Drug Development

Molecular Targets for GI Diseases

Edited by

Timothy S. Gaginella

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DRUG DEVELOPMENT

MOLECULAR TARGETS FOR GI DISEASES

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PREFACE

The application of molecular techniques to gastroenterology continues to yield important advances in the development of drugs to treat gastrointestinal disorders. Important new drugs have emerged through the collaborative and complementary efforts of basic scientists, clinicians, and clinical researchers in academia and the pharmaceutical industry. The challenge has been exciting, with a few surprises along the way. Consider peptic ulcer disease as an example. The discovery of H_2 receptors and the availability of potent and selective H_2-receptor antagonists signaled the beginning of a new era in the treatment of gastric hypersecretory states and peptic ulcers. Introduction of proton pump inhibitors offered another therapeutic option. Though H_2-receptor antagonists and proton pump inhibitors are important and useful drugs, the discovery of the link between *H. pylori* infection and peptic ulcer disease has led to even more effective pharmacotherapeutic regimens. Our intent in *Drug Development: Molecular Targets for GI Diseases* is to bring together hands-on experts to review promising areas of gastrointestinal pharmacology. The contemporary topics covered, from a mechanistic viewpoint, are relevant to gastrointestinal inflammation and motility disorders. Authoritative opinions are offered on both future research directions and potential applications for new therapies.

Although each chapter in *Drug Development: Molecular Targets for GI Diseases* stands alone, many of the experimental approaches and concepts that move drug development forward are interrelated. Just as the response of the gut at any instant depends upon the net effect of a multiplicity of mediators, so the reader may capture key ideas from several or all chapters and integrate them into his or her own research. The issues are complex, and at this time our understanding in many areas covered here remains incomplete.

For example, some arachidonic acid metabolites are clearly important for maintaining normal gastrointestinal functions, whereas others are deleterious and offer opportunities for therapeutic intervention. In this regard cyclooxygenase-2 inhibitors are currently promoted as "safer" nonsteroidal anti-inflammatory drugs, but as pointed out in Chapter 1, these drugs may worsen existing mucosal ulcers. Likewise, nitric oxide has both beneficial and injurious effects on the gut mucosa. The complexities of the nitric oxide pathway, with discussion of the roles of constitutive and inducible nitric oxide

synthase, are presented in Chapter 2. The interplay among cytokines and other mediators of inflammation has a profound influence on the severity of inflammatory bowel disease. Chapter 3 provides an in-depth review of these pivotal regulators of immune function, in the context of new opportunities for pharmacotherapy. Maintenance and protection of the mucosa is influenced by a variety of peptide growth factors. The strengths and weaknesses of these agents as potential new gastrointestinal drugs is discussed in detail in Chapter 4. Peptides classified as tachykinins, particularly substance P and neurokinins, affect gut secretion, motility, and immune and vascular functions. Blocking or potentiating the effects of these mediators may be useful in disorders associated with altered gastrointestinal inflammation, secretion, and motility. Potential novel therapies involving tachykinins are presented in Chapter 5. The importance of cholecystokinin receptors as targets for new peptide and nonpeptide drugs is discussed in Chapter 6. Gut motility is greatly influenced by serotonin (5-hydroxytryptamine [5-HT]), and the existence of several subtypes of the 5-HT receptor offers the hope that subtype-selective 5-HT receptor agonists and antagonists might emerge as new anti-emetics and novel modulators of gut motility. Research in this area is discussed in Chapter 7.

Much of classical pharmacology was founded on the characterization of opiate actions on isolated strips of gut muscle. Subsequent research showed that opiates and opiate-like drugs could influence intestinal fluid secretion. The fact that multiple subtypes of opioid receptors reside in the gut supports the notion expressed in Chapter 8 that novel, selective drugs to act at such sites might be developed for treating diarrhea, certain motility disorders, and visceral pain. Finally, the discovery of H_3 receptors and the possibility that H_3-receptor agonists might find utility in treating gut inflammation or pain is reviewed in Chapter 9. Sadly, Giulio Bertaccini died before completion of the book. He was a pioneer in gastrointestinal pharmacology and a prolific contributor to the literature.

It is our hope that this book will stimulate further interest in bringing to light new, more effective drugs for treating gastrointestinal disorders.

