-intestinal ulcers, renal adverse reactions, pharmacokinetics.

Summary

Frank Degner

Efficacy and gastrointestinal safety of selective COX-2 inhibitors

NSAIDs are among the most commonly prescribed drugs in the world and are used frequently as anti-inflammatory and analgesic agents in the treatment of musculoskeletal conditions. Their use is mainly limited by adverse effects, which are more frequently seen with NSAIDs than with any other prescription drug. The arrival of selective COX-2 inhibitors heralds one of the biggest changes in rheumatological practice. It appears that the COX-2 selective drugs have a similar anti-inflammatory efficacy as standard NSAIDs. For the most part the evidence suggests that COX-2 selective agents are less likely to produce symptomatic gastrointestinal tract adverse events. However, our enthusiasm needs to be tempered by the reality that these drugs are still relatively new, and that possible advantages and disadvantages await further evaluation.

Key Words: NSAID, efficacy, rheumatoid arthritis, selective COX-2 inhibitors, safety, osteoarthritis, meloxicam, ankylosing spondylitis, celecoxib, rofecoxib, gastrointestinal complications.

Summary

Joanne van Ryn and Michel Pairat

Ulcers and ulcers healing: Role of COX-2 inhibitors

Clinical evidence now indicates that cyclooxygenase (COX)-2 selective inhibitors have reduced gastrointestinal (GI) complications as compared to nonselective inhibitors,

presumably by sparing COX-1 inhibition and thereby maintaining GI mucosal integrity. Thus, the advantages of COX-2 selective agents are that the anti-inflammatory activity is maintained, while the amount of COX-1 inhibition is reduced. The implications of these concepts in both GI ulceration and in ulcer healing in an experimental setting will be discussed. It has been demonstrated recently that in addition to COX-1, COX-2 also has a role in maintaining GI integrity and that the role of each is not as clear cut as first imagined. In addition, the implications of COX-2 inhibition and ulcer healing are also discussed.

Key Words: Gastric injury, gastric mucosa, tropical injury, bicarbonate barrier, enteric-coated aspirin, mucosal barrier, restitution, blood supply, mucosal blood flow, neutrophil adhesion, tumor necrosis factor α (TNF α), leukotriene, nitric oxide, *Helicobacter pylori*; COX-1, mucosal integrity: COX-2; mucosal integrity: SC-560, celecoxib, rofecoxib, acid challenge, gastric blood flow, afferent nerve, gastric injury, meloxicam, piroxicam, interleukin (IL)-1 α , interleukin (IL)-1 β , afferent innervation, acid-challenged stomach, adjuvant arthritis, mucosal defense, ulcer, ulcer healing, granulation tissue, angiogenesis, epithelial cells, restitution, basic fibroblast growth factor (bFGF), cell proliferation, indomethacin, NS-398, vascular endothelial growth factor (VEGF), endothelial ERK-2, platelet, endostatin, flurbiprofen, nitric oxide, proton pump inhibitor.

Summary

Rahul Nayak and Brendan F. McAdam
COX-2 and the cardiovascular system

The discovery of the “inducible” isoform of cyclooxygenase (COX-2) as a mediator of inflammatory pathways has not only led to the development of a new class of anti-inflammatory agents but has also afforded new and sometimes unexpected insights into the biology of COX expression. Recent results on vascular events of the Vioxx[®] in the Gastrointestinal Outcomes Trial (VIGOR) have cast a cloud of controversy over their use in certain populations who are at increased cardiovascular risk. Moreover, the finding that these agents suppress the formation of prostacyclin *in vivo* without altering platelet function has provided a mechanistic explanation for their potential to cause vascular thrombosis. In addition, the discovery that both COX isoforms are expressed in atherosclerotic plaque and in diseased myocardium has led to a deeper appreciation of the complexity of prostaglandin metabolism particularly in disease states. This chapter will review current knowledge of the choreography of COX expression and the functional role of eicosanoids in cardiovascular pathophysiology. Current perspectives and possible mechanisms on the potential for cardiovascular thrombotic effects with treatment of this class of agents will be discussed.

Key Words: Prostaglandins, cyclooxygenase (COX), NSAIDs, selective COX-2 inhibitors, coxibs, platelet activation, endothelial dysfunction, thromboxane A₂, prostacyclin, myocardial infarction.

