

# Ghrelin and oxidative stress in gastrointestinal tract

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**Oxidative stress is a major cause of the gastrointestinal damage under physical or psychological stress. Ghrelin exhibits gastroprotective effects and they are supposed to be derived from antioxidant effects. In gastroduodenal mucosal injury, the plasma ghrelin levels increase in response to the demand for gastroduodenal cytoprotection. However, in the condition of *Helicobacter pylori*-induced gastric mucosal severe atrophy, the plasma ghrelin concentration shifted to lower levels. In diabetic gastroparesis, the regulation of ghrelin secretion is impaired with vagal nerve dysfunction. Selective ghrelin agonist is expected to represent a new class of prokinetic agent. In addition, the plasma ghrelin levels are also enhanced by systemic oxidative stress, and ghrelin exhibits antioxidant effects in many organs, such as heart, pancreas, and lung. This suggests that ghrelin would be an important player as a sensor of systemic oxidative stress.**

**Key Words:** oxidative stress, ghrelin, peptic ulcer, gastroparesis

The physiological response to stressor includes an increased activity of the hypothalamic-pituitary-adrenal axis as well as changes in gastrointestinal damage. According to Selye's formulation of the general adaptation syndrome, an increase in adrenocortical activity should be related to an increase in the incidence of gastric ulceration.<sup>(1)</sup> The strong candidate for the cause of stress ulcer would be oxidative stress. There are some evidences that not only physical stress, such as surgery and infection, but also psychological stress leads to oxidative stress.<sup>(2,3)</sup>

Oxidative stress, which refers to a state of elevated levels of reactive oxygen species (ROS), forms a variety of conditions that stimulate either ROS production or a decline in antioxidant defenses. Oxidative stress is involved in the pathogenesis of life-style-related diseases, including atherosclerosis, hypertension, diabetes mellitus, ischemic diseases, and malignancies.<sup>(4)</sup> Several gastrointestinal diseases, such as peptic ulcer disease and gastroparesis, are known to be related with the dysfunction of the antioxidative properties.<sup>(5)</sup>

Ghrelin, produced and secreted by the A-like cells of the oxyntic glands of the stomach, stimulates growth hormone (GH) secretion, gastric motility, and food intake.<sup>(6)</sup> Many researchers reported the relationship between oxidative stress and the expression or function of ghrelin.<sup>(7,8)</sup> Moreover, ghrelin administration is expected to reduce oxidative stress and control diseases.<sup>(9)</sup> Previous studies have reported that ghrelin has an anti-inflammatory action on the oxidative injury of the diverse organs, such as the heart, liver and pancreas.<sup>(10-14)</sup> In the present article, we discuss the association of oxidative gastrointestinal damages with the potential role of ghrelin.

## Effects of Ghrelin against Gastric Mucosal Injury

Recent studies have shown that ghrelin exhibits gastroprotective

effects.<sup>(15-19)</sup> Ghrelin administration reduced ethanol-induced gastric ulceration,<sup>(15,17,18)</sup> acetic acid-induced chronic gastric and duodenal ulceration,<sup>(16)</sup> and ischemia-reperfusion (I/R)-induced gastric ulceration<sup>(18,19)</sup> in rats. In addition, ghrelin administration increased mucosal cell proliferation<sup>(16)</sup> and mucosal microvascular flow<sup>(16,18,20)</sup> in rats. These effects could be observed by intracerebroventricular,<sup>(15,17,18)</sup> subcutaneous,<sup>(15)</sup> intraperitoneal,<sup>(18)</sup> and peripheral intravascular<sup>(19)</sup> administration of synthetic ghrelin.

