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ROLE OF MUCUS IN GASTRIC MUCOSAL PROTECTION

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Even though there is no general agreement as to the mechanism of gastric mucosal protection, the consensus is that the initial brunt of luminal insults falls on the mucus layer which constitutes the only identifiable physical barrier between the gastric lumen and the mucosal surface. The continuous renewal and resilient nature of this layer efficiently counters peptic erosion of the gel, assures its viscoelastic and permselective properties, and provides a milieu for containment of the diffusing luminal acid by mucosal bicarbonate. Disturbances in this delicate balance lead to the impairment of the protective function of mucus resulting in gastric disease. Indeed, the weakening of gastric mucosal defense is intimately associated with the diminished viscoelastic qualities of mucus, decrease in hydrogen ion retardation capacity, and the extensive proteolysis of its mucin component. Although until recently the disintegration of the mucus coat was attributed exclusively to the enhanced activity of intragastric pepsin, our studies provided strong argument that a bacterial factor, namely infection by Helicobacter pylori, through the action of its protease and lipase enzymes also is highly detrimental to the integrity of gastric mucus. Hence, agents capable of interfering with the pathogenic activity of this bacteria are becoming the drugs of choice in peptic ulcer therapy.

Key words: Gastric mucus protection, Helicobacter, pylori mucolytic action, antiulcer agents

INTRODUCTION

The mechanism involved in the maintenance of gastric mucosal protection under the adverse environment of luminal contents which pose continuous threat to the integrity of its defense elements is complex in nature and appears to be multicomponential. Among the mucosal components most often implicated in the maintenance of the mucosal integrity are the viscous and slimy layer of mucus that tenaciously adheres to the epithelial surfaces, the cell membranes of gastric epithelium, and the muco-

sal blood flow (1—3). Hence, the initial brunt of luminal insult falls on the mucus layer which constitutes the only identifiably physical barrier between the gastric lumen and the surface epithelial cells of the mucosa. Under normal physiological conditions, the continuous renewal and resilient nature of this layer efficiently counters peptic erosion of the gel, assures its viscoelastic and permselective properties, and provides a milieu for containment of the diffusion luminal acid by mucosal bicarbonate (4, 5). Disturbances in this delicate balance lead to the impairment of the protective function of mucus layer resulting in gastric disease.

Indeed, the weakening of gastric mucosal defense is intimately associated with the diminished viscoelastic qualities of mucus, decrease in hydrogen ion retardation capacity, and the extensive peptic erosion of its mucin component (2, 5). While until recently the disintegration of the mucus coat was attributed exclusively to the enhanced activity of intragastric pepsin, ample of evidence now exists that a bacterial factor, namely, infection by Helicobacter pylori, may be responsible for the weakening of gastric mucosal integrity.

Although the transmission route for H. pylori is not well understood, the bacteria apparently finds its way to the mucosal surface and thus occupies a niche bordering two major perimeters of gastric mucosal defense, and therefore is capable of exerting its detrimental action on mucus layer, as well as cell surface of gastric epithelium.

H. Pylori colonization factor

Colonization of gastric mucosa by H. pylori is viewed as a causative factor in gastritis and the development of gastric an duodenal ulcers, though the course of pathogenic events is not well explored. The available data indicate that the bacterial attachment to gastric epithelial cells involves a surface-associated adhesin with properties similar to colonization factor antigens commonly found in many pathogenic bacteria. Indeed, H. pylori adhesin like those of other bacteria exhibits a strong hemagglutinin activity towards human and animal erythrocytes (6—8). Discrepancies, however, exist as to the exact nature of the carbohydrate chains involved in this process. While one study suggests that the receptor may bear NeuAcα2, 3Galβ1, 4Glc structure (6), the results of another investigation point towards the involvement of GM_1 ganglioside (Galβ1, 4GalNAcβ1, 4(NeuAcα2, 3) Galβ1, 4Glcβ1, 1Cer) in this phenomenon (7), yet other studies indicate the participation of gastric glycerolipid (8).

The results of our investigations (9) obtained with a variety of glycolipids derived from gastric mucosa. demonstrated that H. pylori agglutinin

specificity is not confined only to sialoglycolipids, but also recognizes sulfated glycolipids. Among sialoglycolipids, the most potent inhibitor of the agglutinin activity was found to be GM_3 ganglioside the carbohydrate chain of which contains NeuAcα2, 3Galβ1, 4Glcβ1, 1Cer structure, while GM_1 and GD_1 gangliosides were clearly less effective. Of the sulfated glycolipids, the highest specificity for H. pylori agglutinin was exhibited by lactosylceramide sulfate with SO_3H, 3Galβ1, 4Glcβ1, 1Cer structure, followed by galactosylceramide sulfate and triglucosyl monoalkylmonoacylglycerol sulfate. Since GM_3 gangloside and lactosylceramide sulfate bear a common Galβ1, 4Glc carbohydrate structure with acidic substituent at C—3 of galactose (NeuAc or sulfate ester group), it appears that H. pylori colonization factor antigen has a high degree of specificity towards carbohydrate structures with terminal lactosyl moieties bearing acidis substituents (*Fig. 1*).

