REVIEW ARTICLE

Drugs 2006; 66 Suppl. 1: 1–5
0012-6667/06/0001-0001/$44.95/0

Current Understanding of the Mechanisms of Gastro-oesophageal Reflux Disease

Roy C Orlando

Department of Medicine, Tulane University Medical School, New Orleans, Louisiana, USA

Abstract

Gastro-oesophageal reflux disease (GERD) covers a broad range of signs and symptoms arising from the orad movement of gastric contents into the oesophagus, oropharynx, larynx or airway. Most commonly, contact with and damage to the oesophageal epithelium by acidic refluxate causes micro or macroscopic defects leading to the symptom of heartburn. However, GERD can also give rise to extra-oesophageal manifestations such as pharyngitis, laryngitis, asthma and other disorders, identifiable as acid-mediated events by a favorable response to acid suppression.

Only one-third of individuals with heartburn have endoscopic evidence of erosive oesophagitis; the remainder have endoscopy-negative or non-erosive reflux disease (NERD). Improved investigative technologies are increasing our understanding of the pathophysiology of NERD. For example, although a number of microscopic abnormalities have been identified, oesophageal damage in NERD has been shown to be characterized by the presence of 'dilated intercellular spaces' within oesophageal stratified squamous epithelium. Dilated intercellular spaces that reflect damage to the intercellular junctions enable levels of acidity that would be considered innocuous when present in the oesophageal lumen to initiate pathological responses within oesophageal nociceptors when present within the intercellular spaces. This effectively gives rise to the symptom of heartburn.

Excessive acidity within the intercellular spaces in NERD also presages its evolution to erosive disease, the latter through inflammation-mediated disruption of the antireflux and luminal clearance mechanisms. Support for this scenario is evident by the ability of effective acid control with proton pump inhibitors both to control symptoms, and lead to resolution of dilated intercellular spaces in patients with both erosive and non-erosive disease. This article examines these concepts and how they shape our current understanding of GERD.

1. Introduction

Our increasing understanding of the pathophysiology of gastro-oesophageal reflux is likely to influence clinical practice and improve the management of gastro-oesophageal reflux disease (GERD). This article will focus on our current understanding of some of the mechanisms through which GERD takes place. GERD as a term encompasses a broad range of signs and symptoms that arise from the orad movement of gastric contents into the oesophagus, oropharynx, larynx or airway. This can give rise to oesophagitis, pharyngitis, laryngitis, and asthma, among other disorders. In its most common embodiment an acidic refluxate contacts and damages the oesophageal epithelium, giving rise to either microscopic or macroscopic mucosal defects and the symptom of heartburn.

2. Categorization of Reflux Disease

The description of heartburn as a symptom of substernal burning discomfort, worse after meals and on reclining, and alleviated at least temporarily by antacids gives credence to the idea that reflux symptomatology is an acid-driven process. When patients with heartburn are endoscoped they can be characterized broadly into two categories. In the first category, erosive oesophagitis, there is clear evidence of gross endoscopic abnormalities in the form of breaks or erosions in the oesophageal epithelium. However, in those that have heartburn but do not have any mucosal breaks on endoscopy, the condition is defined as non-erosive reflux disease or NERD. There are two requirements for heartburn, regardless of a diagnosis of erosive disease or non-erosive disease. First is the need for acid in high concentrations within the oesophageal lumen, and this takes place through the process of reflux. Second, there is also a need to have in place a damaged oesophageal epithelium. Such damage is critically important to allow the luminal acid to enter the tissue where stimulation of the nociceptors generates the symptom of heartburn. Although breaks in the oesophageal epithelium are visible endoscopically in those individuals with erosive oesophagitis, in patients with NERD the break in the mucosa is only apparent microscopically, on oesophageal biopsy.

