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Gastroesophageal Reflux Disease and Airway Hyperresponsiveness: Mechanisms and Mediators Involved GERD and Asthma

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Abstract

Gastroesophageal reflux disease (GERD) is clearly explained as the unintentional passage of stomach contents through the esophagus that takes place many times during the day both in children and in adults. GERD leads to symptoms of heartburn and regurgitation, these defined esophageal symptoms are in dichotomy with extra-esophageal symptoms of GERD. These extra-esophageal symptoms include several respiratory manifestations that include chronic cough, bronchoconstriction and inflammation of airway, main features of asthma. Asthma is a chronic disease defined by variable degree of airflow obstruction, bronchial hyper-responsiveness (AHR) and chronic airway inflammation. Recent papers demonstrated an association between GERD and asthma. There are a lot of mechanisms through GERD can alter the reactivity of airway and lead to bronchoconstriction. Two hypotheses are proposed to explain this effect and different mechanisms may be involved. However many authors suggest bidirectional effect between asthma and GERD. In fact, asthma can lead to onset of GERD through an increase of intrathoracic pressure during breathing and a reduction of lower esophageal sphincter (LES) pressure due to asthma therapy. The correlation between GERD and asthma is more complicated and has not yet been fully elucidated and understood, leaving this field of research open to further investigations.

Keywords: Gastroesophageal reflux disease; Asthma; Airway hyperresponsiveness; Tachykinins; Nociceptin/Orphanin FQ

Introduction

Gastroesophageal reflux disease (GERD) is clearly explained as the unintentional passage of stomach contents through the esophagus that takes place many times during the day both in children and in adults [1].

The diagnosis of GERD is made through the assessment of reflux symptoms by monitoring of esophageal pH [1]. In literature, there are few studies based on the correlation between GERD and age, and then on the onset of the disorder in both adults and children [1]. The prevalence rate is tightly linked with age, with adults aged 60 to 70 being the most commonly affected [2]. In adults, the estimate of the prevalence of GERD, defined as the onset of an episode a week, it is between 10% and 20% in Western countries, while it is less than 5% in Asian countries. Instead, the prevalence of GERD in children is less than 10%. Nevertheless, a specific populations of children has a greater risk of developing GERD, such as those with esophageal atresia, or respiratory diseases, or even children suffering from obesity or born prematurely [1].

GERD leads to symptoms of heartburn and regurgitation, these defined esophageal symptoms are in dichotomy with extra-esophageal symptoms of GERD [3]. These extra-esophageal symptoms include a variety of respiratory manifestations that include chronic cough, bronchoconstriction and airway inflammation, main features of asthma [4].

Asthma is a chronic disease defined by variable degree of airflow obstruction, bronchial hyper-responsiveness (AHR) and chronic airway inflammation [5]. According to World Health Organization (WHO) the most recent revised global estimate of asthma suggests that 334 million people suffer from asthma in the entire world, and this number is rising. World-wide, deaths from this condition have reached over 250,000 annually. Estimates suggest that the number of people suffering from this condition will further increase by over 100 million by 2025 [6,7]. Usually, respiratory symptoms and AHR are connected with eosinophilic inflammation of airways, hallmark of asthmatic patients [8]. Moreover, structural changes of asthmatic airways as sub epithelial fibrosis, mucous metaplasia, wall thickening and hypertrophy and hyperplasia of smooth muscle modify airways mechanical properties [9].

GERD in Asthma: Mechanisms

GERD is a general state associated with several symptoms of respiratory tract, such as chronic cough and asthma exacerbation [10]. The prevalence of this disorder in 25.7 million people with asthma is estimated to be 32-82% [3]. Many experimental studies demonstrated that an amount of acid in the oesophagus may induce mild bronchospasm in dogs and plasma extravasation in guinea-pigs. It has been clearly demonstrated by recent papers an association between GERD and asthma [11,12].

In fact, the authors suggest the relationship between the two conditions, showing airway hyper responsiveness to inspiration of methacholine in non-asthmatic subjects with GERD and in asthmatic subjects after oesophageal hydrochloric acid (HCl) instillation [10].

