Lung Interactions With Other Organs And Systems

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Objectives

Introduction

Lung-Brain axis

Lung-Kidney axis

Lung-Gastrointestinal axis

Metabolic, Immunological, Endocrine Lung regulatory function

Interaction between the Lung and the Endocrine system

Conclusion

References

Introduction

The lungs are the only organs that receive all cardiac output, and in turn, all the blood volume that passes through the pulmonary circulation reaches the systemic circulation. They are in close and continuous contact with the external environment, and other internal organs in our body.

Lung tissue is rich in cells of the mononuclear immune and phagocytic system, and the pulmonary endothelium is a highly active entity, with well-established functions in the regulation of the inflammatory, immunological, metabolic and endocrine response.

Given their central location and anatomically close and interconnected with the central nervous system, bidirectional relationships of control and self-regulation are established between these two organs, which are vital for the maintenance of health and life.

In the same way, it has been established both in experimental models in animals and in research in humans, the existence of bidirectional axes, often simultaneous, that interconnect lung function with that of distant organs such as the kidney, the intestine, the endocrine system. These interconnections (crosstalk) occur through complex mechanisms that involve the exchange of cells, cytokines, enzymes, pro-apoptoic elements, hormones, specific receptors, among other elements.

The lung microbiome, with important anti-inflammatory modulatory effects, fulfills regulatory functions both in the lung and in distant organs. There is an interrelationship between the lung and intestinal microbiota that has been demonstrated over the last few years. Proven pathophysiological relationships have been established between certain acute and chronic pulmonary entities and changes in the gut microbiota and vice versa.

During mechanical ventilation with positive pressure, especially if it is non-protective, a series of physiological phenomena occur that translate into local pulmonary and distant effects on various organs.

The lung is a complex organ, which is not only involved in the function of ventilation. The full extent of its influence on the normal functioning of the organism, and its role in the various pathological processes of the different systems is still to be elucidated.

Lung-Brain Axis

Both the brain and lungs are vital organs that play essential roles in maintaining health and life. These organs maintain a complex interaction through sophisticated bidirectional pathways known as the lung-brain axis.

The brain is an organ with a high demand for oxygen and glucose, from which it obtains the energy necessary for the metabolic processes that guarantee its proper functioning. The anatomical proximity and complex network of blood vessels between the lungs and the brain facilitate the efficient transport of oxygenated blood, crucial for maintaining proper body homeostasis.

The basic neural circuits for the control of breathing are found in the brainstem (respiratory center located in the medulla oblongata and pons), while voluntary breathing is determined by the cerebral cortex, the hypothalamus and other areas of the brain.

The Central Nervous System and the Peripheral Nervous System regulate the respiratory rhythm by adjusting alveolar ventilation to the metabolic requirements of the body. It is for this reason that the concentrations of blood gases pH, oxygen and carbon dioxide remain practically stable in a healthy subject, regardless of the physical activity performed.

Ambient air contains 21% oxygen at sea level (PO_2 = 21 kPa), as it passes through the airways and reaches the level of the pulmonary alveoli, PO_2 decreases to 14 kPa, in arterial blood PO_2 reaches 13 kPa, and when it reaches brain tissue PO_2 is 3.9 kPa. This gradient of environmental oxygen reduction to brain tissue constitutes what is called the oxygen cascade.

Blood flow in the cerebral gray matter is > 80 mL/100 g/min and in the white matter it ranges from 20 - 25 mL/100 g/min, on average the cerebral blood flow is 50 mL/100 g/min. The gray matter has greater capillary density than white matter for metabolic reasons, since neurons consume energy to a greater degree than nerve fibers. The adult brain consumes only glucose as an energy source, but the availability of oxygen is essential (there is a relationship between glucose consumption and oxygen utilization: six oxygen molecules are required for the oxidation of each glucose molecule). Thus, for every 50 mL of blood flow per 100 g of nervous tissue per minute, 25 micromoles of glucose and 150 micromoles of oxygen are extracted simultaneously.

These mechanisms are fully automatic and allow the control of pulmonary ventilation in the healthy individual through CNS structures, chemoreceptors, arterial gas concentrations (O_2 and CO_2) and pH.

Acid-base balance regulatory system operates to keep the pH value stable. The brain plays a crucial role in this regulation by controlling CO_2 levels in the blood. When pH falls below normal values, the brain's respiratory centers stimulate an increase in the speed (breathing rate) and depth of breathing (tidal volume), leading to increased gas exchange in the lungs, helping to normalize pH values.

These physiological mechanisms are altered in cases of pulmonary, restrictive or obstructive parenchymal diseases that can reduce the oxygen level of the inspired air and can lead to alterations at the neuronal level such as memory alterations, disorientation, delirium, strokes, Alzheimer's disease and Parkinson's disease. (Figure 1)

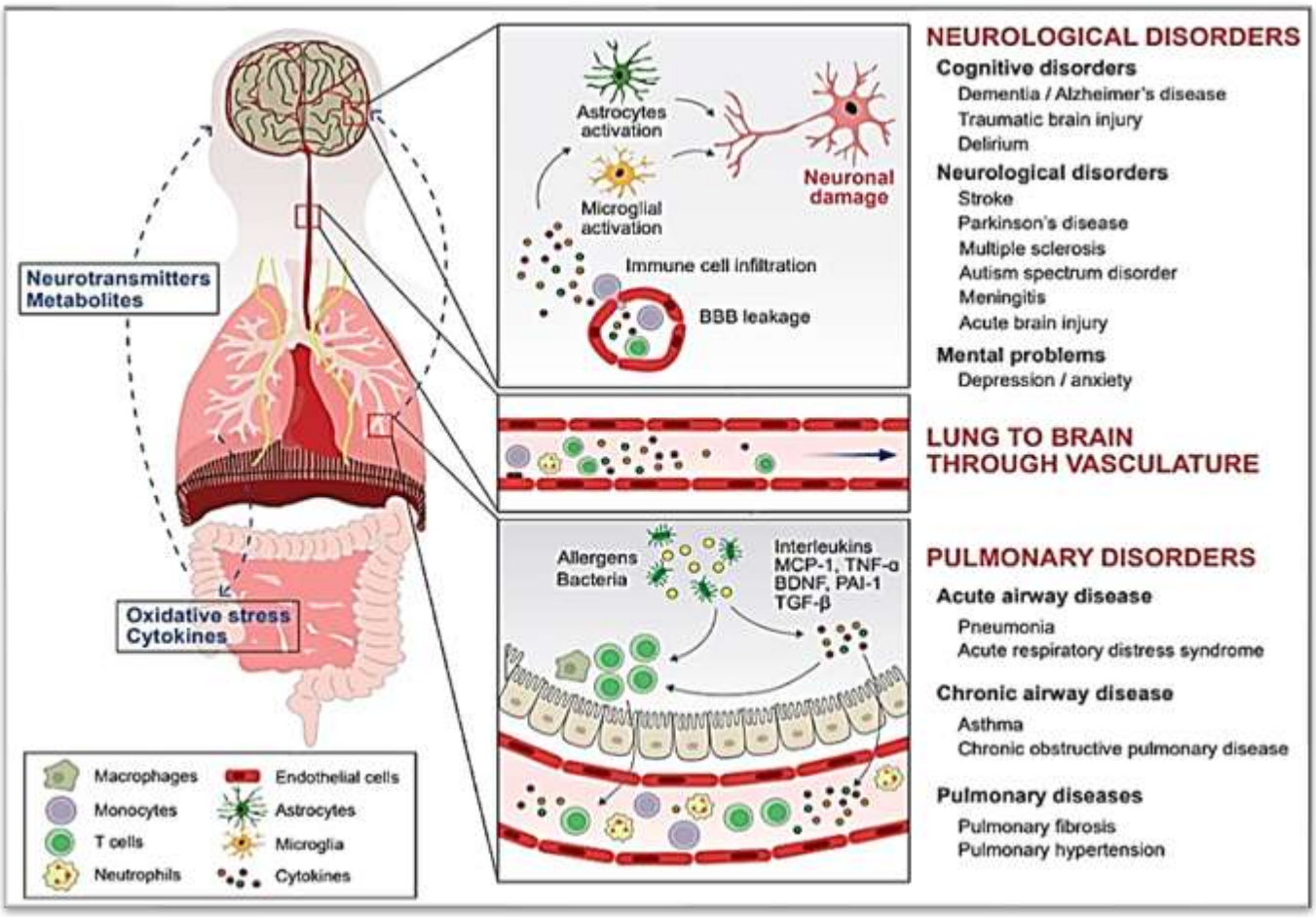

Figure 1: Schematic representation of the lung-brain axis, highlighting the complex relationships between pulmonary inflammatory pathologies and neurological dysfunction.

