Ghrelin and Stress Protection

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Ghrelin Attenuates Inflammation and the Generation of Reactive Oxygen Metabolites

Glossary

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<th>Term</th>
<th>Definition</th>
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<tr>
<td>D cells</td>
<td>Endocrine cells belonging to the amine precursor uptake and decarboxylation (APUD) system known to release the hormone, somatostatin.</td>
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<tr>
<td>Endocrine cells (EC)</td>
<td>Release the hormone motilin and the neurotransmitter serotonin.</td>
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<tr>
<td>Enterochromaffin-like cells (ECL)</td>
<td>Known to release histamine, a potent stimulant of gastric acid secretion in the stomach. They are the predominant endocrine cell-type of the oxyntic (acid-producing) mucosa of the stomach. Histamine acts as the positive paracrine stimulator of the release of hydrochloric acid from the parietal cell.</td>
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<tr>
<td>Gastric blood flow (GBF)</td>
<td>Defined as the flow of the blood through submucosal vessels in the gastric mucosa. Ghrelin-producing cells identified in the gastric mucosa.</td>
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<tr>
<td>NG-nitro-L-arginine (L-NAME)</td>
<td>A nonselective inhibitor of the enzyme nitric oxide synthase. It has been used experimentally to induce hypertension. Small proteins (peptides) comprised of a chain of amino acids that are synthesized in, and secreted by, nerves and serve as neurotransmitters (when released at synapses) and neurohormones (when released into the bloodstream).</td>
</tr>
<tr>
<td>Nitric oxide (NO)</td>
<td>Intracellular gaseous mediator released from vascular endothelium, sensory nerves, and gastrointestinal epithelial cells. It contributes to the mechanism of gastrointestinal mucosal integrity by increasing gastrointestinal microcirculation and protective mucus and bicarbonate secretion.</td>
</tr>
<tr>
<td>Prostaglandins (PG)</td>
<td>Metabolites of enzyme cyclo-oxygenase activity, the derivatives of arachidonic acid that exhibit cytoprotective activity. A group of compounds derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway. They are extremely potent mediators of a diverse group of physiological processes. These compounds play an essential role in the control of gastrointestinal circulation and gastrointestinal mucosal defense. A group of arachidonic acid metabolites which include mainly prostaglandins and thromboxanes.</td>
</tr>
<tr>
<td>Prostanoids</td>
<td>One of the important growth factors, responsible for angiogenesis and acceleration of ulcer healing and process of gastrointestinal mucosal repair.</td>
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<td>Vascular endothelial growth factor (VEGF)</td>
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Pathogenesis of Stress-Induced Gastric Ulcerations

Stress ulcerations are defined as acute gastric mucosal lesions occurring as complications in severely ill patients after burns, sepsis, major surgery, or trauma to the central nervous system. Critically ill patients are at increased risk of developing stress-related gastric mucosal lesions and gastrointestinal bleedings. Stress can induce acute gastric mucosal lesions by a complex of psychological factors, psychosis, or brain trauma, influencing individual vulnerability and specific brain pathways regulating autonomic functions. These stress-induced gastric microbleeding erosions are accompanied by a marked decrease in the gastric blood flow (GBF), a substantial decrease in the
gastric mucosal prostaglandin (PG) content and nitric oxide (NO) release, inhibition of gastric mucus and bicarbonate secretion, and the increased formation of free oxygen radicals in the gastric mucosa leading to gastric ischemia and inflammation. Among various stress models used in animals, the most reproducible results can be obtained by water immersion and restraint stress (WRS), which appear to act synergistically in the production of gastric ulcerations.

