Cardiac Metabolism as a Target for the Treatment of Heart Failure

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Few things in life are more irritating than failing to recognize the obvious. A case in point is energy substrate metabolism as a potential target of pharmacological agents for improving function of the failing heart. The complexities of hemodynamics, coronary flow, and cardiac structure obscure the simple fact that the heart is an efficient converter of energy. The reasoning is straightforward: In a series of highly regulated, enzyme-catalyzed reactions, heart muscle converts chemical energy into mechanical energy. Although metabolism and function in the heart are inextricably linked (Figure), few investigators have considered energy substrate metabolism and the first law of thermodynamics (which states that all energy is conserved) as paradigms for the treatment of heart failure. However, interest in this area is growing.

The Present Study in Perspective

A report in this issue of Circulation joins a canon of papers from Richard Shannon’s laboratory in Pittsburgh describing metabolic derangements and interventions in heart failure. In the present study, the authors show that recombinant glucagon-like peptide 1 (rGLP-1) dramatically improves left ventricular, systemic, and coronary flow hemodynamics in dogs with advanced dilated cardiomyopathy. The basis for this functional improvement appears to be related to the restoration of insulin sensitivity in the failing heart, but these are difficult studies to perform and the mechanism is unclear. The authors were unable to prove that direct metabolic effects on the heart were the cause for the improvement in myocardial contractile performance, because such proof can only be provided by an isolated, perfused-heart preparation. However, the effects of GLP-1 on contractile performance, myocardial oxygen consumption, and myocardial uptake of glucose and fatty acids strongly suggest a direct metabolic action of GLP-1, including a tighter coupling of oxidative metabolism and contraction of the heart.

Possible Modes of Action of GLP-1

What is GLP-1, and how can this hormone achieve such a feat? At this time, one can only speculate and refer to the substantial literature that already exists on the hemodynamic actions of glucagon, which was amassed during the “golden age” of cardiovascular pharmacology. GLP-1, like glucagon, is one of the 5 separately processed domains of pre-proglucagon. It is tempting to speculate that the cellular and hemodynamic actions of GLP-1 are similar to those of glucagon. Indeed, inotropic effects of glucagon are well documented in experimental (pentobarbital-induced) heart failure, as are the G-protein–coupled receptor activation and effect of glucagon on heart adenylate cyclase. For a “classic” pharmacologist, a side-by-side comparison of GLP-1, glucagon, glucose-insulin-potassium, and a β-adrenergic receptor agonist would determine whether administration of GLP-1 represents a new principle for the treatment of heart failure.

The half-life of glucagon is ~5 minutes. The need for continuous infusion of GLP-1 suggests that it has a similar short half-life. What happens when the GLP-1 infusion is turned off? GLP-1 would be an ideal agent for the treatment of heart failure if it were able to induce both short-term and sustained (ie, transcriptional) effects on heart muscle. However, the ill-fated experience with “dobutamine holidays” for patients with advanced heart failure serves as a reminder that there are no quick fixes for the failing heart. In brief, the “short-term” results presented here are not totally unexpected, but much more work is needed before the metabolic principle can be accepted as a therapeutic principle for the long-term treatment of heart failure.

Cardiac Metabolism in Heart Failure

The mammalian heart has been described as a “metabolic omnivore” because of its capacity to oxidize fat and carbohydrates, either simultaneously or vicariously. The dominance of fatty-acid metabolism by the heart in the fasted state gave rise to the concept of the “glucose–fatty-acid cycle,” when the heart is acutely stressed, it readily switches from fat to carbohydrate as fuel for oxidative energy production. When the heart is exposed to sustained changes in ventricular pressures, it reactivates the fetal gene program. Reactivation of these fetal genes includes a switch from fat to glucose oxidation, which though initially adaptive, ultimately results in a loss of insulin sensitivity and hence, a loss of metabolic flexibility. This loss of flexibility then becomes an early feature of metabolic dysregulation in the failing heart, which also exhibits all the features of insulin resistance, as Dr Shannon and his laboratory staff have elegantly shown.