The data on the distribution of sulfated and sialylated glycolipids in human gastric mucosa revealed that antral mucosa in comparision to that of fundus exhibits significantly higher content of gangliosides and

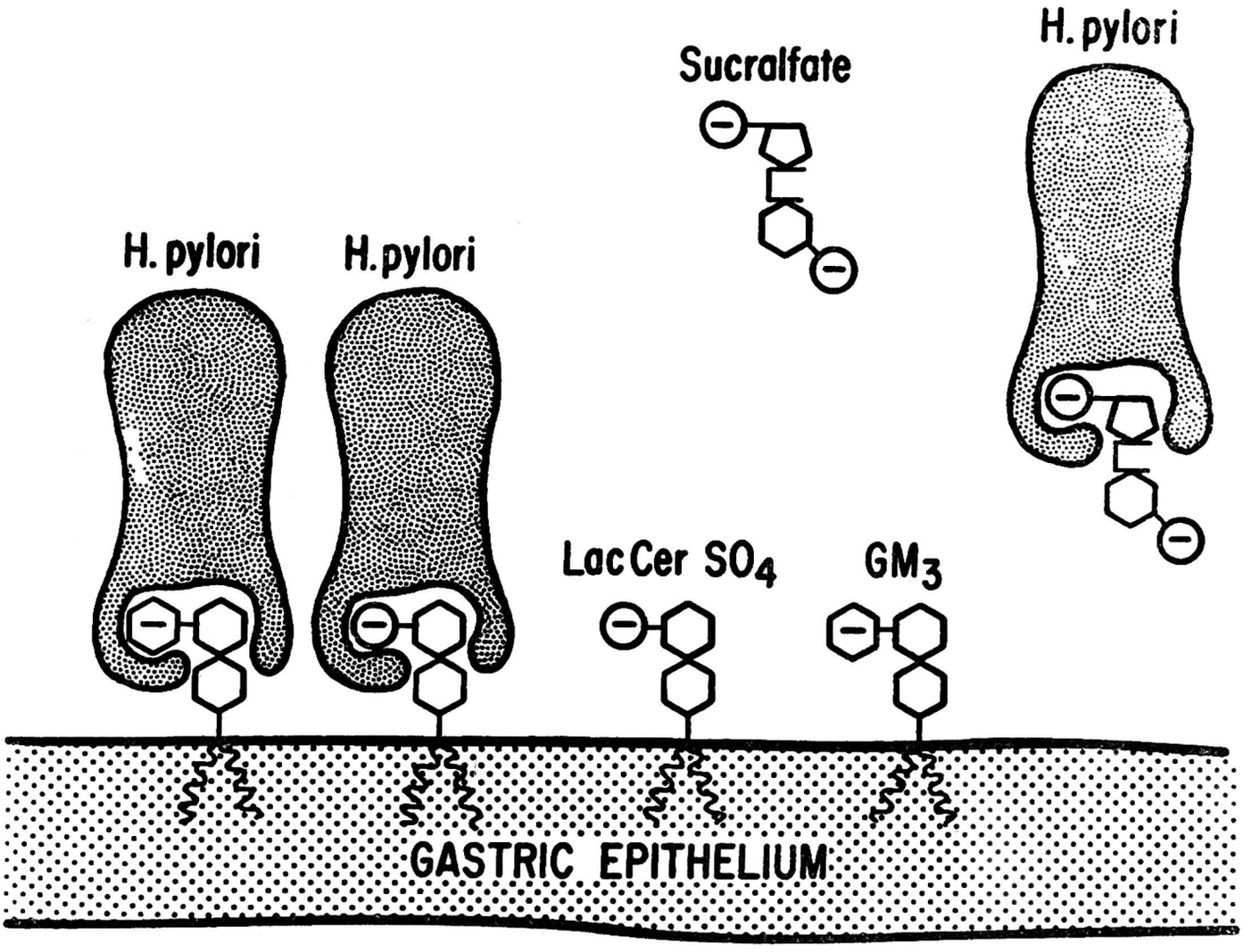

Fig. 1. Schematic representation of H. pylori attachment to gastric mucosa and the mechanism of interference with this interaction by sucralfate.

Table 1. Ganglioside and sulfatide content of human gastric mucosa

Glycosphingolipid	μmol/g dry mucosa	
	Fundus	Antrum
Ganglioside		
GM_3	0.07	0.12
GD_3	0.20	0.28
GM_1	0.10	0.14
Sulfatide		
Galactosylceramide	0.18	0.48
Lactosylceramide	0.15	0.27
Triglycosylceramide	0.06	0.09

sulfatides implicated in H. pylori attachment (*Table 1*). The antral content of GM_3 ganglioside is about 72% higher than that of fundus, while the lactosylceramide sulfate level in antrum is 1.8-fold greater than that of fundus. It is our contention that these differences in the receptor glycolipid levels may be the reason why H. pylori shows preference for colonization of antral epithelium over fundus.

Mucus gel organization

Understanding of the intricacy of the multitude of protective functions of mucus gel and how these properties can be advantageously affected by the antiulcer drugs requires a novel approach to the composition and structure of this seemingly disordered extracellular layer that is of paramount importance in the protection of underyling epithelium. While it has been recognized that drugs which affect ulcer healing also stimulate mucus production, the component of mucus receiving primary attention until recently was mucus glycoprotein or mucin. This situation has changed drastically in recent years as a result of mounting evidence that proteins and lipids also play an important role in defining the integrity and strength of the gel (3, 5). As a result, it is becoming increasingly apparent that mucus gel is not a single entity, but a heterogeneous mixture of proteins, glycoproteins and lipids. Together, these constituents account for 10—15% of the gel weight and arrive at the mucosal surface either through glandular secretion, serum element transudation, or cell exfoliation. The proteins constitute about 65% dry weight of gastric mucus, carbohydrates 15% and lipids 20% (10, 12).

