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Effects of *Helicobacter pylori* and Non-Steroidal Anti-Inflammatory Drugs on Peptic Ulcer

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1. Introduction

Peptic ulcer (PU) was a local gastrointestinal lesion due to gastric fluid, gastric acid and pepsin insult. The lesion may involve in mucosal layer, submucosal or even muscle and plasma layer in duodenum and stomach. It was characterized as not only easy to relapse but also hard to prevent (Wang *et al.*, 1998). Its etiology and mechanism was very sophisticated due to the imbalance between offensive factors (gastric acid, pepsin, *H. pylori* and NSAIDs) and defensive factors (gastric mucus, bicarbonates and blood flow of gastric mucosa) (Hoogerwerf & Pasricha, 2006). There were at least 3 defensive barriers in the gastric wall to resist gastric acid and pepsin: the mucus-bicarbonates barrier that includes mucus and the bicarbonates grade in the mucus, the mucosa barrier that is the tight conjunction structure among gastric epithelial cells, and the blood flow in mucosa that provides oxygen and nutrition to mucosa and support the turnover of gastric epithelium and mucus. *H. pylori* and NSAIDs were gastric mucosa's offensive factors (Tytgat, 2000). Although they cause peptic ulcer by destroying the gastric barrier function, the mechanism was not clear. There were arguments for their simultaneous effects on peptic ulcer (Fendrick *et al.*, 2001). Therefore, it is important to clarify the relationship between *H. pylori* and NSAIDs, especially when both cause simultaneously the damage to gastric mucosa.

2. *H. pylori* and peptic ulcer

H. pylori results in peptic ulcer through damaging gastric mucus and mucosa barriers, and enhancing gastric acid secretion.

2.1 Damages of gastric mucus and mucosa barriers

When *H. pylori* infects the stomach, it can produce cytotoxin-associated gene A protein (CagA), vacuolating cytotoxin A (VacA), urease, mucus enzyme, lipase and phospholipase to injure the gastric mucus and mucosa barriers, and finally results in the peptic ulcer with the combination of gastric acid and pepsin.

Vacuolating cytotoxin and cytotoxin-associated protein: VacA is expressed in *H. pylori* and results in vacuolar degeneration in gastric epithelium through interfering ion transport protein, eg. vacuolar ATPase (Leunk *et al.*, 1988). CagA is up-regulated in VacA⁺ strain and related to VacA activity. 60~70% of *H. pylori* strains express CagA and thereby induce host

cells to produce cytokines, enhance inflammatory reaction and damage the gastric mucosa (Ghira *et al.*, 1995). CagA is immunogenic and induces gastric epithelial cell to produce interleukine-8 (IL-8) that causes strong immunoreactions and results in gastric mucosa injury (Ernst *et al.*, 1994).

Urease: *H. pylori* can produce urease. This enzyme locates on the *H. pylori*'s surface and introcytoplasma (Phadnis *et al.*, 1996; Bode *et al.*, 1989) and hydrolyses urea into ammonia. Ammonia can decrease the content of mucin in mucus and destroy the integrity of the ion in mucus, and finally decline the function of mucus barrier that results in the diffusion of hydrogen ion back to the stomach wall and the erosion of mucosa layer (Hazell *et al.*, 1986). Ammonia can also deprive alpha-ketoglutaric acid that is a middle metabolic substance in Kreb's cycle, and thus, this cycle is blocked and the metabolism of cells is interfered, and finally the ATP production decreases and the Na⁺-K⁺ pump on the cellular membrane is out of order. It may result in cellular edema, degeneration and necrosis, and the barriers of mucus and mucosa are finally destroyed and the ulcer is formed (Marshall, 1994). The hydroxy created from ammonia and water has cytotoxic effect on gastric mucosa. A high concentration of ammonia can cause cellular vacuolar degeneration (Xu *et al.*, 1990). Urease can also cause directly the tissue damage of host (Windsor *et al.*, 2000). *H. pylori* can stimulate neutrophils and cause oxidative burst, and thereby result in the production of H₂O₂ and oxygenate oxy-chloride ion. This ion can further combine ammonia and form more toxic monochloramine that participates in the process of mucosa injury (Sarosiek *et al.*, 1989). The urea may serve as leukocyte chemotactic factor to attract inflammatory cells, cause local inflammation in the stomach, and damage indirectly the gastric epithelium.

