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Gastric Cytoprotection Beyond Prostaglandins: Cellular and Molecular Mechanisms of Gastroprotective and Ulcer Healing Actions of Antacids

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Abstract: This article updates current views on gastric mucosal defense, injury, protection and ulcer healing with a focus on mucosal protective and ulcer healing actions of antacids. The gastric mucosa is continuously exposed to a variety of noxious factors, both endogenous such as: 0.1N hydrochloric acid, pepsin, bile acids, lysolecithin, *H. pylori* toxins and exogenous such as NSAIDs, ethanol and others. Gastric mucosal integrity is maintained by pre-epithelial, epithelial and post-epithelial defense mechanisms permitting the mucosa to withstand exposure to the above damaging factors. When mucosal defense is weakened or overwhelmed by injurious factors, injury develops in the form of erosions or ulcers. In the late 1970s Andre Robert and coworkers discovered that microgram amounts of a prostaglandin E2 analog protects the gastric mucosa against a variety of ulcerogenic and necrotizing agents ─ even such strong inducers of injury as 100% ethanol and boiling water. They proposed a new concept of cytoprotection. Subsequently, other compounds, such as sulfhydryls, sucralfate and epidermal growth factor were shown to exert protective action on gastric mucosa. Additionally, some antacids have been shown to exert a potent mucosal protective action against a variety of injurious factors and accelerate healing of erosions and gastric ulcers. These actions of antacids, especially hydrotalcite ─ the newest and the most extensively studied antacid ─ are due to activation of prostaglandin synthesis; binding to and inactivation of pepsin, bile acids and *H. pylori* toxins; induction of heat shock proteins; and, activation of genes encoding growth factors and their receptors.

Keywords: Gastric, protection, injury, healing, antacid, hydrotalcite, mucosal defense.

INTRODUCTION

In previous papers we extensively reviewed the cellular and molecular mechanisms underlying gastrointestinal mucosal defense, injury, protection and ulcer healing [1-5]. Here we have briefly summarized and updated this information; and, with this background, we have focused the present article on the mucosal protective and ulcer healing actions of antacids.

The gastric mucosa is frequently exposed to HCl, pepsin, bile acids, lysolecithin, ethanol, non-steroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori (Hp*) toxins and other noxious factors [1-3, 6,7]. Despite this exposure, under normal conditions the gastric mucosa maintains structural integrity and resists injury by 0.1 mol/L HCl and pepsin present in the gastric lumen [1-3,7]. This is due to an entire array of defense mechanisms (Fig. **1**), which include a pre-epithelial component (mucus-bicarbonate-phospholipid "barrier") ─ the first line of defense; and, the epithelial component [a continuous layer of surface epithelial cells connected by tight and gap junctions, which generates bicarbonate, mucus, phospholipids, trefoil peptides, prostaglandins (PGs), and heat shock proteins] constituting the second line of mucosal defense [1-3,7]. Other defense mechanisms of the gastric mucosa include continuous epithelial cell renewal (accomplished by proliferation of progenitor cells regulated by growth factors, PGE2 and survivin); continuous blood flow through mucosal microvessels; an endothelial microvascular "barrier;" the generation of nitric oxide and hydrogen sulfide; and, sensory innervation (Fig. **1**) [1-3, 7]. Mucosal defense is also regulated, in part, by the central nervous system (vagal stimulation, CRF, TRF, melatonin), hormones (gastrin, CCK, ghrelin, adrenal corticosteroids), sulfhydryls and growth factors, e.g. EGF [2, 8-10] (Fig. **1**). For an in-depth review of basic gastric mucosal defense mechanisms and clinical implications with respect to mucosal injury and ulcer healing, readers are referred to references [1-9].