The matrix of the gel arises through noncovalent interaction between mucus glycoprotein molecules, each of which appears to be composed of subunits joined together at their nonglycosylated regions (2). In gastric lumen environment, the glycoprotein polymer exists in an expanded,

highly hydrated form, capable of entering into heterotypic interaction with other constituents of the gel, particularly lipids (3, 11). Two types of interactions between lipids and mucus glycoprotein can be distinguished within the gastric mucus gel; one in which lipids remain associated with the glycoprotein through hydrophobic forces and the other in which lipids exist in a covalent linkage with the glycoprotein (13—16).

The data on topography of lipids within the mucus glycoprotein polymer indicate that phospholipids interact with the glycoprotein through the nonglycosylated regions, while the interaction with glycolipids and neutral lipids appears to involve the peripheral regions of the glycoprotein molecule that are resistant to proteolytic cleavage (13). The extent of mucus glycoprotein interaction with the associated lipids is apparently determined by the content and distribution of covalently bound fatty acids. At least 4 covalently bound fatty acids are present in the nonglycosylated regions of the glycoprotein polymer and one in proximity to the amino terminal of each subunit (3). From this, a concept is emerging according to which mucus glycoprotein polymer through its various hydrophobic and hydrophilic regions forms a dynamic continuum with other components of mucus (*Fig. 2*). The concept of dynamic organization of gastric mucus implies that the integrity and strength of mucus gel could be disrupted not only through mucin degradation, but also through changes in mucus gel lipids.

Although the involvement of gastric mucosal lipids in mucosal defense has been recognized since late seventies (10), there are differences of opinions a to the way by which the lipids contribute to this function. While some investigators assign the lipid protective function to the so-called „surface active phospholipids" (*Fig. 3*) supposedly forming an entity separate from other components of the mucus gel (17—19), our dat

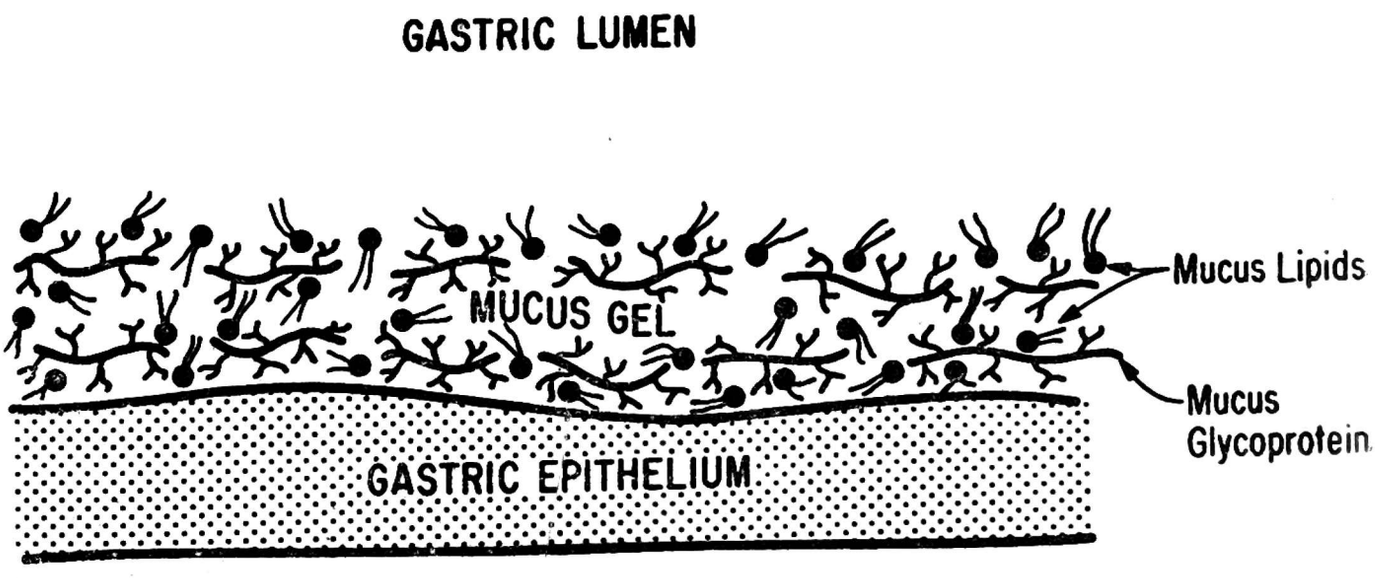

Fig. 2. „Dynamic Continuum" gastric mucus barrier model.

