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Chronic diarrhea caused by idiopathic bile acid malabsorption: an explanation at last

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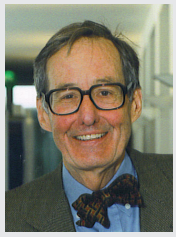

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"There has been enormous progress in our understanding of both the components of the enterohepatic circulation and its derangements in disease."

Bile acids, the multifunctional end products of cholesterol metabolism, have a key role in digestion. They form mixed micelles with fatty acids and monoglycerides, and these mixed micelles, in turn, solubilize fat soluble vitamins. Micelle formation accelerates dietary lipid absorption [1]. Bile acids also denature dietary proteins, thereby accelerating their cleavage by pancreatic proteases [2].

Both of these effects require a high luminal concentration of these detergent molecules. After their synthesis from cholesterol, bile acids are conjugated with either glycine or taurine (in an amide linkage). This conjugation step converts weak acids to strong acids, which are fully ionized at biliary and intestinal pH and, therefore, are membrane impermeant. Bile acids are actively and efficiently absorbed by the terminal ileal enterocytes. Efficient absorption leads to a recycling mass of bile acids of 2–3 g, which cycles between the liver and the intestine multiple times each day. In the healthy adult, approximately 12 g of bile acids are secreted into the intestine each day, whereas fecal loss (which is equivalent to the synthesis rate) averages approximately 0.3 g/day. Thus, absorption is highly efficient – approximately 97%. The efficient reclamation of bile acids by the distal intestine diminishes the requirement for bile acid synthesis [3]. Most of the bile acids passing through the liver after a meal are conjugated bile acids returning from the intestine. Newly synthesized bile acids join the recycled bile acids but make up only a very small fraction of the total bile acids secreted by the liver.

There has been enormous progress in our understanding of both the components of the enterohepatic circulation and its derangements in disease. This brief editorial will summarize some of the major advances that have been made in our understanding of the components in the enterohepatic circulation, as well as their regulation. I will also describe a very recent and exciting clinical discovery that explains the pathogenesis of idiopathic bile acid malabsorption, a common cause of chronic diarrhea.

The enterohepatic circulation of conjugated bile acids requires carrier-mediated transport by the ileal enterocyte and the hepatocyte [4]. Both cell types have apical and basolateral transporters that mediate vectorial transport of bile acids. The genes for these transporters have been cloned and 'knocked out' in mice. The apical transporter of the ileal enterocyte is a sodium-dependent cotransporter that takes conjugated bile acids into the enterocyte. Their exiting from the ileal enterocyte into portal venous blood is mediated by a basolateral transport system consisting of two proteins – organic solute transporter-α and organic solute transporter-β. This transporter is believed to be an antiporter; that is, as a bile acid anion exits the cell, another anion (as yet unidentified) enters the cell. Mice in which the gene encoding either transporter is knocked out have profound bile acid malabsorption [4].

Conjugated bile acids return to the liver in portal blood and are efficiently extracted as they pass down the hepatic sinusoid by one or more basolateral transporters of the hepatocyte. Extraction is greatest as bile acids enter the sinusoid, that is, by the periportal hepatocytes. The major conjugated bile acid transporter is a sodium-dependent cotransporter that shares homology with the apical

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transporter of the ileal enterocyte. Bile acids pass rapidly through the hepatocyte, and are then pumped uphill by the canalicular transporter, the ATP-dependent bile salt export pump. Bile acids then pass down the biliary tract with or without storage in the gall bladder, depending on the pressure relationships of the biliary tree. Canalicular secretion of bile acids may be considered analogous to the power required to transport a roller coaster car to the summit of the roller coaster track. Subsequent movement is all downhill!

Not all bile acids are absorbed in the terminal ileum. A small fraction passes into the cecum, where bile acids are quickly altered by bacteria. Bacteria remove the glycine or taurine moiety (deconjugation) and also the 7-hydroxy group (dehydroxylation). The result of this bacterial biotransformation is the production of bile acids that are less water soluble and are membrane permeant. A fraction of these secondary bile acids is absorbed by the colonic epithelium, as evidenced by the finding that deoxycholic acid (the 7-deoxy derivative of cholic acid) is a major biliary bile acid in adults [5].

It seems likely that bile acids have a function in the colon in addition to their important functions in the small intestine. Recent studies with a polarized, colonic cell line (T84) suggest that low concentrations of bile acids downregulate colonic secretion, promoting fluid and electrolyte absorption [6]. Normally, the human colon absorbs 1 l or more of fluid daily, and such absorption may well be promoted by this antisecretory effect, mediated by a low concentration of secondary bile acids. When luminal concentrations of bile acids are high, such as in patients with bile acid malabsorption, bile acids with two α-hydroxy groups induce secretion [7,8]. This prosecretory effect of bile acids is the major reason why bile acid malabsorption induces diarrhea.

"When luminal concentrations of bile acids are high...bile acids with two α-hydroxy groups induce secretion. This prosecretory effect of bile acids is the major reason why bile acid malabsorption induces diarrhea."

The mass of bile acids circulating enterohepatically is termed the bile acid pool. The size of the bile acid pool is determined, first, by the input of bile acids (either synthesis of primary bile acids or absorption of newly formed secondary bile acids) and, second, by the efficiency of ileal conservation. Both of these physiological processes are regulated. The discovery of the components of the regulatory processes has been a major advance during the past decade.

