ISSN: 2378-2951

Babu. Int J Clin Cardiol 2019, 6:145
DOI: 10.23937/2378-2951/1410145
Volume 6 | Issue 3
Open Access

International Journal of Clinical Cardiology

REVIEW ARTICLE

Molecular Basis of Pulmonary Hypertension

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Abstract

Pulmonary hypertension is a life threatening incurable disorder. The advances in physiology, genetics, and molecular biology have greatly improved our understanding of the cellular and molecular mechanisms underlying the disorder. In this review, the recent progresses in the understanding of molecular mechanism are presented. Many studies show that pulmonary hypertension is caused due to mitochondrial dysfunction, endothelin-1, prostacyclin and serotonin. These findings and their exploitation will hold promise to find novel treatment options for patients.

Keywords

Molecular mechanism, Pulmonary Hypertension, Mitochondrial dysfunction, Endothelin-1, Prostacyclin, Serotonin

Introduction

Disease overview

Pulmonary hypertension (PH) is a type of high blood pressure that affects the arteries in the lungs and the right side of the heart. It reflects the pressure the heart must exert to pump blood from the heart through the arteries of the lungs. This is in contrast with the systemic blood pressure (commonly known as blood pressure, high blood pressure or hypertension) which measures the pressure in the brachial artery while the left side of the heart pumps oxygen-rich blood from the lungs into the rest of the body, measured with a traditional arm cuff [1]. The symptoms of the disease include irregular heartbeat, racing pulse, passing out or dizziness, progressive shortness of breath during exercise or activity, and difficulty breathing at rest [2]. The classification of PH and their causes are shown in Table 1. PH is clinically diagnosed when mean pulmonary artery pressure is greater than 25 mmHg at rest or 30 mmHg during exercise. It is characterized by an increase in pulmonary vascular resistance that ultimately leads to right-heart failure and death. Although it is a rare disease, it is a progressive and often a fatal lung disorder for which there is no cure [3].

This review focusses on some recent studies of the molecular causes of PH. A greater understanding of the cellular and molecular biology of the disease may provide a useful platform to devise novel treatment options for patients.

Mitochondrial dysfunction

Mitochondria plays an important role in disease pathogenesis. Iqbal, et al., 2001 [4] hypothesised that mitochondrial dysfunction contributes to pulmonary hypertension. Mitochondria, despite being a major site of cellular oxygen consumption, is also a major site of cellular oxidative stress. This is due to the generation of reactive oxygen species (ROS), which can thereby contribute to oxidative stress observed with pulmonary hypertension [5-8]. Rather than being completely reduced to water, it has been estimated that 1 to 4% of oxygen consumed by mitochondria is incompletely reduced to ROS (e.g., O_2 - and H_2O_2) due to leakage of electrons from the respiratory chain [9,10].

Thus, due to the great demand that is placed on mitochondria to support the rapid rates of growth, combined with the propensity of mitochondria to produce ROS, mitochondria may be extremely important in contributing to oxidative stress associated with pulmonary hypertension [4].

The tissues and organs affected by pulmonary hypertension were found to share a common metabolic anomaly linked to mitochondrial dysfunction: The suppression of the mitochondrial glucose oxidation (pro-

Citation: Babu AF (2019) Molecular Basis of Pulmonary Hypertension. Int J Clin Cardiol 6:145. doi.org/10.23937/2378-2951/1410145

Accepted: May 29, 2019; **Published:** May 31, 2019

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Table 1: Classification and causes of PH [36].

Types	Causes
Group 1 Pulmonary Arterial Hypertension	• No known cause: Idiopathic (IPAH) • Inherited: Heritable (HPAH) • Caused by drugs/toxins • Caused by conditions(APAH): HIV, Liver disease etc.,
Group 2 Pulmonary Hypertension	• PH with left heart disease • Caused by conditions that affect the left side of the heart: Mitral valve disease, High blood pressure
Group 3 Pulmonary Hypertension	• PH associated with lung diseases: COPD, Interstitial lung disease
Group 4 Pulmonary Hypertension	• Caused by blood clots in the lungs • Caused by blood clotting disorders
Group 5 Pulmonary Hypertension	• Caused by unclear multifactorial mechanisms: Blood disorders System disorders Metabolic disorders Other conditions like tumor

cess through which sugar glucose is converted into energy) and a subsequent increase in cytoplasmic glycolysis. In this sense, the authors suggest that the increase in mitochondrial glucose oxidation may improve PAH pathogenesis. In fact, it has been shown that treatment with dichloroacetate or trimetazidine (both drugs that stimulate glucose oxidation) can improve the right-ventricular function, which is the most important predictive factor for PAH [11].

