Carnitine Deficiency Disorders in Pediatrics

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Fatty Acid Oxidation and Its Relation with Insulin Resistance and Associated Disorders

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Key Words

Carnitine · Insulin resistance · Cardiomyocyte · Carnitine acyltransferase · Treatment · Glucose oxidation · Fatty acid oxidation

Abstract

Alterations in muscle fatty acid metabolism have been implicated in mediating the severity of insulin resistance. In the insulin resistant heart fatty acids are favored as an energy source over glucose, which is thus associated with increased fatty acid oxidation, and an overall decrease in glycolysis and glucose oxidation. In addition, excessive uptake and beta-oxidation of fatty acids in obesity and diabetes can compromise cardiac function. In animal studies, mice fed a high fat diet (HFD) show cardiac insulin resistance in which the accumulation of intra-myocardial diacylglycerol has been implicated, likely involving parallel signaling pathways. A HFD also results in accumulation of fatty acid oxidation by-products in muscle, further contributing to insulin resistance. Carnitine acetyltransferase (CrAT) has an essential role in the cardiomyocyte because of its need for large amounts of carnitine. In the cardiomyocyte, carnitine switches energy substrate preference in the heart from fatty acid oxidation to glucose oxidation. This carnitine-induced switch in fatty acid oxidation to glucose oxidation is due to the presence of cytosolic CrAT and reverse CrAT activity. Accordingly, inhibition of fatty acid oxidation, or stimulation of CrAT, may be a novel approach to treatment of insulin resistance.

Alterations in muscle fatty acid metabolism have been implicated in mediating the severity of insulin resistance. As muscle fatty acid uptake and oxidation is increased in insulin-resistant and diabetic individuals, increased fatty acid metabolism can thus directly impair glucose metabolism in muscle. In addition, accumulation of fatty acid metabolites in muscle can impair insulin signaling, and as will be explained later, L-carnitine supplementation can prevent the accumulation of these metabolites and directly stimulate muscle glucose metabolism. Carnitine acetyltransferase (CrAT) is also a key player in these pathways.

Metabolism in the Aerobic and Insulin Resistant Heart

Energy metabolism in the aerobic heart differs from that in the insulin-resistant heart (fig. 1). In the latter, fatty acids are favored as an energy source over glucose, which is thus associated with increased fatty acid oxidation, and an overall decrease in glycolysis and glucose oxidation.

This has also been shown in animal studies where the contribution of fatty acid oxidation to ATP production is increased in high fat diet (HFD) obese mice hearts [1, 2]. Importantly, an excessive reliance on fatty acid oxidation as a source of energy can increase the oxygen cost of contractility [3]. Moreover, inhibition of fatty acid oxidation and stimulation of glucose oxidation increases cardiac efficiency in the failing heart as has been demonstrated in a

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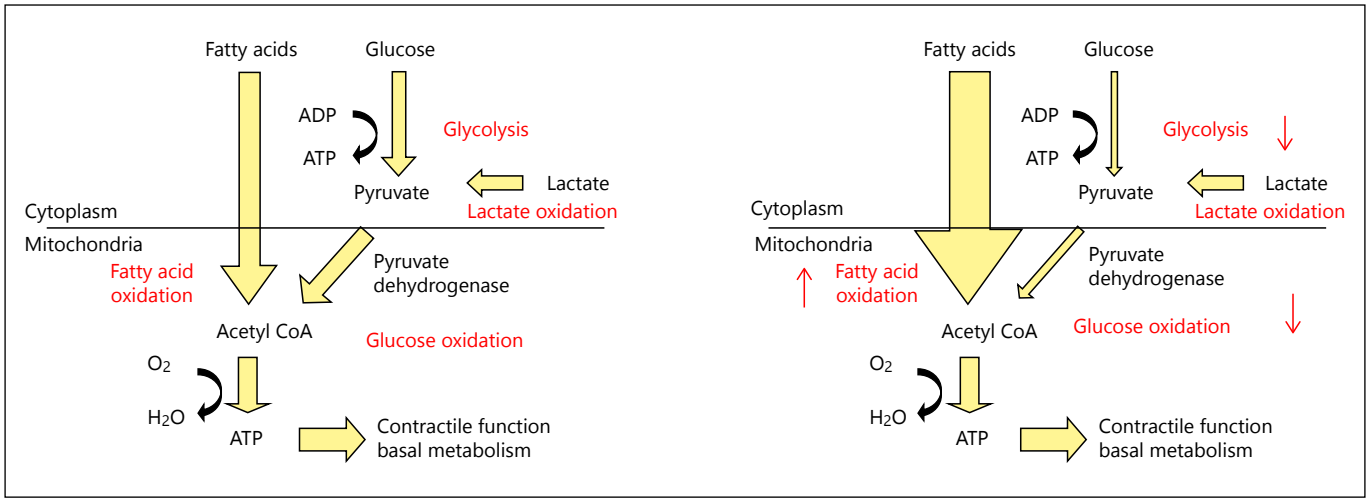