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The mechanisms and presentation of acute gastric mucosal injury. Gastric mucosa exposed to ulcerogenic and necrotizing agents such as aspirin, indomethacin, bile acids, alcohol, ischemia or corrosive agents develops characteristic morphologic, ultrastructural and functional changes reflecting injury [1,2,11]. The development and extent of mucosal injury depend on the nature and concentration of the damaging agent. As presented in (Fig. **2**), injury encompasses disruption of the unstirred mucus/bicarbonate /phospholipid layer, exfoliation of the surface epithelium with loss of its barrier and electrical functions; and, injury of the deeper gastric mucosal layers including microvascular endothelial cells, progenitor cells and parietal and chief cells. Damage to the capillary endothelium leads to microvascular stasis resulting in cessation of oxygen and nutrient delivery and hypoxia [1,3,11,12]. Microvascular damage occurs early during mucosal injury, leading to hypoxia and necrosis of glandular cells, thus adding an ischemic component to the direct toxic injury of cells [1,3,11,12]. Vascular changes (e.g. vasoconstriction) produced by release of vasoactive and pro-inflammatory mediators from damaged mast cells, macrophages and endothelial cells further impair the mucosal microcirculation and ultimately result in mucosal necrosis in form of erosions or ulcers [1,3].

Repair of mucosal injury. Once mucosal necrosis develops, all mucosal components, including microvessels and glandular epithelial cells are destroyed within the necrotic lesions [1,3,11]. Healing of deep mucosal erosions requires reconstruction of the surface epithelium, glandular epithelial structures; and, restoration of the lamina propria and the mucosal blood microvascular network [1,10]. The repair and restoration of the blood microvascular capillary network occurs through angiogenesis ─ formation of new capillary blood vessels ─ from existing endothelial cells of preserved microvessels at the border of injury [3,13,14]. These endothelial cells migrate, proliferate and join through a process of tubulogenesis to re-establish a microvascular network [13,14]. Angiogenesis is triggered by angiogenic growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and angiopoietins [13,14].

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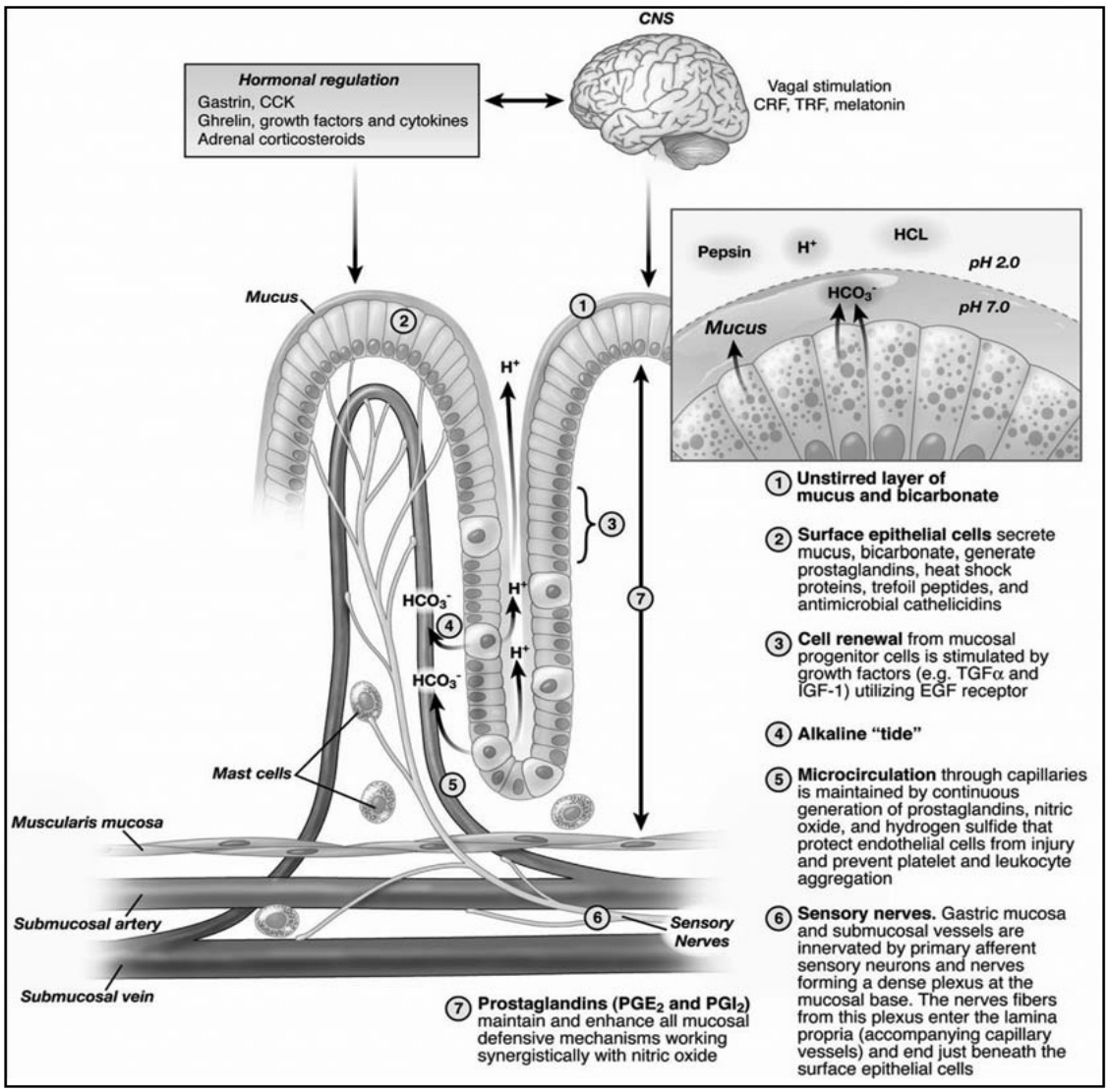