Prostacyclin

Prostacyclin belongs to the endogenous prostanoids family. It is produced from arachidonic acid in a multistep process involving the enzymes prostacyclin synthase and cyclooxygenase (COX) [12-14]. In the pulmonary circulation, prostacyclin is released by endothelial cells in the pulmonary artery [15].

Prostacyclin synthesis is decreased in endothelial cells from PAH patients. Analysis of urinary metabolites of prostacyclin showed a decrease in the amount of excreted 6-ketoprostaglandin F1α, a stable metabolite of prostacyclin, in patients with idiopathic PAH [16]. Moreover, pulmonary endothelial cells of PAH patients are characterized by reduced expression of prostacyclin synthase [17], and prostacyclin therapy has been shown to improve hemodynamics, clinical status, and survival of patients displaying severe PAH [18].

Endothelin-1

Endothelin-1 (ET-1) is a peptide isolated from vascular endothelial cells. It has the most potent vasoconstricting activity and is also a mitogen for smooth-muscle cells *in vitro* [19,20]. It is found to be elevated in heart failure states as well as in pulmonary arterial hypertension (PAH). The pulmonary production of ET-1 may contribute to the vascular abnormalities associated with PH [21]. Patients with PH have significantly higher plasma ET-1 concentrations than healthy controls [22,23]. Hence ET-1 receptor blockade could be used for treatment.

Nitric Oxide

Nitric oxide is a low molecular weight, oleophilic, very fast reacting endogenous free radical. It is a vasodilator and can inhibit platelet aggregation, thrombosis, and remodelling [24]. It is capable of modulating vascular injury and interrupting the elevation of pulmonary vascular resistance selectively. However, it can also produce cytotoxic oxygen radicals and exert cytotoxic and antiplatelet effects. The balance between the protective and adverse effects of nitric oxide is determined by the relative amount of nitric oxide and reactive radicals. Nitric oxide has been shown to be clinically effective in the treatment of pulmonary hypertension and other heart diseases. Additionally, new therapeutic modalities for the treatment of pulmonary hypertension, phosphodiesterase inhibitors, natriuretic peptides and aqueous nitric oxide are also effective for treatment of elevated pulmonary vascular resistance [25].

Serotonin

Serotonin, also known as 5-hydroxytryptamine, is a mitogen secreted from neuroendocrine cells in the gut, and carcinoid tumours are a source of increased production [26,27]. Serotonin from the gastrointestinal tract is normally metabolised by the liver before it reaches the lungs, and it is also effectively removed by the lungs. Both these organs usually localise the effects of serotonin to the circulation of origin, except when abnormal channels of communication exist, as in portal hypertension, or when metabolic capacity is overwhelmed. Lack of removal of vasoactive substances by the liver could help to explain the association between pulmonary hypertension, portal hypertension, and liver diseases [28,29].

On a molar basis, serotonin is the most potent

pulmonary vasoconstrictor identified to date in humans [30], but in the systemic vasculature it causes profound vasodilation [31]. These differing effects on the two circulations are similar to those of hypoxaemia and the effects of serotonin are intensified under hypoxaemic conditions and by the administration of catecholamines.

The vascular adverse effects of serotonergic amines such as ergotamine are exacerbated in liver disease [32]. The ability of the endothelial cells of the lungs to metabolise amines may also be reduced in disease states, probably because of impairment of amine oxidase enzymes [33,34]. Such impairment results in raised circulating amine levels, which may provide early evidence of endothelial dysfunction in pulmonary hypertension before morphological changes are apparent (Table 1).

Conclusion

A great progress has been made in the identification and the understanding of the molecular basis of PH. However, we are still far away from a comprehensive understanding of this deadly disease. This is true for the proliferative abnormalities of the pulmonary vasculature and is even truer for the pathogenetic sequelae underlying right ventricular hypertrophy and failure [35]. There is a need for a greater understanding of the mechanisms of PH. This would, in the future, yield improved treatments options for patients.

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