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Protective Effects of Gastric Mucus

Takafumi Ichikawa and Kazuhiko Ishihara
Kitasato University Graduate School of Medical Sciences
Japan

1. Introduction

The gastric mucosa is continuously exposed to many noxious factors and substances. How the gastric mucosa maintains structural integrity and resists auto-digestion by substances such as acid and pepsin puzzled clinicians and investigators for more than 200 years. The gastric epithelium must also resist damage from extrinsic agents, including *Helicobacter pylori* (*H. pylori*) and noxious ingestions such as ethanol and nonsteroidal anti-inflammatory drugs (NSAIDs). The luminal surface of the stomach is covered by a viscoelastic mucus gel layer that acts as a protective barrier against the harsh luminal environment. The structural characteristics of this barrier are primary indicators of its physiological function and changes of its composition have been identified in gastrointestinal pathologies. This chapter presents recent insights into the implication of the gastric mucus barrier as “no mucus, no protection”.

While acid, pepsin, and *H. pylori* are thought to be major factors in the pathophysiology of gastritis, the importance of the mucosal defense system has also been emphasized. Gastric ‘cytoprotection’ refers to a reduction or prevention of chemically induced acute hemorrhagic erosions by compounds such as prostaglandin (PG) and SH derivatives without inhibiting acid secretion in rodents (Robert, 1979; Szabo et al., 1981). Since the concept of ‘cytoprotection’ was introduced, increasing attention has been paid to the effect of medications on the gastric mucosal defensive mechanisms. Although the exact mechanisms of the mucosal defense system are unknown, it involves one or more of the naturally occurring gastric mucosal defensive factors such as mucus metabolism. For estimation of the gastroprotective function, many drugs have been investigated for their activity to protect the gastric mucosa from a variety of necrotizing agents such as ethanol and HCl. Considerable information has accumulated about the gastroprotective function of the mucus that covers the mucosal surface of the stomach.

2. Fundamental aspects of gastric mucus

2.1 Constituent of gastric mucus

Mucus is produced in mucus-producing cells, secreted and extensively covers the surface layer of the mucosa by forming a mucus gel layers. As shown in Figure 1, mucus is a complex mixture containing mucin, water electrolytes, sloughed off cells, enzymes and various other materials, including bacteria and bacterial products depending on the source and location of the mucus (Hotta, 2000).

Gastric mucus is present in the mucus granules of the mucus-producing cells, the insoluble mucus gel layer adhering to the mucosal surface and the gastric lumen in a solubilized

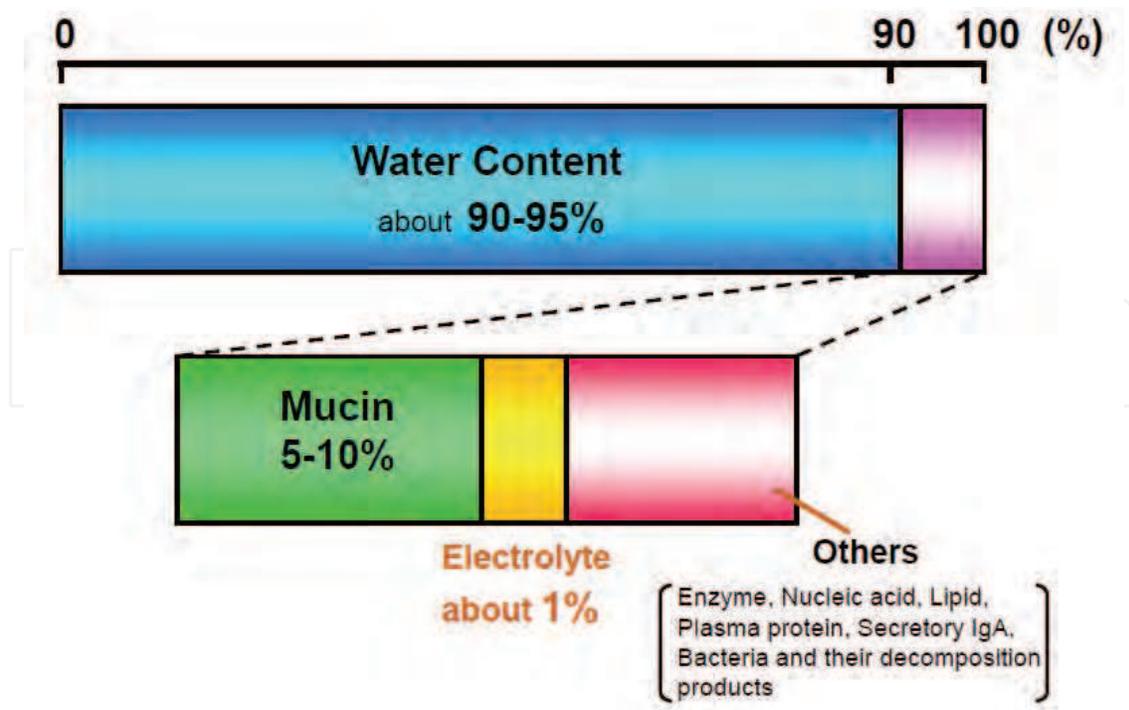


Fig. 1. Composition of gastric mucus.

condition. Mucus rapidly responds to pathological and physiological changes in the stomach. Moreover, mucus present in the stomach exhibits various actions such as maintaining lubrication of the mucosal surface, covering ingested foods to mix them, helping digestion, and protecting the surface epithelium from irritation by forming a thick mucus gel layer.

Mucin, the major constituent of the mucus, is biosynthesized by the mucus-producing cells and secreted from them. Mucus-producing cells of the mammalian gastric mucosa are classified mainly as surface mucus or gland mucus cells (Fig. 2) and respective mucins differ in their peptide sequences and chemical composition of the carbohydrate moieties. The core peptides of the mucins from the surface and gland mucus cells of the human stomach are characterized as MUC5AC and MUC6, respectively. Mucins from these two types of cells have distinct roles in the physiology of the gastric mucosa. In the studies using experimental animals, the appearance of specific mucin was observed in the regenerating epithelia during the healing process from gastric mucosal damage (Hayashida et al., 2001; Ikezawa et al. 2004).

2.2 Outline of gastric mucin

Electron microscopy has indicated 200 to 4000 nm fibers to be present in a gastric mucin molecule. Mucins are composed of glycoprotein subunits (monomer molecular weight : 3 to 5×10^5) joined by disulfide bridges, to form high-molecular-weight polymers (having a molecular weight of millions). Each glycoprotein subunit consists of a central peptide core, with many closely packed carbohydrate side chains attached (Fig. 3). Each carbohydrate chain is composed of several sugar residues (up to 19 in length) in gastric mucus, and many will carry a negative charge because of the presence of ester sulfate and sialic acid residues. It is these negatively charged carbohydrate chains that give the mucin its acidic-staining

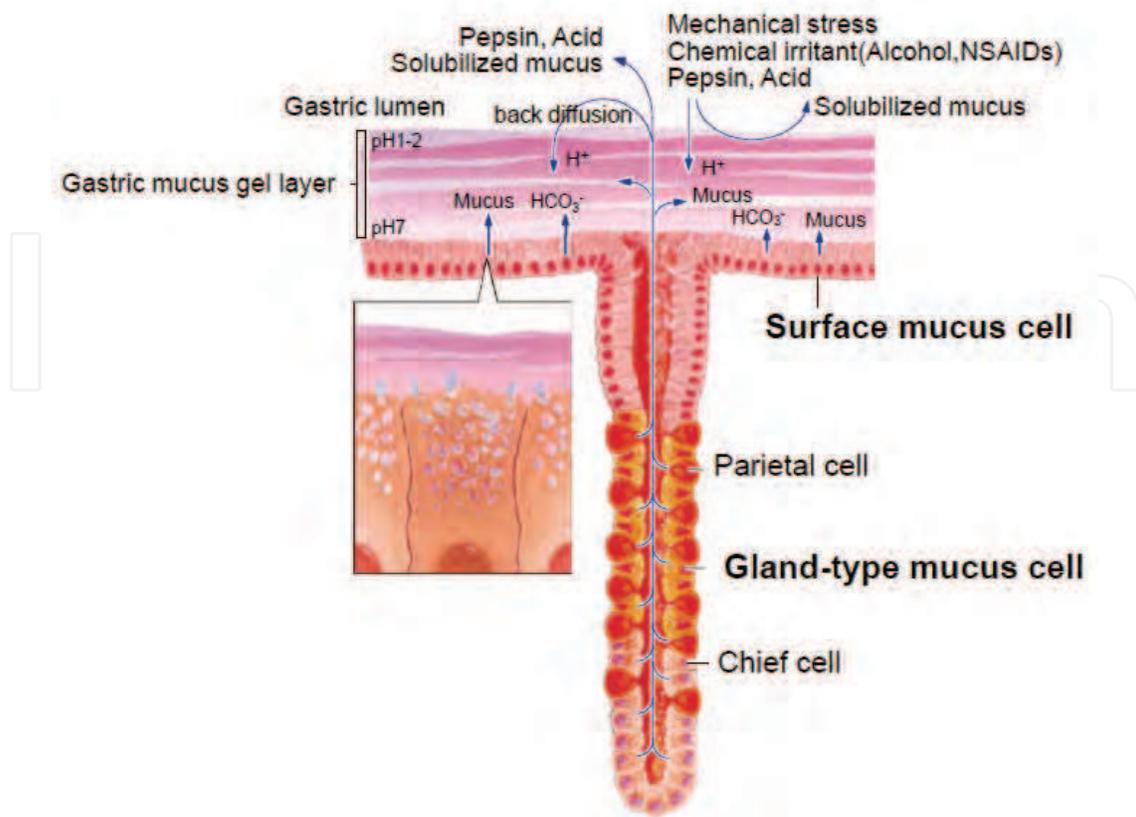


Fig. 2. Distribution of cells constituting the oxyntic gland.