High levels of CO_2 secondary to deterioration of ventilatory function, as can be seen in acute or chronic lung diseases (chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), among others), directly cause an increase in cerebral arterial vasodilation, a phenomenon known as CO_2 cerebral vasoreactivity, with the consequent increase in intracranial blood volume and Intracranial Pressure (ICP). This physiological response, in the presence of limited brain compliance, will eventually have a direct deleterious effect on neurons causing cerebral edema and a greater increase in ICP.

Even though the brain maintains a high degree of immune privilege, it remains vulnerable to systemic inflammatory responses incited by lung inflammation due to environmental exposures.

The mechanism by which these events occur is described through three main pathways:

A) The humoral pathway, which consists of the recruitment of monocytes or macrophages into the lungs, which increases the levels of inflammatory mediators that can directly reach the Central Nervous System through the circulation. Patients with lung diseases with specific cytokine profiles have been shown to develop certain neurological disorders.

In lung infections such as pneumonia, elevated levels of inflammatory cytokines are found in brain hippocampal tissue along with an increase in microgliosis and astrogliosis due to decreased integrity of the Blood-Brain Barrier (BBB).

In patients with ARDS, the mRNA related to Caspase-1 (interleukin-1-b converting enzyme, responsible for the maturation of pro-interleukin-1-b to its pro-inflammatory and biologically active form), IL-1β and IL-18 is elevated, which mediated by acute changes in cerebral blood flow and deterioration of the integrity of the blood-brain barrier, could lead to neurodegenerative diseases. Tetracyclines, and nonsteroidal anti-inflammatory drugs such as ibuprofen, naproxen, and aspirin suppress Caspase-1 activation, thus may alleviate several neurological disorders associated with this mechanism, including stroke, multiple sclerosis, and Parkinson's disease (PD).

People with COPD are at high risk of stroke, especially after exacerbation, and have high levels of plasminogen activator-1 (PAI-1) inhibitor. PAI-1 is a fibrinolysis inhibitor, so it contributes variably to the obstruction of cerebral blood flow and therefore predisposes these patients to the onset of ischemic strokes.

B) The neural pathway, which is based on the existence of the connection between the brain and the nuclei of the solitary tract by means of the afferent pathways of the Vagus nerve, allowing cytokines derived from the lungs to reach the brain and potentially alter brain homeostasis.

C) The cellular pathway, which explains how acute lung inflammation triggers the recruitment of immune cells, such as neutrophils and eosinophils, which activate lung macrophages. These cells potentially lead to further immune responses by producing additional immune cells from the bone marrow through the secretion of Granulocyte Colony-Stimulating Factor from the airways induced by IL-17 and TNF-α. The release of chemotactic protein-1 from monocytes at the brain level is also stimulated, which in turn increases the recruitment of activated monocytes at the level of the central and peripheral nervous system. The influx of immune cells into the bloodstream can lead to widespread inflammation and make the brain more susceptible to inflammation. For example, the likelihood of developing a stroke in asthma patients correlates with the population of these immune cells in the blood, indicating that acute lung inflammation can lead to brain damage. (Table 1)

Table 1: Relationship between the main pulmonary pathologies and their neurological expression through the different pathophysiological pathways

Lung disease	Mechanism/Pathway	Cooccurrence of the neurological disorders in human
Common	Hypoxia	Delirium, dementia, Alzheimer´s disease, stroke, acute brain injury, hemorrhagic stroke, hypoxic-ischemic brain injury, cognitive impairment, epilepsy
	Systemic inflammation which can cause neuroinflammation	Delirium, dementia, Alzheimer´s disease, stroke, acute brain injury, hemorrhagic stroke, hypoxic-ischemic brain injury, epilepsy, cognitive impairment, depression and anxiety
Pneumonia	Disruption of the blood-brain barrier	Delirium, dementia, Alzheimer's disease, stroke
	Secondary or direct infections weaken the immune system through pneumonia	Delirium
	Bacterial infectious agent-induced infection	Meningitis
Acute respiratory distress syndrome	Disruption of the blood-brain barrier	Acute brain injury, hemorrhagic stroke, hypoxic-ischemic brain injury, cognitive impairment
	Cerebral vascular dysfunction and blood flow changes	Cerebral edema, hemorrhagic stroke. Alzheimer´s disease, delirium, stroke, hypoxic-ischemic brain injury
	Cytokine storm	Alzheimer´s disease, Parkinson´s disease, amyotrophic lateral sclerosis
Asthma	Vascular edema and changes in blood flow to the brain	Cognitive impairment, stroke
	Altered synaptic connections	Autism spectrum disorder, cognitive impairment, dementia, Alzheimer´s disease
	Release of stress hormones and activation of brain regions involved in the stress response	Stroke
Chronic obstructive pulmonary disease (COPD)	Chronic oxidative stress-induced brain structure change	Cognitive impairment, depression and anxiety, dementia
	Genetic association	Alzheimer´s disease
	Disruption of the blood-brain barrier	Depression and anxiety, stroke, Alzheimer´s disease

Bacterial pneumonia has a variable impact on the development of different types of neurological impairment such as delirium, dementia, Alzheimer's disease (AD), vascular dementia and unspecified dementia, depending on the types of bacteria; Haemophilus has a 3.8 times higher risk for AD and Staphylococcus has a 5.4 times higher risk for vascular dementia.

Impact of the lung microbiome on the brain

The human body is not only composed of human cells but also has between 10 and 100 trillion cells belonging to the microbiota. The lungs were long considered sterile organs until Hilty in 2010, using culture-independent techniques, demonstrated otherwise. The estimated microbiota in human lungs is approximately 1011 cells and is a diverse community of microorganisms such as bacteria, viruses, and fungi.

The bacterial composition in the upper left lobe of the lung, detected through the 16S rRNA polymerase chain reaction, is distinct from the nasal and pharyngeal microbiota, with a higher abundance of Haemophilus species. The phyla of abundant bacteria are Firmicutes and Bacteroidetes, similar to the gut microbiome.

There is a strong association between changes in the lung microbiome and CNS inflammation, influencing CNS susceptibility to autoimmune diseases. Bacteria such as Firmicutes and Bifidobacterium are less frequently detected in older people or patients with Alzheimer's disease or Parkinson's disease. The mechanism by which the lung microbiota and its metabolites could exert a protective effect against neurodegenerative diseases is not yet fully clarified.