Fig. (1). Schematic presentation of gastric mucosal defense mechanisms (revised and updated from Refs 1 and 2).
(1) Unstirred layer of mucus/ bicarbonate/phospholipids constitutes the first line of defense. It maintains a "neutral" pH of ~ 7.0 at the luminal interface of the surface epithelial cells, while pH in the lumen is about 1.0 – 3.0.
(2) The surface epithelial cells are capable of secreting mucus, bicarbonate and synthesizing prostaglandins and heat shock proteins.
(3) Continuous mucosal cell renewal from mucosal progenitor cells (driven by growth factors and EGF receptors) maintains structural integrity of epithelial structures. Expression of survivin in progenitor cells prevents apoptosis and is the key for immortality of these cells under normal conditions.
(4) "Alkaline tide" - parietal cells secreting HCl into the gastric gland lumen concurrently secrete bicarbonate into the lumen of adjacent capillary blood vessels. It is transported to the surface, where it contributes to the first line of defense.
(5) Mucosal microcirculation through the capillary microvessels is essential for delivery of oxygen and nutrients. Endothelial cells of microvessels generate prostaglandins, mainly PGI_2 (prostacyclin) and nitric oxide, which exert mucosal protective actions.
(6) Sensory nerve stimulation leads to the release of neurotransmitters such as calcitonin gene related peptide (CGRP) and substance P in nerve terminals, which cause vasodilatation and enhance mucosal blood flow.
(7) Continuous generation of prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) by gastric mucosal cells is crucial for the maintenance of mucosal integrity. Almost all of the above (1-6) mucosal defense mechanisms are stimulated or facilitated by endogenous or exogenous prostaglandins.

GASTROINTESTINAL ULCERS AND ULCER HEALING

An ulcer in the gastrointestinal tract is a deep necrotic lesion penetrating the entire mucosa and muscularis mucosae [4,5]. The major difference between an **ulcer** and an **erosion** is that **an ulcer** penetrates through the muscularis mucosae while an **erosion** does not. **Ulcer healing was discussed extensively in our previous papers** [4,5]**. This process** requires filling of the defect with cells and connective tissue, which is accomplished by cell migration, proliferation, angiogenesis and remodeling ultimately leading to scar formation [4,5]. All of these processes are controlled by growth factors – proteins capable of stimulating cell proliferation and division [4,5]. At the ulcer margin, epithelial cells proliferate and migrate onto the granulation tissue to cover (re-epithelialize) the ulcer and initiate reconstruction of the glands within the ulcer scar [4,5]. The processes of re-epithelialization and gland reconstruction are controlled by growth factors including epidermal growth factor (EGF), hepatocyte growth factor (HGF) and insulin-like growth factor -1 (IGF-1), as well as trefoil factors, prostaglandins generated through activated cyclooxygenase-2 (Cox2), and other cytokines produced locally by regenerating cells in an orderly

