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Metabolic Modulation to Treat Cardiac Diseases: Role for Membrane Substrate Transporters

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Abstract

There is growing recognition of the importance and multiple roles of substrate energy metabolism in both cardiac health and disease. Cardiac diseases are frequently accompanied by altered myocardial metabolism, while chronic changes in the type of myocardial substrate utilization are found to elicit cardiac contractile dysfunction. Examples are the increased glucose utilization, at the expense of fatty acids, in cardiac hypertrophy and ischemic heart failure, and the increased fatty acid utilization, at the expense of glucose, in obesity and diabetes-related cardiac dysfunction. Modulation of cardiac metabolism has emerged as a suitable therapeutic intervention in cardiac disease. Insights obtained during the past decade have revealed sarcolemmal substrate transport, facilitated by CD36 for fatty acids and by GLUT4 for glucose, to represent the main rate-governing kinetic step of substrate utilization, over-ruling intracellular sites of flux regulation. This suggests that manipulating the presence of substrate transporters in the sarcolemma may be an effective approach for metabolic modulation therapy. The present mini-review provides a short summary of the functioning of substrate transporters CD36 and GLUT4 in the heart, and discusses their application as targets for metabolic intervention.

Abbreviations

CD36: Cluster of Differentiation 36; FABPc: Cytoplasmic Fatty Acid-Binding Protein; FABPpm: Plasma Membrane Fatty Acid-Binding Protein; FATP: Fatty Acid Transport Protein; GLUT4: Glucose Transporter-4; SR-B2: Scavenger Receptor B2; VAMP: Vesicle-Associated Membrane Protein; v-ATPase: vacuolar-type H+-ATPase

Introduction

Cardiac energy metabolism is increasingly being recognized to play multiple roles in the cardiovascular system. Specifically, the unimpeded functioning of cardiac metabolism appears an important prerequisite for proper myocardial functioning. Consequently, metabolic changes that cause a progressive impairment of high-energy phosphate production often lead to heart failure. For instance, metabolic changes that occur in obesity and diabetes directly affect the cardiac contractile function and may explain why cardiovascular disease is the main cause of morbidity and mortality in patients with diabetes[1,2]. In general, heart failure – defined as a myocardial derangement causing systolic and/or diastolic ventricular dysfunction – is commonly associated with metabolic alterations, especially with regard to substrate preference, whereby distinct metabolic signatures are observed depending on the cause of heart failure (e.g. pressure-overload versus hypoxia/ischemia)[2,3].

Evidence is accumulating that modulation of cardiac metabolism is a useful therapeutic approach in cardiac disease[4]. Such so-called 'metabolic modulation' intervention is directed towards counteracting the energy deprivation commonly seen in heart failure and towards re-installing the flexibility of the heart to adapt its energy provision to environmental influences (referred to as metabolic flexibility). Specific agents have been described that optimize cardiac substrate metabolism without exerting negative haemodynamic effects. These include metabolic agents stimulating or inhibiting fatty acid β-oxidation such as L-carnitine, etomoxir, perhexiline and trimetazidine, and agents stimulating glucose utilization such as dichloroacetate[4-8]. Importantly, while these metabolic modulators have shown promising results in experimental animal studies and some clinical trials [4], other trials did not reveal any significant benefit or, in the case of etomoxir, even showed unacceptable side-effects that caused early termination of the trial[9]. It should be realized however, that these various agents are directed towards intracellular metabolic processing of a single type of substrate rather than securing the intracellular availability of a proper mixture of substrates that is needed for optimal energy provision[10,11]. Indeed, modulating such a mixture of substrates, for instance, through manipulating the entry of metabolic substrates into cardiomyocytes, is emerging as a novel therapeutic approach.