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Fig. 1. Differences in energy metabolism in the aerobic and insulin-resistant heart.

variety of animal models [4]. As an example, in a mouse model, altered myocardial substrate use and reduced myocardial efficiency were found to be early abnormalities in the hearts of obese mice and preceded the onset of hyperglycemia [5].

The fact that excessive uptake and beta-oxidation of fatty acids in obesity and diabetes can compromise cardiac function has also been demonstrated in young women where obesity and insulin resistance affected myocardial substrate metabolism and efficiency [6]. In particular, obesity is a significant predictor of increased myocardial oxygen consumption and decreased efficiency, and insulin resistance is a robust predictor of fatty acid uptake, utilization and oxidation. Moreover, increased myocardial fatty acid metabolism has been observed in patients with type I diabetes who showed increased fatty acid uptake and beta-oxidation along with reduced myocardial glucose utilization, consistent with experimental models of diabetes [7]. Interestingly, in an animal model of type 2 diabetes, the db/db mouse, treatment with Ang 1-7 led to a reduction in cardiac hypertrophy and lipotoxicity, adipose inflammation and upregulation of adipose triglyceride lipase [8]. Treatment with Ang 1-7 also completely rescued the diastolic dysfunction in the same mouse model.

The Effects of a HFD

In animal studies, mice show fed a HFD cardiac insulin resistance in which the accumulation of intra-myocardial diacylglycerol has been implicated [2]. The same authors proposed a pathway in which a HFD induces the development of cardiac insulin resistance. Instead of upregulating the rate of fatty acids oxidation and enhancing the biosynthesis of ceramide, HFD-induced accumulation of myocardial long-chain acyl coenzyme A (CoA) triggers the GPAT pathway for biosynthesis of diacylglycerol. Also, cardiac DGAT2 activity is decreased, and as a consequence, diacylglycerol accumulates. This, in turn, triggers the translocation of protein kinase Cα (PKCα) to the plasma membrane. Translocation of PKCα not only activates PLD1, but also modifies IRS1 phosphorylation. Thus, parallel signaling pathways may contribute to the development of HFD-induced cardiac insulin resistance.

Incomplete Fatty Acid Oxidation Contributes to Muscle Insulin Resistance

A HFD results in accumulation of fatty acid oxidation byproducts in muscle. Metabolomic studies have found that mice fed a HFD demonstrate incomplete oxidation of fatty acids, which is also accompanied by an increase in whole body fatty acid oxidation [9]. This, in turn, contributes to insulin resistance in skeletal muscle. In this model, inhibition of malonyl CoA decarboxylase (MCD) increases glucose oxidation. Ussher et al. [1] studied the effects of diet-induced obesity in wild-type mice and mice deficient for MCD (–/–) on insulin-sensitive cardiac glucose oxidation. MCD deletion was found to increase cardiac insulin sensitivity in HFD mice; diet-induced obe-

