

Inhibition of Cyclooxygenases-1 and -2. What Do We Know and Where Do We Go From Here?

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Plant extracts or non-steroidal anti-inflammatory drugs (NSAIDs) have been used for centuries to treat the symptoms of pain, fever, and inflammation. As the molecular targets for their action were identified as cyclooxygenase-1 (COX-1) then cyclooxygenase-2 (COX-2) more potent and selective drugs were developed and are currently on the market worldwide. COX-2 is an important contributor to carcinogenesis in many different solid tumors so COX-2-selective inhibitors (COXIBs) are being investigated as potential agents for cancer prevention and adjuvant therapy. Recent clinical trials indicate that COXIBs and NSAIDs exhibit cardiovascular side effects that may limit their application particularly among individuals with preexisting vascular disease. The molecular basis for the interaction of NSAIDs and COXIBs with COX enzymes is amazingly diverse given the small number of chemical classes represented and the similarity of the active sites of the two target proteins. The results of structural and functional analyses will be presented to illustrate the diversity and subtlety of interactions responsible for COX inhibition. The predictive utility of this mechanistic utility will be highlighted. The mechanisms of gastrointestinal and cardiovascular toxicity also will be considered along with the implications of these adverse effects on future drug discovery.