MALNUTRITION IMPAIRS BILE ACID SYNTHESIS THROUGH ALTERED HEPATIC HEME HOMEOSTASIS

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Background: Bile acids act as detergents for dietary lipid emulsification and as hormones that regulate numerous metabolic pathways. In malnutrition, bile acid synthesis is impaired, leading to fat malabsorption and metabolic abnormalities that result from altered nuclear receptor signaling. In our mouse model of early postnatal malnutrition, we reported that impaired bile acid synthesis leads to decreased farnesoid-X-receptor (FXR) activation and decreased expression of FXR-dependent coagulation factors, resulting in coagulopathy. It is unknown why bile acid synthesis is impaired in malnutrition. The rate-determining enzyme in the classic pathway of bile acid synthesis is CYP7A1, which converts cholesterol into the bile acid intermediate 7α-hydroxycholesterol. Our malnourished mice have normal expression of CYP7A1 with 2-fold increased cholesterol, suggesting that impaired CYP7A1 activity might underlie the buildup of cholesterol and decreased bile acid synthesis. CYP7A1 activity requires a single prosthetic moiety, heme. We hypothesized that malnutrition impairs the classic pathway of bile acid synthesis by inhibiting heme synthesis, thus reducing the availability of the essential cofactor for CYP7A1 activity.

Materials/Methods: C57BL/6 mice were malnourished by low-protein low-fat diet or were maintained on control chow. After 8 weeks, mice received intraperitoneal heme or vehicle, then primary hepatocytes were isolated for heme quantification and for CYP7A1 activity by mass spectrometry. Total fecal bile acids were quantified. In vitro bile acid synthesis was assessed in HepG2 hepatocytes incubated with heme or succinylacetone, a potent inhibitor of heme synthesis.

Results: Malnutrition reduced hepatic CYP7A1 activity by 65% ($p=0.023$) and heme concentrations by 44% ($p=0.002$). Inhibiting heme synthesis in vitro with succinylacetone decreased bile acid production by 61% ($p<0.0001$); bile acid synthesis was restored by adding free heme to succinylacetone-treated cells. Strikingly, treating malnourished mice with heme completely restored intestinal bile acid levels.

Conclusions: We present the first direct evidence that impaired CYP7A1 activity is responsible for decreased bile acid synthesis in malnutrition. Supplementation with heme increases bile acid synthesis both in vitro and in vivo. These results suggest a novel, unexplored link between heme homeostasis and bile acid synthesis that ultimately could be leveraged to combat malnutrition-induced liver dysfunction.

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