Featured research

Abstracts and commentaries

Recruitment of compensatory pathways to sustain oxidative flux with reduced carnitine palmitoyltransferase I activity characterizes inefficiency in energy metabolism in hypertrophied hearts

Sorokina N, O'Donnell JM, McKinney RD, et al. *Circulation*. 2007;115:2033–2041.

Transport rates of long-chain free fatty acids into mitochondria via carnitine palmitoyltransferase I relative to overall oxidative rates in hypertrophied hearts remain poorly understood. Furthermore, the extent of glucose oxidation, despite increased glycolysis in hypertrophy, remains controversial. In the present study we explored potential compensatory mechanisms to sustain tricarboxylic acid cycle flux that resolve the apparent discrepancy of reduced fatty acid oxidation without increased glucose oxidation through the pyruvate dehydrogenase complex in the energy-poor, hypertrophied heart. We studied flux through the oxidative metabolism of intact adult rat hearts subjected to 10 weeks of pressure overload (hypertrophied; $n = 9$) or sham operation ($n = 8$), using dynamic carbon-13 nuclear magnetic resonance. Isolated hearts were perfused with 2,4,6,8,10,12,14,16-[^{13}C]palmitate (0.4 mmol/L) plus glucose (5 mmol/L) in a 14.1 T nuclear magnetic resonance magnet. At similar tricarboxylic acid cycle rates, flux through carnitine palmitoyltransferase I was 23% lower in hypertrophied hearts ($P < 0.04$) than in sham-operated hearts, and corresponded to a shift toward increased expression of the L-carnitine palmitoyltransferase I isoform. Glucose oxidation via pyruvate dehydrogenase complex did not compensate for reduced palmitate oxidation rates. However, hypertrophied hearts displayed an 83% increase in anaplerotic flux into the tricarboxylic acid cycle ($P < 0.03$) that was supported by glycolytic pyruvate, coincident with increased levels of mRNA transcript for malic enzyme. We conclude that, in cardiac hypertrophy, fatty acid oxidation rates are reduced, whereas compensatory increases in anaplerosis maintain tricarboxylic acid cycle flux and account for a greater portion of glucose oxidation than previously recognized. The shift away from production of acetyl coenzyme A toward carbon influx via anaplerosis bypasses energy-yielding reactions, contributing to a less energy-efficient heart.

Commentary

Cardiac hypertrophy is associated with marked alterations in energy metabolism that may be important contributors to contractile dysfunction. Previous experimental and clinical studies have shown that fatty acid oxidation can decrease in the hypertrophic myocardium. However, there is confusion as to what happens to glucose metabolism in the hypertrophied heart. Although glucose uptake and glycolysis increase during cardiac hypertrophy, the subsequent oxidation of the pyruvate generated from glycolysis does not appear to increase. As a result, the pyruvate must either be converted to lactate or metabolized by some other pathway.

The study by Sorokina et al confirms that fatty acid oxidation is decreased in the hypertrophic heart, and that glucose oxidation rates do not increase to compensate for this decrease in fatty acid oxidation. Of importance is that this study also shows that pyruvate from glycolysis can be metabolized by an alternative metabolic pathway in the hypertrophied heart, in which carbons enter the tricarboxylic acid (TCA) cycle via a pathway called anaplerosis. The recruitment of this compensatory intermediary pathway, while less efficient in energy synthesis, may allow maintenance of TCA cycle activity in the hypertrophied heart. However, the most efficient pathway for pyruvate metabolism is entry into the TCA cycle via the pyruvate dehydrogenase complex (ie, glucose oxidation). There is now considerable evidence showing that shifting metabolism from fatty acid to glucose oxidation is a therapeutic strategy for treating the ischemic heart.