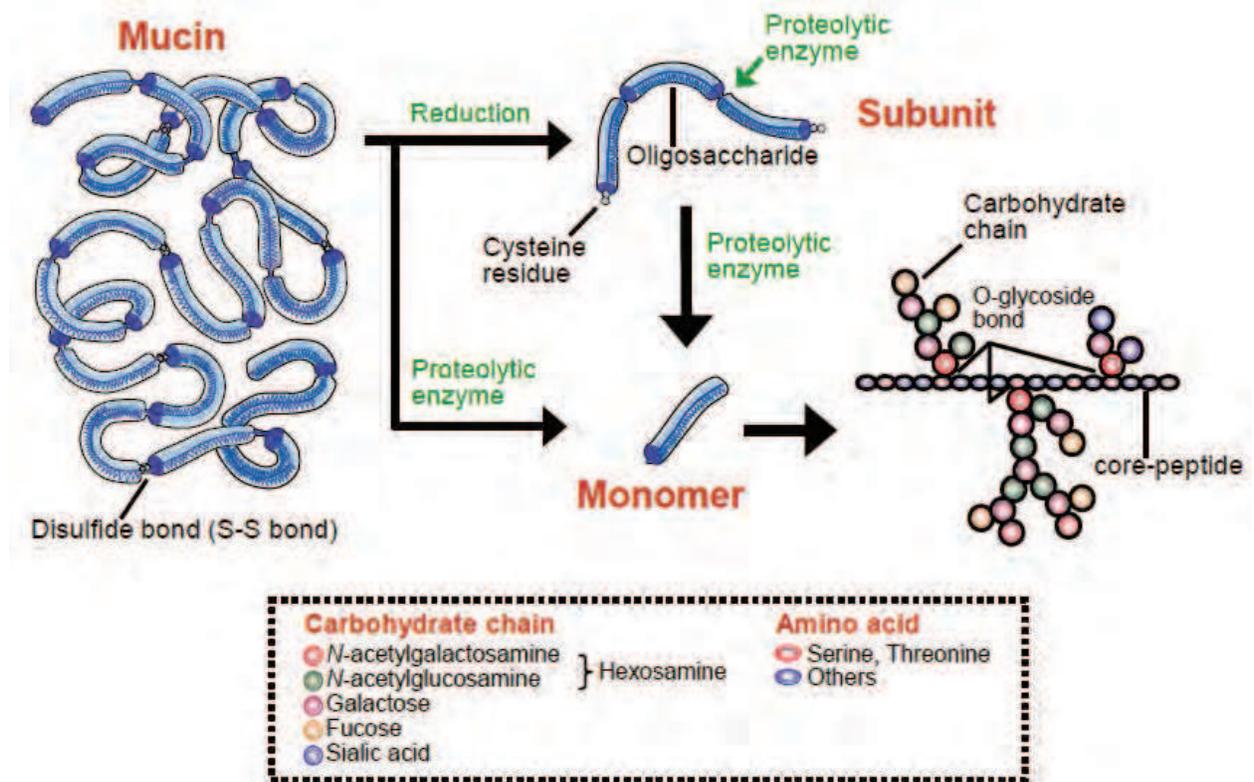


Fig. 3. Polymeric structure of mucin molecules.

properties. Each glycoprotein subunit can be divided into two functional regions on the basis of the peptide core: (1) glycosylated regions in which carbohydrate chains form a closely packed sheath around the central peptide core, protecting it from proteolytic attack; and (2) other nonglycosylated regions of the peptide core that have little or no carbohydrate attached, which are therefore accessible to proteolytic attack by pepsin and other proteolytic enzymes. These nonglycosylated regions of the peptide core are also the site of the disulfide bridges that join the glycoprotein subunits together to form the polymeric mucin structure.

Gel formation between intact polymeric mucin molecules occurs at high concentration (15 to 50 mg/ml) by noncovalent interactions. For gel formation to take place, the mucin must be in its polymeric form. This is the reason why proteolytic enzymes such as pepsin, which degrades the mucin polymeric structure, will dissolve mucus gels. Proteolysis digests the nonglycosylated regions of the peptide core, hence that part containing the disulfide bridges that join the glycoprotein subunits together. The resulting proteolytically degraded subunit consists of the glycosylated region, which is resistant to further proteolytic digestion. There is no detectable loss of carbohydrate during proteolysis and, since it is more than 80% by weight of the glycoprotein subunit, the proteolytically degraded glycoprotein is still quite large.

3. Method and tools for mucus research

3.1 Biosynthesis of mucin

Mucin is produced within mucus-producing cells. To serine or threonine in the polypeptide core synthesized in ribosomes, sugars are transferred one after another in the Golgi complex. Dekker & Strous (1990) have indicated the biosynthesis of gastric mucin to occur as follows. A polypeptide (molecular weight: about 270,000) is synthesized in ribosome and the mucin precursor is synthesized in the rough endoplasmic reticulum (RER). A small portion of an *N*-glycoside sugar chain is connected to each end of the peptide in the RER and is required for efficient oligomerization of the precursor. Three to 4 molecules of this precursor are polymerized in an ATP-unrelated manner in the RER to form an oligomer. *N*-acetylgalactosamine is subsequently transferred to serine and threonine in the late RER compartment (transitional elements) or in cisternae of the Golgi complex. The three-dimensional structure of the polypeptide core changes to an elongated random coil as a result of this transfer. The other sugars are transferred to mucin intermediates before they can reach the trans-cisternae of the Golgi complex and the mucin intermediates form mature mucin. Following biosynthesis in mucus-producing cells, mucin accumulates as mucus granules in the cells and is subsequently secreted through exocytosis. Consequently, a mucus gel layer is formed, which is degraded or directly secreted (Fig. 4).

3.2 Methods for isolation of gastric mucus

The distribution in the stomach, localization and composition of mucus were mainly determined by histochemical methods. By virtue of the development of new staining methods, it has become possible to determine the histochemical characteristics of the produced mucus. However, this method is not suitable for a quantitative assay to grasp the disposition of mucus as a whole. To continue our mucus research, the development of some biochemical assay methods was needed. Gastric mucus is a mixture with a complicated

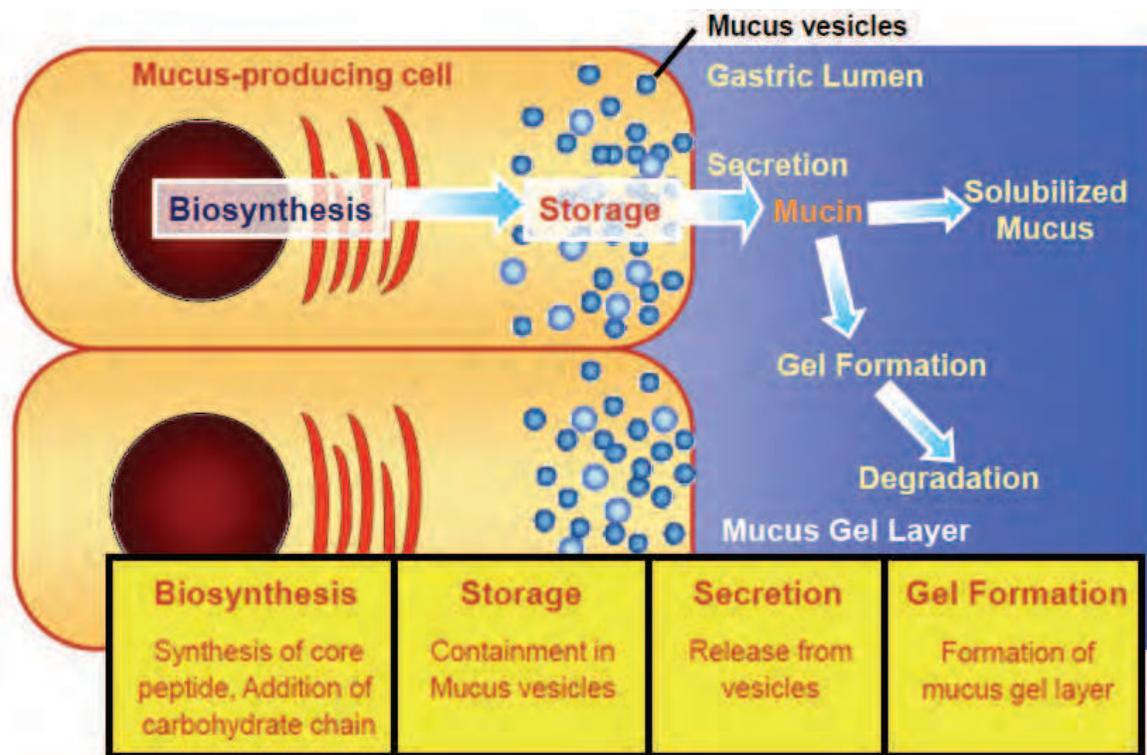


Fig. 4. Biosynthesis and secretion of mucin on mucus-producing cell.

composition. It is not easy to quantify this substance. To overcome this difficulty, we decided to determine the major constituent of mucus, mucin, alone for quantitative evaluation of the gastric mucus. As mucin is a highly glycosylated macromolecule, we developed a method to efficiently extract and isolate mucin from the gastric mucus and established the method to quantify its constituent sugars.

Mucus is isolated from corpus and antral mucosa of rat stomach (Fig. 5). To determine mucus content, lyophilized tissues are subjected to extraction with Tris-HCl buffer containing 2% Triton X-100 and separated by gel filtration. The first peak eluted with the void volume is characterized as mucin and the change in mucin content is determined by measurement of hexose (Azumi et al., 1980). The amount of hexose per dry tissue weight is calculated and the results expressed relative to the control. To investigate the biosynthetic activity of mucin, 2 x 2 mm tissue samples are incubated in a medium containing a labelled precursor and the mucin fraction is isolated. The radioactivity is determined and given as levels per tissue protein (Ichikawa et al., 1993).

These biochemical methods are suitable for quantification of the total mucin content in the entire mucosal layer. With the use of these methods, it became possible to quantify the amount of mucus and the extent of biosynthesis in each portion of the stomach (corpus and antrum). Moreover, it became possible to determine the physiological changes and also changes in the amount of mucus and qualitative changes due to pathological changes such as an experimental ulcer. However, when using this described method, it was impossible to determine the disposition of mucin in the mucus gel layer which is important for the gastric defense mechanism. We normally mechanically scraped the gel layer from the mucosa, and therefore, it was impossible to make a precise determination due to the loss of surface epithelial cells. To solve this problem, various methods for removal of the gel layer were

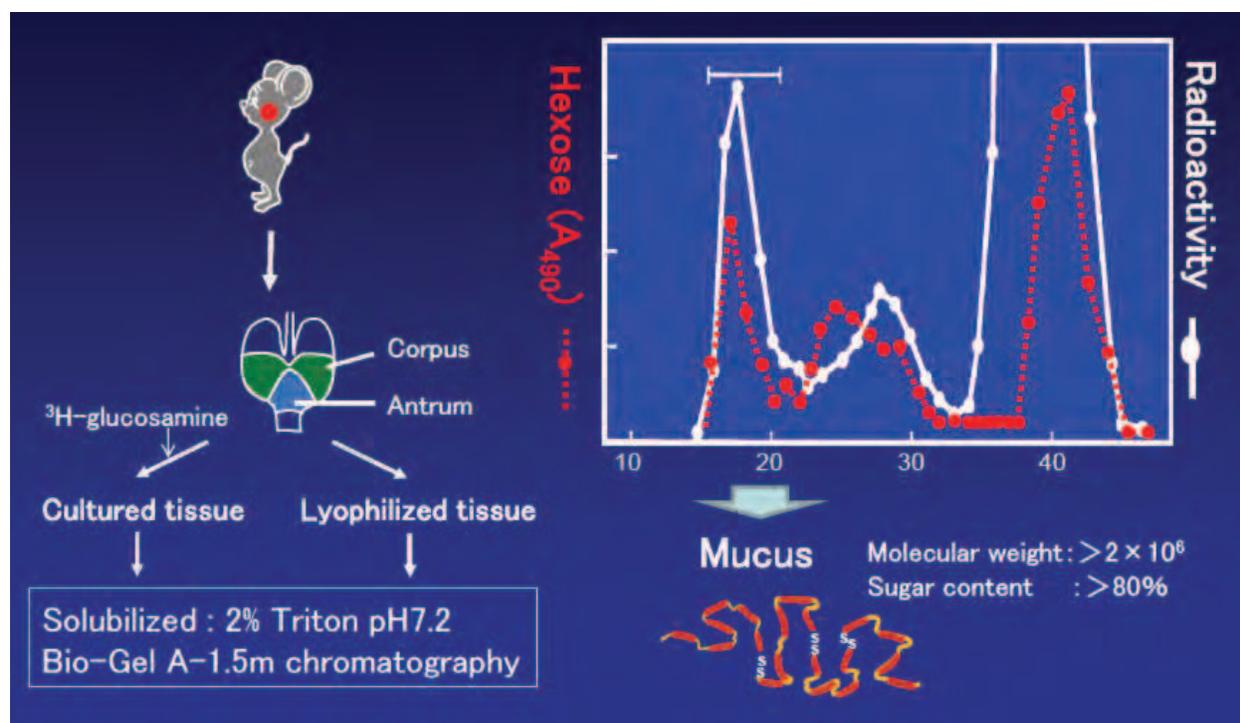


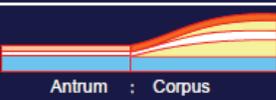
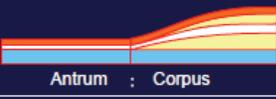
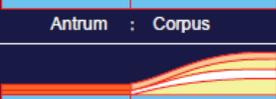
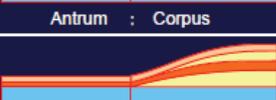
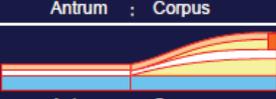
Fig. 5. Preparation of labeled and unlabeled mucus.