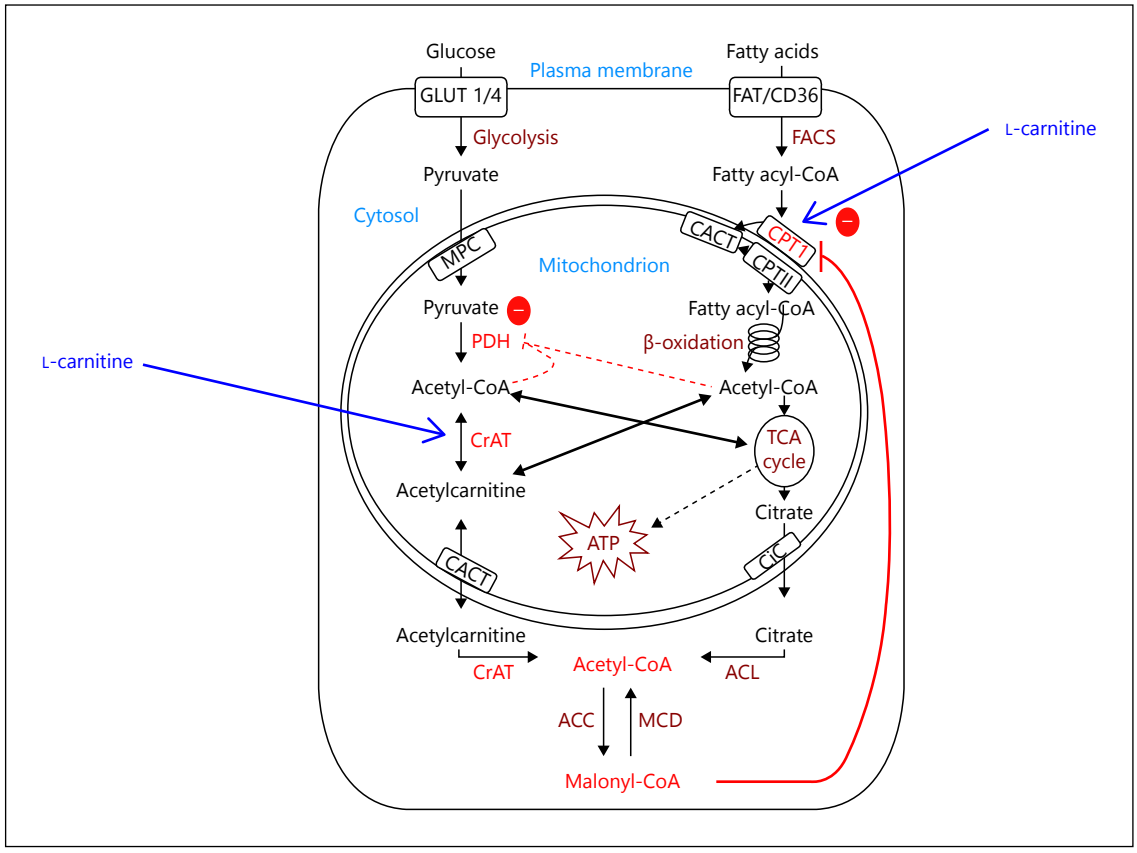

Fig. 2. Proposed roles of CrAT in the cardiomyocyte.

sity is associated with reduced insulin-stimulated glucose oxidation compared to low fat-fed WT mice. Moreover, MCD (–/–) mice subjected to diet-induced obesity display increased insulin-stimulated glucose oxidation and less incomplete fatty acid oxidation. This is associated with a decrease in long-chain acylcarnitines compared with wild-type mice.

Role of CrAT in the Cardiomyocyte

Carnitine has clear effects on CPT1, but in many disease states such as insulin resistance, this pathway is excessively active. However, there is another pathway in which carnitine is important, namely that involving CrAT (fig. 2). CrAT is particularly relevant because of its need for higher concentrations of carnitine. In the cardiomyocyte, carnitine switches energy substrate preference in the heart from fatty acid oxidation to glucose oxidation.

In perfused rat heart supplemented with carnitine, acute carnitine levels are increased, which was associated with a situation in which there is increased glucose oxidation and decreased fatty acid beta-oxidation, thus switching oxidation to a more preferable substrate (fig. 3) [10].

CrAT and Metabolic Flexibility

This carnitine-induced switch in fatty acid oxidation to glucose oxidation may occur due to the presence of cytosolic CrAT, and in particular reverse CrAT activity, wherein acetylcarnitine is transformed into acetyl CoA which ultimately inhibits production of malonyl CoA to inhibit CPT1 (fig. 2). Our group has shown that the heart, in fact, has a high level of reverse CrAT activity (fig. 4). Thus, in the heart, CrAT can act as a buffer by influencing the levels of acetyl CoA in the mitochondria and cytosol. Stimulating CrAT has the potential to create a large amount of metabolic flexibility in the heart as also suggested by other authors [11]. In fact, CrAT plays an essential role in regulating substrate switching and glucose

