Chapter

The Role of Increased Gastric Acid Secretion and Reactive Oxygen Species in the Pathophysiology of Reflux Esophagitis

Mohamed-Amine Jabri and Hichem Sebai

Abstract

Gastroesophageal reflux (GER) disease is a chronic disease characterized by the recurrent ascension of some of the gastric contents in the esophagus. Indeed, gastric acid secreted by parietal cells and the gastric pepsin activity, but not the intestinal alkaline content, are the most important pathogenic factors of GER. Several pathophysiological mechanisms are involved, the most important of which is the imbalance of the redox state of the esophageal tissue. Indeed, several studies have shown that reflux esophagitis is mediated by oxygen-derived free radicals. In this chapter, we describe the pathophysiology and important pathways, especially acid gastric contents and reactive oxygen species involved in pathology of GER.

Keywords: esophagus, parietal cells, pepsin activity, reactive oxygen species

1. Introduction

Gastroesophageal reflux (GER) is defined as the passage through the cardia of the contents of the stomach into the esophagus, without any effort of vomiting [1]. The intermittent ascent of the gastric contents, particularly the acid in the esophagus, is the main determinant of the esophageal mucosa lesions [2, 3]. The alteration of gastric or esophageal motility, the aggressiveness of the refluxing fluid, and the alteration of esophageal mucosal resistance are also important factors in the genesis of esophagitis lesions [4]. Disturbances of the inflammatory and immune response reported during reflux esophagitis are numerous [5]. It is well established that oxidative stress, by excessive production of oxidizing mediators or by a deficiency of certain nutrients essential to the maintenance of a suitable antioxidant defense, contributes to cellular dysfunctions and to the esophagus tissue destruction [5, 6]. This chapter gives a detailed insight about the role of acidic gastric secretions and the involvement of oxidative stress as well as reactive oxygen species (ROS) in the pathophysiology of reflux esophagitis.

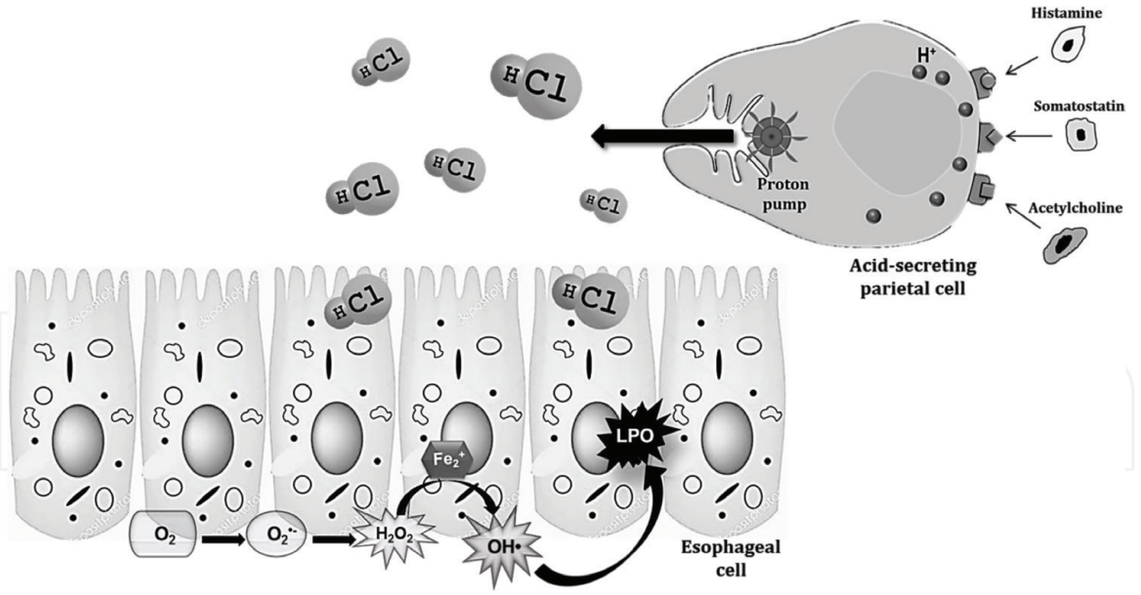

Figure 1.
Mechanism of acidic gastric secretion and production of reactive oxygen species in the esophageal mucosa.

2. Mechanism of acidic gastric secretion

Gastric secretion is essentially characterized by its high concentration of hydrochloric acid. This acidity makes it possible to sterilize the food bowl and initiate digestion, especially food proteins. Gastric acid secretion is permanently modulated by the endocrine (gastrin), paracrine (histamine and somatostatin), as well as nerve (acetylcholine) pathways (**Figure 1**). Gastrin is secreted at the basal pole of the G cells of the pyloric glands of the antrum into the bloodstream. It acts by binding membrane receptors of enterochromaffin-like cells (ELC) by stimulating the secretion of histamine and on the membrane receptors of parietal cells by stimulating the secretion of hydrochloric acid [7, 8].

