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REVIEW

"Gastric cytoprotection" is still relevant

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Abstract

Although Andre Robert's historic article on "gastric cytoprotection" in 1979 introduced this new name and concept, gastroprotective drugs (e.g. sofalcone, sucralfate), which prevent and/or accelerate healing of gastric ulcers without inhibiting acid secretion, were known in Japan before or around that time. But since Robert's studies were solely focused on prostaglandins (PG), they became the center of gastrointestinal research for more than 30 years. As endogenous products, PG were implicated in mediating the gastroprotective effect of other drugs such as sofalcone and sucralfate, despite that the cyclooxygenase inhibitor indomethacin diminished but never abolished gastroprotection by other drugs. Another group of endogenous substances, that is, sulfhydryls (SH), investigated in parallel with PG, also seem to play a mechanistic role in gastroprotection, especially since SH alkylators like N-ethylmaleimide counteract virtually any form of gastroprotection. In Robert's terms of "prevention of chemically induced acute mucosal lesions," so far no single mechanism could explain the beneficial effects of diverse protective agents, but I argue that these two endogenous substances (i.e. PG, SH), in addition to histamine, are the main mechanistic mediators of acute gastroprotection: PG and histamine, because as mediators of acute inflammation, they increase vascular permeability (VP), and SH scavenge free radicals. This is contrary to the search for a single mechanism of action, long focused on enhanced secretion of mucus and/or bicarbonate that may contribute but cannot explain all forms of gastroprotection. Nevertheless, based on research work of the last 30 years, in part from our lab, a new mechanistic explanation of gastroprotection may be formulated: it's a complex but orderly and evolution-based physiologic response of the gastric mucosa under pathologic conditions. Namely, one of the first physiologic defense responses of any organ is inflammation that starts with rapid vascular changes (e.g. increased VP and blood flow), followed by cellular events (e.g. infiltration by acute and chronic inflammatory cells). Thus, PG and histamine, by increasing VP create a perivascular edema that dilutes and delays toxic agents reaching the subepithelial capillaries. Otherwise, damaging chemicals may induce severe early vascular injury resulting in blood flow stasis, hypoxia, and necrosis of surrounding epithelial and mesenchymal cells. In this complex response, increased mucus and/or bicarbonate secretion seem to cause luminal dilution of gastrotoxic chemicals that is further reinforced by a perivascular, histodilutional component. This mechanistic explanation would encompass the protective actions of diverse agents as PG, small doses of histamine, motility stimulants, and dilute irritants (i.e. "adaptive cytoprotection"). Thus, although markedly increased VP is pathologic, slight increase in VP seems to be protective, that is, a key element in the complex pathophysiologic response during acute gastroprotection. Over the years, "gastroprotection" was also applied to accelerated healing of chronic gastroduodenal ulcers without reduction of acid secretion. The likely main mechanism here is the binding of angiogenic growth factors (e.g. basic fibroblast growth factor, vascular endothelial growth factor) to the heparin-like structures of sucralfate and sofalcone. Thus, despite intensive research of the last 30 years, gastroprotection is incompletely understood, and we are still far away from effectively treating *Helicobacter pylori*-negative ulcers and preventing nonsteroidal anti-inflammatory drugs-caused erosions and ulcers in the upper and lower gastrointestinal tract; hence "gastric cytoprotection" research is still relevant.

It's not widely known that gastroprotective drugs (e.g. sofalcone, sucralfate) which prevent and/or accelerate healing of gastric ulcers, without inhibiting acid secretion, were first introduced in Japan, before or around Andre Robert's historic article on "gastric cytoprotection" in 1979.[1,2] Furthermore, some poorly defined and locally acting "protective" drugs (e.g. carbenoxolone and bismuth salts) were empirically used in Europe and North America, but their mechanisms of action were not widely investigated.[3] Since Robert's studies were solely focused on prostaglandins (PG), they became the center of gastrointestinal (GI) research for more than 30 years, preceding the popularity of *Helicobacter pylori* investigations. As endogenous products, PG were implicated in mediating the gastroprotective effect of other drugs such as sofalcone and sucralfate[4,5] despite that the cyclooxygenase inhibitor indomethacin diminished but never abolished gastroprotection by other drugs. Another group of endogenous substances, that is, sulfhydryls (SH), investigated in parallel with PG, also seem to play a mechanistic role in gastroprotection, especially since SH alkylators like N-ethylmaleimide (NEM) counteract virtually any form of gastroprotection.[6,7]