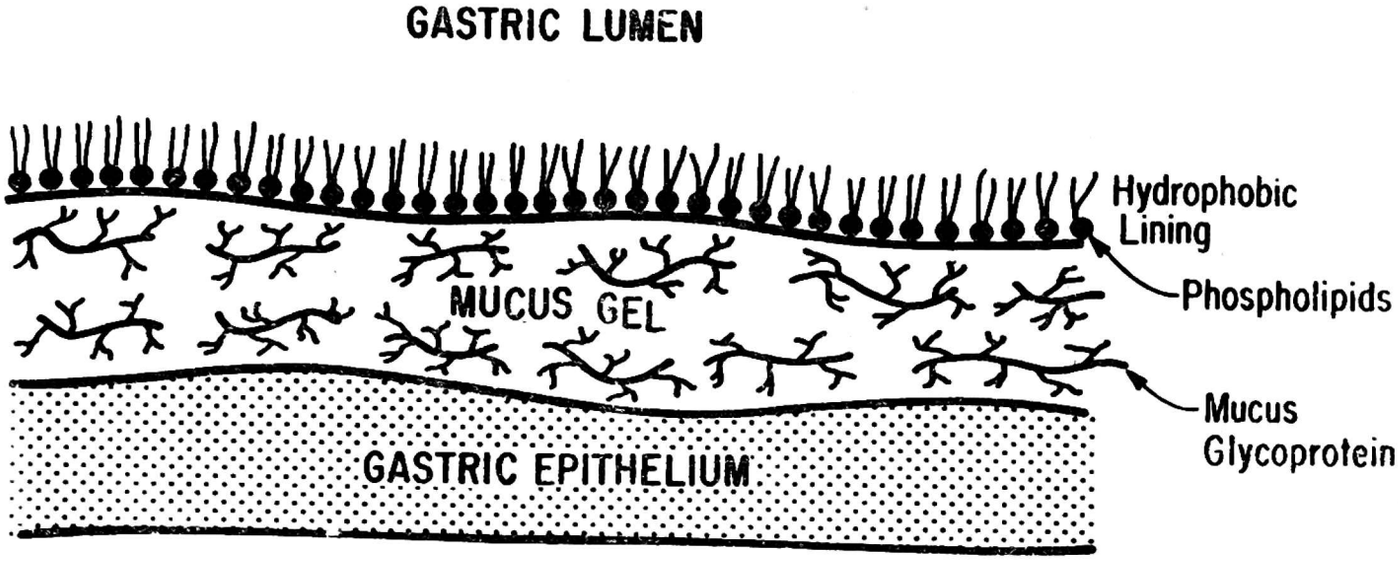

Fig. 3. „Surface Active Phospholipid" gastric mucus barrier model.

and that of others (3, 5, 20) indicate that lipids are integral part of mucus gel where together with mucins form a dynamic continuum and that this complex is responsible for the maintenance of gastric mucosal hydrophobicity as well as its integrity (5, 21). Thus, the maintenance of gastric mucosal defense system depends upon a delicate balance, controlled by factors affecting the elaboration and breakdown of all mucus constituents and not just that of „surface active phospolipids or for that matter mucins (*Fig. 4*), as implied by some investigators (2, 22).

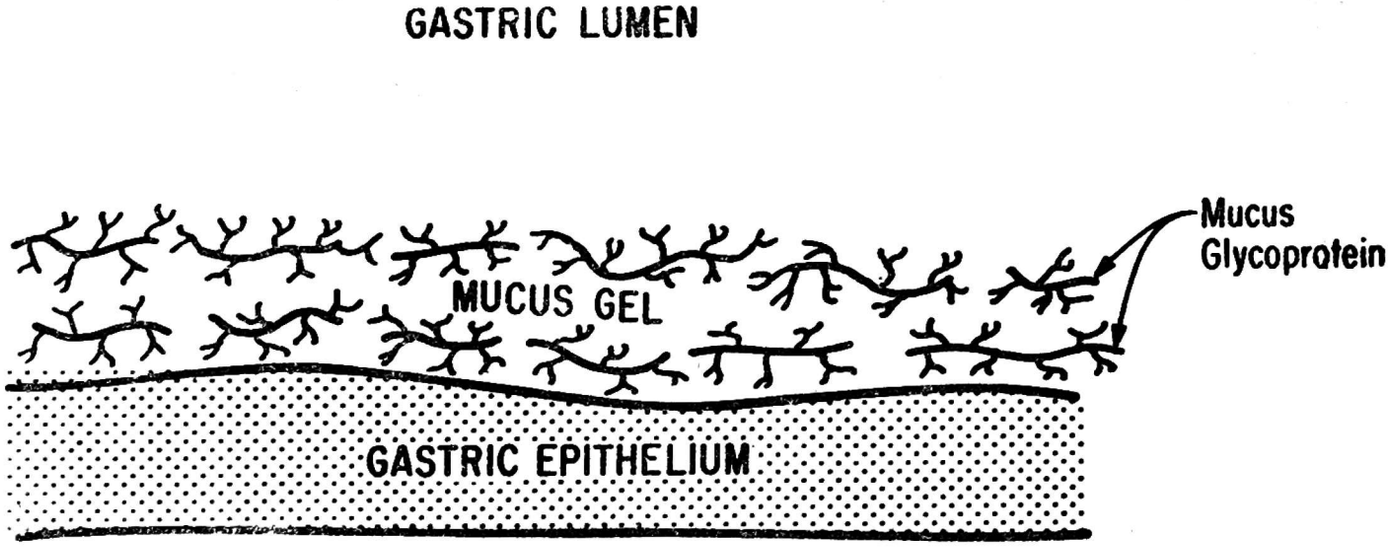

Fig. 4. „Mucin Only" gastric mucus barrier model.

