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THE PATHOPHYSIOLOGICAL ROLE AND THERAPEUTIC SIGNIFICANCE OF ENDOTHELIN-1 IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT
Endothelin-1 (ET-1), a potent vasoconstrictor peptide composed of 21 amino acids and primarily synthesized by vascular endothelial cells, is regarded as a key biological mediator in the pathogenesis of respiratory diseases. Recent studies indicate that ET-1 is actively involved not only in the regulation of vascular tone but also in inflammatory processes, oxidative stress, cell proliferation, and the development of fibrosis. Elevated levels of ET-1 have been detected in pathologies such as chronic obstructive pulmonary disease, bronchial asthma, pulmonary arterial hypertension, and acute respiratory distress syndrome. This increase has been proven to be directly correlated with disease severity, the degree of hypoxemia, and systemic inflammation markers. By interacting with interleukin-6, tumor necrosis factor-alpha, transforming growth factor-beta, and other cytokines, ET-1 activates the inflammatory cascade, intensifies structural changes in lung tissue, and induces vasoconstriction and remodeling in the pulmonary vessels. Furthermore, signaling pathways mediated through endothelin receptors (ETA and ETB) play a crucial role in pulmonary vascular hypertrophy and smooth muscle cell proliferation. Consequently, the endothelin system is considered a promising therapeutic target for the treatment of respiratory diseases. This article analyzes current scientific data on the biological properties, molecular mechanisms, and pathophysiological role of Endothelin-1 in major respiratory diseases and highlights its clinical significance.
Keywords: Endothelin-1; COPD; pulmonary hypertension; inflammation markers; vascular remodeling; cytokines; molecular mechanisms.

INTRODUCTION

Respiratory diseases are distinguished by high morbidity and mortality rates worldwide, placing a significant economic and social burden on healthcare systems. Chronic inflammation, oxidative stress, endothelial dysfunction, and tissue remodeling play an important role in the pathogenesis of pathologies such as chronic obstructive pulmonary disease (COPD), bronchial asthma, pulmonary arterial hypertension, and acute respiratory distress syndrome (ARDS). In recent years, the activation of the vascular endothelium and the imbalance of biological mediators in these processes have become a focus of particular attention.

Among the biologically active substances synthesized by the endothelium, the endothelin system, particularly Endothelin-1 (ET-1), is of special significance. ET-1 is a potent vasoconstrictor peptide composed of 21 amino acids that participates in regulating vascular tone, cell proliferation, inflammation, and fibrosis. Under pathological conditions, the excessive production of ET-1 leads to pulmonary vascular constriction, hypertrophy of smooth muscle cells, and fibrotic changes in tissues.

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Scientific research indicates an increase in ET-1 levels in plasma and local lung tissues during respiratory diseases. This increase has been found to correlate with disease severity, the degree of hypoxemia, and inflammatory markers. Furthermore, ET-1 engages in complex molecular interactions with cytokines such as interleukin-6, tumor necrosis factor-alpha, and transforming growth factor-beta, which intensifies the inflammatory cascade and promotes structural remodeling processes in the pulmonary parenchyma and vessels. In this regard, the endothelin system is not only a significant scientific area for explaining the pathogenesis of respiratory diseases but also holds great promise in clinical practice as a diagnostic marker and therapeutic target.

The purpose of this article is to systematically analyze existing scientific data on the biological properties, molecular mechanisms, and pathophysiological role of Endothelin-1 in major respiratory diseases, and to elucidate its clinical significance.

Metabolism and Biological Effects of Endothelin-1

Endothelin-1 (ET-1) is a 21-amino acid, biologically active peptide belonging to the endothelin family, synthesized primarily by vascular endothelial cells. The endothelin system consists of three isoforms: ET-1, ET-2, and ET-3. Among these, ET-1 is considered to have the most significant biological importance in the respiratory and cardiovascular systems.

Synthesis and metabolism; The synthesis of ET-1 occurs in several stages. First, preproendothelin is synthesized in the cell, which is converted into proendothelin (Big endothelin-1) through proteolytic cleavage. In the next stage, the biologically active form, ET-1, is produced under the influence of the endothelin-converting enzyme (ECE). ET-1 synthesis is intensified by hypoxia, inflammatory cytokines (IL-6, TNF-α), angiotensin II, oxidative stress, and mechanical injury. Chronic hypoxia, particularly that observed in respiratory diseases, is one of the primary factors that increases ET-1 expression**.** ET-1 primarily exerts its effects through paracrine and autocrine mechanisms. Although its half-life is short, it demonstrates high biological activity in tissues.

Receptors and signaling pathways:

ET-1 exerts its effects through two main receptors: ETA receptors and ETB receptors.

ETA receptors are primarily located in smooth muscle cells and produce the following effects: potent vasoconstriction, cell proliferation, development of fibrosis, and vascular remodeling.

ETB receptors have two different functions: in endothelial cells, they cause vasodilation (through the release of NO and prostacyclin), while in smooth muscle cells, they cause vasoconstriction.