Histamine is secreted by ELC, in the vicinity of parietal cells, in response to stimulation by gastrin and parasympathetic activation. This secretion is inhibited by somatostatin. Histamine stimulates the HCl secretion by action on the histamine H2-type receptors of parietal cells [9].

Acetylcholine, released by postganglionic neurons from the parasympathetic system, stimulates the parietal cells, gastrin, and histamine secretions. Somatostatin is the main inhibitor of gastric acid secretion: its secretion by D cells is stimulated by increasing the concentration of H^+ ions in the gastric cavity [8].

3. Physiopathology of gastroesophageal reflux

3.1 Failure of the anti-reflux barrier

Generally, GER is related to a failure of the anti-reflux barrier. This anti-reflux barrier is composed of the lower esophageal sphincter (LES), which plays the role of an internal sphincter, and the diaphragmatic muscle that plays the role of an external sphincter. The LES is a zone of high pressure, 2–4 cm long, with no individualized thickening of the circular layer of the muscularis. This area of high pressure separates the thoracic esophagus subjected to negative pressure from the stomach that supports the positive pressure prevailing in the enclosure of the abdominal cavity [1, 10]. The pressure of the LES is influenced by several dietary factors, certain drugs, and circulating hormones. Chocolate, fats, alcohol, and caffeine reduce the pressure of the LES

[4, 10]. Tobacco also lowers the pressure of the LES, and in smokers, the periods of smoking are marked by an increased GER frequency. Many medications affect also the LES pressure. Indeed, anticholinergics, nitrates, theophylline, and anticalcics lower it, while cisapride and metoclopramide increase it [4, 10].

3.2 The reflux material composition

The reflux that reaches the esophagus may be of variable acidity, may be depending on the case of a pure liquid or a mixture of gas and liquid [11]. The role of pepsin in the occurrence of esophageal lesions during GER is uncertain. Animal studies have shown that the toxicity to the esophageal mucosa of an HCl-pepsin mixture is higher than that of a pure acid solution [4, 12]. The reflux of duodenal contents into the stomach is a postprandial physiological phenomenon. It is therefore not unusual for GER to contain duodenal, pancreatic, and bile secretions. In experimental models, conjugated bile acids are toxic to the esophagus at acidic pH, whereas nonconjugated bile acids have a toxicity that is observed mainly at neutral pH. But the human bile acid concentrations in the reflux liquid never reached the concentrations used in these experimental models [11, 12].

Studies in humans have shown that the frequency of duodeno-gastroesophageal reflux is particularly high in patients with severe esophagitis and especially an endobrachy-esophagus, notably in those who respond to treatment with proton pump inhibitors [12].

4. Involvement of oxidative stress in the pathophysiology of reflux esophagitis

Several recent studies have shown that esophagitis induced by gastroesophageal reflux is mediated by reactive oxygen species (ROS) [13–16]. The role of ROS has been extensively studied in gastric and esophageal mucosal lesions induced by the administration of NSAIDs such as aspirin [17] or ethanol [18] as well as by ischemia [6].

4.1 Oxidative stress and production of oxygenated free radicals

Oxidative stress is defined as an excessive intracellular oxidation due to an imbalance between the production of oxidizing species or reactive oxygen species (ROS) and that of antioxidant systems [16, 19]. The equilibrium or redox homeostasis is then disrupted, and the cells become vulnerable to free radical attacks, resulting in oxidative damage to cellular components [20, 21]. Indeed, ROS are responsible for denaturation and degradation of biomolecules and are involved in tissue lesions observed during inflammatory processes [22]. They are produced during various biological processes by a large number of cells, particularly phagocytic cells [23].

4.2 Free oxygen derivatives and caustic injuries of esophagus during GER

According to recent studies on animal models [14, 24, 25], it has been shown that gastroesophageal reflux promotes the production of ROS, which leads to lesions of the esophageal mucosa. Reactive oxygen species appear to be a major cause of esophageal lesion during GER. In point of fact, it has been shown that the administration of a free radical scavenger effectively inhibits esophagitis in rats [6]. The increased production of free radicals derived from oxygen has been accompanied by increased lipid peroxidation of the esophageal mucosa, which is a sensitive marker of membrane damage caused by free radicals [24]. In addition, several previous

studies have shown that GER induced experimentally in rats caused an increase in the level of malondialdehyde, a final product of lipid peroxidation, as well as a decrease in the activity of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase in the esophageal mucosa tissues [5, 13, 14]. GER has also induced the decrease of reduced glutathione and thiol group levels as well as plasma scavenging activity, an indicator of free radical generation in tissues [13]. Other studies have shown that blocking acid secretion or administering an antioxidant compound effectively reduced the severity of reflux esophagitis. Indeed, the administration of the various free radical scavengers prevented the esophageal mucosa damage, by stimulating the activity of antioxidant enzymes and inhibiting lipid peroxidation [5, 14].

5. Conclusion

Several mechanisms are involved in the occurrence of GER and in its severity, especially the gastric secretion of acid and pepsin as well as the role of reactive oxygen species. Therefore, the ROS-scavenging compounds should be considered in the prevention and treatment of reflux esophagitis, in accordance with the current antisecretory treatment.

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