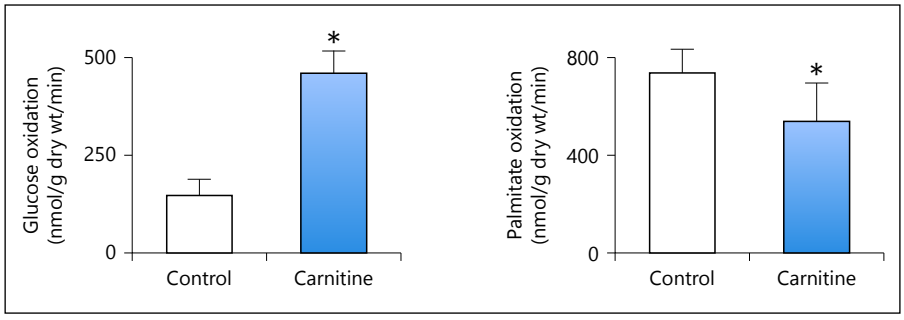

Fig. 3. Carnitine switches energy substrate preference in the heart from fatty acid oxidation to glucose oxidation. Adapted from [10].

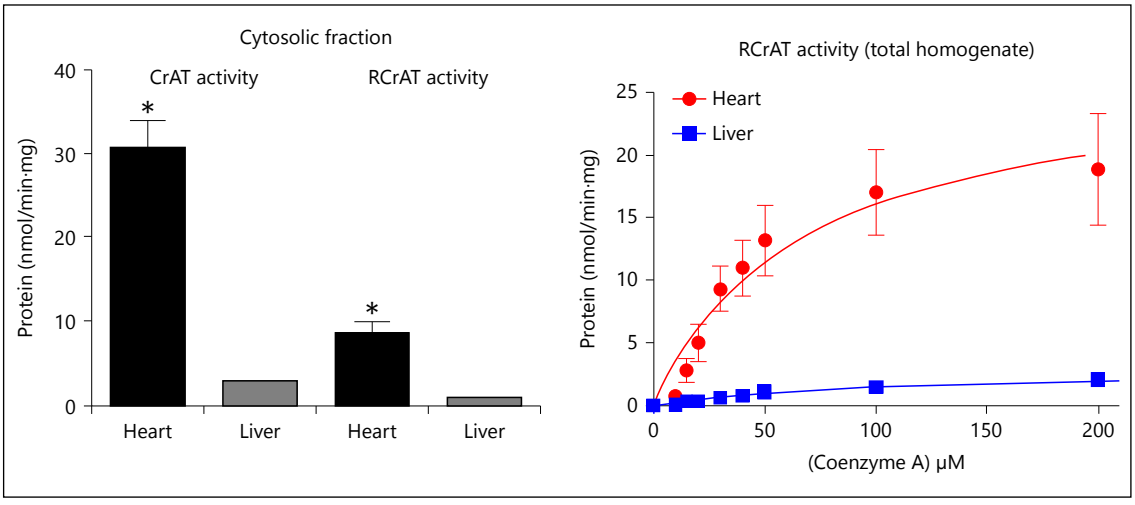

Fig. 4. Reverse CrAT activity is present in the cytoplasm of the heart (Altamimi and Lopaschuk, unpublished data).

tolerance. By converting acetyl-CoA to its membrane permeant acetylcarnitine ester, CrAT regulates mitochondrial and intracellular carbon trafficking. Several studies have indicated that CrAT combats nutrient stress and enhances insulin action by permitting mitochondrial efflux of excess acetyl moieties that otherwise inhibit key regulatory enzymes such as pyruvate dehydrogenase.

L-Carnitine Supplementation Affects Fatty Acid Beta-Oxidation

In further investigations, whole body carnitine diminution was identified as a common feature of insulin-resistant states such as advanced age, genetic diabetes and diet-induced obesity. In particular, rodents fed a 12-month HFD, show a compromised carnitine status that is accompanied by increased skeletal muscle accumulation of acylcarnitine and decreased hepatic expression of carnitine biosynthetic genes [12]. The diminished reserves of carnitine in muscle of obese rats is accompanied by low rates of complete fatty acid beta-oxidation, elevated incomplete beta-oxidation and impaired substrate switching from fatty acid to pyruvate. Interestingly, these abnormalities were reversed by 8 weeks of oral carnitine supplementation, in concert with increased tissue efflux and urinary excretion of acetylcarnitine and improvement of whole body glucose tolerance. A role for CrAT in reversing glucose intolerance was further supported by the finding that CrAT overexpression in primary human skeletal myocytes increases glucose uptake and attenuates lipid-induced suppression of glucose oxidation. Thus, carnitine insufficiency and reduced CrAT activity may be considered as reversible components of metabolic syndrome.

