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Challenges to Unravel Mechanisms of GERD

Shouji Shimoyama

Abstract

Gastroesophageal reflux disease (GERD) encompasses a spectrum of disorders caused by a reflux of gastric contents into the esophagus or complications of gastroesophageal reflux. Although depending on the definition, the prevalence of GERD is higher in the West than in the East, and the prevalence has been slightly increasing, so that the clinicians, even though they are not gastroenterologists, must encounter GERD patients and treat them. However, the clinicians do feel difficulty in treating GERD patients, since prescription of acid neutralizing agents, such as proton pump inhibitors (PPIs), sometimes fail to resolve their complaints. This may be partly explained by the discrepancies between clinical complaint and endoscopic findings; some patients present endoscopic esophagitis while some do not, and be partly explained by the potentially wide spectrum of pathophysiological etiologies than has been thought. This chapter describes current knowledge on heterogeneous mechanisms of GERD development. Clarifying the mechanisms of GERD on the individual basis may realize conceptual shift from uniform prescription of acid neutralizing agents to establishment of patient-oriented therapies.

Keywords: gastroesophageal reflux disease, nonerosive reflux disease, esophagitis, reflux hypersensitivity, functional heartburn, central sensitization, proton pump inhibitors

1. Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition with at least weekly troublesome symptoms due to the abnormal reflux of stomach contents into the esophagus [1]. Heartburn and/or acid regurgitation are ranked 7th on the list prompting visits to doctors, and GERD is the most common diagnosis given in outpatient visits [2]. GERD appears worldwide with some geographic variation. Prevalence estimates are 18–28% in North and South America, 9–33% in the Middle East, 12% in Australia, but less than 10% in East Asia [3]. In addition, an analysis of temporal trends suggests a particular increase in GERD prevalence in North America and Europe [4], while such a trend in Asia is indeterminable [4–6], partly due to the regional variation of prevalence being much higher in Southwest and Western Asia than in Eastern Asia [6]. In Japan, the prevalence of GERD was below 10% in the 1980s but has shown a two- or three-fold increase in the twenty-first century [7]. Although such time-trends or steady increases in the rise in the number of patients might be attributable to an increased awareness of the disease, and the prevalence of GERD varies between studies, the worldwide disease burden confirms that the numbers of patients suffering from GERD is substantial. Since

the symptoms do compromise patient quality of life (QOL) [8], clinicians, even if they are not gastroenterologists, may frequently encounter such patients and should treat them.

Acid-suppressing agents, such as proton pump inhibitors (PPIs), are a main choice of medication [9]; however, it is also true that while most patients do respond it, some do not. A recent study of PPI use has demonstrated that 20–26% of GERD patients showed persistent heartburn of any intensity for 2 or 3 days or more per week [10]. Recent systematic reviews found that 17–45% of GERD patients experienced persistent troublesome heartburn or regurgitation despite PPI therapy [11, 12]. That not all GERD patients can attain complete relief of GERD symptoms suggests that GERD is likely to be a heterogeneous disease entity which may explain the above unmet clinical needs. In light of the fact that patient QOL deteriorates by PPI refractoriness [13] as well as GERD symptoms *per se*, even if persistent symptoms are mild [14], clarifying the mechanisms of GERD or PPI refractoriness enables clinicians to prescribe medications according to the underlying mechanism on a patient-by-patient basis, which subsequently realizes clinical improvement.

This chapter discusses the current knowledge on the underlying mechanisms of PPI refractory GERD, and considers potential research directions attempting to resolve its symptoms, especially those among PPI refractory patients.

2. Reflux symptoms do not necessarily coincide with endoscopic findings

One of the complex phenomena that impedes the understanding of GERD is that reflux symptoms, endoscopic findings, and treatment results do not necessarily coincide with each other, despite the fact that GERD symptoms are by definition caused by the abnormal reflux of gastric contents into the esophagus. GERD is divided into reflux esophagitis and nonerosive reflux disease (NERD), which is a condition of reflux symptoms with no endoscopically apparent damage to the esophageal mucosa. A substantial proportion (50–70%) of GERD patients demonstrates endoscopically negative findings [15, 16], suggesting that NERD forms the main body of GERD. Curiously, endoscopic healing of erosive esophagitis does not necessarily result in symptom relief. In the same sense, a novel potassium-competitive acid blocker, vonoprazan, achieved improvement of heartburn in only approximately 20% of NERD patients [17]. These results suggest that the association of esophageal acid exposure with patient symptoms is tenuous in a certain fraction of GERD patients. On the other hand, some patients with endoscopically confirmed esophagitis are asymptomatic. Consequently, the prevalence and treatment success rate of GERD are greatly influenced by its definition, i.e., whether or not the study body includes NERD patients, whether or not it includes asymptomatic erosive reflux esophagitis patients, and whether or not treatment success includes only complete symptom relief or extends an even partial response.