tried. As a result, it was confirmed that the mucus gel layer alone can be separated without damaging the surface epithelium when *N*-acetylcysteine is used as a mucolytic agent (Komuro et al., 1991). At present, it has become possible to remove the gel layer, to scrape the surface mucosa and deep mucosa, and then to determine the mucin content in the mucus for each region and each layer (Komuro et al., 1992a, 1992b). Our scraping method enables us to biochemically assess the mucin content of the gel layer by separating it from the deep mucosa of the stomach, and we have demonstrated that quantitative changes in the gastric mucin are closely related to mucosal protective activity (Kojima et al., 1992, 1993; Ichikawa et al., 1994a; Komuro et al., 1998).

3.3 Development of monoclonal antibody against gastric mucin

Previous studies have shown that different types of mucin, differing in their carbohydrates and core protein structure, are expressed in different regions of the gastrointestinal tract. In the stomach, the corpus mucin differs from the antral mucin, and in each region the surface-type mucins (surface mucus cell-type mucins) differ from the gland-type mucins, synthesized in deeper layers of the gastric mucosa (Corfield et al. 2000). Histochemical studies revealed that surface-type mucins have different carbohydrate chains from gland-type mucins in the stomach. For instance, surface-type mucins were stained by galactose oxidase-cold thionine Schiff (GOTS) staining, while glandular mucins were stained by paradoxical concanavalin A staining (PCS) (Ota et al., 1991; Ota & Katsuyama, 1992). On the other hand, studies using gene technology revealed that, in the stomach, the mucin bearing MUC5AC core protein was expressed in the surface mucosa, while MUC6 was expressed in the glandular mucosa (De Bolos et al., 1995; Ho et al., 1995a, 1995b; Buisine et al, 2000). The biochemical characterization of individual mucin molecules is important to understand their functions, and specific tools to recognize particular mucin species are essential. For these

purposes, many monoclonal antibodies (mAbs) against mucins have been developed and used in our laboratory (Ishihara et al., 1993). Representative anti-mucin monoclonal antibodies are shown in Figure 6. The mAbs RGM21 and HIK1083, which recognize a specific carbohydrate portion of rat gastric surface- and gland-type mucins, respectively (Ishihara et al., 1996a, 1996b), are frequently used to characterize the different mucin molecular structures. From histological studies and epitope analyses, the characteristics of each antibody have been elucidated (Goso et al., 1999, 2003, 2009; Tsubokawa et al., 2007, 2009).

Group	Abs	Species	Detectable mucus cells	Immunohistochemical staining (Rat stomach)	Epitope	Class	
Carbo- hydrate antigen	I	RGM11	Corpus (SMC)		Blood-group H type carbohydrate moiety	Ig M	
		RGM21	Corpus (SMC)	Antrum : Corpus			
	II	RGM24	Rat	Corpus / Antrum (SMC)		Peripheral sugar residues	IgM
		HGM75	Human	Corpus / Antrum (SMC)		Peripheral sugar residues	IgG
	III	RGM26	Rat	Antrum (SMC)		Peripheral α-linked GalNAc	IgM
		RGM22	Rat	Antrum (SMC/GMC)		Peripheral α-linked GalNAc	IgM
	IV	HIK1083	Human, Rat, Frog	Corpus / Antrum (GMC)		Peripheral α-linked GlcNAc	IgM
	V	HCM31	Rat	Cardia (SMC), Small intestine, Colon		Oligosaccharides with the sialic acid residue	IgG
		PGM34	Rat	Small intestine		Sulfated oligosaccharides	IgM
	Peptide antigen	RGM23	Rat, (Human)	Corpus / Antrum / Cardia (SMC)		Peptide moiety of the mucin molecule	IgG

SMC : Surface mucus cell, GMC : Gland mucus cell

Fig. 6. Representative anti-mucin monoclonal antibodies.

4. Changes of gastric mucus and mucosal protection

4.1 Gastric mucosal protection

The gastric mucosa acts to maintain homeostasis through the physiological mechanism naturally given to it in the presence of endogenous irritants such as gastric acid, pepsin, and exogenous irritants such as NSAIDs, stress, and alcohol (Fig. 7). During the protection of the mucosa, various factors such as bicarbonate ion, mucosal blood flow and cell turnover are involved other than the mucus. In recent years, the roles played by indirect factors such as prostaglandin and superoxide dismutase have also been clarified. These factors interact with each other, and damage to the mucosa occurs through an imbalance between the aggressive factors and protective factors (Fig. 7).

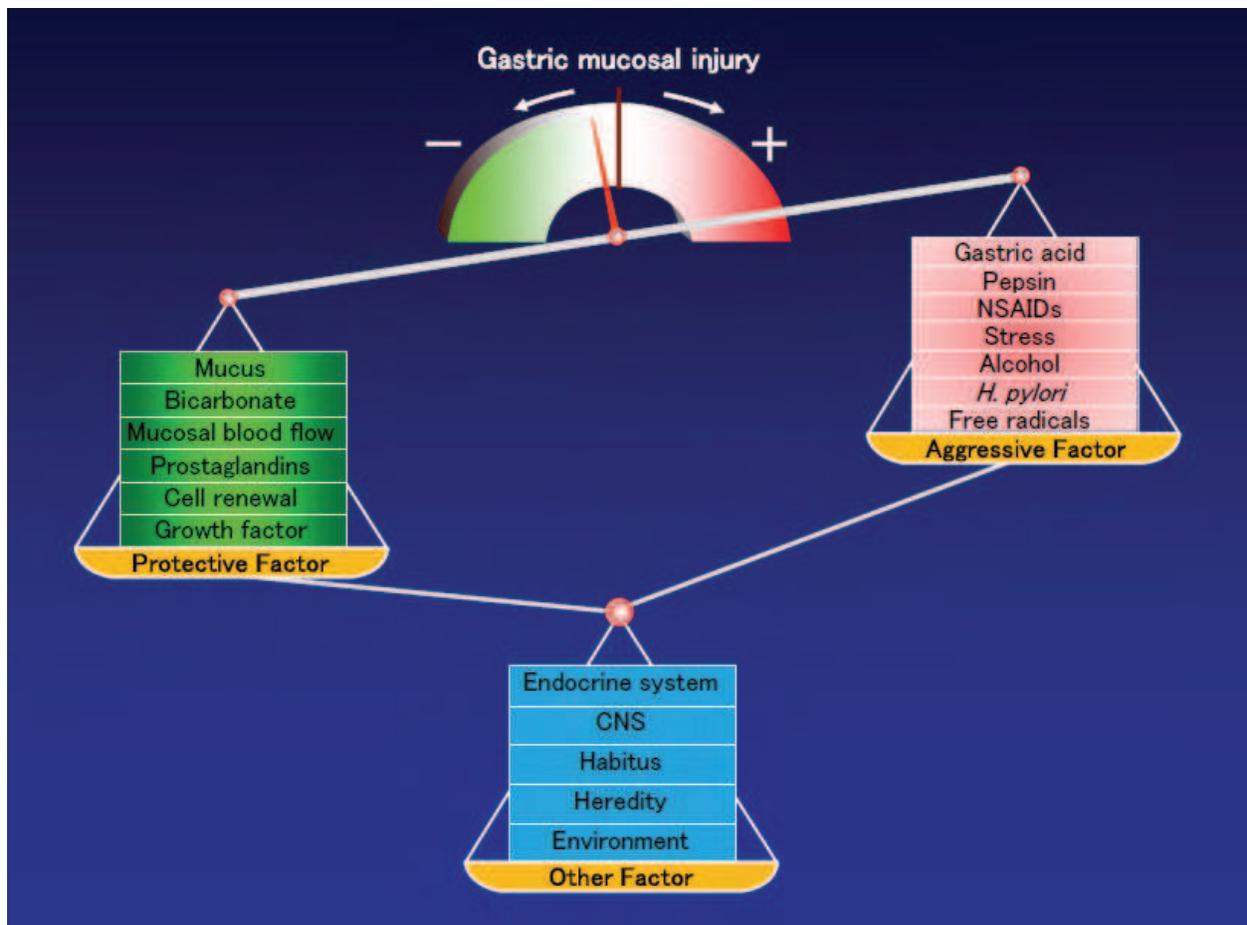


Fig. 7. Gastric protection: which is stronger, aggressive factor or protective factor?

4.2 Changes of gastric mucus

The response of the gastric mucosa to acute injury is uniform regardless of the damaging agent; it usually results in exfoliation of the surface epithelium and injury of deeper mucosal layers. Deep mucosal injury is most likely caused, at least in part, by injury to the gastric mucosal microvasculature. Acute injury is most often produced by alcohol, aspirin, indomethacin, and other NSAIDs.

Figure 8 shows the changes of rat gastric mucosa after orally administration of aspirin (100 mg/kg in 0.15N HCl). In the control rat, after fasting for 24 hr, surface mucus cells of the corpus were strongly stained by RGM21 (Fig. 8a). After the administration of aspirin, the immunohistochemical reactivity of RGM21 in the corpus of the rat stomach had decreased when compared with the control situation (Fig. 8b). Figure 8c shows the gastric mucosa treated with teprenone (geranylgeranylacetone) 3 hr after aspirin administration. Teprenone is a gastric mucosal protective drug without affecting gastric acid secretion and clinically used in Japan for treatment of gastritis. This drug has been reported to reveal various pharmacological actions including the promotion of gastrointestinal mucus (Iwai et al., 2011; Rokutan et al., 2000).

