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Reprogramming of Energy Metabolism in Kidney Disease

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Abstract

Kidney tubules have high metabolic activity to support solute transport and other cellular functions. Energy generation in the kidney is largely dependent on mitochondrial oxidative phosphorylation, particularly in the proximal tubules. Important alterations in the pathways of energy generation and cellular metabolism have been identified in early and late stages of kidney disease. This review provides a succinct summary of the current literature on the central role of energy metabolism in the pathophysiology of acute and chronic kidney disease.

Introduction

Renal energy metabolism has enjoyed renewed attention in recent years. It's important role in the pathophysiology of kidney disease has been underscored in pre-clinical and clinical literature. Particularly, the primacy of proximal tubular metabolism in acute and chronic kidney disease has been increasingly demonstrated. As is well known, proximal tubules are amongst the most metabolically active segments of the nephron and utilize mitochondrial oxidative phosphorylation (OXPHOS) for ATP generation to support the high rates of tubular transport of various ions. Preferential substrates for ATP production in proximal tubules include fatty acids, amino acids and lactate to generate metabolites for the tricarboxylic acid cycle (TCA) within the mitochondria.

Under physiological conditions, kidneys filter large amounts of glucose (180g/day). Nearly all of this is reabsorbed by the proximal tubule via sodium-glucose cotransporters on the apical side and released into the circulation through facilitative glucose transporters on the basolateral membrane. The tubular glucose concentration exceeds the plasma concentration at any given time to allow the facilitative transport out of the proximal tubular cells to the peritubular capillaries. Proximal tubules also generate glucose via gluconeogenesis, with about 60% of endogenous glucose release in the postprandial period. Thus, proximal tubules are exposed to high glucose flux (~20mmol/L/min) but have limited capacity to catabolize glucose as a metabolic fuel under physiological conditions [1]. Of the three segments of

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the proximal tubules, the S3 segment has the highest glycolytic capacity. Other nephron segments can utilize glucose as a substrate and it's catabolism in the process of glycolysis generates pyruvate in the cytosol. Pyruvate can have different fates depending on availability of ambient oxygen. It can be converted to acetyl CoA and transported to the mitochondria for TCA cycle under normoxic conditions or converted to lactate in hypoxic conditions.

Renal Energy Metabolism and Metabolic Reprogramming in Kidney Disease

In recent years, altered metabolism has been described in a variety of kidney diseases. Specifically, fatty acid oxidation, glycolysis and oxidative metabolism has received significant attention in the pathogenesis and pathophysiology of kidney disease. Increased metabolic flux with upregulation of glycolysis, fatty acid oxidation and TCA cycle in cortex of diabetic mice has been reported [2]. This was accompanied by evidence of mitochondrial dysfunction. Similar findings were observed in kidney biopsy samples of patients with type2 diabetes on transcriptomic analyses [2]. Moreover, increased glycolytic and TCA metabolites in urine of patients with diabetes have been found and, in fact, predicted disease progression [2].

There is extensive literature on dysregulated metabolism in polycystic kidney disease (PKD)[3]. In animal models and in kidney tissue from patients with PKD, upregulated glycolytic genes have been observed [4]. Inhibition of glycolysis with 2-deoxyglucose reduced cystogenesis in animal models and human PKD cells [4, 5]. Besides a metabolic reprogramming toward aerobic glycolysis, changes in lipid metabolism have also been reported in PKD. Transcriptomic and metabolomic analyses has revealed reduced fatty acid oxidation in PKD models [3]. Treatment with fenofibrate, peroxisome proliferator–activated receptor alpha (PPARα) agonist which regulates fatty acid oxidation, reduced cystogenesis in PKD [6]. In targeted metabolomic analyses of serum from patients in the HALT-PKD study, alterations in fatty acid metabolism were observed [3].

In models of advanced fibrosis, reduced enzymes and regulators of fatty acid metabolism have been described [7]. In patient kidney biopsy samples, expression of genes involved in fatty acid metabolism and their transcriptional regulator were lower in CKD [7]. Interestingly, regulators of glycolysis were also lower in CKD kidney samples, suggesting an overall downregulation of renal metabolism. A reduction in fatty acid oxidation has been shown to play a causative role in the pathogenesis of renal fibrosis using genetic and pharmacological approaches [7]. In a recent study, conditional and inducible overexpression of key fatty acid oxidation enzyme, carnitine palmitoyl-transferase 1A (CPT1A), in renal tubules was protective in models of fibrosis with improved renal function and decreased fibrosis markers [8]. It also increased mitochondrial DNA copy number indicative mitochondrial biogenesis, mitochondrial bioenergetics and ATP levels.