In short, the anatomical proximity between brain structures and the lungs allows cytokines derived from the latter to reach the brain, altering its homeostasis. The coexistence of neurological alterations in patients with acute or chronic respiratory diseases and recent findings related to the lung microbiome enhance the close interaction between the lungs and the brain in physiological and pathological conditions, which is why cognitive evaluation is highly recommended in this specific population. In addition, understanding and addressing the lung-brain axis presents new therapeutic opportunities for lung and neurological diseases.

Just as lung disorders have a significant neurological impact, the fact that acute brain injuries cause ventilatory disorders is also notorious. A classic example is traumatic brain injury in which neurogenic pulmonary edema is the main serious respiratory complication. The first to describe the relationship

between traumatic brain injury and pulmonary edema was Brown-Sequard in 1871 during an experiment in which he injured the pontine structures of Guinea pigs, causing hemorrhages and pulmonary edema.

The excess of catecholamines that accompanies acute brain injury of any etiology, produces a positive regulation of the transduction of sympathetic signals, which causes an increase in pulmonary venous pressures with the subsequent transudate. The systemic inflammatory response also plays an important role in this section. The intracranial inflammatory response that takes place immediately after acute brain injury is mediated by pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF), which are produced locally in damaged brain tissue. Astrocytes and microglia are the main source of inflammatory mediators. The altered blood-brain barrier, with increased permeability, allows it to pass into the systemic circulation.

Additionally, there is sympathetic overload causing vasoconstriction. It is due to these mechanisms that a redistribution of blood flow from the systemic circulation to the pulmonary circulation occurs, resulting in pulmonary hypertension, with increased hydrostatic pressure in the pulmonary capillary. These changes in lung pressures are responsible for the extravasation of fluid from the intravascular space into the alveolus and into the interstitial space of the lung parenchyma, either by the mechanism of Starling forces, or by changes in the permeability of the capillary wall.

Lung-Kidney Axis

The central position, as well as the extensive pulmonary capillary network that receives the entire cardiac output, allows the lung to interact with other organs. Thus, mediators released from a damaged lung can remotely affect the kidney (lung-kidney interaction) and conversely, the lung is exposed and responds to mediators released from other organs such as the kidney (kidney-lung interaction). In critically ill patients, lung-kidney communication is reciprocal and simultaneously.

From applied physiology, Oxygen delivery (DO_2) at the tissue level is defined as:

$DO_2 = CO \times CaO_2$

Where DO_2 corresponds to the oxygen-carrying capacity, CO is cardiac output and CaO_2 is the oxygen content in arterial blood. Oxygen delivery is directly proportional to cardiac output (cardiac function) and arterial oxygen content (lung function). It seems that the kidney is not involved in this equation; however, this organ is central to the delivery of oxygen to the tissues and does so through the control of fluid balance (cardiac preload, according to Starling's law), the regulation of vascular tone in response to variable flow demands (hormonal regulation through the renin-angiotensin system (RAS), afterload, (ejection volume), hydro-electrolyte and acid-base balance (regulation of oxygen consumption at the tissue level, deviation from the curve of hemoglobin dissociation, vascular resistance, and enzyme function) and erythropoietin production (hemoglobin concentration, directly related to oxygen-carrying capacity).

Lung-kidney interaction in mechanical ventilation:

The influence of mechanical ventilation on kidney function can be divided into three types:

1. Hemodynamic changes (cardiopulmonary interactions)
2. Alterations in gas exchange (PaO_2 and $PaCO_2$)
3. Biotrauma

Regardless of the main mechanism proposed, alterations in the inflammatory response, oxidative stress and cell necrosis/apoptosis are important components of this intercommunication.

1. Hemodynamic changes (cardiopulmonary interactions): In 1947, the effect of the use of positive pressure ventilation on renal perfusion and function in healthy individuals was demonstrated for the

first time. From a hemodynamic point of view, the use of mechanical ventilation with positive pressure can cause a decrease in venous return, which can cause a drop in cardiac output, causing arterial hypotension. It also determines an increase in right ventricular afterload related to the increase in intrapulmonary pressures, this being independent of the effect on venous return. Likewise, the increase in intrathoracic pressure causes a drop in renal plasma flow, glomerular filtration rate and urinary output, with redistribution of intrarenal blood flow.

Moore and colleagues described for the first time that after six hours of mechanical ventilation use, the distribution of intrarenal blood flow is reversed, with the flow of the inner renal cortex being greater than that of the outer cortex as a result of the release of vasoactive agents.

The interaction between positive pressure mechanical ventilation and renal function was subsequently examined extensively with the use of positive end expiratory pressure (PEEP). In a canine model, the use of 10 cmH_2O of PEEP caused a drop in urinary flow, sodium excretion, and creatinine clearance in response to the decrease in cardiac output and intrathoracic blood volume, with a redistribution of intrarenal blood flow, with maintenance of total blood flow.

2. Alteration in gas exchange: under normal conditions, the combination of a high oxygen consumption by the renal concentrator system (especially Henle's loop and proximal tubule) and the relatively low total renal blood flow, which could also be reversed in hypovolemic patients, in shock of various causes or with mechanical ventilatory support with positive pressure, it causes areas susceptible to hypoxic damage. In addition, in critically ill patients, the development of severe hypoxemia alone causes an increase in renal vascular resistance and a consequent decrease in blood flow to that organ. In experimental animal models, the activation of vasoactive factors such as Angiotensin II and Endothelin have been demonstrated. On the other hand, endogenous Nitric Oxide (NO) plays a significant role in the maintenance of baseline renal hemodynamics.

The level of carbon dioxide also affects the regulation of renal vascular tone, such that hypercapnia is inversely correlated with renal blood flow. There is a first direct mechanism through the release of norepinephrine which is a powerful vasoconstrictor. The other indirect mechanism occurs by the activation of the Renin-Angiotensin-Aldosterone axis in response to the drop in renal blood flow, caused by systemic vasodilation due to elevated CO_2 levels. These changes observed with hypercapnia are independent of changes in blood oxygen pressure.

3. Biotrauma: There is a close relationship between mechanical ventilation and the development of renal dysfunction, which can be caused by the underlying disease or as a consequence of the therapy used (e.g., vasopressors, nephrotoxic drugs, etc.). Today it is known that mechanical ventilation per se can be a direct cause of kidney damage, an entity that is increasingly being paid attention to and has been recognized as Ventilator Induced Kidney Injury (VIKI).

In patients with ARDS, the use of non-protective mechanical ventilation results in local and systemic release of proinflammatory mediators (IL-1, IL-6, IL-8, TNF). This is associated with alteration of renal vascular tone mediated by the release of NO, and loss of viability of epithelial renal cells through the release of pro-apoptotic agents such as Caspase-3, among others. In these patients, there is also an increase in the renal expression of Endothelin-144 and Endothelial Nitric Oxide Synthetase, which are responsible for microvascular leakage in the renal parenchyma.

Experimental models in rats showed that plasma from animals ventilated in this deleterious manner caused renal tubular apoptosis in healthy animals to a greater extent than plasma from animals ventilated under a protective modality. In rabbits subjected to non-protective ventilation, the presence of renal tubular apoptosis and biochemical markers of renal dysfunction was demonstrated, supporting the causal association between mechanical ventilation and the development of remote renal damage.

4. Neurohumoral mechanisms: The aforementioned mechanisms only partially explain the effects of mechanical ventilation on the development of oliguria and renal dysfunction. Stimulation of sympathetic and hormonal pathways also play a significant role in the pathophysiology of Mechanical Ventilation-Induced Kidney Injury.

The use of mechanical ventilation has effects on the sympathetic system, Renin-Angiotensin axis, non-osmotic vasopressin release (ADH), and Atrial Natriuretic Peptide (ANP) production. Activation of these neurohormonal pathways will result in the development of oliguria.