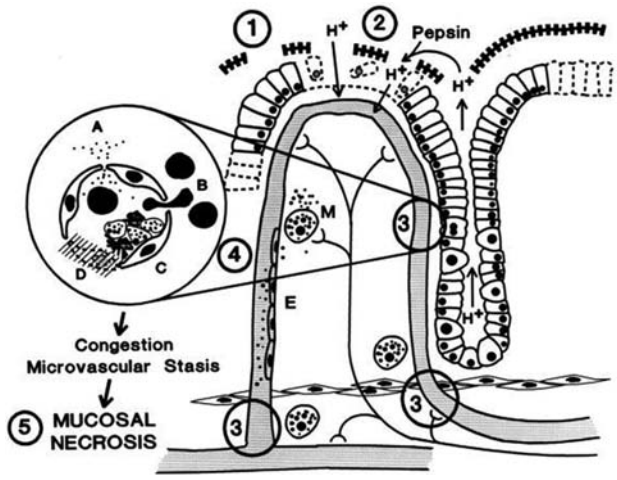

Fig. (2). Diagrammatic representation of gastric mucosal injury (revised and updated from Ref **1**). **Acute gastric mucosal injury consists of:**
(1) disruption of the unstirred mucus/bicarbonate/phospholipid layer,
(2) injury and exfoliation of the surface epithelium with loss of its barrier and electrical functions
(3) injury of the deeper gastric mucosal layers including: (**a**) microvascular endothelial cells, (**b**) progenitor cells and (c) parietal and chief cells.
(4) Microvascular damage occurs early during mucosal injury, leading to hypoxia and necrosis of glandular cells, and adds an ischemic component to the direct toxic injury of cells, ultimately resulting in mucosal necrosis in the form of erosions or ulcers.

and integrated manner [4,5,15]. These - factors, mainly EGF and prostaglandins, trigger cell proliferation via signal transduction pathways involving both direct activation and transactivation of the EGF-receptor [3,4,10,15-17]. **Granulation tissue** develops at the ulcer base. It consists of fibroblasts, macrophages and proliferating endothelial cells forming microvessels under the control of angiogenic growth factors: VEGF, bFGF and angiopoietins. The ensuing angiogenesis - capillary blood vessels formation – is essential for the restoration of the blood microcirculation in the mucosa and is thus crucial for oxygen and nutrient supply [4,5,13]. The major mechanism underlying the activation of angiogenic growth factors and expression of their receptors is hypoxia, which activates the transcription factor, hypoxia-inducible factor 1 (HIF-1α). HIF-1α, in turn, upregulates VEGF transcriptional expression and thus increases the local production of VEGF essential for angiogenesis [4,5]. Primary functions of granulation tissue are therefore to supply: (a) microvessels for the restoration of the microvascular blood network; and, (b) connective tissue cells for the restoration of the lamina propria within the mucosal scar [4,5]. The final outcome of the healing process reflects a dynamic interaction between the epithelial component from the "healing" zone at the ulcer margin and the connective tissue component (including microvessels) originating from the granulation tissue and from bone marrow derived stem cells attracted to the site of injury [4,5].

Quality of Ulcer Healing. In our previous studies, we demonstrated that re-epithelialized mucosa of grossly "healed" experimental gastric ulcers has prominent histologic and ultrastructural abnormalities: reduced height, marked dilation of gastric glands, increased connective tissue, a disorganized microvascular network and increased capillary permeability [18,19]. These prominent abnormalities may interfere with mucosal defense and cause ulcer recurrence when ulcerogenic factors are present. Therefore, the quality of mucosal structural restoration may be the most important factor in determining future ulcer recurrence [18,19].

