A unifying hypothesis for the mechanism of NSAID related gastrointestinal toxicity

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used; in the United Kingdom alone there are more than 26 million prescriptions for them each year (100 million in the USA). Although their side effects are diverse, the main clinical problems are gastrointestinal, including ulceration, haemorrhage, and perforations, in addition to chronic blood and protein loss. It is widely believed that both the therapeutic and toxic effects of NSAIDs result from the inhibition of cyclo-oxygenase (COX) activity.1 While this longstanding view is simple and logical, it may be incomplete.2 Recently, an alternative hypothesis has been suggested to explain the initiation and perpetuation of NSAID induced gastrointestinal damage.3

The hypothesis proposes a two stage mechanism of NSAID gastrointestinal damage. In its simplest form, the pathogenesis can be visualised as an initial 'topical' biochemical action of NSAIDs (stage I) which is then transformed into an inflammatory tissue reaction (stage II) because of increased intestinal permeability (a transitional stage) that allows luminal aggressive factors access to the mucosa (table). NSAIDs uncouple mitochondrial oxidative phosphorylation, with consequent decreases in intracellular ATP.4,5 This, in turn, causes loss of cytoskeletal control over tight junctions and increased mucosal permeability. Concomitant leakage of calcium from mitochondria initiates a cascade of free oxygen species damage, further potentiating the permeability changes.4,6 Locally and systemically mediated inhibition of COX, which occurs at a much smaller concentration of NSAIDs than that required for uncoupling (picomolar and micromolar, respectively), further prevents mucosal repair by its effect on blood flow, cell proliferation, and mucus and bicarbonate production.

The transition from the initial biochemical injury to tissue reaction is reflected in a transformation from ultrastructural to macroscopic damage. In the stomach, the increased mucosal permeability allows acid, pepsin, bile, and possibly Helicobacter pylori, access to the mucosa. In the small bowel, the luminal aggressive factors include proteolytic and hydrolytic enzymes, ingested foodstuffs, bacteria and their degradation products, pancreatic secretions, and bile. Many of these substances are chemotactic for neutrophils (the defining feature of NSAID enteropathy), which consequently release lysosomal enzymes and generate oxygen reactive species, resulting in macroscopic changes. It has been suggested that development of frank ulcers may be predominantly the result of severe restriction in mucosal vascular blood flow, which, at least in part, is mediated by reduction in prostaglandins. The proposed framework thus requires

Summary of supporting evidence for the involvement of mitochondria in the overall pathogenesis of NSAID induced gastrointestinal toxicity

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that drugs (i) uncouple oxidative phosphorylation and (ii) inhibit COX, in order that they cause gastrointestinal macroscopic injury.

There is a difference between the mechanisms of the biochemical and the macroscopic damage. The biochemical effects of NSAIDs are not site specific, but are related to the local concentration of drug. Drug absorption is determined by size, solubility, pKa (which determines the degree of ionisation), formulation, and local factors such as gastric pH or acidity, gastric and intestinal dilution, transit times, etc. In contrast to the biochemical damage, the mechanism of the tissue injury phase of the damage is clearly site specific. This suggests that conventional attempts to reduce and heal NSAID damage may be effective only in the stomach, or in the small bowel, but not in both.

Inhibition of COX by NSAIDs in this pathogenic framework perpetuates, rather than initiates, gastrointestinal injury. This view is supported by several observations: (a) unlike the anti-inflammatory action of these agents, there is no clear correlation between the extent of their inhibition of COX and intestinal damage; (b) COX activity has often returned towards normal by the time ulcers are observed; (c) COX activities can be inhibited by more than 95% without apparent gastrointestinal damage; (d) though small doses of aspirin almost completely inactivate gastric COX, there is progressive increase in gastric damage with increasing aspirin dose; this is not accompanied by any further COX inhibition; (e) nabumetone and aspirin, unlike all other NSAIDs, cause no small intestinal injury in experimental animals, even in massive doses. Despite this, 6-methoxy-2-naphthylacetic acid (6-MNA) (the active metabolite of nabumetone) and aspirin are effective inhibitors of COX; (f) damage has been observed within five to 10 minutes of oral administration of aspirin; this is considered to be too rapid to reflect a prostaglandin mediated process.

Supportive evidence for the involvement of mitochondria in NSAID induced damage comes from a variety of sources. Subcellular organelle marker enzymes and electron microscopic studies after ingestion of NSAIDs in rats show characteristic mitochondrial changes consistent with uncoupling of oxidative phosphorylation or inhibition of the electron transport along the respiratory chain. In vitro studies show that NSAIDs, unlike paracetamol, uncouple mitochondrial oxidative phosphorylation, and this correlates with drug pKa. Drugs with high pKa (for example indomethacin) are more potent uncouplers than those with a lower pKa (for example aspirin), while low pKa drugs are relatively poor COX inhibitors (compared with high pKa NSAIDs), requiring gram rather than 10–100 mg doses. Free plasma concentrations of these acidic, highly protein bound drugs are in the picomolar range; this would be sufficient to inhibit COX systemically, but not enough to uncouple oxidative phosphorylation.

The demonstration that uncoupling of mitochondrial oxidative phosphorylation is an important early pathogenic event in the toxicity of NSAIDs suggests that it may be possible to develop safer drugs. The ability of NSAIDs to uncouple oxidative phosphorylation stems from their extreme lipid solubility and possession of a carboxylic group that acts as a proton translocator. The carboxyl moiety is open to chemical modification, and this has inadvertently been achieved by butyric-nitric oxide (ENO) ester linkage to form NO-flurbiprofen, or by linking two flurbiprofen molecules by an acid anhydride bond to form dimero-flurbiprofen (figure). Nitric oxide NSAIDs have been claimed to have little or no gastrointestinal toxicity, and it has even been suggested that NO-flurbiprofen accelerates healing of experimental gastric ulcers. Further work is required to define the clinical value of these drugs. There is abundant esterase activity in the small intestine; esterification of NSAIDs may therefore be protective only of the stomach, rather than of the small bowel. As the carboxylic group is essential for uncoupling and COX inhibition, an alternative approach is to disguise this group within a pro-NSAID. Classical NSAID pro-drugs such as sulindac, etodolac, and fenbufen all have a carboxyl group and, predictably, all are associated with significant gastrointestinal toxicity. Nabumetone, in contrast, does not possess a proton translocating moiety, and though 6-MNA is a potent uncoupler, it never achieves micromolar concentrations within the intestine because it is not excreted in bile. There is evidence that nabumetone is much less toxic to the gastrointestinal tract than conventional NSAIDs.

Another strategy for developing safer anti-inflammatory agents relates to the discovery of isoenzymes of COX. The two forms have different relative tissue distribution: inducible COX II is predominantly expressed in inflamed tissue and brain, whereas the constitutive COX I is normally present in many organs, including the kidney and gastrointestinal tract. Selective COX II inhibitors with anti-inflammatory action are being developed, and early results indicate good gastrointestinal tolerability. Significantly, COX II inhibitors are ineffective as proton translocators, and therefore do not uncouple oxidative phosphorylation. However, until COX II inhibitors have been shown to be clinically efficacious and are in routine use, attempting to limit the gastrointestinal toxicity of conventional NSAIDs remains an important objective. We suspect that this is possible and can be based on an understanding of the pathogenic mechanisms outlined.

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