Understanding mouse bile acid formation: Is it time to unwind why mice and rats make unique bile acids?¹

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ARE MCAS OF INTEREST IN HUMAN MEDICINE?

The long and complex pathways for the synthesis of bile acids are classic examples of where it has been recognized that the level of synthesis is suppressed by the end products made, the bile acids. How this occurred was not well understood until the discovery that the farnesoid X receptor (FXR) serves as a specific receptor for bile acids in this negative feedback regulation (7, 8). This knowledge has in turn led to an increased awareness that the FXR agonistic activity varies greatly between different bile acids. Thus, CDCA and deoxycholic acid (DCA) are clearly more potent than cholic acid (CA) and UDCA, the latter two being poor FXR activators when studied alone in vitro (8, 9). However, when UDCA is used in the presence of potent FXR activating agonists such as DCA or CDCA, it can dampen the FXR stimulation from the agonists (9). In this respect, the MCAs are of particular interest. Although never mentioned in the report by Makishima et al. (7), it could be seen that the CYP7A1 protein in HepG2 cells was dose-dependently increased when cells were exposed to MCAs. Later studies on germ-free mice have highlighted that such animals have an enlarged pool of bile acids rich in MCAs and that Tβ-MCA and Tα-MCA can serve as antagonists to CDCA as determined with a coactivator recruitment assay with recombinant human FXR (10). Germ-free mice have been shown to have an improved resistance to high-fat feeding (11). Interestingly, cholic acid free CYP8B1−/− mice and mice treated with antibiotics share several features with germ-free mice. They have an induced bile acid synthesis and increased expression of the intestinal ASBT protein, an enzyme that transports bile acids. How this occurs was not well understood until the discovery that the farnesoid X receptor (FXR) serves as a specific receptor for bile acids in this negative feedback regulation (7, 8). 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CYP8B1−/− mice are also less prone to develop steatosis (12). Further, feeding WT mice with α- or β-MCAs reduces the intestinal absorption of cholesterol from 38 to 11% (15). The present identification of Cyp2c70 as key for the synthesis of MCAs from CDCA or UDCA should now make it

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feasible to synthesize MCAs in vivo in species other than rats and mice. One may thus speculate whether the production of significant quantities of MCAs by human intestinal microbiota or in liver may result in beneficial metabolic effects such as reduced body weight, improved insulin sensitivity, and reduced liver lipids. One important substrate for this, CDCA, is certainly highly available in humans.

Other conditions where it may be of interest to generate MCAs in humans are different situations with cholestasis associated with high systemic levels of the potentially toxic CDCA. In bile duct-ligated rats, the urinary excretion of the water soluble MCAs increases about 400-fold (16) to become CDCA. In bile duct-ligated rats, the urinary excretion of the potentially toxic CDCA that dampens the expected suppression of bile acid synthesis is induced.

Although such approaches may at first appear attractive, the fact that administered bile acids are often rapidly converted in vivo may result in unexpected responses. Thus, the administration of CDCA to mice induces the formation of MCAs from CDCA that dampens the expected suppression of bile acid synthesis by this treatment, while on the other hand, administration of the weak FXR agonist CA suppresses CYP7A1 strongly, presumably due to the pronounced reduction of FXR antagonistic MCAs that is seen during such treatment (5, 6).

FURTHER UNDERSTANDING OF THE PHYSIOLOGIC FUNCTION OF MCAS IN RATS AND MICE

It is well known that mice and rats are relatively resistant to high-fat feeding and that mice with boosted levels of MCAs, such as germ-free, Cyp8b1−/−, and antibiotic-treated mice, show even stronger such resistance. The question of whether MCAs are important for this resistance may now be investigated by high-fat feeding of MCA-deficient mice. Will these mice respond more like humans?

It is also known that basal bile acid synthesis in mice is about double that seen in humans. Are the FXR antagonistic MCAs important for this species difference? In the present study, there was a clear trend for higher CYP7A1 mRNA in the WT animals but due to small animal numbers, this did not reach statistical significance. Another issue that also will be of interest is how MCA-deficient mice will respond to bile duct ligation. Will bile acid synthesis be suppressed as in humans or will it be induced as in WT mice? These and many other questions to clarify the physiologic functions of MCAs should now be possible to answer.

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