As mentioned in the introduction, the integrity of gastric mucosa is critically dependent on continuous generation of prostaglandins (PGs) by cyclooxygenase enzymes, Cox-1 (expressed constitutively) and Cox-2 (expressed in response to injury and/or inflammation) [2,20]. PGs maintain mucosal integrity and offer protection against ulcerogenic and necrotizing agents [1-3]. Almost all of the mucosal defense mechanisms are stimulated or facilitated by endogenous or exogenous PGs [1-3]. The suppression of PG synthesis by NSAIDs renders the mucosa more susceptible to injury [1,2,20-22]. PGs inhibit acid secretion, stimulate mucus and bicarbonate secretion, increase mucosal blood flow and accelerate ulcer healing. PGs also inhibit mast cell activation and leukocyte adherence to the vascular endothelium [2]. Additionally, PGs maintain and enhance cellular defense mechanisms by stabilization of lysosomal, mitochondrial and cell membranes, prevention of apoptosis and/or preservation of the cell cytoskeleton and cellular transport of ions [23].

The concept of cytoprotection was developed in late 1970s and early 1980s by Andre Robert and his colleagues at Upjohn Co, Kalamazoo, MI [24]. Cytoprotection was defined as the ability of pharmacological agents (originally prostaglandins) to prevent gastric and intestinal mucosal injury produced by a variety of ulcerogenic agents, such as aspirin, indomethacin, and bile acid salts; and, by necrotizing agents, such as boiling water, absolute alcohol, 0.6M hydrochloric acid, and 0.2M sodium hydroxide [24]. Pretreatment of animals (e.g. rats) with a microgram amount (0.1 to 1 μg/kg) of 16,16 dimethyl prostaglandin E_2 given orally or subcutaneously 15-30 minutes prior to insult almost completely prevented severe gastric mucosal necrosis from occurring after intragastric instillation of 100% alcohol or boiling water [24]. This remarkable protection (cytoprotection) has been confirmed by several independent investigators. Moreover, cytoprotection was accomplished by mechanisms other than reduction of gastric acid secretion, which is indicated by the fact that certain prostaglandins protect the gastric mucosa in non-antisecretory doses; and, that even complete inhibition of gastric acid secretion with cimetidine, ranitidine or omeprazole does not prevent necrosis produced by necrotizing agents (e.g. 100% alcohol, overdistension) [23-25]. Interestingly, omeprazole increases duodenal damage caused by alcohol [26]. Therefore, the mechanisms of cytoprotection are distinct and separate from inhibition of acid secretion. The cytoprotective action of prostaglandins, demonstrated in experimental animals by a number of laboratories, has also been found to apply to the human gastric and duodenal mucosa [27,28] and to other tissues and organs, e.g. liver, pancreas, kidney, blood vessels and heart [23]. Our direct endoscopic studies with simultaneous assessment of mucosal appearance, histology and ultrastructure demonstrated that 16, 16 dimethyl prostaglandin E_2 effectively protects the human gastric and duodenal mucosa against injury produced by concentrated (40% - 60%) alcohol [27,28].

Since the first demonstration of cytoprotection by prostaglandins, some other agents have been shown to be cytoprotective. They include sulfhydryl agents; growth factors; and peptides such as EGF, TGFα, TFFs, gastrin, cholecystokinin, thyrotropin-releasing hormone, bombesin, CRF, peptide YY, neurokinin A, somatostatin, gastric pentadecapeptide BPC 157, leptin, ghrelin, NO, hydrogen sulfide, agonists of adenosine and agonists of proteinase activated receptor-1, and topically active antiulcer drugs such as sucralfate, antacids and rebamipide [2,6-9,29]. Interestingly, our resent studies demonstrated that accumulation of the cell cycle regulator and anti-apoptosis protein, survivin, contributes to gastric cytoprotection likely as a result of increased phosphorylation/stabilization via the cell cycle-dependent kinase, $p34^{cdc2}$ [30]; and, that one of the main reasons for the increased susceptibility of gastric microvascular endothelial (vs. epithelial) cells to injury is reduced expression levels of survivin [31].

