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Review

The role of the lung-brain axis in asthma exacerbations

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Abstract: Asthma is a heterogeneous pulmonary disease characterized by airway hyperresponsiveness and chronic inflammation, and affects from 1% to 29% of the population in different countries. The pathogenesis of this disease is multifaceted; in addition to the crucial role of the immune system, its development involves environmental and genetic factors. Asthma is manifested by wheezing, shortness of breath, and chest tightness, and characteristic of this disease is that symptoms vary over time and in intensity. Studies have suggested that the special communication, lung-brain axis, has a potential role in the course of pulmonary diseases, including asthma. This term relates to the bidirectional relationship between the brain and the lung, which has communication comprising the central and peripheral nervous systems, the endocrine system, the immunological systems, and microbiota. These elements cooperate to create a complex system of bilateral interactions between the lung and the central nervous system. Our aim of this article was to summarize and organize knowledge about the role of the lung-brain axis during asthma exacerbation, a state which is defined as the worsening of a patient's symptoms and lung function parameters over a defined period.

Keywords: allergy; asthma; lung-brain axis; atopic diseases; exacerbation

Abbreviations: ACC: Anterior cingulate cortex; ACT: Asthma control test; AEs: Asthma exacerbations; ATP: Adenosine triphosphate; BALF: Bronchoalveolar lavage fluid; BBB: Blood–brain barrier; BDNF: Brain-derived neurotrophic factor; CCL11: C-C motif chemokine ligand 11, eotaxin-1; CFU: Colony-forming unit; CGRP: Calcitonin gene-related peptide; CMV: Cytomegalovirus; CNS: Central nervous system; CRSwNP: Chronic rhinosinusitis with nasal polyps; CS: Cytokine storm; CXCL-1, -2, -8, -9, -10: Chemokine (C-X-C motif) ligand -1, -2, -8, -9, -10; E: Epinephrine; EAACI: European Academy of Allergy and Clinical Immunology; ECM1: Extracellular matrix protein 1; ERS: European Respiratory Society; FEF25–75%: Forced Expiratory Flow 25–75%;

FEV1: Forced Expiratory Volume in 1 second; FRC: Functional Residual Capacity; GERD: Gastroesophageal reflux disease; GINA: Global Initiative for Asthma; HBI: Hypoxic brain injury; HPA axis: Hypothalamic–pituitary–adrenal axis; ICS: Inhaled corticosteroids; IFN: Interferon; IgE: Immunoglobulin E; IL-1α: Interleukin-1α; IL-1β: Interleukin-1β; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-13: Interleukin-13; IL-17: Interleukin-17; IL-22: Interleukin-22; IL1R1: Interleukin-1 receptor type 1; IMV: Invasive mechanical ventilation; LBA: Lung–brain axis; LPS: Lipopolysaccharide; MDD: Major depressive disorder; MERS-CoV-1: Middle East respiratory syndrome coronavirus-1; MIP-1β: Macrophage inflammatory protein-1 beta; MMP-9: Matrix metalloproteinase 9; NE: Norepinephrine; NGF: Nerve growth factor; NIV: Non-invasive ventilation; NK cells: Natural killer cells; NMDA: N-methyl-D-aspartate; NO: Nitric oxide; NOS: Nitric oxide synthetase; NOTCH-1: Notch receptor 1; NPY: Neuropeptide Y; NT3: Neurotrophin 3; NT4: Neurotrophin 4; NTs: Neurotrophins; OMVs: Outer-membrane vesicles; PCFs: Bronchopulmonary C-fibres (PCFs); PD-L1: Programmed death-ligand 1; PDLIM4: PDZ and LIM domain protein 4; PEF: Peak Expiratory Flow; PGD2: Prostaglandin D2; PNECs: Pulmonary neuroendocrine cells; ROS: Reactive oxygen species; RS: Respiratory system; SAE: Sepsis-associated encephalopathy; SARS-CoV-1: Severe Acute Respiratory Syndrome coronavirus 1; SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus 2; SBP-Ag: Staphylococcal bacterial protein antigen; SP: Substance P; SpO2: Peripheral Capillary Oxygen Saturation; Treg cells: Regulatory T cells; TNF-α: Tumour necrosis factor alpha; TRPV1: Transient receptor potential vanilloid 1; V/Q: ventilation-perfusion ratio; VEGF-A: Vascular endothelial growth factor A; VIP: Vasoactive intestinal peptide; VN: Vagus nerve; VNS: Vagus nerve stimulation; WHO: World Health Organization

