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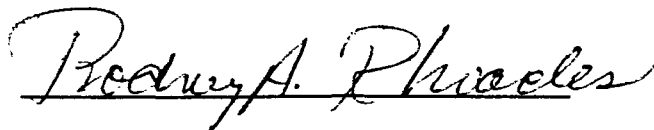
THE ROLE OF RHO-KINASE AND MYOSIN PHOSPHATASE IN
HYPOXIC PULMONARY VASOCONSTRICTION

Zhiqian Wang

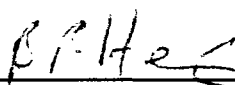
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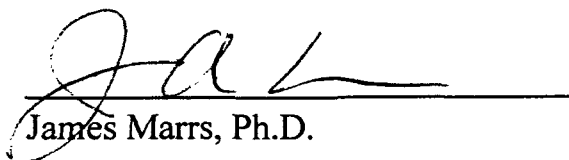


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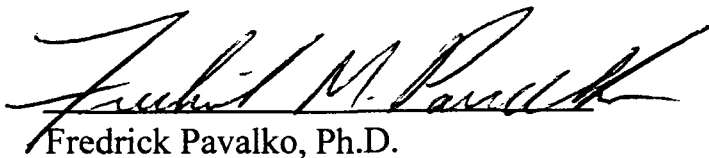


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Abstract

An oxygen paradox exists in vascular biology. In the systemic circulation, hypoxia causes vasodilation. In the pulmonary circulation, hypoxia causes vasoconstriction. The hypoxia pulmonary vasoconstriction (HPV) plays a critical role in the regulation of pulmonary blood flow during normal and abnormal conditions. Hypoxia-induced MLC phosphorylation seen in pulmonary arterial smooth muscle cells (PASMCs) is the underlying molecular/cellular mechanism of HPV. The current work studied the role of Rho, Rho-kinase and myosin phosphatase (MP) in the regulation of hypoxic pulmonary vasoconstriction. Rat intrapulmonary arteries and cultured rat PASMCs were used. Hypoxia caused both a significant increase in myosin light chain (MLC) phosphorylation in PASMCs and vasoconstriction in isolated pulmonary arterial ring. Hypoxia-induced MLC phosphorylation was inhibited by Y-27632 (a Rho-kinase inhibitor) or exoenzyme C3 (a specific Rho inhibitor) or toxin B (a Rho proteins inhibitor). Y-27632 caused a significant relaxation during the sustained phase of HPV in a concentration-dependent manner. Rho-kinase is activated by hypoxia in PASMCs; In addition, hypoxia-induced Rho-kinase activation was blocked by C3 and toxin B. Hypoxia caused an increase in the phosphorylation of the myosin binding subunit of MP resulting in a concomitant inhibition of MP activity; a response that was blocked by Y-27632. The results indicate that Rho, Rho-kinase, and myosin phosphatase forms a closely linked intracellular signaling pathway that is functionally linked to hypoxia-induced MLC phosphorylation and plays a specific role in the sustained phase of HPV.

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