Aluminum-magnesium containing antacids (e.g. hydrotalcite) have been shown to exert a potent mucosal protective action against

a variety of injurious factors including ethanol, NSAIDs, pepsin, bile acids, stress, and ischemia/reperfusion [32-34].

These actions of antacids, especially hydrotalcite (the newest and the most extensively studied antacid) are due to activation of prostaglandin synthesis; binding to and inactivation of pepsin, lysolecithin, bile acids and *H. pylori* toxins; activation of heat shock proteins (which protect cells and their proteins from damage); and, activation of the genes encoding EGF, bFGF and their receptors [34-45] (Table **1**).

Table 1. The Mechanisms of Mucosal Protective Actions of Hydrotalcite

The Mechanisms of Mucosal Protective Actions of Hydrotalcite
1). Activates Cox1 and Cox2 in gastric mucosa and increases prostaglandin synthesis and release
2). Increases bicarbonate and mucus secretion
3). Binds and inactivates pepsin, lysolecithin, bile salts and *H. pylori* toxins.
4). Activates heat shock response leading to increased levels of heat shock protein (HSP), especially HSP-70 in gastric mucosal cells.
5). Activates Cox2 and bFGF in endothelial cells resulting in protection of microvascular endothelium and maintenance of mucosal blood flow.
6). Stimulates nitric oxide synthase
7). Stimulates macrophages (cytokines ?)
8). Stimulates sensory nerves (?) leading to increased release of calcitonin gene related peptide (CGRP), which in turn leads to activation of Nitric Oxide and vasodilation

Hydrotalcite protects gastric mucosa against injury caused by a variety of injurious factors, accelerates ulcer healing and significantly improves (vs. omeprazole) quality of mucosal restoration in the ulcer scar.

Hydrotalcite is the main active component of the newest, third generation of antacids, e.g. Talcid, which has a novel "layer-lattice" structure. Hydrotalcite contains aluminum hydroxide, magnesium hydroxide, carbonate and water [36]. It is a single chemical entity and exists in nature in the form of a mineral. Hydrotalcite's layer-lattice consists of layers of aluminum hydroxide and magnesium hydroxide ions (in radio of 1 $Al(OH)_3^+$ to 3 $Mg(OH)_2$); these ions provide the buffering capacity with the aluminum ions providing these layers with a positive charge Additionally, water-containing interlayers of carbonate anions (CO_3); contain a negative charge [36] (Fig. **3**). Hydrotalcite forms a crystalline lattice or grid structure, which is insoluble in water, organic solvents and solutions with pH >5. Due to its special 'layer-lattice' grid structure, hydrotalcite differs from other antacids in that it buffers the stomach lumen between pH 3 and 5, rather than making it alkaline [36-40]. Hydrotalcite protects the stomach and its protective properties have been documented in both animal and human studies [34-45]. It improves the quality of mucosal repair; and, its binding to the ulcer crater results in "trophic" effects, which have only recently been discovered [39]. Thus, hydrotalcite imitates the natural unstirred layer of mucous gel and bicarbonate to protect the stomach with its layer-lattice [39].

MUCOSAL PROTECTIVE ACTIONS OF HYDROTALCITE

Clinical and experimental data indicate that antacids enhance protective and reparative properties of the gastric mucosa [34-46].