Using Robert's terms of "gastric cytoprotection: prevention of chemically induced acute mucosal lesions," so far no single mechanism could explain the beneficial effects of diverse protective agents, but I argue that these two endogenous substances (i.e. PG, SH), in addition to histamine, are the main mechanistic mediators of acute gastroprotection: PG and histamine, because as mediators of acute inflammation, they increase vascular permeability, and SH scavenge toxic free radicals. This is contrary to the search for a single mechanism of action, long focused on enhanced secretion of mucus and/or bicarbonate that may contribute but cannot explain all forms of gastroprotection, as direct (*in vitro*) cytoprotection is also of limited value. Nevertheless, based on research work of the last 30 years, in part from our lab, a new mechanistic explanation of gastroprotection may be formulated (see below).

This short review is written with three goals: (i) to argue that the mechanism of gastroprotection is still poorly defined, although I will propose a new, multifactorial, and contemporary mechanistic explanation for the surprisingly potent gastroprotective action of wide variety of drugs. (ii) Although the original "gastric cytoprotection" experiments of Robert[1,2] and the deluge of subsequent similar studies worldwide referred to prevention of acute gastric mucosal lesions or erosions, without reducing gastric acidity, I suggest that almost 35 years after Robert's seminal work, there is a new possibility to accelerate the healing of chronic gastroduodenal ulcers without inhibiting gastric acid secretion. (iii) There is a growing clinical need to find novel gastroprotective drugs which prevent and/or accelerate the healing of nonsteroidal anti-inflammatory drugs (NSAID)-induced and both *H. pylori*-positive and negative gastroduodenal ulcers.[8,9]

The search for mechanism of acute gastroprotection: Single or multiple components?

Since the initial studies of Robert used pretreatment with very small doses of PG in rats to prevent acute hemorrhagic erosions caused by concentrated ethanol, HCl, NaOH, hot water, or hypertonic NaCl2,[1,2] "gastric cytoprotection" became a magnet to search for mechanistic explanation(s) for this unexpected effect of tiny doses of Prostaglandin E2 (PG-E2) (i.e. about 10–100 times smaller than the dose required to inhibit gastric acid secretion). Furthermore, even PG from the F series that have no effect on gastric acidity exert gastroprotection, as revealed by our initial studies.[6,7]

The biggest surprise in this field, however, has come from first studies of Paul Guth who demonstrated that "gastric cytoprotection" is not unique to PG molecules since non-antisecretory doses of cimetidine and probanthine also exert similar acute gastric mucosal protective effects.[10] After reading this article in the most recent issues of *Gastroenterology* on the day when it arrived to the library of Harvard Medical School late December 1979, I had the idea (shortly after arriving from the institute of Hans Selye who was obsessed with specificity *vs* non-specificity of stress response) that if tree molecules very different in structures and mechanisms of action exert some common effect (i.e. gastroprotection), there must be some common neuroendocrine and/or other chemical mediators (e.g. glutathione and other antioxidants) in their mechanism of action. Fortunately, that was one of the about 10% of my hypotheses when I was right, since our subsequent experiments soon demonstrated that not only ethanol dose-dependently depleted glutathione in the gastric mucosa of control, but not in PG-pretreated rats, but other SH containing endogenous (e.g. L-cysteine, D,L-methionine) and exogenous chemicals (e.g. dimercaprol, N-acetylcysteine or Mucomyst) also prevented the ethanol-induced acute gastric mucosal hemorrhagic lesions.[6,7] Furthermore, the PG or cimetidine-induced gastroprotection was lost in adrenalectomized (but not in thyroidectomized or ovariectomized) female rats, and this was restored by replacement therapy with gluco- but not with mineralocorticoids.[11]

These findings were soon followed by revelations from Mozsik and Miller who independently demonstrated that the PG-induced gastroprotection was also lost in vagotomized rats[12,13] and by the findings of Holzer, Mozsik and Szolcsanyi that capsaicin-sensitive neurons play a critical role in the mechanisms of gastroprotective drugs.[14] All these implications about the neuroendocrine factors suggested that the PG-induced prevention of acute gastric mucosal lesions is relative, and this was further reinforced by the relativity of morphologic "protection." Namely, in almost parallel but independent studies of Ito and Lacey at the Department of Anatomy as well as of Szabo and Trier in the Departments of Pathology and Medicine, at Harvard Medical School, respectively, revealed that although grossly the stomachs 1 h after intragastric administration of damaging chemicals in PG-pretreated rats appeared intact, histologically by light microscopy, especially if examined 1–5 min after concentrated ethanol, most of the superficial gastric mucosal cells were missing but were rapidly "restituted" (Fig. 1).[11,15] This implied that for yet mysterious reasons, the chemically induced gastric mucosal lesions in the properly pretreated animals did not progress deeper than the superficial one fifth of the gastric mucosa, sparing the subepithelial capillaries from rapturing and hemorrhaging, and leaving the surviving gastric foveolar cells to rapidly migrate and without divisions (i.e. proliferation) rapidly replace the lost surface necrotic cells,[15] resulting in macroscopically normal looking gastric mucosa 1 h after the administration of toxic chemicals (Fig. 1).

