New Approaches to Pulmonary Hypertension
Will Therapies in Mice Work in Humans?

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Gene manipulation in mice is now a routine approach to the investigation of disease pathophysiology. Examination of cardiovascular physiology in mice has required the development of miniaturized hemodynamic monitoring systems, or essentially mouse “cath labs,” in which catheters and guidewires are manipulated in mouse vessels often <1 mm in size. Cardiovascular integrative physiology has become miniaturized in scale but magnified in impact. Studies testing the pharmacological or physiological effects of infused drugs, which once could be done only in large animals, are now performed in mice by genetic manipulation and/or gene transfer, with equally rigorous hemodynamic monitoring. The potential for defining disease pathophysiology and developing new therapies is enormous.

Given these advances in technology, what have we learned about cardiovascular biology from mouse models? And importantly, will we be able to translate these discoveries into novel therapies for humans? The study by Champion et al in this issue of Circulation brings these questions under close scrutiny. These investigators examine the function of prepro-calcitonin gene–related peptide (CGRP) in a mouse model of pulmonary hypertension. CGRP is a neuropeptide produced by alternative splicing of the calcitonin gene and is located within nerve fibers of lung airways. CGRP receptors are highly expressed by vascular smooth muscle cells within the pulmonary vasculature. These receptors are regulated by hypoxia. During hypoxic conditions, CGRP levels are reduced and vasoconstriction of pulmonary arteries occurs, leading to pulmonary hypertension and its sequelae on right ventricular mass and function. The mechanism for CGRP mediated vasodilation involves activation of K⁺ channels.

In the present study, the authors expressed a prepro-CGRP gene within lung epithelial cells of mice by introducing an adenoviral vector encoding CGRP, termed AdRSVCGRP, under pressure into mouse trachea. Peak levels of recombinant CGRP protein were detected in the lung 5 days later and persisted for 21 to 25 days, consistent with the time course of gene expression with adenoviral vectors. Five days after CGRP gene transfer, the mice were subjected to hypoxia through a hypobaric chamber (10% O₂) for 16 additional days. At day 21, experimental and control groups of mice were tested with pulmonary vasodilators and vasoconstrictors. The responses of control mice exposed to hypoxia, control mice transfected with a reporter gene β-galactosidase (AdRSVβgal) exposed to hypoxia, and control mice kept in normobaric conditions (21% O₂) were compared with the AdRSVCGRP group. Not surprisingly, mice subjected to hypoxia for 16 days developed pulmonary hypertension and vascular remodeling. Evidence of right heart failure was also present. Transfection of a reporter gene, AdRSVβgal, into the lungs before hypoxic exposure did not alter the development of pulmonary hypertension, which suggests a benign effect of the reporter gene and adenoviral vector on disease pathophysiology.

Expression of the prepro-CGRP gene in mice exposed to hypoxia (AdRSVCGRP group), however, resulted in relief of pulmonary artery vasoconstriction and prevention of pulmonary hypertension. CGRP expression led to a significant attenuation of vasoconstriction responses to intravenous infusions of endothelin-1, angiotensin II, the nitric oxide synthase inhibitor L-NAME (N⁶-nitro-L-arginine methyl ester), and acute hypoxia. The authors detected elevated levels of CGRP locally in the lung but not in the circulation. These levels of CGRP, although sufficient to alter responses to vasoconstrictors, did not saturate CGRP receptors on vascular smooth muscle cells, because infusions of CGRP and adrenomedullin (a precursor/analog of CGRP) into AdRSVCGRP mice resulted in further decreases in mean pulmonary artery pressure and pulmonary vascular resistance. Furthermore, infusions of rolipram (a type IV cAMP-selective phosphodiesterase inhibitor) or zaprinast (a type V cGMP-selective phosphodiesterase inhibitor) did not modify lowering of mean pulmonary or systemic arterial pressures. Perhaps most striking, however, were the effects of prepro-CGRP expression on pulmonary artery remodeling. Lower right arterial pressures, smaller right ventricular masses, and fewer muscle pulmonary arteries were observed in the AdRSVCGRP groups, which suggests an attenuation of the development of pulmonary hypertension.

What are we to learn from this study? There are at least 3 messages. Modification of K⁺ channel activation alone or in combination with phosphodiesterase inhibitors may be a possible approach to attenuate vasoconstriction of pulmonary arteries in pulmonary hypertension, thereby providing new therapies. Second, these studies in mice suggest that delivery of recombinant genes by inhalation, as is done with the phosphodiesterase inhibitors, may be effective. Whether the physiology and pharmacology observed in this study in mice will also be applicable to humans is clearly open to specula-
tion, but the positive findings imply that further testing in larger animal models is warranted. Third, from a research standpoint, these sophisticated physiology experiments in mice are a tour de force. The field of cardiovascular integrative physiology has been reinvented on a miniaturized scale in mice, and studies such as this portend great promise for future investigations of gene function in genetically manipulated mice and for the development of new therapies.

References

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