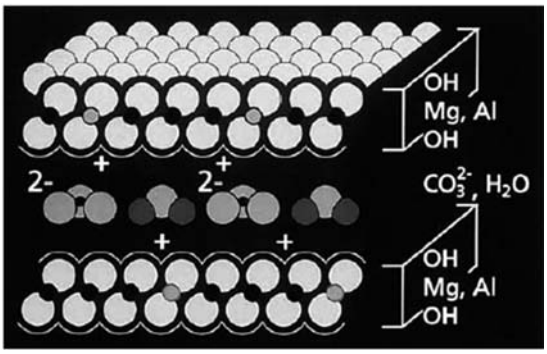

Fig. (3). The layer-lattice structure of hydrotalcite (reprinted from Ref 44). Positively charged layers containing aluminum hydroxide ions ($Al(OH)_2^+$) and magnesium hydroxide ($Mg(OH)_2$) alternate with the negatively charged interlayers containing water (H_2O) and carbonate anions (CO_3), forming a grid or 'layer-lattice'

Hydrotalcite prevents alcohol-, indomethacin- and bile acid-induced gastric mucosal injury and stimulates mucosal restitution and secretion of prostaglandin by the normal stomach. Hydrotalcite's ability to prevent ethanol-induced gastric mucosal injury (Fig. **4**) is an important finding because this form of injury is independent of gastric acid and therefore cannot be prevented by H_2 receptor antagonists [25] or proton pump inhibitors.

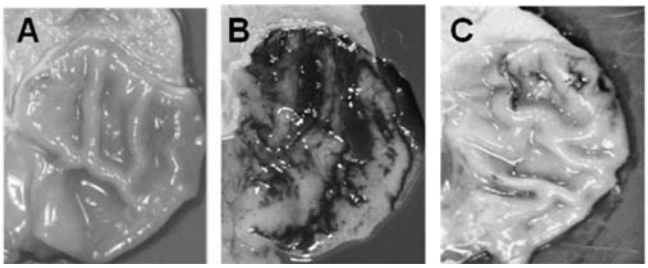

Fig. (4). Hydrotalcite protects gastric mucosa against injury by concentrated (70%) ethanol. Macroscopic appearance of gastric mucosa in rats. **(A)** normal mucosa (stomach was opened along greater curvature and a half of the luminal mucosa is shown). **(B)** 3 hours after ethanol administration in control, placebo pretreated rats. Intragastric administration of ethanol caused longitudinal necrotic lesions - erosions. **(C)** 3 hours after ethanol administration in hydrotacite pretreated rats the gastric mucosa has only minimal injury, reflecting a potent protective action of this drug. Moreover, when hydrotalcite is acidified with hydrochloric acid, it still protects gastric mucosa against alcohol-induced injury (A. Tarnawski, unpublished data and Ref 46).

The mechanisms of mucosal protective actions of Talcid are summarized in Table **1**. They include: **a**) activation of Cox2 with increased generation and release of cytoprotective prostaglandins E_2 and I_2; **b**) activation of heat shock proteins; **c**) neutralization of acid; **d**) binding and inactivation of pepsin, lysolecithin, bile salts and *H. pylori* toxins; **e**) activation of the genes encoding Cox1 and Cox2; EGF, bFGF, their receptors and trefoil factor 2; and, increased nitric oxide production within the gastric mucosa [34-47]. Studies from Peskar's group demonstrated that hydrotalcite induces dose dependent protection against gastric mucosal damage caused by ethanol or indomethacin in rats [46]. This effect was enhanced by hydrotalcite's acidification. Hydrotalcite significantly reduced the gastric mucosal injury caused by indomethacin even when it was administered up to 2 hours after indomethacin [46]. Ablation of afferent neurons with capsaicin and/or inhibition of endogenous nitric oxide decreased, in part, the protective effect of hydrotalcite [46]. Interestingly, the authors did not find a detectable effect of

hydrotalcite on PGs generation, which is in contrast to several other studies cited in that paper [46,47].

MUCOSAL INJURY AND EROSIONS HEALING ACTION OF HYDROTALCITE.

Hydrotalcite accelerates healing of acute gastric mucosal injury, e.g. alcohol-induced erosions [48]. This is accomplished by several different mechanisms such as protection from acid and pepsin injury of cells that survived insult, by activating genes encoding EGF, its receptor and trefoil factor 2, all of which promote re-epithelialization; and, by stimulating angiogenesis via upregulation of the genes encoding pro-angiogenic factors [48] (Table **2**).

