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Exercise training contributes to H_2O_2/VEGF signaling in the lung of rats with monocrotaline-induced pulmonary hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling and right ventricle overload. Given that angiogenesis is a key factor involved in the reduction of vascular resistance to blood flow, we tested the hypothesis that aerobic exercise exerts a positive impact on hydrogen peroxide (H_2O_2) and protein kinase B (Akt) levels in the lung parenchyma. To study the effects of aerobic exercise on lung angiogenesis signaling, Wistar rats were administered monocrotaline (MCT) (60 mg/kg i.p.) or the same volume of saline (0.9% NaCl i.p.). There was an increase in H_2O_2 (43%) in PAH-trained animals (TM) compared to control animals (SM). H_2O_2 showed a positive correlation ($r = 0.77$) with vascular endothelial growth factor (VEGF). VEGF was higher (4.7 fold) in TM animals compared to SM. VEGF and angiopoietin-1 (Ang-1) showed positive staining in the lung parenchyma of TM and SM. Glutathione peroxidase showed higher activity in the TM group (49%) compared to trained control (TC). Aerobic exercise increased the activity of peroxiredoxin ($P < 0.05$). The increase in VEGF was positively correlated with Akt phosphorylation ($r = 0.73$). p-Akt was shown to be increased in TM animals when compared to SM animals (2.5 fold). The change in fractional area, fractional shortening and systolic tricuspid annular plane excursion showed improvement after exercise training. Therefore, aerobic exercise promotes H_2O_2/VEGF/p-Akt signaling for pulmonary physiological angiogenesis. It is associated with an improvement in RV function, as evaluated by echocardiography.

1. Introduction

Administration of the drug pyrrolizidine alkaloid monocrotaline at specific doses can cause pulmonary arterial hypertension (PAH) due to pulmonary mononuclear vasculitis, which may in turn lead to right ventricular hypertrophy (RVH) [1]. PAH is a progressive and fatal disease characterized by vascular remodeling and pathological angiogenesis. Pathological angiogenesis is caused by hyperplasia and hypertrophy of the tunica media of arterioles, resulting in the reduction or obliteration of its lumen, increased afterload imposed on the right ventricle (RV) and progression to right heart failure (RHF) [2].

Vascular remodeling is a complex process that varies over time and is dependent on coordinated biochemical events between endothelial cells and smooth muscle cells [2]. However, the molecular and cellular mechanisms that modulate angiogenesis in PAH are still not completely understood. The molecular signals leading to angiogenesis are dependent on the vascular endothelial growth factor (VEGF) and angiopoietins. Physiological angiogenesis is initiated by signals triggered by shear stress and hypoxia, causing an increase in the expression of VEGF and a change in the proteolytic balance, leading to degradation of the basement membrane and endothelial cell proliferation. The signal triggered by VEGF causes an increase in the expression of angiopoietin-1 (Ang-1), which binds to its membrane receptor (Tie-2), stimulating an intracellular signal for cell survival and nitric oxide (NO) synthesis. This intracellular signal seems to depend on phosphoinositide-3 kinase (PI3K)-protein kinase B (Akt) [3]. Pathological angiogenesis shares many of the intracellular signals of physiological angiogenesis. However, VEGF and angiopoietins are also released by macrophages attracted by local inflammation. During inflammation, there is an increase in the release of angiopoietin-2 (Ang-2), which acts by antagonizing the effects of Ang-1, causing malformation, instability, apoptosis and luminal obliteration of vessels [1,2].

Among the mediators of angiogenesis, reactive oxygen species (ROS) are of particular interest. ROS can be produced under tissue

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