There are many mechanisms by which esophageal contents can alter airway reactivity and result in bronchoconstriction. Two hypotheses are proposed to explain this effect and more than one mechanism may be involved:

Reflux mechanism: It is mostly sustained by the fact that bronchoconstriction happens after the instillation of stomach contents into the esophagus with subsequent aspiration into the lungs. This conducts to direct mucosal damage through the stomach contents leading to extra-esophageal symptoms, chronic inflammation of lung tissue, which can lead to airway obstruction. GERD promotes the release of pro inflammatory mediators such as T-helper type 2 cytokines, which cause an increase of the resistance and inflammation of the airways. Airways inflammation induced by GERD leads to infiltration of macrophages, neutrophils, eosinophils and lymphocytes. In several animal studies was demonstrated the release of several interleukins that increase the release of TNF-α. Finally, it was observed that subjects with respiratory disorders and pathologic acid exposure of distal esophagus, can show a progress in their respiratory symptoms after antireflux treatment [3].

Vagal reflex: It operates on the principle that embryologically, the esophagus and bronchial tree have an origin similar and a neural innervation via the vagus nerve. Reflex theory is mediated through stimulation of esophageal mucosal receptors by a low pH and esophageal distention, which can lead to extra-esophageal symptoms as as well as hyper responsiveness of airways and hyperactive of bronchial smooth muscles [3].

Both mechanisms probably contribute to asthma in varying degrees (Figure 1) [13,14].

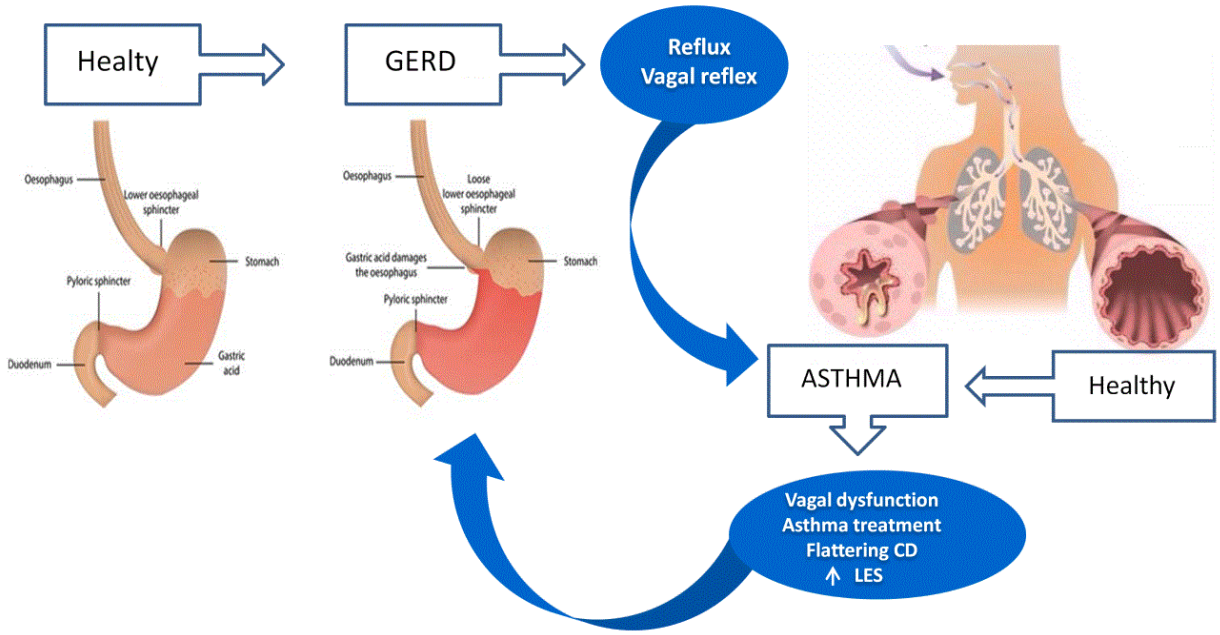

Figure 1: Mechanisms of GERD in asthama and asthama in GERD.

GERD in Asthma: Mediators

This section discusses involved mediators that might conduct to the evolution of GERD in asthmatics subjects (Table 1).