Numerous studies have demonstrated the usefulness of cold-restraint stress and proved it to be a clinically relevant experimental model for studying of pathomechanism of acute gastric damage and protection. It has been shown that gastric acid plays an important role in the development of stress-induced gastric ulcer and is the most common endogenous factor responsible for the destruction of epithelial cells. Gastric mucosal lesions induced by different time-dependent exposures to WRS trigger time-course dependent changes of the ultrastructure of gastric parietal cells secreting gastric acid. Many physiological agents such as PG, NO donors, calcitonin gene-releasing factor (CGRP), and gastrointestinal hormones such as cholecystokinin (CCK) and leptin have been reported to attenuate the gastric erosions induced by stress of different origin and durations. The mechanism of the recovery of gastric mucosa from stress injury is not fully understood and the underlying healing of stress-induced gastric lesions appears to be multifactorial. It has been proposed that mucosal integrity and mucosal repair after stress damage, involve the enhancement of GBF and increased cell proliferation mediated by expression and subsequent release of growth factors such as epidermal growth factor (EGF) and transforming growth factor (TGF)-β.

Discovery, Receptors, and Physiological Functions of Ghrelin

Ghrelin is a recently described 28-amino acid peptide that has been discovered in rat and human gastrointestinal tracts, particularly in gastric mucosa, as an endogenous ligand for growth hormone (GH) secretagogue receptor (GHSR). Ghrelin stimulates food intake and body weight gain exerting a modulating effect on energy expenditure acting through afferent nerves and directly on hypothalamic feeding centers. This peptide was also shown to enhance the gastric motility and gastric secretion. Recent studies revealed that ghrelin is produced by special neuroendocrine cells located mainly in oxyntic mucosa but not in enterochromatoffin-like cells (ECLs), endocrine cells (ECs) or D cells. Ghrelin has no relevant homology with any known gastrointestinal peptides but potently stimulates the release of GH and acts as a natural ligand for the GHSR which is the endogenous counter of the family of synthetic, peptidyl and non-peptidyl GH secretagogues. Ghrelin stimulates food intake and body weight gain exerting a modulating effect on energy expenditure. Administration of ghrelin causes weight gain via appetite stimulation and reduced fat oxidation. The release of ghrelin may be influenced by the status of fasting and nutrient feeding because central and peripheral administration to rats results in an increase in their feeding behavior.

Recent studies in humans revealed that gastrectomy produced a dramatic fall in the plasma ghrelin levels, whereas fasting and anorexia nervosa were accompanied by elevated plasma ghrelin concentrations supporting the notion that the gastrointestinal tract, primarily the stomach, is a major source of circulating ghrelin, which could be considered as a starvation-related hormone. Interestingly, obestatin, which is encoded by the same gene as ghrelin has recently been reported to counteract physiological effects of ghrelin.

A recent study revealed that endocrine Gr cells of the stomach are a major source of circulating ghrelin acting via activation of two receptor subtypes. Two GHS-R subtypes are generated by alternative splicing of a single gene: the full-length type 1a receptor (GHS-R1a); and a carboxyl-terminally truncated GHS-R type 1b (GHS-R1b). The GHS-R1a is the functionally active, signal-transducing form of the GHS-R, while the GHS-R1b is devoid of high-affinity ligand binding and signal transduction activity. Ghrelin molecules, produced by endocrine cells of gastric glands exist in two major molecular forms, ghrelin and des-n-octanoyl ghrelin (des-acyl ghrelin). The acylation by n-octanoic acid of the hydroxyl group of their third residue, which is either serine or threonine, is essential for binding of ghrelin to GHS-R1a. The anorexia associated with cancer chemotherapy in rodents is reported to be alleviated by exogenous ghrelin and similar effects have been described in humans. This may be due to a reduction in activity of ghrelin-producing cells, present predominantly in the oxyntic mucosa.

Role of Ghrelin in Maintenance of Gastric Mucosal Integrity

Little is known about the factors that might affect ghrelin release in the stomach and whether this peptide can contribute the mechanism of gastric mucosa integrity. The role of ghrelin in the mechanism of gastric mucosal defense and gastroprotection has been investigated by revealing that peripheral administration of ghrelin reduces the formation of lesions induced by ethanol and cold stress (Figure 1).
In agreement with the original hypothesis that prostanoids, NO, and sensory neuropeptides cooperate in the mechanism of maintenance of gastric integrity, it was proposed that NO and sensory neuropeptides may mediate these gastroprotective effects because the blockade of NO synthase (NOS) activity with NG-nitro-L-arginine (L-NAME) and the functional ablation of sensory afferent nerves with capsaicin were both found to attenuate them. It is of interest that centrally applied ghrelin can influence gastric acid secretion, while attenuating lesions caused by stress and this effect is mediated by the vagal innervation and the expression of calcitonin gene related peptide (CGRP) messenger ribonucleic acid (mRNA), an important neuropeptide released from sensory nerve endings. Both these events are considered as important components of the brain-gastrointestinal tract axis involved in the gastroprotective effects of ghrelin especially against stress-induced gastric lesions.