Summary

Dirk O. Stichtenoth
Effects on the kidney: Role of COX-2 inhibitors

The results of *in vitro* and *in vivo* experimental work and clinical trials consistently demonstrate that COX-1 plays a leading role in the synthesis of vasoactive prostanoids in the kidney. In contrast, it has been shown that COX-2 is the critical enzyme for sodium excretion

and renin release. Anti-diuretic hormone (ADH)-antagonism is apparently also COX-2 dependent, but more detailed studies are required here.

In clinical practice, improvement of renal safety in terms of renal perfusion by selective COX-2 inhibitors is small. Moreover, selective COX-2 inhibitors cause sodium and water retention and inhibit renal renin release to the same extent as COX-unselective NSAIDs. Thus, edema, hypertension, hyperkalemia and probably water intoxication due to enhanced ADH actions remain as typical NSAID side effects of selective COX-2 inhibitors. As a consequence, to avoid renal side effects of selective COX-2 inhibitors the same precautions as for conventional NSAIDs must be used.

Key Words: Cyclooxygenase, renal side effects, NSAIDs, prostaglandins, COX-2 selective Renin, hypertension, hyperkalemia, edema.

Summary

R. Stokes Peebles, Jr. and Koichi Hashimoto

Effects on the lungs: Role of COX-2 inhibitors

The importance of COX-2 in regulating lung biology is evident from the impressive results using specific COX-2 inhibitors and COX-2 deficient mice in animal models of pulmonary disease. These studies reveal that COX-2 may regulate the genesis and pathobiology of lung cancer, radiation sensitivity, allergic airway inflammation and asthma, sepsis, ischemia/reperfusion injury, pulmonary fibrosis, and pancreatitis-induced lung disease. Whether COX-2 inhibitors will impact these disease states in humans is still largely unknown as clinical trials are either currently ongoing or are still in the planning stages. It is probable that other lung conditions will also be beneficially impacted by COX-2 inhibition, providing motivation for further investigation into the examination of the modulatory role of COX-2 inhibition in lung disease.

Key Words: Cyclooxygenase-2, lung, asthma, lung cancer, sepsis, angiogenesis, interstitial pulmonary fibrosis, angiogenesis, infection, radiation, reperfusion injury.

Summary

Phillip R. Bennett and Aarthi R. Mohan

Reproduction: Role of COX-2 and its inhibition

Prostaglandins play a central role in human reproduction. They are involved, not only in the processes of term and preterm labor, but also in menstruation, ovulation and blastocyst implantation, as well as having a function in male reproduction. This chapter reviews the physiological significance of COX-2 and prostaglandins in reproduction, and discusses the implications of COX-2 inhibition with regard to tocolysis.

Key Words: Cyclo-oxygenase, COX-2; COX-1, prostaglandins, menstruation, ovulation, implantation, placentation, labour, prematurity, amnion, tocolysis.

Summary

Kirsi Saukkonen, Christianne J. Buskens, Anna Sivula, Bastiaan P. van Rees, Tiina-Liisa Erkinheimo, Johanna Rintahaka, Leena Pohjola, J. Jan B. van Lanschot, G. Johan A. Offerhaus, Caj Haglund and Ari Ristimäki
Cyclooxygenase-2 in cancer

Expression of COX-2 is elevated in a variety of malignancies and in their precursor lesions. In humans, elevated COX-2 expression associates with poor prognosis in certain types of adenocarcinomas. Furthermore, genetic deletion or pharmacological inhibition of COX-2 suppresses tumor growth in several animal models of carcinogenesis, and a selective COX-2 inhibitor celecoxib reduces polyp burden in patients who suffer from familial adenomatous polyposis. Thus, COX-2 seems to be a relevant target in chemoprevention. Our aim is to review data on COX-2 expression in several adenocarcinomas and evaluate the role of COX-2 in human carcinogenesis.

Key Words: Cyclooxygenase-2, nonsteroidal anti-inflammatory drugs, celecoxib, prostaglandin, prostanoid, cancer, adenocarcinoma, metastasis, prognosis, survival, colon, esophagus, stomach, lung and breast.



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