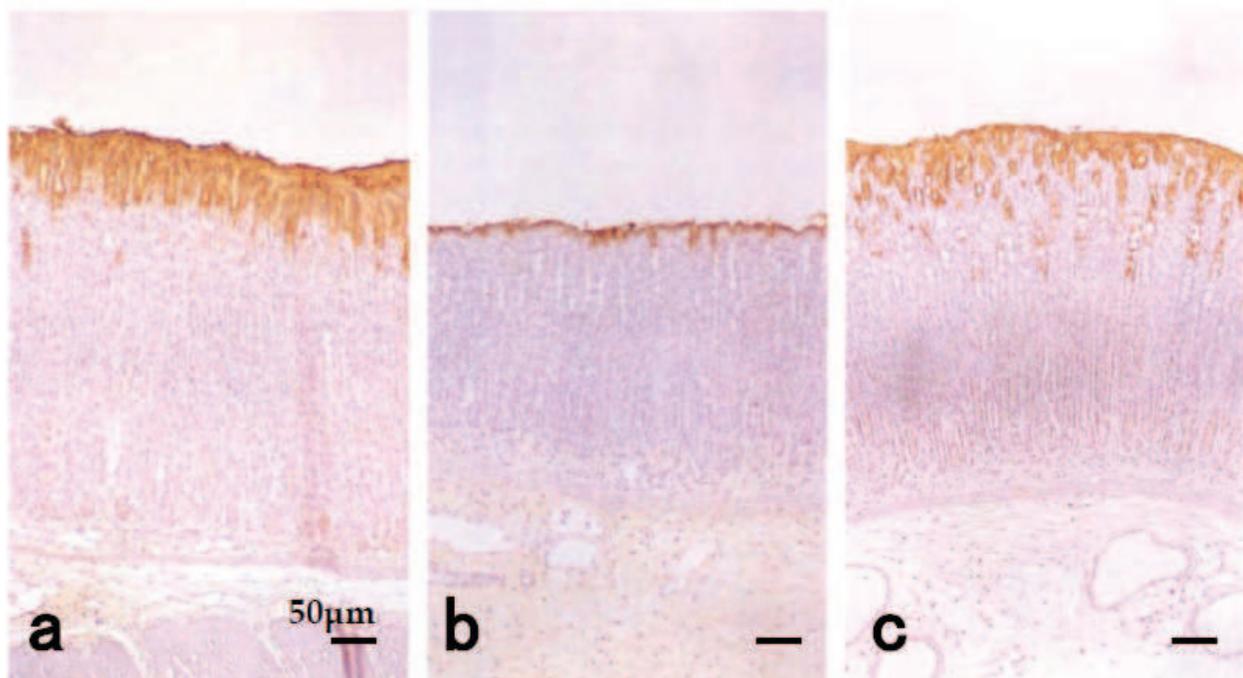


Fig. 8. Immunohistochemical staining with RGM21 in the gastric mucosa. (a) Normal control rat. (b) Aspirin (100 mg/kg) was administered orally and lesion formation was assessed 3 hr later. (c) Rat treated with teprenone (200 mg/kg) after aspirin administration.

4.3 Regulatory mechanism of gastric mucus metabolism

It has been elucidated that various factors are involved in the regulation of the mucus metabolism and each of these factors acts on some specific kind of mucus cells (Fig. 9). Among the endogenous regulatory factors of the stomach, gastrin, histamine and carbachol, which have an acid secretory action, EGF and HGF, which are growth factors and PG, which is an autacoid, are all able to increase the biosynthesis of the gastric mucin. However, a difference is seen in the mucin synthetic reactions based on these factors. Thus, the increase in mucin biosynthesis induced by gastrin among these acid secretagogues can be observed in the surface mucus cells of the gastric oxyntic mucosa, indicating that it occurs by way of specific gastrin receptors independent of the acid secretion mechanism (Ichikawa et al., 1993). Moreover, gastrin stimulates the process of glycosylation without any change in the backbone peptide elongation, and the stimulation is mediated by nitric oxide (NO). Histamine activates the peptide biosynthesis process of mucin, but this process is not mediated by NO. On the other hand, carbachol stimulates the biosynthesis of the mucin peptide as well as the glycosylation step, both in the corpus and the antrum (Ichikawa et al., 1998). As shown in Figure 9, EGF and HGF have distinct effects on the mucin biosynthesis in a specific region of gastric mucosa without their trophic effects (Ichikawa et al., 2000a, 2000b). In other words, endogenous regulatory factors act on the mucus-producing cells through different modes of action, thus regulating their biosynthesis. It has also been indicated that different regulatory mechanisms are present at various sites in the stomach, and that NO and neuropeptides are involved in part of the regulatory process (Ichikawa et al., 2000c).

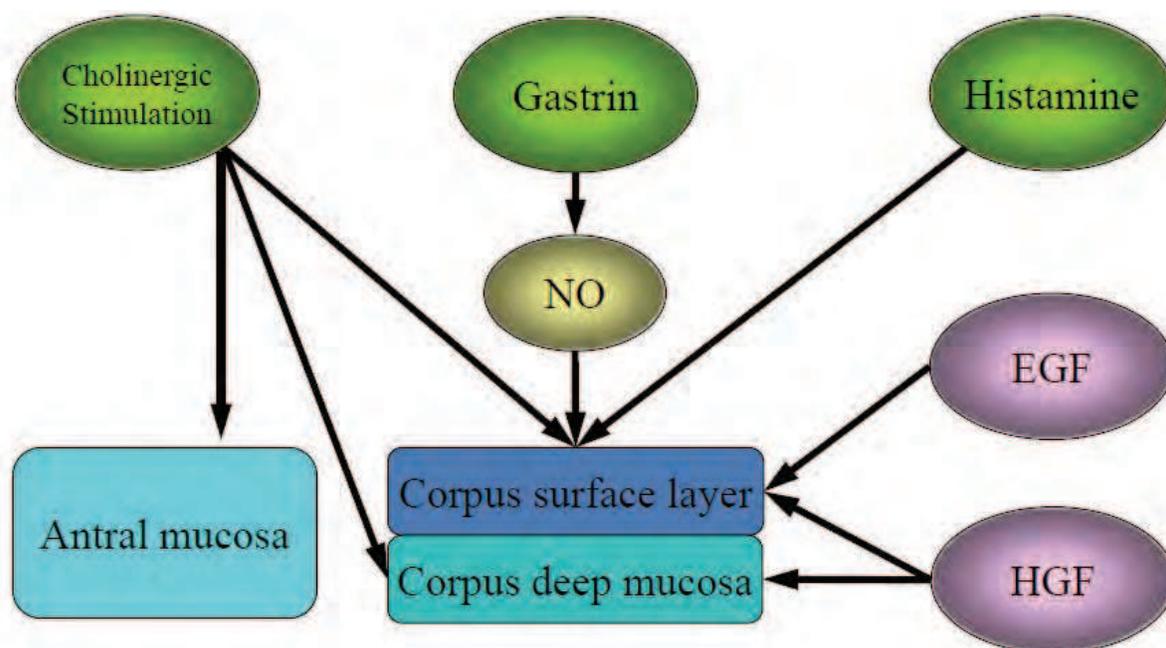


Fig. 9. Regulation of gastric mucin biosynthesis.

5. Second-generation H₂-blockers

5.1 Structure of second-generation H₂-blockers

The H₂-blockers are widely used these days in the treatment of gastritis. The chemical structures of some frequently used H₂-blockers are shown in Figure 10. All the known H₂-blockers comprise an aromatic ring with a flexible chain joined to a polar group. Despite considerable diversity, these compounds can be grouped into two main series according to the nature of the aromatic rings, namely five-membered and six-membered aromatic ring series. Cimetidine and ranitidine belong to the conventional group characterized by a five-membered aromatic ring. Recently, some of the newer H₂-blockers (so-called second-generation H₂-blockers) have been reported to promote the gastric mucosal defense mechanisms (Fukushima et al., 2006; Harada et al., 2007; Marazova et al. 1998; Murashima et al., 2009; Saegusa et al., 2008; Ichikawa et al., 2009a). Second-generation H₂-blockers contain a six-membered aromatic ring, instead of a five-membered heterocyclic ring.

Of the four H₂-blockers shown in Figure 10, lafutidine and roxatidine have a stimulant effect on mucin biosynthesis in the rat gastric mucosa. In contrast, first-generation H₂-receptor antagonists such as cimetidine, ranitidine and famotidine, failed to stimulate mucin biosynthesis (Ichikawa et al., 1994b, 2009b). Second-generation H₂-blockers, lafutidine and roxatidine, have been reported to prevent the formation of gastric mucosal lesions induced by necrotizing agents in rats (Fukushima et al., 2006; Shiratsuchi et al., 1988), and this effect may be due not only to the inhibition of aggressive factors such as acid, but also to the maintenance of defensive factors such as mucus. On the other hand, many reports have indicated that cimetidine and ranitidine lack a protective effect against necrotizing agent-induced gastric mucosal damage in the rat (Shiratsuchi et al., 1988; Tarnawski et al., 1985).

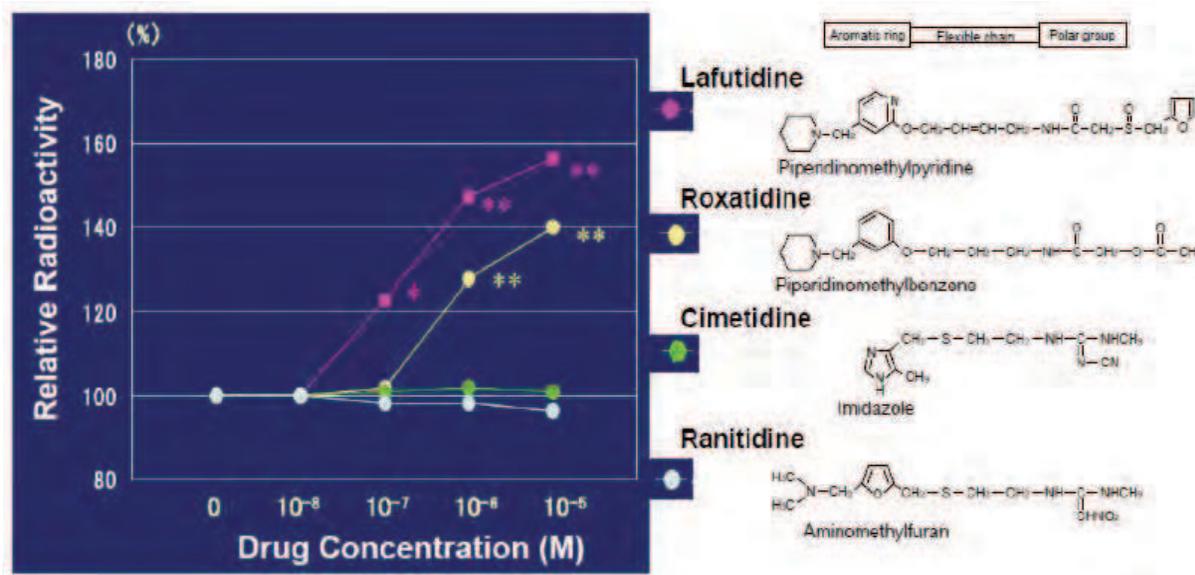


Fig. 10. Effects of representative H₂-blockers on mucin biosynthesis.