Mediator/Mechanism	Receptor	Effect
Tachykinins: SP, NKA, NKB	NK1, NK2, NK3	Vasodilatation, bronchoconstriction, increase in microvascular permeability, glandular secretions production, facilitation of cholinergic neurotransmission and recruitment and activation of inflammatory cells
N/OFQ	NOP	Reduce bronchoconstriction and airway inflammation
Low pH and distention	Esophageal Mucosal Receptors	Airway hyperresponsiveness and overactive bronchial smooth muscles

HCl microaspiration	Muscarinic (M3) receptor	Mucosal injury, chronic inflammation of lung tissue, airway obstruction
Th2 cytokines: IL-4, IL-5, IL-6, IL-13	Type II Cytokine Receptors	Increase resistance and inflammation of airway infiltration of macrophages, neutrophils, eosinophils and lymphocytes
Increase intrathoracic pressure		Worsening GERD
Vagal dysfunction		Worsening GERD
Altered CD function		Worsening GERD
Decreased LES pressure		Worsening GERD

Table 1: GERD in asthma and viceversa: mediators/mechanisms. CD: Crural Diaphragm; LES: Lower esophageal sphincter.

Some experimental studies performed in animal models highlighted that the infusion of HCl into airways and the reflux of gastric contents can cause bronchoconstriction [15] Moreover, both animal and human studies demonstrated the involvement of the vagus nerve and cholinergic neurotransmission in GERD-induced bronchoconstriction [16] Neurogenic inflammation mediated by tachykinins can hold a key role in these mechanisms. Tachykinins are present in several types of peripheral tissues, including gastro-intestinal tract, lung and bladder [17]. The activation of C-fiber afferent nerves in the airways conducts to local release of tachykinins, such as substance P (SP), neurokinin A (NKA) and neurokinin B (NKB). The biological actions of tachykinins are mediated via three types of receptors, denoted tachykinin NK1, NK2 and NK3, which have the highest affinity for SP, NKA and NKB, respectively. They are particularly responsible for several biological effects in the airways, such as vasodilatation, bronchoconstriction, increase in microvascular permeability, glandular secretions production, facilitation of cholinergic neurotransmission and the recruitment and activation of inflammatory cells [10] Some experimental models of GERD showed that airway plasma extravasation or bronchoconstriction induced by HCl instillation is eliminated through the pretreatment with capsaicin, a substance that leads to a reduction of tachykinins from sensory nerves or by treatment with neurokinin receptor antagonists [17].

Moreover, several studies have highlighted the involvement of other mediators in the relationship between GERD and asthma such as nociceptin/orphanin FQ (N/OFQ).

N/OFQ is a ligand for a specific opioid like G-protein coupled receptor called N/OFQ peptide receptor (NOP) and plays a key role in more central functions as well as in the periphery on the cardiovascular, renal, gastrointestinal and airway systems.

In fact, Rouget et al., [16] demonstrated that N/OFQ reduces the airway inflammation induced by esophageal HCl infusion in guinea pig [18,19].

Asthma in GERD

Given the evidence of GERD leading to asthma, many authors have felt that asthma can lead to worsening GERD through several mechanisms than can coexist: the increase of intrathoracic pressure, vagal dysfunction, altered Crural Diaphragm (CD) function and the decreased of lower esophageal sphincter (LES) pressure due to asthma therapy. In asthmatics, especially during severe episodes of bronchoconstriction, the increase of pressure gradient between the esophagus and the stomach can overcome LES pressure, leading to GERD. On the contrary, it's known that asthmatics have an increase of vagal responsiveness [1]. Therefore, asthma may also affect GERD by autonomic dysregulation, that would lead to a lower LES pressure gradient, supporting GERD episodes. Furthermore, the alteration of the CD function has been considered another mechanism through asthma may influence GERD [2,3]. Also, during inhalation, CD can contribute to the LES pressure gradient. Episodes of hyperinflation associated with bronchoconstriction in asthma can affect the function of the CD through the alteration of its geometry [1].

Moreover, another mechanism is due to mechanical changes. In particular, the obstructive pattern of asthma leads to increased negative intrathoracic pleural pressure. In turn this leads to increased diaphragmatic pressure, which would promote the regurgitation of gastric content across the LES due to the pressure difference. During asthma attacks, the negative intrathoracic pressure surpasses the protective effect of the LES and leads to reflux (Figure 1) [20].

Conclusion

The correlation between GERD and asthma is more complicated and has not yet been fully elucidated and understood. This is partly due to the difficulty to affirm the diagnosis and assess the severity of conditions. Nevertheless, several experimental studies have showed some mediators at the basis of this disease, such as tachykinins and have underlined the possible role of N/OFQ on the tachykinergic neurotransmission. Therefore, this field of research remains open to further investigations.

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