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Themed Section: Eicosanoids 35 years from the 1982 Nobel: where are we now?

REVIEW ARTICLE

Eicosanoids in the gastrointestinal tract

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Eicosanoids play important roles in modulating inflammation throughout the body. The gastrointestinal (GI) tract, in part because of its intimate relationship with the gut microbiota, is in a constant state of low-grade inflammation. Eicosanoids like PGs, lipoxins and leukotrienes play essential roles in maintenance of mucosal integrity. On the other hand, in some circumstances, these mediators can become major drivers of inflammatory processes when the lining of the GI tract is breached. Drugs such as nonsteroidal anti-inflammatories, by altering the production of various eicosanoids, can dramatically impact the ability of the GI tract to respond appropriately to injury. Disorders such as inflammatory bowel disease appear to be driven in part by altered production of eicosanoids. Several classes of drugs have been developed that target eicosanoids.

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Abbreviations

GI, gastrointestinal; IBD, inflammatory bowel disease; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; NSAID, nonsteroidal anti-inflammatory drug

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The discovery by Sir John Vane that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibited the formation of PGs led to a burst of research into the role of this group of lipid mediators in gastrointestinal (GI) function (Vane, 1971). Prior to that, Andre Robert and his colleagues at The Upjohn Company, in the USA, had discovered that PGs were potent inhibitors of gastric acid secretion, and these lipid mediators could also prevent experimental ulcer formation (Robert *et al.*, 1968). Robert's group went on to characterize the effects of several longer acting synthetic PG analogues in animals and humans (Konturek *et al.*, 1974; Robert *et al.*, 1979), and in a landmark paper in 1979, described the powerful 'cytoprotective' effects of these agents in the stomach and duodenum (Robert *et al.*, 1979). Remarkably, these very low doses of PGs were reported to protect the lining of the rat stomach from damage induced by oral administration of high concentrations of hydrochloric acid or sodium hydroxide, absolute alcohol and even to boiling water (Robert *et al.*, 1979).

The first PG analogue to reach the marketplace was **misoprostol**, a PGE_1 derivative developed by Searle and launched in 1986. Misoprostol was shown to significantly reduce the incidence of NSAID-induced gastric ulcers, but only at doses that suppressed gastric acid secretion (Graham *et al.*, 1988). At such doses, misoprostol significantly increased the incidence of diarrhoea, consistent with known stimulatory effects of PGs on GI epithelial secretion (Matuchansky and Coutrot, 1978).

COX-1 and COX-2

In 1972, another very important discovery was made by Roderick Flower and Sir John Vane that would only be fully appreciated two decades later. They observed that **acetaminophen**, which was known not inhibit peripheral tissue COX activity at therapeutic doses, was able to suppress PG synthesis in the brain (Flower and Vane, 1972). They speculated that there may be more than one form of COX, differentially affected by anti-inflammatory drugs. This notion lingered in the background until 1991, when two groups in the USA reported a previously unrecognized, inducible COX enzyme, which would come to be known as '**COX-2**' (Kujubu *et al.*, 1991; Xie *et al.*, 1991). These publications resulted in a burst of research into the factors regulating expression of the two COX enzymes and their sensitivity to inhibition by the many NSAIDs already on the market, as well as to many new NSAIDs designed to selectively inhibit COX-2 (Masferrer *et al.*, 1994; Mitchell *et al.*, 1994; Warner *et al.*, 1999). The latter was based on the notion that PGs derived from COX-2 accounted for pain and inflammation, while PGs from **COX-1** accounted for the cytoprotective effects that Robert and his colleagues had first observed in the late 1960s (Robert *et al.*, 1968). Several of the world's largest pharmaceutical companies raced to develop selective COX-2 inhibitors. The first to succeed was Searle in 1999 (**celecoxib**; Celebrex®), followed less than a year later by Merck (**rofecoxib**; Vioxx®). Both were hugely successful from a commercial standpoint, but less than 5 years after its launch, Merck removed rofecoxib from worldwide markets because of evidence that it caused serious cardiovascular events (Bombardier *et al.*, 2000; Bresalier *et al.*, 2005). Celecoxib, which was less selective for COX-2 than rofecoxib (Warner *et al.*, 1999), has remained on the market and is one of the most commercially successful drugs. Concerns that the selective COX-2 inhibitors increased the risk of serious cardiovascular events led to recommendations from regulators and medical associations for concomitant use of low-dose aspirin in patients deemed to be at increased risk for serious cardiovascular events. However, there is clear evidence that co-administration of aspirin with celecoxib greatly diminishes any reduction of significant GI adverse events that may have been achieved through use of celecoxib versus a conventional NSAID (Silverstein *et al.*, 2000; Wallace *et al.*, 2000).

