REVIEWS

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The Role and Mechanism of Action of Bile Acids Within the Digestive System – Bile Acids in the Liver and Bile

Rola i mechanizm działania kwasów żółciowych w obrębie układu pokarmowego – kwasy żółciowe w wątrobie i żółci

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Abstract

Bile acids are considered as the most important and most specific bile components. The variety of their types and forms with different physicochemical properties occurs in mammalian organisms. Type and strength of bile acid actions are related to these properties. Bile acids are synthetized *de novo* in the liver, secreted into the bile and excreted into the duodenum. In the gut they can subject to bacterial biotransformation and reabsorption into the blood; their major part returns into the liver and is secreted again into the bile. They are the natural driving force for bile secretory process because actively secreted from the hepatocytes into the bile canaliculi cause the passive water flow at the rate of about 7–15 µl of water for 1 µmol of secreted bile acids. Bile acid metabolism in the liver is dependent of bile acid inflow and concentration in the hepatocytes. Bile acids affect also the lipid metabolism in the liver. Types and amounts of bile acids in bile determine bile properties including bile acid and mixed micele formation. However, the influences of bile acids in the gut are related to bile acid profile in bile delivered into the duodenum and to the period of bile inflow into the intestinal lumen (**Adv Clin Exp Med. 2007, 16, 6, 793–799**).

Key words: liver, bile, bile acids, secretory process.

Streszczenie

Kwasy żółciowe uważa się za najważniejsze i najbardziej specyficzne składniki żółci. W organizmach ssaków występuje wiele ich rodzajów i postaci, które różnią się właściwościami fizykochemicznymi. Od tych właściwości zależy rodzaj i intensywność ich oddziaływania. Kwasy żółciowe są syntetyzowane *de novo* w wątrobie, wydzielane do żółci, a następnie wydalane do dwunastnicy. W jelitach mogą podlegać biotransformacji bakteryjnej oraz zwrotnemu wchłonięciu do krwi; drogą tą większa ich część wraca do wątroby, ulegając resekrecji do żółci. Są naturalną siłę napędową procesu wydzielania żółci, gdyż wydzielane aktywnie do kanalików żółciowych powodują bierne wydzielanie wody przez hepatocyty przeciętnie w ilości 7–15 µl na 1 µmol wydzielonych kwasów żółciowych. Metabolizm kwasów żółciowych w wątrobie zależy od ich napływu z krwi i stężenia w hepatocytach. Kwasy żółciowe wpływają także na przemiany lipidowe w wątrobie. Właściwości żółci, w tym także powstawanie miceli żółciowych i mieszanych, zależą od rodzaju i ilości kwasów żółciowych znajdujących się w żółci. Wpływy kwasów żółciowych w jelicie natomiast zależą z jednej strony od profilu kwasów żółciowych w żółci napływającej do dwunastnicy, a z drugiej – od okresu, w jakim żółć napływa do światła jelita (**Adv Clin Exp Med 2007, 16, 6, 793–799**).

Słowa kluczowe: wątroba, żółć, kwasy żółciowe, wydzielanie.

Bile acids (BAs) are synthetized *de novo* exclusively in the liver, where the so-called primary bile acids (mostly cholic acid and chenodeoxycholic acid) are formed. Following the conjugation with taurine and glycine the majority of them is secreted into the bile, then into the duodenum and they are transported along the gastrointestinal tract. Small portion of BAs is passively absorbed

from the small intestine and most of them is actively absorbed from the ileum. The remaining BAs enter the hindgut in which they undergo the bacterial biotransformation resulting in the formation of the so-called secondary BAs (mostly deoxycholic acid and litocholic acid). Part of them is absorbed and uptaken by the liver where they can be conjugated with glycine and taurine or they can be trasformed into the so-called tertiary BAs and resecreted into the bile. Thus, the liver BA synthesis is only supplementary to prevent the decrease of BA pool by BA loss with the feces and also the trace amounts with the urine [1].

