Gastroduodenal Mucosal Integrity and Influencing Factors

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ABSTRACT

Gastroduodenal mucosal integrity has important role in the pathogenesis of gastroduodenal ulcer. It depends on imbalance between aggressive and defensive factors. However, many experts believe that defensive factors has more dominant role. Maintenance of gastrointestinal endothelial integrity appears to define the "cytoprotection" phenomenon and, as discussed below, is a critical component of NSAID-induced GI injury and a potential target for therapeutic intervention.

***Keywords**: mucosal integrity, aggressive factors, defensive factor, cytoprotection*

INTRODUCTION

Since many centuries ago, experts had continued to study gastrointestinal (GI) tract function and its protective mechanism. For many years, a lot of works had been done in search of how intestine and stomach can prevent damage from endogenous aggressive substance such as digestive enzymes, gastric acid and bile acids. Gastrointestinal tract always has direct contact to external environment, and that is why it must have some mechanism that can protect it from dangerous substances and pathogenic microorganism which enter digestive system together with food.

In normal condition, there is a balance between aggressive factors and defensive factors which maintain gastrointestinal mucosal integrity. In peptic ulcer, defensive mechanism is outweighed by intraluminal aggressive factors such as acids, pepsin, NSAID and *Helicobacter pylori.*

Three hundreds and fifty years BC, Hypocrates had mentioned about the symptoms of gastritis. In 1772 Hunter outlined first hypothesis of gastric protective mechanism to autodigestion through adequate blood flow. This was supported by Virchow (1853) who believed that blood flow has acid neutralization effect. The opinion that gastric mucosa produces acid had been delivered by Prout (1823) and Beaumont (1826). The role of acid in the pathogenesis of ulcer was supported by Schwartz (1910) who conveyed *No Acid, No Ulcer* dictum.

The role of mucus as one of defensive factors had been endorsed by Glover (1800) and Harley (1860). Paplov (1898) believed that mucus layer was alkali and could neutralize acids. This was countered by Heatly (1959) who stated that back diffusion of gastric acid was neutralized by bicarbonate secreted by gastric mucosa.[1,2,3,4] Although recently it has been postulated that peptic ulcer is due to imbalance between aggressive and defensive factor, however, many experts had concluded that defensive factors has dominant role in maintenance of gastroduodenal mucosal integrity.[5]

THE THREE LEVELS OF MUCOSAL DEFENSE

Almost in the last 3 decades, studies on defensive mechanism of gastrointestinal tract were intensively conducted. Recently, it has been widely accepted that defensive mechanism involves 3 elements:[1,4]

1. Pre-epithelial factors that are secreted into the lumen including mucus, acids, bicarbonate and antibacterial substance like immunoglobulin, and lactoferin. In this matter, the main function of acid is to reduce amount of bacteria that entering intestinal lumen. Mucus layer that covers gastrointestinal tract from gaster to colon is the frontline defense mechanism to aggressive factors. Mucus functions as barrier to noxious substances diffusion, trap for microorganism, interact with immune system of gastrointestinal tract and also acts as lubricant. Mucus is cohesive compound of water (95%) and mucinous glycoprotein (5%). Lipid is pressumed to have important role in the formation and strengthening of mucus.[1,6]
2. Epithelial factors consist of cell membrane,

intercellular tight junction, plasma membrane and restitution. Restitution is a rapid improvement process of damaged epithelial cells by migrating normal epithelial cells to damage epithelial cells.[1,7,8]

3. Subepithelial factors consist of mucosal blood flow, nervous system, some inflammatory mediators and immune system like macrophage and mast cells.

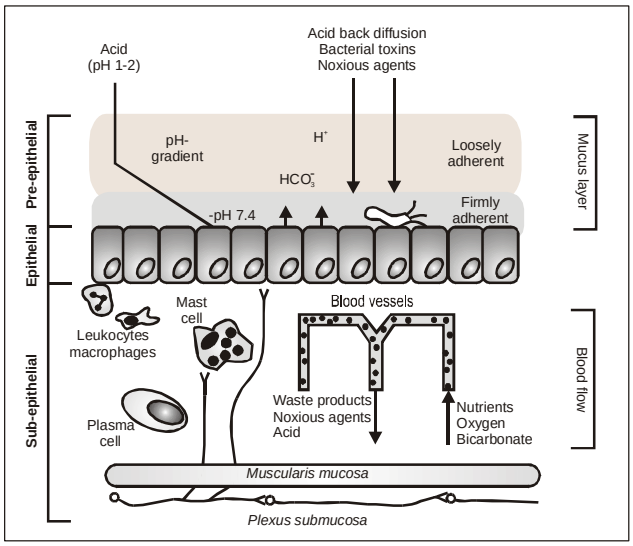

Figure 1. The three levels of mucosal defense.[1]

CONCEPT OF CYTOPROTECTION

The findings of H_2 receptor antagonist and proton pump inhibitor can accelerate healing process of gastro duodenal ulcer. However, recurrent ulcer can not be fully prevented. The formation of ulcer is not always induced by high acidity of gastric acid, especially in the elderly which sometimes known to have low acidity level of gastric acid.