Mechanical ventilation causes an increase in sympathetic tone, which secondarily activates the RAS, with the consequent drop in renal blood flow, glomerular filtration and finally the appearance of oliguria. The increase in ADH release is multifactorial in nature and evidence suggests that it is due, in part, to less atrial transmural stretching and pressure, due to the absolute or relative depletion of the intravascular component, associated with the use of mechanical ventilation. This is confirmed by the rapid restoration of diuresis and natriuresis upon withdrawal of mechanical ventilation.

However, increased urinary osmolarity is not frequently found in ventilated patients, which indicates that increased ADH secretion is not the main mechanism responsible for the decrease in urine output.

The other mechanism involves the suppression of the release of the ANP. It has been demonstrated in animal experimental models that there is a decrease in plasma levels of ANP with the initiation of mechanical ventilation.

Kidney-lung interaction

The concept of uremic lung was described by Lange more than a century ago and his radiological findings were reported three decades later. The alveolar epithelium shares characteristics with the renal tubular epithelium, specifically in terms of its polarization (apical-basolateral), location of water channels, ion transporters and the existence of adhesion between epithelial cells through the tight junction complex.

Traditionally, fluid overload caused by acute kidney injury (AKI) is considered to be the cause of pulmonary involvement, obviously, excess fluids cause an increase in the hydrostatic pressure of the pulmonary capillary (cardiogenic edema) and alteration of gas exchange. However, AKI also directly causes lung inflammation and alterations in the epithelial transporters of sodium and water.

Acute kidney injury is associated with epithelial damage and pulmonary edema mediated by macrophage-derived products, which peak in potency at 48 hours. The Na+ channels and Na(+)-K(+)-Adenosine triphosphatase, components of the active Na+ absorption transport system, are very important in opposing fluid accumulation in the lungs and operate as an anti-edema safety factor. In the event of ischemia-reperfusion phenomena, a negative regulation of the Na+, Na(+)-K(+)ATPase and Aquaporin-5 channels occurs due to perpetuation of the endothelial lesion (post-reperfusion lesion), which finally results in a lower clearance of the alveolar fluid and pulmonary edema. It is by this same mechanism that an increase in pulmonary edema occurs through the administration of Amyloride (Na channel blocker) or Ouabain (Na(+)-K(+)-ATPase blocker. If endothelial damage associated with ischemia-reperfusion persists, the transport processes, even if operational, are insufficient to prevent the continuous accumulation of alveolar fluid and the formation of pulmonary edema.

Ischemic AKI causes inflammatory changes in the lung, with activation of transcription factors such as Nuclear Factor kappa-Beta (NF-κB). In experimental studies of ischemic AKI, an increase in the levels of circulating cytokines (TNF, IL-1, IL-6), chemokines and activated leukocytes has been observed, the latter being the ones that infiltrate, among other organs, the lung parenchyma. A significant increase in

pulmonary extravascular water was evidenced in a pediatric animal model of renal ischemia-reperfusion, with an early onset. The protective effect of the anti-inflammatory cytokine Melanocyte-Stimulating Hormone (MSH) has been demonstrated in mice in AKI induced respiratory failure, which decreases the levels of inflammatory cytokines, NO production and expression of neutrophil adhesion molecules.

Finally, both bilateral renal ischemia and nephrectomy have been shown to alter gene expression of the Angiotensin-Converting Enzyme gene at the pulmonary level (54).

In summary, the combination of effects of ischemic AKI results in an edematous, inflamed lung with a variable predisposition to face a potential second injury.

Mechanical ventilation in patients with ARDS through the use of a pulmonary protective strategy should maintain adequate gas exchange in addition to avoiding a decrease in renal blood flow and reducing the increase in inflammatory and pro-apoptotic mediators. This conceptual model may give rise to new therapeutic strategies to be considered in patients with Multiple Organ Dysfunction Syndrome (DOMS).

Lung-Gastrointestinal Axis

The microorganisms that inhabit both the intestine and the lung live mutualistically with the host, benefiting from a stable microenvironment rich in nutrients. There is growing evidence explaining the critical role of microbiomes in maintaining immune system homeostasis. In the gut microbiota, Bacteroidetes and Firmicutes predominate (Tables 2 and 3), while in the lungs, Bacteroidetes, Firmicutes and Proteobacteria predominate (Table 4). However, in terms of species level, they are significantly different. The largest and most diverse community of the mammalian microbiome counts about 1014 bacteria and is found in the intestinal tract. Emerging evidence has revealed that dysbiosis of the gut microbiota is associated with several local and distant chronic diseases. A balanced microbial community in the gut is of great importance for immune, lung, and overall health.

Table 2: General characteristics of the microbiota of the small and large intestine in healthy adult subjects

Small Intestine	Large Intestine
Low microbial density	High microbial density
Low population density	High population density
Aerotolerant microorganisms abound	Anaerobic microorganisms abound
Predominance of lactobacilli/ **Rare bifidobacteria**	Few lactobacilli/ Abundant bifidobacteria
Increased immune function/ **Reduced metabolic function**	Reduced immune function/ Increased metabolic function

Table 3: Gut microbiota in healthy adult subjects

Domain	Kingdom	Filo	Examples
Archaea	Archaea	Euryarchaeota	Methanogenic microorganisms
Bacteria	Bacteria	Proteobacteria	E. coli (gut), Helicoacter (stomach)
		Firmicutes	Lactobacillus, Staphilococcus, Streptococcus (small intestite), Faecalibacterium, Ruminococcus, Clostridium, Roseburia (large intestine)
		Bacteroidetes	Bacteroides, Prevotella
		Actinobacteria	Bifidobacterium
		Verrucomicrobia	Akkermansia
Eukaryota	Protista	Amoebozoa	Amoebas
	Fungi	Ascomycota	Candida

Table 4: Location and composition of the respiratory system microbiota in healthy adult subjects

Localization	Strain
Anterior nostrils	Staphilococcus ssp.
	Propionibacterium spp.
	Corynebacterium spp.
	Moraxella spp.
	Streptococcus spp.
Nasopharynx	Moraxellaspp.
	Staphilococcus spp.
	Corynebacterium spp.
	Dolosigranulum spp.
	Haemophilus spp.
	Streptococcus spp.
Oropharynx	Streptococcus spp.
	Neisseria spp.
	Rothia spp.
	Veillonella spp.
	Prevotella spp.
	Leptotrichia spp.
Lungs	Prevotella spp.
	Veillonella spp.
	Streptococcus spp.
	Trophermyma Whipplei

The gut microbiota affects lung immunity through a vital crosstalk known as the gut-lung axis (Figure 2). This axis allows the passage of endotoxins, microbial metabolites, cytokines, and hormones into the bloodstream, connecting the intestinal niche to the pulmonary niche. The gut-lung axis is bidirectional. When inflammation occurs in the lung, the lung-gut axis can induce changes in the gut microbiota and vice versa.

During non-protective mechanical ventilation, a series of proinflammatory cytokines are released that cause epithelial apoptosis in the intestine, an expression of crosstalk between distant organs (crosstalk).

