Point:Counterpoint: Release of an endothelium-derived vasoconstrictor and RhoA/Rho kinase-mediated calcium sensitization of smooth muscle cell contraction are not the main effectors for full and sustained hypoxic pulmonary vasoconstriction

POINT: RELEASE OF AN ENDOTHELIUM-DERIVED VASOCONSTRICTOR AND RHOA/RHO KINASE-MEDIATED CALCIUM SENSITIZATION OF SMOOTH MUSCLE CELL CONTRACTION ARE THE MAIN EFFECTORS FOR FULL AND SUSTAINED HYPOXIC PULMONARY VASOCONSTRICTION

The ability of an organism, or an organ therein, to respond appropriately to episodes of hypoxia is a key evolutionary determinant. In mammalian lungs, the response to acute hypoxia involves constriction of the intrapulmonary arteries (IPA) in the hypoxic region of the lung. This response, termed hypoxic pulmonary vasoconstriction (HPV), effectively matches regional perfusion of the lung to regional ventilation and constitutes a pivotal homeostatic mechanism (25). HPV has, therefore, been the subject of intensive research for many years, although little consensus exists regarding its underlying sensor(s) and effector(s) mechanisms. Indeed, heated debates abound once one mentions trigger words and phrases such as “redox,” “reactive oxygen species,” “potassium channels,” etc., in relation to HPV (1, 28). This article focuses attention on another incendiary trigger phrase, namely “the endothelium.”

To consider the role of the endothelium in HPV, we must first define the hypoxic constrictor response itself. In vivo and in isolated blood-perfused lungs, HPV is usually immediate in onset and sustained. In contrast, HPV in isolated arteries is often biphasic, consisting of an initial transient constrictor response superimposed on a more slowly developing, sustained contraction (10). It has been argued that the latter, sustained, response is more physiologically relevant as it would appear to define the hypoxic constrictor response itself. In vivo and in isolated blood-perfused lungs, HPV is usually immediate in onset and sustained.

In the context of sustained HPV, one potential mediator of the Ca\(^{2+}\) sensitization observed during HPV, protein kinase C, was eliminated and it was not until the availability of the specific inhibitor of Rho-associated coiled coil-forming serine/threonine kinase (Rho kinase), Y-27632, that the activation of Rho kinase was first promulgated as a pivotal step in sustained HPV (19). Since the first isolation of Rho kinase (11), it has become apparent that, upon activation by the binding of the small monomeric G-protein RhoA, Rho kinase inhibits myosin light chain phosphatase (MLCP), resulting in Ca\(^{2+}\)-independent contraction of vascular smooth muscle. Since this initial report, converging lines of evidence have pinpointed Rho kinase activation and subsequent inhibition of MLCP (27) as being a vital step in the initiation and maintenance of increased pulmonary artery pressure in response to acute hypoxia (6, 23), chronic hypoxia (6, 8, 13, 15), and pulmonary hypertensive states per se (3, 13, 14). Moreover, Rho-kinase inhibitors appear to show much promise as potential therapeutic agents in pulmonary hypertension (9). It is, therefore, possible that the activation of Rho kinase during sustained HPV represents the bridge between physiological HPV (i.e., that which occurs in response to brief and reversible hypoxia) and the pathophysiological consequences of chronic hypoxia.

It would seem logical to assume that since sustained HPV and the associated Ca\(^{2+}\) sensitization are both endothelium dependent then the activation of Rho kinase during hypoxia should be similarly endothelium dependent. However, it was reported that hypoxia can directly activate Rho kinase in...
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cultured pulmonary artery smooth muscle cells (PASMC; Ref. 26). At first glance, this appears to scupper any idea of an EDCF-mediated increase in Rho kinase activation during sustained HPV. However, the increase in Rho kinase activity in cultured PASMC was a rather meager ~20% after 40 min of hypoxia, rising to a rather disappointing ~40% after 1 h. This is in stark contrast to the rather impressive ~260% increase in Rho kinase activity recently reported in isolated pulmonary arteries of the rat during sustained HPV (16). Moreover, this activation of Rho kinase in rat pulmonary arteries was endothelium dependent and in endothelium-denuded arteries the increase in Rho kinase activity was similar (~40%) to that reported for cultured PASMC. Furthermore, the translocation of RhoA to the plasma membrane of the pulmonary smooth muscle, a causal event in the activation of Rho kinase, was similarly dependent on the presence on an intact endothelium.

In closing, the case for the EDCF-Rhoa/Rho kinase-Ca2+-sensitization axis being responsible for the maintenance of sustained HPV is solid. My most worthy opponent will probably try to convince the reader that the endothelium merely “modulates” the hypoxic constrictor response. However, when disruption of said axis results in removal of the hypoxic constrictor response, then “modulate” must surely be changed to “mediate”!

REFERENCES

14. Tom P. Robertson Department of Physiology and Pharmacology Institute of Comparative Medicine College of Veterinary Medicine The University of Georgia Athens, Georgia e-mail: troberts@vet.uga.edu

COUNTERPOINT: RELEASE OF AN ENDOTHELIUM-DERIVED VASOCSTRCTOR AND RHoA/RHOKINASE-MEDIATED CALCIUM SENSITIZATION OF SMOOTH MUSCLE CELL CONTRACTION ARE NOT THE MAIN EFFECTORS FOR FULL AND SUSTAINED HPV

The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact

Thomas H. Huxley (1825–1895)

With a simple experiment 15 years ago, Jane Madden et al. (9) slayed the beautiful (then unborn) hypothesis that a (still mysterious) vasocostrctor secreted from the endothelium in response to hypoxia causes hypoxic pulmonary vasocostric-

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