In 1979, Robert et al reported that pretreatment of gastric mucosa with oral or subcutaneous prostaglandin (PGs) might prevent gastric necrosis after contact with damaging substance such as ethanol, HCl, NaOH, hypertonic NaCl and even heat. This phenomenon is known as cytoprotection.

Cytoprotective mechanism is not related to acid secretion. Although cytoprotective mechanism is not wholly understood, it is presumed to have included several points:[3,5,7]

- Prevent damage of gastric mucosal barrier
- Stimulate mucus production and bicarbonate secretion
- Enhance mucosal blood flow to maintain adequate oxygen supply for aerobic metabolism
- Induce cellular transport process and eliminate H^+ back diffusion
- Stimulate macromolecule system
- Increase role of phospholipids and sulphydril at cell surface

There are 2 cytoprotective mechanisms, adaptive mechanism and direct cytoprotection. Adaptive cytoprotection occurs because of formation of endogenous prostaglandin due to contacts with mild irritant substances, while direct cytoprotection is due to exogenous prostaglandin.[5,7]

Several studies showed various factors that influence cytoprotective mechanism. In 1985, Itoh and Guth had proved that free radicals like superoxide had important role in gastroduodenal mucosal damage. This can be reduced by treatment using free radicals scavenger such as superoxide dismutase (SOD). Recently, it has been demonstrated the role of heat shock protein/stressprotein in gastroduodenal mucosal protection.[5,6,7]

THE ROLE OF INFLAMMATORY MEDIATORS

Gastroduodenal mucosal integrity depends on the balance between defensive and aggressive factors in the lumen. Some of components of gastroduodenal mucosal defense are influenced by various inflammatory mediators like nitric oxide (NO), eicosanoid (prostaglandin, leucotrien, thromboxan), platelet activating factor (PAF), neuropeptides, cytokines and some proteinase enzymes.

1. Nitric oxide (NO)

There are some controversies regarding the role of NO in GI tract whether it is protective or destructive. However, many experts believe that NO together with prostaglandin has become one part of defensive factors through the following mechanism:[3,10]

a. Modulate immunocytes activity of mucosa such as mast cells and intestinal endothelial permeability
b. Inhibit infiltration to GI mucosa
c. Reduce neutrophils adherence and secretion
d. Increase mucus and electrolyte secretion

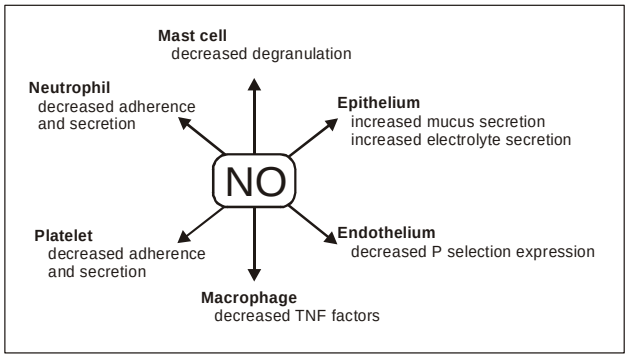

Figure 2. NO contributes to mucosal defense in a number of different ways.[3]

2. Eicosanoid

a. Prostaglandin

Prostaglandin is formed from arachidonic acid through cyclooxygenase (COX) enzyme activity. There are 2 isoform of COX; COX-1 and COX-2. Prostaglandin that is produced by COX-1 pathway has defensive factor properties on GI tract:

- Stimulate mucus secretion and bicarbonate
- Maintain optimal mucosal blood flow
- Increase resistance of epithelial cells to damage due to cytotoxin
- Inhibit leukocyte infiltration if there is mucosa inflammation

Meanwhile, prostaglandin which is produced through COX-2 pathway has detrimental effect because of its pro-inflammatory property will cause edema, fever and pain. In this context, recently, new class of drugs that selectively inhibit COX-2 have been developed, so that they may have more potent anti inflammation and analgesic effect but less ulcerogenic.

