Energy Metabolism and Cytotoxicity

By Didier Portilla

Fatty acids constitute a major source of metabolic fuel for energy production in kidney tissue. During acute renal failure (ARF) injury to the proximal tubule and medullary thick ascending limb leads to structural and functional alterations that result in reduced expression and activity of mitochondrial and peroxisomal fatty acid oxidation (FAO) enzymes. Reduced DNA binding activity of peroxisome proliferator activated receptor-α (PPARα) to its target genes and decreased expression of its tissue-specific coactivator PPAR-γ-coactivator-1 (PGC-1) in the mouse proximal tubule and the medullary thick ascending limb, represent 2 potential mechanisms that account for the observed alterations of FAO during ARF. Pretreatment with PPARα ligands restores the expression and activity of renal FAO enzymes, and this metabolic alteration leads to amelioration of acute tubular necrosis caused by ischemia/reperfusion or cisplatin-induced ARF. More studies are needed to examine further the cellular mechanisms of substrate inhibition, and to determine if metabolic pathways, in addition to the recovery of FAO, account for the protective effect (s) of PPARα ligands during acute renal failure.
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THE USE OF FATTY ACIDS for energy production varies significantly among various tissues depending on the metabolic status of the body. Although nervous tissues oxidize fatty acids to a minimal degree, cardiac, skeletal muscle, and kidney cortex depend heavily on fatty acids as a major energy source.[1-4] Fatty acids delivered to renal epithelial cells are taken up via the basolateral membrane and used for energy production primarily by mitochondria and peroxisomes in a process intimately integrated with energy generation from other sources. The process of oxidation of fatty acids occurs by biochemical mechanisms in which 2 carbon fragments of the fatty acid molecule are removed sequentially from the carboxyl end of the acid after dehydrogenation, hydration, and oxidation to form a β-keto acid, which is split by thiolysis. The reactions involved in mitochondrial β oxidation are identical to those for peroxisomal β oxidation, except that peroxisomes do not use carnitine as the carrier system for the entry of fatty acids into the inner matrix.[5-9]

In the mitochondria, the first step in the oxidation of a fatty acid is its activation to a fatty acyl CoA. This is similar to the reaction involved in the synthesis of triacylglycerol and occurs in the endoplasmic reticulum or the outer mitochondrial membrane. To cross the inner mitochondrial membrane, which is impermeable to CoA derivatives, fatty acid acyl groups use the carnitine carrier system. The steps involved in this system are outlined in Figure 1.

On the outer mitochondrial membrane the acyl group is transferred to carnitine catalyzed by the enzyme carnitine palmitoyltransferase I. Acyl carnitine then exchanges across the inner mitochondrial membrane with free carnitine by a carnitine-acylcarnitine antiporter translocase. Finally, the fatty acyl group is transferred back to CoA by carnitine palmitoyltransferase II, located on the matrix of the inner membrane. This process functions primarily in mitochondrial transport of fatty acyl CoAs with chain lengths of C12 to C18. By contrast, entry of shorter chain fatty acids is independent of carnitine because they cross the inner mitochondrial membrane and become activated to their CoA derivative in the matrix.[10] The 4 chemical reactions involved in mitochondrial β oxidation of fatty acids that occur inside the inner mitochondrial membrane are presented in Fig 2.

In the first reaction, the fatty acyl CoA formed at the inner surface of the inner mitochondrial membrane can be oxidized by acyl CoA dehydrogenase, a flavoprotein that uses flavin adenine dinucleotide (FAD) as the electron acceptor (reaction 1). The products are enoyl CoA with a trans-double bond between the C-2 and C-3 atoms and enzyme-bound $FADH_2$. At least 4 enzymes are involved in the first dehydrogenation step. These are referred to as very long chain, long-chain, medium-chain, and short-chain acyl CoA dehydrogenases. Very long chain acyl CoA dehydrogenase, which is thought to handle straight-chain acyl CoAs ranging from

From the Department of Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR; and the Department of Renal Medicine, Central Arkansas Veterans Healthcare System, Little Rock, AR.