Animal studies clearly demonstrated that selective inhibition of COX-2 did not result in significant damage in the stomach (Masferrer *et al.*, 1994). However, selective inhibition of COX-1 also did not result in mucosal damage (Wallace *et al.*, 2000). Selective inhibition of one isoform of COX results in rapid up-regulation of the other, at least in the GI tract (Davies *et al.*, 1997; Wallace *et al.*, 2000). Thus, suppression of both COX enzymes was necessary for gastric damage to be induced (Wallace *et al.*, 2000) (Figure 1). These observations from animal models were consistent with the clinical observations on co-administration of celecoxib and low-dose aspirin (Silverstein *et al.*, 2000). The 'COX-2 hypothesis' was also challenged by evidence that COX-1-derived PGs contribute significantly to inflammation (Wallace *et al.*, 1997), and gastric COX-1 is inducible (Ferraz *et al.*, 1997).

Most of the research in the early 'COX-2 era' was focused on ulceration and bleeding in the stomach and proximal duodenum. These are the regions most easy to examine with an endoscope and where the damage is

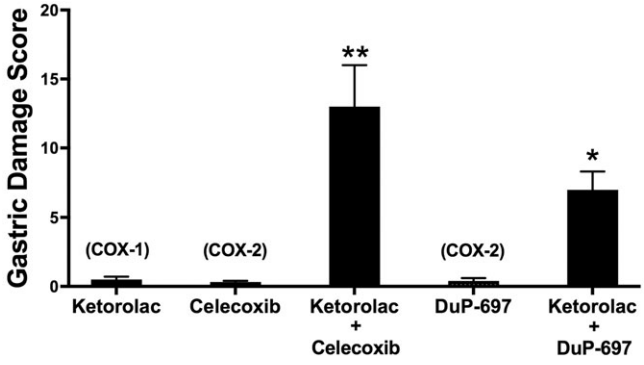

Figure 1

Induction of haemorrhagic, gastric damage by NSAIDs requires inhibition of both COX-1 and COX-2. Ketorolac at a dose (3 $mg \cdot kg^{-1}$) that inhibited COX-1 but not COX-2 did not cause significant gastric damage. Likewise, celecoxib or DuP-697 at doses that selectively inhibit COX-2 (15 $mg \cdot kg^{-1}$ and 10 $mg \cdot kg^{-1}$, respectively) did not cause significant gastric damage. However, the combination of a COX-1 and COX-2 inhibitor resulted in extensive haemorrhagic damage in the stomach (*$P < 0.05$, **$P < 0.01$ compared with the groups treated only with a single drug). This figure was constructed from previously published data (Wallace *et al.*, 2000).

clearly dependent upon the presence of acid. However, NSAIDs can cause clinically significant ulceration and bleeding throughout the GI tract (Bjarnason *et al.*, 1993; Graham *et al.*, 2005; Lanas *et al.*, 2009; Watanabe *et al.*, 2013; Washio *et al.*, 2016). Several clinical studies demonstrated that there was no reduction in incidence or severity of more distal small intestinal damage with a selective COX-2 inhibitor as compared to that with a conventional NSAID (McCarthy, 2009; Graham *et al.*, 2011). These observations were surprising given that selective COX-2 inhibitors do not block platelet aggregation, which would contribute to GI bleeding. Indeed, endoscopic studies of selective COX-2 inhibitors in healthy volunteers, who typically exhibit greater resistance to NSAID-induced GI damage than arthritis patients, have revealed very high rates of intestinal damage and bleeding (Maiden *et al.*, 2005; Maiden *et al.*, 2007). Also, while selective COX-2 inhibitors were commercially promoted on the basis of vastly improved GI safety, they are commonly co-prescribed with agents that suppress gastric acid secretion. However, administration of selective COX-2 inhibitors with proton pump inhibitors or histamine **H_2 receptor** antagonists has been shown to markedly increase the severity of damage in the distal intestine (Wallace *et al.*, 2011; Satoh *et al.*, 2012; Blackler *et al.*, 2014, Washio *et al.*, 2016). This is in part due to dramatic shifts in the intestinal microbiome (Wallace *et al.*, 2011).

