

● 雑誌

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## IV. 研究成果の刊行物・別刷

# Roles of oxidative stress in stomach disorders

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The stomach is a sensitive digestive organ that is susceptible and exposed to exogenous pathogens from the diet. In response to such pathogens, the stomach induces oxidative stress, which might be related to the development of gastric organic disorders such as gastritis, gastric ulcers, and gastric cancer, as well as functional disorders such as functional dyspepsia. In particular, the bacterium *Helicobacter pylori* plays a major role in eliciting and confronting oxidative stress in the stomach. The present paper summarizes the pathogenesis of oxidative stress in the stomach during the development of various stomach diseases.

**Key Words:** gastric mucosa, oxidative stress, *Helicobacter pylori*

## Oxidative Stress in the Process of Gastric Mucosal Injury

Physiological responses to stressors include increased activity of the hypothalamic-pituitary-adrenal axis as well as changes in gastrointestinal tissue. According to Selye's formulation of the general adaptation syndrome, an increase in adrenocortical activity is related to an increase in the incidence of gastric ulceration. The main candidate for the cause of stress ulcers is oxidative stress. There is some evidence that psychological stress, in addition to physical stress such as surgical intervention and microbial infection including *Helicobacter pylori* (*H. pylori*),<sup>(1)</sup> leads to oxidative stress in the stomach. Oxidative stress, which is a state of elevated levels of reactive oxygen species (ROS), causes a variety of conditions that stimulate either additional ROS production or a decline in antioxidant defenses. Oxidative stress is not only involved in the pathogenesis of gastric inflammation, ulcerogenesis, and carcinogenesis in *H. pylori* infection, but also in that of lifestyle-related diseases including atherosclerosis, hypertension, diabetes mellitus, ischemic heart diseases, and malignancies.<sup>(2)</sup> Several phenotypes of gastrointestinal diseases, such as peptic ulcer disease and gastroparesis, are known to be related to antioxidant property dysfunction.

**Ethanol.** The effects of ethanol on gastric mucosa are complicated and multifaceted. They may be associated with a disturbance in the balance between gastric mucosal protective and aggressive factors. Gastric mucosa is exposed to gastric acid, pepsin, and stimulants among others, while gastroprotective factors maintain the integrity of the gastric mucous layer, microcirculatory system, HCO<sub>3</sub><sup>-</sup>, prostaglandins (PGs), epidermal growth factor synthesis, and epithelial cell restitution. Ethanol injures the vascular endothelial cells of the gastric mucosa and induces microcirculatory disturbance and hypoxia, linking to the overproduction of oxygen radicals.

Pan *et al.*<sup>(3)</sup> report the role of mitochondrial energy charge in the pathogenesis of ethanol-induced gastric mucosal injury. The gastric mucosal lesion index is correlated with the thiobarbituric acid (TBA)-reactive substance (TBARS) content in gastric mucosa. As the concentration of ethanol increases and the

exposure time to ethanol is extended, the TBARS content in gastric mucosa and the extent of gastric mucosal damage increase. The ultrastructural pathological changes in mitochondria are positively related to ethanol concentration and exposure time. The expressions of mitochondrial DNA ATPase subunits 6 and 8 mRNA decline with increasing TBARS content in gastric mucosa produced as a result of ethanol gavage. As mentioned above, ethanol-induced gastric mucosal injury is related to oxidative stress, which disturbs the energy metabolism of mitochondria and plays a critical role in the pathogenesis of ethanol-induced gastric mucosal injury.

**Ischemia/reperfusion injury.** Ischemia/reperfusion damages the gastric mucosa by inducing oxidative stress. Specifically, ROS such as superoxide (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) induce inflammatory responses and tissue damage by fragmenting cellular DNA. In the gut, ROS can also be generated by non-steroidal anti-inflammatory drugs (NSAIDs), cold stress, ethanol, and *H. pylori* infection. NADPH oxidase found in phagocytic cells, vascular smooth muscle cells, endothelial cells, fibroblasts, and adipocytes convert oxygen into superoxide anions. Nakagiri *et al.*<sup>(4)</sup> recently reported that NADPH oxidase activity is elevated in ischemia and ischemia/reperfusion and is involved in the resultant gastric mucosal damage. This increased NADPH oxidase activity may also upregulate cyclooxygenase-2.