In contrast, the *Helicobacter pylori* (*H. pylori*) infection of the human gastric mucosa which is now considered to play a role as the causal factor in the pathogenesis of gastritis and peptic ulcer was found to attenuate the mucosal expression and release of ghrelin and to reduce appetite. This was confirmed in *H. pylori*-infected gastric mucosa of Mongolian gerbils, which is now widely accepted as an appropriate model to study the mechanism of *H. pylori* infection under experimental conditions. It is of interest, that after successful cure of *H. pylori* in healthy asymptomatic subjects the plasma ghrelin concentration increased, which in turn led to enhanced appetite and weight gain. This implies that increase in ghrelin in *H. pylori* cured gastric mucosa may contribute to the increasing obesity seen in Western populations, where the prevalence of *H. pylori* is low.

**Mechanism of Gastroprotection Induced by Ghrelin**

Recently, endogenous PGs have been implicated in the control of food intake and appetite but the possibility that these cytoprotective arachidonic acid metabolites could also play an important role in the gastroprotective effect of ghrelin has not been explored. Moreover, the question remains whether ghrelin contributes to gastroprotection against gastric lesions caused not only by artificial irritants such as ethanol, but also can protect against those caused by vascular disturbances resulting from stress or ischemia-reperfusion (I/R) that lead to severe microbleeding erosions and the fall in the microcirculation (*Figure 2*). Therefore it was important to confirm whether endogenous PGs as well as the expression of cyclooxygenase (COX)-1 and COX-2 are involved in the possible gastroprotective activity of ghrelin against stress-induced gastric erosions.

Our study supports the notion that ghrelin-induced protection and hyperemia involves co-activation of NO and sensory afferents and endogenous PG.
Arachidonic acid metabolites were believed to act as the classic mediators of cytoprotection but recent studies revealed that in contrast to NO, endogenous PG do not appear to contribute to the observed gastroprotection by peptides such as leptin and CCK against ethanol-induced gastric lesions. Questions arose whether the suppression of COX by nonselective COX inhibitor, indometacin, or the highly selective COX-2 inhibitor, rofecoxib, could influence the gastroprotective and hyperemic activity of ghrelin. It has been documented that ghrelin-induced protection and hyperemia is accompanied by the enhancement in the mucosal PGE2 generation. Both, indometacin and rofecoxib greatly attenuated the protective and hyperemic effects of ghrelin, indicating that endogenous PG possibly derived from COX-1 and COX-2 PG pathway may mediate these beneficial effects of this hormone on the stomach (Figure 3).

Ghrelin applied centrally exhibits comparable gastroprotective activity as when administered peripherally against the mucosal damage induced by corrosive substance such as ethanol and nontopical ulcerogen such as stress. This suggests that exogenous ghrelin could be considered as an important protective factor for the gastric mucosa. This notion is supported by observation that ghrelin attenuated the gastric lesions induced by ethanol in various concentrations and those provoked by stress while producing an increase in gastric mucosal blood flow and the plasma level of this hormone. The results of secretory studies revealed that ghrelin applied by the intracerebroventricular (ICV) and intraperitoneal (IP) routes in doses that were gastroprotective against stress and ethanol injury significantly raised gastric acid secretion suggesting that the protective effect of this peptide occurred despite an increase of the gastric secretory function, thus representing genuine gastroprotective activity as previously proposed for the phenomenon of cytoprotection. The ghrelin-induced protection after its central administration was accompanied by a significant and dose-dependent rise in the plasma ghrelin concentrations by WRS suggesting that ghrelin-evoked gastric hyperemia could be an important mechanism of the protective effect of this peptide in rat stomachs (Figure 1).

