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EDITORIAL

Role of Phospholipids in Protection of the GI Mucosa

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The focus of peptic ulcer disease research has evolved over the past 50 years. In the past, the greatest interest understandably has been in studying the regulation of gastric acid secretion, following the century-old Schwarz's dictum of "no acid, no ulcer" [1]. As a consequence, understanding the regulation of gastric acid section and the potential causes of gastric acid hypersecretion became a central research focus until 1970, with major scientific advances including the elucidation of the role of gastrin, acetylcholine, and histamine as physiological stimulants of acid secretion and the identification of luminal acid and somatostatin as physiological inhibitors [2]. Afterwards, the emphasis was on the development of pharmacological inhibitors of gastric acid secretion, with the clinically important discovery of highly effective H_2 receptor antagonists (H_2RAs) followed by the even more efficacious proton pump inhibitors (PPIs) [3–7]. During this same period came the major discovery by Robert and associates of the role of prostaglandins in inhibiting gastric acid secretion, and more importantly in protecting the gastric mucosa from a damaging agents and ulcerogenic conditions (e.g., stress), a remarkable finding at the time, termed "cytoprotection" [8]. The multi-factorial mechanism that underlies prostaglandin's cytoprotective action appears to involve increasing and/or maintaining tight junctional integrity, increasing intestinal mucus and bicarbonate section, and increasing mucosal hydrophobicity, mitochondrial integrity, and blood flow [9, 10]. The development of prostaglandins as clinical cytoprotective agents, however, has been disappointing due to the side-effect profile of these biologically active lipids to stimulate uterine and intestinal smooth muscle contraction and intestinal secretion, which may result in miscarriages, bloating, and diarrhea [11]. Lastly, the discovery of *Helicobacter pylori* by Marshall and Warren [12] revolutionized the field of peptic ulcer disease by implicating a micro-organism in its pathogenesis, leading to novel antibiotic combination therapeutic approaches which not only remarkably reduced the incidence of peptic ulcer disease but of gastric cancer as well [13, 14]. The mechanism by which *H. pylori* causes peptic ulcer disease surprisingly has yet to be fully resolved, but appears to be dependent on the gastric localization of the infection (antrum vs. body), gastric acid hypersecretion (mostly linked to antral infection), and defects in gastroduodenal barrier function [15, 16].

Nonsteroidal anti-inflammatory drugs (NSAIDs), which are regularly consumed by a large percentage of our populace, represent the other major cause of GI ulceration, with gastroduodenal erosions and/or ulcers affecting between 15 and 40 % of those regularly taking NSAIDs [17], and lower gut pathology being present in >50 % of chronic NSAID users [18]. The mechanism by which aspirin and related NSAIDs injure the GI mucosa was once thought to be strictly due to disruption of the biosynthesis of cytoprotective prostaglandins via inhibition of constitutive cyclooxygenase- 1 (COX-1) [19], leading to the development of highly selective COX-2 inhibitors (coxibs) as safer anti-inflammatory drugs. However, over time this concept has been challenged, with the demonstration that NSAIDs can induce GI injury by COX-independent mechanisms [20], and the demonstration that a number of highly selective coxibs have unanticipated and potentially

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life-threatening cardiovascular, renal, and hepatic side effects [21], eventuating in their withdrawal from the US market.

Although prostaglandins clearly fall in the class of biologically active lipids, the appreciation of the role of dietary and intrinsic lipids in mucosal protection has not been readily accepted by the GI community. This is particularly surprising, in light of the long-term and widely accepted use of milk and other dairy products in reducing ulcer pain and promoting ulcer healing during the first half of the 20th century [22]. The use and acceptance of this form of natural therapy, called the Sippy diet, fell into disfavor in the mid 1970s when it was demonstrated that milk stimulated gastric acid secretion due to its high calcium content [23] and concern about the possible linkage of a diet enriched in dairy products and the development of cardiovascular disease due to the diet's high concentration of saturated lipids and cholesterol, which then led to the widespread use of antacids followed by the aforementioned anti-secretory drugs. It is also worthy to note, that certain diets, enriched in omega-6 fatty acids can promote the biosynthesis of prostaglandins and thereby fortify the GI mucosal barrier, as originally suggested by Hollander and Tarnawski [24].

