ABSTRACT

Hypoxic pulmonary vasoconstriction (HPV) is a physiological mechanism that maintains optimal oxygenation of blood in the lungs. However, chronic hypoxia causes hypoxic pulmonary hypertension (HPH). Increased reactive oxygen species (ROS) participate in the pathogenesis of HPH. Oxidative stress can cause NO synthase uncoupling and subsequent production of superoxide instead of NO.

Increase in intracellular Ca^{2+} concentration in pulmonary smooth muscle cells is required for pulmonary vasoconstriction. However, vessel tone can also be regulated by vascular smooth muscle cells' calcium sensitivity (without Ca^{2+} concentration changes). Increase of calcium sensitivity plays a role in HPV and HPH. This study focuses on three mechanisms to influence the increased calcium sensitivity in HPV a HPH: (1) Rho kinase inhibition, (2) effort to re-couple NO synthase, and (3) vasorelaxant effect of tyrosine kinase inhibitors.

Normobaric hypoxic chamber (10% O_2) or the combination of hypoxia and vascular endothelial growth factor receptor blockade was used to induce pulmonary hypertension in rats.

(1) The effect of acute and chronic Rho kinase inhibition was studied on pressure-flow relationship (P/Q) in isolated perfused lungs. Acute Rho kinase inhibition decreased the basal tone of pulmonary vessels in HPH animals. Chronic Rho kinase inhibition during hypoxia lowered the increase in pulmonary vascular resistance according to this model.

(2) The effect of exogenous tetrahydrobiopterin administration (BH4, NO synthase cofactor) was studied in isolated perfused lungs, isolated pulmonary vessels, and on exhaled NO concentrations in live animals. BH4 had a vasorelaxant effect that was bigger in controls than in hypoxic animals. BH4 also increased exhaled NO concentrations. These effects were blocked by NO synthase inhibitors.

(3) Tyrosine kinase inhibitors had potent vasorelaxant effects on both normal and hypertensive isolated pulmonary arteries. Activation of myosin light chain phosphatase (calcium desensitisation) plays a role in these effects. Acute imatinib administration reduced right ventricle pressure in live rats with pulmonary hypertension.

Increased calcium sensitivity in chronic hypoxia can be influenced by Rho kinase inhibitors and tyrosine kinase inhibitors. Both have potent pulmonary vasorelaxant effects.

BH4 administration increases NO production. The smaller increase in NO production in hypoxic lungs can be due to NO synthase uncoupling in chronic hypoxia. Impaired NO production in chronic hypoxia can participate in calcium sensitivity increase.

The regulation of vascular smooth muscle cells' calcium sensitivity is an important mechanism in vascular tone regulation.