3. Mechanisms

3.1 Conventional theory: acid as a direct contributor

Traditionally, reflux esophagitis is thought to be a condition resulting from a caustic, chemical injury inflicted by refluxate components such as hydrogen ions and pepsin. Hydrogen ions injure the superficial layer of the esophageal mucosa and cause esophagitis, and pepsin destroys the tight junction of the esophageal epithelium.

These chemical injuries lead to dilatation of the intracellular spaces (DIS) and an increase in paracellular permeability, which eventually allows acid to penetrate into deep layers of the esophagus, followed by the attraction of inflammatory cells, and finally stimulates nocireceptors [18]. In this theory, the epithelial injury triggers the pathophysiological cascade of GERD, beginning at the luminal surface of the esophageal epithelium, and then proceeds to the deeper layer. This mechanism is readily plausible for GERD patients with esophagitis; however, acid penetration through DIS as a main causative mechanism of GERD cannot explain why PPI refractory patients still exist as do symptomatic patients without esophagitis.

3.2 New theory: GERD is an immune mediated injury

On the other hand, the literature contains some experimental data which cannot necessarily be explained by the conventional theory, namely, acid penetration through DIS as a cause of GERD. In a rat reflux esophagitis model, inflammatory cells appeared at the deep layer of the epithelium, and then infiltrated upward to the superficial layer of the esophagus [19]. Basal cell and papillary hyperplasia preceded the development of esophagitis [19]. Consistent results were demonstrated in a human study, where stopping the PPI therapy in successfully PPI treated patients was associated with T-lymphocyte infiltration in the deep layer of the esophagus as well as basal cell and papillary hyperplasia without apparent surface erosions [20]. Degrees of DIS in patients with reflux esophagitis or NERD did not differ from those of asymptomatic healthy volunteers [21].

Evidence has been accumulated that pro-inflammatory cytokine release from esophageal epithelium, mesenchymal cells, and endothelial cells is an initial event of GERD. The participants of pro-inflammatory cytokines are interleukin (IL)-8 [19, 22, 23], IL-1 beta [19, 23], monocyte chemoattractant protein 1 (MCP-1) [24], IL-6 [25], IL-33 [26], tumor necrosis factor (TNF)-alpha [27], prostaglandin E2 [28, 29], hypoxia inducible factor (HIF)-2alpha [30], and platelet activating factor (PAF) [31, 32]. These pro-inflammatory cytokines attract immune cells—lymphocytes and polymorphonuclear cells—into the esophageal mucosa and submucosa. Interestingly, antineutrophil serum was found to inhibit inflammatory markers in rat acute esophagitis [33].

Another source of pro-inflammatory cytokines is the proteinase-activated receptor 2 (PAR2) localized on the surface of epithelial cells. PAR2 is activated by trypsin and weak acid, then stimulates pro-inflammatory cytokine release such as IL-8 from the epithelial cells, induces a neuroinflammatory effect mediated by neurotransmitters such as substance P and calcitonin gene-related peptide (CGRP), and subsequently establishes visceral hypersensitivity [34]. Indeed, PAR2 expression increases in patients with erosive esophagitis as well as NERD [34]. PAR2 activation has been correlated with IL-8 expression and further with DIS, papillary hyperplasia, and intraepithelial lymphocyte density [34]. These mechanisms mediated by pro-inflammatory cytokines would partly explain why PPI solely cannot necessarily resolve GERD symptoms and why a protease inhibitor, i.e., camostat mesilate, is effective in patients in whom GERD symptoms are caused by weakly acidic episodes.

Weak acid activates acid-sensing nocireceptors such as the transient receptor potential channel vanilloid subfamily receptor-1 (TRPV-1) [35, 36] and acid-sensing ion channels (ASIC) [37]. TRPV-1 is also activated by pro-inflammatory cytokines. TRPV-1 is a detector of various noxious stimuli including heat, acid, and irritant pollutants [38, 39]; it thus has been recognized as an initial molecule of nociceptive transmission. Once activated, neurotransmitters such as substance P and CGRP are released, afferent neurons evoke a sensation of burning pain, and finally peripheral and central sensitization is established. The activation of TRPV-1

also produces PAF [31] and adenosine triphosphate (ATP) [40], the former acting as a chemoattractant of inflammatory cells [41], while the latter stimulates both substance P and CGRP release from esophageal submucosal neurons [40] as well as the secretion of pro-inflammatory cytokines at the esophageal epithelium [35]. ATP *per se* is also a neurotransmitter [42] involved in the sensation of pain. Interestingly, an increased expression of TRPV-1 was observed not only in erosive esophagitis but also in NERD patients without correlation with acid exposure [43].