1. Introduction

Asthma is a pulmonary disease characterized by chronic inflammation (T2—high or T2—low) with episodes of exacerbations [1,2]. The global prevalence of asthma is estimated at 9.1% among children, 11.0% among adolescents, and 6.6% among adults, with more than 450,000 deaths each year [3,4]. Common symptoms of asthma include wheezing, dyspnoea, chest tightness, and, in some cases, cough [5,6]. Asthma is a syndrome characterized by underlying mechanisms and thus is divided into several phenotypes [6]. Asthma exacerbations (AEs) are characterized by worsening symptoms that result in difficulty breathing. A universally accepted definition is lacking, and definitions vary across scientific societies. Additionally, the Global Initiative for Asthma (GINA) 2025 report indicates that the term “exacerbation” is not suitable for clinical practice, underscoring the importance of the term “flare-up”. According to GINA, exacerbation represents a change in symptoms from the patient’s usual status. In 2019, the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) defined severe exacerbation as an event in which the patient requires 3 or more days of systemic corticosteroids and is treated in the emergency department, or is hospitalized [1,7]. Asthma attacks can occur suddenly, but are usually triggered by upper respiratory tract infections or environmental triggers like allergens, which result in airway obstruction and dynamic hyperinflation [8,9]. The risk factors for AE include individual characteristics like age (≥50), high short-acting beta-agonist (SABA) use, inadequate inhaled corticosteroids (ICS) therapy, and comorbidities, such as obesity, gastroesophageal reflux disease (GERD), chronic rhinosinusitis with nasal polyps (CRSwNP), food allergy, smoking exposure, and previous exacerbation history. Behavioral and socioeconomic conditions (for instance, medication costs or access to healthcare) are

also critical because they influence the likelihood of AEs. [1,10,11]. The life-threatening form of severe AE is *status asthmaticus* characterised by hypoxemia, hypercapnia, and secondary respiratory failure. All asthma patients can develop this condition, which also manifests in progressive decline in mental status, as neurological deterioration is a sign of inadequate blood oxygenation [12]. Standard pharmacologic management of AE includes treatment of bronchospasm and airway inflammation. Repetitive or continuous SABA administration is the mainstay of therapy for acute AE symptoms. [9].

There is extensive research linking asthma to changes in brain structure and function. In a 2021 study by Huang, et al., patients with chronic asthma showed distinct functional changes across brain regions, primarily in the cerebellum and the frontal, temporal, and occipital lobes [13]. Moreover, 45% of patients with asthma have cognitive impairment of various intensities [14]. Comorbid depression or anxiety disorders are associated with a higher risk of AEs in adults, with more than 30% of the patients with persistent asthma experiencing those diseases [15,16]. In the acute state, neuropsychiatric symptoms in AE are mainly anxiety- and panic-related, with more severe cognitive symptoms in hypoxic cases [17]. Regarding children, due to vague data on adults, Morin, et al. illustrated that among children aged 7–17 years, 53% of them experienced symptoms of depression, anxiety or both for hospitalization due to AE [18]. Other neurologic symptoms of patients, like agitation, confusion, and mental drowsiness, are extreme signs of fatal asthma, and they can mirror general hypoxia. These manifestations are considered markers of critical illness and are often reflective of underlying hypoxia rather than primary psychiatric pathology [17]. The new concept, combining the connection between the lungs and the central nervous system (CNS), the lung–brain axis (LBA), is an emerging area of study inspired by the gut–brain axis pathway. The LBA concept represents bidirectional communication between the respiratory system (RS) and the CNS. The communication can occur through several pathways: Neural via the vagus nerve (VN) or with the participation of transient receptor potential vanilloid 1 (TRPV1) nociceptors, immunological through activity of cytokines and cells, microbial, endocrine, and via direct influence of hypoxemia [14,19,20]. The relationship between chronic asthma and neuroinflammatory processes has been extensively investigated in LBA. However, the acute state and activity of LBA remain comparatively understudied. Therefore, we aim to review and summarize the role of certain elements of the LBA during AEs. In this review, we present and describe the parts of LBA that are involved in AE and how this communication could work. We hypothesize that the LBA plays an important role in triggering and sustaining AE through interdependent neural, immunological, hormonal, and microbial changes.

2. The lung-brain axis

2.1. Neural pathway

Neural pathways are essential for bidirectional communication between the respiratory system and the CNS, primarily mediated by the autonomic nervous system. The VN plays a dominant role, with parasympathetic activation promoting bronchoconstriction, mucus secretion, and mucosal edema, while sympathetic activation counteracts these effects through bronchodilation and inhibition of secretion [20,21]. Evidence from studies on allergic rhinitis suggests that asthma involves activation of the LBA, in which airway inflammation stimulates specific brain regions that subsequently modulate peripheral neural outputs. This process leads to the release of neuropeptides and mediators that exacerbate bronchoconstriction, amplify inflammation, and contribute to neurological symptoms [14].