Peskar *et al.*<sup>(5)</sup> report that during ischemia/reperfusion, inhibitors of the cyclooxygenase and lipoxygenase pathways increase gastric mucosal damage in a dose-dependent manner. The synergism observed as a result of the combination of cyclooxygenase and lipoxygenase inhibitors suggests that both pathways are important in gastric mucosal defense during ischemia/reperfusion. PGE<sub>2</sub> theoretically antagonizes the effects of cyclooxygenase and lipoxygenase inhibitors. Similarly, lipoxin A<sub>4</sub>, a lipoxygenase-derived product of arachidonate metabolism, also antagonizes the effects of cyclooxygenase and lipoxygenase inhibitors; moreover, it could replace PGE<sub>2</sub> for the prevention of gastric mucosal damage caused by cyclooxygenase inhibitors during ischemia/reperfusion.

**Portal hypertensive gastropathy.** Portal hypertensive gastropathy (PHG) is a common complication of liver cirrhosis and is associated with impaired gastric mucosal healing. PHG may be related to increased ROS and lipid peroxide (LPO) production. Kinjo *et al.*<sup>(4)</sup> report increased levels of LPO and nitrotyrosine, an indicator of nitration of tyrosine residues due to peroxynitrite, in the gastric mucosa of portal hypertensive rats; in addition, they report impaired ERK1/2 phosphorylation related to increased nitration by peroxynitrite. The gastroprotective, anti-inflammatory agent rebamipide prevents free radical production by scavenging

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He received "SFRR Japan Award of Scientific Excellent" in 2011 in recognition of his outstanding work.

hydroxyl radicals.<sup>(5,6)</sup> Rebamipide decreases LPO and nitrotyrosine levels, normalizes ERK1/2 phosphorylation, and improves the ulcer index; this suggests that defects in the mitogen-activated protein kinase (MAPK) pathway are involved in the increased susceptibility to gastric mucosal injury observed in portal hypertensive gastropathy, indicating a potential role of rebamipide for treatment.

**NSAIDs and aspirin.** In addition to inhibiting cyclooxygenase and decreasing prostaglandin production, NSAIDs induce mucosal damage *via* ROS produced by recruited leukocytes. ROS-mediated mitochondrial damage as well as lipid, protein, and DNA oxidation lead to apoptosis and mucosal injury. Proton pump inhibitor (PPI) therapy is thought to primarily protect gastric mucosa by inhibiting gastric acid secretion. Nevertheless, Maity *et al.*<sup>(7)</sup> recently demonstrated that a PPI, lansoprazole, also inhibits NSAID-induced gastropathy by inhibiting mitochondrial and Fas-mediated apoptosis pathways. Lansoprazole's anti-apoptotic activity appears to be mediated by preventing NSAID-induced reductions in anti-apoptotic genes (e.g., Bcl and Bcl-2) while inhibiting increases in Fas and Fas ligand as well as pro-apoptotic genes (e.g., Bax and Bak).

On the other hand, aspirin increases the permeability of cultured gastric epithelial cell monolayers. The disruption in barrier integrity is mediated by p38 MAPK and involves the downregulation of claudin-7, a protein component of tight junctions.<sup>(8)</sup> This differs from the effects of other NSAIDs (i.e., non-aspirin NSAIDs), which increase epithelial permeability coupled to cyclooxygenase-1 inhibition; this increase can be restored by PGE<sub>2</sub> administration.

**Heat shock proteins.** Heat shock proteins, especially HSP70, provide cellular protection against stressor-induced tissue damage by refolding or degrading denatured proteins produced as a result of these stressors. Otaka *et al.*<sup>(9)</sup> recently used affinity chromatography to identify cytoskeletal myosin and actin as the first molecules bound by HSP70 after gastric mucosal injury in rats. Transcriptional upregulation of HSPs occurs via the binding of the transcription factor, heat shock factor 1 (HSF1), to heat shock element, which is located upstream of the HSP genes. In HSF1 null and HSP70-expressing transgenic mice, HSPs protect against irritant (e.g., ethanol or NSAIDs)-induced gastric lesions; moreover, geranylgeranylacetone (GGA), a gastroprotective agent, induces HSPs. Furthermore, HSP70 protects the gastric mucosa by inhibiting apoptosis, proinflammatory cytokines, and cell adhesion molecules involved in leukocyte infiltration. After induction by GGA, HSPs exhibit protective effects in mouse models of inflammatory bowel disease as well as in NSAID-induced lesions of the small intestine. Therefore, HSP inducers such as GGA may have therapeutic benefits in numerous diseases.