3. Pathophysiology of Non-erosive Reflux Disease

Over the past 25 or 30 years, a whole series of abnormalities has been identified in reflux-damaged patients with non-erosive disease. These include basal cell hyperplasia, elongation of the rete pegs, the presence of inflammatory cell infiltrates, cell oedema and microscopic cell necrosis. However, the most important lesion in NERD has only recently been recognized and accepted, and that is the presence of 'dilated intercellular spaces' within oesophageal stratified squamous epithelium. Although dilated intercellular spaces can be seen on light microscopy, they are clearly and dramatically apparent on electron microscopy. As shown in figure 1,[1] patients with NERD have dilated intercellular spaces, which show as white areas, filled with salt and water in between the multiple layers of stratified squamous cells. These spaces are far less apparent in patients who have healthy oesophageal epithelium. The dilated spaces have an important implication, indicating that these individuals have a break in the intercellular junctions between the cells of the upper barrier layers. Impaired resistance of the oesophageal mucosal barrier allows luminal acid to diffuse between the intercellular spaces, access the oesophageal nociceptors in the intraepithelial sensory nerve endings, and trigger off a signal by virtue of

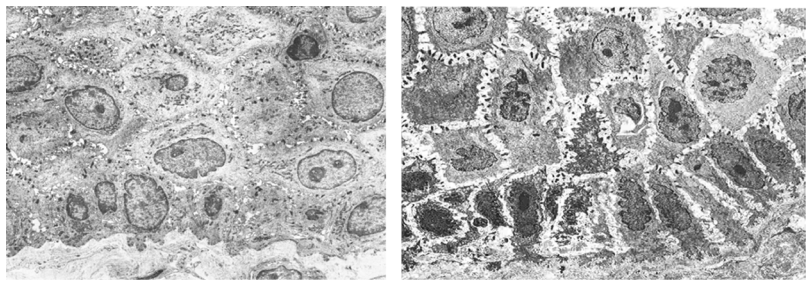

Fig. 1. Transmission electron microscopy of the oesophageal epithelium in healthy subjects and patients with non-erosive reflux disease. Adapted with permission from Pope.[1]

changing the pH in the intercellular environment. Central processing of this signal in the brain in turn elicits the symptom of heartburn.[2]

The study of vagal sensory afferents in various tissues has been very instructive to this whole process of acid sensitivity and response in the oesophagus. Vagal sensory afferents have been shown to contain a variety of different channels, among them acid-sensing ion channels (ASIC), which can respond to pH as high as 7 and even as low as pH 5.[3] These are pH levels that would be considered relatively innocuous when present in the lumen, but when present in the intercellular spaces these pH levels are pathological and will stimulate nociceptor firing, leading to the symptom that we recognize as heartburn.

3.1. Acid-mediated Effects

This helps us to understand, then, why heartburn is an acid-mediated symptom. First, hydrogen ions are the smallest molecules known. Second, when there is a process of acid reflux, the refluxate contains huge concentrations of hydrogen ions, which produce enormous gradients for their diffusion from the lumen into the tissue towards the blood. For example, a gradient of approximately 1 million to 1 is produced at a pH of 1 in the refluxate, and a gradient of 100 000 to 1 at pH 2. Consequently, very efficient conditions are produced for small molecules to pass between the damaged intercellular junctions, driving through the intercellular space down towards the sensory nociceptors. Finally, vagal afferents possessing ASIC are uniquely poised to sense changes in environmental pH, even when very, very modest in terms of acidity, leading to activation and giving rise to heartburn.

The break in the intercellular junction has another important function essential to the understanding of GERD. Not only does it allow acid in the intercellular space to generate the symptom of heartburn, but it also allows acid to access a very vulnerable part of the squamous epithelial cell, and that is its basolateral cell membrane. Unlike apical cell membranes, which are highly acid impermeant, basolateral cell membranes are acid permeable. The entry of acid into the cell acidifies the intracellular compartment and begins a process of cell destruction, thereby allowing for the evolution of non-erosive patients to erosive oesophagitis. One of the mechanisms that makes the basolateral membrane so vulnerable to acidity is called a chloride–bicarbonate exchanger. This is a sodium-independent ion transporter that carries excess chloride into the cell and, when acid is in the intercellular space, a gradient is created for bicarbonate to move out of the cell. This process of chloride in and bicarbonate out in effect is equivalent to hydrochloric acid absorption, essentially creating the acidic environment leading to cell destruction (figure 2).[4]

Support for this composite idea or concept is provided by therapeutics. The healing rate of erosive oesophagitis by acid-suppressive therapy such as histamine H_2 blockers (H_2 receptor antagonists) or more powerful proton pump inhibitors is directly related to the time gastric acid suppression is maintained above pH 4 over a 24-h period, an almost linear relationship.[5] The greater the acid control, the more patients are successfully managed with resolution of their signs of erosive disease. Not only is erosive disease resolved but, as shown recently, effective acid control with proton pump inhibitors leads to the resolution of the dilated intercellular spaces.[6] This is true of patients both with erosive and with non-erosive disease, indicating that these are acid-mediated changes that are resolved upon the control of oesophageal acidity.

