



PEPTIC ULCER: A REVIEW ON ETIOLOGY AND PATHOGENESIS

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ABSTRACT

A peptic ulcer is a sore on the lining of the stomach or duodenum. The two most common types of peptic ulcer are called “gastric ulcers” and “duodenal ulcers”. Peptic ulcers are found to be due to an imbalance between aggressive factors such as hydrochloric acid (HCL), pepsin, refluxed bile, leukotrienes (LTs), reactive oxygen species (ROS) and defensive factors, which include the function of the mucus-bicarbonate barrier, prostaglandins (PGs), mucosal blood flow, cell renewal and migration, nonenzymatic and enzymatic antioxidants and some growth factors. *H. pylori* infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the predominant causes of peptic ulcer disease. Also, a numbers of factors are implicated in the pathogenesis of gastric ulcer, among which major factors involved are bacterial infection (*Helicobacter pylori*), certain medications (NSAID), chemicals (Hcl/ethanol), gastric cancer and minor factors are stress, smoking, spicy food and nutritional deficiencies. The idea behind treating ulcers is to lower the amount of acid that your stomach makes, to neutralize the acid that is made and to protect the injured area so it can have time to heal. The main aim of this review article has to summarize the ulcerogenic mechanisms of various mediators involved in Peptic ulcer disease.

KEYWORDS: Peptic Ulcer, Types, Pathogenesis and Mediators.

INTRODUCTION

Ulcers are deep lesions penetrating through the entire thickness of the gastrointestinal tract (g.i.t) mucosa and muscularis mucosa. Peptic ulcer has unquestionably been a disease of the twentieth century. Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence. There are different types of ulcers most common are peptic ulcer: gastric ulcer, which appeared to be due to damage to the lining of the stomach, and duodenal ulcer, which was associated with excessive acid secretion by the stomach. The aetiology of peptic ulcer was fiercely debated. It is believed that peptic ulcers develop due to an imbalance between aggressive factors (*Helicobacter pylori*, NSAIDs, gastric acid) and protective factors (mucin, bicarbonate, prostaglandins), leading to an interruption in the mucosal integrity. Various factors are implicated that play a pivotal role in the pathogenesis of ulcerations like, sedentary life style, alcohol intake, spicy food, drugs and various bacterial infections. Moreover, several endogenous substances have been identified and are reported to be involved in the production of gastrointestinal lesions in animals. The more important ones include some of the bacterial infection, various drugs and chemicals, gastric secretion, lipid metabolites, neuropeptides, inflammatory mediators and reactive free radicals. Oxidative stress has emerged as one of the major pathogenic factors in progression of ulcer that directly impaired the cellular functions and promotes cellular organelles damage in the cells, including mitochondria, lysosomes, and nucleus. Also, NO is accepted as vital mediator of GIT mucosal defense as decreased NO generation or synthesis contribute to the pathogenesis of ulceration. The present study summarizes the ulcerogenic mechanisms of these substances and the enable us to understand better the etiology of peptic ulcer.

TYPES OF ULCER

Peptic Ulcer: Peptic ulcer is a broad term which includes ulcers of digestive tract in the stomach or the duodenum. Earlier it was believed that one developed this type of ulcers due to stress and spicy food. However, recent research has shown that these are just the aggravating factors. The

causative agent is infection caused by the bacteria *H. pylori* or reaction to certain medicines like non-steroidal anti-inflammatory drugs (NSAIDs)¹. Symptoms of peptic ulcers include abdominal discomfort and pain. Other symptoms include weight loss, poor appetite, bloating, nausea, and vomiting. Some may also experience blood in stool and vomit, and black stools that indicate gastrointestinal bleeding².

Aphthous Ulcers: Sores that develop in the inner lining of the mouth are referred to as mouth ulcers. Mouth ulcers are common and are usually due to trauma such as from ill fitting dentures, fractured teeth, or fillings. Anemia, measles, viral infection, oral candidiasis, chronic infections, throat cancer, mouth cancer and vitamin B deficiency are some of the common causes of ulcers or sores in the mouth³. Aphthous minor is amongst the most common form of oral ulcerative diseases and affects an estimated 15-20% of the population worldwide. In some populations, the prevalence has been documented as being as high as 50-66% and it is especially common in North America⁴⁻⁵. The incidence of aphthous ulcers has been found to be lower in smokers than in non-smokers⁶.