5.2 Structure-activity relationship for gastroprotective actions

The above findings have clarified that the second-generation H₂-blockers have a unique structure, and not only inhibit acid secretion but also enhance the protective mechanisms of the gastric mucosa. This should stimulate new interest in the chemical analysis of these drugs to determine the structural requirements for their gastroprotective actions.

Compared with the structural requirements of the acid-inhibitory mechanisms of the H₂-blockers, only a few detailed analyses have been reported of the structural aspects of their gastroprotective actions (Ichikawa et al., 1996, 1997; Sekine et al., 1998; Hirakawa et al., 1998) because of the complicated mechanisms of mucosal protection. However, the cardinal chemical features of lafutidine that determine its mucin biosynthetic activity, as a quantitative index of its gastroprotective action, were identified by considering the structural analogs (Fig. 11) of this drug using a rat stomach organ culture system (Ichikawa et al., 1996). As shown in Figure 11, compounds A, B and C bear the pyridine ring and compounds D and E bear the furan ring, which are commonly present in the structure of lafutidine. Mucin biosynthetic activity was increased by the addition of two pyridine derivatives, lafutidine and compound A. In contrast, compounds D and E, lacking a pyridine ring, failed to stimulate mucin biosynthesis. Similar results were obtained for compounds B and C, which have a pyridine ring but lack an amide structure. These results indicate that pyridine-based compounds containing an amide structure may be essential for activating the gastroprotective function. Furthermore, comparison with the H₂-receptor antagonistic activities of these compounds suggests that H₂-receptor antagonism is not directly correlated with lafutidine-induced stimulation of mucin biosynthesis.

A more detailed analysis has been performed using roxatidine and its structural analogs to reveal the structural requirements of second-generation H₂-blockers for the stimulant effect on rat gastric mucin biosynthesis, particularly with regard to whether the cardinal features of roxatidine are only the six-membered aromatic ring and amide structure, and its relation to H₂-receptor antagonism (Ichikawa et al., 1997). Of six compounds containing both a benzene ring and an amide structure, analogs A and B, but not C, stimulated mucin biosynthesis in a manner similar to that of roxatidine. These three compounds contain a

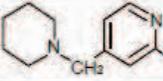
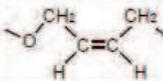
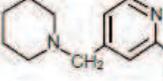
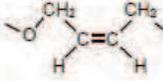
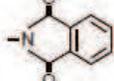
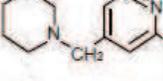
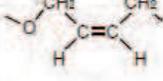
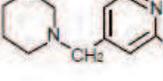
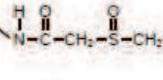
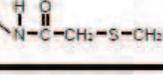
	[A] – [B] – [C]			Histamine H ₂ -receptor antagonistic activity	Mucin biosynthetic activity
	[A]	[B]	[C]		
Lafutidine				+++	+++
Compound A				-	++
Compound B			-OH	+	-
Compound C		Cl	-	-	-
Compound D	-	H		-	-
Compound E	-	CH ₃ -C=O		-	-

Fig. 11. Structures and pharmacological activities of lafutidine and its analogs. Mucin biosynthetic activity was evaluated in an organ culture system of the rat stomach. Score was divided into the following 4 groups: -, no effect at 1×10^{-6} M; +, under 20% increase from the baseline at dose of 1×10^{-6} M; ++, significant 20-30% increase of biosynthetic activity ($p < 0.05$) at 1×10^{-6} M; +++, significant over 30% increase of mucin biosynthesis ($p < 0.01$) at 1×10^{-6} M. Histamine H₂-receptor antagonistic activity was investigated on the histamine-induced positive chronotropic responses in the isolated guinea-pig right atria. Score was divided into the following 4 groups: -, no effect at 1×10^{-5} M; +, under 70% inhibition at 1×10^{-6} M; ++, 70-90% inhibition at 1×10^{-6} M; +++, over 90% inhibition at 1×10^{-6} M. Data are taken from the reference (Ichikawa et al., 1996).

piperidine ring (indicated by R₁ in Figure 12) attached to the benzene ring via a methylene bridge, but the length of the flexible chain (indicated by R₂ in Figure 12) of analog C differs from that of roxatidine. This means that the length of the flexible chain between the benzene ring and the amide structure is essential for this stimulation of mucin biosynthesis. Analogs D, E and F, having different ring structures or no ring structure at R₁ of the roxatidine molecule, failed to activate mucin biosynthesis. Analogs D, E and F contain the same flexible chain as roxatidine. Thus, the piperidine ring is also important for their activity. These results indicate that the structural requirements for the stimulant effect of roxatidine on mucin biosynthesis are not only the six-membered aromatic ring and amide structure, but the attachment of the piperidinomethyl group and the appropriate length of the flexible chain are also important for this function. With regard to their H₂-receptor antagonistic properties, the six analogs were investigated using competition with the binding of the radiolabeled H₂-receptor antagonist [¹²⁵I]iodoaminopotentidine to membranes of the guinea pig striatum (Leurs et al., 1994; Ruat et al., 1990). All compounds, except analog F in Figure 12, displaced the specific [¹²⁵I]iodoaminopotentidine binding to H₂-receptor sites. The

relative potencies of these antagonists were: analog B > A > roxatidine > D > C > E. Compared with the IC₅₀ value (concentration required to inhibit 50% of specific binding) for cimetidine obtained under similar experimental conditions, roxatidine and analogs A, B, C and D were 4.6, 9.5, 13.7, 1.6 and 2.7 times more potent than cimetidine, respectively (Ichikawa et al., 1997). These results suggest that H₂-receptor antagonism does not directly correlate with roxatidine-induced stimulation of mucin biosynthesis.

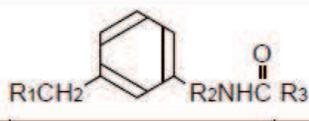
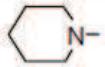
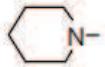
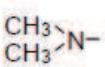
				Histamine H ₂ -receptor antagonistic activity	Mucin biosynthetic activity
	R ₁	R ₂	R ₃		
Roxatidine		-OCH ₂ CH ₂ CH ₂ -	-CH ₂ OCOCH ₃	+++	+++
Analog A		-OCH ₂ CH ₂ CH ₂ -	-CH ₂ OH	+++	+++
Analog B		-OCH ₂ CH ₂ CH ₂ -	-CH ₃	++++	++
Analog C		-OCH ₂ CH ₂ CH ₂ CH ₂ -	-CH ₃	++	-
Analog D		-OCH ₂ CH ₂ CH ₂ -	-CH ₃	++	-
Analog E		-OCH ₂ CH ₂ CH ₂ -	-CH ₃	+	-
Analog F		-OCH ₂ CH ₂ CH ₂ -	-CH ₃	-	-

Fig. 12. Structures and pharmacological activities of roxatidine and its analogs. Mucin biosynthetic activity was evaluated in an organ culture system of the rat stomach. Score was divided into the following 4 groups: -, no effect at 1×10^{-6} M; +, under 20% increase from the baseline at dose of 1×10^{-6} M; ++, significant 20-30% increase of biosynthetic activity ($p < 0.05$) at 1×10^{-6} M; +++, significant over 30% increase of mucin biosynthesis ($p < 0.01$) at 1×10^{-6} M. Histamine H₂-receptor antagonistic activity was investigated on the competition studies with [¹²⁵I]iodoaminopotentidine binding to membranes of the guinea-pig striatum. IC₅₀ values (concentration required to inhibit 50% of specific binding) were determined and divided into the following 5 groups: -, IC₅₀ > 4000 nM; +, 800 > IC₅₀ > 500 nM (similar to cimetidine in the antagonism); ++, 500 > IC₅₀ > 200 nM; +++, 200 > IC₅₀ > 50 nM; +++++, 50 nM > IC₅₀. Data are taken from the reference (Ichikawa et al., 1997).

Taken together, these data indicate that the structural requirements for mucosal protective activity in the second-generation H₂-blockers are their amide structure and six-membered aromatic ring, such as benzene and pyridine derivatives. The cardinal chemical features of roxatidine for the activation of mucin biosynthesis are the appropriate length of the flexible chain between the amide structure and the aromatic ring system bearing the methylpiperidinyl group at the meta position. The thioether function can confer increased gastroprotective activity on lafutidine.

5.3 Effects of lafutidine on the mucus barrier

The adherent mucus gel layer is the functionally important component of the mucus barrier in the human stomach. However, it cannot be demonstrated by routine histological techniques because of its susceptibility to dehydration and shrinkage, which has hampered research. The developed method of stabilizing this layer with Carnoy's solution revealed that its laminated structure was composed of two types of mucin in alternating layers; one mucin is derived from the surface mucus cells and the other from the gland mucus cells. The surface mucus gel layer in Carnoy-fixed tissue sections is shown in the hematoxylin and eosin (HE) preparation (Figs. 13A, C) of the human gastric mucosa. This layer is well preserved and appeared as a thick eosinophilic band. The galactose oxidase/thionine Schiff reaction/paradoxical concanavalin A (GOTS-PCS) procedure stained surface mucus cells blue and gland mucus cells brown (Figs. 13B, D). The surface mucus gel layer consistently shows the laminated structure in the samples of gastric corpus mucosa from both the lafutidine positive and negative groups (Figs. 13B, D). The mucin produced by human gastric gland mucus cells appears to function as a natural antibiotic, protecting the host from *H. pylori* (Kawakubo et al., 2004). Figure 13 demonstrates that after administration of lafutidine there is thickening of the surface mucus gel layer. In other studies using experimental animals, lafutidine has been shown to possess gastroprotective properties, such as strengthening the mucus gel layer, apart from its antisecretory activity (Ichikawa et al., 1994a; Onodera et al., 1999a; Sato et al., 2003).

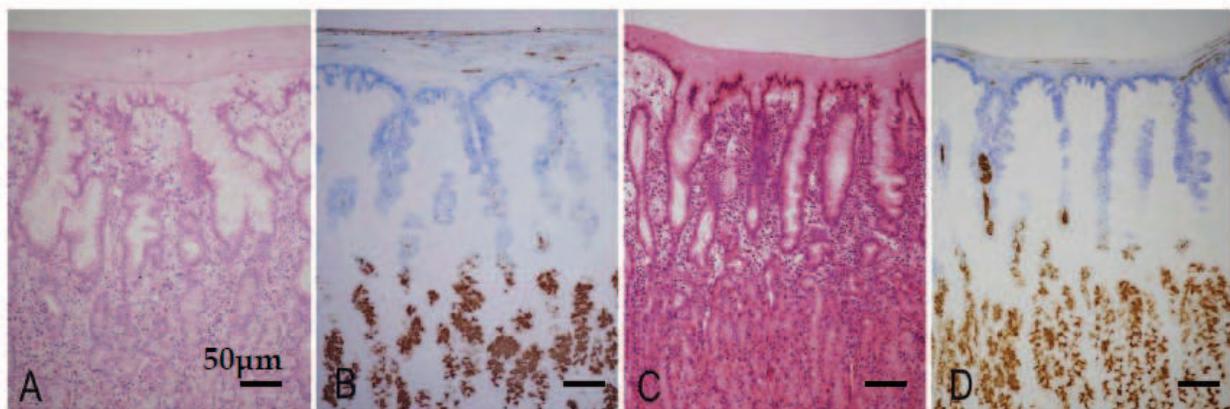


Fig. 13. Surface mucus gel layer of the human gastric mucosa from (A, B) lafutidine positive and (C, D) lafutidine negative groups stained with (A, C) HE and (B, D) GOTS-PCS.

