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Overview/Abstract

Sepsis is a major cause of mortality and a common risk factor for acute kidney injury (AKI) among preterm and term newborns, contributing up to 78% of AKI cases in this population and potentially impacting on long-term renal function among survivors (1-10). High rates of chronic kidney-related problems including decreased glomerular filtration rate, proteinuria and/or hypertension have recently been reported among former extremely preterm newborns (< 28 completed weeks gestation at birth), many of whom had encountered sepsis and/or AKI during their initial hospitalization (11). The mechanisms how neonatal systemic infection can lead to AKI and/or CKD and what makes neonates so vulnerable to sepsis-induced kidney injury remain however poorly understood. Furthermore, currently available antimicrobial therapies alone do not prevent sepsis-induced AKI and/or subsequent CKD (12), and may even exert nephrotoxic effects (13).

To address this gap, we recently developed and published a murine model of neonatal bacterial sepsis-induced AKI (14). Preliminary findings on young adult survivors employing this model demonstrated histological proximal tubular injury as well as decreased glomerular filtration rate, which was accompanied by downregulation of renal mitochondrial energy metabolism genes, including fatty acid oxidation, peroxisome proliferator-activated receptor (PPAR) and AMP-activated protein kinase (AMPK) signaling pathways.

Caffeine, which is used in preterm newborns to treat apnea of prematurity, has been associated with decreased incidence and severity of AKI among very low birth weight and preterm neonates (15,16). Discontinuation of caffeine at a later postmenstrual age was associated with decreased risk of reduced estimated GFR at 2 years of age in former extremely preterm newborns without a diagnosis of chronic lung disease, however not among the entire cohort of extremely preterm neonates (17). Recent reports have shown that caffeine stimulated AMPK, PPAR-β/δ and mitochondrial biogenesis, thus improving cellular energetics and oxidative metabolism (18). In this regard, the PPAR-γ receptor is now emerging as a potential target to improve outcomes of preterm neonates such as chronic lung disease, necrotizing enterocolitis and lipopolysaccharide-induced brain injury (19).

Based on these reports and our own preliminary data, we hypothesize that neonatal sepsis-induced AKI leads to impairment of renal energy metabolic pathways and development of CKD. We further hypothesize that caffeine when administered in addition to antibiotics during neonatal bacterial sepsis can mitigate the development of CKD through enhancement of oxidative metabolism pathways such as PPAR and AMPK.

The aims of our project are therefore to

(1) examine the effects of neonatal sepsis on the metabolome of renal tissue, specifically the expression of energy metabolism promoting enzymes and their substrates during the recovery from sepsis, i.e., after 24 hours, 7 days, and 8 weeks from the time of sepsis initiation.
(2) determine if caffeine has a rescuing effect on renal tissue energy metabolic enzyme and metabolome expression during and following the acute sepsis episode, and to evaluate its potential impact on renal structural and functional outcome.

We anticipate that these experiments will validate our hypothesis, and find that neonatal sepsis leads to dysregulation of energy metabolism promoting-enzymes and their substrates during sepsis recovery. We further anticipate that adjunctive caffeine treatment in addition to antibiotics will improve energy metabolism in the post-sepsis period, as evidenced through enhanced expression of energy metabolism promoting enzymes and their substrates, accompanied by mitigation of histological tubular injury and renal excretory function.

These experiments will introduce the PI to proteomics and metabolomics, and at the same time provide the preliminary data for an NIDDK NIH R01 application.