Extracellular Adenosine Attenuates Left Ventricular Hypertrophy Through Its Impact on the Protein Kinase and Phosphatase Interaction

Rainer Schulz, Gerd Heusch

Left ventricular (LV) hypertrophy (LVH) is a major determinant of cardiovascular morbidity and mortality; LVH develops in response to valvular disease and hypertension and is part of the remodeling process after myocardial infarction. Initially LVH may serve to reduce wall stress and preserve cardiac output, but more chronically LVH can progress into cardiac decompensation and failure.

Transverse aortic constriction is an established animal model to study chronic pressure overload and LVH. In this model, local and/or systemic neurohumoral activation occurs, and circulating norepinephrine and renin concentrations are increased. These neurohumoral mediators activate platelets to release ADP and form reactive oxygen species (ROS), endothelial cells to express adhesion molecules and form ROS, fibroblasts to proliferate and synthesize collagen, and cardiomyocytes to synthesize proteins and grow. These divergent effects on different cell types are closely interrelated in that, eg, extracellular ROS contribute to cardiomyocyte hypertrophy and interstitial fibrosis. Cardiomyocyte growth and adaptive and maladaptive LVH involve activation of phosphoinositol 3-kinase (PI3K; Figure 1). Activation of PI3K-α/β by growth factor receptors and receptor tyrosine kinases is thought to mediate adaptive LVH, whereas PI3K-γ is activated by neurohumoral mediators via G protein–coupled receptors and thought to mediate maladaptive LVH. Once activated, PI3Ks generate phosphatidylinositol 3,4,5-triphosphate, leading to the recruitment and activation of Akt/protein kinase B (PKB), which, in turn, activates downstream targets, such as the mammalian target of rapamycin and p70 ribosomal S6 kinase. The phosphatase and tensin homolog on chromosome 10 (PTEN) is the main negative regulator of PI3K activity by dephosphorylating phosphatidylinositol 3,4,5-triphosphate to phosphatidylinositol 4,5-diphosphate. Phospholipase C uses phosphatidylinositol 4,5-diphosphate to generate inositol 1,4,5-triphosphate and diacylglycerol and consequently activate protein kinase C-α, -ε, and -δ. PTEN is highly expressed in adult hearts, however, mostly in its phosphorylated, inactivated form. ROS also inactivate PTEN, contributing to the activation of Akt/PKB, thus highlighting the close interaction between protein kinase and phosphatases in cardiovascular physiology and disease. This important study leaves us with several questions, as described below.

First, what exactly is the stimulus for adenosine formation and which cellular compartment(s) contribute to the increase in extracellular purines (ATP, ADP, AMP, and adenosine) at which time point during the development of pressure overload and LVH? ATP is released in response to increased shear stress from endothelial cells and as a cotransmitter from sympathetic nerve endings. ADP is released from platelets preactivated by hypertension, and, finally, cardiomyocytes within the hypertrophied LV release adenosine. Especially with increased extravascular compression of the coronary circulation by the hypertrophied myocardium in the coronary effluent is increased. Extracellular adenosine is derived in part by phosphohydrolysis of AMP via ecto-5’-nucleotidase (CD73; Figure 1). Adenosine inhibits sympathetic norepinephrine release, attenuates the activation of the renin-angiotensin system, and counteracts cytokine effects. During pressure overload in mice, exogenous adenosine (or stable adenosine analogues) attenuates LV dilatation, improves LV systolic function, and reduces cardiomyocyte hypertrophy and interstitial fibrosis through adenosine-A1 receptor activation.

