Case 44

Bile Acid Deficiency: Ileal Resection

Paul Bostian is a 39-year-old high school guidance counselor who was diagnosed with Crohn's disease (an inflammatory bowel disease) when he was a teenager. For 20 years, he was treated medically with antidiarrheal agents and strong anti-inflammatory drugs, including glucocorticoids. During that time, Paul had two spontaneous remissions. However, after these remissions, his disease always returned "with a vengeance." Last year, he had a small bowel obstruction that could not be relieved with nonsurgical approaches, and he underwent emergency surgery that removed 80% of his ileum.

Since the surgery, Paul has had diarrhea. His stools are oily, pale, and foul-smelling. He takes the drug cholestyramine to control his diarrhea. However, he continues to have steatorrhea. Paul also receives monthly injections of vitamin B_{12}.

QUESTIONS

1. What steps are involved in the biosynthesis of bile acids? What is a primary bile acid? What is a secondary bile acid? What are bile salts? What purpose is served by converting bile acids to bile salts?

2. Describe the enterohepatic circulation of bile salts.

3. What role do bile salts play in the absorption of dietary lipids?

4. Why did Paul have oily stools (steatorrhea) after his ileal resection?

5. Paul has "bile acid diarrhea." Why do bile acids cause diarrhea? (Big hint: They stimulate colonic Cl^- secretion.) Why don't healthy persons have bile acid diarrhea?

6. Cholestyramine is a cationic resin that binds bile salts. Propose a mechanism that explains its effectiveness in treating Paul's diarrhea.

7. Why did Paul need monthly injections of vitamin B_{12}? What conditions can lead to vitamin B_{12} deficiency?

ANSWERS AND EXPLANATIONS

1. The **primary bile acids** (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol in the liver. The rate-limiting enzyme in this biosynthetic pathway is cholesterol 7α-hydroxylase, which is feedback-inhibited by cholic acid. These primary bile acids are secreted in bile into the intestinal lumen, where they are dehydroxylated by intestinal bacteria to form the **secondary bile acids** deoxycholic acid and lithocholic acid. In the intestine, a portion of each primary bile acid is dehydroxylated to form a secondary bile acid, and a portion is left unchanged (Figure 5–9).

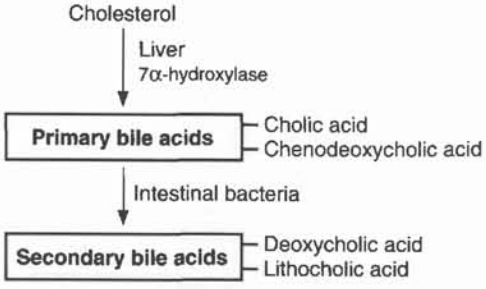

Figure 5–9 Biosynthetic pathways for bile acids.

Bile salts are conjugated forms of bile acids. Each primary bile acid may be conjugated in the liver with the amino acid glycine or taurine, yielding a total of *eight bile salts*. The bile salts are named for the parent bile acid and the conjugating amino acid (e.g., taurocholic acid, glycolithocholic acid).

The purpose of conjugating bile acids to bile salts is to decrease the pK of the compounds, making them more soluble in the aqueous solution of the intestinal lumen (where bile salts act). The reasoning is as follows. The duodenal contents have a pH of 3–5. The bile acids have a pK of approximately 7. Therefore, in the range of duodenal pH, most bile acids are present in their nonionized (HA) forms, which are *water-insoluble*. The bile salts have a pK of 1–4. Consequently, at duodenal pH, most bile salts are present in their ionized (A^-) forms, which are *water-soluble*. Therefore, in aqueous solution (e.g., the intestinal lumen), bile salts are more soluble than bile acids. The discussion of Question 3 explains why the solubility of bile salts is very important.

2. **Enterohepatic circulation** of bile salts refers to their circulation between the intestine and the liver. But we need to back up in the story. How did the bile salts reach the intestine in the first place? Recall from the previous question that two primary bile acids are synthesized in the liver and conjugated with glycine or taurine to form their respective bile salts. The hepatocytes continuously produce bile, approximately 50% of which is bile salts. Bile flows through the bile ducts to the gallbladder, where it is concentrated (by absorption of ions and water) and stored. Within 30 minutes of ingestion of a meal, the gastrointestinal hormone cholecystokinin (CCK) is secreted. CCK simultaneously causes the gallbladder to contract and the sphincter of Oddi to relax. As a result, bile is ejected from the gallbladder into the lumen of the intestine. In the intestinal lumen (as discussed earlier), the four bile salts become eight bile salts as a result of bacterial dehydroxylation. Now the bile salts are ready to assist in the process of absorbing dietary lipids (discussed in the next question). (Incidentally, a portion of each bile salt is converted back to its bile acid by bacterial deconjugation. Hence, when we speak of enterohepatic circulation of bile salts, we mean bile salts *plus* bile acids.)