Dysregulated metabolism has also been implicated in various forms of AKI [9]. Downregulation of fatty acid oxidation enzymes has been consistently shown in ischemic, nephrotoxic and sepsis associated AKI as recently reviewed [10]. Impaired fatty acid oxidation in the mitochondria and peroxisomes has been demonstrated in both ischemic and cisplatin induced AKI [11, 12]. This is accompanied by accumulation of free fatty

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acids in tubules which depolarize mitochondrial membrane potential and uncouple oxidative phosphorylation [12]. Upregulation of transcription factors such as PPARα which activate fatty acid oxidation, pharmacologically (fenofibrate) and genetically (proximal tubule specific), is protective against AKI [11]. In the cecal ligation and puncture (CLP) model of sepsis associated AKI, we observed decreased expression of rate limiting fatty acid oxidation enzymes including CPT 1 and 2 and acyl-CoA oxidase 2 [13].

Regarding glucose metabolism, the literature is rather variable. Early upregulation of different glycolytic enzymes within the first 24 hours after ischemia has been seen in some studies but not others [10]. The S3 segment has higher glycolytic capacity than the S1 and S2 segments of the proximal tubule but is also the segment that shows the most injury after ischemia. Under ischemic conditions, the glycolytic capacity of the S3 segment is inhibited resulting in tubular cell death. Altered levels of glucose, lactate and pyruvate have been reported after ischemia [14], but these can have different interpretations as both glucose utilization (glycolysis) and glucose generation (gluconeogenesis) occur in the kidney and may be impacted in AKI. In fact, decreased expression gluconeogenesis enzymes have been reported at 24 hours after ischemia and impaired gluconeogenesis was demonstrated by reduced glucose production and lactate conversion to glucose [15]. Decreased expression of some gluconeogenesis and increased expression of some glycolysis genes were also observed at 24 hours with RNA sequencing [15].

In models of sepsis-AKI, enhanced hexokinase activity has been shown along with increased phosphoenol pyruvate, pyruvate, and lactate levels [10]. We observed increase in expression of rate-limiting glycolytic enzymes at 24 hours after CLP along with decreased expression of pyruvate dehydrogenase which facilitates conversion of pyruvate to acetyl- CoA for the mitochondrial TCA cycle [13]. However, when functional glycolysis was assessed in proximal tubules, all parameters including basal and compensatory glycolysis as well as glycolytic capacity and reserve were lower in CLP. This could indicate depleted glycolysis due to it’s overconsumption as a source of energy generation or impaired glucose availability for glycolysis to proceed. Hence, detailed functional assessment beyond expression of enzymes can provide important insights into the metabolic changes in AKI.

Recent studies have examined the role of metabolic reprogramming in AKI to CKD transition, mostly using animal models of ischemia-reperfusion. At 2 weeks after ischemia, while several tubules appeared to have recovered, discreet tubules with atrophied morphology and surrounding fibrosis also showed the highest expression of glycolytic enzymes [14]. This suggests increased glycolytic capacity of tubular cells may be associated with a lack of recovery or maladaptive repair phenotype. Recently, in a longitudinal model of AKI with transition to CKD after aristolochic acid administration, there was downregulation of several genes involved in glycolysis, TCA cycle and fatty acid oxidation pathways which were sustained from early to late stages [16]. Interestingly, fatty acid biosynthetic pathways were upregulated and associated with hyperlipidemia, suggesting this renal metabolic reprogramming may result in lipid abnormalities seen in CKD.

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Summary and Perspective

The role of energy metabolism has been increasingly recognized in various etiologies of kidney disease. While recent literature has provided important insights into the dysregulation and reprogramming of energy metabolism, several unanswered questions remain regarding the significance, temporal effects and adaptive vs. maladaptive impact in AKI and CKD. It could be postulated that since glycolysis enables biomass synthesis, which is important for cellular repair and proliferation, that the glycolytic phenotype is induced as an adaptive mechanism after tubular injury. This may be beneficial in the early post0injury phase to support repair and recovery. However, persistence of this phenotype appears to be associated with increases fibrosis. Additional research on the adaptive or maladaptive impact of metabolic reprogramming during injury, repair and recovery is warranted and will enhance the development of potential therapeutics to target energy metabolism dysregulation in kidney disease.

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