Mucus enzyme and pepsin: *H. pylori* can produce mucolytic enzyme that causes the gastric mucous degradation. The degraded mucus losses its viscosity and elasticity and thus, allows the diffusion of hydrogen ion back to the stomach wall and the erosion of mucosa layer. The decreased viscosity of mucus benefits the movement of *H. pylori* and makes *H. pylori* easier to plant on the stomach wall. The decomposed mucus can also provide nutrition necessary to *H. pylori* (Beales *et al.*, 1996). *H. pylori* can also generate an extracellular protease that was able to split the polymer of glycoprotein in gastric mucus and wipe out the gastric mucous barrier so as to allow the gastric epithelium to contact directly with attack factors such as gastric acid, pepsin, cholic acid and drugs. Finally, the gastric epithelial erosion appears (Kawano *et al.*, 1990).

Lipase and phospholipase: the normal cell membrane is composed of double phospholipid layers. *H. pylori* can produce phospholipase A that hydrolyzes palmityl lecithin into free palmitic acid and lysolecithin and thereby destroy the integrity of the cellular membrane (Goggin *et al.*, 1991). The lipid and phospholipid in the gastric mucus play an important role in the maintenance of mucous viscosity and hydrophobic characters and in the prevention of hydrogen ion from diffusion back to the stomach wall (Goggin *et al.*, 1991). The lipase and phospholipase A can hydrolyze lipid and phospholipid in the mucus and thus obliterate the function of mucous barrier. Phospholipase A can also enhance the release of arachidonic acid and generate inflammatory media such as prostaglandin and thromboxane that induce inflammatory reaction. The metabolism of phospholipid, such as lysolecithin, also has cytotoxic effect (Lewis *et al.*, 1990).

Alcoholic dehydrogenase: Alcoholic dehydrogenase generated by *H. pylori* can oxygenate alcohol into acetaldehyde that is a strong oxidizer and causes the injury of mucosa.

Lipopolysaccharide (LPS): LPS produced by *H. pylori* can stimulate gastric epithelial cell to secrete IL-8 that can induce local inflammatory reaction in infected stomach. LPS also stimulates the pepsinogen secretion in gastric epithelium. Pepsin hydrolyses the protein in gastric epithelium, originates epithelial injury and causes ulceration (Young *et al.*, 1992). LPS from *H. pylori* has similar antigenic determinants to human being, such as Lewis type 2, e.g. Lewis X and Lewis Y. These similar antigenic determinants also distribute in the surface of parietal cell and gastric gland. The patient with *H. pylori* infection may generate antibody for Lewis antigenic determinants. Therefore, the mucosa barrier will be injured by autoimmune reaction (Appelmelk *et al.*, 1996).

Free radical: When *H. pylori* infects the stomach, it can adhere to gastric epithelium via its surface structure such as N-acetylneuraminic lactose fibril haemagglutinin, extra cellular S adhesin and Lewis B blood-group antigen adhesin, etc (Lundstrom *et al.*, 2001; Domingo *et al.*, 1999; Dundon *et al.*, 2001; McGee *et al.*, 1999). Neutrophil chemotactic factors such as VacA, CagA and neutrophil activating protein (NAP) are released (Atherton *et al.*, 1997; Naito *et al.*, 2002; Satin *et al.*, 2000; Yoshikawa *et al.*, 2000). Furthermore, *H. pylori* stimulates gastric epithelium to secrete interleukin-8 (Shiotani *et al.*, 2002; Bhattacharyya *et al.*, 2002) that is a strong neutrophil chemotactic factor. These white blood chemotactic factors result in the occurrence of inflammation. Neutrophils, monocytes, lymphocytes and macrophage may infiltrate into mucosa and release a big amount of free radicals. Lipids and proteins in epithelium are peroxidized, and the cellular structure and function were damaged, and finally the epithelial barrier was destroyed.

Hemolysin: *H. pylori* can secrete hemolysin that has cytotoxic effects, induces inflammatory reaction, and results in the injury of epithelial barrier (Wetherall *et al.*, 1989).

In addition, *H. pylori* inhibits the expression of constitutive nitric oxide (cNOS) and enhances the expression of inducible NOS (iNOS) that may lead to the overproduction of NO and the excessive generation of toxic radical peroxynitrate that is involved in the gastric cell inflammatory response and cellular damage (Brzozowski *et al.*, 2006).

2.2 Increases of gastric acid

H. pylori causes the release of urease and the formation of ammonia. Ammonia increases the pH on the surface of epithelial. Consequently, the gastrin secretion increases. Gastrinemia stimulates parietal cell to secrete gastric acid. Persistent gastrinemia causes the proliferation of parietal cell and the further production of gastric acid. Gastric acid is a strong attack factor and causes ulceration formation (Levi *et al.*, 1989). Other study demonstrated that *H. pylori* inhibit the secretion of somatostatin (SS) in sinus ventriculi D cells. SS inhibits the secretion of gastrin in sinus ventriculi G cells. The reduction of somatostatin weakens the control of gastrin secretion and thus prolongs the postprandial gastric acid secretion and causes ulceration (Kaneko *et al.*, 1992). *H. pylori* has a growth inhibitory factor that inhibits the turnover of mucous epithelial cells.