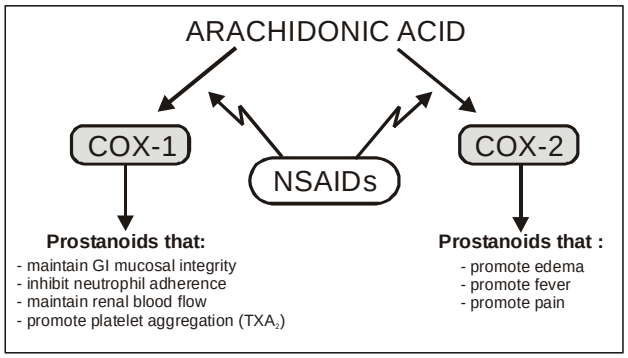

Figure 3. Schematic diagram of the relative roles of COX-1 and COX-2[3]

However, nowadays there are still questions on the role of COX, especially known as COX-2 hypothesis, because evidences were rather against the theory above:[3,11]

a. Some COX-2 inhibitors only induce anti-inflammatory effect on experimental rats if it was given at dose that also inhibit COX-1
b. Giving the selective inhibitor COX-2 to experimental rats had minimal effect to GI tract, but in fact, there are still many reports on the incidence of ulcer or bleeding or perforation even after consumption of these drugs

b. Leukotrien [3,10]

Leukotrien is synthesized from arachidonic acids through 5-lypooxygenase enzyme activity. There are 2 kinds of leukotriens B4 (LTB_4) and peptidoleukotrien. Synthesis of leukotrien occurs mainly in immnunocytes especially mast cells, epithelial cells and endothelial cells. The two leukotrients have bad impact on GI mucosa. The impacts of LTB_4 on GI tract:

1. Induce leukocyte infiltration
2. Stimulate oxygen reactive metabolite secretion from neutrophils which will cause mucosal inflammation
3. In the pathogenesis of NSAID gastropathy, LTB_4 will stimulate leukocyte adherence to epithelial vascular vessel. The same thing happens in the pathogenesis of ulcer due to *Helicobacter pylori* infection
4. Has role in pathogenesis of inflammatory bowel disease (IBD)

The bad influence of peptidoleukotrien on GI mucosa is presumed through increased endothelial vascular permeability and increased secretion of selectin P and mast cell activation.

c. Thromboxan

Thromboxan is main metabolite of arachidonic acid produced by thrombocytes (through COX-1). Thromboxan is a potent vasoconstrictor and anti thrombocyte aggregation. It has role in inducing gastroduodenal ulcer because it can reduce mucosal blood flow, stimulate formation of LTB4, increase leukocyte adherence and thus increase inflammatory response.

3. Platelet Activating Factor (PAF)

PAF is produced from phospholipids through activation of phospholipase enzyme. PAF is a potent ulcerogenic factor. The role of PAF in the destruction of gastroduodenal mucosa is believed through its effects to increase leukocyte adherence of endothelial vessel and activation of granulocytes to secrete oxygen reactive metabolite. In small intestine, PAF is presumed to have role in process of neutrophils infiltration to lamina propria in the case of helminthiasis. PAF is also presumed to have role in the pathogenesis of neonatal necrotizing enterocolitis and IBD.

4. Neuropeptides

Peptide mediators produced by intrinsic and extrinsic nerve fibers of GI tract. One of neuropeptides that has important role in defensive mechanism of GI tract is calcitonin-gene related peptide (CGRP). If there are irritant substances in gastric lumen, CGRp is released by the sensory afferent nerve fibers whichinduce NO release from endothelial vascular and cause dilatation of submucosal arterioles. This will increase mucosal blood flow which helps dilute, neutralize or even hamper back diffusion of acid and toxins/irritants. Mucosal defensive mechanism through CGRP is inhibited by capcaisin.[1,3]

Mast cell has role in defensive mechanism of gastric mucosa like CGRP. Afferent sensory nerves in GI tract can release P substance which will activate mast cell to release histamine that causes submucosal arteriole dilatation/hyperemic mucosa of GI tract as part of defensive mechanism to intraluminal irritant substances.

5. Cytokine

Cytokine has important role in regulation of mucosal GI immune system especially in the intestine and colon. One of main factors in the pathogenesis of IBD is presumed due to imbalance production between pro and anti-inflammatory cytokines. Three widely known cytokines are interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α) which have pro-inflammatory properties and interleukin-10 (IL-10) which has the anti-inflammatory property. In patients with IBD, there is increased level of plasma IL-1. IL-β, and TNF-α that are released in early phase of inflammation and infection, have effects on appetite and induce fever. As mater of fact for the upper GI tract, for example in cases of NSAID gastropathy, IL-1, on the contrary, could reduce mucosal damage by inhibiting to leukocyte adherence, stimulate prostaglandin and NO release. IL-1 also inhibits the release of ulcer promoting mediators such as PAF and histamine from mast cells. Meanwhile, TNF-α has role in mechanism of gastric mucosal damage in association with *Helicobacter pylori* infection.[2,6] Prostaglandin is a potent inhibitor of TNF-α release by macrophage and mast cells. TNF-α is also assumed to have role in the pathogenesis of IBD.