Table 2. The Mechanisms of Hydrotalcite's Healing Action on Acute Gastric Mucosal Injury

1). Protects the surviving cells at the erosion margin from acid and pepsin injury
2). Activates genes encoding EGF, EGF-receptor and Trefoil factor 2, which promote cell proliferation, migration and re-epithelialization.
3). Activates genes encoding bFGF and its receptor, which promote angiogenesis – new blood vessel formation – essential for delivery to oxygen and nutrients to the healing site.

ULCER HEALING ACTION OF HYDROTALCITE – CLINICAL IMPLICATIONS

Clinical double bind trials indicate that eight week treatment with low dose of hydrotalcite (Talcid) was as effective as ranitidine in healing gastric ulcers and achieving pain relief [49]. Another study indicated that a single 1g dose of hydrotalcite (Talcid) relieves symptoms of gastroesophageal reflux disease much faster that OTC famotidine [50]. As demonstrated in that study, hydrotalcite was significantly superior ($p<0.001$) to famotidine in increasing the proportion of responders within the first 45 minutes, starting 10 minutes after drug intake [50]. These data showed that hydrotalcite is a safe and effective self-medication for on-demand treatment of heartburn, a major symptom of reflux esophagitis [50].

Experimental data indicate that hydrotalcite accelerates healing of experimental gastric ulcers in rats (in two models: cryoulcers and acetic acid-induced ulcers) and provides better restoration of glandular structures within gastric ulcer scars than the omeprazole [34,51,52]. The mechanisms underlying the mucosal healing actions of hydrotalcite are summarized in Table **3**. They include: a) activation of the genes encoding EGF and its receptor, which promote epithelial growth; b) regeneration and ulcer healing; and, c) activation of genes encoding bFGF and its receptors, which results in increased angiogenesis [35,45,48]. Additionally, the, unique lattice structure of hydrotalcite binds pepsin, bile acids and lysolecithin and protects the healing site from acid and pepsin digestion [39,40,46]. Moreover, hydrotalcite adsorbs and neutralizes all proteins secreted by *H. pylori*, including VacA (+) cytotoxin [44], which has been shown to interfere with the ulcer healing process and impair quality of the scar [53-55]. To date, hydrotalcite is the only anti-ulcer drug with proven ability to adsorb and neutralize all harmful proteins secreted by *H. pylori*, including VacA (+) cytotoxin [44].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Table 3. The Mechanisms of Ulcer Healing Actions of Hydrotalcite

1. Acid neutralization, binding and deactivation of lysolecithin, bile acids and *H. pylori* toxins.
2. Increases mucosal blood flow at the ulcer margin
3. Stimulation of angiogenesis in granulation tissue
4. Increased bicarbonate and prostaglandin production
5. Activation of genes encoding epidermal growth factor (EGF) and its receptor, which increases epithelial cell proliferation, migration, re-epithelialization and reconstruction of gastric glands within the ulcer scar.
6. Increased expression of genes encoding basic fibroblast growth factor (bFGF) and likely VEGF and their receptors in granulation tissue, which promotes angiogenesis
7. Interaction with macrophages (stimulation of production/release of cytokines).
8. Stimulation of sensory neurons (release of calcitonin gene related peptide and stimulation of nitric oxide production, both resulting in vasodilatation).

ABBREVIATIONS

bFGF	=	basic fibroblast growth factor
CCK	=	cholecystokinin
CGRP	=	calcitonin gene related peptide
COX1	=	cyclooxygenase 1
COX2	=	cyclooxygenase 2
CRF	=	Corticotrophin Releasing Factor
EGF	=	epidermal growth factor
H.P.	=	helicobacter pylori
IGF-1	=	insulin-like growth factor -1
MAPK	=	mitogen activated protein kinase
NO	=	nitric oxide
NSAIDs	=	non-steroidal anti-inflammatory drugs
PGI2	=	Prostacyclin
PGs	=	prostaglandins
PI-3K	=	Phosphatidylinositol 3-kinase
TRF	=	thyrotropin-releasing factor
VEGF	=	Vascular endothelial growth factor

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