It was long known that bile acid synthesis was under negative feedback regulation. In animals and patients, interruption of the enterohepatic circulation by creation of a biliary fistula or resection of the ileum caused bile acid synthesis to increase. The converse, bile acid feeding, was shown to decrease bile acid synthesis [9,10]. The mechanism by which bile acids downregulate their own biosynthesis has turned out to be quite complicated. A nuclear receptor (farnesoid X receptor) was found, for which bile acids were identified as the ligand [11–13]. Activation of this receptor by bile acids induces the synthesis of a repressor protein which directly or indirectly downregulates the rate-limiting enzyme in bile acid biosynthesis [14,15].

Two groups working independently found that parenteral infusion of bile acids did not return upregulated bile acid biosynthesis to normal, whereas intestinal infusion of bile acids convincingly turned off the upregulated synthesis [16,17]. This observation raised the possibility that an unknown factor was released by the small intestine and was required for negative feedback suppression of bile acid biosynthesis.

This unknown factor by which the ileal enterocyte signals to the hepatocyte was identified by a group led by Steven Kliewer and was found to be a known protein named FGF19 [18]. Formation and release of this protein was shown to be stimulated by bile acids in the ileal enterocyte acting via the farnesoid X receptor. FGF19 released by the ileal enterocyte travels to the liver in portal venous blood. There, FGF19, acting together with yet another protein known as β-klotho, activates its receptor (FGF receptor 4) on the hepatocyte [19–23]. Such activation leads to a phosphorylation cascade, which ultimately downregulates bile acid biosynthesis. FGF19 and β-klotho activation of FGF receptor 4 of the hepatocyte appear to be absolute requirements for the downregulation of bile acid biosynthesis by bile acids.

This very complex regulatory pathway has recently been shown to have clinical relevance. Historically, my laboratory and others have shown that patients with ileal resection have bile acid malabsorption and increased bile acid biosynthesis [24–28]. Diarrhea is induced by the increased flux of bile acids entering the colon and is improved by administration of a bile acid sequestrant [29]. We had no idea that an additional player, FGF19, was involved.

Eigel Hess Thaysen, working in Denmark, described a group of patients with bile acid malabsorption who responded to bile acid sequestrants, yet had an ileum that appeared normal by light microscopy [30]. Such patients were considered to have 'idiopathic' bile acid malabsorption. Other investigators identified such patients as a subset of patients with irritable bowel syndrome, diarrhea predominant, and showed that bile acid malabsorption was present (based on more rapid excretion of ^{75}Se-tagged bile acid) [31–34]. The patients responded symptomatically to a bile acid sequestrant. Dutch [35] and Swedish groups [36] examined bile acid transport in ileal biopsies from these patients and found it was normal or even increased. Thus, it was a continuing puzzle as to why bile acids were malabsorbed when bile acid transport by the ileum appeared to be quite normal.

The mystery of why bile acid malabsorption occurs in at least some patients with idiopathic bile acid malabsorption has at last been solved by studies led by Julian Walters at the Hammersmith Hospital in London, UK [37]. Walters and his colleagues have found that such patients have a marked decrease in their plasma levels of FGF19, suggesting that either FGF19 is not formed or not released by the ileal enterocyte. As a result of deficiency of FGF19, the hepatocyte cannot downregulate its bile acid synthesis. When bile acid synthesis is markedly increased, the bile acid pool expands and ileal absorption is downregulated by the high flux of bile acids through it, but absorption is saturated. In this new steady state, an

increased flux of bile acids passes into the colon, causing diarrhea. FGF19 has recently been shown to be present in the human hepatocyte [38], and it is not known whether patients with idiopathic bile acid malabsorption form FGF19 in the liver. We might dare to predict that there are other patients with idiopathic bile acid malabsorption who will prove to be deficient in FGF receptor 4 or do not form the required cofactor, β-klotho. In mice, knockout of the genes encoding FGF receptor 4 [22] or of β-klotho [23] results in a phenotype of increased bile acid synthesis, which is analogous to that present in patients with idiopathic bile acid malabsorption.

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The diagnosis of bile acid malabsorption in the patient with chronic diarrhea is not easily made, as measurement of either fecal bile acid excretion or postprandial plasma levels of bile acids is not performed in most clinical chemistry laboratories. A Swedish group has proposed the measurement of plasma levels 7α-hydroxy-cholest-4-ene-3-one (termed 'C4' for convenience) [39]. This intermediate in bile acid biosynthesis spills over into plasma in direct proportion to its synthesis rate. Thus, plasma C4 levels increase when bile acid biosynthesis increases, and C4 levels are markedly increased in patients with bile acid malabsorption [40–42]. As yet, this interesting and potentially valuable diagnostic test is only available in research laboratories.

This advance in our understanding of idiopathic bile acid malabsorption does not change the clinical management of such patients. At present, they are treated by administration of a bile acid sequestrant, and it can be argued that a clinical response is sufficient to establish the diagnosis. Cholestyramine and colestipol have been used in the past, but a newly developed sequestrant, colesevelam, is available in tablet form and seems to be better tolerated by patients [43]. New sequestrants that are still more potent may be developed. Specific therapy would be an FGF19 agonist. For someone who began the study of patients with bile acid malabsorption over 40 years ago [44], elucidation of the defect in patients with idiopathic bile acid malabsorption is a very exciting advance.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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