However, VN activity, as part of LBA in AEs, is inconsistent. According to a systematic review by Di Flumeri, et al., vagus nerve stimulation (VNS) may represent a potential intervention for acute asthmatic bronchoconstriction. Limited human studies suggest that VNS can transiently improve pulmonary function in adults with AE when administered alongside standard anti-asthmatic therapy [22]. Mehmed, et al., reported that transcutaneous VNS increased Forced Expiratory Volume in 1 second (FEV1) by 10.2% compared with 1.7% in the sham group, with concomitant improvements in Peak Expiratory Flow (PEF) and Forced Expiratory Flow 25–75% (FEF25–75%). However, this study included only 30 participants, which limits the strength of the conclusions [23]. The available evidence remains limited and is based mainly on small studies of insufficient methodological quality, often lacking appropriate control groups and involving concomitant pharmacological treatment, which makes it difficult to determine the independent effect of VNS. Additional concerns include the limited translatability of animal findings and the overall low level of clinical evidence [22,23]. Beyond its neural function, the VN is a component of the cholinergic anti-inflammatory pathway, linking pulmonary inflammation to central neuroimmune regulation via α7 nicotinic acetylcholine receptors on immune cells [21]. The pulmonary parasympathetic inflammation reflex, involving VN terminals, brain integration centers, acetylcholine, and α7 nicotinic acetylcholine receptor-expressing cells, modulates lung and brain functions, with release of acetylcholine, neuropeptides, substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neuromedin U, and adenosine triphosphate (ATP) [20,24]. Experimental evidence indicates that proper activation of this pathway can limit pulmonary inflammation, whereas dysregulation may promote immunosuppression, infection, or fibrotic remodeling [21].

During AEs, neuropeptides released from vagus afferents, sensory neurons, and pulmonary neuroendocrine cells (PNECs) further mediate lung-brain communication by modulating neurogenic inflammation by bronchopulmonary C-fibers (PCFs), immune cell recruitment, and airway hyperresponsiveness [21,25]. In terms of sensory receptors, lung TRPV1 can detect lipopolysaccharide (LPS) from bacteria. Malaise, fatigue, and anorexia are symptoms resulting from neural signals from these receptors that are transmitted to the hypothalamus [20].

The aforementioned PNECs are the only innervated respiratory epithelial cells capable of accumulating neuropeptides. Their abundance is increased in the bronchi of patients with asthma. When triggered by allergens, PNECs can release neuropeptides such as tachykinins, eliciting immune responses [21,26,27].

Inflammatory cytokines can generally promote neurotrophins (NTs) expression in airway smooth muscles. They are substances produced by neural and non-neural cells. The family of NTs consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BNDF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4). Elevated levels of NTs are associated with asthma prevalence. For example, NGF, a mediator of asthma pathogenesis, is responsible for chemotaxis, mast cell degranulation, and enhanced neutrophil and macrophage phagocytosis. NGF can aggravate airway inflammation by activating eosinophils, and higher levels are correlated with a more severe disease course. However, further studies are needed to clarify the mechanisms underlying NGF's effects [28–31].

2.2. Immunological pathway

The immune system regulates and sustains stability of the internal environment by acting through immune organs, cells, and molecules in multiple body systems, providing immunological defense

against infections and tumors. However, an incorrect immune response can lead to inflammatory diseases such as asthma. [21,32,33]. Airway inflammation in asthma could be an effect of three kinds of cell-mediated immune responses, type 1, 2, or 3, dividing asthma into four inflammatory phenotypes: Eosinophilic, neutrophilic, pauci-granulocytic, and mixed-granulocytic asthma. Type 2 high asthma, which includes the allergic and non-allergic phenotype, is most prevalent and characterized by the activity of eosinophils and IL-4, IL-5, and IL-13 cytokine profiles (eosinophilic phenotype). Type 2 low (type 1 and 3) asthma encompasses neutrophilic and pauci-granulocytic phenotypes. Neutrophilic asthma is associated with Th1/Th17-driven inflammation with IL-1α, IL-1β, IL-6, tumor necrosis factor alpha (TNF-α) and chemokine (CXCL-1, -2, -8, -9, -10) profiles, and pauci-granulocytic is described with a low number of eosinophils and neutrophils along with a poor cytokine-related profile. In the pathogenesis of mixed-granulocytic asthma, eosinophils and neutrophils contribute to airway inflammation [34–36].

Airway inflammation in asthma may activate agents that influence brain activity. Dill-McFarland, et al., in 2024 demonstrated that during bronchial inflammation induced by allergen provocation (*Staphylococcal* bacterial protein antigen, SBP-Ag) in patients with mild asthma, the release of molecules associated with T2-type inflammation correlated with enhanced reactivity of the salience network. This network comprises the frontoinsular and paralimbic anterior cingulate cortices and is responsible for task selection, executive functions, sleep, and emotional regulation [36–38]. After allergen provocation, the released IL-17 contributes to the activation of notch receptor 1 (NOTCH-1), a protein involved in promoting brain neuroinflammation and neurodegeneration and is associated with increased expression of vascular endothelial growth factor A (VEGF-A), a protein that increases blood-brain barrier (BBB) permeability [39–41]. Th17 inflammation and NOTCH-1 with VEGF-A signaling could be responsible for cognitive dysfunction in asthma patients during AE, also suggesting new therapeutic targets [39].