In the present issue of Hypertension, Xu et al now demonstrate that endogenous adenosine derived from CD73 attenuates LV systolic dysfunction, cardiomyocyte hypertrophy, and interstitial (especially perivascular) fibrosis after aortic banding in mice, because pressure-overload–induced functional and morphological alterations were more pronounced in CD73 knockout mice. In isolated cardiomyocytes, increased protein synthesis and cell size during phenylephrine stimulation were blunted by a stable adenosine analogue, confirming previous findings, but adenosine also reduced protein synthesis and proliferation of stimulated fibroblasts. Along with the functional and morphological findings, the phosphorylation of protein kinase C-α, Akt/PKB, and p70 ribosomal S6 kinase in cardiac homogenates from these CD73 knockout mice during aortic banding was increased. Also, PTEN phosphorylation was increased and most likely contributed to the activation of Akt/PKB, thus highlighting the close interaction between protein kinase and phosphatases in cardiovascular physiology and disease. This important study leaves us with several questions, as described below.

Correspondence to Rainer Schulz, Institut für Pathophysiologie, Westdeutsches Herzcentrum, Universitätsklinikum Essen, Hufelandstrasse 55, 45122 Essen, Germany. E-mail rainer.schulz@uk-essen.de

Hypertension is available at http://hypertension.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.108.112144

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Institute of Pathophysiology, University of Duisburg-Essen, Essen, Germany.

Hypertension. 2008;51:1474–1475.)

© 2008 American Heart Association, Inc.
myocardium and increased perivascular fibrosis and, thus, increased diffusion distances for oxygen, cardiomyocytes might be rendered hypoxic and increasingly release adenosine at higher work loads. Finally, hypertrophy might be initially compensated by angiogenesis, and, again, adenosine may be involved in angiogenesis.

Second, are the observed effects distributed homogeneously throughout the left ventricle and are they operative under all circumstances? CD73 is primarily expressed in the subendocardium and the subepicardium but to a lesser extent in the midmyocardium. With increasing age, the activity of CD73 declines, whereas the activities of adenosine degrading enzymes remain unaltered. Thus, the rate of AMP conversion and the ratio of AMP:adenosine will differ across the LV at a different age and are expected to result in altered cellular responses. Adenosine, eg, inhibits fibroblast growth and collagen synthesis, whereas AMP, via activation of AMP kinase, enhances proliferation of cardiac fibroblasts during neurohumoral stimulation.

Third, does the activation of the PI3K/PTEN signaling cascade differ, depending on the duration of pressure overload and the cell type involved? Although increased expression of activated PTEN by recombinant adenovirus inhibits cardiomyocyte growth, chronic lack of PTEN (in knockout mice) contributes to maladaptive LVH during the development of pressure overload and consequently aggravates LV dilatation and dysfunction.

The present article by Xu et al., thus, opens the avenue for a series of challenging experiments that will further define the stimulus and origin of enhanced adenosine formation in hypertrophied myocardium, the interaction of different cellular compartments and their protein kinase and phosphatase signaling modules in response to adenosine, and finally the specific morphological and functional targets of these signaling events, ie, cardiomyocyte hypertrophy and dysfunction, fibrosis, inflammation, and so on.

Figure 1. Extracellular adenosine is produced by CD73 during pressure overload and activates the PI3K signaling pathway in different cell types leading to cardiomyocyte hypertrophy and interstitial fibrosis. mTor indicates mammalian target of rapamycin; p70S6K, p70 ribosomal S6 kinase; PKC, protein kinase C.

Figure 2. Pressure overload increases PTEN expression via increased p53 expression. However, at the same time, activation of PKC and, subsequently, LKB1 phosphorylates PTEN, thereby reducing PTEN activity and stability. Similarly, activation of reduced nicotinamide-adenine dinucleotide phosphate oxidase and increased ROS formation (potentially, in addition, also derived from mitochondria) during pressure-overload oxidizes and inactivates PTEN. Tumor suppressor p53, LKB1.STK11 indicates serin/threonine kinase 11; PKC, protein kinase C.

Disclosures

None.

References

Extracellular Adenosine Attenuates Left Ventricular Hypertrophy Through Its Impact on the Protein Kinase and Phosphatase Interaction

Rainer Schulz and Gerd Heusch

*Hypertension*. 2008;51:1474-1475; originally published online April 7, 2008;
doi: 10.1161/HYPERTENSIONAHA.108.112144

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/51/6/1474

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/