Recent insight into the regulation of myocardial substrate metabolism has revealed a pivotal role for membrane substrate transporters. The utilization of long-chain fatty acids, which form the predominant substrate for myocardial energy provision, is primarily determined by the rate of myocellular fatty acid uptake as facilitated by the presence of the fatty acid transporter CD36 (SR-B2) in the sarcolemma, and overrules the regulation of mitochondrial oxidation of fatty acids by the enzyme carnitine palmitoyl-transferase-1 (CPT-1)[12]. This molecular mechanism fully resembles the regulation of myocardial utilization of the other major substrate, i.e., glucose, which is dependent on the sarcolemmal presence of glucose transporters (GLUT1 and GLUT4)[13]. Importantly, both CD36 and GLUT4 have been implicated in dysregulated cardiac metabolism in pathophysiological conditions such as high-fat diet induced insulin resistance/diabetic cardiomyopathy and pressure-overload induced heart failure. These recent observations suggest that membrane substrate transporters may be preferable targets for metabolic modulation therapy to treat cardiovascular diseases.

In the present mini-review, we will explain the role of membrane substrate transporters in cardiac metabolism and contractile function in more detail, and examine their application as targets to treat cardiovascular diseases.

Myocardial Fatty Acid Uptake

The uptake of fatty acids into cardiomyocytes is facilitated by membrane-associated proteins with a predominant role for the transmembrane glycoprotein cluster-of-differentiation 36 (CD36; officially known as scavenger receptor SR-B2), which functions in cooperation with plasma membrane fatty acid-binding protein ($FABP_{pm}$). The extracellular loop of CD36 contains a hydrophobic binding pocket that operates as an acceptor of fatty acids to promote the partitioning of the fatty acids and their delivery to the outer leaflet of the lipid bilayer (**Fig. 1**). Thereafter, the fatty acids 'flip–flop' to the inner leaflet of the membrane, which

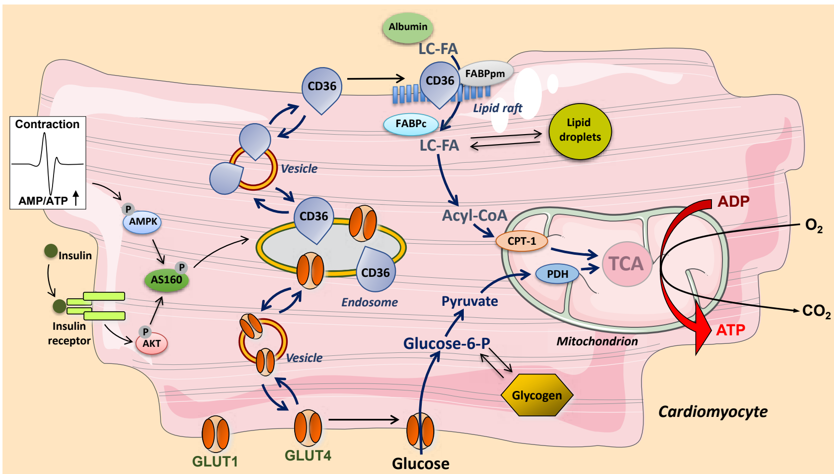

Figure 1: Regulation of long-chain fatty acid (LC-FA) and glucose utilization by cardiac myocytes. LC-FA uptake is mediated by fatty acid transporter CD36 (scavenger receptor (SR)-B2) and glucose uptake by glucose transporters GLUT1 and GLUT4. During increased contractile activity (mediated by AMP-activated kinase, AMPK) or in response to insulin both CD36 and GLUT4 reversibly translocate from an endosomal storage compartment to the sarcolemma to increase fatty acid and glucose uptake, respectively. The glucose transporter GLUT1 is constitutively expressed in the sarcolemma and contributes up to 25% of glucose uptake. Mitochondrial oxidation of LC-FA is controlled by the activity of carnitine palmitoyltransferase-1 (CPT-1) and that of glucose by pyruvate dehydrogenase (PDH). TCA, tricarboxylic acid cycle.

process occurs very fast and does not need assistance from membrane proteins[12]. The final step in the transmembrane transportation process is the desorption of the fatty acids from the inner leaflet and their binding to the cytoplasmic fatty acid carrier $FABP_c$, which transfer is assumed to occur in specific membrane domains designated 'lipid rafts'. The desorption is regarded as the rate-limiting step of overall transmembrane transport. CD36 is considered to facilitate this step by providing a docking site for $FABP_c$ or for acyl-CoA synthetases resulting in a highly efficient uptake process.