This background of neuroendocrine mechanistic factors and the relativity of morphologic protections suggested to us that the term

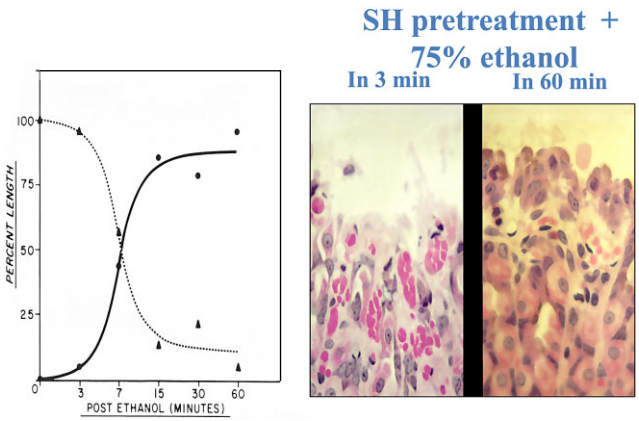

Figure 1 Graphical (left) illustration of rapid epithelial restitution in the gastric mucosa after intragastric administration of ethanol in a rat pretreated with prostaglandins (modified from Reference 15). Light microscopic histology of the same phenomenon after pretreatment with a sulfhydryls-containing drug (modified from Reference 71). ▲, DAMAGED; ●, RESTITUED.

"gastric cytoprotection" is inappropriate for this phenomenon, especially since thousands of surface epithelial cells would die even in the "protected" stomach, yet the majority of gastric mucosa and the entire stomach remain relatively normal, that is, without bloody lesions and deepening erosions that may lead to ulcer formation. Thus, we suggested that it's much more appropriate to speak about organ or gastroprotection than to use the misleading term of "cytoprotection."[16]

The fact that only the hemorrhagic component of gastric mucosal lesions is prevented suggested early to us that most of the protection may be related to the preservation of subepithelial capillary endothelial cells, resulting in maintenance of mucosal blood flow that allows the energy-dependent epithelial cell migration/restitution to replace the early necrosis of millions of surface epithelial cells.[16–18] We also suggested that early endothelial injury may precede the development of mucosal necrosis, that is, hemorrhagic gastric erosions induced by ethanol and other toxic chemicals. Indeed, using specific vascular tracers in light microscopic and ultrastructural studies, we detected endothelial damage and increased vascular permeability within 1–3 min after intragastric instillation of 75% ethanol, while superficial hemorrhagic mucosal lesions could be seen only 5–10 min later in rats.[17–19] Tarnawski was the first to electron microscopically confirm these early vascular lesions in gastric biopsy samples of human volunteers.[20]

Other early mechanistic implications originated from the studies of Flemstrom and Garner as well as Allen and LaMont in relationship to the discovery that gastroprotective doses of PG-enhanced gastric bicarbonate[21] and mucus[22,23] secretion. This effect of PG was widely confirmed in subsequent publications from several labs, our joint experiments with LaMont actually confirmed a "true-true but unrelated" fallacy often encountered in mechanistic research studies. Namely, gastroprotective doses of PG indeed stimulated mucus secretion in the rat stomach, but pretreatment with SH alkylators like NEM completely blocked the protective effect of PG without interfering with the enhanced mucin release.[23]

In addition to these *in vivo* animal studies, a possible direct protection by PG was also investigated *in vitro*. Using cultured epithelial cells and isolated gastric glands, Terano and Tarnawski could demonstrate only limited direct tissue protection.[24,25] We confirmed and expanded these findings by using isolated rat gastric mucosal cells and employing not only trypan blue exclusion but also other markers of cell membrane permeability, mitochondrial and nuclear viability,[26] and demonstrated that *in vitro* pretreatment with PG and other gastroprotective compounds have no or minimal protective effects against diluted ethanol and other gastrotoxic chemicals.[26,27]