4. Does Non-erosive Reflux Disease Progress to Erosive Disease?

There has been some debate in gastroenterology about whether NERD and erosive reflux disease are indeed part of the same disease spectrum. Fass and Ofman[7] proposed dividing GERD into three pathologically separate groups: NERD, erosive oesophagitis, and Barrett's oesophagus. However, more recent evidence from long-term follow-up of patients with NERD supports the concept presented here that they form a continuum.[8] Non-erosive disease is a milder form of histopathological injury that can evolve into a major form of gross

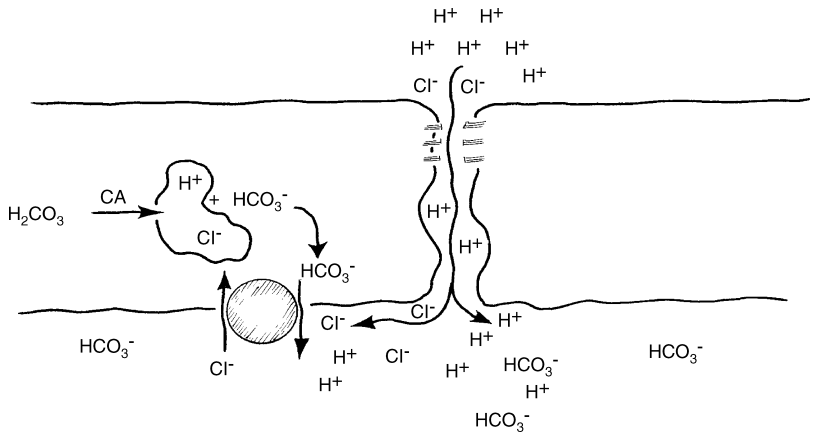

Fig. 2. Cell acidification in the oesophageal epithelium. CA, Carbonic anhydrase. Adapted with permission from Orlando.[4]

macroscopic injury. However, only 15–20% of patients followed in the clinical setting are likely to progress from non-erosive to erosive oesophagitis. Transition between one stage and the other may be dependent on a transition factor not present in the majority of patients.

4.1. Role of the Inflammatory Process

This transition factor is likely to revolve around the transforming power of the inflammatory process, a process highly dependent on host genetics, and that determines who remains with non-erosive disease and who migrates over to the erosive form of oesophagitis. An inflammatory cascade is generated after acid injury to the squamous epithelium. Many of the components of the inflammatory cascade in oesophagitis have been defined. They include such cytokines as IL-6, IL-1β and IL-8. IL-8, when present in high concentrations in acid-damaged oesophageal mucosa, drives a neutrophil influx that can produce such products as hydrogen peroxide, prostaglandin-2 and platelet-activating factor. These products are important because they all affect circular smooth muscle, altering the neuromuscular apparatus in a way that promotes lower oesophageal sphincter (LES) weakness and peristaltic dysfunction (figure 3), which in turn promotes greater acid damage by increasing the number of reflux events and prolonging the duration of the presence of acid within the oesophagus by delaying luminal clearance.

In summary, acid injury to squamous epithelium may lead to inflammation. If inflammation is not severe, the patient may not progress beyond non-erosive disease. However, if the inflammatory process, by virtue of host genetics, leads to sufficient inflammation and the release of chemical mediators that drive neuromuscular dysfunction, there will be low LES pressure and greater reflux, and impaired peristalsis with prolonged acid contact as a result of delayed clearance. In effect, both of these actions promote more acid exposure

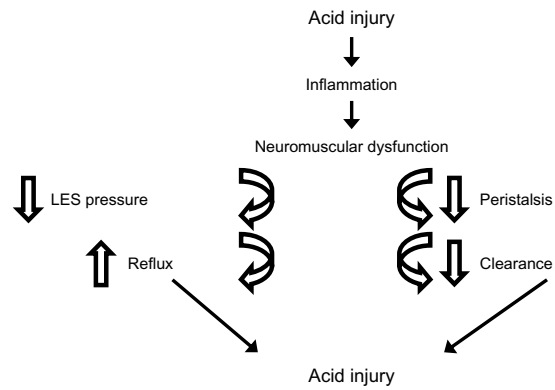

Fig. 3. Non-erosive reflux disease to erosive oesophagitis: cycle of cell necrosis. LES, Lower oesophageal sphincter.

and consequently more acid injury, which then sequentially results in further inflammation and more neuromuscular dysfunction successively until erosive disease evolves in a select minority of patients.