Eosinophils are involved in the development of asthma exacerbation. Studies have suggested that sputum and blood eosinophil counts are important factors for predicting asthma exacerbation. In type 2 high asthma, stimulation of eosinophils, for instance in AE, contributes to neuronal damage and death by activating eotaxin-1 (CCL11), which crosses the BBB and binds to CCL11 receptors on microglial cells. This connection results in the induction of oxidative stress, increased glutamate-induced neurotoxicity, and elevated levels of intracellular reactive oxygen species (ROS) [14,42,43].

In 2025, Morera P, et al. evaluated the role of neutrophils and eosinophils in inducing behavioral alterations and neuroinflammation in the brain. They checked changes in mouse behavior induced by mixed granulocytic airway inflammation. The mice, after ovalbumin with Complete Freund's Adjuvant challenge, were characterized by increased neutrophil and eosinophil levels in bronchoalveolar lavage fluid (BALF). The study showed learning deficits and elevated interleukins IL-6, IL-1β, and tumor necrosis factor alpha (TNF-α) levels in the prefrontal cortex, IL-1β and IL-6 in the hippocampus, and TNF-α and IL-6 levels in the hypothalamus in those mice after provocation. The study suggests that lung inflammation, regardless of eosinophilic or neutrophilic predominance, can drive neuroinflammatory responses [44].

The phenomenon of lung disease-induced effects on the CNS, regulated by immune responses, also applies to infectious diseases. Lung diseases can initiate an immunological response to pathogens, and circulating inflammatory markers like matrix metalloproteinases -9 (MMP-9) and TNF- α can activate glial cells and exacerbate nerve cell death. In rats, these molecules lead to brain grey matter volume reduction and anxiety-like behaviors [30]. A hyperactivated inflammatory reaction, such as a cytokine storm (CS),

occurs when cytokines released into the bloodstream evoke pro-inflammatory systemic effects. CS storms have been observed in a diverse range of infectious diseases (influenza, SARS-CoV-1, MERS-CoV-1, SARS-CoV-2). The effect of CS on the nervous system, which can be observed in some cases during infection among asthma patients, includes confusion, seizures, aphasia, and delirium states [45].

2.3. Gas Pathway

In the gas pathway, oxygen, carbon dioxide, and nitric oxide have importance and functions. Oxygen plays a crucial role in cell metabolism, and when its concentration in the blood is within the normal range, this condition is referred to as normoxemia; if the oxygen level decreases, it is called hypoxemia. Hypoxemia results from inadequate oxygen delivery to tissues due to reduced blood supply or low oxygen saturation and may lead to tissue hypoxia, defined as reduced oxygen availability at the tissue level [21,46]. The role of hypoxemia in brain injury is well-documented, and results from the lung-brain connection show that the brain has high metabolic demands based on oxidative phosphorylation [20]. Hypoxic Brain Injury (HBI) is a condition resulting from insufficient oxygen delivery to meet the brain tissue's metabolic needs. The main pathophysiologic pathway leading to cell death involves activation of calcium influx through N-methyl-D-aspartate (NMDA) receptors, triggered by glutamine release in response to brain ischemia. Hypoxemia leads to excitotoxicity as calcium influx exacerbates neuronal injury by activating lysosomal enzymes, promoting free radical formation, and impairing mitochondrial function [47]. In the case of AE, HBI can result from a critical reduction in laminar airflow in the airways, such as during *status asthmaticus.* Airway closure during exhalation leads to an increased respiratory rate and respiratory alkalosis. This is accompanied by an increase in functional residual capacity (FRC) and air trapping, which further worsens hypoxemia. Progressive hypoxemia can impair consciousness and lead to neurological deterioration [48,49].

Carbon dioxide is a gas and a byproduct of metabolism. It is transported in the bloodstream from cells to the lungs, where it is removed through exhalation. CO_2 regulates blood pH, pace of breathing, and hemoglobin's affinity for oxygen (O_2) [50]. In severe AE, elevated CO_2 levels lower blood pH, which alerts the brain via chemoreceptors in the medulla. In response, the brain signals the pulmonary stretch receptors in the lungs to increase the respiratory rate [47]. The compensation for decreasing CO_2 concentration in blood and tissues via rapid breathing has its own limitations. When this mechanism fails with additional comorbid lung diseases, neurological disorders can be manifested with seizures, papilledema, depression, and muscle twitches [50,51].

Nitric oxide (NO) is a molecule produced by nitric oxide synthetase (NOS) by alveolar macrophages in response to stimulation by endotoxins and cytokines. Its function during asthma consists of promoting vesicle formation and bronchial dilation, mediating ciliary beat frequency, promoting mucus secretion, and participating in the transmission of neural signals by non-adrenergic, non-cholinergic neurons [52]. Given that nitric oxide exhibits a very short half-life of 1–10 seconds under physiological conditions and a limited diffusion range of 50–1000 μm before undergoing oxidation, it is unlikely that it exerts direct effects on CNS signaling. However, in the form of nitrite and nitrate, it can be transported via circulation to make NO available for recipient tissues [53,54]. Presley, et al. have shown that a high nitrate diet increases blood flow in specific brain areas in older patients, and that a high nitrate load is linked to elevated nitrate and nitrite concentrations in blood and tissues [55]. These substances can be reduced back to nitric oxide in the brain, and astrocytes can produce nitric oxide via mitochondrial nitrite reduction, thereby increasing cerebral blood flow [56].