A new proposal for a pathophysiologically sound mechanism of acute gastroprotection

The emerging new studies that showed the importance of capsaicin-sensitive neurons in maintaining gastric mucosal blood flow[12,14,28] as well as the critical role of vasodilatory nitric oxide (NO) and vasoconstrictory endothelins confirmed[29–32] that the mechanisms of gastroprotection is most likely happening only at the tissue (not at the cellular level), and vascular factors are crucial in this phenomenon. Then I realized that PG are actually mediators of acute inflammation which consists of vascular (e.g. increased vascular permeability leading to edema and increased blood flow) and cellular components (e.g. infiltration of leukocytes).[33] This prompted us to use other modulators of vascular permeability, histamine, and bradykinin that dose dependently increase vascular permeability to test the hypothesis that a PG-induced perivascular edema in the top part of the gastric lamina propria creates a "histodilutional barrier" which dilutes intraluminal toxic chemicals, delays their absorption, and preserves the integrity of subepithelial vascular endothelial cells allowing the maintenance of mucosal blood flow. Indeed, pretreatment of rats with small amounts of histamine dose and time dependently prevented the ethanol-induced gastric hemorrhagic erosions, while large doses of histamine aggravated the chemically produced mucosal lesions (Fig. 2).[34,35] The summary of these results with the modulation of gastric mucosal vascular permeability showed a good linear correlation between vascular permeability and the development of hemorrhagic mucosal erosions (Fig. 2). Special histologic and light microscopic examination of thin (1 um) acrylate-embedded sections of gastric mucosa (instead of the usual 6 um cuts of paraffin-embedded tissue), with a better resolution than the standard histologic methods, showed that pretreatment of rats with gastroprotective doses of histamine resulted in clearly visible perivascular edema (Fig. 3). This might explain the slight delay in the absorption of NSAID after pretreatment with gastroprotective drugs, such as sucralfate, as demonstrated in rats[36] and clinical studies (Fig. 3). This also confirms what Andre Robert described: "cytoprotection occurs in spite of penetration of absolute ethanol into the gastric mucosa."[37]

It appears thus that the tissue-level mechanism of acute gastroprotection is a multicomponent physiologic defensive reaction under pathologic conditions. Namely, evolution showed us that the first physiologic defense in any organ is inflammation which starts with rapid vascular changes (i.e. increased permeability and blood flow), followed by cellular events (e.g. infiltration by acute and chronic inflammatory cells). Otherwise, damaging