It has been shown that ghrelin, primarily produced in the stomach, but also in the hypothalamus, is an orexigenic peptide and affects both feeding at the levels of hypothalamus (arcuate nuclei) and GH secretion partly due to an activation of gastric vagal afferents transmitting visceral sensory signals to the brain. The observation that ghrelin stimulates gastric acid secretion is in keeping with the original observation that an increase in gastric secretion was achieved after parenteral but not topical administration of ghrelin. The mechanism by which ghrelin increases gastric acid secretion after peripheral as well as central administration could be related to elevation of plasma gastrin concentration, since a considerable increase in this hormone level was notified following ghrelin application. Gastrin could contribute, at least in part, to the secretory as well as protective and hyperemic effects of ghrelin but its effect on histamine release should also be considered. The notion that the protective activity of ghrelin depends, at least in part, on gastrin release is at variance with some studies claiming that ghrelin release does not operate under gastrin; however, these studies failed to directly address the effect of ghrelin on gastrin release. It is not excluded that ghrelin, which is known for the release of GH, acts via GH release to protect gastric mucosa against stress damage as GH was shown to...
enhance the healing of gastric ulcers, while increasing plasma gastrin level.

**Neural Aspects of Gastroprotective Activity of Ghrelin**

Ghrelin is an orexigenic peptide and affects both feeding at the levels of hypothalamus (arcuate nuclei) to stimulate neuropeptide Y (NPY) and Agouti-related peptide (AgPP)-related neurons and to release GH partly due to an activation of gastric vagal afferents transmitting visceral sensory signals to the brain. An experimental study in a stress model of gastric injury revealed that ghrelin mRNA was upregulated in the gastric mucosa exposed to WRS. This was followed by an increase in the plasma ghrelin level indicating that endogenous ghrelin might act as local integrity peptide to limit the extent of gastric damage provoked by WRS. This was followed by an increase in the plasma ghrelin level indicating that endogenous ghrelin might act as local integrity peptide to limit the extent of gastric damage provoked by WRS. This is similar to leptin, another gastric hormone involved in the control of food intake though acting in opposite direction than ghrelin. As expected, ghrelin-induced protection after its central administration was accompanied by a significant and dose-dependent rise in the plasma ghrelin concentrations and marked attenuation of the fall in the GBF caused by WRS suggesting that ghrelin-evoked gastric hyperemia could be an important mechanism of the protective effect of this peptide in the rat stomach. This notion is based on the well-documented facts that an appropriate microcirculatory blood supply helps to orchestrate various lines of mucosal defense system in gastric mucosa. In addition, as mentioned before, ghrelin significantly increases the expression of mRNA for CGRP, which is known to increase the gastric mucosal blood flow. The mechanism by which ghrelin improves this gastric mucosal blood flow could be related to a direct effect of ghrelin on blood vessels due to a potent vasodilatory activity of this peptide. It is assumed that the direct protective effect of ghrelin can not be ruled out; however, no study has been yet undertaken to demonstrate that ghrelin exerts direct effects on vasculature.

Since the mechanism of gastric mucosal defense include NO that could be released from vascular endothelium, sensory nerves, or gastric epithelial cells, the hypothesis was tested that ghrelin-induced gastroprotection involving NO could originate from the activation of afferent sensory neurons by this peptide. The deactivation of rat primary afferent nerves, using a neurotoxic dose of capsaicin about 2 weeks before the stress experiment, aggravated WRS-induced gastric damage as compared to rats without capsaicin denervation and significantly reduced the GBF

