EFFECTS OF CYCLOOXYGENASE INHIBITORS ON MOLECULAR MECHANISMS IMPLICATED IN GASTRIC ULCER HEALING

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Introduction. Cyclooxygenase-2 (COX-2) inhibitors were developed to down-regulate inflammation and preserve gastric mucosa. This study investigated the effects of different COX inhibitors on molecular mechanisms involved in ulcer healing. **Methods**. Gastric ulcers were induced in Wistar rats by 20% acetic acid, and treatment with COX inhibitors started 4 days later. Indomethacin (1 mg/kg/day, COX-1/COX-2 inhibitor), DFU (5 mg/kg/day, COX-2 inhibitor), celecoxib (1 mg/kg/day, COX-2 inihibitor) were administered orally for 1, 3 or 7 days. Ulcer area was measured and surrounding tissues were processed to evaluate: a) COX-1, COX-2, cleaved caspase-3 and PCNA (western blot); b) phosphorylation of ERK-1/2, p38, JNK, CREB and Akt (western blot). **Results**. At 1, 3 or 7 days ulcer area was 59.3±4.3, 57.4±4.8 and 18.7±4 mm^2, respectively. Indomethacin and DFU, but not celecoxib, delayed ulcer healing. At day 1, COX-2 was induced and this response was enhanced by celecoxib, reduced by indomethacin, and unaffected by DFU. Western blot data are shown in table (fold changes). Ulceration was associated with CREB activation and up-regulation of apoptotic (caspase-3) and proliferation (PCNA) markers. Indomethacin blunted CREB activation, down-regulated proliferation and maintained a pro-apoptotic condition. Celecoxib enhanced CREB activation, suppressed apoptotic pathways and promoted proliferative responses. DFU partly reduced CREB activation and was less effective than celecoxib in decreasing apoptosis. **Conclusions**. Gastric ulcer healing is characterized by a combination of apoptotic and proliferative processes driven by activation of CREB pathways. The ability of celecoxib to enhance CREB-dependent anti-apoptotic and proliferative signals can account for its lack of influence on ulcer repair.

	Normal untreated	Ulcer untreated	Ulcer+indomethacin	Ulcer + DFU	Ulcer + celecoxib
ERK-1/2	1	1.8	2.5	2.5	4.5
JNK	1	2	0.5	0.7	0
p38	1	0.2	0.4	0.1	0
CREB	1	3.4	0.8	1.7	6
COX-2	1	3	0.4	2.5	7
Akt	0	1	0.5	1.8	2.6
Caspase-3	1	1.8	2.5	0.8	0
PCNA	1	2	0.9	4	3