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Department of Paediatrics, Medical University of Lublin
Department of Surgical Oncology, Medical University of Lublin

GRAŻYNA POLKOWSKA, WOJCIECH P. POLKOWSKI

The clinical role of the bile acids in selected paediatric and surgical diseases

Bile acids (BA) and their salts are chemical compounds that belong to steroids and in humans, are synthesised from cholesterol. They are characterised by the presence of four cycles of the cyclo-pentano-perhydro-fenantrene and a side chain at the C-17 position of various length that is terminated with a carboxyl group. The three major human BA have 24 carbon atoms with the basic structure of 5β-cholan-24-oic acid, and differ in position of hydroxyl groups at C-3, C-7 or C-12. About 60% of all BA constitutes 3α,7α12α-trihydroxy-5β-cholan-24-oic acid (cholic acid), and the rest are mainly 3α,7α-dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid) and 3α,12α-dihydroxy-5β-cholan-24-oic acid (deoxycholic acid). Bile in man however, contains small amounts of lithocholic (3α-hydroxy-5β-cholan-24-oic) acid and ursodeoxycholic (3α,7 β - dihydroxy-5β-cholan-24-oic) acid (8).

Primary BA that are produced in the liver, under normal circumstances are enzymatically conjugated with either of the amino acids glycine or taurine by peptide linkage at the C-24 position, thus forming bile salts. The ratio of glycine-conjugated to taurine-conjugated BA is around 3:1 (7). The conjugation of BA determines their polarity, good solubility in water, and formation of the micelle (stable emulsion) with insoluble lipids. Most BA are ionised and conjugated and temporarily stored in the gall bladder. Contraction of the gall bladder causes passage of the BA into the lumen of duodenum and small bowel, where they act in digestion and absorption of the lipids. After doing this, bile salts are in majority (99%) actively absorbed in the ileum into the bloodstream, passing the portal system into the liver (BA hepato-intestinal cycle).

BA non-absorbed in the ileum are subsequently metabolised by bacterial flora of the large bowel (Bacteroides, Lactobacillus) into the secondary bile acids. This process is catalysed by bacterial enzymes and involves deconjugation and dehydroxolation of the BA. Thus, deoxycholic acid is made from cholic acid, and lithocholic from chenodeoxycholic acid. Afterwards the secondary BA are in part passively reabsorbed from the colonic lumen into the bloodstream, entering the hepato-intestinal circulation cycle; and in part they are excreted with faeces (300-800 mg/day, less than 5% of the total BA pool in adults).

Hepatic biosynthesis of the BA is regulated by negative feedback control. The amounts of BA absorbed in the ileum and transported with bloodstream to the liver, as well as the amount of absorbed cholesterol are regulators of this process. Both excess of the absorbed BA and excessive supply of exogenous cholesterol lead to decrease of the endogenous synthesis of the BA. On the other hand, disturbed re-absorption or excessive excretion of the BA with faeces causes manifold increase of their synthesis in the liver.

In contrast to composition of the bile in adults, in newborns and in infants up to 6 months, taurine conjugates requiring vitamin B_6 are dominant, while secondary BA are present in bile before their contact with the bowel (5). In newborns and in infants, there is developmental immaturity of BA carriers in brush border of the enterocytes in the terminal ileum. This causes decreased re-absorption and lack of active transport of the BA and insufficient bacterial deconjugation in the colon. As a result, a large portion of the primary and secondary BA is lost with faeces. This leads in newborns to so-called negative pool of the BA (4). Total pool of the BA increases with age. Within the bowel BA have several functions: 1) micelle formation for lipids digestion; 2) accelerate transport of lipids, cholesterol, and lipid soluble vitamins; 3) regulation of the bowel motor activity; 4) regulation of entero-hormonal secretion; 5) induction of ion and water secretion into the large bowel lumen (1).

Primary BA molecule is of carbohydrate cyclic character with internal side being hydrophobic while the external is hydrophilic, containing the hydroxyl groups and terminal, highly polar, carboxyl or sulfonyl group. Above a certain critical concentration (2mmol/l), BA molecules aggregate to form small particles called micelles. Therefore, BA have detergent properties. The polar groups of BA are located on the surface of their molecular particle and interact with the aqueous environment. Thus, admixture of even small amounts of BA causes marked decrease of the water surface tension and enables the creation of stable emulsions with apolar, water insoluble substances. BA play an important role in fat digestion in the alimentary tract, especially in the process of absorption of fatty acids and other water insoluble substances (several vitamins, cholesterol) through the intestine wall. Consequently, fine emulgation of the lipids facilitate their direct contact with lipolytic enzymes on much greater surface than in the case of insoluble lipid solid phase.

