Role of the gallbladder

Mammals

In mammals (rats) that do not have the gallbladder, only the hydrophilic hepatoprotective bile acids are only synthesized; as for the secondary hydrophobic hepatotoxic bile acids, they are formed in small quantities or are poorly absorbed in the ileum and the colon (table 2).

Table 2.

Presence of gallbladder and type of bile acids.

Mammals	Presence of gallbladder	Type of bile acids or bile alcohols
Rats	No	Hydrophilic bile acids
Camels	No	?
Deers	No	?
Elephants	No	Hydrophilic bile alcohols
Rhinoceros	No	Hydrophilic bile alcohols
Whales	No	Hydrophilic bile alcohols
Bears	Yes	Hydrophilic bile acids
Rabbits	Yes	Hydrophobic bile acids
Primates	Yes	Hydrophilic and hydrophobic bile acids
Human	Yes	Hydrophilic and hydrophobic bile acids

Since a long stagnation in the gallbladder may promote the formation of gallstones, the gallbladder may be absent in mammals which can manage without food and water for a long period of time (camels, deer) (1). Since the size of the gallbladder must be proportional to the size of the liver, the gallbladder may be absent in big mammals (elephants, rhinoceros, whales) because of their anatomical peculiarities (2). In these mammals there is a considerable synthesis of bile alcohols, which are poorly solubilize cholesterol (2). In mammals that have the gallbladder (humans, monkeys, rabbits) both the hydrophilic and hydrophobic bile acids may be synthesized (table 2). The secondary hydrophobic hepatotoxic bile acids can be formed in large quantities, but they are poorly absorbed in the ileum and the colon (1-3). Since a long stagnation in the gallbladder may promote the formation of gallstones, only the hydrophilic bile acids are synthesized in mammals that fall into long hibernation (bears), but the secondary bile acids are also hydrophilic (1-3).

Therefore, the basic role of the gallbladder in mammals in which hydrophobic hepatotoxic bile acids are synthesized or formed, is the protection of the liver from their effect by means of bile acids accumulation in the gallbladder and lowering the number of the cycles of enterohepatic circulation. The mammals in which the hydrophobic hepatotoxic bile acids are synthesized or formed must have the gallbladder. Those mammals in which the hydrophilic hepatoprotective bile acids are synthesized and the hydrophobic hepatotoxic bile acids are formed in small quantities, may manage without it. The mammals, in which bile alcohols are synthesized in large amounts, do not have the gallbladder.

Human

The excessive hepatic bile passage from the liver into the duodenum increases the frequency of the gallbladder independent enterohepatic circulation of bile acids. The gallbladder-independent enterohepatic circulation of bile acids in patients with the cholesterol gallstone disease or after cholecystectomy is raised (fig. 10).