Despite these systemic effects, the role of NO produced in the lungs and its direct effect on the brain during acute asthma exacerbations appears to be limited. Evidence is primarily derived from isolated studies that do not specifically address the pathophysiological environment of asthma exacerbations, and instead rely on a rather systemic, cause-and-effect description across studies; thus, its clinical relevance in this context needs to be fully elucidated.

2.4. Microbiome pathway

The microbiome consists of all the microbes (archaea, bacteria, viruses, fungi) and their gene sequences in a specific habitat at a specific time. In the lung microbiome, the dominant phyla are *Firmicutes* and *Bacteroidetes*, and the major bacterial genera are *Prevotella*, *Veillonella*, *Porobacteria*, and *Streptococcus* [21]. The virome mainly consists of *Anelloviridae*, and the mycobiome is made up of *Ceriporia*, *Saccaromyces*, and *Penicillium* [57]. The biomass of the pulmonary microbiome is low in comparison to the gut's, with the value of the 10^3–10^5 CFU/g of lung tissue [58,59]. The bacteria originate from the oral cavity microbiome and migrate to the lungs via microaspiration and mucosal translocation [60]. On the one hand, direct inhalation and micro-aspiration from the upper airways enable bacteria to settle in the lower airways; on the other hand, coughing and mucociliary clearance movements eliminate microbes from that site [61]. The microbiota is a crucial component of the LBA. Lung microbiota influences brain activity via direct translocation or signalization by immunological, VN, hormonal, and metabolic pathways [62].

Patients with asthma exhibit distinct bacterial profiles compared with healthy patients. The microbiota in asthma is not consistent, varying with disease severity, clinical phenotype, current clinical status, and underlying inflammation [59]. Overall, the microbiome profile of asthma patients is characterized by the enrichment of *Proteobacteria*, particularly *Haemophilus*, *Neisseria*, and *Moraxella*, and type-2-low asthma is more diverse and contains more bacteria than type-2-high [57,63,64]. In children, lower relative abundances of the bacteria *Bifidobacterium*, *Faecalibacterium*, *Lachnospira*, *Roseburia*, *Ruminococcus*, and *Bacteroides*, as well as the fungus *Malassezia,* are associated with asthma or atopic wheeze prevalence [65].

The main point is to differentiate bacterial colonization without symptoms from respiratory infection. We can distinguish two situations: Bacterial, fungal, or viral infections that exacerbate asthma, or commensal activity that can lead to AEs. In the first case, Hwang assessed airway infections in AE in 2023 and detected respiratory pathogens in 53% of the patients. Moreover, 24.6% of the patients had positive results for bacteria (most prevalent *Pneumococcus* infection). Viruses were detected in 37.3% of the patients, with Influenza A virus as the most common viral pathogen, followed by rhinovirus [66]. In the latter case, the resident microbiota can modulate the course of AE. Dysbiosis in commensal bacteria seems to promote AE in asthma patients. In the 2023 review by Valverde-Molina, et al., a higher abundance of *Proteobacteria* in bronchial brushings and nasal samples was associated with more frequent exacerbations among adults. *Prevotella buccalis*, *Dialister invisus*, *Gardnerella vaginalis*, and *Alkanindiges hongkongensis* were more prevalent in nasal probes from patients with exacerbations, suggesting their role in the pathogenesis of AEs [67]. In another study by Kim in 2021, a group of 95 children was analyzed by examining the bacterial constitution of induced sputum during AE. The microbial candidates were assessed for their association with the production of inflammatory cytokines. *Campylobacter*, *Capnocytophaga*, *Haemophilus*, and *Porphyromonas* were associated with acute AE by production of increased levels of macrophage inflammatory protein-1

beta (MIP-1β), programmed death-ligand 1 (PD-L1), and granzyme B, which are involved in the pathogenesis of asthma [68].

Microbial factors may also contribute to neuropsychiatric symptoms. Viruses can directly infect neurons by reverse axonal transport through the VN; by infecting the breath centre in the brain stem, they can aggravate respiratory distress [21]. In severe cases, bacteremia, which is the presence of bacteria in the blood, can progress to septicemia, a life-threatening condition that may result in sepsis [69]. Sepsis-induced brain dysfunction is manifested as sepsis-associated encephalopathy (SAE), delirium, sickness behavior with cerebral ischemia, and hemorrhage, leading to progressive cognitive impairment [70]. Bacterial products can also enter peripheral blood as outer membrane vesicles (OMVs) [21]. OMVs carry LPS, which can cross the BBB and activate microglial cells, astrocytes, and dendritic cells in the brain. LPS-induced neuroinflammation reinforces oxidative stress affecting mitochondrial function in brain tissues, leading to memory impairment, dysfunctional locomotor function, muscle weakness, paralysis, learning deficits, and dementia [71–73].