Address reprint requests to Didier Portilla, MD, Department of Nephrology, University of Arkansas for Medical Sciences, 4301 W. Markham St, Little Rock, AR 72205. E-mail: DPortilla1@uams.edu

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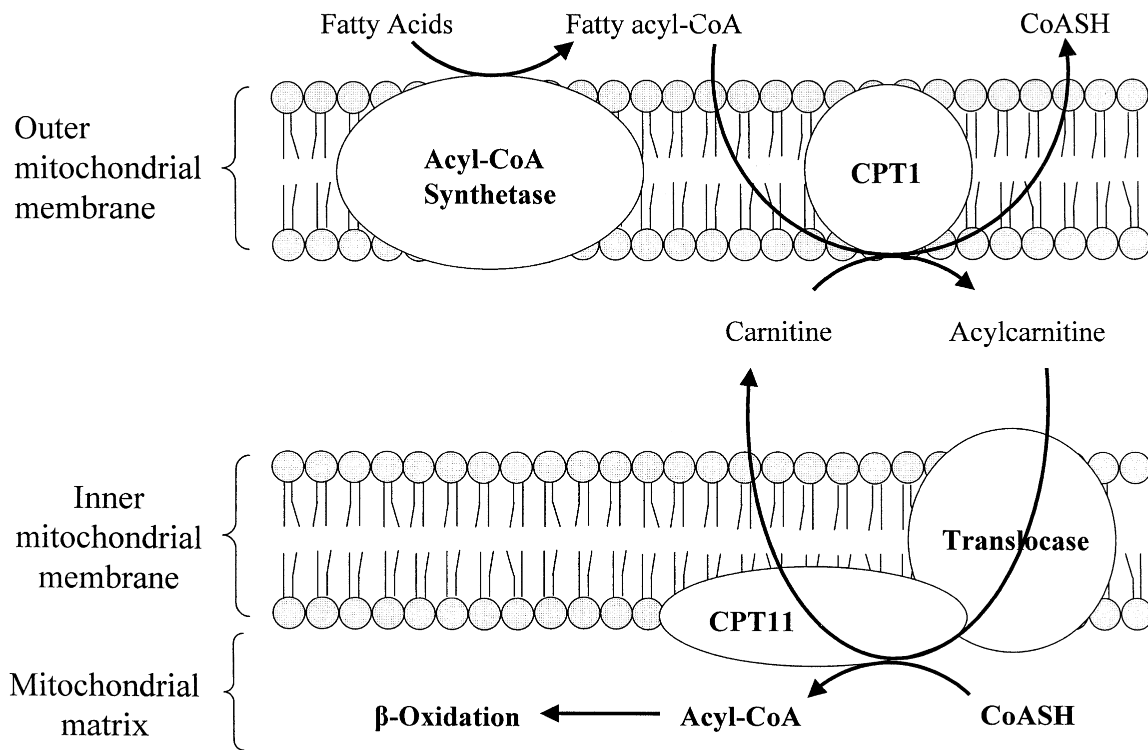

Fig 1. Mechanisms for transfer of fatty acids from the cytosol through the inner mitochondrial membrane for oxidation.

C-12 to C-24, differs from the other family members in that it is membrane associated. Medium-chain acyl CoA dehydrogenase has broad chain length specificity but is mostly active toward C-6 and C-8 substrates, while the order of preference for short-chain acyl CoA dehydrogenase is C4 > C6 > C8. Long-chain acyl CoA dehydrogenase primarily is involved in initiating the oxidation of branched-chain fatty acids. The second step in β-oxidation of fatty acids is the hydration of the trans-double bond to a 3-L-hydroxyacyl CoA. This reaction is stereospecific in that the L-isomer is the product when the trans-double bond is hydrated. The stereospecificity of the oxidative pathway is governed by the enzyme catalyzing the third reaction, which is specific for the L-isomer as its substrate. The final step is the cleavage of the 2-carbon fragment by a thiolase. Each set of fatty acid oxidation results in the production of one acetyl CoA molecule, one reduced flavoprotein and one reduced form of nicotinamide-adenine dinucleotide (NADH). In the oxidation of palmitoyl CoA, for example, 7 cleavages take place, and in the last cleavage 2 acetyl CoA molecules are formed.[11]

