Enterobacteria Regulate Hepatic Bile Acid Synthesis via Fibroblast Growth Factor

Antibacterial drugs affect enterobacterial populations that have synergistic relationships with the production of secondary bile acids such as deoxycholate. The bile acids have important nutrient and vitamin uptake roles, and they also have key signaling roles in networks that regulate metabolic pathways. In this issue, Miyata et al., study the effects of antibiotics on the production of secondary bile acids. The study shows that treatment of mice with antibiotics, such as ampicillin or the nonabsorbed bacitracin/streptomycin/neomycin agents, markedly down-regulates expression of fibroblast growth factor-15 (FGF15) in the ileum. The drugs also increase mRNA expression and activity of hepatic CYP7A1 mRNA and total hepatic and intestinal bile acids. The studies demonstrate a loss of secondary bile acids in the small intestine lumen in antibiotic-treated animals, despite an increase in total bile acids. Treatment of control mice with dietary cholic acid markedly increases intestinal primary taurocholic acid and secondary taurocholic acid (TDCA) bile acids and markedly potentiate ileal FGF15 mRNA, the ortholog of human FGF19. Treatment of ampicillin-treated mice with TDCA restores the intestinal secondary bile acids and increases FGF15 expression in the ileum. Experiments in farnesoid X receptor (FXR)-null mice show that FGF15 mRNA levels are decreased in vehicle-fed mice but are even further decreased in ampicillin-treated FXR-null mice. These data support the hypothesis that intestinal secondary bile acids act, perhaps via FXR, to up-regulate FGF15 expression in the ileum with subsequent inhibitory effects on hepatic bile acid synthesis. The results also show that increased levels of hepatic bile acids are not as important in the regulation of hepatic CYP7A1 as are the levels of secondary bile acids and ileal FGF15 expression. These results are consistent with current view that intestinal FGF15 plays a major role in inhibition of bile acid synthesis in hepatocytes and that intestinal bacteria play a key role in regulation of bile acid synthesis.


Interplay Between Eicosanoids and Heme Oxygenase in Metabolic Syndrome

Heme oxygenase (HO) isoforms degrade heme into carbon monoxide and bilirubin, and both affect renal function and attenuate vasoconstriction in the blood vessels. HO has two isoforms: HO-1 and HO-2. HO-1 is an inducible isoform, whereas HO-2 is a constitutive isoform. The arachidonic acid metabolites, such as epoxyeicosatrienoic acids (EETs), are cytochrome P450-derived eicosanoids that have many potent biological activities in the kidneys and vascular system. Although it is thought that HO and EET both might affect hypertension, the interaction between HO and EET pathways in the obesity that is often linked with hypertension in some patients is not well established. In this issue, Sodhi et al., studied the consequences of HO-2 knockout on EET production in the kidneys and whether EET agonist combined with soluble epoxide hydrolase (sEH, enzyme responsible for EET degradation) inhibitor affects the physiological parameters of HO-2 knockout mice. It was found that the HO-2 mice are obese, insulin-resistant, and hypertensive. In addition, the HO-2 knockout is associated with decreased CYP2c expression, decreased renal EET levels, increased HO-1 expression and activity, impairment of endothelial function in mouse aorta, and increased superoxide production. Finally, treatment of HO-2 knockout mice with a chemical agent, containing the activities of both EET agonist and sEH inhibition, increased renal and vascular EET levels, increased HO-1 expression, lowered blood pressure, reduced body weight and fat tissue, decreased serum TNF-α and MCP-1, increased adiponectin levels, and improved endothelial function in the aorta. Based on these results, the authors conclude that deficiencies in either the HO or EET system might contribute to the adverse effects and clinical progression of metabolic syndrome.

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