3. NSAIDs and ulceration

NSAIDs, such as aspirin and indometacin, are effective drugs for anti-inflammation, anti-rheumatics, antipyretics and analgesics. Furthermore, NSAIDs, due to their effect on anti platelet aggregation, are regular prophylaxis drugs for cardiac and brain vascular diseases (Tarnawski *et al.*, 2003). NSAIDs can also decrease the rate of colonial and rectal cancer (Husain *et al.*, 2002) and Alzheimer disease (Tarnawski *et al.*, 2003b). Therefore, NSAIDs

are widely used. NSAIDs, however, have a serious side-effect causing gastric mucosa damage.

3.1 NSAIDs direct mucosa damage

Most of NSAIDs are weak organic acids as non-ion status under acidic environment in the stomach. NSAIDs can freely pass cellular membrane to intracellular where the environment is neutral. Intracellular NSAIDs can be dissociated into water soluble ion status. The intracellular concentration of NSAIDs is much higher than the extracellular one. Therefore, NSAIDs have a direct cytotoxic effect on gastric mucosa cells (Scheiman, 1996). Furthermore, NSAIDs inhibit mitochondrial oxidative phosphorylation so as to interfere energy metabolism, inhibit the expression of heat shock proteins (HSP) related to cellular membrane integrity (Wallace, 1997), originate the injury of epithelium and the cellular exfoliation, induce the release of various inflammatory factors, such as leukotriene B4 and histamine, and finally damage capillary vascular, increase vascular permeability and reduce blood flow into the mucosa (Wallace *et al.*, 1990; Wallace *et al.*, 1995). Another effect is that NSAIDs trigger gastric epithelium to release tumor necrosis factor alpha (TNF- α). TNF- α increases adhesive molecules and activates neutrophils (Wallace *et al.*, 1995), which result in the gastric mucosa neutrophil infiltration, the submucosa capillary vascular constriction, the mucosa ischemia and hypoxia, the abnormal metabolism in epithelial cells, and finally the functional damage of mucus and mucosa barrier.

3.2 NSAIDs inhibit the syntheses of prostaglandin

Arachidonic acid may be produced from phospholipids in the membrane under catalysis of phospholipase A₂. Arachidonic acid generates leukotrienes through lipoxidase and generates PGI₂ and PGE₂ through cyclo-oxygenase. Leukotrienes are involved in allergic reaction, leukocyte chemotaxis and inflammation. PGI₂ has the effects on vasodilatation and platelet aggregation. PGE₂ is capable of inducing inflammation, fever, pain, vasodilatation and gastric mucosa protection (Scheiman, 1996).

NSAIDs may inhibit COX activity, interfere the metabolism of arachidonic acid, and decrease PG syntheses (Figure 1). Therefore, NSAIDs have the effects of anti-inflammation, antipyretics and analgesics. COX has two isoforms, one is constitutive or COX-1 and another is inducible or COX-2. COX-1 constantly expresses in gastrointestinal tract and platelets, controls the syntheses of PGI₂, PGE₂ and TXA₂, regulates angiotasis, protects the mucosa of digestive tract from assault factors, and maintains the mucosa's integrity. There is little or almost no COX-2 in the mucosa of stomach and intestine and the platelets in healthy people. LPS, interleukin-1 (IL-1) and many other inflammatory factors, however, can induce its production. COX-2 can increase dramatically in local inflammatory lesion. It may result in the increase of PGI₂ and PGE₂ that also participate in inflammatory reaction. The classic NSAIDs had no selective inhibition effect on COX-1 and COX-2. The inhibition of COX-2 results in anti-inflammation, while inhibition of COX-1 causes side effects, i.e. to decrease PGI₂ and PGE₂ that have mucosa protective effects, decline the blood flow in gastric mucosa, decrease the provision of oxygen and nutrition, slow the turnover of mucosa cells, lessen the syntheses and secretion of mucus, damage the mucus and mucosa barriers, prolong the mucosa reparation, and finally cause mucosa erosion, ulceration and hemorrhage (Pawlik *et al.*, 2002). Besides above effects, aspirin prolongs the recovery of ulceration. Its mechanism underlies on the inhibition of PG syntheses (Wang *et al.*, 1989), the reduction of cellular

proliferation (Penney *et al.*, 1994) and the decrease of blood flow at the ulcer margin (Hirose *et al.*, 1991).