When the bile salts finish their lipid-absorption work in the duodenum and jejunem, they are *recirculated* to the liver instead of being excreted in the feces. This process (enterohepatic circulation of bile salts) occurs as follows (Figure 5–10). Bile salts are transported from the lumen of the intestine into the portal blood on an **Na^+-bile salt cotransporter** located in the terminal small intestine (**ileum**). This portal blood supplies the liver, which extracts the bile salts and adds them to the total hepatic bile salt pool. In this way, 95% of the bile salts secreted in each circulation are returned to the liver (rather than being excreted). Twenty-five percent of the total bile salt pool is excreted daily and must be replaced.

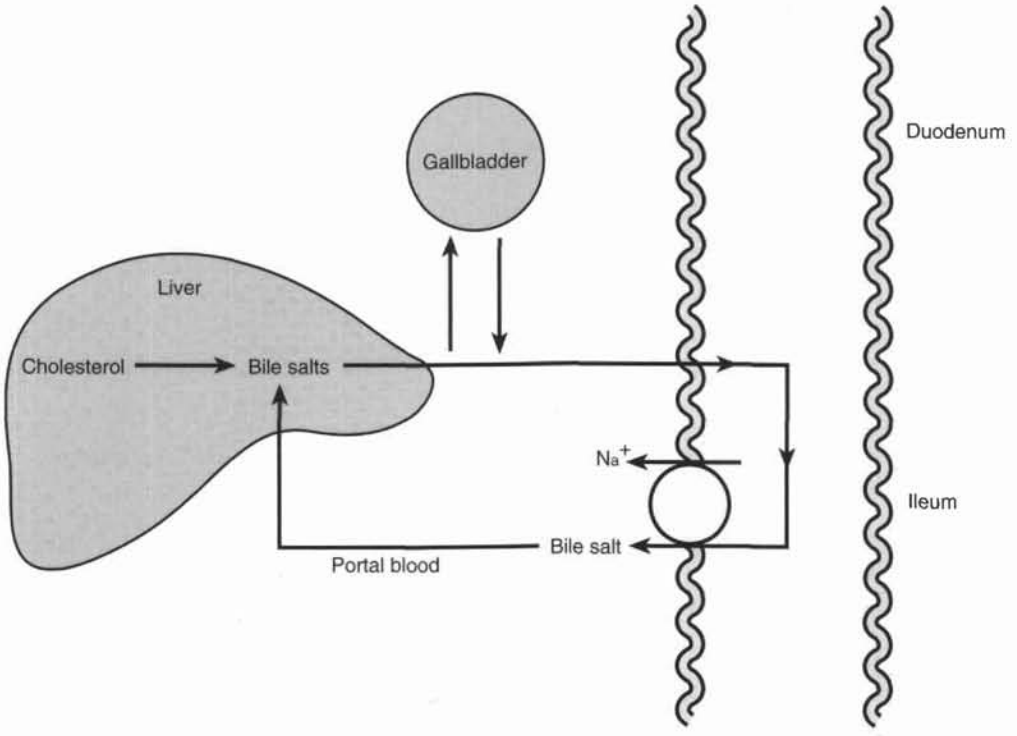

Figure 5–10 Enterohepatic circulation of bile salts.

3. The function of bile salts in the intestinal lumen is to emulsify and solubilize dietary lipids so that the lipids can be digested and absorbed by intestinal epithelial cells. Why do the dietary lipids need this help? Because lipids, which are hydrophobic, are insoluble in aqueous solutions such as that present in the lumen of the small intestine.

The first role of the bile salts is to **emulsify** dietary lipids. The negatively charged bile salts surround the lipids, creating small lipid droplets in the aqueous solution of the small intestinal lumen. The negative charges on the bile salts repel each other so that the droplets disperse, rather than coalesce. In this way, the surface area available for pancreatic digestive enzymes is increased. If emulsification did not occur, dietary lipids would coalesce into large lipid "blobs," with relatively little total surface area for digestion.