Esophageal Ulcers: Esophageal ulcers are lesions that occur in the esophagus (the food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Esophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSAIDs, and smoking⁷.

ETIOLOGY AND PATHOGENESIS OF ULCER

H. Pylori

H. Pylori is the main cause of stomach ulcers, was first identified by the two Australian scientists in 1982. *H. Pylori* is a gram negative bacillus, motile, microaerophilic, flagellated and spiral shaped bacteria⁸. Type I strains of *H. Pylori* possess a pathogenic activity, that encodes the effector protein cytotoxin-associated gene A (cagA). After translocation into the host cell, cagA effects cell shape, increases cell motility, disturbs cell junctional activity and thus responsible for gastric carcinomas and gastric ulcers⁹. *H. Pylori* causes increases expression of cytokines such as

TNF- α in gastritis. Further, IL-1 β is too overexpressed in the H. Pylori-induced gastritis¹⁰. H. pylori-infected gastric mucosa showed infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells in the lamina propria, and intraepithelial severe neutrophil infiltration¹¹. The appropriate antibiotic regimens can successfully eradicate the infection with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers¹². Triple therapy regimens comprising of a proton pump inhibitor or ranitidine bismuth citrate and two antibiotics (amoxicillin and clithromycin) are the standard therapy to treat H. pylori infection¹³.

Gastric acid secretions

Gastric acid is established as one of the major ulcerogenic factor for the induction of gastric ulcer disease. It has been reported that about 50% of gastric ulcer patients are pepsin and acid hypersecretors¹⁴. But, on the other hand, gastric acid plays a stringent role in gastric defense. It is the first line of mucosal defense to prevent bacterial colonization and reduced their ability to entrance in the mucosal layer¹⁵. Acid secretion is suggested to be stimulated by three principle secretagogues histamine, acetylcholine and gastrin. The receptors on the surface of parietal cell include H₂ receptors responding to histamine released from specialized mast cells, receptors that are sensitive to the muscarinic effects of acetylcholine released from the vagus nerve and probably receptors responsive to endogenous circulating gastrin¹⁶. Gastrin stimulates acid secretion either by direct stimulation of parietal cells or by the release of histamine from ECL cells¹⁷⁻¹⁸. In the 1972, Black et al, postulated that histamine stimulated acid secretion through a novel histamine receptor, the H₂ receptor¹⁹. Moreover, various studies indicate numerous epithelial cells at the base of pyloric glands contain histamine and histidine decarboxylase (HDC), the enzyme responsible for the synthesis of histamine²⁰.

The only source of the acetylcholine (Ach) that can act directly on the parietal cell is from the postganglionic fibres of the enteric nervous system. The muscarinic-1 agonist McN-A-343 stimulates acid secretion without affecting histamine release, thus suggesting that the muscarinic receptor on the parietal cell²¹.

NSAIDs (Non-steroidal anti-inflammatory drugs)

NSAIDs are valuable therapeutics that acts not only as anti-inflammatory, but also as analgesics and antipyretics. They are used in a wide variety of clinical conditions, including arthritis and other musculoskeletal disorders. Unfortunately, their use has been limited by their gastric ulcer-inducing effects. Nearly 25% of chronic users of these drugs develop gastric ulcer disease²². Various studies indicates that NSAIDS helps in the progression of ulceration by overcoming the expression of enzyme cyclo-oxygenase (COX) which has been documented to inhibit the conversion of AA to PG's, that impairs the mucosal barrier and results in corrosive action with pepsin and results in the progression of peptic ulcers²³⁻²⁴. Further, COX-1 inhibition by the NSAIDS leads to the significant release of the endothelin-1(ET-1) which is a potent vasoconstriction which has been shown to induce mucosal injury. NSAIDs by inhibiting the prostaglandin synthesis prostaglandins causes the activation of neutrophils and the local release of reactive oxygen species (ROS) and thus initiates the gastric injury²⁵. Further NSAID also causes marked reduction in mucosal blood flow, mucus-bicarbonate secretions, impaired platelet aggregation, reduced epithelial cell renewal and increased leukocyte adherence that are responsible for pathogenesis of ulceration²⁶. Gastric acid

worsen the NSAID effects by deepening superficial lesions, interfering with platelet aggregation, and impairing the ulcer healing process²⁷⁻²⁸.