Leukotrienes and ulcers

When pharmacological tools for studying leukotrienes (LT) first became available, there were numerous studies suggesting a role for these mediators in upper GI injury, but most involved animal models of injury, such as administration of high concentrations of ethanol, with questionable relevance to the injury that is most commonly observed in humans. However, there were some studies identifying increased mucosal levels of **LTB_4** and **LTC_4** in biopsies from humans infected with *Helicobacter pylori* (Fukuda *et al.*, 1990; Ahmed *et al.*, 1992). NSAID-induced ulceration was shown to be a neutrophil-dependent process in animal studies (Wallace *et al.*, 1990), leading to the proposal that blockade of COX activity may result in a shunting of **arachidonic acid** to **lipoxygenase (LOX)** enzymes and that LTs might be key mediators in activating leukocyte adherence and activation, as well as contributing to mucosal injury. Indeed, NSAID-induced leukocyte adherence was shown to be markedly reduced in rats by a 5-LOX inhibitor and by an **LTB_4 (BLT_1) receptor** antagonist (Asako *et al.*, 1992), and gastric mucosal synthesis of LTB_4 was shown to be significantly increased in humans taking NSAIDs (Hudson *et al.*, 1993). The availability of selective antagonists of LT receptors facilitated several studies of the role of LTs in animal models of gastric damage. Suppression of LT synthesis by inhibitors of 5-LOX was found to significantly reduce the severity of gastric damage induced by an NSAID (Vaananen *et al.*, 1992). However, treatment with LTB_4 or LTC_4/**LTD_4** antagonists had no effect in these studies.

There does not appear to have been any clinical testing of LT antagonists or selective 5-LOX inhibitors with respect to GI safety. Licofelone (ML3000) is a dual COX/5-LOX inhibitor that was proposed to be a 'balanced inhibitor' of 5-LOX and COX with improved GI safety (Jovanovic *et al.*, 2001), but it ultimately failed in phase III clinical development.

Prostaglandins and intestinal secretion

The 'cytoprotective' effects of PGs can be observed throughout the GI tract in various animal models of injury. Some of these effects may be in part attributable to stimulation of secretion in the gut, which can result in dilution of luminal irritants or toxins, and contribute to the process of expelling such agents. Thus, **PGE_2** can relax colonic circular muscle *via* actions on **EP_2** and **EP_4** receptors (Martinez-Cutillas *et al.*, 2014), while smooth muscle contraction can be increased by PGs acting through the **EP_1 receptor** (Chan and Mashimo, 2013). With respect to the latter, a PGE_1 analogue, **lubiprostone**, has been employed in humans as a treatment for constipation-predominant irritable bowel syndrome (Owen, 2008) and for opioid-induced constipation (Jamal *et al.*, 2015). On the other hand, EP_2 and EP_4 receptor antagonists have been used to suppress diarrhoea, such as that induced by cholera toxin in infected ileal loops (Satitsri *et al.*, 2016).

Duodenal bicarbonate secretion is particularly important for protection of the tissue from high concentrations of gastric acid, and its mechanisms have been well characterized. PGE_2 stimulates duodenal bicarbonate secretion in rats *via* activation of EP_3 and EP_4 receptors (Takeuchi *et al.*, 2010; Said *et al.*, 2015).