ETB receptors are also involved in the clearance of ET-1. When ET-1 receptors are activated, intracellular G-protein-coupled signaling pathways are initiated. This results in the activation of phospholipase C, the formation of IP3 and DAG, an increase in calcium ion concentration, and the activation of protein kinase C. These processes enhance smooth muscle contraction, cell proliferation, and the secretion of inflammatory mediators.

Biological Effects on the Respiratory System

- ET-1 in Lung Tissue:
- Increases bronchial smooth muscle tone
- Causes vasoconstriction in pulmonary vessels
- Exacerbates endothelial dysfunction
- Stimulates fibroblast activation

This leads to the narrowing of pulmonary vessels, thickening of the alveolar wall, and impaired gas exchange. Furthermore, the biological effects of ET-1 are mediated through G-protein-

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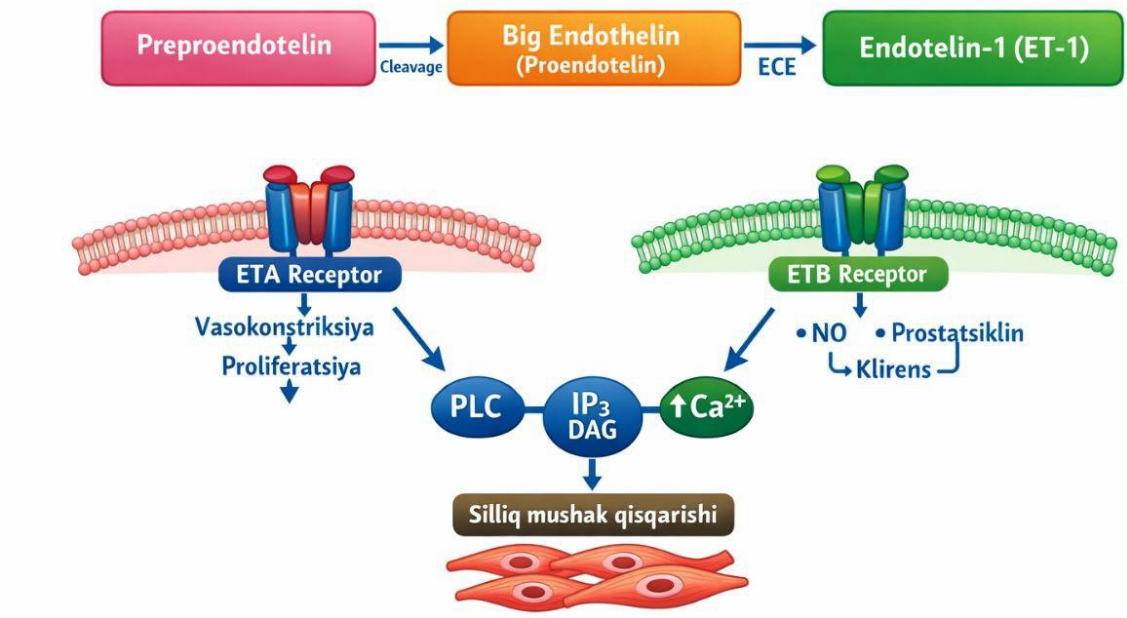
coupled receptors (GPCRs). The ETA and ETB receptors bind to Gq/11 proteins, activating phospholipase C-β (PLC-β), which results in the formation of inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 stimulates the release of Ca2+ from the sarcoplasmic reticulum, which in turn leads to the activation of calmodulin and myosin light-chain kinase (MLCK). This causes the contraction of smooth muscle cells.

Scheme 1: Mechanism of action of Endothelin-1



The Role of Endothelin-1 in Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a progressive pathology characterized by irreversible airflow limitation and develops on the basis of chronic inflammation. The pathogenesis of the disease involves thickening of the bronchial walls, alveolar destruction, loss of the lung parenchyma's elastic properties, and remodeling processes in the pulmonary vessels. In recent years, the endothelin system, specifically Endothelin-1 (ET-1), has been regarded as one of the key mediators in the pathogenesis of COPD.

Increased ET-1 levels and their clinical significance: Studies show that ET-1 levels in the plasma and bronchoalveolar fluid of patients with COPD are higher than in healthy individuals. ET-1 concentration correlates with disease severity (GOLD stages), a decrease in the FEV1

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index, and the degree of hypoxemia. Particularly under conditions of chronic hypoxia, EDN1 gene expression is enhanced via HIF-1α, leading to increased ET-1 production.
In severe forms of COPD, high levels of ET-1 may be associated with an increase in pulmonary arterial pressure and the development of pulmonary hypertension.

Remodeling in pulmonary vessels: In COPD, ET-1 stimulates vasoconstriction and proliferation in the smooth muscle cells of pulmonary vessels via ETA receptors. As a result, thickening of the vessel wall, hypertrophy of the medial layer, intimal fibrosis, and narrowing of the vessel lumen are observed. These changes increase resistance in the pulmonary circulation and create a basis for the development of pulmonary arterial hypertension. ET-1 also activates the Rho-kinase and MAPK signaling pathways, enhancing cell migration and proliferation.