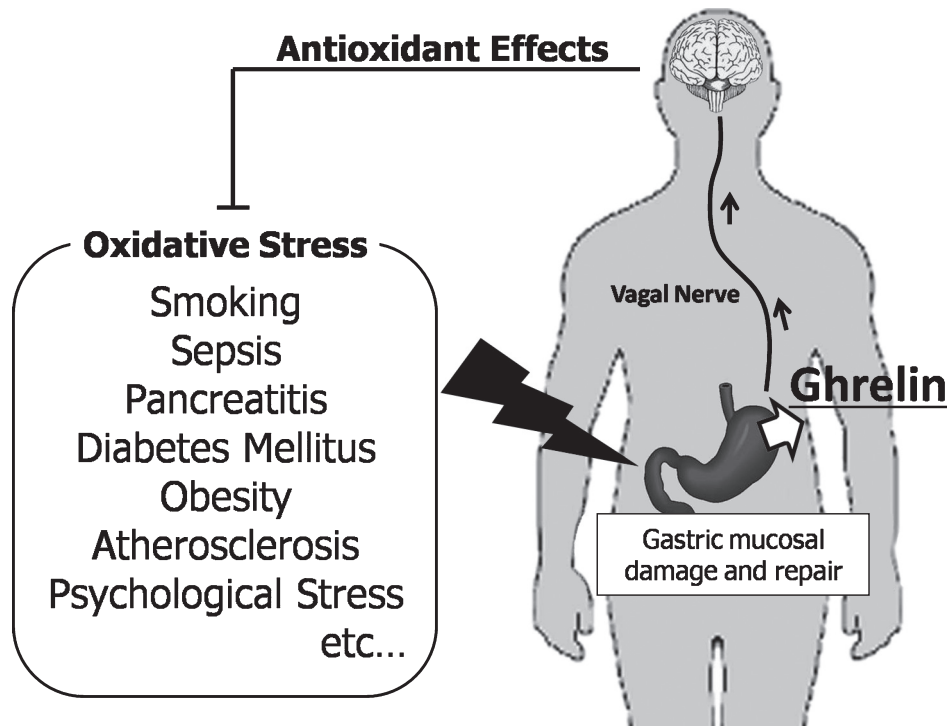
The mechanism of the gastroprotective effects of ghrelin remains unclear. Sabilia *et al.* reported that such effects of ghrelin are mediated by endogenous nitric oxide (NO) release and requires the integrity of sensory nerve fibers.<sup>(15)</sup> Sabilia *et al.*<sup>(17)</sup> also reported that cyclooxygenase-1-derived prostaglandins (PGs) are mainly involved in ghrelin-associated gastroprotection and that NO derived from constitutive source, together with PGE<sub>2</sub>, are involved in its activity. Ceranowicz *et al.*<sup>(16)</sup> reported that the gastroprotective effects of ghrelin are mediated by the release of endogenous GH and insulin-like growth factor-1. Brzozowski *et al.*<sup>(18)</sup> reported that these effects involved vagal nerve integrity, partially depending upon afferent nerves and hyperemia mediated by sensory neuropeptides such as calcitonin gene-related peptide released from these nerves.

The most remarkable gastroprotective effects of ghrelin are supposed to be derived from its antioxidant effects. Eter *et al.*<sup>(19)</sup> reported that peripheral administration of ghrelin attenuated I/R-induced gastric mucosal injury by reducing ulceration, tissue congestion, cellular infiltration and vascular permeability in rats. Serum level of LDH and tissue content of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) were markedly reduced by the ghrelin administration. In their study, a decrement of thiobarbituric acid reactive substance (TBARS) and an increment in glutathione were observed, which suggested that ghrelin has an antioxidant activity. *In vitro* studies, using human polymorphonuclear cells incubated with ghrelin, showed that ghrelin inhibited ROS generation as measured by chemiluminescence.<sup>(19)</sup> Iseri *et al.*<sup>(21)</sup> reported that although alendronate induces oxidative gastric damage by a local irritant effect, ghrelin ameliorates this damage by its possible antioxidant and anti-inflammatory powers.

## Ghrelin Secretion and Gastric Mucosal Injury

The most common causes of gastric mucosal injury and peptic ulceration are *Helicobacter pylori* (*H. pylori*) infection and the consumption of non-steroidal anti-inflammatory drugs (NSAIDs). *H. pylori* induces a strong inflammatory response, generating large amounts of ROS during the process of colonizing the host.<sup>(20,22-29)</sup> In the pathogenesis of NSAID-induced gastric mucosal injury, oxygen radicals also play an important role.<sup>(30)</sup>

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**Fig. 1.** Ghrelin has antioxidant effects on systemic oxidative stress. Many kinds of systemic oxidative stress could lead to gastric mucosal injury. Ghrelin would be released when the A-like cells were damaged or repaired. Secreted ghrelin send a signal to the brain through the vagal nerve, and enhance the antioxidant reaction in the body.

Although ghrelin secretion would be required to protect gastric mucosa against ROS-induced injury, the number of the gastric A-like cells is decreased simultaneously by gastric mucosal injury.<sup>(31,32)</sup> Therefore, the status of ghrelin secretion in gastric mucosal injury is complicated. The plasma total and active ghrelin levels are known to be increased by the formation of duodenal ulcers, which induced by administration of cysteamine, a somatostatin inhibitor, in rats.<sup>(33)</sup> In a human study, enhanced plasma ghrelin levels were observed in patients, not only with duodenal ulcers, but also with gastric ulcers.<sup>(34)</sup> According to the report by Isomoto *et al.*,<sup>(35)</sup> among plasma ghrelin levels of the patients with chronic gastritis, gastric ulcer, duodenal ulcer, acute gastritis, and normal mucosa, the levels of acute gastritis group were the highest, and then that of chronic gastritis group were the lowest. Within the *H. pylori*-positive population, the plasma ghrelin levels of duodenal ulcer group were higher than gastric ulcer group or chronic gastritis group.<sup>(35)</sup> The plasma total and active ghrelin levels correlated with the serum pepsinogen I levels, as well as the serum pepsinogen I/II ratio, and decreased with increasing extent of gastric mucosal atrophy.<sup>(36,37)</sup> These results suggest that the plasma ghrelin levels increase in response to the severe gastric mucosal oxidative stress. However, in the condition of *H. pylori*-induced gastric mucosal severe atrophy, the number of A like cells as well as the plasma ghrelin concentration shifted to lower levels with the reduction of other component cells in gastric fundic gland due to inflammatory cell infiltrations.