5.4 Mechanisms of gastroprotective actions

Although the exact mechanisms that underlie the gastroprotective activity of the second-generation H₂-receptor antagonists are not well understood, recent findings suggest that the activation of capsaicin-sensitive sensory neurons is associated with their maintenance of gastric mucosal integrity (Fukushima et al., 2006; Harada et al., 2007; Murashima et al., 2009; Sugiyama et al., 2008). The gastrointestinal tract is known to possess a rich neural network, among which afferent neurons of extrinsic origin are reported to operate as the emergency protective system. The discovery of these sensory neuron functions was made possible by capsaicin, a pharmacological tool with which the activity of certain primary afferent neurons can be manipulated selectively. Capsaicin is an excitotoxin that acutely stimulates a group of afferent neurons with unmyelinated (C) or thinly myelinated (A δ) nerve fibers. This

excitotoxic action is restricted to neurons with C- and A δ -fibers because only these cells express receptor-binding sites (vanilloid receptor type 1: VR1) for capsaicin and structurally related ligands. The mammalian stomach, particularly the submucosa, is densely innervated with capsaicin-sensitive afferent neurons. These neurons not only serve a sensory and afferent role, but also display a local effector function initiated by the release of neuropeptide transmitters, such as calcitonin gene-related peptide (CGRP) and substance P, from their peripheral nerve endings. CGRP is reported to exhibit significant mucosal protective roles in the gastrointestinal tract (Ichikawa et al., 2000c; Mizuguchi et al., 2005; Ohno et al., 2008). The action of CGRP is in part mediated by endogenous NO.

The gastroprotective action of lafutidine has been reduced or abolished by treatment with tetrodotoxin, CGRP₈₋₃₇, or chemical defunctionalisation of afferent nerves (Mimaki et al., 2002; Onodera et al., 1999a), indicating that capsaicin-sensitive nerves contribute significantly to the mechanisms underlying the actions of lafutidine (Nishihara et al., 2002). Moreover, lafutidine has been shown to significantly increase CGRP release in both experimental animal models and humans (Harada & Okajima, 2007; Nishihara et al., 2002; Ikawa et al., 2006; Shimatani et al., 2006). Several reports indicate that the VR1 of capsaicin-sensitive afferent nerves may not contribute the CGRP release by lafutidine, suggesting the existence of yet unidentified sites for lafutidine other than VR1 on these nerves (Fukushima et al., 2006; Nishihara et al., 2002). The gastroprotective effects of lafutidine are decreased by treatment with NO synthase inhibitors or NO antidotes (Nishihara et al., 2002; Ichikawa et al., 1998), indicating the involvement of NO generation in lafutidine function. Similar results have been obtained with another second-generation H₂-receptor antagonist, roxatidine (Ichikawa et al., 1997, 1999).

Lafutidine has been shown to enhance the healing of gastrointestinal mucosal lesions in a manner independent of its antacid secretory action (Kato et al., 2000; Onodera et al., 2004). However, lafutidine by itself does not have any direct effects on cell migration or proliferation. An earlier study demonstrated that lafutidine does not influence the impaired healing of epithelial wounds in RGM1 cells under *in vitro* conditions without neuronal innervations (Murashima et al., 2009), again confirming the importance of sensory neurons in the healing-promoting action of this agent. Several studies show that luminal lafutidine stimulates capsaicin-sensitive afferent nerves via presumably direct diffusion rather than after its absorption from intestine followed by via circulation, suggesting the rapid local diffusion reaching to the afferents before H₂-receptor blockade from the circulation (Onodera et al., 1999b; Nagahama et al., 2003). Second-generation H₂-receptor antagonists such as lafutidine are thought to facilitate capsaicin-sensitive sensory afferent nerves and exert gastroprotective effects through CGRP and in part via NO release in the stomach.

6. Summary and perspectives

The gastric mucus barrier constituted by the layer of viscous mucus is crucial to the defense of gastric mucosa. In this review, we have shown a new perspective on the ability of certain therapeutic agent for gastritis to strengthen gastric mucosal defense system. The development of mAbs against the carbohydrate moiety of gastric mucin with a different specificity is really a significant event. With the use of these mAbs, it would be possible to separately identify and determine the various mucins. Through the establishment of the mucus determining method, which utilizes mAbs, the roles of the mucus with different origins as protecting factors would be made clearer.

Second-generation H₂-blockers offer the possibility of more effective prevention of gastritis through the activation of mucosal defense mechanisms (Fig. 14). The structural requirements for mucosal protective activity in these antagonists were shown to be the amide structure and six-membered aromatic ring, such as benzene and pyridine derivatives. The cardinal chemical features of roxatidine for the activation of mucin biosynthesis are the appropriate length of the flexible chain between the amide structure and the aromatic ring system bearing the methylpiperidinyl group at the meta position. Although the exact mechanism underlying the gastroprotective action associated with these agents is unknown, capsaicin-sensitive nerves and CGRP/NO pathway are considered responsible for their anti-ulcer effects in experimental animal models of various gastric mucosal injuries. These mechanisms are also involved in the cytoprotective properties of gastrin, which is a physiologically important bioactive peptide (Ichikawa et al., 1998, 2000c). Taken together, these findings suggest the gastroprotective effects of second-generation H₂-blockers may be of physiological relevance.

Enhanced understanding of the mechanisms of gastric mucosal defense and injury provides new insight into potential therapeutic targets, which contributes towards the development of more well tolerated and more effective therapies.

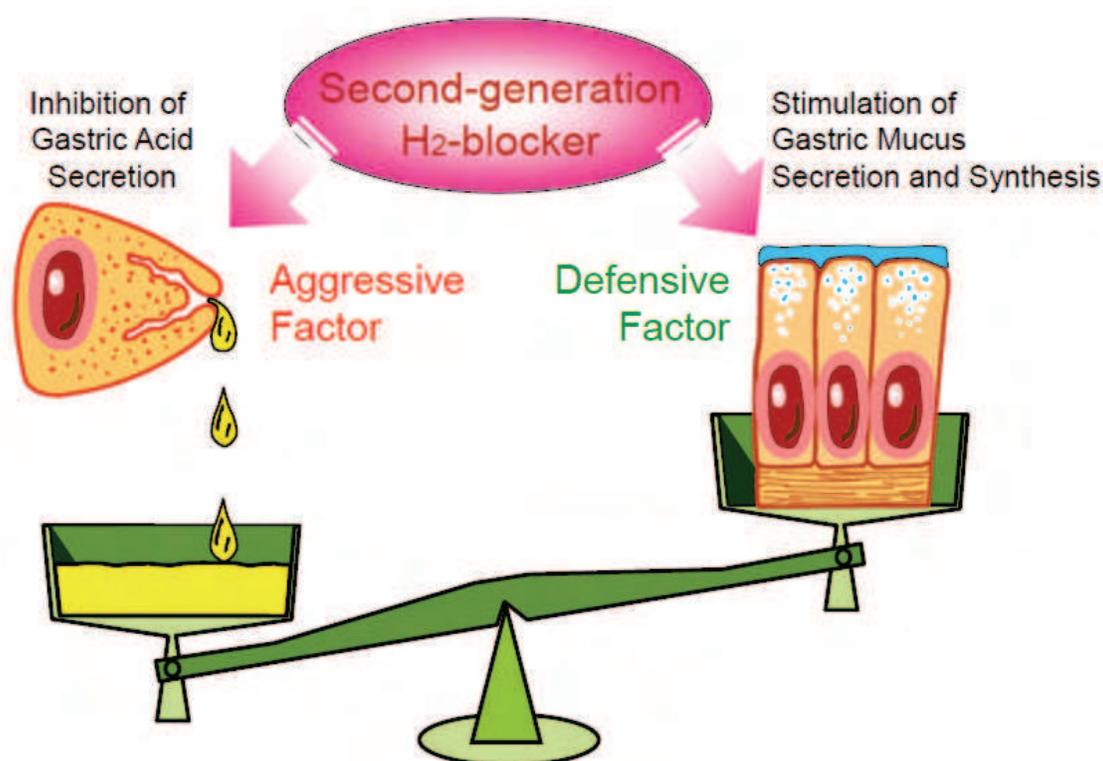


Fig. 14. Dual action of second-generation H₂-blockers.

7. References

- Azuumi, Y.; Ohara, S.; Ishihara, K.; Okabe, H. & Hotta, K. (1980). Correlation of quantitative changes of gastric mucosal glycoproteins with aspirin-induced gastric damage in rats. *Gut* Vol.21, No.6, pp.533-536, ISSN 0017-5749