BA Properties and Actions in the Body

BAs along with bile pigments represent the most characteristic bile components although the bile properties are basically related to the properties of BAs which determine the roles of BAs in the body. The different BAs exhibit various physicochemical properties, thus also their physiological roles in the organism vary. Detergent BA properties related to their structure seem to be the most important. The BA molecule expresses the hydrophobic and hydrophilic poles and, for example, the BAs solubility in water is dependent upon the mutual relationship between the molecular poles [2] and is inversely proportional to BA hydrophobicity. The BA hydrophobic-hydrophilic balance can be considered as well [3]. The litho-cholic acid represents the example of hydrophobic BAs while the ursodeoxycholic acid represents the hydrophilic BA. BA properties influence also physiological BA functions and role in the body. These influences are multidirectional [2]. Since BAs can modify the structure and function of their target organs, thus acting directly upon the liver, biliary tract and the intestines, possibly also on the stomach. Stimulating the gastrointestinal mucosal nerve endings and modulating the gut hormone release, BAs can indirectly regulate function of other organs including the pancreas or additionally modulate the function of the liver, biliary and the gastrointestinal tract. There are several BAs in the body and the BA composition in bile is species-dependent. In spite of it, the BA composition in bile can change markedly within the animal species what may depend upon the physiological and pathological conditions. Many factors stimulate or hamper the BA action and the mutual influences of BAs also exist. The effects of BAs in the body can also be harmful which, in most cases, is linked with BA hydrophobic properties [3, 4]. The role of BAs in the body has not been fully elucidated. The detailed recognition of their physiology enables to understand several pathological states based especially upon the genetic or immunological disturbances linked with BA metabolism. Pathogenesis of these diseases remains largely unknown so far. Some of BAs like ursodeoxycholic acid, and their derivatives are also applied as drugs. This discipline has been developing gradually for many years. Thus, more and more new facts and phenomena related to BA physiology and pathology justify this elaboration.

Roles of BAs in the Liver and Biliary Tract

Role of BAs in Bile Secretion

The majority of BAs circulate in the body between the liver and the gastrointestinal tract and this process is known as their enterohepatic circulation [5]. Therefore, BAs are tightly linked with the liver function that can be presented in three principal groups of physiological phenomena: uptake of BAs by the liver from portal blood, intracellular processes occurring in hepatocytes and BA secretion into bile. These processes are summarized in Fig. 1.

BA synthesis is conducted in the liver cells, however its intensity is limited to the supplementary range since the amount of BAs synthesized *de novo* roughly is equal to their loss from the body, i.e. about 5% of the total body BA pool. The dynamics of BA synthesis can be enhanced about twice. Thus, the majority of BAs present in the hepatocytes originates from hepatic BA uptake and is transported into bile. The mechanism of hepatocytic BA transport is not entirely recognized [6]. It has been reported that it runs from one cellular pole (i.e. from the basolateral site – the Disse space) to the facing pole where the biliary canaliculus occurs. This study indicates that the BA transport does not exhibit the vesicular character whereas other data indicate that this is a carrier-related transport. Furthermore, in the liver the BAs (especially the BAs synthesized *de novo*) undergo the conjugation with taurine and glycine while in normal conditions this process is so effective that in normal bile, BAs are conjugated almost exclusively. The long-term BA depletion or loss from the organism may exhaust the hepatic stores of, for example, taurine and therefore the portion of BAs will be secreted into bile in non-conjugated form [4]. BAs can influence intrahepatic lipid metabolism. This effect comprises either the relationship between BAs and low-density lipoproteins (LDL) or the direct effect of BAs on intrahepatic cholesterol homeostasis. In the