### Enlarged Fold Gastritis and Oxidative Stress

*H. pylori* eradication therapy increases Runt domain transcription factor 3 (RUNX3) expression in glandular epithelial cells in enlarged-fold gastritis. Recently, we reported that RUNX3 is expressed in gastric epithelial cells and that *H. pylori* eradication significantly increases RUNX3 expression in the glandular epithelium of the corpus; however, no changes were observed in the antrum.<sup>(10)</sup> The mucosal chemiluminescence value, a marker of oxidative stress, is 4-fold higher in the corpus than in the antrum. *H. pylori* eradication significantly decreases the mucosal chemiluminescence values in both portions of the stomach to nearly undetectable levels. We conclude that the glandular epithelium is exposed to high levels of carcinogenic oxidative stress and expresses low levels of the tumor-suppressing molecule, RUNX3; however, RUNX3 expression was restored after eradication, suggesting a high risk of carcinogenesis associated with *H. pylori*-induced enlarged-fold gastritis of the corpus.<sup>(10)</sup>

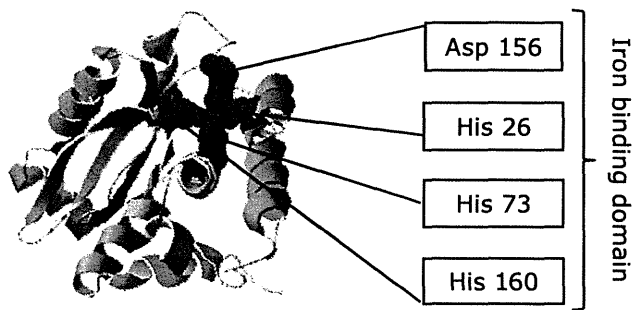
### Oxidative Stress during *H. pylori* Infection

**Antioxidant ability of *H. pylori* to establish chronic infection.** *H. pylori* infection induces a strong inflammatory host response, leading to the generation of a number of ROS and reactive nitrogen species (RNS), which are mediated by neutrophils and macrophages.<sup>(11)</sup> The generation of ROS and/or RNS is an important host immune response against persistent pathogens. Therefore, *H. pylori* must combat oxidative stress generated by the host immune response using an antioxidant protein in order to establish long-term colonization.<sup>(12,13)</sup> The mechanisms for ROS detoxification are of particular interest in understanding the *H. pylori*-associated pathogenesis. It is well known that *H. pylori* has a variety of enzymes acting as antioxidant systems to combat the toxic effects of ROS including catalase (KatA), iron-cofactored superoxide dismutase (SodB), and alkyl hydroperoxide reductase (AhpC).<sup>(13,14)</sup>

Superoxide dismutase (SOD) catalyzes the conversion of superoxide anions to hydrogen peroxide, which is degraded to oxygen and water by catalase.<sup>(13,15)</sup> SOD is a metalloenzyme; 3 structurally different forms have been identified depending on the metal cofactor. In general, organisms encode different sets of SOD enzymes. For example, *Escherichia coli* has 3 SODs: Fe-SOD (SodB) and Mn-SOD (SodA) in the cytoplasm and Cu/Zn-SOD in the periplasm.<sup>(16)</sup> On the other hand, *H. pylori* produces only a single SodB encoded by the *sodB* gene.<sup>(17,18)</sup> It was recently reported that *sodB* deletion in *H. pylori* causes the bacterium to lose its capacity for gastric mucosal colonization in mice.<sup>(19)</sup> This indicates that SodB is an important determinant of the host colonization capability of *H. pylori*. The regulation of *sodB* mRNA expression is also important for ROS detoxification. The mRNA expression of *sodB* in *H. pylori* is directly regulated by ferric uptake regulator (Fur) protein.<sup>(20)</sup> Fur functions as a global transcriptional regulator in *H. pylori*.<sup>(21-24)</sup> It is reported that Fur binds to ferrous iron (Fe<sup>2+</sup>) and that the genes for iron uptake are suppressed by the iron-binding form of Fur.<sup>(25,26)</sup> On the other hand, *sodB* expression is suppressed by the iron-free form of Fur (apo-Fur).<sup>(20)</sup> Apo-Fur binds to a specific consensus sequence called Fur-Box located on the *sodB* promoter, blocking the binding of RNA polymerase.<sup>(20,27,28)</sup> It was recently reported that nucleic-acid mutations in Fur-Box and/or amino-acid mutations in Fur decrease the affinity of apo-Fur for Fur-Box in *H. pylori*, halting the suppression of *sodB* mRNA expression.<sup>(29-31)</sup> In particular, stopping the suppression of *sodB* mRNA expression in *H. pylori* by amino-acid mutations in Fur (i.e., C78Y and P114S) determines the development of metronidazole (Mtz) resistance.<sup>(31)</sup> This is because, when Mtz enters cells, its antimicrobial toxicity is dependent on the reduction of its nitro group to nitro anion radicals and the generation of superoxide.<sup>(32,33)</sup>