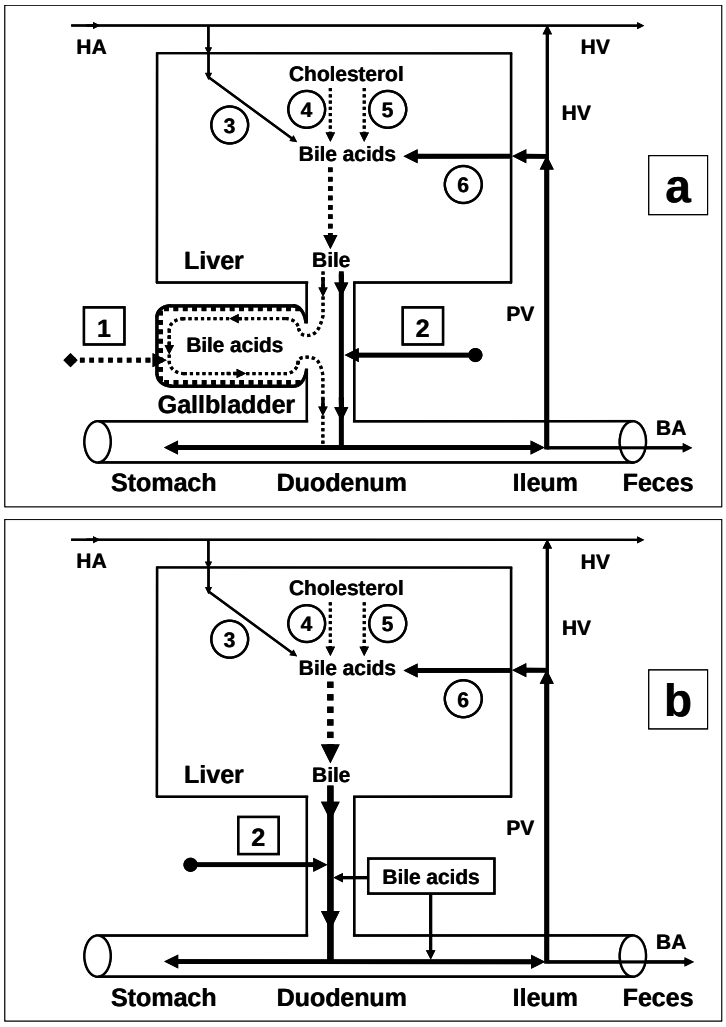

Fig. 10. Enterohepatic circulation of bile acids in patients with chronic calculous cholecystitis **(a)** and patients after cholecystectomy **(b)**.
1 = gallbladder-dependent enterohepatic circulation of bile acids;
2 = gallbladder-independent enterohepatic circulation of bile acids;
3 = bile acids entering the liver through the hepatic artery;
4 = synthesis of cholic acid: cholesterol-7α-hydroxylase;
5 = synthesis of chenodeoxycholic acid: cholesterol-27-hydroxylase;
6 = bile acids entering the liver through the portal vein.

BA = bile acids;
HA = hepatic artery;
HV = hepatic vein;
PV = portal vein.

It results in: 1) the increase of the hydrophobic hepatotoxic deoxycholic bile acid (DCA) formation and its accumulation in hepatocytes (table 3) (4), 2) the formation of morphological changes in the liver (nonspecific reactive hepatitis) (5) and 3) the appearance of cholestasis (6).

Table 3.
Percentage of hydrophobic deoxycholic acid (DCA) in bile of rabbits, primates and human.

Mammals	% of DCA
Rabbits	up to 90%
Primates	up to 50%
Human (healthy)	up to 10-20%
Human (patient with gallstone disease)	up to 30-40%
Human (after cholecystectomy)	up to 30-60%

The risk of cancer of the liver, the pancreas, the small intestine, and the colon increases as well (7-15). The increases of deoxycholic acid, participating in the enterohepatic circulation, and of other toxic agents in the hepatic bile can result in chronic pancreatitis and duodeno-gastral reflux (16-19).

Hence, the basic role of the gallbladder in a human is a protective. The gallbladder decrease the formation of the secondary hydrophobic hepatotoxic bile acids (DCA and LCA) by accumulating the primary bile acids (CA and CDCA) in the gallbladder and by reducing their concentration in the

gallbladder-independent enterohepatic circulation, thereby protecting the liver, the mucosa of the stomach, the gallbladder, and the colon from their effect.

Besides, the increase of the cycles of enterohepatic circulation in a human can determine the raised enterohepatic circulation of estrogens, progesterons and the formation of their active metabolites: 1. a) 16α-hydroxy-estrone (it activates proliferation and induces breast cancer); b) 4-hydroxyestrone (proliferation, cancer); c) 2-hydroxy-estrone (it stimulates fat accumulation in the body of a human) (20-22); 2. a) pregnanolone (inflammation, cholestasis) (23); b) pregnandiol (inflammation, cholestasis) (23).

Probably, the excessive formation of these "active" metabolites and deoxycholic acid determine the increased risk of cancer of various sites (13). 9.4% of the patients with gallstones and cholecystectomized patients have cancer of various sites (cancer of the liver, the pancreas, the colon and the small intestine, breast cancer in women) (13, 14).

For women, who underwent cholecystectomy before the age of 50 (i.e. before menopause), the risk of colon cancer is higher than for women who underwent cholecystectomy at the age over 50 (11). Estrogens intensify the cancer effect of the hydrophobic deoxycholic acid (24). The concentration of total bile acids in blood serum is 3 times higher and the risk of intrahepatic cholestasis is 2.5 times higher in cholecystectomized pregnant women (19%) than in noncholecystectomized pregnant women (25). Children with inborn absence of the gallbladder have infringements of the function of the liver and lag behind in physical development (6). Probably, the evolution of a human lacking the gallbladder would have been extremely difficulty.

