

typic much
 O₂ dep
 -Hydrogen peroxide
 -single

SY2 THE COX-2 CONCEPT: AN UPDATE

Pravit Akarasereenont, MD.Ph.D

Department of Pharmacology, Faculty of Medicine, Siriraj Hospital, Mahidol University

Cyclooxygenase (COX) is the first enzyme in the pathway in which arachidonic acid is converted to prostaglandins (PGs) which have numerous cardiovascular and inflammatory effects. COX exists in at least two isoforms, the constitutive (COX-1) and inducible isoforms (COX-2). COX-1, which is constitutively expressed in many tissues (including vascular endothelium, gastrointestinal tract, platelets, and kidney) is responsible for producing prostanoids that regulate normal physiological functions. In contrast, COX-2 is the inducible isoform responsible for the production of prostanoids in response to a variety of stimuli in different tissues and for mediation of inflammation and pain in certain diseases. Since the identification of COX-2, a lot of researches have been devoted to elucidating and understanding its molecular and physiologic characteristics. As a result of research into the differences between COX-1 and COX-2, new insights into the role of each isoform in normal homeostasis and in their responses to exogenous stimuli have emerged. Recent evidences suggest that COX-2 has diverse physiologic and pathophysiologic functions. It is expressed constitutively in the developing kidney and brain, playing a role in their proper maturation and function. Furthermore, COX-2 expression may be upregulated at certain sites besides its induction in cells at inflammatory sites. COX-2 is known to be induced in the kidney in response to sodium depletion or in hyperfiltration states; in postsynaptic excitatory neurons in the brain after electroconvulsive stimulation, in the ovary and uterus during ovulation and implantation; in intestinal epithelium after bacterial infection; as well as in colon adenoma and carcinoma cells. These findings have suggested a broader spectrum of biological activity of COX-2 and potential alterations of specific physiologic or protective mechanisms by inhibition of COX-2, as well as potential new clinical targets of therapy with COX-2 inhibitors. As COX-2 appears to play an important role in pathologic processes other than pain and inflammation, ongoing research is investigating the potential utility of COX-2 inhibitors in other conditions, such as colonic polyposis, colorectal cancer, and Alzheimer's disease. Despite this apparently optimistic outlook for future uses of COX-2 inhibitors, most of the findings supporting this perspective are based on in vitro and in vivo models and must be rigorously corroborated in human studies, some of which are already planned. Thus, the development of specific COX-2 inhibitors will clearly provide important advances in the therapy of pain and inflammation as well as a diverse array of other conditions. However, it is important to bear in mind for the side effects of COX-2 inhibitor from inhibiting the role of COX-2 in physiological stress or pathological defences which are waiting for elucidation.