H. Pylori and gastric mucus

As the loss of mucus gel integrity due to excessive degradation of mucus constituents is a prominent feature in pathology of gastric disease, our efforts were focused on the enzymatic activities of H. pylori towards

lipids and glycoprotein constituents mucus coat. Hence, the extracellular material elaborated by H. pylori was examined for its capability of mucin, protein, and lipid degradation.

Assays of exoglycosidase enzyme activities conducted with a battery of synthetic substrates revealed only feeble β-galactosidase activity, and furthermore, the H. pylori filtrate did not cause hydrolysis of gastric mucin carbohydrate chains, as evidenced by the absence of free sugars release (23). However, when the incubate was examined on gel chromatography, a shift in mucin elution profile characteristic for proteolytic degradation of mucus glycoprotein was observed. Parallel experiments with albumin indicated that the enzyme also caused extensive degradation of this protein. The protease activity of H. pylori appears to be associated with a low molecular weight (< 50 K) protein fraction and shows behavior typical of metalloproteinase.

Since the result of H. pylori protease action on gastric mucin is disintegration of the polymeric structure of the glycoprotein and formation glycopeptides which no longer possess the viscous and gel-forming properties, and exhibit only limited hydrogen ion retardation capacity (24), the erosion of mucus glycoprotein polymer, which constitutes the gel matrix, may, indeed, be of dire consequence to the mucosal integrity. Furthermore, the challenge on the luminal side by acid and pepsin, and on the mucosal side by H. pylori protease, renders the stomach epithelium vulnerable to damage by luminal contents.

Two lipolytic enzymes, triglyceride lipase and phospholipase A_2 were identified in the extracellular material elaborated by H. pylori. By following the relase of fatty acid, it was found that the lipase attains its maximum activity at 37°C and the pH of 7.2. In the case of phospholipase A_2 maximum conversion of phosphatidylcholine substrate to free fatty acid and lysophosphatidylcholine was attained at the pH range of 7.0—7.4 and 37°C (25, 26). The incubation of gastric mucus neutral lipids with H. pylori enzymes led to a 15% increase in free fatty acids, 2.8-fold increase in mono- and diglycerides, and a 4.8-fold decrease in triglycerides. Examination of gastric mucus phospholipids following incubation with H. pylori filtrate showed the conversion of phosphatidylcholine and phosphatidylethanolamine to the corresponding lysophospholipids. Thus, with respect to its lipolytic activities, H. pylori shares characteristics common to the majority of pathogenic microorganisms, which are known to produce large amount of extracellular lipase and phospholipase enzymes (27, 28). These enzymes apparently play an important role, not only in pathogen proliferation, but also appear to be active components of toxins and, hence, influence the pathogenic potential of the microorganism (27—29).