This work would not have been possible without the efforts of the authors, and the support from our families, to whom we are grateful.

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CONTENTS

1 The Arachidonic Acid Pathway

New Molecules and Enzymes

John L. Wallace

CONTENTS

1. INTRODUCTION

Arachidonic acid can be liberated from membrane phospholipids via the action of phospholipase A_2 or phospholipase C. The liberated arachidonic acid can then be metabolized via several enzymes to yield a vast array of vasoactive and immunomodulatory substances, termed "eicosanoids" (Fig. 1). Included in this group are the prostaglandins (PGs), leukotrienes (LTs) and thromboxanes (TXs). In general, eicosanoids have a short half-life (seconds to minutes), and act in a paracrine or autocrine manner. The enzymes that catalyze the formation of eicosanoids have been well characterized, and several new drugs have been

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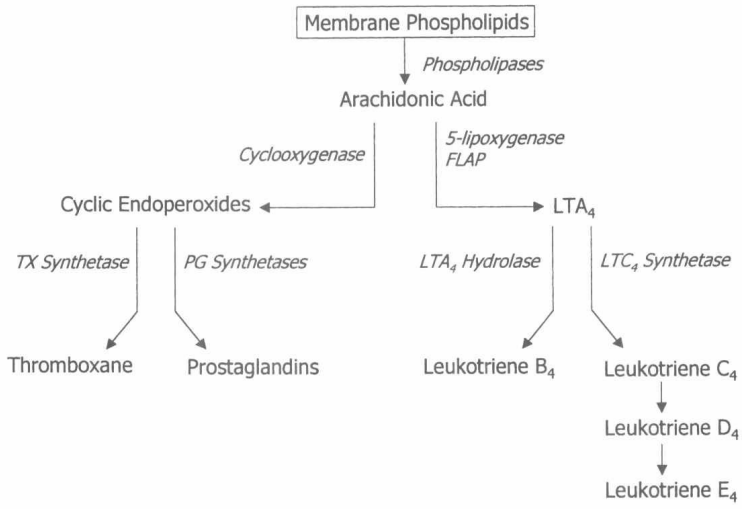

Fig. 1. Schematic diagram of the arachidonic acid cascade. Each of the enzymes shown represent potential targets for anti-inflammatory drugs, and selective inhibitors have been developed.

developed that inhibit their activity. In addition, the receptors for the eicosanoids have been identified and specific antagonists have been developed as potential therapies for a number of inflammatory conditions. This subject has been reviewed in detail by Halushka et al. (1989). In this chapter, the biological actions of the eicosanoids are reviewed, as are the enzymes through which they are formed, and the receptors through which they act. The potential of drugs that block the activity of these enzymes or the eicosanoid receptors is reviewed, particularly with respect to their potential utility in the treatment of inflammatory diseases of the gastrointestinal (GI) tract.

2. PROSTAGLANDINS

PGs are 20-carbon fatty acids produced from arachidonic acid through the actions of the enzyme. cyclo-oxygenase (COX) (Fig. 1). It is now clear that there are at least two isoforms of COX, and selective inhibitors of each have been developed. This is discussed in more detail

below. The recognition of the ability of PGs to reduce or prevent GI injury induced by topical irritants, or cytoprotection (Robert et al., 1976), resulted in an explosion of research into the physiological roles of these substances in GI mucosal defense. It is now well established that suppression of PG synthesis, through inhibition of COX, is a key component of the mechanism underlying gastric ulceration caused by nonsteroidal anti-inflammatory drugs (NSAIDs) (Vane, 1971; Wallace, 1993), as well as the ability of these drugs to exacerbate mucosal injury (Kaufmann and Taubin, 1987; Wallace et al., 1992b). Although the mechanism through which PGs exert their cytoprotective actions has never been firmly established, it is known that these substances can stimulate mucus and bicarbonate secretion, maintain mucosal blood flow, and, through mechanisms that are not yet fully understood, enhance the resistance of epithelial cells to injury induced by cytotoxins (Wallace, 1997). PGs also exert a number of anti-inflammatory effects. This is exemplified by the fact that NSAIDs can greatly exacerbate mucosal inflammation in animal models of colitis (Woolverton et al., 1989; Wallace et al., 1992b; Reuter et al., 1996), and in human inflammatory bowel disease (IBD) (Kaufmann and Taubin, 1987).