The SodB of *H. pylori* shares 53% sequence identity with the corresponding protein from *E. coli*. Interestingly, *H. pylori* SodB is significantly different from other Fe-SODs; its most distinguishing characteristic is its extended C-terminal tail,<sup>(34)</sup> although the role of this tail remains unclear. The structure of SodB has been clarified; it is now known to exist as a dimer composed of 2 identical subunits.<sup>(34)</sup> Furthermore, it is identified as having 4 ferrous ion (Fe<sup>2+</sup>)-coordinating residues (i.e., an iron-binding domain; His 26, His 73, His 160, and Asp 156) (Fig. 1). In fact, SodB needs to recruit ferrous ion (Fe<sup>2+</sup>) to express its activity.<sup>(15,34)</sup> It is expected that SodB activity might be suppressed by preventing the uptake of iron ion (Fe<sup>2+</sup> and/or Fe<sup>3+</sup>).

**Generation of oxidative stress as a virulence factor in *H. pylori*-infected hosts.** ROS released from activated neutrophils are also potential virulence factors involved in *H. pylori*-infected host cells. In *H. pylori*-infected host cells, hypochlorous anions (OCl<sup>-</sup>) are generated from H<sub>2</sub>O<sub>2</sub> in the presence of Cl<sup>-</sup>. The hypochlorous anions subsequently react with ammonia (NH<sub>3</sub>), which is derived from urea by urease produced by *H. pylori*,



**Fig. 1.** Homology modeling of *Helicobacter pylori* SodB. Four amino acids (His 26, His 73, His 160, and Asp 156) of SodB are ferrous ion ( $\text{Fe}^{2+}$ )-coordinating residues (i.e., an iron-binding domain).

ultimately yielding monochloramine ( $\text{NH}_2\text{Cl}$ ).  $\text{NH}_2\text{Cl}$  induces mucosal cytotoxicity due to its lipophilic properties and freely penetrates biological membranes to oxidize intracellular components.<sup>(35-37)</sup>

In addition, it is well known that *H. pylori* produces a  $\gamma$ -glutamyltranspeptidase (EC 2.3.2.2; GGT) in the periplasm.<sup>(38)</sup> *H. pylori* GGT catalyzes the transpeptidation and hydrolysis of the  $\gamma$ -glutamyl groups of glutamine and glutathione. Interestingly, these findings indicate that *H. pylori* GGT performs 2 functions. First, GGT functions in the physiological functioning of *H. pylori*. *H. pylori* is unable to take up extracellular glutamine and glutathione directly; GGT hydrolyzes these substances to glutamate. The glutamate is then transported into *H. pylori* cells via a  $\text{Na}^+$ -dependent reaction and is mainly incorporated into the TCA cycle.<sup>(39)</sup> Second, GGT acts as a virulence factor by disrupting the antioxidant ability of host cells. Although glutathione has antioxidant potential in host cells, *H. pylori* GGT reduces extracellular glutathione levels. In fact, *H. pylori* GGT reduces the ROS resistance of the host cells and induces apoptosis or necrosis.<sup>(38,40)</sup>

Excess ROS are produced in *H. pylori*-colonized human stomachs; this induces oxidative stress to both the gastric mucosa and *H. pylori*. Because *H. pylori* has a deft capability of detoxifying ROS using a variety of enzymes to establish long-term colonization,<sup>(12,13)</sup> excess ROS leads solely to host cell damage.

### Oxidative Stress in the Progression of Gastric Motility Disorders

Gastric motility disorders can occur in many clinical settings with a wide variety in the severity of symptoms with or without gastric mucosal injuries. Gastric motility disorders are attributable to either damage within the smooth muscle itself or dysfunctions within the neuromuscular components including the enteric nerves and interstitial cells of Cajal (ICC), which regulate smooth muscle function. How oxidative stress is involved in these dysfunctions is discussed in the following situations.