The role of the gallbladder and gallbladder bile in digestion

The evacuation volume of the gallbladder depends on the quality and quantity of accepted food. The gallbladder is emptied to a greater extent when the fat food is accepted (1). Since the gallbladder is contracted in 5-20 minutes after food is available in a stomach, and "the gastric chyme" moves from the stomach into the duodenum only 1-3 hours later, the role of the gallbladder bile in digestion may be insignificant. The gallbladder bile, coming into the duodenum, stimulates the peristalsis of the intestine and promotes the cleaning of the intestine for "a new gastric chyme". The hepatic and gallbladder bile volumes and the bile acids concentration, participating in the first circle of gallbladder-dependent and gallbladder-independent enterohepatic circulation, determine the bile acids-stimulated secretion of the hepatic bile that in a greater extent participates in digestion.

Conclusion:

Thus, the basic role of the gallbladder in a human is the protection of the liver, the mucosa of the stomach, the gallbladder and the colon from the effect of hepatotoxic hydrophobic bile acids and the regulation of serum lipids level. If the genetics of the biosynthesis of bile acids in a human had evolved in a different way (by analogy with bears [presence of cholesterol-7β-hydroxylase instead of cholesterol-7α-hydroxylase] or rats [presence of cholesterol-6β-hydroxylase instead of cholesterol-12α-hydroxylase]), a human being would have probably never suffered from gallstone disease, some hepatic and colon diseases (liver cirrhosis, colorectal cancer) (2, 26, 27, 28).

This model of the gallbladder bile formation that we have worked out provides a better understanding of the causes of the diseases of the hepatobiliary zone. It also allows to foresee various trends in their treatment and prevention and to make prognosis of the appearance of various disorders in hepato-biliary-cholecysto-pancreatico-duodeno-gastro-esophageal region after cholecystectomy.

References:

1. **Gorshkowa SM**, Kurtsin IT. Mechanisms of the bile excreting. Leningrad: Science, 1967: 34-137.
2. **Carey MC**, Duane WC. Enterohepatic circulation. In: Arias IM, Boyer JL, Fausto N, Jakoby WB,