As this transformation from dietary to pharmacological therapy was taking place, our lab demonstrated that the mammalian gastric mucosa possessed unique hydrophobic properties making the tissue non-wettable to luminal acid [10]. Furthermore, this property appeared to be attributable to the synthesis and secretion of surfactant-like phospholipids, notably phosphatidylcholine by the surface mucous cells which were recruited to the luminal interface of mucus gel layer [10]. We also demonstrated that this protective layer could be compromised by NSAIDs and *H. pylori*-related bacteria [10], the latter findings being translated to humans by Northfield and associates [25]. Furthermore, other groups demonstrated that a similar mechanism of GI phospholipid secretion may occur in the small bowel [26] and colon [27], and that a decrease in colonic mucosal phospholipid concentration and hydrophobicity may contribute to the pathogenesis of ulcerative colitis [28]. These observations led to the exploration of novel therapeutic approaches to gastrointestinal mucosal injury. Revisiting the Sippy diet approach, our lab demonstrated the importance of phospholipids in milk in ulcer protection and healing (overriding the effects of increased gastric acid secretion) [29], and also demonstrated that synthetic and soy lecithin-derived (PC) could protect against damaging agents or conditions (e.g., stress) [10]. This work led to reports by our lab and those of other investigators that NSAIDs can induce surface injury to the GI mucosa by chemically associating with PC present in mucus and cell membranes [30, 31], thereby compromising these important barriers. These findings ultimately led to the development of a family of soy-derived PC–NSAIDs that have been demonstrated to have reduced GI toxicity in rodents [30] and in a number of clinical endoscopic trials, while fully maintaining the therapeutic activity of the NSAIDs [32, 33].

In addition to phospholipids playing an important structural role in the extracellular and membrane barriers of the GI mucosa, a body of work has demonstrated that metabolites of PC and related phospholipids may play a key role in cell signaling and defense. The study by Tanaka and associates in the current issue of this journal [34] represents an extension of these interesting observations, demonstrating that phosphatidic acid (PA) and lysophosphatidic acid (LPA) provide protection against aspirin-induced gastric injury in rats. This agrees with studies of Deng et al. [35] and others that LPA has potent anti-apoptotic activity via a PI3K–AKT pro-survival pathway ultimately leading to inactivation of caspase-9 [36]. They also demonstrated by immunohistochemistry the presence of the LPA_2 receptor, the key G-protein coupled receptor involved in the anti-apoptotic response [35], on the luminal surface of rodent gastric epithelial cells (most likely surface mucous cells) and that aspirin-treatment markedly decreased this immunoreactivity. Furthermore, they reported that PA and LPA were present in the gastric contents of rats fed a normal diet, which was expected since these same phospholipids are present in soybean extracts, a usual constituent of rodent chow, and cruciferous vegetables such as cabbage [37]. Tanaka and associates also reported that the activity of phospholipase A_2 (PLA_2), which converts PA to LPA in the stomach, was enhanced by bile acids. Although the authors assumed that bile acids are not normally present in the stomach in order to enhance PLA_2 activity and LPA formation, duodenogastric reflux of bile acids and increases in PLA_2 in gastric juice has been described in rodents treated with GI damaging agent, endotoxin, or lipopolysaccharide (LPS) [38, 39]. These results suggest a potential mechanism by which cruciferous vegetables (cabbage) enriched in PA and LPA can promote ulcer healing as demonstrated in a clinical trial using cabbage juice in the late 1940s [40], providing potentially important insight into a new family of GI protective agents "rooted" in traditional medicine.

In conclusion, biologically active lipids, notably phospholipids (e.g., PC) and their metabolites (e.g., LPA) are an attractive organic means to enhance the barrier properties of the GI mucosa and to reduce the toxicity of pharmacological (e.g., NSAIDs) and natural damaging agents (e.g., bile acids, LPS), which induce tissue injury and disrupt membranes. This, indeed is a lesson one can learn from nature from the study of the phylogeny of biliary PC, whose presence in bile increases in general proportion to

the biliary concentration of hydrophobic bile acids, to counterbalance the highly membrane disruptive activity of these natural detergents [41].

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