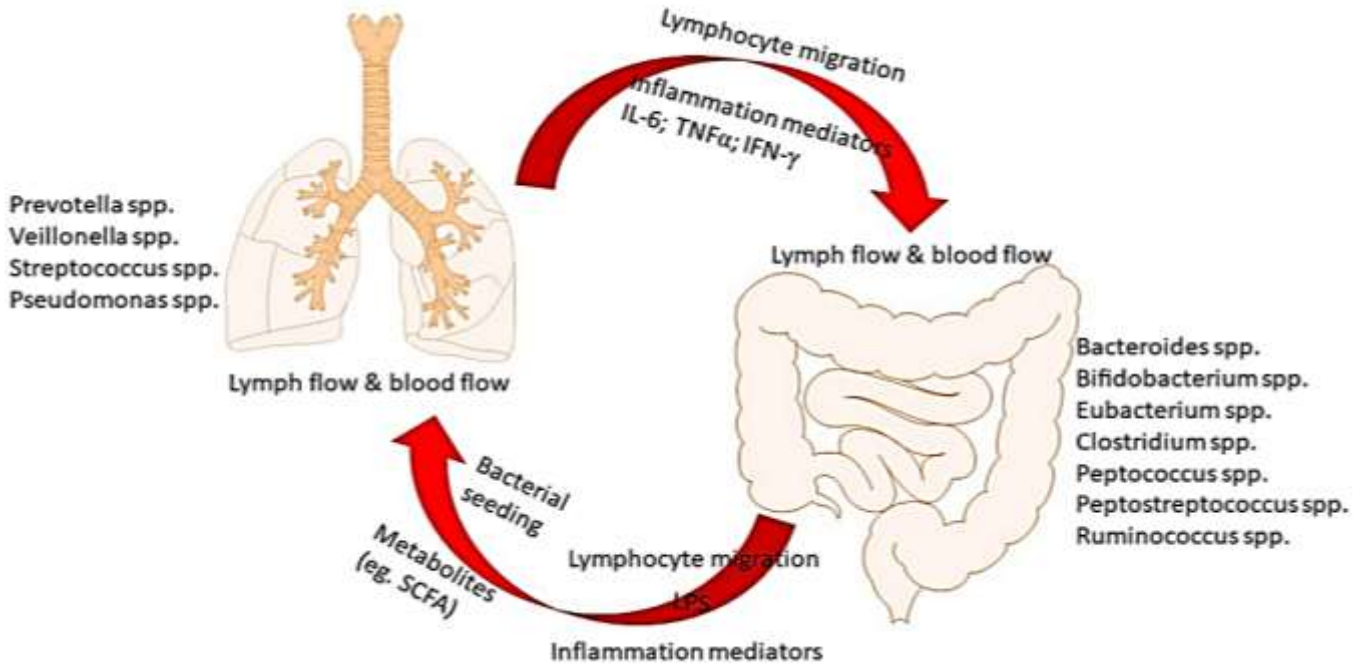

Figure 2: Schematic representation of the lung and gut microbiota, as well as their complex interactions that are bidirectional and simultaneous.

Role of the gut-lung axis in the pathogenesis of lung diseases:

A growing number of studies indicate that alterations in gut microbial species and their metabolites have been linked to changes in immune responses and inflammation, as well as to the development of various acute and chronic pulmonary pathologies.

The risk of developing allergic respiratory tract disease is increased due to antibiotic-induced changes in the gut microbiota in the first years of life, which facilitates our understanding of the links between exposure to the gut microbiota and respiratory tract allergy. On the other hand, intestinal alterations are also common in individuals with lung diseases such as allergies, asthma, chronic obstructive pulmonary disease, cystic fibrosis and lung cancer.

The mechanisms by which the gut microbiota influences immune responses and inflammation in the lungs, and vice versa, are being studied extensively. The involvement of subsets of regulatory T cells and Toll-like receptors (TLRs), cytokines and mediators of inflammation, surfactant protein D, and several other factors have been proposed as some of the underlying mechanisms, but many details are still unknown. Inflammatory processes spread from the lungs to other organs through cytokines and activated immune cells. Similarly, Para-Aminobenzoic Acid (PABA) or short-chain fatty acids (SCFAs) produced

by the gut microbiota, or the cytokines themselves, can reach the lung and regulate some of its functions. It is well documented that exposure to carbon and ozone, or viral infections that lead to lung inflammation, can influence the composition of the gut microbiome through oxidative stress, resulting in increased SCFAs production by gut microbes. Consequently, the existence of a possible mediation in the lung by the intestine during inflammation can be considered.

On this pathophysiological basis, new therapeutic strategies have been tried aimed at manipulating the intestinal microbiome through antibiotics, probiotics, prebiotics, natural products or diets in various lung diseases through clinical and laboratory studies.

Lungs and intestine, in addition, are organs that are in continuous contact and exchange with the external environment, and both have innated and adaptive immune systems. Human lungs comprise 38% immune cells, including B cells (0.8%), Plasma cells (0.3%), T-CD4 (3.6%), T-CD8 (5.0%), NK (2.9%), Dendritic cells (0.1 to 1.6%), alveolar Macrophages (11.7%), Monocytes (1.5 to 4.8%), and Mast cells (1.1%). Similarly, the adult human intestine contains B cells (9.0%), T-CD4 (2.9%), T-CD8 (2.3%), NK (0.5%), Dendritic cells (0.7%), Macrophages (1.6%), Monocytes (0.3%) and Mast cells (0.1%).

Comparatively, the lungs have a higher proportion of T-CD8 lymphocytes than the intestine and a lower proportion of B lymphocytes, and a larger population of Myeloid cells. Despite these differences, both organs have similar immunological functions and share mucosal-associated immune systems that can develop tertiary lymphoid organs in response to chronic inflammation, such as Peyer's patches in the intestine and lymphoid tissues associated with the bronchi. Immunoglobulin is produced in the lung and intestine via B cells, and they harbor memory B cells, which are advantageous for long-term protection and rapid responses to antigens that are already familiar.

In the context of certain inflammatory lung conditions, dysbiosis of the lung microbiota occurs. This finding has been of particular importance in lung cancer, where specific microbiomes have been proposed as biomarkers to predict metastasis. The oropharyngeal, pulmonary, and gut microbiome can spread to other organs, and metabolites from it, along with activated immune cells and secreted cytokines, can affect other systems.

Bronchial Asthma and Gut Microbiome

Asthma is a very common chronic respiratory disease, affecting people of all ages, but usually begins in childhood and has multiple phenotypes with different pathophysiological and clinical features. Since the involvement of immunity in the pathogenesis of asthma was recognized, as well as the involvement of regulatory T cell subsets, the hypothesis of a link between gut microbes and allergy was hypothesized.

In one study, bacterial DNA isolated from the stool samples of 92 children diagnosed with asthma and 88 healthy children were detected. Akkermansia Muciniphila and Faecalibacterium Prausnitzii were found to be decreased in the asthma group compared to the healthy group. Both bacterial species can suppress inflammation through modulation of secreted metabolites, such as increased IL-10 and decreased IL-12. Levels of inflammatory factors, such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) in the peripheral serum of children with asthma, were significantly higher than those of controls. In particular, CRP was positively correlated with total bacterial load, indicating that with increased levels of inflammatory factors in peripheral serum, the likelihood of gut dysbiosis and gastrointestinal symptoms will increase in children with asthma.

In adults with diagnosed asthma, there are significant relationships between the composition of the gut microbiota, sensitization to aeroallergens, and lung function in asthmatics. The reduction in total fatty acid content and absolute concentrations of specific short-chain acids (acetate, butyrate, and propionate), as well as the isoacid content in the feces of these patients compared to normal controls is remarkable.

Microbes, bile salts, and other immune stimuli in the digestive tract may play a vital role in mucosal immunity in the respiratory system. The epithelium controls local respiratory immune activities that are also mediated by thymic stromal lymphopoietin, IL-25 and IL-33, thus facilitating the development of asthma. The gut microbiome contributes to the generation of regulatory T cells, making the lung more susceptible to oral allergens. Peripherally generated regulatory T cells, known as induced T-regulatory cells (iT-regs), are predominantly stimulated in the mesenteric lamina propria, Peyer's patches, and lymph nodes in the small and large intestine. There is growing evidence to suggest that the gut microbiome plays an important role in coordinating the innate and adaptive immunity involved in the development of asthma.

