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# Recent advances in gastric ulcer therapeutics

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In developed countries at least, ulcers related to *Helicobacter pylori* infection are becoming rarer. However, ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) remain a major clinical problem, which has not been solved through the introduction of selective inhibitors of cyclooxygenase (COX)-2. Recent studies suggest that NSAID-induced ulcers can be prevented largely through co-administration of a proton pump inhibitor to block acid secretion in the stomach. In patients requiring aspirin therapy to prevent cardiovascular diseases, co-administration of aspirin plus a proton pump inhibitor was found to be safer than using another anti-platelet therapy that does not block gastric prostaglandin production (e.g. clopidogrel). Several recent papers have clarified further the contribution of COX-2 to gastric mucosal defence and to the healing of ulcers. In some circumstances, COX-2 produces a highly potent gastroprotective substance (15-R-lipoxin  $A_4$ ), and analogues of this substance could have therapeutic value for preventing gastric ulceration. Nitric oxide-releasing NSAIDs continue to show promise in terms of limiting damage to the gastrointestinal tract, even when given in combination with aspirin. Recent studies support the notion that platelets make a major contribution to ulcer healing, and the release of several key growth factors from platelets appears to be regulated by proteinase-activated receptors.

## Addresses

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## Introduction

The stomach is exposed to a wide range of substances that have the capacity to cause epithelial damage, as well as to hydrochloric acid, digestive enzymes and bile. However, significant damage to the mucosal rarely occurs. Better understanding of the mechanisms underlying ‘mucosal defence’ has led to the development of novel anti-ulcer therapies. Discoveries in the past two years have continued to improve our understanding of mucosal defence,

of the pathogenesis of gastric ulcer disease, and of the processes contributing to the healing of ulcers.

## Ulcer prevention

The realization in recent years that selective cyclooxygenase (COX)-2 inhibitors were not as ‘GI safe’ as their promotional materials suggested led to several evaluations of alternative methods for preventing gastric ulceration induced by non-steroidal anti-inflammatory drugs (NSAIDs). Proton pump inhibitors (PPIs) have long been suggested to reduce the incidence of serious gastrointestinal complications during NSAID use. A study by Pilotto *et al.* [1] added further support to this notion by reporting that the use of PPIs was associated with a significant reduction in the risk of ulcer in both acute and chronic users of NSAIDs. Moreover, the ‘number needed to treat’ to avoid one peptic ulcer in the elderly was low: three for both acute and chronic NSAID users. Chan *et al.* [2••] examined the utility of PPIs for prevention of recurrent ulcer bleeding in patients taking aspirin to prevent vascular diseases. Patients who presented with ulcer bleeding were randomized, after their ulcers had healed, to receive aspirin plus a PPI (esomeprazole), or another anti-platelet drug (clopidogrel). Clopidogrel is an ADP receptor antagonist that inhibits platelet aggregation and is recommended for patients who have major gastrointestinal intolerance of aspirin. All patients in the study were negative for *Helicobacter pylori*. The results of this study were startling; in patients receiving clopidogrel, the cumulative incidence of recurrent bleeding during the one-year study period approached 9%. In the patients receiving aspirin plus esomeprazole, the cumulative incidence of ulcer bleeding was only 0.7%. Another member of this class of drugs, ticlopidine, was shown to impair the healing of gastric ulcers induced in rats by serosal application of acetic acid [3]. These effects appeared to be related to a previously unrecognized ability of ticlopidine (and possibly other ADP receptor antagonists) to impair new blood vessel growth (angiogenesis) by altering platelet and serum levels of anti-angiogenic factors [3].

## Ulcer healing

Although suppressors of acid secretion (e.g.  $H_2$  receptor antagonists, PPIs) have been a mainstay for promotion of ulcer healing for three decades, there is increased interest in recent years in the mechanisms through which ulcers heal, and the possibility that both the speed and quality of healing may be pharmacologically modulated. Healing requires angiogenesis in the granulation tissue at the base of the ulcer, together with replication of epithelial cells at the ulcer margins and subsequent re-establishment of glandular architecture. Epithelial and endothelial cell

proliferation is largely driven by growth factors. In the case of angiogenesis, vascular endothelial growth factor (VEGF) appears to be among the most important. VEGF is released by endothelial cells themselves, and by platelets. Indeed, release of VEGF is likely to be a primary mechanism through which platelets contribute to ulcer healing [3].