- Buisine, M.P.; Devisme, L.; Maunoury, V.; Deschodt, E.; Gosselin, B.; Copin, M.C.; Aubert, J.P. & Porchet, N. (2000). Developmental mucin gene expression in the gastroduodenal tract and accessory digestive glands. I. Stomach. A relationship to gastric carcinoma. *J Histochem Cytochem* Vol.48, No.12, pp.1657-1666, ISSN 0022-1554
- Corfield, A.P.; Myerscough, N.; Longman, R.; Sylvester, P.; Arul, S. & Pignatelli M. (2000). Mucins and mucosal protection in the gastrointestinal tract: new prospects for mucins in the pathology of gastrointestinal disease. *Gut* Vol.47, No.4, pp.589-594, ISSN 0017-5749
- De Bolos, C., Garrido, M. & Real, F.X. (1995). MUC6 apomucin shows a distinct normal tissue distribution that correlates with Lewis antigen expression in the human stomach. *Gastroenterology* Vol.10, No.3, pp.723-734, ISSN 0016-5085
- Dekker, J. & Strous, G.J. (1990). Covalent oligomerization of rat gastric mucin occurs in the rough endoplasmic reticulum, is N-glycosylation-dependent, and precedes initial O-glycosylation. *J Biol Chem* Vol.265, No.30, pp.18116-18122, ISSN 0021-9258
- Fukushima, K.; Aoi, Y.; Kato, S. & Takeuchi, K. (2006). Gastro-protective action of lafutidine mediated by capsaicin-sensitive afferent neurons without interaction with TRPV1 and involvement of endogenous prostaglandins. *World J Gastroenterol* Vol.12, No.19, 3031-3037, ISSN 1007-9327
- Goso, Y.; Ikezawa, T.; Kurihara, M.; Endo, M.; Hotta, K. & Ishihara, K. (2003). Characterization of rat gastric mucins using a monoclonal antibody, RGM23, recognizing surface mucous cell-type mucins. *J Biochem* Vol.133, No.4, pp.453-460, ISSN 0021-924X
- Goso, Y.; Ishihara, K.; Kurihara, M.; Sugaya, T. & Hotta, K. (1999). Rat gastric mucins recognized by monoclonal antibodies RGM21 and HIK1083: isolation of mucin species characteristic of the surface and glandular mucosa. *J Biochem* Vol.126, No.2, pp.375-381, ISSN 0021-924X
- Goso, Y.; Tsubokawa, D. & Ishihara, K. (2009). Evaluation of conditions for release of mucin-type oligosaccharides from glycoproteins by hydrazine gas treatment. *J Biochem* Vol.145, No.6, pp.739-749, ISSN 1756-2651
- Harada, N. & Okajima, K. (2007). Inhibition of neutrophil activation by lafutidine, an H₂-receptor antagonist, through enhancement of sensory neuron activation contributes to the reduction of stress-induced gastric mucosal injury in rats. *Dig Dis Sci* Vol.52, No.2, 469-477, 0163-2116
- Hayashida, H.; Ishihara, K.; Ichikawa, T.; Okayasu, I.; Kurihara, M.; Saigenji, K. & Hotta, K. (2001). Expression of a specific mucin type recognized by monoclonal antibodies in the rat gastric mucosa regenerating from acetic acid-induced ulcer. *Scand J Gastroenterol* Vol.36, No.5, pp.467-473, ISSN 0036-5521
- Hirakawa, N.; Matsumoto, H.; Hosoda, A.; Sekine, A.; Yamaura, T. & Sekine, Y. (1998). A novel histamine 2 (H₂) receptor antagonist with gastroprotective activity. II. Synthesis and pharmacological evaluation of 2-furfuryl-thio and 2-furfurylsulfinyl acetamide derivatives with heteroaromatic rings. *Chem Pharm Bull (Tokyo)* Vol.46, No.4, pp.616-622, ISSN 0009-2363
- Ho, S.B.; Robertson, A.M.; Shekels, L.L.; Lyftogt, C.T.; Niehans, G.A. & Toribara, N.W. (1995a). Expression cloning of gastric mucin complementary DNA and localization of mucin gene expression. *Gastroenterology* Vol.109, No.3, 735-747, ISSN 0016-5085

- Ho, S.B.; Shekels, L.L.; Toribara, N.W.; Kim, Y.S.; Lyftogt, C.; Cherwitz, D.L. & Niehans, G.A. (1995b). Mucin gene expression in normal, preneoplastic, and neoplastic human gastric epithelium. *Cancer Res* Vol.55, No.12, pp.2681-2690, ISSN 0008-5472
- Hotta, K. (2000). "Gastric mucus", a mysterious and interesting substance. *Trends in Glycoscience and Glycotechnology* Vol.12, No. 63, pp.59-68, ISSN 0915-7352
- Ichikawa, T.; Endoh, H.; Hotta, K. & Ishihara (2000a). Hepatocyte growth factor region specifically activates mucin synthesis in rat stomach. *Eur J Pharmacol* Vol.392, No.1-2, pp.87-91, ISSN 0014-2999
- Ichikawa, T.; Endoh, H.; Hotta, K. & Ishihara (2000b). The mucin biosynthesis stimulated by epidermal growth factor occurs in surface mucus cells, but not in gland mucus cells, of rat stomach. *Life Sci* Vol.67, No.9, pp.1095-1101, ISSN 0024-3205
- Ichikawa, T.; Hotta, K. & Ishihara, K. (2009a). Second-generation histamine H₂-receptor antagonists with gastric mucosal defensive properties. *Mini Rev Med Chem* Vo.9, No.5, pp.581-589, ISSN 1389-5575
- Ichikawa, T.; Ishihara, K.; Komuro, Y.; Kojima, Y.; Saigenji, K. & Hotta, K. (1994a). Effects of the new histamine H₂ receptor antagonist, FRG-8813, on gastric mucin in rats with or without acidified ethanol-induced gastric damage. *Life Sci* Vol.54, No.10, pp.PL159-164, ISSN 0024-3205
- Ichikawa, T.; Ishihara, K.; Kusakabe, T.; Hiruma, H.; Kawakami, T. & Hotta, K. (2000c). CGRP modulates mucin synthesis in surface mucus cells of rat gastric oxyntic mucosa. *Am J Physiol* Vol.279, No.1, pp.G82-89, ISSN 0193-1857
- Ichikawa, T.; Ishihara, K.; Kusakabe, T.; Kawakami, T. & Hotta, K. (1999). Stimulant effect of nitric oxide generator and roxatidine on mucin biosynthesis of rat gastric oxyntic mucosa. *Life Sci* Vol.65, No.4, pp.PL41-46, ISSN 0024-3205
- Ichikawa, T.; Ishihara, K.; Kusakabe, T.; Kurihara, M.; Kawakami, T.; Takenaka, T.; Saigenji, K. & Hotta, K. (1998). Distinct effects of tetragastrin, histamine, and CCh on rat gastric mucin synthesis and contribution of NO. *Am J Physiol* Vol.274, No.1, pp.G138-146, ISSN 0002-9513
- Ichikawa, T.; Ishihara, K.; Saigenji, K. & Hotta, K. (1993). Stimulation of mucus glycoprotein biosynthesis in rat gastric mucosa by gastrin. *Biochem Pharmacol* Vol.46, No.9, pp.1551-1557, ISSN 0006-2952
- Ichikawa, T.; Ishihara, K.; Saigenji, K. & Hotta, K. (1994b). Effects of acid-inhibitory antiulcer drugs on mucin biosynthesis in the rat stomach. *Eur J Pharmacol* Vol.251, No.1, pp.107-111, ISSN 0014-2999
- Ichikawa, T.; Ishihara, K.; Saigenji, K. & Hotta, K. (1997). Structural requirements for roxatidine in the stimulant effect of rat gastric mucin synthesis and the participation of nitric oxide in this mechanism. *Br J Pharmacol* Vol.122, No.6, pp.1230-1236, ISSN 0007-1188
- Ichikawa, T.; Ishihara, K.; Shibata, M.; Yamaura, T.; Saigenji, K. & Hotta, K. (1996). Stimulation of mucin biosynthesis in rat gastric mucosa by FRG-8813 and its structural analogs. *Eur J Pharmacol* Vol.297, No.1-2, pp.87-92, ISSN 0014-2999
- Ichikawa, T.; Ito, Y.; Saegusa, Y.; Iwai, T.; Goso, Y.; Ikezawa, T. & Ishihara, K. (2009b). Effects of combination treatment with famotidine and methylmethionine sulfonium chloride on the mucus barrier of rat gastric mucosa. *J Gastroenterol Hepatol* Vol.24, No.3, pp.488-492, ISSN 1440-1746

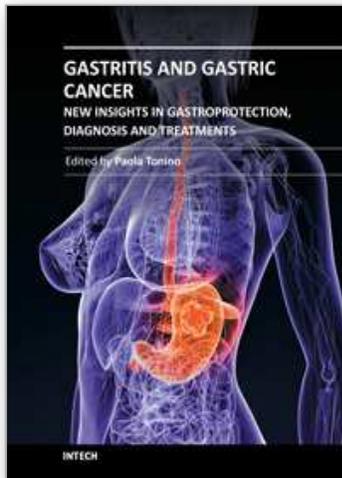
- Ikawa, K.; Shimatani, T.; Azuma, Y.; Inoue, M. & Morikawa, N. (2006). Calcitonin gene-related peptide and somatostatin releases correlated with the area under the lafutidine concentration-time curve in human plasma. *J Clin Pharm Ther* Vol.31, No.4, pp.351-356, ISSN 0269-4727
- Ikezawa, T.; Goso, Y.; Ichikawa, T.; Hayashida, H.; Kurihara, M.; Okayasu, I.; Saigenji, K. & Ishihara, K. (2004). Appearance of specific mucins recognized by monoclonal antibodies in rat gastric mucosa healing from HCl-induced gastric mucosal damage. *J Gastroenterol* Vol.39, No.2, pp.113-119, ISSN 0944-1174
- Ishihara, K.; Kurihara, M.; Eto, H.; Kasai, K.; Shimauchi, S. & Hotta, K. (1993). A monoclonal antibody against carbohydrate moiety of rat gastric surface epithelial cell-derived mucin. *Hybridoma* Vol.12, No.5, pp.609-620, ISSN 0272-457X
- Ishihara, K.; Kurihara, M.; Goso, Y.; Ota, H.; Katsuyama, T. & Hotta, K. (1996a). Establishment of monoclonal antibodies against carbohydrate moiety of gastric mucins distributed in the different sites and layers of rat gastric mucosa. *Glycoconj J* Vol.13, No.5, pp.857-64, 0282-0080
- Ishihara, K.; Kurihara, M.; Goso, Y.; Urata, T.; Ota, H.; Katsuyama, T. & Hotta, K. (1996b). Peripheral alpha-linked N-acetylglucosamine on the carbohydrate moiety of mucin derived from mammalian gastric gland mucous cells: epitope recognized by a newly characterized monoclonal antibody. *Biochem J* Vol.318, No.2, pp.409-416, ISSN 0264-6021
- Iwai, T.; Ichikawa, T.; Kida, M.; Goso, Y.; Kurihara, M.; Koizumi, W. & Ishihara, K. (2011). Protective effect of geranylgeranylacetone against loxoprofen sodium-induced small intestinal lesions in rats. *Eur J Pharmacol* Vol.652, No.1-3, pp.121-125, ISSN 1879-0712
- Kato, S.; Tanaka, A.; Kunikata, T.; Umeda, M. & Takeuchi, K. (2000). Protective effect of lafutidine against indomethacin-induced intestinal ulceration in rats: relation to capsaicin-sensitive sensory neurons. *Digestion* Vol.61, No.1, pp.39-46, ISSN 0012-2823
- Kawakubo, M.; Ito, Y.; Okimura, Y.; Kobayashi, M.; Sakura, K.; Kasama, S.; Fukuda, M.N.; Fukuda, M.; Katsuyama, T. & Nakayama, J. (2004). Natural antibiotic function of a human gastric mucin against *Helicobacter pylori* infection. *Science* Vol.305, No.5686, pp.1003-1006, ISSN 1095-9203
- Kojima, Y.; Ishihara, K.; Komuro, Y.; Saigenji, K. & Hotta, K. (1993). Effects of the muscarinic receptor agonist carbachol and/or antagonist pirenzepine on gastric mucus secretion in rats. *Scand J Gastroenterol* Vol.28, No.7, pp.647-651, ISSN 0036-5521
- Kojima, Y.; Ishihara, K.; Ohara, S.; Saigenji, K. & Hotta, K. (1992). Effects of the M1 muscarinic receptor antagonist pirenzepine on gastric mucus glycoprotein in rats with or without ethanol-induced gastric damage. *Scand J Gastroenterol* Vol.27, No.9, pp.764-768, ISSN 0036-5521
- Komuro, Y.; Ishihara, K.; Ishii, K.; Ota, H.; Katsuyama, T.; Saigenji, K. & Hotta, K. (1992a). A separating method for quantifying mucus glycoprotein localized in the different layer of rat gastric mucosa. *Gastroenterol Jpn* Vol.27, No.4, pp.466-472, ISSN 0435-1339
- Komuro, Y.; Ishihara, K.; Kojima, Y.; Saigenji, K. & Hotta, K. (1998). Distinct effects of tetragastrin in rat gastroduodenal mucosa on mucin content and mucosal