Chronic Obstructive Pulmonary Disease and Lung-Liver-Intestine Axis

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease that causes chronic obstruction to airflow as a result of prolonged exposure to pollutants, primarily tobacco. The gut-liver-lung axis plays a vital role in the pathogenesis of COPD. The liver is a key organ for orchestrating innate immunity in the gut and lung, through the generation of inflammatory cytokines and mediators.

Elevated systemic inflammatory mediators due to the overactive innate immune response, such as C-reactive protein (CRP) and IL-6, directly contribute to both morbidity and mortality in COPD. IL-6 activates the innate immune response to maintain systemic inflammation as part of the normal immune system in response to smoking or repeated exposure to bacterial invasion. In response to elevated serum IL-6, acute phase proteins such as CRP are generated in the liver. (Figure 3) A high-fiber diet was associated with a lower risk of COPD and improved lung function.

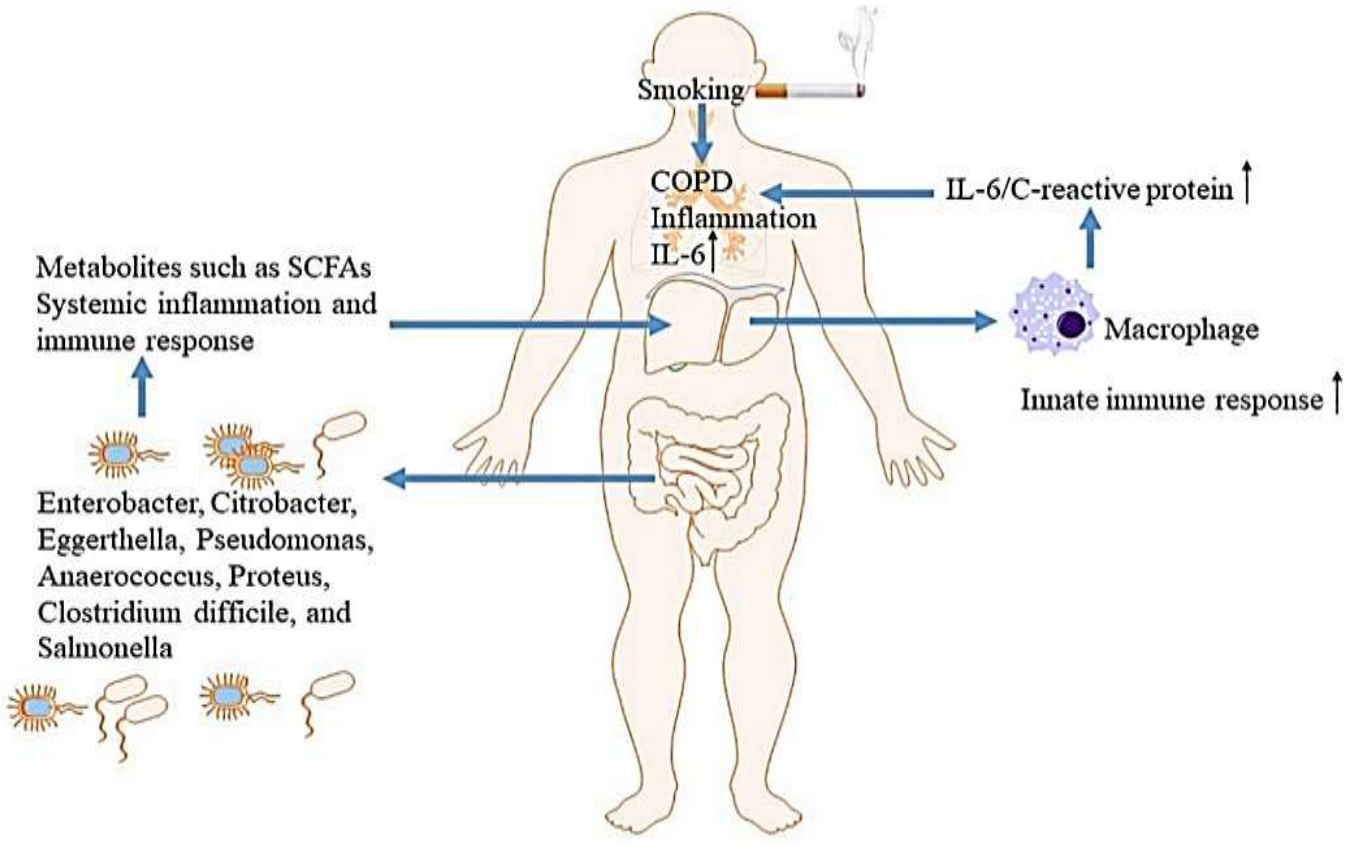

Figure 3: Schematic representation of the interaction between the components of the Lung-Liver-Gut axis in COPD

The gut microbiota of COPD patients is characterized by the presence of representatives of Proteobacteria, such as Enterobacter cloacae, Citrobacter, Eggerthella, Pseudomonas, Anaerococcus, Proteus, Clostridium difficile, and Salmonella. In a rat model with COPD generated by exposure to cigarette smoke for 6 months, structural and dysfunctional changes were observed in the intestinal mucosal barrier, associated with aggravation of intestinal and pulmonary inflammatory responses.

Lung cancer and gut microbiota

Lung cancer is one of the deadliest malignancies and with a dizzying increase in morbidity worldwide. Increased levels of Enterococcus spp. and decreased levels of Bifidobacterium spp. and Actinobacteria spp. are associated with lung cancer. In addition, the deterioration of the normal function of the gut microbiome has an impact on the rapid progression of lung cancer.

In one study, lower levels of Dialister, Enterobacter, Escherichia-Shigella, Fecalibacterium, and Kluyvera were found, but higher levels of Veillonella, Bacteroides, and Fusobacterium compared to those of controls.

In patients with lung cancer, after receiving treatment with anti-PD-1 antibodies (programmed cell death protein), a variation in the gut microbiota is observed that is directly correlated with the risk of developing chronic diarrhea. Phascolarctobacterium, Bacteroides and Parabacteroides were the microbes found in greater abundance, while Veillonella spp. is found in significantly lower density in those patients who do not present with diarrhea.

Regulatory function of the lung

Metabolic, Immunological, Endocrine

Pulmonary endothelium

The pulmonary endothelium is formed by a heterogeneous cellular monolayer that covers the luminal surface of the entire pulmonary vasculature. As such, this cell layer is located at a critical interface between the blood, airways, and lung parenchyma. Lung endothelial cells can produce and secrete mediators, display surface receptors, cell adhesion molecules, and metabolize circulating hormones to influence vasomotor tone, local and systemic inflammation, and coagulation functions. In this way, they actively intervene by producing vasodilation, platelet disaggregation and activating anti-inflammatory mechanisms. The endothelium also acts as a semipermeable selective barrier that regulates the exchange of gases, fluids, solutes, and cells between the plasma and the interstitial space.

The pulmonary endothelium, historically considered a passive barrier, is now recognized as a metabolically active tissue with multiple regulatory functions.

Regulatory function of the pulmonary endothelium

The pulmonary circulation receives the entire cardiac output, and subsequently 100% of this blood volume is poured into the peripheral circulation. With this we intend to highlight the fact that the metabolic transformations that will occur in the pulmonary circulation will reach the entire organism where their effects will take place. In addition, due to the pulmonary anatomy itself, the external environment comes into contact with the cells of the alveolar capillaries through the function of ventilation, making it possible for external factors to affect the internal biochemistry with pharmacodynamic consequences.