2.5. The endocrine pathway

The endocrine pathway plays a crucial role in AE by releasing hormones in response to stress. The HPA axis comprises the hypothalamus, pituitary, and adrenal glands, which communicate through a feedback loop. Stress can activate the HPA axis, which is responsible for glucocorticoid release, and stimulate the sympathetic nervous system to release norepinephrine (NE) and epinephrine (E) [74]. Stress also affects the parasympathetic system; efferent cholinergic nerve endings are activated, releasing acetylcholine to promote mucus production and airway remodeling [75]. Stressors also induce brain structures such as the anterior cingulate cortex (ACC), insula, and limbic system to release substance P (SP), histamine, and neuropeptide Y (NPY), which are then transported to the airways, exacerbating the course of asthma [14].

Sex hormones, as part of the endocrine pathway, can also modulate the course of asthma. For instance, severe asthma and frequent AE are more likely to occur in females. The mechanism of this phenomenon may be explained by estrogen's effects on enhancing type 2 inflammatory responses, increasing eosinophil infiltration, and elevating IL-4 and IL-13 levels [76]. Moreover, the occurrence of depression and anxiety in patients with asthma is higher in females [77]. This may be linked to the correlation between increased levels of inflammatory mediators, including IL-4, IL-6, TNF-α, and depression. Moreover, this communication is bidirectional, as depression may increase the frequency of AE. Papaporfyriou, et al. demonstrated that patients with mild and moderate depression, rates of AE were significantly higher in females compared to males [78].

Asthma patients under stress are more susceptible to infection. During stressful situations, released NE increases bacterial pathogenicity by enhancing their mobility and proliferation. Additionally, glucocorticoids have a dual effect on immune function. In the short term, they enhance the activity of natural killer cells (NK cells) and promote the production of pro-inflammatory cytokines. Conversely, during chronic exposure, high concentrations of this hormone can lead to immunosuppression [79]. Beyond their crucial role in asthma treatment, steroids are also responsible for the apoptosis of epithelial cells and can weaken the epithelial layer [21,80,81]. Disruption of the epithelial barrier facilitates the translocation of allergens or bacteria, promoting an inflammatory response in the airways [82]. Additionally, prolonged or chronic stress exposure leads to downregulation of beta-2 adrenergic receptors and alterations in glucocorticoid receptor function, reducing responsiveness to inhaled

corticosteroid therapy and complicating AE management [83]. Stress also influences immunological pathways; it skews the T2-type response by reducing regulatory T cells (Treg cells) [75,81].

Comorbid depression or anxiety disorders are psychiatric disorders where stress is one of the crucial factors in their pathogenesis [84]. Overactivity of the HPA axis occurs in major depressive disorder (MDD), leading to cognitive dysfunction and reduced mood [85]. Individuals with depression have an increased risk of AE due to poorer adherence to treatment, greater tobacco consumption, and a higher prevalence of being overweight, all of which adversely influence asthma control [83,86].

3. Discussion

Thorough research was conducted using Google Scholar, PubMed, Wiley Online Library, and the Cochrane Library databases for articles published between 2015 and 2025. Older publication was mentioned to describe mechanism of the LBA due to a lack of actual data. We also cite information from the National Library of Medicine, the GINA document, and the World Health Organization (WHO) document to describe physiological phenomena during asthma. The initial search in each database included the following terms: "lung-brain axis" and "asthma exacerbation", with a total of 20 articles, regardless of the time of publication, fulfilling those criteria. After reviewing the knowledge on LBA and AE, we expanded the search criteria to include terms related to immunity, microbiota, hormones, gases, and the brain. The inclusion criteria were: A valid publication date, a direct relation to AE, and inclusion in LBA. Exclusion criteria included studies focusing solely on chronic asthma without acute exacerbation and studies not involving the CNS. The chosen abstracts were read, and only relevant ones were analyzed and summarized. Peer-reviewed original studies, review articles, and case reports only in the English language were considered. In total, we obtained 89 articles.

In this review, we focus on the "lung–brain axis" as an emerging conceptual framework that assumes a bidirectional relationship between the respiratory and nervous systems. Its components are being investigated across a range of pulmonary diseases, while offering a potential explanatory model for neurodegenerative processes observed in patients with chronic respiratory conditions [31]. In this review, we summarize the knowledge on asthma exacerbations in the context of lung–brain axis function. Due to the limited number of studies in this area, the evidence remains preliminary, except those for gaseous and hormonal pathways, which have been studied extensively. However, despite these limitations, we attempt to formulate conclusions. Asthma exacerbations result from a complex interplay of factors that collectively contribute to a unified clinical phenotype, which can be conceptualized partially as components of the lung–brain axis. Separately, this model may help explain certain neurological manifestations observed during asthma attacks. The immune, nervous, and endocrine systems, as well as gaseous mediators and microbiota, all participate in the exacerbation process, with each component posing reciprocal influence on the others (Table 1). Unfortunately, some data remain speculative, and it seems that no single dominant pathway can be identified, as all mechanisms are interdependent in the context of neurological symptoms in patients with asthma.