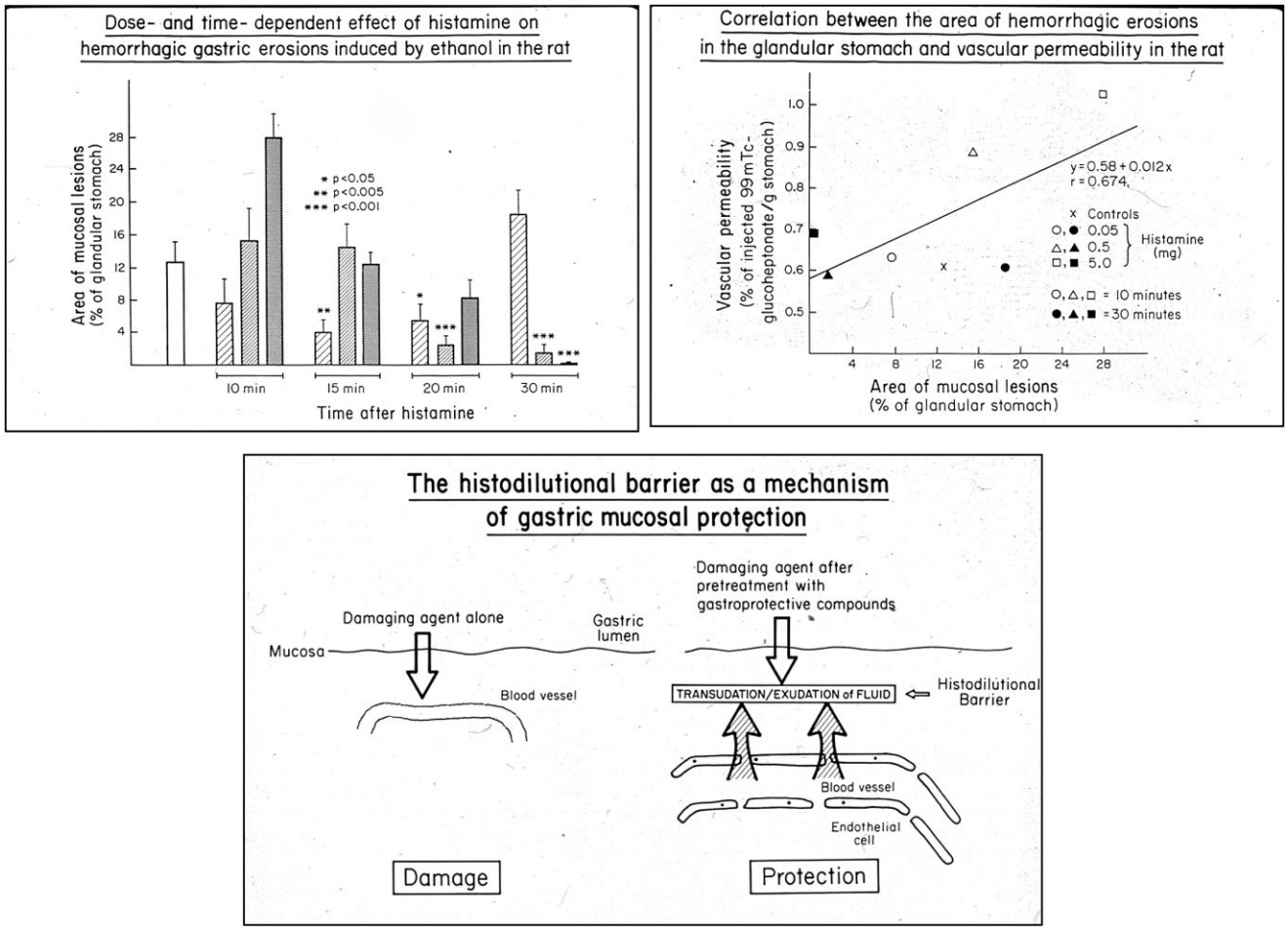

Figure 2 Dose- and time-dependent effect of pretreatment with histamine on ethanol-induced gastric hemorrhagic erosions in the rat (top left); correlation of vascular permeability and hemorrhagic mucosal lesions in rats (top right); and illustration of histodilutional barrier as a mechanism of acute gastric mucosal protection (bottom). □, Controls; ▨, 0.05; ▨, 0.5; ▩, 5.0.

chemicals may induce severe early vascular injury, resulting in microcirculatory stasis, hypoxia, and necrosis. This new mechanistic explanation of gastroprotection is consistent with previous findings like "adaptive cytoprotection" (originally described by Robert *et al.*), that is, when pretreatment of rats with—low concatenations of ethanol or HCl or NaOH prevented the hemorrhagic erosions caused by concentrated solutions of these chemicals.[38] Namely, these "mild irritants" cause mild acute inflammation in the gastric mucosa where the first event is slightly increased vascular permeability and tissue edema. Furthermore, the well-demonstrated increased bicarbonate and mucus secretion by PG and numerous other gastroprotective drugs could also result in luminal dilution of damaging agents whose access to subepithelial blood vessels may be further delayed by the perivascular edema created in this mild hyperacute inflammation that Andre Robert called "gastric cytoprotection." It may well be that gastric motility stimulants which also prevent the ethanol-induced hemorrhagic mucosal erosions also contribute to this pre-epithelial mucosal defense mechanism.[39] The new multicomponent physiologic defense mechanism is also consistent with previous vascular studies, that is, although markedly increased vascular permeability is pathologic, slight increase in this permeability seems to be protective, that is, a key element in the complex pathophysiologic response during acute gastroprotection.

Long-lasting gastroprotection and its likely mechanism

Although "gastric cytoprotection," as originally described,[1,2] is strictly an acute phenomenon which is related to the prevention of mucosal lesions. Over the years, more and more investigators used "gastroprotection" for the accelerated healing, that is, treatment of chronic gastric ulcers without the involvement of reduced gastric acidity. Actually, the clinically proven ulcer healing effects (without reducing gastric acidity) of sofalcone and sucralfate[3–5] suggested this possibility in the very early stages of gastroprotection research. In parallel studies, to search the mechanism(s) of acute gastroprotection, these drugs were also found to increase mainly gastric mucus secretion and to strengthen the poorly defined "mucosal barrier." Yet, for accelerated healing of existing gastroduodenal ulcers, strengthening the already broken

