Functional Gastroenterology Bolus

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The Sterolbiome – The Essential, But Overlooked Enterohepatic Endocrine System

The human ecosystem consists mostly of microorganisms. The genetic contribution of the microbiome dwarfs the 23,000 genes in the human genome. These organisms and their genes control much of the human endocrine system through their interactions with bile (and vice versa). Decades of research attest to the hormonal effects of bile acids on energy (glucose, lipids, and lipoproteins) and inflammation – the sterolbiome.

A Quick Review of the Biliary System

The liver synthesizes and secretes hydrophilic primary bile acids, which are converted in the gut by Clostridia into numerous secondary hydrophobic bile acids. With gastric emptying after a meal, gradual gallbladder emptying occurs. Gallbladder contraction and Sphincter of Oddi relaxation is mediated by the enteric hormone cholecystokinin, which delivers bile to the small intestinal lumen. Bile acids (BA) are absorbed by active and passive mechanisms, returned to the liver via the portal vein, processed by hepatocytes and re-secreted into the bile ducts. During overnight fasting, bile accumulates in the gallbladder where it is concentrated and stored.[1]

Primary bile acids (synthesized from cholesterol in hepatocytes) include cholic and chenodeoxycholic acid. About 16 enzymes are needed to convert cholesterol to bile salts. Hepatocytes also conjugate bile salts with glycine or taurine**.** Bile salts may also be sulfated or glucuronidated or – in the case of ursodeoxycholic acid (UDCA) – undergo N-acetylglucosamination. UDCA makes up only 2% of the biliary pool but has unique beneficial properties.[2]

Primary bile acids have both a hydrophobic and a hydrophilic side. The anions associate to form micelles with phosphatidylcholine and lipids. Mixed micelles increase absorption of fatty acids, monoglycerides and fat-soluble vitamins.

The secondary bile acids are deoxycholic acid (DCA) and lithocholic acid (LCA). Secondary bile acid metabolites influence nuclear receptors. This is the mechanism for most of the endocrine effects of the sterolbiome.

Elevated colonic concentrations of the primary bile acid chenodeoxycholic acid (CDCA) or the secondary bile acid deoxycholic acid (DCA) are known to induce water secretion, causing diarrhea. A decrease in these may be a cause of childhood functional constipation.[3]

The major mechanism for removal of cholesterol is through bile excretion either by direct transport of intact cholesterol to the bile or by conversion into bile acids in the liver, mediated by the enzymes CYP7A1, CYP8B1 and CYP27A1.

The biliary system is a major route of detoxification and bile acids can be used as therapeutic agents.

Bile also has a major influence over the balance of intestinal flora. In the colon, primary bile acids regulate growth of *Clostridium difficile***.** Secondary bile acids (formed by bacterial action) suppress the growth of *C. diff.* By killing bacteria, most antibiotics are risk factors for C. difficile enterocolitis. Antibiotics inhibit production of secondary bile acids by altering intestinal flora.

Bile Acids…Are They Hormones?

"The gut microbial community through their capacity to produce bile acid metabolites distinct from the liver can be thought of as an ***endocrine organ*** with potential to alter host physiology, perhaps to their own favor."[4]

The gut microbiome (sterolbiome) produces endocrine molecules from endogenous and exogenous steroids in the gut. BAs are also known to fundamentally shape the gut microbiome and vice versa.

Bile Acids Activate Nuclear Receptors

As stated above, secondary bile acids influence nuclear receptors. Bile acids are hormones that regulate their own synthesis and transport, glucose and lipid homeostasis, energy balance, inflammation and microbial growth. These nuclear receptors include the Farnesoid X receptor (FXR), the Pregnane X receptor (PXR), G-protein coupled receptors (GPCR) and the Vitamin D receptor (VDR).

Farnesoid X receptor (FXR): "FXR is the bridge between the liver and the small intestine to control BA levels and regulate BA synthesis."[4] By doing so it regulates glucose, lipoproteins, lipid metabolism, inflammation, tumor suppression, drug metabolism, hepatic regeneration, fibrosis, cell differentiation and neoplasia.

Pregnane X receptor (PXR): PXR turns on sulfation in phase 2 detoxification, regulating the processing of xenobiotic and endogenous compounds. It is especially important in the detoxification of carcinogenic lithocholic acid (LCA). LCA can induce double stranded breaks in DNA!

Rifaximin, the SIBO drug, also increases PXR-mediated inhibition of angiogenic factors in colorectal cell lines and may be a promising anticancer tool. Treatment with rifaximin also causes "significant and concentration-dependent reduction of cell proliferation, cell migration, VEGF secretion, NO and MMP release."[5] This activation of PXR (by rifaximin) can enhance intestinal epithelial repair and down-regulate gut microbe inflammatory responses. The specifics include inhibiting the activation of the nuclear factor-κB *via* the pregnane X receptor (PXR) as well as reduced interleukin-1B and tumor necrosis factor-alpha.[6] Rifaximin is uniquely bile soluble.

G protein coupled receptors (GPCR): GPCR are found in the gallbladder, spleen, intestinal neuroendocrine cells, macrophages, cholangiocytes and brown adipose cells. Secondary bile acids (and primary BA to a lesser degree) are potent stimuli for GPCR. This leads to enhanced glucose regulation by modulation of incretin hormones, glucagon and insulin.[7] One might hypothesize that chronic low-grade inflammation which is associated with insulin resistance, may inhibit bile acid signaling and disrupt lipid metabolism. The disruption of these signaling pathways may increase the risk of fatty liver and non-alcoholic fatty liver disease.[8]

Vitamin D receptor (VDR): Lithocholic acid metabolites are agonists for the vitamin D receptor, enhancing the myriad effects of this essential fat-soluble vitamin/hormone.

In addition to the nuclear receptor activity discussed above gut bacteria secrete β-glucuronidase, an enzyme that deconjugates estrogens. The deconjugated forms of estrogen are more active, so in this way, estrogen is more efficiently absorbed into the blood and is therefore able to bind to receptors and induce physiological activities. *Clostridium scindens*, one of the major species involved in the bio-transformation of BA, also converts glucocorticoids to androgens.[9]

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