EFFECTS OF NSAIDs AND COXIBS ON MECHANISMS OF GASTROPROTECTION AND ULCER HEALING: MOLECULAR BASIS

Blandizzi Corrado

Division of Pharmacology and Chemotherapy, Department of Internal Medicine
University of Pisa, Pisa, Italy

The use of non steroidal anti-inflammatory drugs (NSAIDs) is associated with adverse digestive effects, consisting of erosions, ulcerations and bleeding. The injuring effects of NSAIDs on digestive mucosa are ascribed to suppression of prostaglandin synthesis through a blockade of cyclooxygenase (COX), with consequent reduction of mucosal blood flow, enhancement of gastric secretion, and decrease in cell turnover. Following the identification of two COX isoforms (COX-1, COX-2), COX-2 was characterized as an inducible enzyme deputed to biosynthesis of prostanoids implicated in inflammation and pain, but lacking significant involvement in the defence of digestive tract against damaging stimuli. Based on this rationale, selective COX-2 inhibitors (coxibs) were developed to obtain anti-inflammatory and analgesic effects comparable to conventional NSAIDs (COX-1/COX-2 inhibitors), with a reduced risk of injurious actions on digestive mucosa. Molecular and pharmacological studies on preclinical models, including animals with COX-1 or COX-2 gene suppression, have shown that both COX isoforms are expressed and active in the gastric mucosa, and that a concomitant blockade of COX-1 and COX-2 (as it occurs with traditional NSAIDs) is required to induce mucosal damage, thus providing a convincing rationale for the ability of coxibs to preserve the mechanisms of digestive protection. COX-2 has been also found induced in chronic gastric ulcers, and it has been claimed that COX-2 blockade in this setting might interfere with healing processes. However, the exact roles played by COX-2 as well as the molecular mechanisms underlying the effects of NSAIDs or coxibs in ulcer repair remain unclear. We have recently investigated the effects of different COX inhibitors, including indomethacin (COX-1/COX-2 inhibitor) and celecoxib (COX-2 inhibitor) in rats with gastric ulcers induced by acetic acid. In this study, indomethacin delayed ulcer healing and down-regulated COX-2 expression in the ulcerated area, while treatment with celecoxib enhanced COX-2 expression and was without effects on ulcer healing. Moreover, indomethacin down-regulated proliferation and maintained a pro-apoptotic condition in the ulcerative lesions, while celecoxib suppressed apoptotic pathways and promoted proliferative responses. Thus, it appears that differential effects of COX inhibitors on molecular mechanisms regulating proliferation and apoptosis in digestive ulcers may account for different effects of these drugs on ulcer repair. However, beside knowledge gained by preclinical experiences, the clinical significance of COX-2 in the digestive mucosa remains an open field for future investigations.