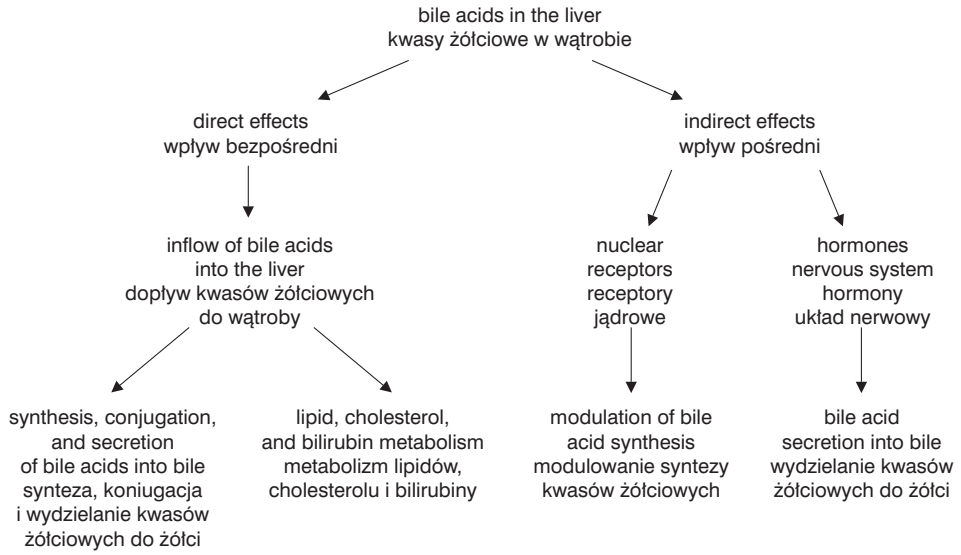

Fig. 1. The effects of bile acids on liver functions [5, 7–11]

Ryc. 1. Wpływ kwasów żółciowych w wątrobie na jej czynności [5, 7–17]

course of *in vivo* and *in vitro* studies it was shown that ursodeoxycholic acid stimulated LDL uptake and this effect was mediated by specific LDL receptor [7]. Alterations in BA metabolism result also in the differences in very low density lipoprotein (VLDL) concentrations [8]. It was also noticed that in some animal species the enrichment of food with cholesterol stimulates BA synthesis and the presence of ursodeoxycholic acid in the fodder also enhances BA synthesis and HMG CoA reductase activity. Notwithstanding, the administration of chenodeoxycholic acid decreases activity of the key enzymes for cholesterol and BA synthesis, i.e. the HMG CoA and 7α-hydroxylase [7, 9]. In consequence, the biliary cholesterol secretion and bile cholesterol saturation are lowered that is the meaningful event in the pathogenesis of cholelithiasis [10]. However, some authors suggested that the action of ursodeoxycholic acid is similar to the effects triggered by chenodeoxycholic acid, at least, as the response to its long-lasting application [11].

BAs are secreted into bile *via* active transmembrane transport. There is the BA-specific pump within the biliary canalicular membrane and its action can be modified by some ligands like the metabolites of estrogen hormones [12]. The active canalicular BA secretory process is important for bile formation as bile volume and composition is dependent mostly upon the efficacy of this process, particularly upon the amount and type of BA secreted into bile [5]. It was estimated that 1 μmol of BAs secreted into bile is responsible for secretion of 7–15 μl of biliary water. The biliary secretion of BAs, i.e. their presence in biliary canaliculi just after secretion is related not only to the magnitude of the bile acid-dependent bile fraction but also to the bile acid-independent bile fraction as well as it depends upon the secretion of biliary lipids, notably the phospholipids and cholesterol. It is self-evident that these effects are stimulatory. Nevertheless, the influences of freshly secreted BAs into the bile canaliculi upon the biliary lipid secretion are confirmed only in part [12]. It is conceivable that there are species differences in this process. The recent studies revealed that BAs might act as the ligands affecting the synthesis of the proteins transporting BAs into the hepatocytes and to the bile and also the synthesis of the cytochrom 450 system enzymes involved in BA and cholesterol metabolism [13]. In these processes farnezoid X receptors, present in hepatocytic nuclei, are engaged and they can be activated by BAs that leads to the inhibition of the transcription of the gene encoding the cholesterol 7α-hydroxylase and stimulation of BA secretion and transport [14, 15]. The micele-forming BAs also stimulate the secretion of conjugated and non-conjugated bilirubin into bile whereas in the latter process the non-micelar BAs participate as well although they are less effective [15]. Secretion of conjugated bilirubin is not affected by such BAs as triketo-BA, dehydrocholic acid and its taurine conjugate amid derivative. The mechanism of this action has not been entirely recognized but it is known, for example, that taurocholate in some experimental conditions enhanced secretion of conjugated bilirubin through the activation of colchicine-dependent vesicular exocytosis [16].