These results have also been supported by additional studies in humans who were receiving L-carnitine supple-

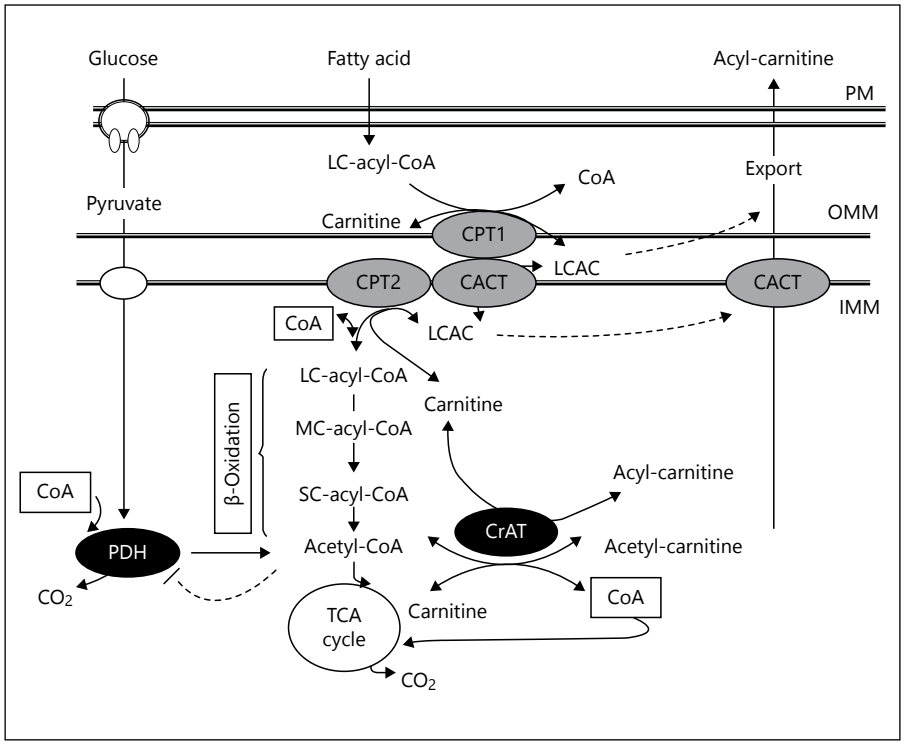

Fig. 5. Proposed role of carnitine and CrAT in regulating mitochondrial energetics.

mentation. In these individuals, free carnitine levels in blood are increased and accompanied by a decreased HOMA score and increased glucose tolerance [11].

Proposed Role of Carnitine and CrAT

Thus, the general concept is that stimulation of CrAT through the presence of higher levels of carnitine can buffer the acetyl CoA to acetylcarnitine and relieve the inhibition of pyruvate dehydrogenase and inhibit incomplete fatty acid oxidation (fig. 5). Inhibition of fatty acid oxidation, or stimulation of CrAT, may thus be an approach to treat insulin resistance.

Lastly, obesity and lipid stress inhibit CrAT activity [13]. This was shown by mass spectrometry-based metabolic profiling, which demonstrated a negative relationship between CrAT activity and muscle content of lipid intermediates. In particular, CrAT activity is diminished in muscles from obese and diabetic rodents, despite increased levels of protein abundance, which is associated with accumulation of long-chain acylcarnitines and acyl CoA along with a decrease in the acetylcarnitine/acetyl-CoA ratio. Accordingly, lipid-induced antagonism of CrAT might contribute to decreased activity of pyruvate dehydrogenase and glucose utilization in obesity and diabetes.

Conclusions

- Obesity and insulin resistance in the heart is associated with high fatty acid beta-oxidation and low glucose oxidation rates. This contributes to diastolic dysfunction in obesity.
- Increases in heart and muscle diacylglycerol are associated with cardiac insulin resistance early in the development of diet-induced obesity.
- Incomplete fatty acid oxidation contributes to insulin resistance in heart and muscle.
- Carnitine deficiency and decreased CrAT activity contribute to the increase in incomplete fatty acid oxidation.
- Inhibition of fatty acid oxidation, or stimulation of CrAT, may be an approach to treating insulin resistance.

Disclosure Statement

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