Interaction with inflammation and oxidative stress: Chronic inflammation plays a central role in the pathogenesis of COPD. ET-1 interacts with interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β), thereby intensifying the inflammatory cascade. By activating the NF-κB signaling pathway, ET-1 increases the synthesis of pro-inflammatory mediators. Furthermore, ET-1 enhances the formation of reactive oxygen species (ROS), which deepens oxidative stress and further aggravates endothelial dysfunction. Endothelial dysfunction, in turn, is accompanied by a decrease in NO synthesis, disrupting the balance between vasoconstrictor and vasodilator factors.

Bronchial Obstruction and Structural Changes: ET-1 increases bronchial smooth muscle tone and exacerbates bronchoconstriction. Concurrently, activation of fibroblasts and increased collagen synthesis lead to bronchial wall thickening and the accumulation of extracellular matrix. These processes result in a worsening of airflow limitation in COPD.

Clinical and Therapeutic Perspectives

The role of ET-1 in the pathogenesis of COPD allows it to be considered a potential biomarker. Measuring ET-1 levels may have additional diagnostic value in assessing disease severity, determining prognosis, and predicting the risk of pulmonary hypertension. Furthermore, scientific research is underway on the potential therapeutic effect of endothelin receptor antagonists (e.g., selective ETA blockers) by reducing vasoconstriction in pulmonary vessels. However, further clinical trials are required to establish their efficacy and safety in COPD.

CONCLUSION

Endothelin-1 (ET-1) serves as a key molecular mediator in the pathogenesis of respiratory diseases, particularly chronic obstructive pulmonary disease (COPD). Its vasoconstrictive, pro-inflammatory, proliferative, and profibrotic properties play a leading role in the development of structural and functional changes in lung tissue. In COPD, elevated ET-1 levels are closely associated with chronic hypoxia, endothelial dysfunction, and systemic inflammation, and correlate with disease severity and changes in pulmonary hemodynamics. ET-1 signaling mechanisms, mediated through its ETA and ETB receptors, lead to smooth muscle cell proliferation, pulmonary vascular remodeling, and worsening bronchial obstruction. Furthermore, ET-1 interacts with inflammatory mediators and oxidative stress factors, thereby sustaining the pathological processes.

Existing scientific data indicate the need to consider the endothelin system as a diagnostic biomarker and therapeutic target. Determining ET-1 levels may have additional significance in assessing the severity of COPD and establishing a prognosis. However, large-scale clinical trials are required to evaluate the efficacy and safety of endothelin receptor antagonists in COPD. Thus, Endothelin-1 is a key component in the pathogenesis of COPD, and an in-depth

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study of its molecular mechanisms will enable the development of new therapeutic strategies and the enhancement of treatment based on an individualized approach.

References

1. Yanagisawa, M., Kurihara, H., Kimura, S., Tomobe, Y., Kobayashi, M., Mitsui, Y., Yazaki, Y., Goto, K., & Masaki, T. (1988). A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature, 332, 411–415.
2. Kedzierski, R. M., & Yanagisawa, M. (2001). Endothelin system: The double-edged sword in health and disease. Annual Review of Pharmacology and Toxicology, 41, 851–876.
3. Dhaun, N., Goddard, J., & Webb, D. J. (2008). The endothelin system and its antagonism in chronic lung disease. British Journal of Pharmacology, 153, 182–190.
4. Barnes, P. J. (2016). Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. Journal of Allergy and Clinical Immunology, 138 (1), 16–27.
5. MacNee, W. (2005). Pathogenesis of chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society, 2, 258–266.
6. Peinado, V. I., Barberà, J. A., Ramírez, J., Gomez, F. P., Roca, J., Jover, L., & Rodriguez-Roisin, R. (1998). Endothelial dysfunction in pulmonary arteries of patients with mild COPD. American Journal of Physiology, 274, L908–L913.
7. Wright, J. L., Levy, R. D., & Churg, A. (2005). Pulmonary hypertension in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine, 172, 189–195.
8. Giaid, A., Michel, R. P., Stewart, D. J., Sheppard, M., Corrin, B., & Hamid, Q. (1993). Expression of endothelin-1 in lungs of patients with pulmonary hypertension. New England Journal of Medicine, 328, 1732–1739.
9. Rubin, L. J., Badesch, D. B., Barst, R. J., Galie, N., Black, C. M., Keogh, A., Pulido, T., Frost, A., Roux, S., Leconte, I., & Landzberg, M. (2002). Bosentan therapy for pulmonary arterial hypertension. New England Journal of Medicine, 346, 896–903.
10. Galiè, N., Humbert, M., Vachiery, J. L., Gibbs, S., Lang, I., Torbicki, A., Simonneau, G., Peacock, A., Vonk Noordegraaf, A., Beghetti, M., & Ghofrani, A. (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal, 46, 903–975.