Taking all these processes into account, while not fully elucidated, it is conceivable that the secretion of pro-inflammatory cytokines, decreased mucosal integrity, exposure of subepithelial nerves to acid, and neuropeptide release to transmit nociceptive stimuli through the peripheral nerve to the brain may interplay to manifest GERD symptoms. Once such a network operates, patients have a lower threshold for pain perception by chemical or mechanical stimulation. The above findings support the hypothesis that an immune mediated neuroinflammatory cascade may underlie the development of GERD symptoms, and that GERD is an immune mediated injury rather than a chemical burn. This hypothesis considers that the secretion of pro-inflammatory cytokines is an initial event, the release of a variety of mediators is the second, and then the transmission of pain through the peripheral nerve to the central nervous system is the last step of the cascade. This cascade contrasts sharply with the conventional theory in which caustic acid-induced direct epithelial injury is an initial event of GERD; it could explain why not all GERD symptoms can be regulated solely by acid suppression. This is an essential background to the clinically reiterating and troublesome claim that there is a distinction between endoscopically-based and symptom-based GERD diagnosis.

4. PPI-refractory GERD comprises heterogeneous pathophysiological conditions

Under the above new theory, the primary focus should be on which factors switch on the cascade. The advent of multichannel intraluminal impedance-pH monitoring enables us to count the number of reflux events, to measure acidity of reflux content, and to differentiate between liquid and air in a refluxate. This technique clarifies that the initial event that triggers the cascade at the esophagus is not only acid exposure but also weak acid or weak alkaline conditions, temperature, electrical stimuli, and mechanical stimuli [44–48]. More detailed analyses of content and pH in the refluxate as well as degrees of symptom-reflux association create challenges to classify PPI-refractory GERD into three subcategories: (1) true GERD, in which symptoms are associated with acid reflux but acid neutralization is incomplete; (2) reflux hypersensitivity, where symptoms are associated with nonacid reflux; and (3) functional heartburn, where symptoms are exerted by nonacid and nonreflux events. The second and third subcategories could be putative factors that are responsible for PPI refractoriness or symptomatic NERD (**Figure 1**). Recently, the Rome IV classification [49] involves these mechanisms as underlying mechanisms of PPI-refractory GERD that allows a paradigm change for understanding this condition.

Reflux hypersensitivity is a heightened perception of physiological reflux which results in persistent GERD symptoms despite PPI therapy [44]. This is characterized by normal acid exposure in the distal esophagus but symptoms are attributable to reflux. On the other hand, functional heartburn is distinct from reflux hypersensitivity, in that functional heartburn is characterized by normal acid exposure in the distal esophagus without any apparent symptom-reflux association. That baseline impedance was reduced in erosive gastritis and acid-associated GERD but not in functional heartburn suggests that functional heartburn is caused by factors other than acid [50].
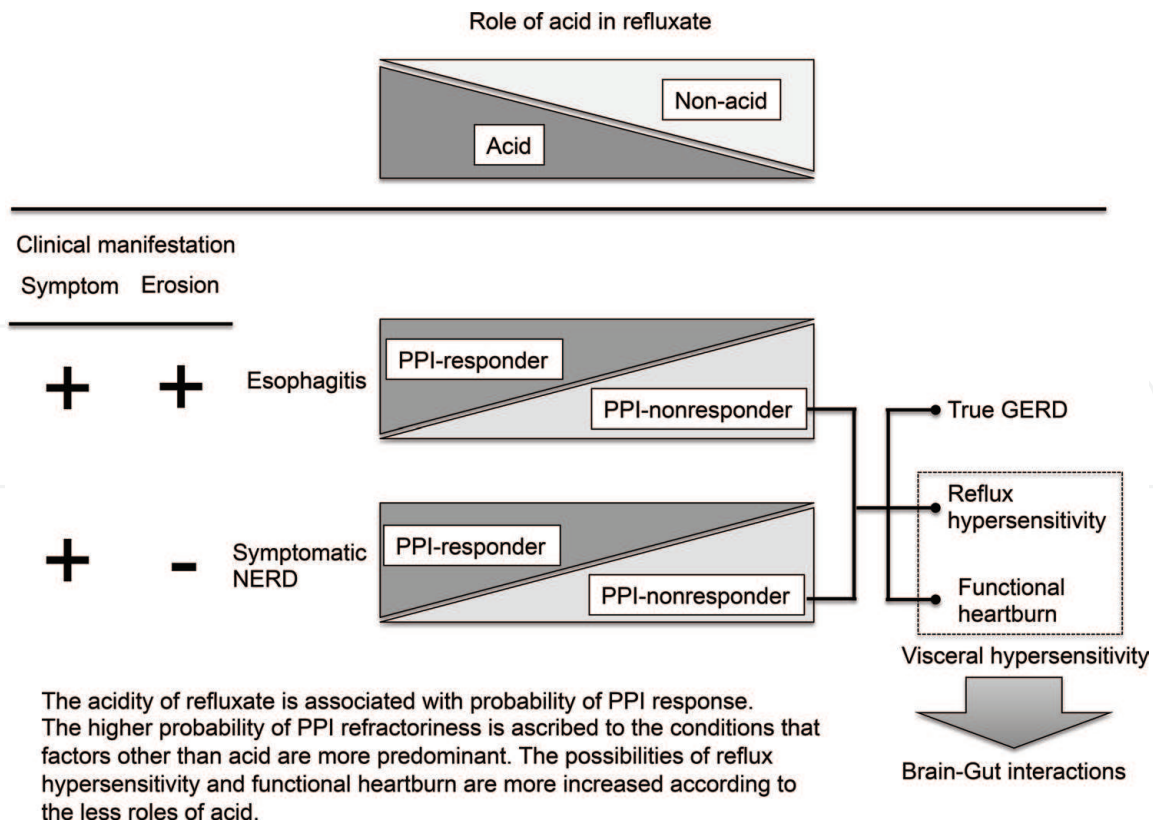
Figure 1.
The acidity of refluxate is associated with probability of PPI response. The higher probability of PPI refractoriness is ascribed to the conditions that factors other than acid are more predominant. The possibilities of reflux hypersensitivity and functional heartburn are more increased according to the less roles of acid.