4. The simultaneous effects of *H. pylori* and NSAIDs on gastric mucosa

From above discussion, we know that *H. pylori* and NSAIDs are two important factors assaulting gastric mucosa and have the pivotal role in the peptic ulcer. Each has a different way to injure the gastric mucosa. It has been confirmed that *H. pylori* and NSAIDs are two independent offending factors (Grymer *et al.*, 1984). However, the exact relationship remains to be clarified (Laine, 2002). *H. pylori* and NSAIDs may be irrelevant, additive or synergistic, or possibly antagonistic (Ji *et al.*, 2003).

4.1 *H. pylori* and NSAIDs are irrelevant

Some studies demonstrated that NSAIDs should not impact *H. pylori*'s plantation (Maxton *et al.*, 1990). The infection of *H. pylori* dose not increase the ulcerative risk in long term NSAIDs user (Kim *et al.*, 1994). The epidemic investigation showed that NSAIDs did not affect the patient's susceptibility to *H. pylori* (Graham *et al.*, 1991; Barkin, 1998; Wilcox, 1997). NSAIDs dose not enhance the gastrointestinal toxicity to *H. pylori* carrier (Rybar *et al.*, 2001). Clinical data demonstrated that *H. pylori* infection did not impinge on the degree and type of gastric mucosa injury by NSAIDs (Barkin, 1998; LANZA *et al.*, 1991).

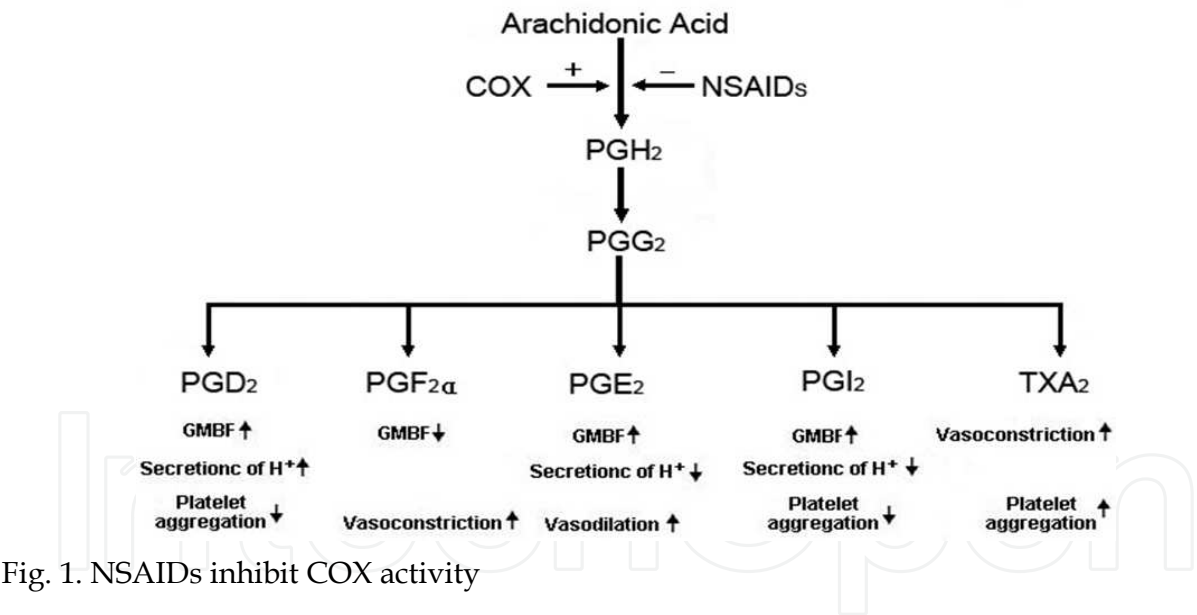


Fig. 1. NSAIDs inhibit COX activity

4.2 There is additive or synergistic relationship between *H. pylori* and NSAIDs

H. pylori and NSAIDs are strong offensive factors (Chan *et al.*, 1998). Both of them can destroy gastric barrier function. Eradication of *H. pylori* before using NSAIDs reduces the ulcerative rate (Bazzoli *et al.*, 2001). The ulceration is easier to relapse in NSAIDs takers with *H. pylori* than those without *H. pylori* infection (Chan *et al.*, 1998b). Furthermore, both *H. pylori* and NSAIDs increase permeability in the gastric epithelial cellular junction, and thus allow the gastric acid, pepsin and other endogenous offending factors to injure the gastric mucosa (Barr *et al.*, 2000). *H. pylori* and NSAIDs act synergistically through pathways of inflammation in the development of ulcers and in ulcer bleeding (Figure 2).