Reserpine

The pathogenesis of gastric ulceration induced by drugs is not yet clear. It has found that histamine, catecholamines and acetylcholine have been implicated in the ulcerogenic activity of a number of drugs viz. phenylbutazone, acetyl salicylic acid, oxyphenbutazone, indomethacin and reserpine²⁹⁻³¹. Reserpine is one of the drugs, derived from the roots of the rawolfia serpentina reported to have pivotal role in the progression of ulcer. Various reports indicate that reserpine causes the degranulation of mast cells with increase in the gastric acid secretion by sympathetic activation³². Reserpine is documented to generate free radicals and inhibit the prostaglandin synthesis. The exact mechanism how reserpine caused gastric ulceration is not clear. It has appeared that peripheral cholinergic and adrenergic mechanisms are involved in the ulceration induced by reserpine³³. It has demonstrated that reserpine produced gastric ulceration due to a release of catecholamines from the sympathetic nerve endings³⁴⁻³⁵. Both at peripheral level and central nervous system, reserpine depletes catecholamine, serotonin (5-HT) and histamine (H₂) stores. Also, it is releasing gastrin and corticosteroids³⁶. From these released endogenous molecules, serotonin can act directly on the gastric mucosa. Also, number of authors explains the formation of ulcers by intervention of reserpine in the metabolism of serotonin. As in is well known, serotonin and its precursors, when applied in larger doses, are capable of causing destructive changes in the stomach wall³⁷. As for the catecholamines, the involvement in the ulcerative process is more complicated. In a first stage, released catecholamines act on gastric blood vessels and later, after the stores are depleted, they generate a functional adrenergic deficit. This phasic action on adrenergic mechanisms is prevalent at the central nervous system level. The result is an imbalance between the adrenergic and the cholinergic tonus with important consequences on gastric function³⁸. Alteration of the adrenergiccholinergic balance is transmitted to the gastric level via the vagus nerve. It is known the fact that vagotomy and muscarinic and nicotinic-cholinolytic drugs decrease the gastric ulcerative action of the reserpine³⁹. Restoration of the adrenergic activity by catecholamine precursors and drugs that stimulate the biosynthesis and release of the precursors also have protective action at gastric level.

Ethanol

The mechanism of ethanol-induced gastric lesions is varied, including the depletion of gastric mucus content, damaged mucosal blood flow and mucosal cell injury. It has been documented that ethanol causes severe damage to the gastrointestinal mucosa starts with microvascular injury results in increase vascular permeability, edema formation and epithelial lifting. Szabo et al suggested that after intragastric administration of ethanol a rapid and time dependent release of endothelin-1 into the systemic circulation preceded the development of the hemorrhagic mucosal erosions by vasoconstriction¹⁴. Moreover, by decreasing the secretion of bicarbonate (HCO₃⁻) and mucus production, ethanol produces the necrotic lesions in gastric mucosa. Further ethanol also has been reported to activate TNF- α and mitogen activated protein kinases (MAPK)⁴⁰. Also, ethanol has also initiate apoptosis which lead to cell death⁴⁰. Further, ethanol after metabolism has been reported to releases superoxide anion and hydroperoxy free radicals

which lead to an increased lipid peroxidation⁴¹. Increase in lipid peroxide content and oxygen-derived free radicals results in marked changes in cellular levels and causes membrane damage, cell death, exfoliation and epithelial erosion⁴¹⁻⁴².