As mucus lipids and phospholipids, in particular, contribute to the

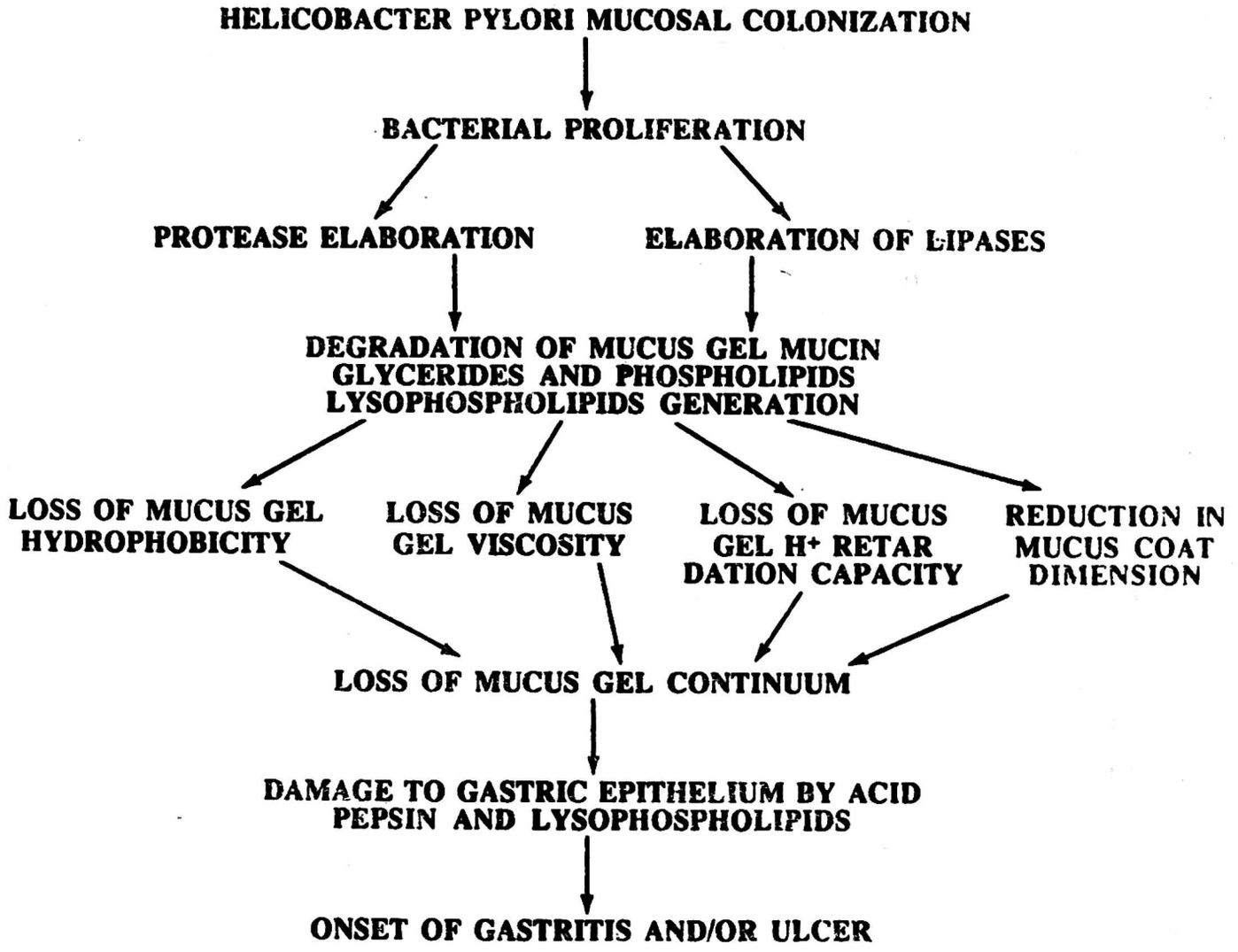

Fig. 5. Mechanism of H. pylori pathogenic action on gastric mucosa.

integrity and resilience of gastric mucosal defense (2, 5, 21), and are involved in the maintenance of the mucosal hydrophobicity (19—21), the alterations in lipids caused by H. pylori lipases my be of serious consequence to the mucosal defense. Furthermore, an increase in lysolecithin level due to H. pylori phospholipase A_2 offsets the ratio of this lipid to other phospholipids, leading to a drastic change in the lytic activity of the lysophospholipid towards gastric epithelium and the mucus coat (30, 31). The lipolytic activity of H. pylori could, thus, be detrimental at the same to the mucus layer and the cell membranes of gastric epithelium (*Fig. 5*).

Mucin and mucosal resistance to H. pylori colonization

The protective role of mucus layer against bacterial colonization is considered to be an essential element of gastric mucosal defense (32). The layer poses not only the passive physical obstacle but also constitute an active defense zone endowed with components capable of interference with bacterial adhesion to the epithelial cells. Indeed, salivary and gastro-

intestinal mucins, because of similarities in the structure of their carbo hydrate chains to those present on the receptor site of cell surface, are potent inhibitors of bacterial adherence and show strong aggregating activity towards many types of bacteria (32).