The GI mucosa contains a substantial number of immunocytes, including mast cells, macrophages, neutrophils, and eosinophils. The number of these cells varies considerably along the length of the GI tract, to some extent reflecting the bacterial load in the lumen of each region. As in other external mucosae (e.g., skin, lungs, urogenital tract), some of these immunocytes play an important role in signaling the entry into the lamina propria of foreign material or antigens. These cells typically release soluble mediators (including eicosanoids) and cytokines which initiate an inflammatory response aimed at limiting the entry of the foreign matter into the systemic circulation. These mediators act on several targets. Some increase the permeability of the vascular endothelium, thereby permitting plasma exudation, and facilitating the movement of antibodies into the interstitium. Some inflammatory mediators also increase expression of adhesion molecules on the vascular endothelium and/or circulating leukocytes, thereby facilitating the recruitment of the white blood cells to a site of injury or infection. Many inflammatory mediators are chemotaxins; that is, after extravasating, the leukocytes will migrate up a concentration gradient of these chemicals, toward the source of their release. Some

inflammatory mediators are also capable of priming or stimulating leukocytes, to release reactive oxygen metabolites, proteases, or other inflammatory mediators.

One of the mechanisms through which PGs downregulate inflammatory responses is through modulation of the activity of mucosal immunocytes. For example, effects of PGs or PG synthesis inhibitors on tumor necrosis factor (TNF-α) release from macrophages have been very well characterized. Prostaglandin E_2 (PGE_2) has been shown to be a potent suppressor of TNF-α release from macrophages (Kunkel et al., 1986b), and also reduces expression of the gene for TNF-α in these cells (Kunkel et al., 1988). NSAIDs, on the other hand, increase the release of TNF-α from macrophages and other cells (Martich et al., 1991; Spatafora et al., 1991; Santucci et al., 1994). For example, administration of indomethacin, at doses that caused gastric mucosal injury in rats, resulted in marked increases in serum TNF-α levels (Santucci et al., 1994; Appleyard et al., 1996). In humans given bacterial endotoxin, prior administration of an NSAID significantly increased the release of TNF-α into the systemic circulation (Martich et al., 1991). PGs also regulate the release of other cytokines, such as interleukin-1, from macrophages (Kunkel and Chensue, 1985; Kunkel et al., 1986a), and are able to suppress the release of other eicosanoids, such as leukotriene B_4 (LTB_4), from activated neutrophils (Ham et al., 1983; Haurand and Floh, 1989).

The anti-inflammatory effects of PGs may also be mediated via inhibition of mast cell degranulation. Raud et al. (1990) demonstrated that PGs could partially suppress acute mast cell-dependent inflammation; Hogaboam et al. (1993), using isolated mast cells from both the peritoneum and the intestinal mucosa, demonstrated that PGE_2 inhibited, in a dose-dependent manner, the release of platelet-activating factor (PAF), histamine, and TNF-α. These effects were observed at very low (i.e., picomolar) concentrations. For example, with the PGE_1 analog, misoprostol, PAF release from peritoneal mast cells was inhibited at concentrations as low as 10^{-10} molar, while PGE_2 suppressed TNF-α release from peritoneal mast cells at concentrations as low as 10^{-11} *M*.

In addition to acting on immunocytes that are resident within the lamina propria, and thereby decreasing the intensity of an inflammatory response, PGs can inhibit the recruitment of leukocytes from the vasculature (Fig. 2). Because infiltrating leukocytes can cause considerable mucosal injury in some circumstances, this effect of PGs may be

