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Myocardial utilization of carbohydrate and lipids â˜†

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Abstract

Fatty acids represent a very important, if not the most important, substrate for myocardial energy metabolism. The heart derives fatty acids from circulating FFA bound to albumin and from plasma triglycerides. The rate of extraction of albumin bound FFA depends upon the albumin: FFA molar ratio and the metabolic state of the tissue. Since the albumin concentration in vivo is fairly constant, the albumin: fatty acid ratio is determined by the concentration of fatty acids in the serum. The fatty acid concentration is in turn regulated by dietary intake, de novo synthesis in the liver and adipose tissue, and the rate of fatty acid mobilization from adipose tissue. Mobilization from adipose tissue is increased during states of substrate deficiency such as fasting, diabetes or during the postabsorptive state and is decreased during periods of substrate excess. The rate of myocardial utilization of circulating triglycerides depends on the activity of lipoprotein lipases. The activity of

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these enzymes is under hormonal control and is increased by fasting or diabetes and is decreased by refeeding.

Although the rate of FFA uptake by the heart is dependent upon the level of circulating FFA, the rate of uptake at any one concentration of exogenous FFA depends upon the metabolic state of the tissue. The rate of uptake and oxidation was increased by epinephrine (probably as a result of a positive inotropic effect) and by increased ventricular pressure development. The rate of uptake was decreased and the incorporation of fatty acids into tissue lipids was increased by reduced oxygen supply to the tissue.

Regulation of fatty acid utilization by the heart is poorly understood. At low concentrations of exogenous fatty acid, the rate-limiting steps for uptake are located prior to formation of acetyl CoA. At 0.4 mM exogenous palmitate, increased ventricular pressure development accelerated the rates of oxygen consumption, CO_2 production from C^{14}-palmitate and palmitate uptake. This faster rate of uptake was associated with an increased tissue content of long-chain acyl carnitine and a decreased content of long-chain acyl CoA and FFA. These data suggest that fatty acid uptake was accelerated by increased cardiac work due to an acceleration of carnitine-palmityl CoA transferase and reduced levels of tissue FFA. The lower intracellular levels of FFA would establish a larger concentration gradient between intracellular binding sites and binding sites on plasma albumin, which would accelerate transfer of exogenous fatty acid into the myocardial cells.

At higher levels of exogenous fatty acids, the citric acid cycle limited the rate of fatty acid oxidation and uptake. The rate of the citric acid cycle was limited at the level of isocitrate dehydrogenase (due to a high NADHNAD ratio) and at the level of citrate synthetase (due to reduced availability of oxaloacetate). The limited rate of isocitric dehydrogenase resulted in increased tissue levels of citrate and isocitrate and decreased levels of Î±-ketoglutarate, succinyl CoA, malate, and oxaloacetate. Accumulation of citrate and isocitrate was limited by the availability of oxaloacetate and a limited rate of citrate synthetase resulted in accumulation of high levels of acetyl CoA. The carbon that accumulated within the cycle as citrate and isocitrate was derived from intermediates in the span of the cycle form Î±-ketoglurate to oxaloacetate and by converting aspartate to oxaloacetate. Low levels of oxaloacetate resulted from a high NADHNAD ratio, a limited availability of malate, due to inhibition of isocitric dehydrogenase, a reduced level of aspartate and from increased utilization by citrate synthetase.

Increased ventricular pressure development accelerated the rate of NADH oxidation as indicated by a faster rate of oxygen consumption, increased the rate of flux through the citric acid cycle as shown by a faster rate of CO_2 production, and deareased the level of acetyl CoA and increased the rate of fatty acid uptake. Increased cardiac work accelerated citrate synthesis by increased levels of oxaloacetate at all levels of exogenous fatty acids that were studied. At low levels of fatty acid, increased production of oxaloacetate resulted from a stimulation of Î±-ketoglutarate dehydrogenase and malate dehydrogenase. At higher levels of exogenous palmitate, the primary effect of increased work was stimulation of isocitric dehydrogenase. The rate of malate dehydrogenase was also increased. These effects of cardiac work resulted from an increased rate of oxidative phosphorylation and a reduced NADHNAD ratio.

Data presented indicated that translocation of long-chain acyl groups from extramitochondrial acyl carnitine to intramitochondrial acyl CoA restricted fatty acid oxidation when the level of exogenous fatty acid was low or when the tissue content of acetyl CoA was decreased by increased cardiac work at high levels of exogenous fatty acid. This restriction was bypassed and a high tissue level of acetyl CoA was maintained in hearts that were perfused with octanoate even when the rate of the citric acid cycle and the rate of octanoate uptake was accelerated twofold by increased cardiac work. With palmitate as substrate, increased cardiac work resulted in lower levels of acetyl CoA, acetyl carnitine and long-chain acyl CoA and in higher levels of long-chain acyl carnitine, indicating that carnitine:acyl CoA transferase was stimulated. Higher levels of acyl carnitine would help overcome the restriction to acyl translocation across the inner mitochondrial membrane and facilitate fatty acid oxidation.

Endogenous triglycerides represent a readily available supply of substrate for energy metabolism. Oxidation of the triglyceride fatty acids stored in the tissue could support normal rates of oxygen consumption for about 45 min. Only about 50% of these fatty acids appeared to be available for oxidation. The rate of triglyceride breakdown was accelerated by increased ventricular pressure development and this effect was reduced by the presence of exogenous long-chain fatty acids, but not by short-chain acids. The rate of triglyceride synthesis was increased by greater availability of circulating fatty acids and higher tissue levels of acyl CoA or by a reduced rate of oxidative metabolism.

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