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EDITORIAL

A Twist in the Tale of a Pig Model of Short-Bowel Syndrome

Short-bowel syndrome (SBS) occurs after a long surgical resection of small intestine. This results in malabsorption of nutrients, especially lipids, and is associated with the development of liver disease. It is particularly serious in infants. The contributions of altered lipid metabolism, bile acid physiology, dysbiosis, and supplemental enteral or parenteral nutrition to the development of this pathology remain unclear, and a piglet model has provided useful evidence due to various similarities with humans.[1]

In the study of SBS-induced liver damage by Pereira-Fantini et al[2] published in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, piglets had resection of 75% of the small intestine, leaving duodenum and terminal ileum in situ, or a sham operation. Animals were fed with oral formula and were studied 2 weeks postsurgery when liver, terminal ileum, bile, and portal blood samples were collected. Half the piglets in each group were given the farnesoid X receptor (FXR) agonist, obeticholic acid (OCA). This is a semisynthetic bile acid, with an additional 6-alpha-ethyl group, which increases its potency at the FXR, in mouse and humans at least, by almost 100-fold. OCA has been shown to be beneficial in many animal models of cholestasis and steatosis, and in clinical trials for primary biliary cholangitis, nonalcoholic steatohepatitis, and primary bile acid diarrhea.[3–5] OCA was a plausible drug to study as previous work by the same authors had suggested impaired FXR responses in SBS piglets.[6] Also, in the parenteral nutrition–fed piglet, the most potent natural bile acid FXR agonist, chenodeoxycholic acid, improved the liver disease.[7]

As expected, in the SBS model weight gain was reduced, feces were unformed and fatty (steatorrhea), and liver changes including lipid droplets and clusters of inflammatory cells were found. OCA treatment reduced stool fat to a large extent, improving absorption. SBS was associated with depletion of biliary taurine and OCA reversed this. There were many changes in the composition of bile acids in the bile in SBS, in particular a large increase in hyocholic acid, which is a major primary bile acid in the pig. There were major decreases in SBS of the secondary bile acids, which result from intestinal bacterial metabolism. OCA treatment partially restored these conjugated secondary bile acids in bile.

The rate-limiting gene for bile acid synthesis by the classical pathway in the liver is *CYP7A1*, and expression of this was potently inhibited by OCA in control and SBS pigs, as reported in other species. OCA up-regulated several other known FXR-responsive genes in the liver and there were only minor differences between its effects in control or SBS animals.

However, there were several unexpected findings. In the SBS animals, OCA resulted in more fat accumulation in the liver and a significant reduction in lobule size. Intestinal FXR target gene expression was surprisingly reduced by OCA—and importantly this was seen in the control group as well as in the SBS group. In the human ileum, FXR agonists such as chenodeoxycholic acid or OCA stimulate expression of specific genes involved in bile acid reabsorption. Particularly, the ileum-derived hormone, fibroblast growth factor 19, is up-regulated by FXR agonists[8] and acts in the liver as the major inhibitor of *CYP7A1*.[9] In the pig, fibroblast growth factor 19 transcripts were also significantly down-regulated by OCA. Expression of FXR itself was increased in SBS in both the liver and the intestine, with OCA stimulating FXR in the control liver but inhibiting FXR in the SBS intestine.

How should we interpret these findings? Probably most importantly, pigs are not human. Hyocholic acid is 1 of the 2 major primary bile acids in pigs, unlike in humans. The effects of hyocholic acid, and the derived hyodeoxycholic acid, at the FXR, as agonists or antagonists, are unknown. Hyocholic acid is a 6-hydroxylated bile acid, in the alpha position. In the mouse, muricholic acid is 6-beta hydroxylated and is a poor FXR agonist, whereas OCA has an ethyl group in the 6-alpha position and is very potent. There are also different spliced variants of FXR, with different effects in pigs and humans.[10] The gut microbiome is critical for production of secondary bile acids and also differs.

Overall, interpretation of the relevance of these findings to human physiology and SBS therapeutics is unclear. Further studies are required to understand these effects in pigs and how these differences affect bile acid and FXR functions. This work has shown clearly the complexities of the bile acid-FXR system in the liver and intestine and will stimulate discussion as to how this can best be targeted for therapy.

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References

1. Lim DW, Turner JM, Wales PW. Emerging piglet models of neonatal short bowel syndrome. JPEN J Parenter Enteral Nutr 2015;39:636–643.
2. Pereira-Fantini PM, Lapthorne S, Gahan CGM, Joyce SA, Charles J, Fuller PJ, Bines JE. Farnesoid X receptor agonist treatment alters bile acid metabolism but exacerbates liver damage in a piglet model of short-bowel syndrome. Cell Mol Gastroenterol Hepatol 2017;4:65–74.
3. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ,

Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T, Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med 2016;375:631–643.

4. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, Chalasani N, Dasarathy S, Diehl AM, Hameed B, Kowdley KV, McCullough A, Terrault N, Clark JM, Tonascia J, Brunt EM, Kleiner DE, Doo E. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956–965.
5. Walters JR, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. Aliment Pharmacol Ther 2015;41:54–64.
6. Pereira-Fantini PM, Lapthorne S, Joyce SA, Dellios NL, Wilson G, Fouhy F, Thomas SL, Scurr M, Hill C, Gahan CG, Cotter PD, Fuller PJ, Hardikar W, Bines JE. Altered FXR signalling is associated with bile acid dysmetabolism in short bowel syndrome-associated liver disease. J Hepatol 2014;61:1115–1125.
7. Jain AK, Stoll B, Burrin DG, Holst JJ, Moore DD. Enteral bile acid treatment improves parenteral nutrition-related liver disease and intestinal mucosal atrophy in neonatal pigs. Am J Physiol Gastrointest Liver Physiol 2012;302:G218–G224.
8. Zhang JH, Nolan JD, Kennie SL, Johnston IM, Dew T, Dixon PH, Williamson C, Walters JR. Potent stimulation of fibroblast growth factor 19 expression in the human ileum by bile acids. Am J Physiol Gastrointest Liver Physiol 2013;304:G940–G948.
9. Keely SJ, Walters JR. The Farnesoid X receptor: good for BAD. Cell Mol Gastroenterol Hepatol 2016;2:725–732.
10. Gray MA, James SE. Investigation of the dominant positive effect of porcine farnesoid X receptor (FXR) splice variant 1. Gene 2015;560:71–76.

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Conflicts of interest
JRFW has served as a speaker, advisory board member, or consultant for Albireo, GE Healthcare, Intercept Pharmaceuticals, NGM Biopharmaceuticals, and Novartis.

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