As a consequence of these metabolic processes in the lung, three possible outcomes can be obtained:

A) Activation

B) Inactivation

C) No change

A) Activation implies that the final metabolic product is more active than the substrate that enters the pulmonary circulation. In this case we have the conversion of Angiotensin I, an inactive decapeptide, into Angiotensin II, a highly active octapeptide, by the converting enzyme, which has its highest concentration in the lungs; so that up to 40% of Angiotensin I is converted to Angiotensin II in a single passage through the pulmonary circulation. The same converting enzyme is responsible for the disappearance of Kinins, with the same enzyme having as substrates the most potent endogenous vasoconstrictor (Angiotensin II) and a vasodilator (Bradikinin).

B) Inactivation is a completely opposite process to the previous one. A typical example is 5-HT (endogenous vasoactive autacoid and inhibitory neurotransmitter of the central nervous system) and Prostaglandins E2 and F2α, which undergo more than 90% inactivation during a single passage through the pulmonary circulation.

C) The No change demonstrates the selectivity of pulmonary metabolic function that can differentiate between PGE2 and PGI2, to inactivate the former and not alter the latter, or between Noradrenaline, Adrenaline and Dopamine, unlike other organs such as the liver where this differentiation does not occur (Table 5).

The lung as an endocrine organ

Due to its central location, the lung has the ability to release endogenous substances into the peripheral circulation, behaving like an endocrine gland. (Table 5)

The release of Von Willebrand factor (VWF) and cell-activating plasminogen from the pulmonary endothelium are examples of this function. In pathological situations, the release of Eicosanoids and Histamine from the lung during an immunological attack, or endotoxins in a state of acute injury, can aggravate a pre-existing cardiovascular collapse situation.

Among the pulmonary vasoactive hormones, we have Platelet Activating Factor (PAF), Endothelial Relaxing Factor (also identified as Nitric Oxide NO), and Endothelin. PAF, released mainly by platelets and leukocytes, has an important pro-inflammatory activity unrelated to lipid mediators derived from arachidonic acid. PAF synthesis may be inhibited with steroid use.

NO is produced directly by endothelial cells. It has been shown to be a potent vasodilator of the pulmonary circulation.

Endothelins are a family of 21 amino peptides that act in the regulation of vasomotor tone, cell proliferation and hormone production. Endothelin undergoes an extensive elimination of more than 50% in a single passage through the pulmonary circulation.

Table 5: Metabolic transformations that occur in the pulmonary circulation by means of activation, inactivation or uptake and non-change reactions. List of endogenous substances produced in the lung

Substrate	Inactivation	No change	Activation	New synthesis
Biogenic Amines	Serotonin	Adrenaline		
	noradrenaline	Isoproterenol		
	Dopamine	Histamine		
	Tyramine			
Peptides and Proteins	Endothelin-1	Angiotensin II	Angiotensin I	Atrial natriuretic peptide (in congestive heart failure) Hepatocyte growth factor
	Bradykinin	Oxytocin	Endothelin	
	Encephalin	Vasopressin	Protein S	
	Atrial natriuretic peptide	Vasoactive Intestinal Peptide	Tissue Plasminogen Activator	
	Substance P			
Eicosanoids and Lípids	Arachidonic acid	Prostaglandin I2 (prostacyclin)	Arachidonic acid	Prostaglandin I2
	Leukotrienes C4 and D4	Prostaglandin A2		Prostaglandin E2 (release)
	Prostaglandins D2	Thromboxane A2		Prostaglandin F2α
	Prostaglandins E1 and E2			Leukotrienes (release)
	Prostaglandin F2α			Surfactant
Adenine derivatives	Adenosine			
	AMP/ADP/ATP			
Steroids	Progesterone		Cortisone	
	beclomethasone			
Xenobiotic compounds	Fentanyl	Morphine	Lidocaine	
	Alfentanil	Isoproterenol		
	Meperidine			
Others			Nitric oxide	

Interaction between Lungs and Endocrine system

This crosstalk between systems is possible because endocrine organs express cytokine receptors and immune system cells express hormone receptors. Cytokines induce alterations in hormone production, by directly affecting the function of endocrine organs, such as IL-1, IL-6 and TNF-α. These cytokines directly increase the activity of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes and reduce that of the hypothalamic-pituitary-gonadal axis, or act indirectly by promoting cellular destruction of endocrine cells, as in the pancreatic dysfunction of type 2 diabetes mellitus.

Corticotropin-releasing hormone (CRH)

CRH is produced primarily by the hypothalamus, but it can also be expressed at peripheral sites where it acts as an autocrine or paracrine inflammatory modulator. CRH binds with a high affinity to the CRH 1 receptor (CRHR1) and CRH-like peptides (CRHR2).

CRHR2 is the main receptor that is expressed in human lungs. CRHR1 mRNA increases and CRHR2 mRNA decreases in dendritic cells, while CRHR2 increases in macrophages in response to stress. CRHR2 mRNA is preferentially expressed in neutrophils in the lungs. Differential expressions of CRHR1 and CRHR2 in phagocytic cells in the lungs could affect the cells' innate function, potentially leading to altered adaptive immune responses.

Among the pulmonary effects of CRHR2 we find the reduction of the pulmonary inflammatory response, the recruitment of neutrophils and monocytes to the lung, bronchodilation and the limitation of lung inflammation induced by lipopolysaccharides (LPS).

Adrenocorticotropic hormone (ACTH)

ACTH is a pituitary hormone that sends signals through melanocortin receptors (MCRs), of which there are five. Among these receptors, MC1R and MC5R are expressed in lung tissues. MC1R, MC3R, and MC5R are expressed in macrophages and lymphocytes, while MC2R and MC4R are expressed in lymphocytes (The cleavage of the first 13 amino acids of ACTH produces melanocyte-stimulating hormone alpha (a-MSH). In experimental models, intraperitoneal a-MSH reduced inflammation of the peribronchial airways, altering leukocyte populations in bronchoalveolar lavage fluid (BAL), and reduced IL-4 and IL-13 levels, effects that depend on IL-10 signaling.

In experimental models with mice with acute lung injury, mice treated with a-MSH showed reduced edema; gene expression of IL-6, TNF-α, and TGF-b, and infiltration of leukocytes into the lung. Therefore, stimulation of RCM in the lung may provide a novel therapeutic target for its anti-inflammatory properties.

Growth Hormone-Releasing Hormone (GHRH) and Growth Hormone (GH)

GHRH is predominantly secreted by the hypothalamus and stimulates GH secretion by the pituitary gland. The lungs also produce GHRH locally and express the GHRH receptor (GHRHR). In normal mouse lung tissue, type 2 cells, fibroblasts, lymphocytes, and dendritic cells express GHRH. GHRH is involved in pulmonary homeostasis, inflammation, and fibrosis. GHRHR antagonists have anti-inflammatory, pro-apoptotic, antioxidant, and antifibrotic effects on the lung. The ability of GHRHR signaling to modulate pulmonary immune responses may be a starting point for new therapeutic strategies.

Adrenal hormones (Glucocorticoids and Mineralocorticoids)

Cortisol is a well-known immune modulator, and synthetic glucocorticoids have been used clinically to manage inflammatory conditions, such as asthma, for decades. High doses of glucocorticoids reduce the number of macrophages in the respiratory tract and impair the functional activity of resident pulmonary macrophages. They are produced in T cells and macrophages in the lung upon stimulation by inflammatory mediators, including TNF-α, LPS, and anti-CD3, acting as an immunoregulatory mechanism to limit uncontrolled inflammatory responses in the lung. Long-term treatment (> 1 year) with inhaled corticosteroids involves an increased risk of developing pneumonia and is associated with the risk of mycobacterial diseases, such as tuberculosis.