Eicosanoids and inflammatory bowel disease

The ability of PGs to stimulate colonic secretion led some investigators to propose that PGs may play an important role in inflammatory bowel disease (IBD) (ulcerative colitis and Crohn's disease). As outlined above, PGs may indeed contribute significantly to IBD-associated diarrhoea. However, studies of inhibitors of COX activity in human IBD or in animal models of colitis overwhelmingly suggest important protective (anti-inflammatory) effects of PGs. Several animal studies convincingly demonstrated that selective inhibition of COX-2 led to a marked exacerbation of colitis (Reuter *et al.*, 1996; McCartney *et al.*, 1999; Morteau *et al.*, 2000).

Use of NSAIDs has also been shown to be associated with microscopic colitis, which is characterized by watery diarrhoea (Masclee *et al.*, 2015). It is not clear if this was directly related to suppression of prostanoid synthesis. Proton pump inhibitors are similarly associated with an increased risk of microscopic colitis (Verhaegh *et al.*, 2016). Significant alterations in the gut microbiome may contribute to induction of microscopic colitis by both NSAIDs and proton pump inhibitors (Wallace *et al.*, 2011; Wallace, 2013).

Leukotrienes in inflammatory bowel disease

The observation by Musch *et al*. (1982) that LOX products of arachidonic acid could potently stimulate colonic secretion drew the attention of other researchers to the possibility of LTs contributing significantly to the pathogenesis of IBD. Subsequently, a marked increase in colonic synthesis of **LTB_4** was documented in patients with IBD (Sharon and Stenson, 1984), as was a marked increase in peptido-LTs (i.e. LTC_4, LTD_4, LTE_4) (Peskar *et al*., 1986). The increase in LTB_4 levels in the colonic mucosa of IBD patients was shown to be due to a significant decrease in ω-hydroxylase activity and a marked increase in 5-LOX activity (Ikehata *et al*., 1995).

Mesalamine (5-aminosalicylic acid) is a commonly used, first-line therapy for IBD, with an unknown mechanism of action. It was shown to markedly reduce peptido-LT synthesis by colonic tissue from patients with IBD (Peskar *et al*., 1986). As discussed above, NSAIDs are known to exacerbate colitis in many IBD patients. Hudson *et al*. (1993) demonstrated that NSAID administration to IBD patients resulted in a significant enhancement of LTB_4 synthesis and suggested that this could be the mechanism underlying the exacerbating effects of NSAIDs in colitis.

As more selective inhibitors of LT synthesis became available, they were tested in rodent models of IBD and were shown to be very effective in suppressing LT synthesis and accelerating resolution of colitis (Wallace *et al*., 1989). On the other hand, intracolonic administration of LTB_4 significantly exacerbated experimental colitis (Wallace and Keenan, 1990).

Despite the promising findings in animal models, results from clinical trials of inhibitors of LT synthesis were disappointing. MK-591 was among the first tested. This inhibitor of LTB_4 synthesis was evaluated in a multi-centre clinical trial in ulcerative colitis patients (Roberts *et al*., 1997). Patients were treated twice daily for 8 weeks and rectal dialysate LTB_4 concentrations and disease activity scores were assessed at the end of that period. The highest dose of MK-591 tested in the study (100 mg twice daily) reduced rectal dialysate LTB_4 levels by ~98%, but lower doses (50 or 12.5 mg twice daily) had no significant effect on LTB_4 levels as compared with placebo-treated patients. None of the doses of MK-591 produced a significant improvement in clinical activity as compared with the placebo-treated group.

The role of LTB_4 in ulcerative colitis was further examined in a 6-month clinical trial of **zileuton**, another selective 5-LOX inhibitor (Hawkey *et al*., 1997). The patients were in remission at the start of the study. Treatment with zileuton (600 mg qid) was compared with treatment with placebo or mesalamine (400 mg qid). The primary endpoint was maintenance of remission over the 6-month period. As in the trial of MK-571, the results of the zileuton trial did not support a significant role of LTB_4 in ulcerative colitis. The remission rate in patients treated with zileuton (54%) was not significantly different from that in patients treated with placebo (43%) or mesalamine (63%). The relapse rate for patients treated with mesalamine was significantly lower than the relapse rate for patients on placebo.

PGD_2: a stop signal in colitis?