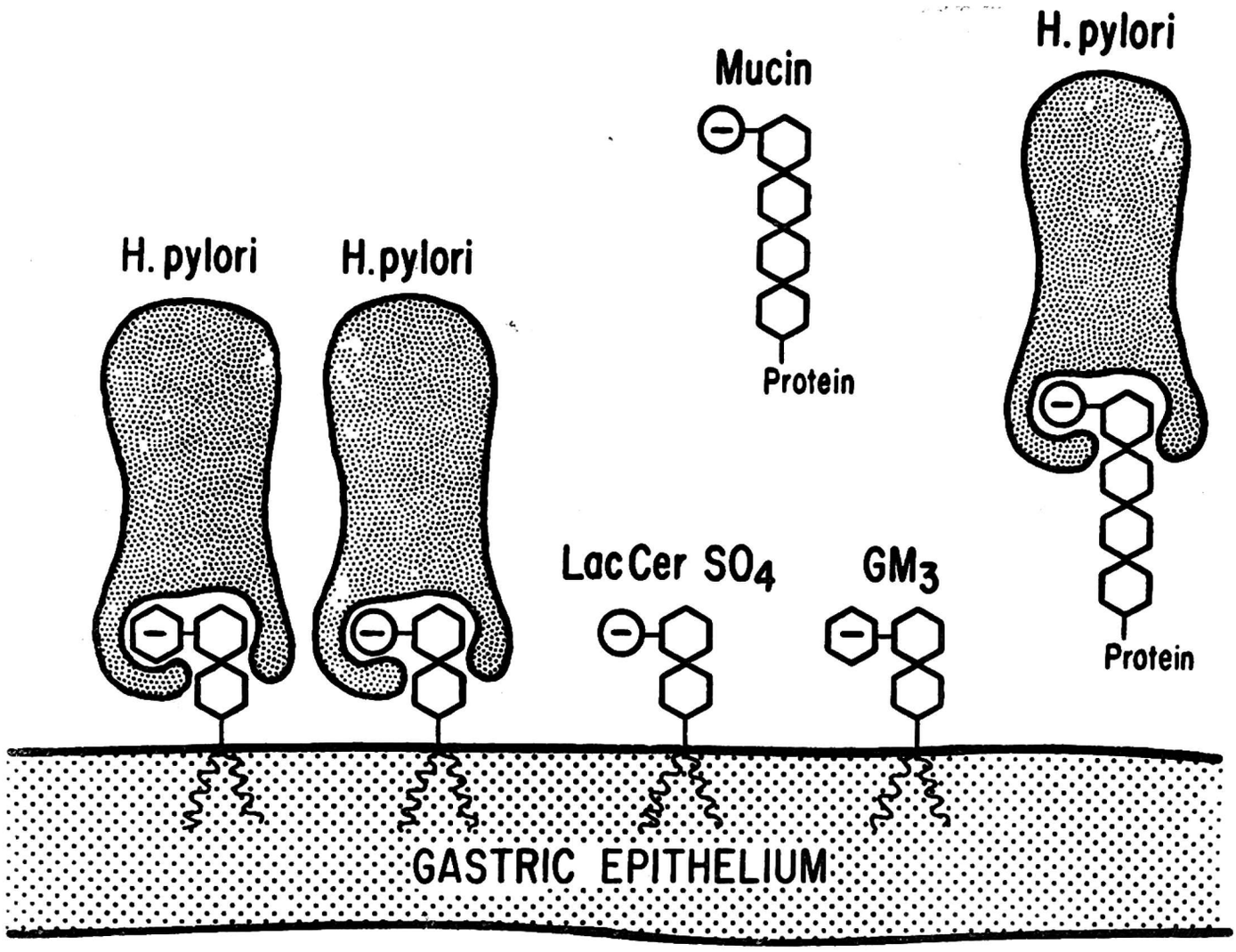

Fig. 6. Mechanism of interference by sulfated gastric mucin in the attachment of H. pylori to gastric mucosa.

Table 2. Effect of gastric and salivary mucins on the agglutination of human erythrocytes by H. pylori

Mucin origin (20 mg/ml)	Hemagglutination inhibition titer
Human gastric (intact)	1:4
Human sulfated gastric	1:64
Human gastric desulfated	0
Pig gastric	1:4
Rat gastric	1:2
Human salivary	1:4
Rat salivary	1:2

Results of the assays conducted with gastric and salivary mucins indicate that these glycoproteins are capable of inhibition of human A, B and O type erythrocytes agglutination by H. pylori (*Table 2*). The most potent inhibitory effect occurs with human sulfated gastric mucin, the activity of which is at least 8-fold higher than that of intact mucin preparation (33). The inhibitory effect of sulfated mucin is, however,abolished by the removal of sulfate ester groups. These findings attest to the importance of sulfated mucin in gastric mucosal defense, and suggest that the resistance of gastric mucosa to H. pylori colonization may strongly depend upon the extent of gastric mucin sulfation (*Fig. 6*).

H. pylori and mucosal strengthening agents

Since successful approach to the therapy of H. pylori associated gastric disease requires understanding whether the drug is capable to interfere with the bacteria, there is a considerable interest in evaluating the anti-H. pylori effects of antiulcer drugs, particularly those directed towards strengthening mucosal defenses. While some of these agents such as colloidal bismuth subcitrate and bismuth subsalicylate are known to be bactericidal (34), the anti-H. pylori value of other agents remains poorly explored. Hence, we concentrated our efforts on the effect of antiulcer agents on their ability to interfere with the bacterial colonization and the activities of the enzymes produced by this pathogen.

Investigations on the attachment of H. pylori to gastric epithelium revealed that one of the antiulcer drugs, namely sucralfate, is capable of reacting with the bacterial colonization factor antigen (*Fig. 1*). The inhibitory titer of sucralfate, although two times lower than that of lactosylceramide sulfate and GM_3 ganglioside, appears to be at least 32-fold greater than that of sulfated gastric mucin of human stomach. The data obtained with colloidal bismuth subcitrate indicate that while alone the drug has no effect on the agglutination titer of H. pylori, the agent caused a marked enhancement in the agglutination inhibitory titer of human gastric sulfated mucin (*Table 3*). Thus, both drugs are clearly capable of interfering with the bacteria gaining access to the mucosal surface.

Another venue explored with respect to antiulcer drugs action is their effect on the mucolytic enzymes elaborated by H. pylori, such as protease and lipases (23—26). The results of H. pylori protease assays in the presence of several mucosal strengthening agents indicate that the highest inhibitory activity towards gastric mucus occurred with nitecapone followed by colloidal bismuth subcitrate and geranylgeranylacetone (Table 4). These drugs, due to their antiproteolytic activity, are thus capable of counteract-

Table 3. Inhibitory potency of sucralfate, colloidal bismuth subcitrate, sulfated gastric mucin, GM_3 ganglioside, and lactosylceramide sulfate on the agglutination of erythrocytes by H. pylori

Type of compund (2 mg/ml)	Hemagglutination inhibition titer
Sucralfate	1:256
Colloidal bismuth subcitrate (CBS)	0
Sulfated mucin	1:8
Sulfated mucin + CBS (20 mg/ml)	1:32
GM_3-ganglioside	1:512
Lactosylceramide sulfate	1:512

ing the excessive degradation of mucus coat by pepsin from the luminal side (35, 36) and by H. pylori protease from the epithelial side (*Fig. 7*).

The data on the effect of antiulcer mucosal strengthening agents on the lipolytic activity of H. pylori are summarized in (*Table 5*). The results obtained with nitecapone indicate that this drug is capable of 85% inhibition of gastric mucus triglyceride degradation and that it has 92% inhibitory effect on the activity of H. pylori phospholipase A_2. Substantial

Table 4. Effect of mucosal strengthening antiulcer agents on the degradation of gastric mucus by H. pylori protease

Antiulcer agent	Concentration (g/l)	% Proteolytic activity inhibition Mucus
Sofalcone	0.1	2
Sucralfate	0.1	3—5
Geranylgeranylacetone	0.1	10—12
Colloidal bismuth subcitrate	0.1	37
Nitecapone	0.1	72

inhibitory activity was also observed with colloidal bismuth subcitrate and sucralfate. In the case of lipase activity, the inhibition of gastric triglycerides degradation in the presence of sucralfate attained the level of 32% and in the presence of colloidal bismuth subcitrate 21%. The respective inhibitory values for phospholipase A_2 activity were 45% and 60%.