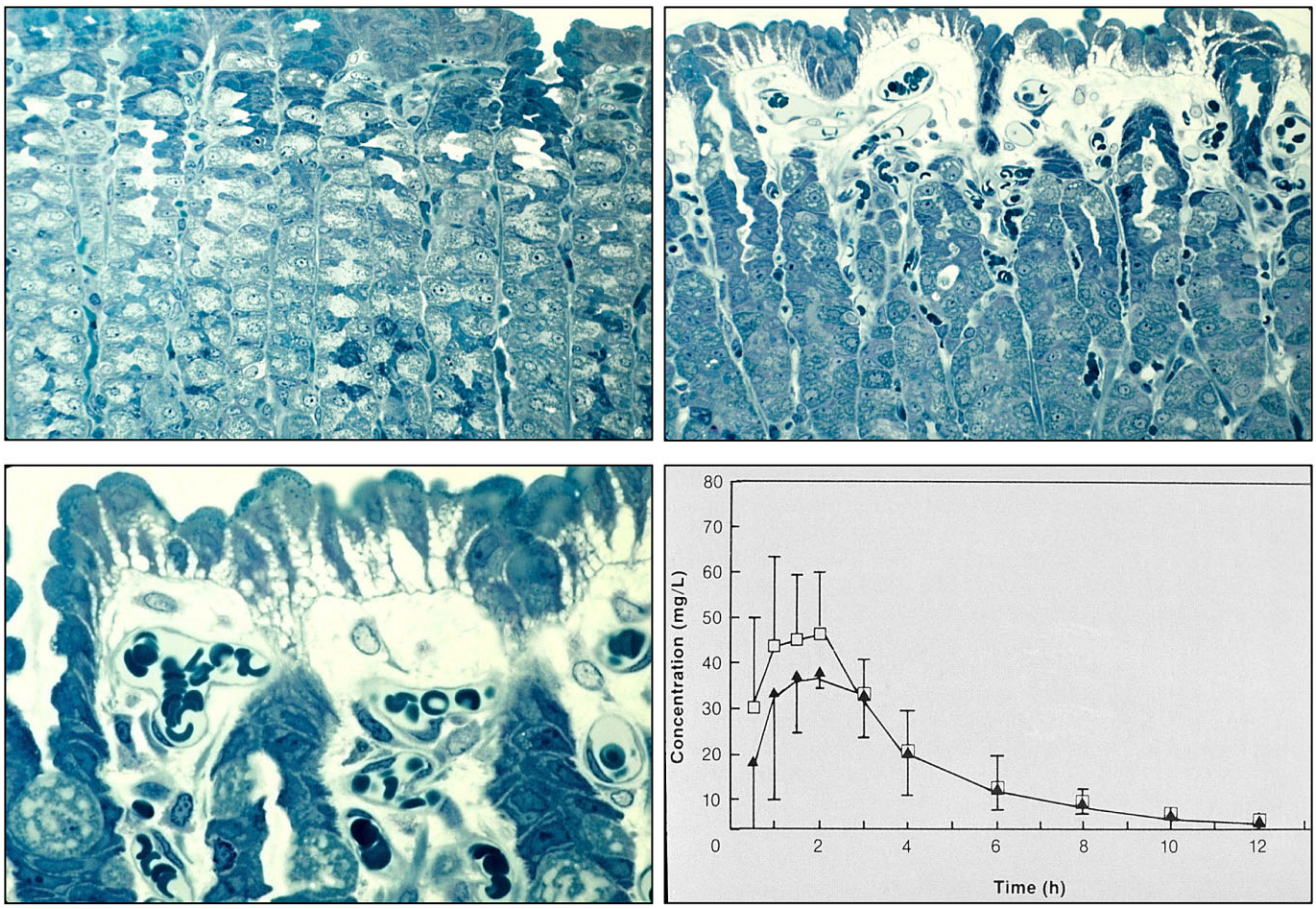

Figure 3 Toluidine blue-stained (1 μm) sections of a rat stomach. Control rat (top left).
After injection of small doses of histamine that created a prominent subepithelial edema due to slightly increased vascular permeability that may result in gastroprotection again ethanol (top right and bottom left). Delayed absorption of ibuprofen in patients pretreated with sucralfate (bottom right). (Modified from References 5 and 71). □, Ibuprofen alone; ▲, Ibuprofen and sucralfate.

mucosal barrier is probably not of much value—or just another example of "true-true but unrelated" fallacy.

