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

Zhiqian Wang

Submitted to the faculty of the University Graduate School
in partial fulfillment of the requirements for the degree
Doctor of Philosophy
in the Department of *Cellular and Integrative Physiology*
Indiana University

July 2001

Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements of the degree of Doctor of Philosophy

Rodney A. Rhoades, Ph.D., Chairman

B. Paul Herring, Ph.D.

Doctoral Committee

James Marrs, Ph.D.

Fredrick Pavalko, Ph.D.

Date of Oral Examination
May 18, 2001

Darl R. Swartz, Ph.D.

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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