Peroxisomes are single membrane bound organelles present in almost every mammalian cell. These organelles contain more than 50 proteins that participate in well-conserved functions including H_2O_2-based respiration, fatty acid β-oxidation, ether lipid (plasmalogen) synthesis, and cholesterol biosynthesis.[12-15] Although short- and medium-chain fatty acids are oxidized in mitochondria, long- and very long chain fatty acids are processed almost exclusively by the peroxisomal β oxidation system.[16] Similar to mitochondrial fatty acid β oxidation, 3 enzymes participate in the peroxisomal α oxidation pathway, namely fatty acyl CoA oxidase, enoyl CoA hydratase/3-hydroxyacyl CoA dehydrogenase (trifunctional enzyme), and 3-keto-acyl-CoA thiolase. Profound defects in peroxisomal β oxidation of fatty acids and peroxisome biogenesis occur in some human peroxisomal genetic disorders, such as Zellweger's syndrome, neonatal adrenoleukodystrophy, and infantile Refsum's disease.[17-19] These disorders are characterized by a lack or substantial reduction in the number of morphologically distinguishable peroxisomes in liver and kidney proximal tubule cells

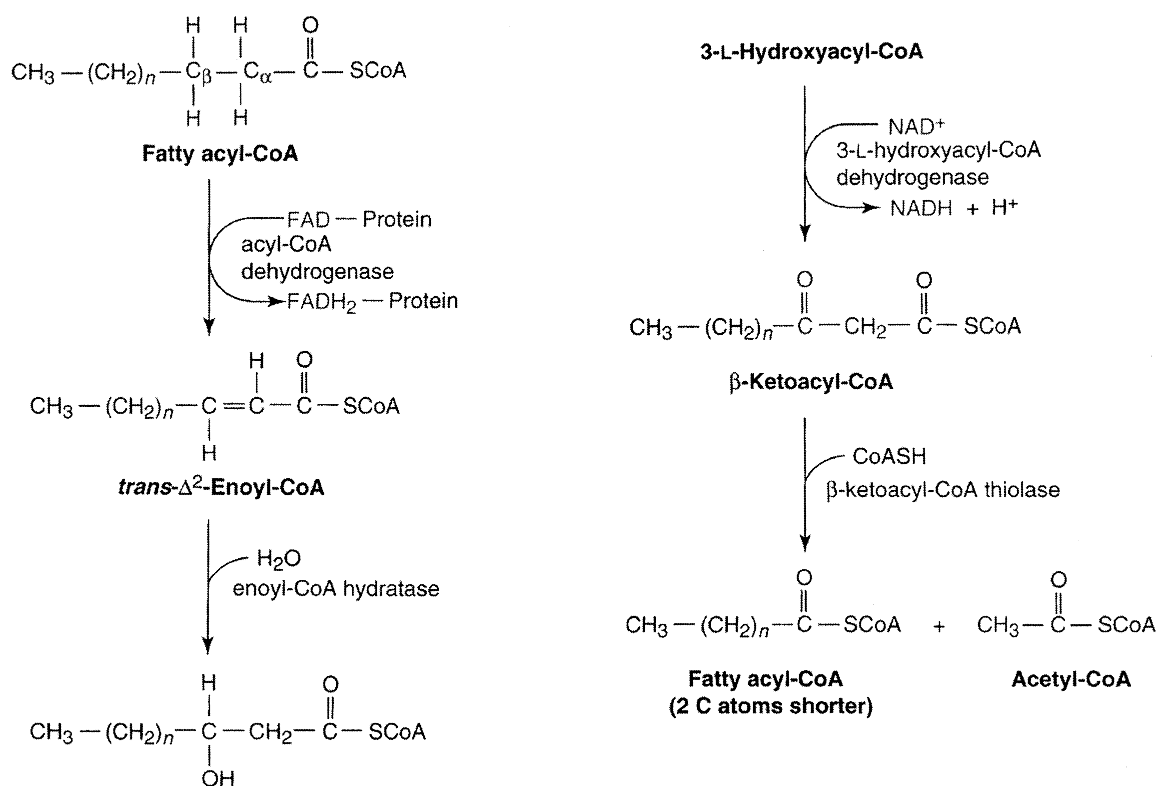

Fig 2. Pathways for fatty acid β-oxidation.

owing to abnormalities in peroxisome assembly. This leads to multiple peroxisomal functional defects including abnormalities in the β oxidation of very long-chain fatty acids.

ENERGY PRODUCTION VIA FATTY ACID OXIDATION

The products of β oxidation of palmitate are 8 acetyl CoAs, 7 reduced flavoproteins, and 7 NADHs. Based on the yield of adenosine triphosphate (ATP) in oxidative phosphorylation, each of the reduced flavoproteins can yield 1.5 ATP and each NADH can yield 2.5 ATP when oxidized by the electron transport chain. Oxidation of each acetyl CoA through the TCA cycle yields 10 ATP, so the eight 2-carbon fragments from a palmitate molecule produce 80 ATP. However, 2 ATP equivalents are used to activate palmitate to palmitoyl CoA. Therefore, each pamitate entering the cell can yield 106 ATP mol-1 by complete oxidation. These stoichiometric measurements underscore the notion that β oxidation of straight-chain fatty acids represent an important energy producing process in the kidney cortex and more specifically in the proximal tubule.

PEROXISOMAL AND MITOCHONDRIAL FATTY ACID OXIDATION ARE INHIBITED IN THE KIDNEY DURING ACUTE RENAL FAILURE

Structural Changes in Mitochondrial and Peroxisomal Compartments During Acute Renal Failure

