Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension

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Abstract

Rationale: The mechanisms of right ventricular (RV) failure in pulmonary arterial hypertension (PAH) are poorly understood. Abnormalities in fatty acid (FA) metabolism have been described in experimental models of PAH, but systemic and myocardial FA metabolism have not been studied in human PAH. We hypothesize the FA metabolic defects are present in human PAH and contribute to RV lipotoxicity.

Methods and Results: We used human blood, RV tissue, and non-invasive imaging to characterize multiple steps in the FA metabolic pathway in PAH subjects and controls. Circulating FAs and long-chain acylcarnitines were elevated in PAH patients versus controls after adjusting for multiple comparisons (both p < 0.001). Human RV long-chain FAs were increased and long-chain acylcarnitines were reduced nearly 100-fold in PAH versus controls (p < 0.001). Using proton magnetic resonance spectroscopy to measure in vivo intramyocyte lipid, we found 7-fold higher triglyceride content in RV tissue (p < 0.001). The long-chain acylcarnitines palmitoylcarnitine (C16), stearoylcarnitine (C18), oleoylcarnitine (C18:1), and linoleoylcarnitine (C18:2) met the Bonferroni-adjusted significance threshold (p < 0.012 for all).

Conclusions: Abnormalities in fatty acid metabolism can be detected in the blood and myocardium in human PAH and are associated with cardiac steatosis and lipotoxicity. Murine data suggest that lipidotoxicity may arise from impaired fatty acid oxidation. This study highlights specific metabolic pathways of potential therapeutic interest in PAH and establishes a tool to study their activity in vivo. Further studies are needed to determine the functional significance of these findings and whether metabolic therapies targeting fatty acid oxidation can favorably modify RV metabolism in PAH.

Results

Figure 1. Elevated Free Fatty Acids and Long-chain Acylcarnitines in PAH Patients Versus Controls

Figure 2. Long chain Fatty Acid and Acylcarnitine Profiles in the Human PAH Right Ventricle

Figure 3. Failure of BMPR2*2899X RV to Augment Oxygen Consumption with Long-chain Acylcarnitine Supplementation

Figure 4. Human Right Ventricular Ceramide in PAH and Controls

Figure 5. Human Proton Magnetic Resonance Spectroscopy in PAH and Controls

Background

• Right ventricular (RV) failure is the predominant cause of death in pulmonary arterial hypertension (PAH). No RV-specific therapies exist, in part because the underlying mechanisms are poorly understood.

• Given the heart’s preference for fatty acids (FA) as an energy source, understanding FA metabolism may be particularly relevant to understanding RV adaptation to elevated afterload in PAH.

• Abnormalities in fatty acid metabolism have been described in experimental models of PAH, but systemic and myocardial FA metabolism have not been studied in human PAH.

• We recently showed that RV failure is associated with myocardial steatosis and accumulation of ceramide in human PAH due to mutation in bone morphogenetic protein receptor type II (BMPR2).

• The generalizability of these abnormalities in fatty acid metabolism to idiopathic PAH (IPAH) and whether they are a systemic feature in human PAH are unknown.

Hypothesis

Fatty acid metabolic defects are ubiquitous in PAH and associated with lipotoxic cardiac steatosis in the RV.

References


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Key Findings

• FFAs were nearly two-fold higher in 19 PAH patients compared with 22 matched control subjects (0.9±0.35 vs. 0.48±0.30, p < 0.001, Figure 1A).

• The long-chain acylcarnitines palmitoylcarnitine (C16), stearoylcarnitine (C18), oleoylcarnitine (C18:1), and linoleoylcarnitine (C18:2) reached the pre-specified significance threshold, measuring 1.5-2-fold higher in PAH patients (Figure 1B, p < 0.003 for all).

• Human RV long chain FAs were increased in PAH compared with control, particularly palmitate (C16) and palmitoleate (C16:1), which were increased >150% (Figure 2A).

• Using high resolution respiration microscopy, the mitochondrial oxygen consumption rate attributable to the oxidation of palmitoylcarnitine in the BMPR2*2899X2 was reduced 9-fold compared to wild type RV (Figure 3). This experiment negates the need for mitochondrial transporter function and therefore directly implicates mitochondrial dysfunction in the PAH RV.

• Immunohistochemistry in 5 PAH and 8 control RVs demonstrated increased in irinotecan (11% on average) in the PAH RV (p = 0.006, Figure 4). This RV was validated by mass spectrometry of a long-chain (C16:0) and a very long-chain (C24:1) (Figure 4).

• Using magnetic resonance spectroscopy to quantitate in vivo myocardial triglyceride content, PAH patients had on average 7 fold higher %TSG compared to matched controls (Figure 5, 1.4±1.3 %TSG vs. 0.2±0.11 %TSG, p = 0.02). We found a moderate inverse relationship between %TSG and six-minute walk distance, however this relationship was not statistically significant (r = -0.7, p = 0.11).

Conclusions

• FA metabolism in PAH are demonstrable in plasma and may influence RV function and functional capacity.

• Abnormalities in fatty acid metabolism are associated with cardiac steatosis and lipotoxicity.

• Murine data implicate a fundamental problem in the utilization of long chain fatty acids to produce energy in the PAH RV and suggest that lipotoxicity may arise from impaired fatty acid oxidation.

• This study highlights metabolic pathways of potential therapeutic interest in PAH and establishes a tool to study their activity in vivo.

• Further studies are needed to determine the functional significance of these findings and whether metabolic therapies targeting fatty acid oxidation can favorably modify RV metabolism in PAH.