Experimental and clinical data suggest that PGs, while contributing to diarrhoea, can also play an important role in dampening inflammation during bouts of colitis. On the other hand, NSAIDs can exacerbate colitis, presumably due to suppression of 'cytoprotective' PGE_2 synthesis. However, while increased PGE_2 production is associated with the promotion of oedema formation and pain (Murakami and Kudo, 2006), **PGD_2** acts in the opposite direction, exerting significant anti-inflammatory effects (Gilroy *et al*., 1999; Ajuebor *et al*., 2000; Rajakariar *et al*., 2007). For example, we demonstrated that in experimental colitis, markedly elevated PGD_2 synthesis was a rapid response to tissue injury, acting as a 'braking mechanism' that countered the pro-inflammatory effects of PGE_2 and other chemotaxins (Ajuebor *et al*., 2000). Remarkably, during the resolution phase of colitis, when tissue structure and function returned to normal, we observed a marked elevation of tissue PGD_2 synthesis that persisted for months after the acute colitis had resolved (Ajuebor *et al*., 2000; Zamuner *et al*., 2003). The PGD_2 produced in this setting was derived primarily *via* COX-2, and selective inhibition of that enzyme resulted in marked increase in granulocyte infiltration into the mucosa. This infiltration was significantly reduced by administration of either PGD_2 or a **DP receptor** agonist (Ajuebor *et al*., 2000). The prolonged up-regulation of PGD_2 synthesis after resolution of a bout of colitis was also accompanied by significant changes in colonic epithelial function. Thus, colonic chloride secretory responses (*in vitro*) were markedly diminished relative to those in controls, but could be recovered to normal by treatment with a selective COX-2 inhibitor (celecoxib), but not selective COX-1 inhibitor (SC-560) (Zamuner *et al*., 2003). This hyporesponsiveness could be mimicked in normal colonic tissue by exposure to PGD_2, but not to its metabolite, 15-deoxy-$\Delta^{12\text{-}14}PGJ_2$. There was also further evidence for substantially altered colonic epithelial function in rats that appeared to have fully recovered from colitis: although appearing healthy and normal, these rats exhibited a 10-fold increase in bacterial colonization of the colon and more than a threefold increase in bacterial translocation. The latter could be reversed by treatment for 1 week with a selective COX-2 inhibitor (rofecoxib). These studies demonstrate an important role for COX-2, apparently *via* generation of PGD_2, in mediating the prolonged barrier and epithelial secretory dysfunction that is evident after apparent resolution of colitis in the rat (Zamuner *et al*., 2003).

There are also human data suggestive of an important role for PGD_2 in the resolution of colitis and particularly in maintenance of remission. Vong *et al*. (2010) analysed colonic biopsies from patients with active ulcerative colitis, looking at pro- and anti-inflammatory PG production, expression of the major enzymes of synthesis and expression of the key receptors. They used two groups as controls: healthy subjects with no prior history of ulcerative colitis and healthy individuals who had previously had ulcerative colitis, but had been in clinical remission for at least 4 years. As expected, the patients with active colitis exhibited significant elevations of colonic synthesis of PGE_2 and increased expression (fourfold to sixfold) of COX-2, **IFN-γ** and **TNF-α** (Figure 2). However, there were some remarkable findings related to PGD_2 when