In this regard, peripheral and central sensitization has recently provided insight into mechanisms establishing of esophageal perception and symptom exacerbation unrelated to acid reflux. Peripheral neuron stimuli triggers repeated neurotransmitter release, and repetitive peripheral firing causes increased excitability of afferent nerves that could establish central sensitization [51]. The upregulated nociceptive pathways could lower resting esophageal pain thresholds, resulting in amplified responses to painful stimuli (hyperalgesia), or resulting in pain perception to non-painful stimuli (allodynia). In this condition, minor physiological noxious stimuli or even innocuous stimuli can be interpreted by the patient as a major symptom, and once hypersensitivity is established, it could continue to potentiate pain even after the stimuli is discontinued, thus "acid" would no longer be a major cause.

In this context, psychiatric comorbidity or psychological stressors could be causes of, or amplifying factors of peripheral and central sensitization. Psychological distress [52], anxiety [53], depression [53], poor sleep quality [54–57], decreased general well-being [58–60], and environmental stress [61] are associated with PPI-refractory GERD. The improvement of reflux symptoms by interventions aimed at reducing stress suggests that the brain-gut interaction and cerebral processing [62] might be responsible for this condition. These psychological factors may compromise esophageal motor function by affecting the enteric nervous system and can modulate esophageal perception, making patients pay excessive attention to intraesophageal events, and consequently cause perception and interpretation of these esophageal events as painful (hypervigilance). By contrast, however, several studies have failed to demonstrate such interaction. Psychological distress was not associated with treatment failure [63]. The relative risk of anxiety or depression in PPI failure was minimal, with the odds ratio being 1.15 [64]. The plausible explanations for these inconsistent results are that the degrees of influence on the enteric nervous system are different between patients

even under the same psychiatric stress. Alternatively, the difference in psychiatric medication given to each patient may play a role. Undoubtedly, the manifestation of GERD symptoms due to a greater psychiatric background should be more likely to be approached by psychotherapy.

This subclassification is clinically important in that true GERD is expected to respond to enhanced or double dose PPI therapy or be a candidate for antireflux surgery, while reflux hypersensitivity and functional heartburn are assumed to show scant response to it. Therefore, it is important to clarify the weight of each component and dominancy in the PPI refractory patients. In a study of 329 NERD patients, 40% showed abnormal acid exposure (true GERD), 36% had reflux hypersensitivity, and 24% had functional heartburn [65]. Another study demonstrated that 40% of 171 symptoms in the PPI refractory GERD patients were considered reflux hypersensitivity, while acid related GERD was only 4.7% [66]. A recent study to explore the composition of 4296 reflux events in 78 PPI refractory patients elucidated that reflux contents are heterogeneous: 24% of reflux events were caused by gas, and 55% of patients were nonacid and reflux unrelated [67]. Finally, as many as 58% of GERD symptoms or 52% of PPI-refractory GERD patients fall into the functional heartburn category [68, 69].