Because of mechanistic uncertainties, and from pathologist's point of view, gastroduodenal ulcers are internal wounds. In the late 1980s and early 1990s, we (Judah Folkman and my lab) proposed the possibility of treating ulcers with angiogenic growth factors (e.g. basic fibroblast growth factor [bFGF], platelet-derived growth factor [PDGF]), which stimulate the formation of granulation tissue that consists of angiogenesis-dependent proliferation of fibroblasts depositing collagen over which surviving and proliferating epithelial cells from the edge of the ulcer migrate and cover the large mucosal defect. Unlike Epidermal growth factor (EGF) which stimulates only the proliferation of epithelial cells—but these cells cannot grow over necrotic debris that is usually on the top of both external and internal wounds. In this respect, bFGF is misnomer, yet probably is the best candidate since it stimulates the division of not only fibroblasts and epithelial cells, but it turned out to be the first angiogenic peptide.[40,41] The targets of PDGF are mainly epithelial cells and fibroblasts, with mild angiogenic action (Table 1). Of course, in this respect, the most potent and specific angiogenic growth factor is the later discovered vascular endothelial growth factor, which unlike bFGF and PDGF, has a differential effect on healing gastroduodenal ulcers *versus* ulcerative colitis.[42,43]

In addition to recognizing the cellular targets of these growth factors, a breakthrough had been the recognition that bFGF-like peptides bind to heparin, and this binding could be used to isolate bFGF from solution and tissue homogenates.[44] Since we previously also investigated the acute gastroprotective effect of not only the entire molecule of sucralfate but also its components (e.g. sucrose octasulfate, sodium sulfate alone),[45] we realized that the structures sucrose octasulfate and heparin are similar (Fig. 4), and thus, sucralfate might also bind bFGF (Fig. 5). Indeed, we found not only a strong *in vitro* binding between these two molecules but also that in rats with cysteamine-induced chronic duodenal ulcers and treated with sucralfate, a large amount of bFGF was recovered from the site, as this associated with a rapid healing of these experimental ulcers (Fig. 5).[46] We thus proposed that sucralfate-like drugs that bind and deliver to ulcer site angiogenic growth factors might be natural alternative not only to antiulcer drugs which inhibit gastric acid secretion, but also for patients who do not respond to traditional antiulcer regimen, including anti-*H. pylori* drugs.[43,47,48]

Table 1 Comparisons of biologic effects and molar potencies of antiulcer doses of growth factors biologic effects

Peptides	Gastric acid	Duodenal bicarbonate	Epithelial cell proliferation	Fibroblast proliferation	Angiogenesis
EGF	↓	↑	++	+/–	+/–
bFGF	–/↓	–	+	++	++
PDGF	–	–	+	++	+
VEGF	–	?	–	–	++

Antiulcer doses in cysteamine-induced chronic duodenal ulcers in rats

	bFGF	PDGF	VEGF	Cimetidine
Antiulcer doses (/100 g)	100 ng	500 ng	1 μg (1 000 ng)	10 mg (10^{10} pg)
Molecular weight	18 000	34 000	45 000	252
1 pmol	18 ng	34 ng	45 ng	252 pg
Antiulcerogenic doses in pmol/100 g	5.6	14.7	22.2	39 682 540.0
Molar comparison	7 086 168	2 699 492	1 787 502	1

bFGF, basic fibroblast growth factor; EGF, Epidermal growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor

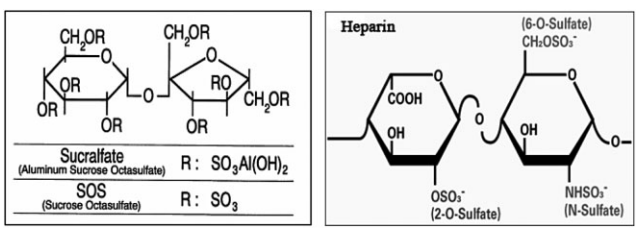

Figure 4 Chemical structures of sucralfate and heparin.

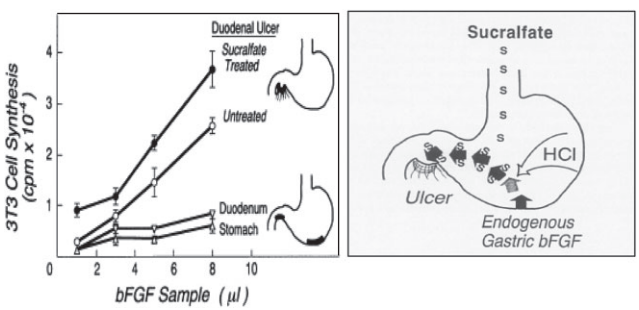

Figure 5 Illustrations of increased bioavailability of basic fibroblast growth factor recovered from sucralfate-treated rats. (Modified from Reference 46).