**Figure 3** The mean number of gastric lesions induced by water immersion and restraint stress (WRS) and accompanying changes in gastric blood flow (GBF) in rats treated with vehicle (saline) and ghrelin (20 µg kg⁻¹ intraperitoneal (IP)) with or without pretreatment with nonselective COX inhibitor, indometacin (5 mg kg⁻¹ IP) or COX-2-selective inhibitor, rofecoxib (10 mg kg⁻¹ intragastric). Mean ± standard error of mean of 6–8 rats. Asterisk indicates a significant decrease as compared to the value obtained in vehicle-control animals. Cross indicates a significant change as compared to the respective value obtained in animals without pretreatment with COX inhibitors. Double cross indicates a significant change as compared to the respective value obtained in ghrelin-treated animals without pretreatment with COX inhibitors. Reproduced from *Regulatory Peptides* 120, Exogenous and endogenous ghrelin in gastroprotection against stress-induced gastric damage. 39–51, 2004, with permission from Elsevier.
when compared to that in animals with intact sensory nerves. Moreover, it has been demonstrated that such a capsaicin-induced deactivation of sensory nerves significantly attenuated the gastroprotective activity of central and peripheral ghrelin and completely abolished the ghrelin-induced rise in GBF. Moreover, the replacement therapy with exogenous CGRP, the major neuropeptide released from sensory afferent nerves, restored the protective and hyperemic activity of ghrelin against the WRS-induced gastric lesions (Figure 4). In addition, the expression of mRNA for CGRP, the major neuropeptide released from sensory afferent nerves, was enhanced in ghrelin-treated animals indicating that this major sensory nerve neuropeptide is essential for microcirculatory response and of crucial importance for the gastroprotective activity of ghrelin.

Involvement of sensory nerves in ghrelin-induced gastroprotection does not exclude the possibility that centrally applied ghrelin enhances the central parasympathetic outflow to the stomach and that also vagal efferent nerves are involved in gastroprotection afforded by centrally and peripherally administered ghrelin. It was proposed, for instance, that the inhibitory effects of ghrelin on gastric acid secretion require intact vagal pathways because vagotomy abolished the increase in gastric secretion induced by this peptide. Indeed, vagotomy significantly attenuated the ghrelin- afforded gastroprotection and the accompanying rise in the GBF after its central and peripheral administration indicating that vagal pathway plays an important role in the mediation of the protective and hyperemic effects of this peptide against lesions evoked by stress. These data could be interpreted that ghrelin induced protection against damage induced by stress might be due to the stimulation of vagal cholinergic pathways that are involved in the recruitment of CGRP from afferent sensory nerves. Thus, evidence was provided that these protective and hyperemic effects of ghrelin may affect vagal nerves, the principal component of brain-gastrointestinal tract axis and involve cooperation between endogenous NO and sensory nerves releasing neuropeptides such as CGRP.

The finding that centrally applied ghrelin raised NO in stress model, is consistent with the observations that protective effects of ghrelin against ethanol can be attenuated by the pretreatment with L-NAME suggesting an involvement of NOS-NO pathway in the gastroprotective effect of ghrelin applied ICV. This excessive gastric NO production by ghrelin may originate from the upregulation of constitutive NOS (cNOS) rather than inducible NOS (iNOS) in the gastric mucosa. It seems likely that NO contributes to gastroprotection afforded by central and peripheral

![Figure 4](image)

**Figure 4** The mean number of WRS-induced gastric lesions and the alterations in the gastric blood flow (GBF) in rats with intact sensory afferent nerves and those with capsaicin denervation with or without pretreatment with vehicle (Veh; control) and ghrelin (20 µg kg⁻¹ intraperitoneal). Please note that ghrelin-induced protection against WRS lesions and the accompanying increase in the GBF are almost completely abolished by functional ablation of afferent sensory neurons by capsaicin. These effects are further restored by the concomitant treatment of ghrelin with exogenous CGRP (10 µg kg⁻¹ subcutaneous) in capsaicin-denervated animals. Mean ± standard error of mean of 6–8 rats. Asterisk indicates a significant change compared to the value in vehicle-treated rats. Cross indicates a significant change compared to the value obtained in rats without capsaicin denervation. Asterisk and cross indicate a significant decrease as compared to ghrelin-treated animals with capsaicin denervation of sensory afferents.
ghrelin as proposed earlier for CCK and leptin, both also implicated in control of appetite and gastroprotection.