Signaling along the lung-brain axis appears bidirectional, although the prevailing mechanisms differ by direction and pathway. Brain-to-lung communication is mediated by stress, which affects signaling pathways, including activation of the HPA axis, action on the microbiome, promotion of Th2 and Th17 inflammatory responses, and influence on brain structures, leading to the release of substance P, histamine, and neuropeptide Y, resulting in AEs. Furthermore, in lung-to-brain signaling, cytokines, including IL-6, IL-1β, and TNF-α, are released in brain regions in response to bronchoinflammation

and play a significant role in promoting neuroinflammation [81]. However, the communication between these organs needs to be more detailed, as little and limited data cannot support formulating the final statement and mechanisms, and not every pathway seems to participate in that bidirectional communication.

This review has some limitations. The knowledge of the role of some elements of LBA remains insufficient. The role of VN has not been fully studied, suggesting further research. Moreover, there is a probable connection between NO produced in the lungs and neural changes in the brain, but this relationship requires further investigation. Moreover, there is a lack of data on the potential roles of the mycobiome and archaea in the pathogenesis of asthma attacks.

The severity of AE should be assessed, as management varies, with severe and life-threatening conditions requiring treatment in acute care facilities. Mild and moderate AE could be controlled in primary care by SABA inhalations (4–10 puffs repeated every 20 minutes for an hour), intravenous corticosteroids-prednisolone (adults 40–50 mg, children 1–2 mg/kg), and oxygenotherapy (SpO2 93–95%, children ≥ 94%). Reassessment after one hour is essential determine whether hospitalization is required or treatment should be discontinued [1].

The brief role of used medications in the treatment of AE and their effect on LBA is presented in Table 2. Although the lung-brain axis provides a conceptual framework, current standard treatment of asthma exacerbations does not directly target all its components. Antibiotics against bacteria, according to GINA 2025, should not be prescribed routinely unless there is strong evidence of a lung infection, as they do not address the microbial effect on AE [1,87]. However, a 2024 meta-analysis indicates that probiotic supplementation (various *Lactobacillus* and *Bifidobacterium* species) may be beneficial for improving asthma symptom control, but only one of the twelve studies observed fewer AE incidents in the studied groups [88]. In cases where the treatments influenced neural transmission, they were limited to agents that relax smooth muscle (SABA, ipratropium bromide, magnesium sulphate, and leukotriene receptor antagonists).

Further research on the lung–brain axis can contribute to the discovery of new approaches to treating asthma exacerbations. For instance, a drug affecting nervous and pulmonary systems is ketamine, a sedative agent that has bronchodilator properties. It exhibits NMDA receptor antagonism, reduces nitric oxide levels, and decreases histamine-induced bronchoconstriction. However, the use of ketamine is not universally recommended in AE due to a lack of major studies on efficacy and safety [9]. A study by Wang, et al. from 2023 pinpointed that receptor interleukin 1 receptor type 1 (IL1R1), glycoprotein extracellular matrix protein 1 (ECM1), and protein PDZ and LIM domain protein 4 (PDLIM4), which were identified in plasma and the brain among asthma patients, could be new therapeutic targets for AE, underlying the importance of further research on LBA in asthma [89].

Table 1. Major evidence in the LBA concept.

Element of LBA	Findings	Source	Study type	Findings	Limitations
Nervous system	Vagal nerve	[20,21]	Review	Neural pathways in LBA are mediated by the vagus nerve. VN promotes inflammation during AE.	Well-designed randomized controlled trials are needed to confirm the role of VN in AEs.
		[22]	Review	Low-voltage vagal nerve stimulation appears to reduce bronchoconstriction in both animal and human subjects.	
	PNECs	[21]	Review	PNECs are part of lung epithelium. They elicit immune responses through neuropeptides.	
	Neurothropins	[29,30]	Review	They promote NO production, bronchoconstriction, acetylcholine release, and induction of interleukin release from eosinophils.	
	Sensory receptors	[21]	Review	$TRPV1^+$ nociceptors are part of LBA and can detect LPS from bacteria.	More research about the role of $TRPV1^+$ during influenza is needed.
Immunology system	T2-low asthma (IL-17)	[39]	Original study	Th17 inflammation could be responsible for cognitive dysfunction in asthma exacerbation.	Insufficient number of study groups.
	T2-high asthma (Eosinophils)	[14,42]	Review	Eosinophils are involved in the development of asthma exacerbations and influence brain function.	
	Cytokine storm	[21,45]	Review	Cytokine storm refers to a spontaneous, dysregulated, and hyperactivated inflammatory reaction that can co-occur during infection in patients with asthma.	
Gaseous pathway	O_2	[48,49]	Mechanistic Description. Chapter of Book	Hypoxic Brain Injury in severe AE.	
	CO_2	[50]	Mechanistic Description. Chapter of Book	Hypercapnia in the pathogenesis of severe AE.	
	NO	[52]	Mechanistic Description. Monograph chapter.	NO promotes bronchi dilatation, mediates ciliary beat frequency, promotes mucus secretion, and acts as a neurotransmitter in AE.	