Schachter DA, Shafritz DA, editors. The Liver, Biology and Pathobiology. 3rd ed. New York: Raven Press, 1994: 719-767.
3. **Hofmann AF.** Bile secretion and the enterohepatic circulation of bile acids. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 6th ed. Philadelphia: Saunders, 1998: 937-948.
4. **Honda A**, Yoshida T, Tanaka N, Matsuzaki Y, He B, Shoda J, Osuga T. Increased bile acid concentration in liver tissue with cholesterol gallstone disease. *J Gastroenterol* 1995; **30:** 61-66.
5. **Geraghty JM**, Goldin RD. Liver changes associated with cholecystitis. *J Clin Pathol* 1994; **47:** 457-60.
6. **Zubovski GA**. Radio and ultrasonic diagnosis of biliary tract diseases. Moscow: Medicine, 1987: 36-174.
7. **Bayerderffer E**, Mannes GA, Richter WO, Ochsenkuhn T, Wiebecke B, Kepcke W, Paumgartner G. Increased serum deoxycholic acid levels in men with colorectal adenomas. *Gastroenterology* 1993; **104:** 145-151.
8. **Bayerderffer E**, Mannes GA, Richter WO, Ochsenkuhn T, Seeholzer G, Kepcke W, Wiebecke B, Paumgartner G. Decreased high-density lipoprotein cholesterol and increased low-density cholesterol levels in patients with colorectal adenomas. *Ann Intern Med 1993*; **118**: 481-487.
9. **Bayerderffer E**, Mannes GA, Ochsenkuhn T, Dirschedl P, Paumgartner G. Variation of serum bile acids in patients with colorectal adenomas during a one-year follow-up. *Digestion* 1994; **55:** 121-129.
10. **Bayerderffer E**, Mannes GA, Ochsenkuhn T, Dirschedl P, Wiebecke B, Paumgartner G. Unconjugated secondary bile acids in the serum of patients with colorectal adenomas. *Gut* 1995; **36:** 268-273.
11. **Ekbom A**, Yuen J, Adami HO, McLaughlin JK, Chow WH, Persson I, Fraumeni JF. Cholecystectomy and colorectal cancer. *Gastroenterology* 1993; **105:** 142-147.
12. **Goldbohm RA**, van den Brandt PA, van Veer P, Dorant E, Sturmans F, Hermus RJ. Cholecystectomy and colorectal cancer: evidence from a cohort study on diet and cancer. *Int J Cancer* 1993; **53:** 735-739.
13. **Johansen C**, Chow WH, Jorgensen T, Mellemkjaer L, Engholm G, Olsen JH. Risk of colorectal cancer and other cancers in patients with gallstones. *Gut* 1996; **39:** 439-443.
14. **Chow WH**, Johansen C, Gridley G, Mellemkjair L, Olsen JH, Fraumeni JF. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. *Br J Cancer* 1999; **79:** 640-644.
15. **Strom BL,** Soloway RD, Rios-Dalenz J, Rodriguez-Martinez HA, West SL, Kinman JL, Crowther RS, Taylor D, Polansky M, Berlin JA. Biochemical epidemiology of gallbladder cancer. *Hepatology* 1996, **23**: 1402-1411.
16. **Barthet M**, Affriat C, Bernard JP, Berthezene P, Dagorn JC, Sahel J. Is biliary lithiasis associated with pancreatographic changes? *Gut* 1995; **36:** 761-765.
17. **Portincasa P**, Di Ciaula A, Palmieri V, Velardi A, VanBerge Henegouwen G.P, Palasciano G. Impaired gallbladder and gastric motility and pathological gastro-oesophageal reflux in gallstone patients. *Eur J Clin Invest* 1997; **27:** 653-661.
18. **Stein HJ**, Kauer WKH, Feussner H, Siewert JR. Bile acids as components of the duodenogastric refluate: detection, relationship to bilirubin, mechanism of injury, and clinical relevance. *Hepatogastroenterology* 1999; **46:** 66-73.
19. **Fukumoto Y**, Murakami F, Andoh M, Mizumachi S, Okita K. Effects of the elevation of serum bile acids on gastric mucosal damage. *Hepatol Res* 1999; **14:** 195-203.
20. **Setchell KDR**. Synthesis of sex hormones. In: Reyes HB, Leuschner U, Arias IM, editors. Pregnancy, Sex Hormones and the Liver. Dordrecht: Kluwer Academic Publishers, 1996: 3-15.
21. **Simon FR**. The role of sex hormones and hepatic plasma membranes in the pathogenesis of cholestasis. In: Reyes HB, Leuschner U, Arias IM, editors. Pregnancy, Sex Hormones and the Liver. Dordrecht: Kluwer Academic Publishers, 1996: 51-59.
22. **Tiribelli C**, Bellentani S. Sex-hormone-induced cholestasis. In: Reyes HB, Leuschner U, Arias I.M, editors. Pregnancy, Sex Hormones and the Liver. Dordrecht: Kluwer Academic Publishers, 1996: 60-66.
23. **Meng LJ**, Reyes H, Palma J, Hernandez I, Ribalta J, Sjovall J. Progesterone metabolism in normal human pregnancy and in patients with intrahepatic cholestasis of pregnancy. In: Reyes HB, Leuschner U, Arias IM, editors. Pregnancy, Sex Hormones and the Liver. Dordrecht: Kluwer Academic Publishers, 1996: 91-100.
24. **Jung B**, Vogt T, Mathieudaude F, Welsh J, McCelland M, Trenkle T, Weitzel C, Kullmann F. Estrogen-responsive RING finger mRNA induction in gastrointestinal carcinoma cells following bile acid treatment. *Carcinogenesis* 1998; **19:** 1901-1906.
25. **Glasinovic JC**, Valdivieso V, Covarrubias C, Marinovic I, Miquel JF, Nervi F. Pregnancy and gallstones. In: Reyes HB, Leuschner U, Arias IM, editors. Pregnancy, Sex Hormones and the Liver. Dordrecht: Kluwer Academic Publishers, 1996: 267-281.
26. **Cooper AD**. Role of the enterohepatic circulation of bile salts in lipoprotein metabolism. *Gastroenterol Clin North Amer* 1999; **28:** 211-229.
27. **Heuman DM**, Hylemon PB, Vlahcevic ZR. Regulation of bile acid synthesis. III. Correlation between biliary bile acid hydrophobicity index and the activities of enzymes regulating cholesterol and bile acid synthesis in the rat. *J Lipid Res* 1989; **30:** 1161-1171.
28. **Tung BY**, Emond MJ, Haggitt RC, Bronner MP, Kimmey MB, Kowdley KV, Brentnall TA. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med* 2001; **134:** 89-95.