Disturbances of BA metabolism may be the reason or one of the reasons in the complex mechanism of diarrhoea. Lack of the bile salts in the lumen of small intestine is the most frequent cause of disturbances in the digestion and absorption of lipids, fatty acids, cholesterol, and fat-soluble vitamins. It is believed that lack of cholic micelle in the intestine content does not clearly interfere with lipid digestion. Protein and lecithin present in the intestine content leads to emulsification, whereas lipase and colipase hydrolyse lipids. A reduced concentration of BA within intestinal lumen impairs the micellar solubilization of lipids, inhibits lipid absorption, whereas products of enzymatic hydrolysis restrain further lipolysis. Because of the deficient cholic micelle, there is inhibition of lipid absorption and excessive fatty acids excretion in the form of chronic steatorrhea. In the case of the complete lack of bile salts, lipid absorption is impaired in nearly 50%. The reduced concentration or lack of BA in the intestinal lumen occurs in the following conditions: 1) biliary obstruction or cholestatic liver disease, which leads to decreased delivery of bile salts to the intestinal lumen; 2) ileal disease or resection, which may lead to an increased intestinal loss of bile salts, which is too large to be compensated for by increased hepatic synthesis; and 3) stasis syndromes which are characterized by bacterial overgrowth in the small intestine with bile salt deconjugation (2). Drugs which bind BA, such as cholestyramine, can also affect micelle formation and lipid solubilization and absorption in the small bowel.

Malabsorption and excessive secretion of the BA into the intestinal lumen may be responsible for incidence, exacerbation or protraction of diarrhoeal symptoms. BA have secretory capacities and are able to stimulate intestinal mucosa to water and electrolyte secretion into the intestinal lumen, and thus they may accelerate peristalsis. On the other hand, increased peristalsis alone in the course of diarrhoea is capable of disturbing BA reabsorption and increasing faecal loss of BA. This is extremely important in dysbacteriosis, in which bacterial overgrowth in the proximal part of the small intestine deconjugate bile salts, and thus generated secondary BA are poorly soluble and can not digest and absorb lipids, as a consequence effect in steatorrhoea. The secondary BA accelerate peristalsis and cause secretory diarrhoea.

Until the 1980's, the only available active treatment for gallbladder stone disease was cholecystectomy. This was changed with the demonstration that two BA can be effective as cholesterol gallstone dissolution agents, when administered orally in the doses ranging from 500 to 1000 mg per day for periods up to two years. The chenodeoxycholic and ursodeoxycholic acids are used as pharmacological agents for the treatment of gallstone disease, and surgery can be avoided (5). Although the cholesterol gallstones of selected patients can be dissolved by BA treatment, the place of gallstone dissolution therapy in the management of patients with gallstone disease is limited. Laparoscopic cholecystectomy is a safe, minimally invasive, and effective treatment for most gall stone patients. A major drawback with dissolution therapy is that gallstone recurrence is frequent 1 to 2 years after successful treatment and the recurrence rate may be as high as 50% (6). Nevertheless, although laparoscopic surgery will remain the main form of treatment for gallstone disease, dissolution therapy is a particularly valuable, alternative treatment for patients with a poor surgical risk because of concomitant diseases.

Biliary BA are supposed to be an indicator for postoperative liver function. The functional recovery of the remnant liver after an extended hepatectomy is critical for the outcome of the patient. Externally drained bile samples obtained from patients with biliary or periampullary carcinomas before and after surgery, were measured for total BA with a 3α-hydroxysteroid dehydrogenase method. After surgery, BA concentration recovered to the preoperative level in all patients but remained low in hepatectomized patients with liver failure (maximum serum bilirubin level >10 mg/dL). Biliary BA concentration had the most predictive power for the occurrence of postoperative liver failure. Therefore, biliary BA concentration could be a simple, real-time, reliable indicator of preoperative and postoperative liver function (3).

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SUMMARY

This article contains basic information on the chemical structure, formation of the micelle, biosynthesis of the bile acids and its control, as well as entero-hepatic circulation of bile acids. Physiological function and the most serious disorders of bile acids in the course of diarrhoea in children are described. Some possibilities of clinical use of the bile acids are also evaluated, such as the conservative treatment of cholecystolithiasis or the monitoring of liver function in hepato-pancerato-biliary surgery.

Kliniczna rola kwasów żółciowych w wybranych chorobach dziecięcych i chirurgicznych

W pracy poglądowej zawarto podstawowe informacje na temat struktury chemicznej, tworzenia miceli, biosyntezy i jej regulacji oraz krążenia jelitowo-wątrobowego kwasów żółciowych. Omówiono także fizjologiczną funkcję kwasów żółciowych, a następnie najpoważniejsze ich zaburzenia w przebiegu biegunek u dzieci. Opisano niektóre możliwości zastosowań klinicznych kwasów żółciowych, takich jak: leczenie zachowawcze kamicy pęcherzyka żółciowego czy monitorowanie wydolności wątroby w chirurgii wątrobowo-trzustkowo-żółciowej.