Under basal conditions, about half of the total cellular amount of CD36 is present in an intracellular storage depot, i.e., endosomes, from where CD36 can be recruited to translocate to the sarcolemma by vesicular transport. Either an increase in cardiomyocyte contraction or the presence of insulin each trigger, within minutes, the reversible translocation of CD36 from endosomes to the sarcolemma, which is paralleled by a proportional increase in the rate of cellular fatty acid uptake (**Fig. 1**)[12,14]. Taken together, CD36 is not merely a facilitator of transmembrane fatty acid transport, but through its reversible recycling between endosomes and the sarcolemma also serves a pivotal role as regulator of the rate of myocellular fatty acid uptake. It has been estimated that about 70% of myocardial fatty acid uptake is mediated and regulated by CD36[15,16].

Control of the overall rate of myocardial fatty acid utilization is classically viewed to be governed by the activity of the mitochondrial enzyme, carnitine palmitoyl-transferase-1 (CPT-1)[17]. However, more recent work has questioned such a role for CPT-1 as it was found that the rate of fatty acid uptake and oxidation is not affected by partial inhibition of CPT-1 activity, yet is directly dependent on the amount of CD36 present in the sarcolemma[18-21]. As a result, while CPT-1 acts as a regulatory site for mitochondrial β-oxidation and merely serves a permissive role in overall fatty acid utilization, CD36-mediated trans-sarcolemmal transport appears the primary site of regulation of myocellular fatty acid flux[12].

Myocardial Glucose Uptake

Glucose uptake into cardiomyocytes is mediated by two glucose transporters, i.e., GLUT1 and GLUT4[13,22], while members of the solute carrier family 2A (SLC2A) are not involved in the heart[23]. GLUT1 is constitutively present in the sarcolemma and mediates basal glucose uptake. GLUT4 is responsible for stimulus-inducible glucose uptake. In the adult heart, GLUT4 is expressed to a substantially higher extent than GLUT1, making the inducible glucose uptake component the quantitatively most important one[13,22]. Thus, it has been estimated that GLUT4 contributes to the rate of glucose uptake for at least 75%, or even more depending on cardiac workload[13].

Substrate Transporters and Cardiac Disease

The corollary is that cardiac fatty acid and glucose utilization are determined largely by the sarcolemmal presence of CD36 and that of GLUT4, respectively. As a consequence, in cases of cardiovascular diseases associated with metabolic alterations, the sarcolemmal presence or functioning of these substrate transporters is altered as well. Numerous examples underline this notion.

Chronic oversupply of fatty acids to the heart, as occurs during high-fat diet consumption and in obesity, triggers a shift in myocardial energy provision towards an increased utilization of fatty acids at the expense of glucose[1,24]. This substrate switch eventually leads to the accumulation of specific lipid species in cardiomyocytes, followed by mitochondrial dysfunction, insulin resistance, and impaired contractile function, together referred to as diabetic cardiomyopathy[25-27]. Interestingly, detailed time-course studies have revealed that this order of events is initiated by a net translocation of CD36 from endosomes to the sarcolemma, which then leads to a concomitant increase in the rate of fatty acid uptake[28,29]. *In vivo*, this subcellular CD36 redistribution occurs rapidly (within days) while the other metabolic changes (e.g. mitochondrial dysfunction) are evident weeks later[28]. The pivotal early role of CD36 in this cascade of events suggests that manipulation of the sarcolemmal presence or activity of CD36 should prevent and/or regress high fat diet-induced toxic lipid accumulation and contractile dysfunction. Indeed, CD36-null mice are protected against high fat diet-induced loss of cardiac function[30,31]. In addition, cardiac-specific overexpression of nuclear receptor PPARα in mice resulting in enhanced cardiac fatty acid utilization and lipotoxic cardiomyopathy could be rescued by deletion of CD36[32]. Finally, isolated rat cardiomyocytes cultured in a high-palmitate containing medium show lipid accumulation, insulin resistance and a marked loss of contractile function, which all can be prevented by the addition of anti-CD36 antibodies to the culture medium[33].

