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Novel insights in the regulation of cardiac substrate metabolism indicate therapeutic options for diabetic cardiomyopathy

Jan F.C. Glatz

Cardiovascular Research Institute Maastricht, The Netherlands

Abstract

Cardiovascular disease is the most common cause of death among obese and diabetic patients. Cardiac contractile dysfunction seen in this condition is referred to as diabetic cardiomyopathy and is caused primarily by the metabolic alterations occurring, i.e., insulin resistance (decreased glucose utilization) and accumulation of lipids (triacylglycerols) and lipid intermediates (diacylglycerols, ceramides) in cardiac myocytes (lipotoxicity). Currently there is no effective treatment counteracting myocardial lipid accumulation. Recent advances in our understanding of cardiac energy metabolism have indicated that specific transporters in the sarcolemma of cardiac myocytes are key players in the regulation of substrate uptake and utilization. The main transporters are GLUT4 for glucose and CD36 for long-chain fatty acids. The regulatory mechanism involves reversible translocation of the transporters from intracellular stores to the membrane to facilitate substrate uptake. In obesity and diabetes, CD36 is permanently located at the sarcolemma while GLUT4 resides intracellularly, which juxtaposition explains the changes in substrate preference. Our recent studies suggest that interventions in the trafficking machinery that regulate cellular GLUT4 and CD36 distribution aimed at increasing sarcolemmal GLUT4 and/or decreasing sarcolemmal CD36 rectify the cardiac substrate balance and restore cardiac contractile function. Thus, overexpression in mouse hearts of protein kinase D, which is involved in GLUT4 but not CD36 translocation, protects against high fat diet-induced insulin resistance. Similarly, overexpression in cardiac myocytes of vesicle-associated membrane protein-3 (VAMP3) prevents the cells from lipid-induced insulin resistance. These novel data disclose (the trafficking of) substrate transporters GLUT4 and CD36 as promising therapeutic targets for diabetic cardiomyopathy.

Biography

Jan F.C. Glatz received his Ph.D in metabolic biochemistry from Nijmegen University (1983). Currently he is Professor of Cardiac Metabolism at CARIM, Maastricht where he studies the regulation of cardiac energy metabolism in the healthy heart and in type 2 diabetes with focus on the role of substrate transporters. He has published >325 papers, organized several international conferences, is editorial board member of a number of journals, and serves as President of the *Society for Heart and Vascular Metabolism* (SHVM).