5. Extra-oesophageal Manifestations of Reflux Disease

Extra-oesophageal manifestations are another aspect of reflux disease, and include asthma, laryngitis, pharyngitis, sinusitis, bronchitis, pneumonia and interstitial pulmonary fibrosis. These processes are also acid mediated, in that acid can access the airways through micro-aspiration, entering the oesophagus and then traveling through the upper oesophageal sphincter into the oropharynx and tracheobronchial tree. Alternatively, acid accesses only the oesophagus, and creates an injury that produces a long vago-vagal reflex, stimulating the contraction of bronchial or oropharyngeal smooth muscle, stimulating airway secretions and leading to asthmatic and bronchial-type symptoms. Support for the pathological basis of this refluxate was provided by So and colleagues,[9] who showed that a positive response to acid suppression predicted the response for controlling extra-oesophageal manifestations. Therefore, the key in the refluxate remains acid, regardless of whether the symptoms produced are heartburn or extra-oesophageal manifestations.

6. Conclusions

The symptoms and signs of GERD result from the contact of a damaged oesophageal epithelium with refluxed gastric acid. In patients with NERD, oesophageal damage is confined to the microscopic level and is characterized by the presence of dilated intercellular spaces. In individuals with erosive oesophagitis, oesophageal damage has progressed from the non-erosive phase, and is apparent at the macroscopic level in the form of erosions. NERD can evolve to erosive disease through inflammation-mediated impairment in the antireflux and luminal clearance mechanisms that set in motion a cycle of increasing rates of cell necrosis. That NERD evolves to erosive oesophagitis infrequently reflects the need for a specific type or severity of inflammation, one that is both host specific and genetically determined.

References

1. Pope CE II. Gastroesophageal reflux disease. In: Sleisenger MH, Fordtran JS, editors. Gastrointestinal disease; pathophysiology, diagnosis, management, 2nd ed. Philadelphia: WB Saunders Company; 1978. pp. 541-68
2. Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology 2005; 128: 771-8
3. Liu M, Willmott NJ, Michael GJ, et al. Differential pH and capsaicin responses of *Griffonia simplicifolia* IB4 (IB4)-positive and IB4-negative small sensory neurons. Neuroscience 2004; 127: 659-72
4. Orlando RC. Pathophysiology of gastroesophageal reflux disease: offensive factors and tissue resistance. In: Orlando RC, editor. Gastroesophageal reflux disease. New York: Marcel Dekker, Inc; 2000. pp. 165-92
5. Bell NJ, Burget D, Howden CW, et al. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 1992; 51 suppl. 1: 59-67
6. Calabrese C, Bortolotti M, Fabbri A, et al. Reversibility of GERD ultrastructural alterations and relief of symptoms after omeprazole treatment. Am J Gastroenterol 2005; 100: 537-42
7. Fass R, Ofman JJ. Gastroesophageal reflux disease – should we adopt a new conceptual framework? Am J Gastroenterol 2002; 97: 1901-9
8. Pace F, Bollani S, Molteni P, et al. Natural history of gastro-oesophageal reflux disease without oesophagitis (NERD) – a reappraisal 10 years on. Dig Liver Dis 2004; 36: 111-5
9. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. Surgery 1998; 124: 28-32

Correspondence and offprints: *Roy C Orlando*, Department of Medicine, Tulane University Medical School, 1430 Tulane Ave., New Orleans, LA 70112, Louisiana, USA.
Tel: +1 504 988 5763; fax: +1 504 988 2675;
e-mail: rorlando@tulane.edu

Dr Orlando has or has had in the recent past relationships (consulting, lecture bureau, research support, stock ownership) with the following companies: TAP Pharmaceuticals, AstraZeneca, Novartis, Proctor and Gamble, Santarus, Sirna, Boston Scientific, Pfizer, Merck.