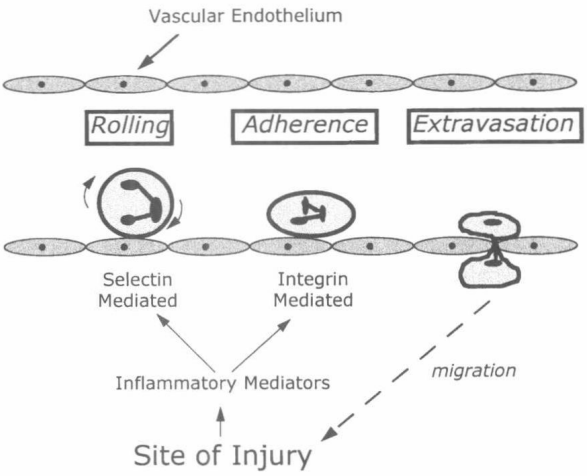

Fig. 2. Key events in the extravasation of leukocytes in response to tissue injury. Inflammatory mediators, including several of the eicosanoids, influence each step of the extravasation and migration process. PGs, particularly PGI_2 and PGE_2, are capable of suppressing most of the adhesive interactions that are depicted, as well as the activation of leukocytes to release free radicals and various enzymes.

one of the underlying mechanisms for the protective effects of these substances in experimental models of mucosal ulceration (e.g., ischemia-reperfusion [Hernandez et al., 1987], NSAID gastropathy [Wallace and Granger, 1992], colitis [Grisham and Granger, 1988; Wallace et al., 1992a]). As mentioned, neutrophils are recruited to a site of injury by the chemotaxins released from immunocytes within the lamina propria. The inflammatory response can also be amplified by the infiltrating neutrophils, because these cells have the capacity to release chemotaxins, such as LTB_4. Once again, PGs serve an important modulatory role by downregulating several neutrophil functions that contribute to inflammation and injury. For example, PGs can suppress the generation of reactive oxygen metabolites, which account for much of the tissue injury caused by neutrophils (Wong et al., 1981; Gryglewski et al., 1987), and the release of the chemotaxins, LTB_4 and interleukin-8 (Ham et al., 1983; Haurand and Floh, 1989; Wertheim et al., 1993). The observation that NSAIDs increase the numbers of neutrophils adhering to the vascular endothelium, and that this can be prevented

by administering exogenous PGs (Asako et al., 1992a; 1992b), suggests that PGs are important physiological regulators of neutrophil adherence.

3. LEUKOTRIENES

The rate-limiting step in the synthesis of LTs from arachidonic acid is the enzyme 5-lipoxygenase (5-LO) (Fig. 1). This activity of this enzyme is in turn dependent on the activation of another protein, named 5-lipoxygenase-activating protein (FLAP), which appears to be involved in the translocation of 5-LO from the cytosol to the membranes from which arachidonic acid is liberated (Miller et al., 1990). The LTs can be conveniently subdivided into two main subclasses: LTB_4 and the peptido-leukotrienes (LTC_4, LTD_4, and LTE_4). As the name suggests, the peptido-LTs include amino acid moieties. LTs are produced chiefly by immunocytes, although there is some evidence for their production by epithelial and endothelial cells as well. In the mucosa, the mast cell appears to be the major source of peptido-LTs; the neutrophil appears to be the predominant source of LTB_4.

LTB_4 is a potent chemotaxin, particularly for neutrophils, and is able to prime a number of different types of immunocytes to secrete other vasoactive and immunomodulatory factors. LTB_4 exerts little, if any, effect on vascular permeability and mucosal blood flow, but can promote the recruitment of leukocytes from the vasculature (Gimbrone et al., 1984) by upregulating the expression on their surface of the β_2-integrins, CD11/CD18 (Lindstrom et al., 1990). LTB_4 can also stimulate neutrophils to release reactive oxygen metabolites, which contribute to tissue injury associated with mucosal inflammation (Schultz et al., 1991). Intra-arterial administration of LTB_4 does not alter the susceptibility of the rat stomach to damage induced by an irritant, but LTB_4 has been suggested to contribute to the pathogenesis of NSAID-induced gastric damage (Asako et al., 1992a; Hudson et al., 1993), probably through its ability to promote leukocyte adherence to the vascular endothelium. This process has been suggested to be an important event in the pathogenesis of NSAID-induced gastric damage (Wallace and Granger, 1992). Administration of LTB_4 receptor antagonists and inhibitors of 5-LO results in attenuation of NSAID-induced leukocyte adherence (Asako et al., 1992a), and a reduction in the severity of NSAID-induced mucosal damage (Vaananen et al., 1992). LTB_4 has also been

suggested to play a role in promoting the leukocyte adherence to vascular endothelial cells that can be induced by water extracts of cultured *Helicobacter pylori* (Yoshida et al., 1993).