Cytokines

Cytokines play a central role in the regulation of the mucosal immune system, and therefore are extremely important in mucosal defense. Several proinflammatory cytokines are involved in the pathogenesis of peptic ulcer, like interleukin (IL)-1 β , IL-2, IL-6, IL-8 and tumor necrosis factor (TNF)- α . When inflammation of the gastric mucosa occurs, it leads to infiltration of neutrophils and mononuclear cells that stimulates the transcription and leads to the synthesis of several proinflammatory cytokines⁴³. IL-1 has been shown to reduce the severity of gastroduodenal damage and increase the resistance to injury⁴⁴⁻⁴⁵. The mechanism underlying the protective actions of IL-1 is not fully understood, but it has been found that IL-1 reduces injury through a paradoxical inhibitory action on leukocyte adherence. Further, IL-1 has also play a role in the inhibition of gastric acid secretion^{44,46,47}. Also, IL-1 stimulates the release of prostaglandin and NO possibly by inducing iNOS expression and COX-2 expression, thus provide a protection to gastroduodenal mucosa⁴⁸. Furthermore, IL-1 has been shown to inhibit the release of other ulcer-promoting mediators like PAF and histamine from mast cells. Also, Lychkova et al, 2007 demonstrate the role of immune system in the pathogenesis of ulcers, mainly T-lymphocytes and cytokines produced by them. Takeuchi et al, 2002 found that NF- κ B activation followed by TNF- α release contribute to tissue damage in gastric ulcer⁴⁹⁻⁵⁰.

VEGF (Vascular endothelial growth factor)

VEGF, a 46-kDa homodimeric glycoprotein, is the most potent stimulator of angiogenesis which is produced by a variety of cell types including macrophages, smooth muscle cells, fibroblasts, megakaryocytes, and neoplastic cells⁵¹⁻⁵³. Angiogenesis and VEGF play a major role in many repair processes such as healing of gastric ulceration resulting from a disturbed balance between factors which damage the gastric mucosa barrier and those which have a protective role. Several studies have provided evidence for a role of VEGF in gastric ulcer healing. Jones et al observed enhanced ulcer healing in rats following a single injection of naked DNA encoding VEGF⁵⁴.

NO (Nitric oxide)

NO is synthesized from L-arginine via the catalytic action of a group of enzymes, the NO synthases (NOS). NO has been studied to play an important role in GI mucosal defense and the pathogenesis of mucosal injury⁵⁵. Also, NO may influence muscle tone as well as endocrine and exocrine secretion. cNOS, nNOS, eNOS are very important in the normal function of the GI tract in that inhibition of these enzymes can result in disturbances of GI motility, blood flow, secretion, etc⁵⁶. On the other hand, the inducible NOS (iNOS), which produces relatively large amounts of NO under certain pathological conditions, contributes to mucosal injury and dysfunction⁵⁷⁻⁵⁸. Suppression of NO synthesis renders the gastric mucosa more susceptible to injury. NO inhibits recruitment of neutrophils to sites of inflammation. NO reduces neutrophil infiltration into the GI tract mucosa⁵⁹. The events related to the gastroprotective effects of nitric oxide include a reduction in acid secretion and promotion of angiogenesis⁶⁰⁻⁶¹. Gastroprotective effects of nitric oxide may be due to its rapid reactivity with various oxygen

species in the biologic system⁶². Also, Nitric oxide inhibits gastric secretion by suppression of histamine release from enterochromaffin-like cells⁶³⁻⁶⁴.

Prostaglandins

Prostaglandins are 20-carbon fatty acids produced from arachidonic acid via the enzyme cyclooxygenase. Hawkey and Rampton found that prostaglandins exert their cytoprotective actions by stimulating the mucus and bicarbonate secretion, maintaining mucosal blood flow, and by enhancing the resistance of epithelial cells to injury induced by cytotoxins⁶⁵. Prostaglandins found to be inhibits the leukocyte recruitment which could contribute to the beneficial effects of these substances in situations in which the GI mucosa is inflamed⁶⁶. Prostaglandin E2 (PGE2) has been shown to be a potent suppressor of release of PAF, histamine and of TNF- α from peritoneal and intestinal mucosal mast cells⁶⁷⁻⁶⁸. Another, it has also found that prostaglandins suppress the generation of reactive oxygen metabolites by neutrophils⁶⁹.