Therefore, it is concluded that ghrelin, besides its recognized function in the control of appetite, energy homeostasis, fat, and carbohydrate metabolism and gastrointestinal motility, could be considered as an important gastroprotective factor, expressed locally in the gastric mucosa in response to mucosal injury. This notion is supported by recent observations that mRNA for ghrelin is upregulated in the gastric mucosa exposed to WRS. Furthermore, it has been demonstrated that beneficial effect of ghrelin involves an activation of the capsaicin-sensitive sensory nerves in the gastric mucosa that are responsible for the increased production of CGRP in gastric mucosa exposed to WRS. This notion is in keeping with the previous studies demonstrating the importance of the activation of capsaicin-sensitive sensory nerves in the protection of gastric mucosa against acute gastric injury. The contribution of CGRP to the ghrelin-induced gastroprotection is further supported by the observation that the functional ablation of sensory nerves by capsaicin attenuated significantly the protective activity of ghrelin and completely abolished the rise in GBF induced by this peptide. The addition of exogenous CGRP to ghrelin in rats with deactivated sensory nerves restored the protection and accompanying rise in the GBF with the extent similar to that observed in ghrelin-treated rats with intact sensory nerves. These results indicate that sensory nerves, and their neuropeptides such as CGRP, are essential for microcirculatory response and of crucial importance for the gastroprotective activity of ghrelin.

Previous studies revealed that CGRP released in response to acute gastric mucosal injury leads also to increased production of NO due to activation of constitutive endothelial NOS. The exposure of rats to WRS that produced gastric lesions was associated with a significant downregulation of cNOS mRNA expression as compared to vehicle-control rats. The treatment with ghrelin of such WRS exposed rats, dose-dependently increased the expression of cNOS which reached the level of this expression comparable to that observed in the vehicle-control gastric mucosa indicating that ghrelin is capable of preventing the decrease in expression of cNOS mRNA caused by the exposure of this mucosa to WRS. The implication of NO in gastroprotection induced by ghrelin was further determined by employing of an inhibitor of NOS, L-NAME injected IP without or with addition of L-arginine, the substrate of NOS. The gastroprotective and hyperemic effects induced by ghrelin were significantly attenuated by L-NAME, but reversed by addition to L-NAME of L-arginine. All these observations support the notion that NO plays a crucial role in the mechanism of gastric protection against WRS damage afforded by ghrelin.

**Ghrelin Attenuates Inflammation and the Generation of Reactive Oxygen Metabolites**

The beneficial effects of ghrelin on the protection of gastric mucosa against injury induced by WRS could be related to the suppression of free oxygen radicals and anti-inflammatory properties of this peptide. Recent studies indicate that ghrelin could be considered as an important mediator in the regulation of inflammation due to its anti-inflammatory activity. Pretreatment with ghrelin just before exposure to WRS and I/R caused a significant reduction in the mRNA expression of proinflammatory cytokine, TNF-α, confirming that anti-inflammatory effect of ghrelin contributes to the gastroprotection and hyperemia exhibited by this peptide. This mechanism seems to be of importance since the upregulation of TNF-α expression represent a central pathophysiological event in the mechanism of acute mucosal injury induced by stress. Further support for the potent anti-inflammatory effects of ghrelin is the fact that ghrelin inhibited the activation of NFκB, which is considered as a critical signaling molecule in inflammation. Previous studies revealed that transcription factor NFκB activation is involved in acute injury of stomach and other organs. In its inactive form, NFκB is sequestered in the cytoplasm and bound by members of IκB family of inhibitor proteins. Phosphorylation of IκB by an IκB kinase complex leads to the translocation of NFκB-p65 into the nucleus. Activation of NFκB induces gene programs leading to transcription of factors that promote inflammation. Therefore, it is assumed that a potential mechanism whereby ghrelin could modulate inflammatory response is blocking of activation of NFκB. This notion was confirmed by observation that ghrelin inhibits an activation of NFκB in human endothelial cells *in vitro*.