Perhaps background causative factors are mixed, and the extent to which each factor contributes to PPI-refractory GERD is different between patients. Those who are currently categorized as PPI refractory GERD with their manifestations deemed uniform may in fact have heterogeneous etiologies, and therefore a more tailored treatment on the basis of each multifaceted pathway is anticipated to resolve their symptoms better.

5. Therapeutics

By gaining increasing recognition of these mechanisms, therapeutic possibilities could be widened by understanding which individual element is dominant in eliciting GERD symptoms and by diminishing the sensory threshold of what is perceived as painful. Several drugs targeting one of these mechanisms are already in phase III trials, while others are in a developmental stage.

Since the prostaglandin (PG) E2 receptor, EP1, mediates pain perception [70], attempts have been made to reduce PGE2 production or to block EP1 for the treatment of GERD symptoms. There are several randomized, placebo-controlled crossover studies using diclofenac (reduce PGE2 production), ONO8539, and ZD6416 (both EP1 antagonists). Acid induced heartburn was attenuated by diclofenac [71], ONO8539 [72], and ZD6416 [73] as compared with a placebo. As discussed earlier, TRPV-1 activation in primary afferent neurons evokes the sensation of burning pain and induces neurogenic inflammation. Thus the TRPV-1 antagonist, AZD1386, is expected to reduce responses to noxious stimuli; however, the effect has been limited. It was able to increase the pain threshold to heat in healthy men [74] but failed to change the threshold in patients with GERD and partial PPI responders [75].

Several randomized trials focusing on modulating neurotransmitters or the downstream central nervous system have been reported. Pregabalin, a pain modulator including substance P, was able to inhibit the development of acid-induced esophageal hypersensitivity [76]. In order to alleviate the central hypersensitivity, antidepressant nortriptyline was investigated in 20 NERD patients [77]. Functional brain imaging by magnetic resonance revealed that nortriptyline was found to reduce more significantly brain response to esophageal acid perfusion than did placebo. However, this reduction could not improve mental outcome. A

randomized controlled trial to investigate the efficacy of antidepressant imipramine in patients with esophageal hypersensitivity or functional heartburn is underway [NCT01753128].

In an animal study, rikkunshito, a mixture of eight herbal ingredients, was able to reduce neuronal activation and peripheral sensitization through the inhibition of substance P and CGRP expression [78].

6. Future perspectives

The mechanisms that exert GERD symptoms in patients lacking esophageal mucosal injury and/or apparent reflux events remain an area of intense research because these patients often show resistance to PPI therapy, and such refractoriness compromises patient QOL. There is increasing evidence that multifactorial determinants including the number of reflux episodes, the acidity of the refluxate, reflux volume, liquid/gas composition, esophageal hypersensitivity, and cognitive hypervigilance form a fine network to generate GERD symptoms. Although acid is corrosive, the less the roles of acid or mucosal injuries are, the more peripheral and central sensitization become important. The advancement of novel diagnostic tools focusing on impedance, neuropathophysiology, and psychometrics could help identify GERD phenotypes more precisely and practically. These novel metrics could also facilitate an understanding that underlying backgrounds of GERD are diverse, response to treatment is variable, and mechanistic phenotypes are heterogeneous, including hypersensitivity and hypervigilance. Therefore, the traditional single approach of focusing solely on acid suppression makes treatment results unsatisfactory and problematic. Otherwise, an expanded consideration of such multifactorial determinants deserves merit. Each determinant could be a potential therapeutic target, and given the wide array of potential therapeutic targets, the development of drugs to control each target could therefore increase treatment possibilities. Therefore, determining which factors are responsible for GERD symptoms on a patient basis can establish more effective and individualized treatments, leading to the treatment concept that there is no longer a "one size fits all." This conceptual shift will realize the prescription of tailored, more effective drugs as well as the performance of behavioral intervention, and ultimately, fill the current therapeutic gaps.

7. Conclusions

The underlying mechanisms of GERD, especially PPI refractory GERD, are multifactorial. Evidence has been accumulated which supports the concept that GERD is established by a cascade starting from cytokine release to central sensitization. Since each component could be a therapeutic target, it is important to develop novel metrics to quantify the weight of each component and to develop drugs to control each component. Clarifying which component is predominant on the patient-by-patient basis could help realize tailored treatment.

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