The 3-ketoacyl coenzyme A thiolase inhibitor, trimetazidine, affords a therapeutic approach that shifts cardiac energy metabolism from fatty acid to glucose oxidation in the heart. The findings of the study by Sorokina et al suggest that a similar approach may be useful in the hypertrophied heart. By stimulating glucose oxidation as a source of TCA cycle carbons, the potential exists to improve cardiac efficiency, as anaplerosis is an inherently inefficient process for energy synthesis compared with glucose oxidation. The authors concluded that ''the potential salutary impact of therapeutic protocols for cardiomyopathy that augment glucose oxidation through pyruvate dehydrogenase complex may derive not only from a shift away from fatty acid oxidation but also from diverting glucose away from the less efficient oxidation via anaplerosis toward the more normal route of the pyruvate dehydrogenase complex''. The study by these authors provides a strong rationale for further examination of the potential benefits of using fatty acid oxidation inhibitors, such as trimetazidine, as an approach to improving cardiac function and cardiac efficiency in the hypertrophied heart.

Gary Lopaschuk

Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes

Steven E. Nissen, Kathy Wolski *N Engl J Med* 2007;356:2457–2471.

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined. Searches of the published literature, the web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline) were conducted. Criteria for inclusion in the meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. All occurrences of myocardial infarction and death from cardiovascular causes were tabulated. Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, compared with the control group, the odds ratio for myocardial infarction was 1.43 [95% confidence interval (CI) 1.03–1.98; $P=0.03$), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI 0.98–2.74; $P=0.06$). Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. The study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

Commentary

This heterogenous meta-analysis of multiple data sources has already received a great deal of commentary in the medical, scientific, lay and financial press. Nonetheless, I thought it useful to emphasize points already expressed by others. There is no doubt the meta-analysis has influenced patients' preferences, doctors' prescribing habits and consequently GlaxoSmithKline's share price [1]. I would argue, however, that these 'knee-jerk' spinal reflexes need to be suppressed by higher centres!

The authors of the above article, and of the covering Editorial, go to some length to point out its failings. Among the most serious of these is the absolute number of events. The conclusions are based on 86 myocardial infarctions in the rosiglitazone group and 72 in the control group. There were 39 deaths from cardiovascular causes in the rosiglitazone group and 22 in the control group. These events were recorded among 27 843 patients, predominantly with overt diabetes, followed for 6–12 months. Based on simple arithmetic, and the worst case scenario, this corresponds to an annualized cardiovascular mortality of only 0.004%, suggesting that the diverse data sources may have resulted in incomplete follow-up and therefore ascertainment bias. The other concern, to me at least, is the underlying biological plausibility. The concerns raised by Nissen and Wolski regarding rosiglitazone have been likened to those raised by Garret FitzGerald over COX-2 inhibitors [2]. The concerns of FitzGerald, however, stemmed from a basic understanding of COX-2 biology underpinned by a long track record of focused and related clinical and basic research. With rosiglitazone the situation is more complex because the authors of the meta-analysis acknowledge in their discussion that the potential adverse cardiovascular effects do not seem to be shared by pioglitazone, another thiazolidinedione and peroxisome-proliferator-activated receptor gamma agonist. One is thus forced to hypothesize

that the potential adverse effects of rosiglitazone are related to 'off-target' actions. Furthermore, these 'off-target' effects seem of too greater a magnitude to be explained by the seemingly modest apparent differences between pioglitazone and rosiglitazone on traditional cardiovascular risk factors such as lipid profiles.

In both the article above and its covering Editorial the US Food and Drug Administration are criticized for licensing glitazones on the basis of their efficacy in lowering blood glucose rather than mortality; the argument being that patients with type 2 diabetes do not die from hyperglycemia but from cardiovascular complications. This is clearly an area that needs to be watched carefully because it could easily become a slippery slope for rationally designed drugs that target a basic fundamental process in disease, in this case insulin sensitivity. Such rational design, based on the careful identification of a biological target and synthesis of a small molecule based on the target's structure, maybe stifled in development by the crippling costs of mortality trials. To a simple clinician-scientist like myself the parachute is rationally designed to lower your terminal velocity, I do not need proof it also saves lives!

REFERENCES

1. Ledford H. Weighing up the evidence. *Nature*. 2007;447:512–513.
2. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci U S A*. 1999;96:272–277.