Myocardial metabolism in experimental infarction and heart failure

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademien
vid Göteborgs Universitet offentlig kommer att försvaras i hörsalen Arvid Carlsson,
Academicum, Medicinaregatan 3, Göteborg
Fredagen den 7. Mars, kl 1300

av

Truls Are Råmunddal

Fakultetsopponent:
Professor Christer Sylvén
Karolinska Institutet

Avhandlingen baseras på följande delarbeten:

I. **In vivo effects of myocardial creatine depletion on left ventricular function, morphology and energy metabolism in mice.**
Lorentzon M., Råmunddal T., Bollano E., Waagstein F., Omerovic E.
Journal of Cardiac Failure, In print

II. **Overexpression of apolipoprotein-B improves cardiac function and increases survival in mice with myocardial infarction.**
T. Råmunddal, M. Lindbom, M. Scharin-Täng, P. Stillemark-Bilton, J. Boren, E. Omerovic, Submitted

III. **Anti-arrhythmic effects of growth hormone- In vivo evidence from small-animal models of acute myocardial infarction and invasive electrophysiology.**
Truls Råmunddal, Sigfus Gizurarson, Malin Lorentzon, Elmir Omerovic
Journal of Electrocardiology, In Print

IV. **Native cardiac reserve predicts survival in acute post infarction heart failure in mice**
Margareta Scharin Täng, Truls Råmunddal, Malin Lindbom and Elmir Omerovic
Cardiovasc Ultrasound. 2007 Dec 2;5(1):46

GÖTEBORG UNIVERSITY
THE SAHLGRENSKA ACADEMY

Abstract

Abstract
The heart is an organ heavily dependent on exogenous lipids for the oxidative production of adenosine-triphosphate (ATP) and therefore maintenance of normal cellular energy homeostasis. However, high energy flux organs such as the heart must closely match lipid import and utilization or otherwise lipids will accumulate in the cardiomyocytes. Intracellular lipid accumulation has detrimental effects on cardiomyocyte function and viability and results in development of lipotoxic cardiomyopathy. Different pathophysiological states such as congestive heart failure (CHF), myocardial ischemia and hypertrophy are associated with myocardial lipid accumulation. The heart, however, produces and secretes apolipoprotein B containing lipoproteins (apoB), which enables the cardiomyocyte to export lipids. It has been proposed that apoB may be involved in cardioprotection by means of elimination of toxic intracellular lipids.
An important part of the patologic cardiac remodelling in CHF is disturbed myocardial energy metabolism. The failing myocardium contains low levels of creatine (Cr), phosphocreatine (PCr), and ATP. Cr depletion in the heart may result in disturbed energy production, transfer and utilisation of chemical energy and therefore compromised left ventricular function. Growth hormone (GH) has been shown to exert numerous positive effects on the failing and remodelled heart suggesting that GH may be an additional agent in the treatment of CHF and myocardial infarction (MI).

The aims of this thesis were:

I. To investigate in vivo the effects of Cr depletion in mice on left ventricular function and morphology, energy metabolism and myocardial lipids.
II. To investigate importance of endogenous lipoproteins in the heart for cardiac function, morphology and survival in the settings of acute and chronic myocardial infarction and doxorubicine induced acute heart failure.
III. To investigate the effects of Growth hormone on arrhythmogenesis
IV. To evaluate the predictive value of native cardiac reserve on outcome after myocardial infarction in mice

Using a mouse model of chemically-induced Cr depletion we show in vivo that myocardial Cr depletion leads to disturbed energy metabolism, left ventricular dysfunction, pathologic remodeling and accumulation of intracellular triglycerides. These alterations are reversible upon the normalization of the creatine levels suggesting that creatine metabolism may be an important target for pharmacological interventions.
Using transgenic animals we show that myocardial apoB may be a cardioprotective system which is activated during ischemia, pathologic remodeling and heart failure and may be important for survival in myocardial infarction and heart failure.
We show that GH possess novel antiarrhythmic properties in the setting of acute MI which adds further evidence to the concept of GH as an additional pharmacological agent in the treatment of CHF and MI.
We demonstrate that native cardiac reserve is a predictor of post-MI survival.

ISBN 978-91-628-7398-1