Previous studies have shown the existence of structural and functional alterations in peroxisomal and mitochondrial organelles after ischemia-reperfusion (I/R) injury. The peroxisomes isolated from normal rat kidney had a density of 1.21 g/cm^3, whereas those isolated from kidneys exposed to ischemic injury yielded 2 populations, one with densities of 1.21 gm/cm^3 (peak I) or peroxisomes of normal density, and a second light density population with a density of 1.14 gm/cm^3 named peak II. Based on immunostaining with catalase the studies showed that the matrix structure was disrupted in the peroxisomes isolated in peak I, but intact in the peroxisomes isolated from peak II.

Those studies have suggested that the population of lighter peroxisomes seen during ischemic injury may be the newly biosynthesized peroxisomes.[20,21]

Two mitochondrial structural abnormalities have been considered to be important pathogenic factors during ischemia. One is characterized by pore formation in the inner mitochondrial membrane, which leads to de-energization and high amplitude swelling (mitochondrial permeability transition).[22] The second involves leakage of cytochrome C from the intermembrane space into the cytosol.[23] Because of its role as an electron shuttle, dislocation of cytochrome C compromises respiration,[24,25] and as a cytosolic factor activates caspase 9 and triggers apoptosis.[23] Cytochrome C may follow the mitochondrial permeability transition or occur independently. After the development of the 2 mitochondrial structural alterations renal epithelial cells can die by necrosis and/or apoptosis. The proximal signaling events that lead to the mitochondrial permeability transition and loss of cytochrome C currently are under investigation. Mitochondrial dysfunction plays an important role in the development of cell injury during I/R or nephrotoxin-induced acute renal failure (ARF).[26,27] The mitochondrial defect that accounts for de-energization during ischemia includes the inhibition of F0-F1 adenosine triphosphatase, leading to impaired function of respiratory complex I.[27] Similar to ischemia, cisplatin has been shown to affect mitochondrial respiratory complexes and function. Kruidering et al[28] showed that exposure of freshly isolated porcine proximal tubules to cisplatin resulted in loss of mitochondrial membrane potential, which preceded cell death. Cisplatin specifically inhibited complexes I to IV of the respiratory chain after 20 minutes of incubation with 50 μmol/L cisplatin, and reduced intracellular ATP by 70% of control values.