Chai *et al.* [4] demonstrated that VEGF-induced angiogenesis is dependent upon the presence of serum response factor (SRF). SRF is a transcription factor that plays an important role in immediate early gene expression and embryonic development. Inhibition of the activity of SRF, through injection of an antisense expression plasmid into gastric ulcers in rats, led to marked inhibition of angiogenesis in the ulcer bed.

Proteinase-activated receptors (PARs) are thought to participate in many functions in the gastrointestinal tract [5]. These receptors are activated in a unique manner: proteolytic cleavage of the N-terminus unmasks the ligand for the receptor itself. PAR1 and PAR4 are the receptors for thrombin on human platelets. A recent report suggests that these receptors may play an important role in regulating the release of pro- and anti-angiogenic factors from platelets, and can therefore affect ulcer healing [6\*\*]. Activation of PAR1 was found to release VEGF from human platelets, but inhibited the release of a potent anti-angiogenic factor, endostatin. By contrast, activation of PAR4 led to suppression of VEGF release, and stimulation of endostatin release. The importance of PAR1 as a potential therapeutic target for modulating ulcer healing was shown by the impairment of gastric ulcer healing in rats treated daily for one week with a PAR1 antagonist. These studies raise the possibility that ulcer healing may be modulated by therapeutics targeting PAR receptors on platelets (and possibly other cells), so as to manipulate the release of growth factors.

Some drugs known to interfere with gastric ulcer healing in a clinical setting have been shown to affect, in a negative way, the expression of growth factors known to promote healing. For example, selective and non-selective COX inhibitors can delay ulcer healing, which might be related, in part, to their ability to reduce the expression of growth factors such as beta-fibroblast growth factor [7]. Moreover, these drugs cause a change in serum and platelet levels of growth factors, resulting in a greater level of anti-angiogenic factors over pro-angiogenic ones. These changes are consistent with the observation that NSAIDs and selective COX-2 inhibitors inhibit angiogenesis in the ulcer bed [7,8].

### Cyclooxygenase-2

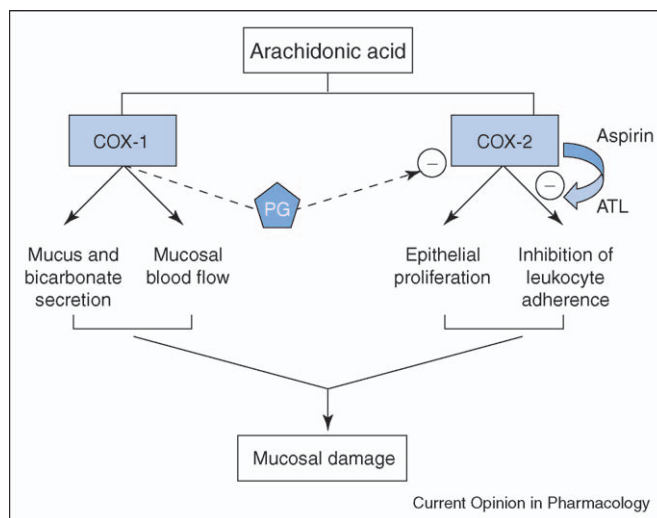
One of the biggest pharmaceutical news stories in recent years was the sudden withdrawal from the marketplace of Vioxx™ (rofecoxib) and, subsequently, Bextra™ (val-

decoxib). Adverse cardiovascular and skin effects, respectively, were the major cited reasons for these withdrawals. However, concerns were also raised in recent years about the putative gastrointestinal safety of this class of drugs. There is now substantial evidence that COX-2 is an important contributor to mucosal defence (Figure 1). This enzyme is rapidly upregulated in response to ischemia, injury or suppression of COX-1 [9,10]. Takeuchi *et al.* [10] reported that suppression of COX-1 led to gastric hypermotility and upregulation of COX-2 expression in the rat stomach. Interestingly, pre-treatment with atropine did not affect the suppression of prostaglandin (PG) synthesis induced by a selective COX-1 inhibitor (SC-560) or by indomethacin, but it did block the hypermotility and the upregulation of COX-2. These data do not prove a causative link between hypermotility and the upregulation of COX-2; nevertheless, these observations could provide clues to help establish the mechanisms responsible for upregulation of COX-2, and thus offer a better understanding of mucosal defence mechanisms. Interestingly, Bhandari *et al.* [11] reported that both COX-1 and COX-2 were upregulated in ulcerated human gastric tissue, with the increases being parallel to the degree of damage. These studies underscore the dynamic nature of mucosal defence, and the fact that many different mediators contribute to the resistance of gastric tissue to injury and to its repair after injury has occurred. The role of COX-2 in gastrointestinal mucosal defence was recently reviewed in detail [12].