LTs (Leukotrienes)

Leukotrienes are derived from arachidonic acid through the action of lipoxygenase and are considered to be important mediators of inflammatory and allergic reactions⁷⁰. Two main subclasses of LTs has been suggested, leukotriene B4 and the peptido-leukotrienes (LTC4, LTD4, and LTE4). LTB4 is a very potent chemotaxin for neutrophils, it stimulate the release of reactive oxygen metabolites from neutrophils and contributes significantly to the tissue injury associated with mucosal inflammation. Goldberg and Subers described the role of LTs) on the stomach⁷¹. It has been shown that LTs induce vasoconstriction in the vascular bed of the stomach followed by leakage of macromolecules from the postcapillary venules. Further, various other studies reported that LTC4 can also induce vasoconstriction in both the venous and arteriolar vessels in rat submucosa, which results in tissue necrosis^{70,72}. Therefore, LTs could serve as a potential proulcerogenic agent. It has been reported that on ethanol administration there is a concentration-dependent increase in gastric mucosal LTC4⁷³ and B4 synthesis which provide the evidence of LTs as mediators in ethanol-induced gastric damage⁷⁴. The mechanism by which ethanol stimulates LT formation by the rat gastric mucosa is not known. It may be caused by the perturbation of cell membranes, resulting in the activation of phospholipase activity and increase in arachidonic acid level, with a subsequent enhancement of LT synthesis. Moreover, LTB4 has been suggested to contribute to the pathogenesis of NSAID-induced gastric damage through its ability to promote leukocyte adherence to the vascular endothelium⁶⁶. Also, LTB4 may play a similar role in the pathogenesis of ulceration associated with *Helicobacter pylori* infection. Interestingly, gastric juice LTB4 levels are significantly higher in patients with gastric *H. pylori* colonization than in those who are *H. pylori* negative⁷⁵.

Endothelin

Endothelin is a 21-amino acid peptide derived from vascular endothelial cells and it has been suggested that it has a pathophysiological role in conditions characterized by vascular spasm. Furthermore, endothelin may act as an endogenous regulator of vascular tone, with opposite actions to endothelium-derived relaxing factors (EDRF) and prostacyclin (PGI2). Vascular congestion is a feature characterizing gastric ulceration induced by substances such as ethanol and aspirin⁷⁶. Several lipid mediators have ulcerogenic actions in the gastric mucosa, and these actions

may affect the vascular endothelium and/or vascular smooth muscle⁷⁷⁻⁷⁸. Endothelin rendered the mucosa more vulnerable to damage induced by ethanol. Endothelin also potentiated gastric damage induced by hydrochloric acid at a concentration tolerated by the gastric mucosa. Further, endothelin produced marked increase in gastric vascular perfusion pressure, presumably a reflection of vasoconstriction. It is entirely feasible that the pro-ulcerogenic actions of endothelin could be attributable to its vasoconstrictor actions in the stomach. It appears that a balance between endothelial constricting and relaxing factors is necessary for the maintenance of gastric mucosal integrity, particularly in the case of challenge with a necrotizing agent⁷⁹.

Apoptosis

Apoptosis was initially defined by Kerr et al. (1972) who suggested that cells dying in this process go through defined morphological changes that involve chromatin condensation, cytoplasmic and nuclear blebbing, and eventual cellular demise without loss of membrane integrity⁸⁰. Under normal physiological conditions, the balance between gastric epithelial cell proliferation and death is of great importance in maintaining gastric mucosal integrity. Since, the balance between cell apoptosis and cell proliferation has important role to keep the gastric mucosa healthy⁸¹. Since, the gastric epithelial cells proliferate in the lower part of the glandular neck and migrate up the crypt towards the surface and then are shed into the lumen by apoptosis⁸². Disturbance of this balance could result in either cell loss, leading to mucosal damage and ulcer formation, or cell accumulation, leading to cancer development⁸³.

CONCLUSION

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

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