An increased utilization of glucose at the expense of fatty acids is seen during pressure overload-induced cardiac hypertrophy and is accompanied by an increased presence of GLUT4 at the sarcolemma[34]. Subjecting mice with transaortic constriction-induced cardiac hypertrophy[30] or mice with genetically induced cardiac hypertrophy[35] to a dietary intervention with a high fat-containing diet, in each case elicited normalization of glucose utilization (due to increased fatty acid utilization) together with the recuperation of contractile function. In both examples, it can be inferred that GLUT4 was redistributed leading to a net relocation towards intracellular stores.

Substrate Transporters as Targets for Intervention

Given the role of membrane substrate transporters in the pathogenesis of the cardiometabolic disease, they may be exploited as suitable targets for therapy with the aim to specifically alter either myocardial fatty acid or glucose utilization (**Fig. 2**). However, targeting their function at the sarcolemma by specific antibodies or inhibitors may not be a preferable systemic approach because such interventions would most likely also impair substrate uptake in other organs. Therefore, a preferable approach is to modulate the subcellular recycling of CD36 and/or that of GLUT4, aiming at manipulating their presence at the sarcolemma, and do so, if possible, specifically in the heart. This would require detailed knowledge of the factors involved in the vesicular trafficking machinery of CD36 and GLUT4 recycling between endosomes and the sarcolemma, and of the triggers that regulate the recycling process. During the last decade, there has been a marked expansion of knowledge in this field, in such a way that the concept of specific modulation of CD36 or GLUT4 recycling in a cardiac-specific manner seems feasible.

Subcellular protein trafficking is a complex process regulated by several proteins, including the family of vesicle-associated membrane proteins (VAMPs) which consists of 8 members. VAMP isoforms bring specificity to both organs and membrane proteins (CD36 vs. GLUT4). Thus, some VAMP isoforms are required for both CD36 and GLUT4 translocation, others are involved in only CD36 or GLUT4 trafficking[36]. These findings suggest the possibility of using VAMPs to manipulate specifically CD36-mediated fatty acid uptake without affecting GLUT4-mediated glucose uptake[36].

Another protein involved in subcellular trafficking of substrate transporters is vacuolar H^+-activated ATPase (v-ATPase), a multimeric protein complex present in the membrane of endosomes. By its proton pumping activity v-ATPase is responsible for the acidic lumen of endosomes[37]. Recent studies have disclosed that excess fatty acids inhibit v-ATPase activity causing the endosomes to lose their acidification, which in turn causes an increased translocation of CD36 from endosomes to the sarcolemma without affecting the sarcolemmal content of GLUT4[38]. As a result, v-ATPase is part of a feed-forward cycle whereby lipid overexposure increases CD36-mediated fatty acid uptake, further impairing v-ATPase activity and increasing the translocation of CD36 to the sarcolemma[12]. Compounds able to re-activate v-ATPase could stop such feed-forward cycle and thus be used to lower sarcolemmal CD36 content and consequently the rate of fatty acid uptake.

Conclusions

Sarcolemmal substrate transporters, in particular, fatty acid transporter CD36 and glucose transporter GLUT4, are now recognized as representing the rate-governing kinetic step of myocardial substrate flux and, therefore, play pivotal roles in myocardial metabolism and energy