4.3 Antagonistic action between *H. pylori* and NSAIDs

NSAIDs have bacteriostatic and bactericidal activity against *H. pylori* (Shirin *et al.*, 2006). NSAIDs inhibit COX-1 and COX-2. This inhibition declines PG synthesis, while *H. pylori* infection stimulates gastric mucosa to express COX-2 (Takahashi *et al.*, 2000) so as to enhance PG syntheses. *H. pylori* accelerates healing of gastric ulcer induced by NSAIDs in rats due to that *H. pylori* stimulates the overexpression of COX-2 and the increase of PG synthesis, and consequently increases the production of vascular endothelial growth factor (VEGF) and the vascular proliferation. Meanwhile, PG also increases transforming growth factor alpha that causes the increase of cellular proliferation and the decrease of gastric acid (Konturek *et al.*, 2002), and finally enhances the recovery of injured gastric mucosa. The clinical trial also demonstrated that the *H. pylori* infection rate was lower in NSAIDs user than those people without NSAIDs administration (Bianchi *et al.*, 1996). It also verifies that there is antagonistic action between *H. pylori* and NSAIDs.

In conclusion, *H. pylori* and NSAIDs are individual strong factors causing peptic ulcer, and their final mechanism is to wipe out barrier function. However, the investigations are conflicts when *H. pylori* and NSAIDs coexist. The reasons leading to this conflict may be the patient's age, the different type of NSAIDs, the administration length of NSAIDs and the different strain of *H. pylori* and so on.

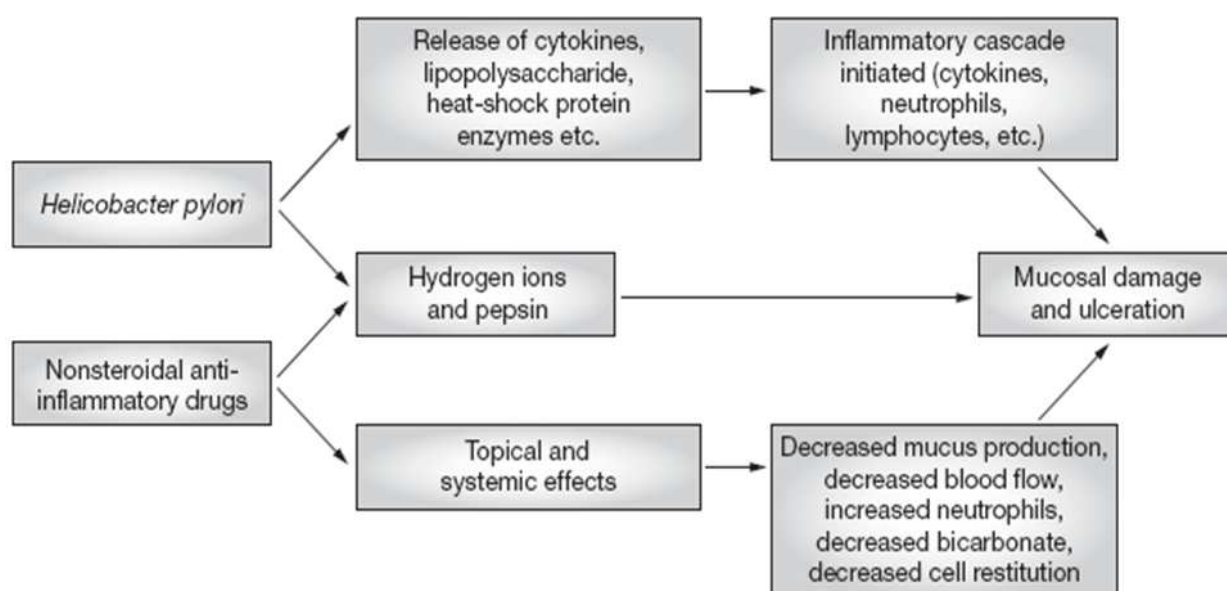


Fig. 2. *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs have synergistic effects on gastric mucosal damage. Both *H. pylori* infection and NSAID use have been found to independently and significantly increase the risk of gastric and duodenal mucosal damage and ulceration. *H. pylori* and NSAIDs act synergistically through pathways of inflammation in the development of ulcers and in ulcer bleeding (Yuan *et al.*, 2006).

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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