It has become clear that one of the products of COX-2 contributes to mucosal defence in a special circumstance; namely, after aspirin administration. Aspirin modifies COX-2 such that it can no longer produce PGs, but it continues to convert arachidonic acid to 15-*R*-hydroxyeicosatetraenoic acid. This product can then be converted, via 5-lipoxygenase, to 15-epi-lipoxin A<sub>4</sub> or 'aspirin-triggered lipoxin' (ATL) [13]. ATL acts to reduce the extent of gastric damage that would otherwise be induced by aspirin [14]. Synthetic lipoxin analogues might therefore represent a novel group of gastroprotective substances. Indeed, two recent papers illustrated the ability of lipoxin analogues to reduce inflammation and promote healing in rodent models of colitis [15,16].

When COX-2 inhibitors are administered together with aspirin, formation of ATL is blocked, resulting in a marked increase in gastric damage. This has been demonstrated in animal and human studies [14,17,18,19\*]. However, in a study of rats with arthritis, Fiorucci *et al.* [20] demonstrated that a nitric oxide-releasing derivative of naproxen was able to suppress COX-2 activity (and thus ATL formation) but, even when given together with aspirin, did not produce gastric injury (Figure 2). This study underscores the potent gastroprotective effects of nitric oxide, as demonstrated in previous studies (for review, see [21]). Elevation of gastric damage in patients

Figure 1



Roles of COX-1 and COX-2 in gastric mucosal defence. PGs generated from COX-1 and COX-2 contribute to mucosal defence in distinct ways. Whereas PGs from COX-1 mediate mucus and bicarbonate secretion and mucosal blood flow, those from COX-2 play a role in regulating epithelial proliferation and leukocyte–endothelial adherence. PGs derived from COX-1 also appear to downregulate expression, and possibly activity, of COX-2. Inhibition of both COX-1 and COX-2 is required for gastric damage to occur in healthy animals. When COX-2 is acetylated by aspirin, it produces ATL, which can inhibit leukocyte–endothelial adherence and thereby counteract the pro-adhesive effects of aspirin. In doing so, ATL limits the extent of gastric damage that would otherwise be caused by aspirin. Indeed, when a COX-2 inhibitor is administered together with aspirin, ATL formation is inhibited and much greater levels of gastric damage are seen.

on low-dose aspirin who are also taking an inhibitor of COX-2 has led to the suggestion that patients needing low-dose aspirin therapy should be receiving a PPI to reduce the risk of gastric injury [22].

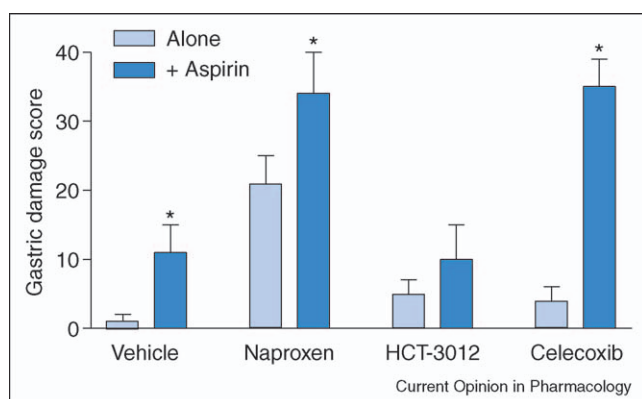
Although a role for COX-2 in ulcer healing has been demonstrated in several studies, downstream enzymes

responsible for PGE<sub>2</sub> synthesis that are important for ulcer healing have not been clearly identified. Gudis *et al.* [23] examined subtypes of PGE synthase in human ulcer specimens. All three isoforms of this enzyme were present, but only mPGES-1 paralleled COX-2 expression (i.e. increased expression in ulcerated versus normal tissue). The mPGES-1 isoform was expressed in mesenchymal cells and in inflammatory cells in the ulcer bed. Selective inhibitors of various isoforms of PGE synthase are in development by several pharmaceutical companies. Potentially, an inhibitor that spared mPGES-1 might not interfere with gastric ulcer healing.