Changes in peroxisomal and mitochondrial function accompany the observed changes in the structure of these 2 organelles during ARF. A significant decrease in the activities of catalase, β oxidation of lignoceric acid in peroxisomes, and the activity of dihydroxyacetone phosphate acyltransferase have been documented.[29-31] Our work using the model of I/R-induced ARF has confirmed that the structural abnormalities present during I/R are accompanied by significant reduction of messenger RNA and protein levels, as well as in the enzymatic activities of peroxisomal and mitochondrial fatty acid oxidation (FAO) enzymes. Our studies have shown at least a 50% reduction in enzyme activity of peroxisomal Acyl CoA oxidase after 45 minutes of ischemia and 24 hours of reperfusion.[32] Using the nephrotoxic model of cisplatin-induced ARF, we also showed decreased expression and enzyme activity of peroxisomal and mitochondrial FAO enzymes in mouse kidney and in proximal tubule cells in culture.[33]

Peroxisome Proliferator Activated Receptor α is the Major Regulator of FAO in Kidney Tissue

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors. One of the first drugs developed for lipid lowering, clofibrate, was noted to induce proliferation of peroxisomals in rodents.[34] The receptor activated by clofibrate subsequently was cloned and given the name PPARα.[35] Subsequently, PPARβ and PPARγ were identified as structural homologs of PPARα that control expression of many genes that participate in several metabolic pathways but do not induce peroxisome proliferation.[36,37] Although PPARα agonists induce FAO in humans, they do not induce proliferation of peroxisomes as in rodents, nevertheless, the name PPAR has remained. The PPAR subfamily of nuclear receptors all bind to peroxisome proliferator response elements such as heterodimers with the retinoid X receptor.[38]

PPARα is expressed in metabolically active tissues including liver, kidney, heart, skeletal muscle, and brown fat.[39,40] In the kidney, PPARα predominantly is expressed in the proximal tubule and medullary thick ascending limbs. Fatty acids are the main natural ligands for PPARα. In the kidney, binding to PPARα by fatty acids, eicosanoid, and fibrate drug ligands leads to the activation of numerous genes involved in the uptake and β oxidative catabolism of fatty acids. In addition to inducing all the genes encoding enzymes of the classic β oxidation pathway (eg, acyl CoA oxidase, very long and medium-chain acyl CoA dehydrogenase, 3 ketoacyl-CoA thiolase),[41] PPARα also activates the genes necessary for cellular uptake of fatty acids (fatty acid transport protein) and their initial derivatization for entry into the β oxidation pathway (acyl CoA synthetase).[42] This leads to increased diversion of fatty acids into β oxidation therefore regulating their availability for triglycer-

ide synthesis and, therefore, very low density lipoprotein secretion by the liver.

In addition to limiting substrate availability for triglyceride synthesis, PPARα has been reported to inhibit the expression of apolipoprotein C-III,[43,44] a protein that inhibits both the triglyceride-hydrolyzing action of lipoprotein lipase and the uptake of triglyceride-rich lipoprotein remnants. PPARα also plays an important role in regulating microsomal ω oxidation of fatty acids and eicosanoids. In particular, putative peroxisome proliferator response elements sites have been reported in the promoter region of CYPA1 genes, and PPARα agonists have been shown to enhance their expression both in vivo and in vitro.[45] Therefore, based on accumulating evidence, PPARα is considered a critical regulator of lipid catabolism in kidney tissue, including mitochondrial and peroxisomal β oxidation, microsomal ω oxidation, ketogenesis, and lipid transport.