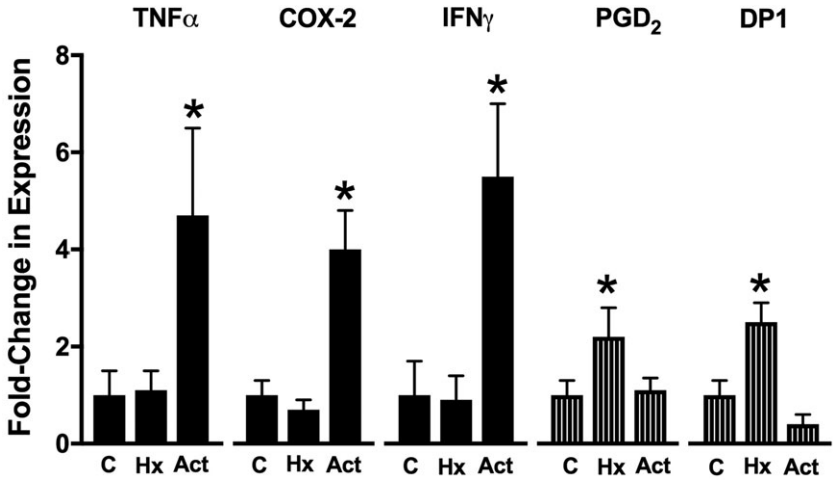

Figure 2

Expression of pro- and anti-inflammatory factors in biopsies from healthy volunteers and ulcerative colitis patients. The 'healthy' groups include subjects with no history (Hx) of ulcerative colitis ('C') and subjects who had previously had ulcerative colitis, but were in long-term remission (more than 4 years). Pro-inflammatory markers such as TNF-α, COX-2 and IFN-γ were significantly elevated in the patients with active (Act) colitis. Anti-inflammatory markers such as PGD_2 and the DP_1 receptor (DP1) were significantly elevated in patients in long-term remission. *$P < 0.05$ versus controls. This figure was constructed from previously published data (Vong *et al.*, 2010).

the group of patients who had been in long-term remission were examined. In that group alone, there were significant increases in PGD_2 synthesis and in expression of mRNA for the **DP_1 receptor**, but not for the **DP_2 receptor**. PGD_2 preferentially binds to DP_1 receptors, and its activation is largely thought to be responsible for the anti-inflammatory effects of PGD_2. These data suggest that the same long-term increase in colonic PGD_2 synthesis that had been observed in rats after resolution of colitis (Ajuebor *et al.*, 2000; Zamuner *et al.*, 2003) are also evident in humans who are in long-term remission after resolution of colitis. Sturm *et al.* (2014) suggested that there may be a role for modulation of colitis through blockade of the other DP receptor, the DP_2 receptor also known as chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells (CRTH2). They demonstrated that blockade of the DP_2 receptor (CRTH2) significantly reduced the severity of colitis in a murine model.

Lipoxins in the GI tract: anti-inflammatory and protective

Lipoxins (LX) are endogenous, anti-inflammatory molecules that contribute significantly to reducing tissue injury and progression from acute to chronic inflammation (Serhan *et al.*, 2007; 2015). The 'classical' LX-generating pathways involve (1) the sequential actions of 5-LOX (in leukocytes) and 12-LOX (in platelets) to produce **LXA_4** and (2) the sequential actions of 15-LOX (in epithelial cells) and 5-LOX (in leukocytes) to produce **LXB_4** (Serhan *et al.*, 2015). A third pathway for LX synthesis, involving aspirin, is described below.

LXA_4 analogues have been synthesized and have shown promising anti-inflammatory effects in models of colitis. For example, Gewirtz *et al.* (2002) demonstrated that LXA_4 analogues reduced pro-inflammatory gene expression in intestinal epithelial cells and significantly attenuated the severity of experimental colitis in mice. LXA_4 and LX analogues have been shown to down-regulate leukocyte degranulation (Gewirtz *et al.*, 1999) and chemokine release (Gewirtz *et al.*, 1998). Moreover, LXA_4 has been shown to dampen intestinal inflammation by inhibiting NF-κB activity (Kure *et al.*, 2010). LXA_4 has also been reported to be important for driving **IL-10** release, thereby producing additional anti-inflammatory effects (Souza *et al.*, 2007), as well as mediating the protective effects of an n-6 fatty acid-enriched diet in ischaemia–reperfusion injury (Gobbetti *et al.*, 2015).

The oral efficacy of ZK-192, a β-oxidation-resistant analogue of aspirin-triggered lipoxin, was examined in experimental colitis. Daily oral administration of ZK-192 at 300 or 1,000 $\mu g \cdot kg^{-1}$ markedly reduced the severity of colitis in rodents, whether given in preventive or therapeutic treatment regimens. This included significant reductions of macroscopic and histological colon injury, weight loss and mucosal neutrophil infiltration. The observed beneficial effects of ZK-192 were comparable with those observed with 3 to 10 $mg \cdot kg^{-1}$ of prednisolone. Expression of a mRNA for several pro-inflammatory mediators (e.g. **inducible NOS**, **macrophage inflammatory protein 2**, COX-2) was significantly decreased by treatment with ZK-192, along with significantly reduced mucosal mRNA and protein levels of TNF-α, **IL-2** and IFN-γ.