The second role of the bile salts is to form **micelles** with the products of lipid digestion (cholesterol, monoglycerides, lysolecithin, and fatty acids). The micellar core contains the products of lipid digestion. The micellar surface is composed of bile salts, which are amphipathic (soluble in both lipid and water). The hydrophobic portions of the bile salt molecules point toward the lipid center of the micelle. The hydrophilic portions of the bile salt molecules are dissolved in the aqueous solution in the intestinal lumen. In this way, hydrophobic lipids are dissolved in an otherwise "unfriendly" aqueous environment.

To complete the process of lipid absorption, the micelles diffuse to the apical membrane of the epithelial cells of the intestinal mucosa. There, they release the lipids, which diffuse across the apical membranes into the cell. (The bile salts remain in the intestinal lumen and are normally recirculated to the liver.) Inside the intestinal cells, the lipids are re-esterified, packaged in **chylomicrons**, and transported into the lymph for absorption.

4. Paul had **steatorrhea** (fat in the stool) because his *bile salt pool was depleted* following the ileal resection. Thus, his biliary secretions contained insufficient bile salts to ensure that all dietary lipid was digested and absorbed. Any nonabsorbed lipid was excreted in the feces, where it appeared as lipid droplets or oil.

   Why did Paul have this apparent bile salt deficiency? Recall that, normally, the liver must replace only 25% of the bile salt pool daily. Because most of Paul's ileum was removed, he lost this recirculatory feature, and most of his bile salt pool was excreted in feces. As a result, Paul's liver had to synthesize nearly 100% of the secreted bile salts daily, compared with 25% in healthy persons. Simply, his liver could not keep up with this large synthetic demand, and as a result, his bile salt pool decreased.

5. Paul's diarrhea was caused in part by the presence of bile salts in the lumen of the colon (so-called **bile acid diarrhea**). These bile salts stimulate colonic Cl^- **secretion;** Na^+ and water follow Cl^- into the intestinal lumen, producing a secretory diarrhea.

   Bile acid diarrhea doesn't occur in healthy persons because, normally, bile salts aren't present in the lumen of the colon. They are recirculated from the ileum to the liver before they reach the colon.

6. **Cholestyramine** is a water-insoluble **cationic resin** that binds bile salts in the intestinal lumen. When bile salts are bound to the resin, they cannot stimulate colonic Cl^- secretion or cause secretory diarrhea. (Incidentally, because cholestyramine binds bile salts in the intestinal lumen, it is also useful as a lipid-lowering agent in persons with hypertriglyceridemia.) When bile salts are bound to the resin, they are not absorbable and therefore are not recirculated to the liver. Thus, cholestyramine treatment depletes the bile salt pool, which impairs lipid absorption from the gastrointestinal tract.

7. In addition to recirculating bile salts to the liver, the **ileum** has another essential function, absorption of **vitamin B_{12}.** Recall the steps involved in vitamin B_{12} absorption. Dietary vitamin B_{12} binds to **R proteins** that are secreted in saliva. In the duodenum, pancreatic proteases degrade the R protein, releasing vitamin B_{12}, which forms a stable complex with **intrinsic factor** that is secreted by the gastric parietal cells. The intrinsic factor–vitamin B_{12} complex, which is resistant to proteolytic degradation, travels to the ileum, where it is absorbed into the blood by transporters in the ileal cells. Vitamin B_{12} then circulates in the blood bound to a specific plasma protein (transcobalamin II). Paul received monthly *injections* of vitamin B_{12} because, in the absence of an ileum, he could not absorb vitamin B_{12} that he ingested *orally*.

   In addition to ileal resection, other conditions that cause vitamin B_{12} deficiency can be understood by considering the steps in vitamin B_{12} absorption from the gastrointestinal tract. **Deficiency of intrinsic factor** (secondary to gastrectomy or to atrophy of the gastric parietal cells) results in inability to form the intrinsic factor–vitamin B_{12} complex that is absorbed in the ileum. Also, one subtle manifestation of **pancreatic enzyme deficiency** is the inability to hydrolyze the R protein from the R protein–vitamin B_{12} complex. In this case, vitamin B_{12} is not "free" to complex with intrinsic factor; therefore, it cannot be absorbed. In these conditions, as with ileectomy, vitamin B_{12} must be administered by injection.

Key topics

Bile acid diarrhea
Bile acids
Bile salts
Cholecystokinin (CCK)
Cholestyramine
Enterohepatic circulation of bile salts
Gallbladder
Ileectomy
Ileum
Intrinsic factor
Lipid absorption
Lipid digestion
Micelles
Na^+-bile salt cotransporter
R protein
Sphincter of Oddi
Steatorrhea
Transcobalamin II
Vitamin B_{12}