The Bile Acid Metabolome in Humans and Rodents

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Humans and rodents differ markedly in respect of bile acid composition, metabolism, and the regulation of their biosynthesis. Despite these differences (vide infra), rodent models (such as knockout, gene overexpression mice, or gnotobiotic mice), “humanized” mice (such as those used for CYP7A1; Li et al., 2012) or basolateral bile acid transporters (Iusuf, Van De Steeg, & Schinkel, 2012) are indispensable to clarify the complex mechanisms regulating the biosynthesis of bile acids and the way bile acid receptors and their effectors, including FGF19 (human) and FGF15 (ortholog in mice) affect cholesterol, glucose, fatty acid, and energy metabolism. Rodents helped to reveal the mode of action of important drugs, including the antidiabetic drug metformin and bile sequestrants, to develop novel drugs targeting bona fide bile acid receptors (TGR5 and FXR) or the apical bile acid transporter (ASBT) as agonists or antagonists. Rodents serve as experimental models for the surgical treatment of obesity/diabetes with procedures like sleeve gastrectomy or severe caloric restriction, and clarify the role of bile acids in these interventions. Exploration of the long-term consequences of gallbladder resection, the role of bile acids for alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), irritable bowel syndrome (IBS), and chronic pruritus are some of many exciting developments in recent times. Finally, intestinal microbiota and bile acids, which are among the key players in communication between the microbiome and its host (and vice versa), are subjects of enormous scientific interest. Interventions to change or correct the human bile acid metabolome via the microbiome have been studied in rodent models, but some of the anticipated benefits were proven in human clinical and pilot studies.

Major Differences between Rodents and Humans with Respect to Bile Acids

1) Regulation of Bile Acid Synthesis
Mice or rats and humans differ in terms of the regulation of bile acid synthesis from the precursor cholesterol (Russell, 2003) (Chiang, 2009). The proximal promoter of the rodent Cyp7a1 gene (CYP7A1 is the key rate-limiting enzyme of bile acid biosynthesis in the liver) binds the oxysterol-activated liver X receptor (LXRα), but the human gene does not bind LXRα. Conversely, the human - but not the rodent - promoter for CYP8B1 (12-α-hydroxylase) possesses a binding site for the farnesoid X receptor (FXR) (Sanyal et al., 2007).

2) Different Pathway Contributions of Synthesis
A much larger portion of the mitochondrial “acidic” pathway (about 25% in rodents versus 5% in healthy humans) via oxysterols contributes to the overall bile acid synthesis in rodents (Russell, 2003).

3) Anatomy
The anatomy of bile compartments may differ; mice - but not rats - have a gallbladder.

4) Intrahepatic Handling
The intrahepatic handling of bile acids differs: basolateral transport of drugs and bile acids into the sinusoidal space is more active in rat hepatocytes than in humans (Yang, Pleifer, Kock, & Brouwer, 2015). This is important in preclinical toxicology, because drug-induced liver injury (DILI) is one of the major reasons for withdrawing previously approved drugs from the market.

5) Different Biophysical Properties
Bile hydrophobicity differs, depending on the structure of bile acids in the different compartments (liver, gallbladder, small and large intestine, feces, serum). Rodents have a much lower bile hydrophobicity index (HI) than humans. (Heuman, 1989).

6) Re-Hydroxylation of Secondary Bile Acids in Rodents but not in Humans
With regard to hydrophobicity, rodents have hepatic enzymes to rehydroxylate microbiota-dehydroxylated bile acids at the C-7 position (mice). Humans lack this rescue mechanism (Dawson & Karpen, 2014).

7) Gender Differences
Bile acid synthesis (measured by plasma levels of 7-hydroxy-4-cholesten-3 one (C4)) is about 30% higher in healthy men than in women. The size of the total bile pool is larger in men by the same factor. Opposite (!) gender differences exist in male and female mice (lower synthesis and pool size in males). As a result, male mice are more...
susceptible to gallstones (Gälman, Angelin, & Rudling, 2011).

8) Humans have only two species primary bile acids, but mice have five. Proportions of bile acids conjugated with glycine and taurine differ in rodents and humans.

The primary bile acids in humans are CA and CDCA, whereas the primary bile acids in mice are CA, CDCA, the muricholic acids α MCA and β MCA, as well as UDCA (Sayin et al., 2013). Human newborns until the age of three weeks almost exclusively conjugate bile acids with taurine. This develops to the adult ratio of 3:1 (glycine:taurine) after about 6-12 months (Lourenço & Camilo, 2002), (Jahnel et al., 2015). Mice almost exclusively conjugate and re-conjugate with taurine.

9) Gut microbiota in mice differ from those in humans, but gnotobiotic mice are helpful to clarify the role of the human gut microbiome and bile acids

Mice have largely different intestinal (colonic) microbiota compared to humans. When ex-germ free (GF) mice were transplanted with human fecal bacteria (gnotobiotic mice), it was possible to identify certain Clostridia strains (including Clostridium scindens) which are just a minute fraction (about 0.0001%) of the colonic flora in humans, but are essential for 7-dehydroxylation and the generation of the secondary bile acids DCA and LCA (Narushima et al., 2006; Ridlon, Kang, & Hylemon, 2006). In contrast to other bacterial transformations (e.g. epimerization), this reaction can only occur for free bile acids. Other bacteria, much more abundant, catalyze the “gateway” reaction by supplying bile salt hydrolase (BSH) (B.V. Jones, Begley, Hill, Gahan, & Marchesi, 2008). A novel approach to the treatment of dyslipidemia (or even obesity and diabetes) is to rearrange the human gut metabolome by altering the gut microbiome. This can be achieved with some success, as shown in human pilot studies with BSH overproducing probiotics, including certain strains of Lactobacillus reuteri (Martoni, Labbé, Ganopolsky, Prakash, & Jones, 2015), (M. L. Jones, Tomaro-Duchesneau, & Prakash, 2014). Gnotobiotic mice also helped to clarify the mechanism by which secondary bile acids suppress the growth of Clostridium difficile (Buffie & Pamer, 2013), (Buffie et al., 2014) which explains the success of fecal transplantation procedures in humans with recurrent C. difficile infection (Kelly, 2013) (Weingarden et al., 2014) (van Nood et al., 2013).

References