Ghrelin not only prevents the acute gastric injury induced by WRS, but also accelerates the healing of these lesions. At 6 h after the end of standard 3.5-h WRS, a significant acceleration of healing of the WRS-induced lesions was observed in rats treated with ghrelin as compared to those treated with vehicle. The mechanism by which ghrelin could stimulate the healing of WRS-induced lesions is poorly understood. Previous studies demonstrated that the growth factors stimulating angiogenesis play a crucial role in the mechanism of healing process. The acceleration of healing of acute WRS-induced gastric erosions was
accompanied by the increased expression of hypoxia-inducible factor-1α (HIF-1α). The increased expression of HIF-1α in the ulcerated mucosa leads to increased expression and activation of vascular endothelial growth factor (VEGF). For instance, the concomitant rise in the expression of HIF-1α and VEGF was observed at day 6 following the combination of ghrelin and I/R and this was accompanied by a marked decrease of the gastric mucosal lesions produced by I/R. At 24 h after the end of WRS and I/R, an increase in expression of HIF-1α, while resulting in downregulation of the VEGF expression was observed in ghrelin-treated animals. This early reduction of VEGF expression despite increased expression of HIF-1α at 24 h after I/R injury or following mucosal recovery from WRS lesions could be attributed to the increased generation of free oxygen radicals and increased lipid peroxidation which can inhibit the activation of VEGF. It is known that healing of WRS and I/R injury involves an activation of antioxidant enzymes resulting in the inhibition of free oxygen species generation and subsequent enhancement in VEGF mRNA expression. This could, at least in part, explain significant increase in the expression for VEGF mRNA at 24 h following WRS damage and at day 6 after I/R-induced gastric injury.

In summary, the administration of exogenous ghrelin applied by the ICV or IP routes that is accompanied by a significant increment in its plasma levels, exhibits dose-dependent gastroprotection against the WRS-induced gastric lesions. Ghrelin is effective not only in gastroprotection against WRS damage but also accelerates the healing of these lesions. Existing evidence indicates that these protective and hyperemic actions of ghrelin may affect brain-gastrointestinal tract axis and involve cooperation between endogenous PG, NO, and sensory nerves releasing neuropeptides such as CGRP (Figure 5). Ghrelin exerts a potent anti-inflammatory activity and inhibits activation of NFκB, an important transcription factor, which seems to be an essential step in the formation of WRS injury. As CGRP and eNOS/NO system are activated in gastric mucosa of ghrelin-treated animals, it is assumed that these two factors could trigger the gastroprotective mechanisms and contribute to the maintenance of gastric mucosal integrity in experimental animals and possibly also in humans exposed to noxious agents and to adverse conditions such as stress.

Further Reading


Date, Y., Kojima, M., Hosoda, H., et al. (2000). Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the


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**Glia or Neuroglia**

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Introduction
Anatomy and Structure  
Physiology and Pharmacology  
Neuron–Glial Cell Interactions

Glossary

**GABA**  
Gamma-aminobutyric acid, the major inhibitory neurotransmitter in the brain.

**CR3**  
Complement receptor 3, a marker for immune cells.

**ED1**  
Product of the ectodermal dysplasia 1 gene, a marker of immune activation.

Introduction

In the past, neuroscientists concentrated almost exclusively on the electroactive components of the nervous system (neurons) because of their direct relationship to function, and neglected the nonelectroactive silent cells (glia), which outnumber them by at least 10 to 1 in much of the nervous system. Classically, glia were named for and relegated to the status of glue responsible for binding together the more important neurons, although Ramón y Cajal and others classified them and made useful proposals about their functions. This neglect has now been partly redressed, and their important roles in development, in maintaining function in the face of physiological stresses, and in the response to injury and infection are now recognized.

Subsequent studies confirmed that there are basically three types of glial cells, namely:

1. **Macroglia:**
2. **Astrocytes:** cells with many processes and possible function
3. **Oligodendrocytes:** cells with few processes that form the myelin of myelinated nerve fibers
4. **Microglia:**
5. **Macrophages:** cells in white matter specifically activated in injury and degeneration

In addition to these glial cells, the normal brain also contains pericytes and perivascular macrophages. Pericyte processes partially cover the basement membrane of brain blood vessels in a way similar to those of astrocytes. Pericytes, however, express smooth muscle actin and are contractile. Both pericytes and perivascular macrophages express immune markers and have sentinel phagocytic functions.

Astrocytes are the most abundant cells in the mammalian brain and consist of (1) those located in white