### Gastrointestinal Complications in Sepsis

Oxygen radicals are implicated as relevant mediators in sepsis and septic shock in animals including humans.<sup>(41,42)</sup> Sepsis is a systemic response caused by bacterial endotoxins such as lipopolysaccharide, which induce the release of ROS and the generation of numerous pro-inflammatory factors and nitric oxide. During sepsis, the most frequent complications within the gastrointestinal tract are gastrointestinal motility disturbances and mucosal barrier dysfunction. Experimental administration of LPS delays gastric emptying and upregulates inducible nitric oxide synthase in order

to downregulate neuronal nitric oxide synthase (nNOS) and synthesize PGs.<sup>(43)</sup> It is also reported that SOD reverses the endotoxin-induced delay in gastric emptying and diminishes the presence of nitrotyrosine, 4-hydroxy-2-nonenal in gastric mucosa, and inducible nitric oxide synthase-positive residential macrophages in the external musculature; these suggest the involvement of oxidative and nitrosative stresses in the pathogenesis of lipopolysaccharide-induced gastrointestinal dysmotility.<sup>(44)</sup>

### Gastrointestinal Complications in Ischemia/Reperfusion Injury

The gastrointestinal tract is one of the most susceptible organ systems to ischemia. Previous investigations demonstrate that ischemia/reperfusion is a major contributor to gastric mucosal injury caused by stresses such as burn stress or hemorrhagic shock, NSAIDs, and *H. pylori* infection. In addition to mucosal injuries, delayed gastric emptying is also reported after gastric ischemia/reperfusion associated with disruption of the ICC network and nNOS-positive neurons.<sup>(45)</sup> ICC play critical roles in gastrointestinal motility in that they are the source of the electrical slow waves underlying the phasic contractions of the gastric musculature and mediate excitatory and inhibitory inputs to the musculature from the enteric motor neurons. Neuronal NOS generates neuronally derived NO, which is the major inhibitory neurotransmitter in the gastrointestinal tract. ICC and nNOS-positive neurons are both important factors for gastric emptying. Oxidative stress produced by the xanthine-xanthine oxidase system after ischemia/reperfusion may play a major role in these events, although the precise mechanism is unclear.

### Diabetes Mellitus

Oxidative stress is a strong pathogenic co-factor involved in the development of complications of diabetes. Increased glucose levels in diabetes react non-enzymatically with proteins and become advanced glycation end products (AGEs); AGEs activate endothelial NADPH oxidase and increase endothelial ROS,<sup>(46)</sup> which occurs in animal models of diabetes<sup>(47)</sup> and diabetes patients.<sup>(48)</sup> Gastric neuromuscular dysfunction occurs in up to 30–50% of patients after 10 years of type 1 or 2 diabetes associated with histological changes including the loss of nNOS and ICC in both humans and animal models. It is reported that increased oxidative stress is attributable to the loss of upregulation of heme oxygenase-1; this results in the loss of ICC, decreased nNOS expression, and delayed gastric emptying in non-obese diabetic mice. These changes can be reversed by heme oxygenase-1 induction, demonstrating an important role of oxidative stress in the development of diabetic gastroparesis.<sup>(49)</sup>

### Aging and Oxidative Stress

Gastrointestinal function declines with aging, including delayed gastric emptying, decreased peristalsis, and slowed colonic transit; these impair quality of life and increase morbidity and mortality. Notable changes in gut neuromuscular function that accompany advanced age are reported in human and animal models.<sup>(50,51)</sup> Cowen *et al.*<sup>(52)</sup> report a 50% reduction in ileal myenteric neurons in 24-month-old Sprague-Dawley rats fed *ad libitum*; this was prevented by caloric restriction, which reduces oxidative stress.<sup>(53)</sup> In the study using progeric mice deficient in the anti-aging peptide Klotho, progeric mice exhibited a gastric phenotype resembling that of human aging involving profound ICC loss with reduced slow wave amplitude and nitroergic inhibitory junction potentials. Klotho protects ICC by preserving their precursors, limiting oxidative stress, and maintaining nutritional status and normal levels of trophic factors important for ICC differentiation.<sup>(54)</sup> Increased oxidative stress in combination with a decrease