In contrast to LTB_4, the peptido-LTs exhibit little chemotactic activity, but they are potent stimulators of smooth muscle contraction, and are also capable of markedly increasing the permeability of the vascular endothelial lining of blood vessels (Ford-Hutchinson, 1990). Moreover, peptido-LTs have been shown to increase the expression of P-selectin on endothelial cells (Kanwar et al., 1995), thereby promoting the rolling (and subsequent extravasation) of leukocytes. Intra-arterial infusion of peptido-LTs can profoundly increase the susceptibility of the rat stomach to injury induced by topical irritants (Wallace et al., 1990), which is probably related to the vasoconstrictor properties of these substances, and could be blocked by pretreating the animals with a LTD_4 receptor antagonist.

One of the principal sources of peptido-LTs in the GI mucosa is the mast cell. Therefore, antigenic activation of mast cells leads to the release of peptido-LTs (Befus et al., 1988), and to effects on various target cells that are probably mediated by these substances. For example, the peptido-LTs have been implicated as mediators of the gastric damage associated with antigenic activation of mucosal mast cells (Rioux et al., 1994). Administration of an antigen to which rats had previously been sensitized resulted in a significant increase in the extent of damage induced by a topically applied irritant. Pretreatment of the rats with a LTD_4 receptor antagonist prevented this injury. Peptido-LTs have also been suggested to mediate the intestinal damage (Perdue et al., 1989) and the motor disturbances (Scott and Maric, 1991) associated with mucosal mast cell activation.

4. THROMBOXANE

TX is the major eicosanoid produced by platelet (via COX-1), which accounts for about 95% of serum TX levels. The neutrophil can also synthesize this substance, although in much smaller amounts (Higgs et al., 1985). In addition to being a potent stimulus for platelet aggregation, TX is a powerful vasoconstrictor. Because any reduction in mucosal blood flow can render the mucosa more susceptible to injury, it has been suggested that TX is an important contributor to the

pathogenesis of ulceration in the GI tract. TX also has the capacity to stimulate LTB_4 release and the adherence of leukocytes to the vascular endothelium (Goldman et al., 1991), and therefore may contribute to mucosal injury throughout the GI tract via amplification of inflammatory responses.

The first evidence to support a role for TX in gastric mucosal defense was reported by Whittle et al. (1981), who showed that close-arterial administration of arachidonic acid into the dog gastric microcirculation resulted in a profound reduction of gastric blood flow. This effect was shown to be attributable to generation of TX from the arachidonic acid. Later, the same group (Whittle et al., 1985) demonstrated similar effects on gastric blood flow with a TX mimetic, and further demonstrated that the susceptibility of the gastric mucosa to injury could be profoundly increased by administration of this mimetic.

With the development of inhibitors of TX synthesis (blockers of TX synthetase), a number of studies were undertaken to determine the contribution of TX to mucosal injury in experimental models of gastric and colonic injury. For example, TX synthase inhibitors were shown to reduce the severity of gastric damage induced by bile salts (Konturek et al., 1983; Walt et al., 1987), ethanol, or indomethacin (Whittle, 1984). Given that indomethacin itself will block TX synthesis, however, it is difficult to implicate TX in the pathogenesis of that particular type of injury. This suggests that the TX synthase inhibitor used in that study may have reduced damage through a nonspecific effect. In support of this, Whittle (1984) showed that greatly reducing the capacity for TX synthesis, by rendering rats thrombocytopenic, did not alter the susceptibility of the stomach to damage induced by ethanol or indomethacin. Very few clinical studies have been performed to evaluate the role of TX in ulcer disease. Hawkey (1986) reported that there were no changes in TX levels in gastric tissue taken from ulcer patients vs controls, irrespective of where the biopsy was taken (at or distant to the ulcer site), or the presence or absence of inflammation at the biopsy site.