Androgens

Dehydroepiandrosterone (DHEA) is produced from cholesterol in the reticular area of the adrenal glands following stimulation of ACTH, and in the gonads following stimulation of Luteinizing hormone (LH) and Follicle-Stimulating hormone (FSH). Treatment with DHEA is associated with a reduction in pulmonary hypertension through the upregulation of soluble guanylate cyclase and by inhibition of the activation of the src/STAT3 pathway, which is key in cytokine-induced cell activation and proliferation. In general, DHEA counteracts the effect of cortisol, and more specifically in alveolar macrophages, it restores the expression of the receptor for activated C kinase (RACK-1) and

the production of TNF-α and IL-8 induced by LPS that is reduced due to aging. Intratracheal administration of 16a-bromoepiandrosterone (BEA; a synthetic sterol related to DHEA) reduces bacterial load and inflammation in the lungs.

Gonadal hormones

Testosterone

Testosterone decreases the release of pro-inflammatory cytokines from monocytes and macrophages and increases the accumulation of cholesterol esters in macrophages derived from human monocytes.

Estrogen

Estrogens comprise three main forms, Estrone, Estradiol, and Estriol. A study investigated the effect of 17-bestradiol (E2) on trauma-hemorrhage-induced lung injury in rats. E2 administration induced increased expression and phosphorylation of endothelial nitric oxide synthase (eNOS), activation of protein kinase G-1, and expression of VASP, resulting in a reduction in lung injury.

Glucagon-Like-1 Peptide (GLP-1)

The GLP-1 receptor (GLP-1R) is expressed in human lungs at a higher level than in other tissues. Numerous studies, reviewed by Lee and Jun, describe the anti-inflammatory effects of GLP-1 and the potential of GLP-1-based therapies. GLP-1R can reduce inflammation by mediating the recruitment and activation of immune cells in the lung, although it has not been shown to be crucial for a balance between pro-inflammatory and anti-inflammatory responses.

Pancreatic hormones

Insulin: The insulin receptor (IR) is expressed to varying degrees in various tissues, including the lungs. In the lungs, IR gene expression predominates in endothelial cells, hair cells, and type 1 and type 2 alveolar cells. During allergic lung inflammation, insulin secretion and IR expression are increased in infiltrating inflammatory cells, predominantly monocytes and macrophages. Insulin treatment improves poor immune cell migration in diabetes, it may also involve pro-inflammatory effects due to leukocyte recruitment.

The response of lung tissue to insulin is still unclear, although some studies indicate anti-inflammatory changes in gene and cytokine expression in insulin-treated alveolar macrophages. Other research suggests that insulin treatment promotes the migration of white blood cells to the lung.

Glucagon

Reports on glucagon receptor (GCGR) expression and function in the lung are scarce. While two studies suggest little or no expression of GCGR in the lungs, administration of nebulized glucagon to the lung improves forced expiratory volume by 22% in asthmatic patients with methacholine-induced bronchospasm. This indicates the responsiveness of pulmonary smooth muscle to glucagon by inducing the activity of cAMP response element binding protein (CREB), eNOS, and cyclooxygenase 1 (COX-1), and the subsequent release of second messengers such as Nitric Oxide and Prostaglandin E2 (109). Glucagon treatment prevents airway hyperresponsiveness and eosinophilia, and reduces levels of IL-4, IL-5, IL-13, TNF-a, CCL11, and CCL24 in hyperreactive lung tissue.

Conclusion

1. The central anatomical position of the lungs, together with their particular characteristic of receiving the entire cardiac output and that all the blood that passes through the pulmonary circulation is subsequently taken to the systemic circulation, means that these organs remain in close relationship with the rest of the organs and systems through cross-communication. bidirectional and often simultaneous.

2. The lungs are in continuous contact with the outside environment through ventilation, which contributes to the regulation of the local and distant immune response.

3. The lung-brain axis plays vital roles in both directions, from the regulation of ventilation and pH, to the expression of acute neurological disorders and neurodegenerative diseases in response to acute or chronic pulmonary inflammatory processes.

4. The anatomical proximity of these organs allows cytokines derived from the lung to reach the brain, altering its homeostasis.

5. Lung-kidney communication is established through an extensive capillary network.

6. Proper renal function is central to the delivery of oxygen to tissues and does so through the control of fluid balance, the regulation of vascular tone in response to variable flow demands, hydroelectrolyte and acid-base balance, and erythropoietin production.

7. In critically ill patients undergoing mechanical ventilation, the development of Mechanical Ventilation-Induced Kidney Injury (VIKI) has been described, which is explained through three main pathophysiological mechanisms (hemodynamic changes (cardiopulmonary interactions), alterations in gas exchange (PaO_2 and $PaCO_2$) and Biotrauma.

8. Stimulation of sympathetic and hormonal pathways also play a significant role in the pathophysiology of Ventilator-Induced Kidney Injury.

9. Acute kidney injury is associated with epithelial damage and pulmonary edema since excess fluids cause an increase in the hydrostatic pressure of the pulmonary capillary (cardiogenic edema) and alteration of gas exchange.

10. In processes of ischemia reperfusion there is a perpetuation of endothelial injury with alteration of the transport processes due to negative regulation of the Na+ channels, of Na(+)-K(+)ATPase, worsening pulmonary edema.

11. The combination of effects of ischemic AKI results in an edematous, inflamed lung with a variable predisposition to face a potential second injury.

12. The gut microbiota affects lung immunity through vital crosstalk known as the gut-lung axis through the passage of endotoxins, microbial metabolites, cytokines, and hormones into the bloodstream, connecting the intestinal niche to the pulmonary niche.

13. When inflammation occurs in the lung, the lung-gut axis can induce changes in the gut microbiota.

14. Alterations in intestinal microbial species and their metabolites have been related to changes in immune responses and inflammation, as well as to the development of various acute and chronic lung pathologies such as bronchial asthma, COPD and lung cancer.

15. The intestine undergoes epithelial apoptosis mediated by the release of pro-inflammatory cytokines from the lung during non-protective mechanical ventilation.

16. The pulmonary endothelium is a metabolically active tissue with multiple regulatory functions that exert through processes of activation (final metabolic product is more active than the substrate), inactivation (the end product is metabolically inactive) and non-change (expression of the selectivity of pulmonary metabolic function so as not to alter some specific metabolites).

17. The lung has the ability to release endogenous substances (Platelet Activating Factor (PAF), Endothelial Relaxing Factor (also known as Nitric Oxide NO), and Endothelin) into the peripheral circulation, behaving like an endocrine gland.

18. Communication between the lung and the endocrine system is possible since the endocrine organs express cytokine receptors and the cells of the immune system express hormone receptors.

19. Hormones with a demonstrated effect on lung metabolic and immune function are CRH, ACTH, a-MSH, GH, GHRH, adrenal hormones (Glucocorticoids and Mineralocorticoids), DHEA, Testosterone, Estradiol, GLP-1, Insulin, Glucagon.

20. The lung microbiome is made up of 10^{11} microorganisms, their metabolites, and genetic material, and fulfills regulatory and anti-inflammatory functions both in the lung and in distant organs.

21. There is an interrelationship between the lung and intestinal microbiota that has been demonstrated in recent years, with important cross-effects between them and towards the brain.

22. The complex interrelationship between the lung and the different organs and systems may form the basis for novel therapeutic strategies and differentiated approaches when addressing mechanical ventilation in critically ill patients.

23. The lung is a complex organ, which is not only involved in the function of ventilation as had been ruled a few years ago. The full extent of its influence on the normal functioning of the organism, and its role in the various pathological processes of the different systems is still to be elucidated.

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