Other investigators not only confirmed our findings with sucralfate and bFGF, but they also expanded to similar results and implications with sofalcone.[49–54] Despite these new advances in understanding the mechanism of ulcer healing effect of sucralfate and sofalcone, no new molecules on the principle of sucralfate + bFGF have been patented so far. Nevertheless, we can now propose a new mechanism of action of antiulcer drugs (e.g. sucralfate, sofalcone) which accelerated ulcer healing without interfering with the natural function of stomach (i.e. secreting HCl which is essential for digestion and maintaining the predominantly sterile environment of gastric lumen): these drugs seem to bind and deliver heparin-binding growth factors (e.g. bFGF, PDGF) to the ulcer site to stimulate angiogenesis, granulation tissue production, leading to re-epithelization and restoration of gastroduodenal mucosal integrity.

The growing clinical need to find novel gastroprotective drugs

There is a clinical need to find and develop new drugs to prevent and/or accelerate the healing of both *H. pylori*-positive and negative gastroduodenal ulcers. The latter is related to the growing problems that reached public health proportions with the widespread use of NSAID drugs with their inherent ulcerogenic "side" effects, even at surprisingly low doses[55,56] and increasing proportion of *H. pylori*-negative ulcers which are resistant to conventional antiulcer drugs.[57–62] With the growing medical need to use NSAID, for example, not only for their traditional anti-inflammatory properties like in rheumatoid arthritis and similar conditions but also for prevention of myocardial infarction and colon cancer[55,56] in the ageing population worldwide, we surely need more specific antiulcer and gastroprotective drugs.

This is reinforced with the well-known side effects of antisecretory and antimicrobial (i.e. anti-*H. pylori*) drugs. Soon after the widespread use of new, potent antisecretory dugs like H2 receptor antagonists, but especially after the availability of proton pump inhibitors (PPI), clinical reports started to appear indicating that use of these drugs for the prevention of stress-induced gastric ulcers in hospital intensive care units (ICU) resulted in marked increase of aspiration pneumonias.[63] This was actually not surprising, since after the virtual elimination of gastric acid, especially by PPI, Gram-negative and positive bacteria start to proliferate in the gastric lumen, the aspiration of bacteria-laden gastric content in ICU settings led to severe, often lethal pneumonias. These complications in hospitalized patients did not happen if sucralfate was used in the ICU. Thus, more and new gastroprotective drugs like sucralfate and sofalcone are needed not only in hospitalized patients but in those whose gastric secretion needs not to be reduced.

It's often overlooked that only about half of "peptic ulcer" patients have higher than normal gastric acid secretion.[3] Furthermore, conceptually and ethically is untenable to suppress the normal physiologic functions of an organ just to treat a very small localized lesion, that is, an internal wound or ulcer. We never treat pulmonary, cardiac, renal, or hepatic patients by suppressing the physiologic functions of these organs. Why would be the stomach and duodenum an exception?

Fortunately, there are other new drug development projects in search of novel gastroprotective medicines which do not influence physiologic gastric acid secretion. After recognizing the gastroprotective effects of endogenous and exogenous SH compounds,[6] we wanted to add SH groups to aspirin and other NSAID derivatives. Unfortunately, aspirin-SH was patented in the 1950s in series poorly defined chemical modification of this drug, but the parallel intragastric administration of SH-containing drugs (e.g. N-acetylcysteine/Mucomyst, D,L-methionine) with ethanol or aspirin in rats was effective[64] and showed promising results even in a single clinical trial, but the sponsoring company did not want to continue the development of new drug combination approach to gastroprotection (unpublished observation). The laboratories of Lichtenberger and Wallace seem to be more successful in new drug developments based on the concept of attaching either phospholipid and NO or H2S molecules, respectively, to NSAID to diminish the gastrotoxicity of NSAID derivatives while preserving their beneficial therapeutic (e.g. anti-inflammatory, pain reducing and inhibition of platelet aggregation) effects.[65–70]

Thus, the concept of "gastric cytoprotection" is not only still relevant, and the underlying mechanisms still need to be investigated, but the future for the introduction of new drugs which protect the stomach without interfering with its physiologic functions (e.g. acid secretion) is very promising. It is hence not surprising that although some conferences on this topic have been discontinued, another series of international symposia devoted to cell injury and cytoprotection are still continuing.[71]

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