TX has also been implicated as a mediator of damage in the small intestine. Boughton-Smith et al. (1989) reported that endotoxin-induced damage in the jejunum was associated with markedly elevated TX and PAF synthesis. TX synthetase inhibitors were able to attenuate both the production of TX and the tissue injury, without affecting PAF synthesis. Bannerjee and Peters (1990) reported that selective inhibitors

of TX synthetase were able to reduce the severity of indomethacin-induced small intestinal injury (epithelial permeability) and inflammation (granulocyte infiltration). However, the dose of indomethacin used to induce injury would itself cause a marked suppression of TX synthesis. It is surprising, given the availability of a number of selective TX receptor antagonists, that these agents have not been employed to further delineate the contribution of TX to the pathogenesis of GI mucosal injury.

5. GI-SPARING ANTI-INFLAMMATORY DRUGS

NSAIDs are among the most prescribed drugs in the world, and are also widely used in over-the-counter preparations. The first NSAID, aspirin, was first commercialized at the end of the nineteenth century. Since that time, dozens of more potent NSAIDs have been marketed. NSAIDs are used primarily for their anti-inflammatory, analgesic, and antipyretic effects, although, more recently, aspirin has been used increasingly for prevention of myocardial infarction and stroke. Although widely used, these drugs are not entirely safe, with well-documented toxicity in the GI tract and kidney.

The discovery, 5 yr ago, of a second isoform of the COX enzyme (Xie et al., 1991; Kujubu et al., 1991) confirmed a theory first suggested in 1972 that there is more than one form of COX (Flower and Vane, 1972). This discovery has led to a re-evaluation of the role of this enzyme in producing PGs in various circumstances. There is now a widely held belief that the PGs produced under normal circumstances, which play such an important role in modulating blood flow and such mucosal defense factors as mucus secretion, are derived from the constitutively expressed isoform, COX-1. PGs produced in the context of inflammation, on the other hand, are thought to be derived from the inducible isoform, COX-2 (Xie et al., 1992). This theory has been somewhat oversimplified to the following: COX-1 produces the PGs that perform beneficial functions, COX-2 produces PGs that exert pro-inflammatory effects. This hypothesis underlies the considerable resources being invested in the development of highly selective inhibitors of COX-2, which have been reported to exert anti-inflammatory and analgesic effects comparable to standard NSAIDs, but to lack ulcerogenic effects. However, there is considerable evidence emerging

Normal	Acute Injury or Inflammation	Ulcer
COX-1-derived PGs •mucus and bicarbonate secretion •mucosal blood flow	COX-1-derived PGs •mucus and bicarbonate secretion •mucosal blood flow	COX-1-derived PGs •unknown
COX-2-derived PGs •negligible (unknown)	COX-2-derived PGs •adaptive cytoprotection (resistance to damage induced by topical irritants)	COX-2-derived PGs •repair: cell proliferation, angiogenesis, maturation of granulation tissue

Fig. 3. Roles of PGs synthesized by COX-1 and COX-2 in gastric mucosal defense and repair in various circumstances. Note that COX-2 appears to become the more important isoform in conditions of mucosal injury.

for physiological roles for PGs produced from COX-2 (Shoda et al., 1995; Slater et al., 1995; Vinals et al., 1997; Gretzer et al., 1998), as well as some evidence that PGs produced from COX-1 contribute to inflammatory responses (Wallace et al., 1998).

Given the evidence that PGs play an important role in limiting inflammatory responses in the GI mucosa, it is perhaps not surprising that several groups have now demonstrated a crucial role for COX-2 in mucosal defense in various models of mucosal injury (Fig. 3). Studies performed recently in this laboratory provide evidence for marked upregulation of COX-2 (protein and mRNA) in the colon of the rat, following induction of colitis (Reuter et al., 1996). The vast majority of PGs produced by the inflamed colon were derived from COX-2. That these PGs were performing a vital function in terms of mucosal defense was confirmed by the finding that selective inhibitors of COX-2 exacerbated the colonic damage in this model of colitis.

There is also considerable evidence that the PGs derived from COX-2 are very important for promoting the healing of ulcers in the stomach. Administration of selective COX-2 inhibitors to rats with preexisting ulcers resulted in a marked retardation of healing (Mizuno et al., 1997; Schmassmann et al., 1998). These studies raise serious concerns about the widespread use of selective COX-2 inhibitors by patients at risk of ulcer disease (i.e., the elderly), particularly when one considers that