Heme oxygenase-1 protects gastric mucosal cells against non-steroidal anti-inflammatory drugs

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Gastric mucosal cell death by non-steroidal anti-inflammatory drugs (NSAIDs) is suggested to be involved in NSAID-induced gastric lesions. Therefore, cellular factors that suppress this cell death are important for protection of the gastric mucosa from NSAIDs. Heme oxygenase-1 (HO-1) is up-regulated by various stressors and protects cells against stressors. Here, we have examined up-regulation of HO-1 by NSAIDs and the contribution of HO-1 to the protection of gastric mucosal cells against NSAIDs both *in vitro* and *in vivo*. In cultured gastric mucosal cells, all NSAIDs tested up-regulated HO-1. In rats, orally administered indomethacin up-regulated HO-1, induced apoptosis and produced lesions at gastric mucosa. An inhibitor of HO stimulated NSAID-induced apoptosis *in vitro* and *in vivo* and also stimulated NSAID-produced gastric lesions, suggesting that NSAID-induced up-regulation of HO-1 protects the gastric mucosa from NSAID-induced gastric lesions by inhibiting NSAID-induced apoptosis. Indomethacin activated the *HO-1* promoter and caused nuclear accumulation of NF-E2-related factor 2 (Nrf2), a transcription factor for the *HO-1* gene. Examination of phosphorylation of p38 mitogen-activated protein kinase (MAPK) and experiments with its inhibitor strongly suggest that the nuclear accumulation of Nrf2 and resulting up-regulation of HO-1 by NSAIDs is mediated through NSAID-dependent activation (phosphorylation) of p38 MAPK. This is the first report showing the protective role of HO-1 against irritant-induced gastric lesions.