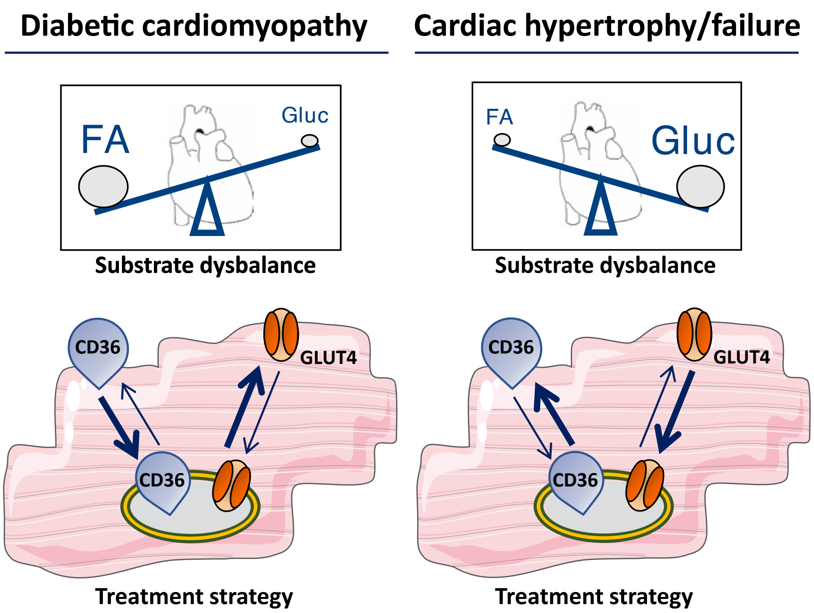

Figure 2: Scheme illustrating the application of substrate transporters for metabolic modulation therapy. Two examples are given. **Left panels**: In case of diabetic cardiomyopathy, cardiac substrate utilization is shifted towards increased utilization of long-chain fatty acids (FA) at the expense of glucose (Gluc). Interventions aimed at net internalization of CD36 and/or net translocation of GLUT4 to the sarcolemma (bold arrows) is expected to normalize substrate utilization and improve contractile function. **Right panels**: In case of hypertrophy and heart failure, cardiac substrate utilization is shifted in the other direction, i.e., towards increased utilization of glucose at the expense of fatty acids. In this case, interventions aimed at net internalization of GLUT4 and/or net translocation of CD36 to the sarcolemma (bold arrows) is expected to normalize substrate utilization and improve contractile function.

provision. While mechanistic insight has been obtained mostly in studies with experimental animals and cell models, importantly, their overall roles also have been confirmed in patient studies[13,39,40]. Given their important roles, not surprisingly, evidence is accumulating that CD36 and GLUT4 also are involved in dysregulated cardiac metabolism associated with the pathogenesis of various cardiac diseases. The latter notion suggests the use of substrate transporters are target for metabolic modulation therapy. Particularly, manipulating the subcellular recycling of CD36 and of GLUT4 appears a promising approach because the involvement of tissue-specific and substrate-specific trafficking proteins in the recycling of CD36 and GLUT4 would allow the separate modulation of fatty acid and glucose uptake. Recent observations underscore the feasibility of this approach.

Alternative approaches to specifically alter either myocardial fatty acid or glucose uptake and utilization may also be worthwile to explore. For instance, PPARα agonists would upregulate specifically the expression of genes implicated in lipid utilization, including CD36, without affecting genes encoding proteins involved in glucose uptake and utilization[12]. Another potential approach is to exploit the emerging role of post-translational modifications of both CD36 and GLUT4 in their localization and functioning. Thus, CD36 undergoes a number of post-translational modifications including palmitoylation, O-GlcNAcylation and ubiquitination, which may influence its subcellular recycling and/or functioning[41], while GLUT4 trafficking (in adipocytes) is regulated, among others, by (de)ubiquitination[42]. Disclosure of the putatively complex role of post-translational modifications on CD36 and GLUT4 functioning is likely to generate additional approaches for their application as metabolic modulation targets.

While long-chain fatty acids and glucose are the main substrates for cardiac energy provision, the heart is known to be a metabolic omnivore and will use virtually all types of substrates so as to assure an optimal cardiac performance[43]. Thus, the healthy heart continuously uses lactate and under certain (patho)physiological conditions also ketone bodies and amino acids. Interestingly, these substrates are also taken up into cardiomyocytes by substrate-specific transporters, i.e., monocarboxylate transporters (MCT) for lactate and ketone bodies, and L-type transporters and/or cationic transporters for amino acids[34]. Although knowledge on the involvement and mechanism of action of these other transporters is only beginning to be obtained, it would be of interest to explore whether these transporters could also be applied as targets for metabolic modulation therapy.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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