PPARα MEDIATED UP-REGULATION OF PEROXISOMAL AND MITOCHONDRIAL FAO PROTECT DURING ARF

Using the clamping model of I/R-induced ARF we recently have shown that: (1) during ARF there is a severe reduction in messenger RNA, protein levels, and enzyme activities of PPARα target genes acyl CoA oxidase and medium-chain acyl CoA dehydrogenase; (2) the administration of PPARα ligands before I/R injury in PPARα wild-type mice reversed the inhibitory effect on messenger RNA, protein levels, and enzyme activities of FAO enzymes, and ameliorated both renal function and histopathologic alterations of acute tubular necrosis; (3) the administration of PPARα ligands to PPARα null mice did not affect the course of ARF or the inhibition of FAO; and (4) that PPARα null mice subjected to a similar degree of I/R or cisplatin injury exhibited enhanced necrosis of the corticomedullary junction and further deterioration of renal function when compared with PPARα wild-type mice.[32] Altogether these observations would suggest a central role for PPARα in controlling activation of FAO in kidney tissue that directly correlates with preservation of kidney morphology and function during I/R-induced ARF. In recent studies using the cisplatin model of ARF we found that cisplatin attenuates PPARα signaling by reducing its DNA binding activity without affecting PPARα or the retinoid X receptor α protein levels. In addition, we found that cisplatin reduces the expression of a recently described tissue-specific coactivator of PPARα named PPAR-γ-coactivator-1 (PGC-1).[33] This nuclear protein has been shown to be a transcriptional coactivator of PPARα,[46] PPARγ,[47] the retinoid X receptor,[48] and other transcription factors such as nuclear respiratory factors, which are important in the regulation of oxidative metabolism, cellular respiration, and adaptive thermogenesis.[49,50] In situ hybridization studies showed the expression of co-activator PGC-1 in the mouse proximal tubule and the thick ascending limb of Henle, 2 nephron segments that also express high levels of PPARα and FAO enzymes. Cisplatin inhibited the expression of PGC-1 in both nephron segments. Transient transfection studies confirmed the expression of PGC-1 in the nuclear compartment of LLCPK1 cells and its expression increased PPARα activity in the proximal tubule. Those studies showed that proximal tubule FAO is reduced in response to cisplatin, suggest that survival of renal tubular epithelial cells depends on intact PGC-1/PPARα function. Maintenance of lipid oxidation for energy balance during toxic injury to renal tubular epithelial cells appears to be an important determinant of cell survival under conditions of ischemia and nephrotic stress.

Although preservation of FAO may not represent the only mechanism by which PPARα ligands protect during acute renal injury, we believe that the anti-apoptotic role of PPARα could represent another potential mechanism of cytoprotection in kidney tissue. Indeed, our most recent studies have shown that the use of PPARα ligand WY 14,643 can prevent proximal tubule cell death by directly inhibiting cisplatin-stimulated caspase 3 activity.[51]

In summary, we believe that PPARα–mediated regulation of FAO plays an important role in the pathogenesis of I/R- and cisplatin-induced ARF. We further propose that PPARα ligands prevent cell death by at least 3 mechanisms: (1) activation of PPARα, preserves fatty acid oxidation, maintains energy, and prevents the accumulation of long-chain fatty acid toxic metabolites; (2) PPARα maintains the expression of antioxidant enzymes including peroxisomal catalase and mitochondrial uncoupled proteins that further spare mitochondria from injury; and (3) PPARα prevents the activation of apoptotic molecules including caspase 3, thus directly preventing apoptotic and necrotic cell death during ARF.

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