The hepatic BA uptake determines the intensity of biliary BA secretion and their concentration in the systemic blood circulation. This process is very effective but saturable, similar to BA hepato-

cytic transport and BA canalicular secretory process [4]. Hepatic BA uptake is not recognized in details, namely little is known regarding the differences in the hepatic uptake between various types of BAs. They are transported into the hepatocytes by means of various transport systems, dependent or independent of Na^+ [17]. The dynamics of this transport is related to BA concentration in the portal blood.

Adverse Effects of BAs in the Liver

BAs are present in the liver cells in the concentration high enough to consider their possible harmful effects. BAs as the powerful natural detergents may damage the cellular membrane structure due to solubilization of cellular lipids and structural proteins. The is greater BA hydrophobicity the stronger is their membrane damaging action. The negative BA influences are enhanced when BA proportions are changed and their intracellular concentration markedly increases. These compounds might also be harmful for other living cells, especially when they are localized inside [18, 19]. Furthermore, BAs can disrupt the intracellular membranes. These actions can result in the development of apoptosis since the specific (death) receptors can be activated [20]. This mode of action is observed during cholestasis when the hepatocytes are injured. In normal conditions the presence of BAs in the hepatocytes is rather not dangerous because of the existence of protetive actions. The mechanism of this phenomenon has not yet been fully explored, however it is known that more hydrophilic BAs and lipids including lecithin-cholesterol intracellular vesicles, in particular present in the similar concentration to that in bile, can prevent the bile canalicular injury caused by BAs [21]. Similar processes most probably undergo also in the hepatocytes. It has been recognized that the Y'-class protein, 3α-hydroxysteroid dehydrogenase represents the main BA binding cytosolic factor. It is believed that it can reduce the damaging actions of BAs on the liver cells [22]. Glycochenodeoxycholic acid is the toxic substance for the hepatocytes and may evoke the mitochondrial injury. The hepatocytic damage was also observed after liver perfusion with unconjugated chenodeoxycholic acid. However, the ursodeoxycholic acid appears to be the best example of the BA preventing the undesirable effects of hydrophobic BAs and it inhibits the apoptosis [23–25]. The ursodeoxycholic acid also exhibits the immunomodulating action and as one of hydrophilic BAs is useful in gastroenterological clinics [25, 26]. It can be mentioned in addition that circulating BAs exert disadvantageous effects on immunoglobulin production and this action is directly proportional to the degree of BA hydrophobicity [27].

Role of BAs in Bile

The BA concentration in biliary canalicular lumen is about 100 times greater than in the hepatocytes. Thus, the influences of BAs upon the canalicular membranes can be stronger than within hepatocytes. However, the concentrations of biliary lipids (principally the phospholipids and cholesterol) in canalicular bile is also greater than in the liver cells what enables to form simple (composed of BAs) and mixed micelles (composed of BAs, biliary lipids and other compounds). Micelle formation process attenuates the potentially disrupting effect of BAs upon the biliary canaliculi but to a limited extent. It is known that some BAs such as taurocholate increase the membrane fluidity [28] affecting its permeability and in consequence affecting the bile formation process. Forming micelles, BAs facilitate the solubilization (dispersion) in water of the water-insoluble substances, especially the cholesterol. Furthermore, BAs can induce the secretion of enzymes and other proteins into bile diminishing their content in canalicular membranes [29]. The most pronounced effects can be ascribed to the evidently hydrophobic BAs, such as lithocholic acid. The biliary BAs present in bile in relatively high concentrations determine the bile properties which are also related to the biliary BA composition. This effect can also be seen in the biliary tract (Fig. 2). It is the long thought that the composition of the hepatic bile during its flow through the biliary ductuli and bile ducts can be modified, apart from other changes, it is gradually enriched in bicarbonates. It is not established whether the bicarbonates are secreted at the canalicular level, however some studies indicate that this process can occur at the ductular level. It was also noticed that ursodeoxycholic acid affects bicarbonate secretion into bile at this level. More precise investigations demonstrated that ursodeoxycholic acid penetrates the biliary epithelium engaging the non-ionic diffusion mechanism and then releases the hydrogen ion. Accordingly, the luminal BA creates the protonated form and the bicarbonate anion is secreted into the bile duct lumen [30]. BAs absorbed on this way are transported to the peribiliary plexus circulation (the circulation between the biliary tract and the liver) and returns to the liver without reaching not only the duodenum but probably also the gallbladder (Fig. 2). Due to this mechanism (the