### Enhancing mucosal defence

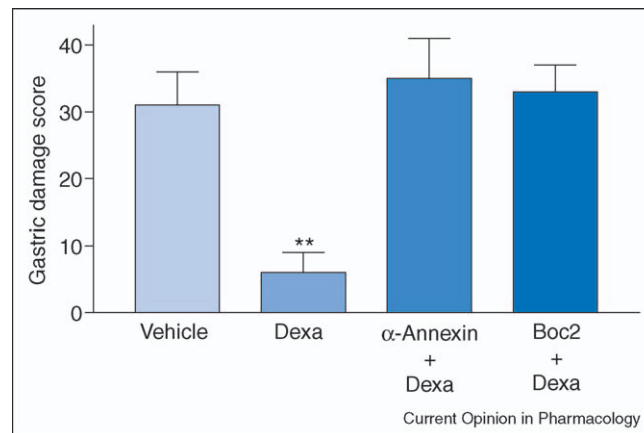
Several recent studies have focused on novel approaches to enhancing the resistance of the gastric mucosa to injury. PGs, nitric oxide and, more recently, lipoxin A<sub>4</sub> [16] have been shown to be important mediators of mucosal defence. Annexin-1 can now be added to this list. Annexin-1 is a protein with a broad range of anti-inflammatory activities that is induced by glucocorticoids [24]. Zanardo *et al.* [25<sup>\*</sup>] demonstrated that annexin-1 is constitutively expressed in the rat stomach; administration of a low dose of glucocorticoid resulted in a marked reduction in the severity of indomethacin-induced gastric damage. Using antagonists to the receptor for annexin-1 (which, interestingly, is the same receptor activated by lipoxin A<sub>4</sub>), and using an immuno-neutralizing antibody, Zanardo *et al.* [25<sup>\*</sup>] demonstrated that the protective effects of the glucocorticoid were mediated via

Figure 2



Gastric damage induced by aspirin in combination with other arthritis drugs. The gastric damage produced in arthritic rats through administration of naproxen or celecoxib was significantly increased by co-administration of aspirin (\* $p < 0.05$ ). However, the nitric oxide-releasing NSAID (HCT-3012) did not cause significant gastric damage, even when co-administered with aspirin. Further details of this study can be found in [20].

Figure 3



Evidence for a role of annexin-1 in gastric mucosal defence. Gastric damage induced in rats by indomethacin was significantly reduced by pre-treatment with dexamethasone (\*\* $p < 0.01$ ). However, immunoneutralization of annexin-1 ( $\alpha$ -annexin) or blockade of the receptor for annexin-1 (with an antagonist called Boc2) reversed the protective effects of dexamethasone. Further details of this study can be found in [25\*].

annexin-1 (Figure 3). Moreover, they showed that annexin-1 contributes to 'basal' gastric mucosal defence.

Alendronate is a bisphosphonate used for the prevention of osteoporosis, but its use is associated with esophageal and gastric ulceration [26]. Alendronate is a topical irritant (i.e. detergent) that induces an inflammatory response in the mucosa. Sener *et al.* [27\*] tested the hypothesis that blockade of the leukotriene D<sub>4</sub> receptor would reduce the degree of inflammation and therefore the severity of alendronate-induced gastric damage. Indeed, treatment of rats with montelukast resulted in a marked reduction in the extent of gastric injury and in the infiltration of neutrophils associated with administration of alendronate.

The identification of *H. pylori* as a major risk factor for gastric ulcer development has changed the management of this disease. Animal models of gastric ulcer have revealed that other species of bacteria will rapidly colonize gastric ulcers and can profoundly alter the natural course of healing [28]. Moreover, both antibiotic and probiotic approaches can be used to accelerate experimental ulcer healing [28,29]. Uchida and Kurakazu [30] further examined this notion using an antral ulcer model in rats. They reported that yogurt containing *Lactobacillus gasseri* dose dependently prevented the formation of antral ulcers induced by combined administration of diethyldithiocarbamate and hydrochloric acid. Interestingly, the yogurt increased the concentrations of PGs in the stomach, possibly explaining its gastroprotective effects.

## Conclusions

Advances continue to be made to understand the mechanisms through which the gastric mucosa is able

to resist autodigestion and damage induced by exogenous agents. Such advances are likely to lead to the development of novel therapies for the prevention of damage to the stomach and elsewhere in the gastrointestinal tract. In the meantime, new evidence from clinical trials is providing important information on how to prevent damage to the stomach induced by agents such as NSAIDs. For example, co-administration of a PPI appears to provide a highly significant level of protection. Better understanding of the mechanisms through which ulcers heal is also providing clues to the development of novel therapies that will accelerate healing and improve the quality of ulcer healing.

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