A significant role for LXA_2 in maintenance of remission in patients with ulcerative colitis was suggested by Vong *et al.* (2012). They observed that there were markedly elevated levels of colonic LXA_2 in the patients who were in remission, but not in healthy controls or in patients with active ulcerative colitis (Figure 3). They also observed significant elevations of 5-LOX expression in the patients with active colitis, but no change in 12- or 15-LOX expression (Vong *et al.*, 2012). These results demonstrated a specific up-regulation of a pro-resolution circuit in patients who were in remission

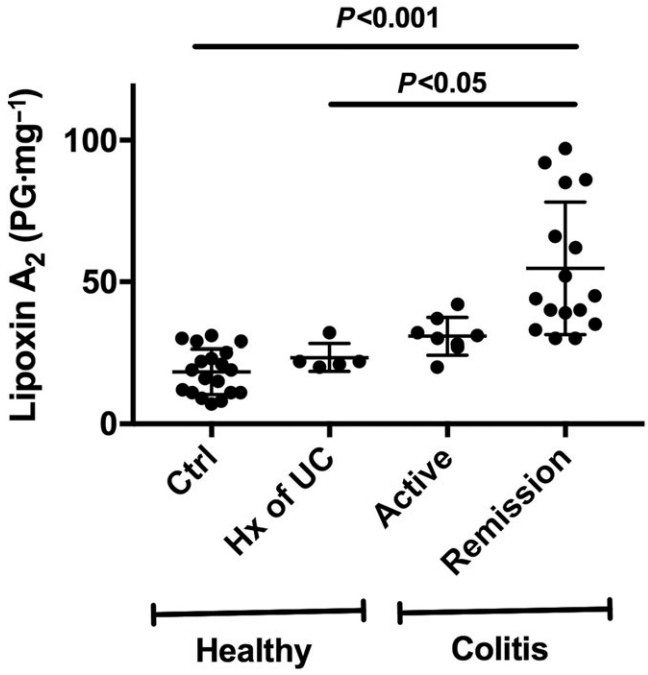

Figure 3

Mucosal lipoxin A_2 levels in biopsies from healthy volunteers and ulcerative colitis patients. The 'healthy' group included subjects with no history (Hx) of ulcerative colitis (Ctrl) and subjects who previously had ulcerative colitis (UC), but had been in long-term remission (more than 4 years). The 'colitis' patients were subdivided into those with active disease and those in medically induced remission. The patients in remission exhibited markedly elevated lipoxin A_2 levels as compared with the two groups of healthy subjects. This figure was constructed from previously published data (Vong *et al.*, 2012).

from ulcerative colitis, with significant contributions of LXA_2 in promoting mucosal homeostasis.

The ability of aspirin to cause damage in the GI tract, particularly in the stomach, is well known. Acetylation of COX-1 by aspirin results in an irreversible inhibition of that enzyme, preventing PG synthesis. However, acetylation of COX-2, while also preventing PG synthesis, does not completely block the function of the enzyme. Arachidonic acid can still be modified by acetylated COX-2, leading to the formation of 15R–HETE (15R–hydroxyeicosatetraenoic acid), which can be further transformed to 'aspirin-triggered lipoxin' (such as 15-epi-LXA_4) *via* the action of 5-LOX (Serhan *et al.*, 2007). In the GI tract, aspirin-triggered lipoxins have been shown to contribute significantly to GI mucosal defence, as well as exhibiting significant anti-inflammatory effects (Fiorucci *et al.*, 2002, 2004).

Closing Comment

As in other tissues, eicosanoids are involved in a wide range of physiological and pathological processes in laboratory animals and humans. There are a wide range of drugs that have been developed to enhance or inhibit the actions of eicosanoids in the GI tract. Despite extensive research for the past five decades, there remains a need for better understanding of the role of eicosanoids in resolution of inflammation in the GI tract. Such research will be an important part of shifting treatment regimens from a target of reducing the magnitude of inflammatory processes (largely symptom control) to an orderly promotion of resolution of inflammation.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2017a,b).

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Conflict of interest

The author declares no conflicts of interest.

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