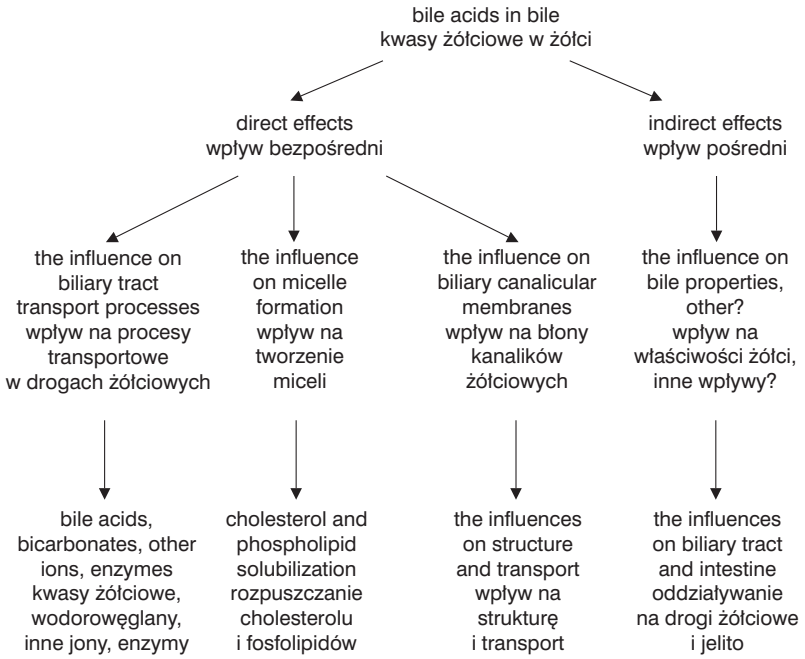

Fig. 2. The effects of bile acids (particularly exhibiting hydrophobic character) in bile on bile properties and their functions within the biliary tract [5, 28–31]

Ryc. 2. Wpływ kwasów żółciowych (zwłaszcza o charakterze hydrofobowym) w żółci na właściwości żółci i czynność w obrębie dróg żółciowych [5, 28–31]

chole-hepatic shunt pathway) the BAs circulating within the biliary tract increase further the bile flow and bicarbonate content in bile that is of the great importance in neutralization of the acidic content inflowing the duodenum from the stomach. However, the BAs can also exert the unfavourable effects in the biliary tract inducing its proliferation and fibrosis [31]. The first step of this pathological process can comprise the activation by BA of the receptor of epidermal growth factor (EGF) *via* the mechanism dependent upon the transforming growth factor-α (TGF-α) in cholangiocytes what accelerates growth of these cells [31]. The described influences take place particularly when the hydrophobic BA concentration is sufficient or for example in the case when the lithocholic acid is given.

Relationship Between the Role of BAs in Bile and in the Gut

Composition of bile flowing down through the biliary tract is modified. The mutual proportions of BAs depend on BA secretion by the liver and on BA absorption within the biliary tract. The definitively formed hepatic bile enters partially the gallbladder where it is stored during the interdigestive period and its composition changes markedly. The most important alterations include the increased bile concentration due to water and electrolyte absorption in the gallbladder. Thus, in the gallbladder bile BA concentration may increase even 10-folds. The final composition of bile inflowing the duodenum determines its effectiveness. The BA content in bile and their hydrophilic-hydrophobic profile seems to be the most important here. The period of the intense bile inflow into the bowel is also important. During the interdigestive period the presence of the greater amount of bile in the duodenum is undesirable and its action in the small-intestinal lumen and the stomach can be too strong and not very helpful, sometimes can be even harmful. In turn, after feeding, when the gastrointestinal tract is not empty, the presence of bile is helpful but not absolutely necessary [32].

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