IL-10 is mainly produced by lymphocyte cells of Th_2, Th1 and monocyte. IL-10 suppresses production of pro-inflammatory cytokines. Akagi et al[2] reported increased TNF-α and interpheron-γ level, decreased IL-10 in patients with Crohn's disease.

6. Proteinase

Proteinase (e.g. thrombin, tripsin, and triptase) has role in protein degradation and cell regulation through breakdown of proteinase activated receptors (PARs) which is part of protein G receptor. We have known 4 kinds of PARs; PARs 1, Pars 2, Pars 3 and PARs 4, generally released by spinal afferent nerve fibers. Activation of PARs causes release of neuro-transmitters that modulate mucosal GI defensive mechanism.

THE ROLE OF NUTRIENT ON GASTROINTESTINAL MUCOSAL INTEGRITY [12,13]

Gastrointestinal acts as barrier to external environment and main entrance of nutrient. In order to maintain both functions, intestinal epithelial depend much on nutrition from lumen and blood flow. In case of maintenance of mucosal integrity, there are some nutrients which have role in it such as glutamine, vitamin A, vitamin E, probiotic and prebiotic.

Glutamine

Glutamine has important role in rapid turn over of cells including intestinal cells. Glutamine from food is assumed to have important role in glutathione synthesis of gastrointestinal and acts as one of antioxidant.

Arginin

Arginin is an amino acid which has role in nitrogen transport and excretion as precursor of NO functioning in maintenance of gastrointestinal mucosal integrity.

Vitamin A

Vitamin A has important role in preservation of epithelial cell integrity, immune function and retinal function. Deficiency of vitamin A cause disturbance of barrier function from gastrointestinal tract. Studies on experimental rats with vitamin A deficiency showed reduced intestinal cells differentiation and reduced goblect cells in crypti and vilus.

Vitamin C and E

In experimental rats which were exposure to X-ray, both vitamin C and E gave protective effect through dual mechanism. First, as the anti oxidant for free radicals and second indirectly strengthen mucosal barrier by increasing synthesis and secretion of prostaglandin which will increase thickness of mucus and phospholipids layer.

Probiotic

Probiotic is defined as microorganism in food which is fermented and has role in maintaining the balance of intestinal microflora such as lactobacillus and bifidobacteria. Probiotic increases immune system of intestinal mucosa both in experimental animal and human. Human study indicated probiotic could prevent traveler diarrhea due to Eschericia coli and presumably also had theurapeutic effect in patients with IBD.

Prebiotic

Prebiotics is nondigestable food which had favorable effect to human body by stimulating selectively certain commensally bacterial growth and activity in colon. Oligosacharydes derived from various plants such as onion or banana can stimulate growth of bifidobacteria and lactobacillus in colon.

Direct actions of prebiotics on gastrointestinal tract are improved intestinal function, increase luminal absorption, increase lipid metabolism and reduce risk of colon cancer.

THE ROLE OF MEDICATION

Recently, many researches had been conducted to find drugs that can increase defensive capacity of gastric mucosa. One of them is teprenone which is a polyisoprenoid derived from vitamin A.[14,15]

Protective effect of teprenone is presumed through following mechanisms:

- Increase glycoprotein content of gastric mucus and mucus layer, preserve normal structure of mucus

and inhibit glycoprotein reduction of mucus by aspirin
- Increase hidrophobicity of gastric mucosa
- Increase endogenous prostaglandine level
- Increase blood flow and gastric mucosa regeneration
- Direct action as free radical scavenger
- Teprenone had been proven to have capacity to induce heat shock protein (HSP) as mucosal cytoprotection

CONCLUSION

- In normal condition, there is balance between aggressive and defensive factors to maintain gastrointestinal mucosal integrity
- Mucosal defensive mechanism of gastrointestinal tract involves three elements which are pre-epithetlial, epithelial, and subepithelial factors
- Various kinds of inflammatory mediators such as NO, eicosanoid (prostaglandin, leukotrien and thromboxan), PAF, neuropeptide, cytokine and proteinase and some nutrients known as functional food have impact on gastrointestinal mucosal integrity
- Some of medications that already known (e.g. teprenone) can increase gastric mucosal defensive capacity

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