### Gastric Motility Dysfunction and Ghrelin

Oxidative stress induces not only gastric mucosal injury, but also gastric motility dysfunction, such as diabetic gastroparesis. Gastroparesis are thought to be caused by ROS-induced damage of the networks of the interstitial cells of Cajal.<sup>(38)</sup> The authors reported that the plasma ghrelin levels and gastric preproghrelin mRNA expression levels are increased in rats with streptozotocin-

induced diabetes, that is known for hyperphagia.<sup>(39)</sup> In a human study, however, the fasting plasma ghrelin level was significantly lower in diabetes mellitus with diabetic gastroparesis than in healthy controls.<sup>(40)</sup> The change in the plasma ghrelin levels with sham feeding in diabetic gastroparesis patients and postsurgical gastroparesis patients were significantly lower than in normal subjects, although the plasma ghrelin levels increased in idiopathic gastroparesis.<sup>(41)</sup> Impaired regulation of the plasma ghrelin levels in diabetic gastroparesis would be caused by vagal nerve dysfunction.<sup>(41)</sup>

Ghrelin administration accelerated gastric emptying of a meal in humans even in the presence of a neural dysregulation by diabetes or surgical vagotomy.<sup>(42)</sup> Also in idiopathic gastroparesis, administration of ghrelin enhances gastric emptying and improves meal-related symptoms.<sup>(43)</sup> Therefore, analogues of ghrelin are expected to represent a new class of prokinetic agents.<sup>(44)</sup> TZP-101, the synthetic, selective ghrelin agonist, is now tested in clinical trials. This new agent was well-tolerated in diabetes patients with moderate-to-severe chronic gastroparesis and showed statistically significant improvements in gastric emptying.<sup>(45,46)</sup>

### Systemic Oxidative Stress and Ghrelin

Systemic oxidative stress is induced by various reasons. In diabetes mellitus, NADPH oxidases, endothelial NO synthase uncoupling, and protein kinase C signaling plays an important roles for mediating increased vascular superoxide production and endothelial dysfunction.<sup>(47)</sup> Smoking stimulates pulmonary alveolar macrophages and increased superoxide production.<sup>(48)</sup> During sepsis, multiple intracellular sites, such as mitochondrial, NADPH oxidase, and Rac1 pathways, are responsible to the superoxide production.<sup>(49)</sup>

Several studies suggested that systemic oxidative stress enhance the plasma ghrelin levels. The plasma ghrelin levels were correlated with vascular super oxide. production and NADPH oxidase

activity in patients with atherosclerosis.<sup>(50)</sup> Plasma ghrelin was elevated in cachectic patients with chronic heart failure, associated with increases in GH and TNF $\alpha$ .<sup>(51)</sup> Smoking acutely increased the plasma ghrelin levels.<sup>(52)</sup> On the other hand, in the early stage of sepsis, ghrelin levels decreased, although the activity of its receptor was markedly elevated in rats.<sup>(53)</sup> In patients with acute pancreatitis, the plasma ghrelin levels increased after patients' recovery, as compared with the levels before therapy.<sup>(54)</sup> Decreased ghrelin levels in the early phase of sepsis or pancreatitis would be caused by the damage of gastric A like cells. With repairment of the A like cells, the plasma ghrelin levels would recover after sepsis or pancreatitis.

Taken together, it is considered that gastric mucosa would play an important role for sensing a systemic oxidative stress (Fig. 1). Exposure to oxidative stress could lead to gastric mucosal injury, and ghrelin would be released when the A like cells were damaged or repaired. Secreted ghrelin would have an anti-inflammatory action on the oxidative injury of the several organs, such as increasing cardiac output,<sup>(55)</sup> vasorelaxation,<sup>(56)</sup> attenuation of acute pancreatic damage,<sup>(57)</sup> and attenuation of acute lung injury,<sup>(58)</sup> as

well as rapid repairment of gastric epithelial cells. Ghrelin would be also secreted from the stomach as an anti-inflammatory player for the systemic oxidative injury.

## Conclusions

Ghrelin has the possible antioxidant and anti-inflammatory effects. Selective ghrelin agonist would be expected as a new agent to treat not only gastrointestinal motility dysfunction, but also gastric mucosal injury, cardiovascular disease, and various systemic diseases induced by oxidative stress. The stomach would be an important organ as a sensor of systemic oxidative stress.

## Abbreviations

ROS	reactive oxygen species
I/R	ischemia-reperfusion
GH	growth hormone
TBARS	thiobarbituric acid reactive substance
NSAIDs	non-steroidal anti-inflammatory drugs

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