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Metabolic Targets for Improved Cardiac Function

Despite these concerns, the work from Shannon’s group is a step in the right direction. The human heart uses several kilograms of ATP per day. Not surprisingly, one third of the cardiac myocyte consists of mitochondria. Given these facts, it is difficult to understand why myocardial energy substrate metabolism has thus far largely eluded the attention of the pharmaceutical industry. An exception, perhaps, is the group of drugs that are supposed to shift the heart’s energy supply from oxidation of fatty acids to the energetically more efficient oxidation of glucose and lactate in the postischemic heart. This shift can be brought about by restoring insulin sensitivity of the heart, by inhibiting fatty-acid oxidation at various levels, or by activating the pyruvate dehydrogenase complex.

A case in point is the success of glucose-insulin-potassium in the treatment of cardiogenic shock after hypothermic ischemic arrest of the heart. Other examples include (1) etomoxir, ethyl-2-tetradecyl glycidate, and oxfenicine, drugs that inhibit long-chain fatty-acid oxidation by inhibiting the entry of long-chain fatty acids into the mitochondria at the level of carnitine palmitoyl transferase I (CPT I). CPT I has become a target for pharmacological intervention in the postischemic, reperfused heart in which rates of fatty-acid oxidation are relatively high and contractile function is (reversibly) impaired. Etomoxir has also generated interest as a drug that may improve energy efficiency in heart failure. However, the therapeutic window of etomoxir seems narrow, because in skeletal muscle, CPT I inhibition leads to excess triglyceride accumulation and lipotoxicity.

(2) The piperazine compound trimetazidine belongs to the group of “partial fatty-acid oxidation” (PFOX) inhibitors and is widely used in France as an antianginal drug. Trimetazidine is thought to inhibit long-chain fatty-acid oxidation by inhibiting one of the terminal steps in the β-oxidation pathway, resulting in a switch of energy substrate preference and improved coupling between glycolysis and glucose oxidation. (3) Ranolazine is another piperazine derivative in the group of PFOX inhibitors. In a recent randomized, controlled trial, ranolazine reduced the frequency and severity of chest pain and improved exercise duration in patients with chronic, stable angina who were already receiving other antianginal therapy. Ranolazine decreases fatty-acid oxidation, promotes glucose oxidation, and acts indirectly by increasing pyruvate dehydrogenase complex activity. The exact mechanism of action of PFOX inhibitors is, however, still unknown.

The list of drugs targeting intermediary metabolism for the treatment of cardiac dysfunction also includes insulin-sensitizing agents such as thiazolidinediones, lipid-lowering agents such as fibrates and statins, as well as propionyl L-carnitine, an anaplerotic agent that raises the level of free coenzyme A. The opportunities for regeneration of normal cardiac myocyte function through metabolic interventions seem unlimited.

Outlook

Who knows what comes next? Given the complexity of metabolic pathways and the multitude of potential targets, pharmacological research has much to explore. It is also clear that investigators have only just begun to understand the importance of modulating metabolic pathways to influence cardiac efficiency. The work presented by Nikolaidis et al. holds the promise of introducing a whole new class of drugs for the treatment of heart failure. On the clinical level, we may witness a long-awaited breakthrough akin to the spectacular results already available in animal models of heart failure subjected to manipulations of metabolic gene expression.

Lastly, a word of caution: One must not underestimate the complexities of intermediary metabolism in the heart. Although the myocardium has certain distinctive biochemical features, many of its basic reaction patterns are similar to those of other tissues. Metabolism is not limited to energy transfer. Its pleiotropic actions include the generation of signals for cardiac growth, programmed cell death and programmed cell survival, the formation of reactive oxygen species, and the regulation of transcription factors. This list further increases our awareness as we begin to identify new metabolic targets for the treatment of heart failure. A reasonable starting point would be to distinguish between drugs that act on one specific enzyme or protein and drugs that, like hormones, act on entire metabolic pathways. Once again, we are reminded of a piece of ancient wisdom: “All is in flux” (παντός ρέει), as Heraclitus (540 to 480 BCE) taught his students in Ephesus 2500 years ago.

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References


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