While the above data provide strong argument that the beneficial action of many ulcer healing agents could be the result of their ability to

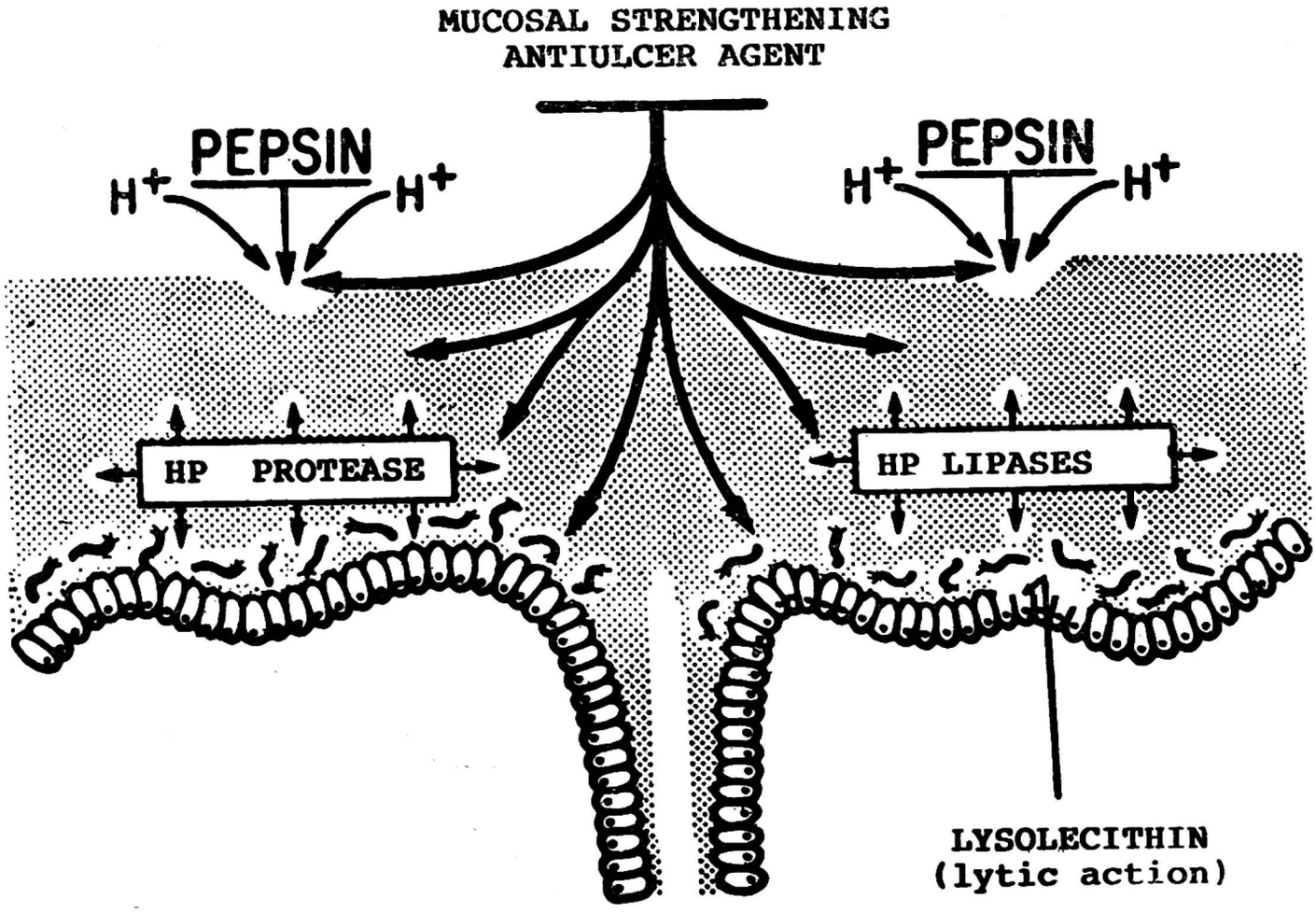

Fig. 7. Diagramatic representation of the inhibitory action of mucosal strengthening antiulcer agents on the aggressive forces affecting gastric mucosal integrity.

Table 5. Effect of mucosal strengthening antiulcer agents on the lipolytic activity of H. pylori

Antiulcer agent	Concentration (μg/ml)	% lipolytic inhibition	
		Lipase	Phospholipase A_2
Sucralfate	200	31.6	45.3
Sofalcone	200	43.0	5.0
Colloidal bismuth subcitrate	200	21.0	60.0
Nitecapone	10	85.0	92.0

counteract the activities of pepsin, and protease and lipase enzymes associated with H. pylori proliferation, it should be also borne in mind that virulence of many microorganisms does not depend on their enzymatic activities alone, as the heat-inactivated lipases are also highly detrimental to the host defense (27, 28).

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