- protective action against histamine-induced injury. *Dig Dis Sci* Vol.43, No.5, pp.1050-1056, ISSN 0163-2116
- Komuro, Y.; Ishihara, K.; Ohara, S.; Saigenji, K. & Hotta, K. (1991). A new method of separation and quantitation of mucus glycoprotein in rat gastric mucus gel layer and its application to mucus secretion induced by 16,16-dimethyl PGE₂. *Gastroenterol Jpn* Vol.26, No.5, pp.582-587, ISSN 0435-1339
- Komuro, Y.; Ishihara, K.; Ohara, S.; Saigenji, K. & Hotta, K. (1992b). Effects of tetragastrin on mucus glycoprotein in rat gastric mucosal protection. *Gastroenterol Jpn* Vol.27, No.5, pp.597-603, ISSN 0435-1339
- Leurs, R.; Smit, M.J.; Menge, W.M. & Timmerman, H. (1994). Pharmacological characterization of the human histamine H₂ receptor stably expressed in Chinese hamster ovary cells. *Br J Pharmacol* Vol.112, No.3, pp.847-54, ISSN 0007-1188
- Marazova, K.; Klouček, E.; Popov, A.; Ivanov, C.; Krushkov, I.; Ichikawa, T.; Ishihara, K. & Hotta, K. (1998). Effect of roxatidine bismuth citrate (MX1) against acetylsalicylic acid- and indomethacin-induced gastric mucosal damage in rats. *Methods Find Exp Clin Pharmacol* Vol.20, No.8, pp.667-672, ISSN 0379-0355
- Mimaki, H.; Kagawa, S.; Aoi, M.; Kato, S.; Satoshi, T.; Kohama, K. & Takeuchi, K. (2002). Effect of lafutidine, a histamine H₂-receptor antagonist, on gastric mucosal blood flow and duodenal HCO₃⁻ secretion in rats: relation to capsaicin-sensitive afferent neurons. *Dig Dis Sci* Vol.47, No.12, pp.2696-2703, ISSN 0163-2116
- Mizuguchi, S.; Ohno, T.; Hattori, Y.; Kamata, K.; Arai, K.; Saeki, T.; Saigenji, K.; Hayashi, I.; Kuribayashi, Y. & Majima, M. (2005). Calcitonin gene-related peptide released by capsaicin suppresses myoelectrical activity of gastric smooth muscle. *J Gastroenterol Hepatol* Vol.20, No.4, pp.611-618, ISSN 0815-9319
- Murashima, Y.; Kotani, T.; Hayashi, S.; Komatsu, Y.; Nakagiri, A.; Amagase, K. & Takeuchi, K. (2009). Impairment by 5-Fluorouracil of the Healing of Gastric Lesions in Rats: Effect of Lafutidine, a Histamine H₂ Receptor Antagonist, Mediated by Capsaicin-Sensitive Afferent Neurons. *Dig Dis Sci* Vol.54, No.1, ISSN 0163-2116
- Nagahama, K.; Yamato, M.; Kato, S. & Takeuchi, K. (2003). Protective effect of lafutidine, a novel H₂-receptor antagonist, on reflux esophagitis in rats through capsaicin-sensitive afferent neurons. *J Pharmacol Sci* Vol.93, No.1, pp.55-61, ISSN 1347-8613
- Nishihara, K.; Nozawa, Y.; Nakano, M.; Ajioka, H. & Matsuura, N. (2002). Sensitizing effects of lafutidine on CGRP-containing afferent nerves in the rat stomach. *Br J Pharmacol* Vol.135, No.6, pp.1487-1494, ISSN 0007-1188
- Ohno, T.; Hattori, Y.; Komine, R.; Ae, T.; Mizuguchi, S.; Arai, K.; Saeki, T.; Suzuki, T.; Hosono, K.; Hayashi, I.; Oh-Hashi, Y.; Kurihara, Y.; Kurihara, H.; Amagase, K.; Okabe, S.; Saigenji, K. & Majima, M. (2008). Roles of calcitonin gene-related peptide in maintenance of gastric mucosal integrity and in enhancement of ulcer healing and angiogenesis. *Gastroenterology* Vol.134, No.1, pp.215-225, ISSN 1528-0012
- Onodera, S.; Nishida, K. & Takeuchi, K. (2004). Unique profile of lafutidine, a novel histamine H₂-receptor antagonist: mucosal protection throughout gastrointestinal tract mediated by capsaicin-sensitive afferent neurons. *Curr Pharm Design* Vol.1, pp.133-144
- Onodera, S.; Shibata, M.; Tanaka, M.; Inaba, N.; Arai, Y.; Aoyama, M.; Lee, B. & Yamaura, T. (1999b). Gastroprotective mechanism of lafutidine, a novel anti-ulcer drug with

- histamine H₂-receptor antagonistic activity. *Arzneimittelforschung* Vol.49, No.6, pp.519-526, ISSN 0004-4172
- Onodera, S.; Tanaka, M.; Aoyama, M.; Arai, Y.; Inaba, N.; Suzuki, T.; Nishizawa, A.; Shibata, M. & Sekine, Y. (1999a). Antiulcer effect of lafutidine on indomethacin-induced gastric antral ulcers in refed rats. *Jpn J Pharmacol* Vol.80, No.3, pp.229-235, ISSN 0021-5198
- Ota, H. & Katsuyama, T. (1992). Alternating laminated array of two types of mucin in the human gastric surface mucous layer. *Histochem J* Vol.24, No.2, pp.86-92, ISSN 0018-2214
- Ota, H.; Katsuyama, T.; Ishii, K.; Nakayama, J.; Shiozawa, T. & Tsukahara, Y. (1991). A dual staining method for identifying mucins of different gastric epithelial mucous cells. *Histochem J* Vol.23, No.1, pp.22-28, ISSN 0018-2214
- Robert, A. (1979). Cytoprotection by prostaglandins. *Gastroenterology* Vol.77, No.4, pp.761-767, ISSN 0016-5085
- Rokutan, K.; Teshima, S.; Kawai, T.; Kawahara, T.; Kusumoro, K.; Mizushima, T. & Kishi, K. (2000). Geranylgeranylacetone stimulates mucin synthesis in cultured guinea pig gastric pit cells by inducing a neuronal nitric oxide synthase. *J Gastroenterol* Vol.35, No.9, pp.673-681, ISSN 0944-1174
- Ruat, M.; Traiffort, E.; Bouthenet, M.L.; Schwartz, J.C.; Hirschfeld, J.; Buschauer, A. & Schunack, W. (1990). Reversible and irreversible labeling and autoradiographic localization of the cerebral histamine H₂ receptor using [¹²⁵I]iodinated probes. *Proc Natl Acad Sci USA* Vol.87, No.5, pp.1658-1662, ISSN 0027-8424
- Saegusa, Y.; Ichikawa, T.; Iwai, T.; Goso, Y.; Ikezawa, T.; Nakano, M.; Shikama, N.; Saigenji, K. & Ishihara, K. (2008). Effects of acid antisecretory drugs on mucus barrier of the rat against 5-fluorouracil-induced gastrointestinal mucositis. *Scand J Gastroenterol* Vol.43, No.5, pp.531-537, ISSN 1502-7708
- Sato, H.; Kawashima, K.; Yuki, M.; Kazumori, H.; Rumi, M.A.; Ortega-Cava, C.F.; Ishihara, S. & Kinoshita, Y. (2003). Lafutidine, a novel histamine H₂-receptor antagonist, increases serum calcitonin gene-related peptide in rats after water immersion-restraint stress. *J Lab Clin Med* Vol.141, No.2, pp.102-105, ISSN 0022-2143
- Sekine, Y.; Hirakawa, N.; Kashiwaba, N.; Matsumoto, H.; Kutsuma, T.; Yamaura, T. & Sekine, A. (1998). A novel histamine 2 (H₂) receptor antagonist with gastroprotective activity. I. Synthesis and pharmacological evaluation of N-phenoxypropylacetamide derivatives with thioether function. *Chem Pharm Bull (Tokyo)* Vol.46, No.4, pp.610-615, ISSN 0009-2363
- Shimatani, T.; Inoue, M.; Kuroiwa, T.; Xu, J.; Nakamura, M.; Tazuma, S.; Ikawa, K. & Morikawa, N. (2006). Lafutidine, a newly developed antiulcer drug, elevates postprandial intragastric pH and increases plasma calcitonin gene-related peptide and somatostatin concentrations in humans: comparisons with famotidine. *Dig Dis Sci* Vol.51, No.1, pp.114-120, ISSN 0163-2116
- Shiratsuchi, K.; Fuse, H.; Hagiwara, M.; Mikami, T.; Miyasaka, K. & Sakuma, H. (1988). Cytoprotective action of roxatidine acetate HCl. *Arch Int Pharmacodyn Ther* Vol.294, pp.295-304, ISSN 0301-4533
- Sugiyama, T.; Hatanaka, Y.; Iwatani, Y.; Jin, X. & Kawasaki, H. (2008). Lafutidine facilitates calcitonin gene-related peptide (CGRP) nerve-mediated vasodilation via vanilloid-1

- receptors in rat mesenteric resistance arteries. *J Pharmacol Sci* Vol.106, No.3, pp.505-511, ISSN 1347-8613
- Szabo, S.; Trier, J.S. & Frankel, P.W. (1981). Sulfhydryl compounds may mediate gastric cytoprotection. *Science* Vol.214, No.4517, pp.200-202, ISSN 0036-8075
- Tarnawski, A.; Hollander, D.; Gergely, H. & Stachura, J. (1985). Comparison of antacid, sucralfate, cimetidine, and ranitidine in protection of the gastric mucosa against ethanol injury. *Am J Med* Vol.79, No.2C, pp.19-23, ISSN 0002-9343
- Tsubokawa, D.; Goso, Y.; Sawaguchi, A.; Kurihara, M.; Ichikawa, T.; Sato, N.; Suganuma, T.; Hotta, K. & Ishihara, K. (2007). A monoclonal antibody, PGM34, against 6-sulfated blood-group H type 2 antigen, on the carbohydrate moiety of mucin. *FEBS J* Vol.274, No.7, pp.1833-1848, ISSN 1742-464X
- Tsubokawa, D.; Nakamura, T.; Goso, Y.; Takano, Y.; Kurihara, M. & Ishihara, K. (2009). *Nippostrongylus brasiliensis*: increase of sialomucins reacting with anti-mucin monoclonal antibody HCM31 in rat small intestinal mucosa with primary infection and reinfection. *Exp Parasitol* Vol.123, No.4, pp.319-325, ISSN 1090-2449

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This book is a comprehensive overview of invited contributions on *Helicobacter pylori* infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in *H. pylori* related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in *H. pylori* infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with *H. pylori* infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and *H. pylori* lipopolysaccharide, as well as the roles of several bacterial genes (*cagA*, *cagT*, *vacA* and *dupA*) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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