Continued on next page

Element of LBA	Findings	Source	Study type	Findings	Limitations
Microbiota	Viruses	[21]	Review	Viruses can directly infect neurons by reverse axonal transport through the VN; by infecting the breath centre in the brain stem, they can aggravate respiratory distress. Viruses can trigger an asthma attack.	
	Bacteria	[66]	Original study	Bacterial infection can trigger AE. The most frequently isolated bacteria from patients with AE are Pneumococcus.	Well-designed prospective studies are needed.
		[67,68]	Original study	Dysbiosis in commensal bacteria amounts seems to promote AE in asthma patients.	There is a lack of robust research on the relationship between dysbiosis and asthma exacerbations, particularly in adult populations and in studies involving bronchoalveolar lavage samples.
		[70]	Mechanistic Description. Chapter of Book	Sepsis-induced brain dysfunction.	
		[71]	Review	Bacterial products can also enter the peripheral blood as OMVs and reach the brain, where they activate microglial cells, astrocytes, and dendritic cells.	
Endocrinal system	Gluco-corticosteroids	[21,79]	Review	Glucocorticosteroids induce the production of pro-inflammatory cytokines, promote apoptosis of epithelial cells, and reduce mucociliary clearance. These changes can promote AE.	During chronic exposure, high concentrations of this hormone can lead to immunosuppression.
	HPA axis	[75]	Review	Stress via the HPA axis skews the response toward the T2-type by reducing regulatory T cells (Tregs).	
	Estrogens	[76]	Review	Estrogen enhances type 2 inflammation, increases eosinophilic infiltration, and upregulates IL-4 and IL-13 expression.	

Table 2. The influence of AE treatment on components of the lung-brain axis [1,9,87].

Intervention:	Effect
Short-acting β2-agonist	relaxation of the smooth muscle (neural pathway)
Oxygen therapy	avoidance of hypoxia and maintaining the right pH blood balance
Corticosteroids	decrease the inflammatory response (immunological pathway)
Ipratropium bromide	relaxation of the smooth muscle and inhibition of mucus secretion (neural pathway)
Magnesium sulphate	relaxation of the smooth muscle (neural pathway)
Leukotriene Receptor Antagonists	relaxation of the smooth muscle (neural pathway) and anti-inflammatory effect (immunological pathway)
Non-invasive ventilation (NIV) or mechanical ventilation	avoidance of hypoxia and maintaining the right pH blood balance

Abbreviations: NIV—non-invasive ventilation.

4. Conclusions

Asthma is a chronic pulmonary disease with episodes of exacerbations. Many mechanisms contribute to the worsening of asthma symptoms, and some possible triggers appear to be involved in the communication between the lungs and brain. Components like the nervous, immunological, and endocrine systems, microbiota, and gases have a meaningful influence on inducing and maintaining AE. The vagus nerve, pulmonary neuroendocrine cells, neuropeptides, and neurotrophins contribute to bronchoconstriction and the modulation of airway inflammation. Eosinophilic, neutrophilic, or mixed-type inflammation act through cytokines, chemokines, and immune cells, leading to blood-brain barrier disruption, microglial activation, oxidative stress, and alterations in brain networks that result in behavioral dysfunction. In acute asthma exacerbation, there is dysregulation of oxygen and carbon dioxide concentrations in the blood, impairing brain function, and nitric oxide modulates mucus secretion and neural signaling. The lung microbiome can interact with the brain regarding asthma, and microbial dysbiosis or infections can trigger neuroinflammation. Stress activates the HPA axis, releasing glucocorticoids and catecholamines, thereby increasing susceptibility to infections, impairing airway clearance, and skewing toward T2 responses. The abovementioned elements can be described in one term, the lung-brain axis, underlying their interrelationship and common effects. The LBA concept may help explain aspects of asthma pathogenesis and neurologic symptoms in these patients. However, more solid research is needed for this connection. The most extensively studied pathways within the LBA in AEs are the gaseous and hormonal pathways. In contrast, pathways involving the microbiota and the nervous and immune systems require research with larger sample sizes using human-based models. The main priority in LBA research is its practical application in asthma therapy, as a deeper understanding of each component of this axis can help optimize the treatment outcomes of AEs.

Use of AI tools declaration

The authors declare that they used Artificial Intelligence (AI) tools in the creation of this article to improve the language quality of their content.

Conflict of interest

All authors declare no conflicts of interest in this paper.

Author contributions

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