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

Rola i mechanizm działania kwasów żółciowych w obrębie przewodu pokarmowego – kwasy żółciowe w jelicie

Abstract
In the small bowel, the principal role of bile acids is emulsification, and thus facilitation of the absorption of lipids as well as lipid-soluble vitamins. However, the physiological importance of this function is limited, since about 60–70% of the normal amount of lipids present in the intestinal content can be absorbed without the participation of bile acid. Bile acids affect intestinal epithelial cells, mucosal nerve endings, and enzyme activity in the intestinal lumen due to their detergent properties. This can cause alterations in gut hormone release, especially of motilin and cholecystokinin. Consequently, bile acids influence pancreatic and gastric secretion as well as gastrointestinal and gallbladder motility. Recent studies indicate that bile acids can act through muscarinic and nuclear cell receptors. Thus it can be stated that bile acids exert multidirectional effects in the digestive system and are of interest not only to biochemists and physiologists, but also to clinicians (Adv Clin Exp Med 2008, 17, 1, 83–89).

Key words: bile acids, intestine, secretion, absorption, motility.

Streszczenie

Słowa kluczowe: kwasy żółciowe, jelito, wydzielanie, wchłanianie, motoryka.
The bile acids can evoke direct or indirect actions in the small bowel. Lipid emulsification is the crucial direct bile-acid function in the small bowel. Since this function is well known, a more detailed description of it is omitted here. However, its importance is often exaggerated, since it has also been established that in the absence of bile in the bowel, about 60–70% of dietary lipids can undergo digestion and absorption [1]. Furthermore, the bile acids, regardless of their concentration, are not very efficient emulsifiers. However, their presence in the intestine is very important. Apart from facilitating the digestive processes, including lipid digestion and absorption, bile acids, interacting with phospholipids, directly increase the absorption of lipid-soluble vitamins and cholesterol [1, 2]. Additionally, bile acids can exert an indirect effect on lipid-soluble vitamin absorption by increasing the activity of such enzymes as oxygenase, which cleaves β-carotene, or esterase, which hydrolyzes tocopherol acetate. The lipid-reesterifying effects of bile acids via enzymes including acylo-CoA synthase and transferases represent other examples [1]. Another considerable effect of bile acids is their activation of pancreatic cholesterol esterase, as this enzyme is absorbed into enterocytes, where it conducts the cholesterol esterification process. In turn, the activity of the microsomal enzyme acetyl-CoA:cholesterol acetyltransferase (ACAT) is inhibited by taurocholate. This enzyme is considered to be the most important in cholesterol esterification within the small-intestinal mucosa [1]. It can therefore be assumed that the bile acids contribute rather to the inhibition of cholesterol absorption. This question was extensively studied, leading to inconsistent results. It appears that only hydrophobic bile acids, including deoxycholic acid, might be responsible for this action. The effect of bile acids on intestinal absorption is summarized in Fig. 1.

The acidity of bile acids is much weaker than that of the hydrochloric acid of the gastric juice. Therefore their role in neutralizing gastric content in the duodenum along with bicarbonates is present, but limited. Bile acids affect the transport processes in the small intestinal mucosa. It has been observed that free and conjugated dihydroxy bile acids inhibit absorption and stimulate water and electrolyte secretion [4]. This action can be direct or indirect, when mediated by neurohumoral mechanisms (Fig. 2). The most pronounced effect of bile-acid monomers was observed in the ileum and under some conditions, for example a small amount of intestinal content, can result in the occurrence of diarrhea. Bile acids can also bind small peptides, thus affecting their absorption in the small intestine, especially in its terminal segments [5]. Perfusion experiments on the rat distal intestinal segment showed that chenodeoxycholic acid inhibited sodium absorption more strongly than equimolar amounts of ursodeoxycholic acid [6]. The bile acids administered in premicellar concentrations, i.e. below the so-called critical micellar concentration, bind iron and calcium ions, thus increasing the solubility of inorganic iron and calcium [7]. This process considerably facilitates their absorption via the transcellular pathway. These properties represent features mainly of bile acids with hydroxyl groups at C7 and/or C12 of their molecule. While taurocholate exhibits such properties, taurodehydrocholate is almost devoid of binding properties to the aforementioned ions and its effect on their absorption is negligible. In the ileum the majority of the bile acids are absorbed and the bulk of the intestinal content also decreases, since the absorptive processes predominate over the secretory processes. In spite of this, unabsorbed bile acids reach the hindgut in relatively significant concentrations [8].

There are relatively few bacteria in the small bowel and their numbers increase with increasing distance from the pylorus; thus the role of bacteria in the biotransformation of bile acid in the small bowel is minimal [8]. It can also be mentioned that numerical data indicate that bile acids inhibit microfloral growth in the small bowel, thus preventing excessive bacterial colonization and excessively intense bile-acid biotransformation processes, especially the bile-acid deconjugation that takes place as its first step [8].
The Regulatory Influences of Bile Acids in the Small Bowel and Their Effect on Motility

These functions comprise mechanisms modulating the neural transmission and alterations in gut hormone release evoked by bile acids. The indirect effects of bile acid, particularly on digestive secretion and motility, result from these influences (Fig. 2–3). It is known that detergent substances are tissue irritants, and it can also be stated that nerve endings are very sensitive not only to specific, but also to above-threshold, unspecific stimuli. Therefore it can be expected that bile acids can exhibit stimulatory action upon the receptors and mucosal cells of most gastrointestinal regions. Bile acids are present in the highest concentration in the duodenum and jejunum, and in the distal regions their concentration decreases. Thus it can be assumed that they are absent in the stomach. However, they are usually present there because of the antiperistaltic duodenal contractions moving the duodenal content back to the stomach, and the recurrent character of this event is known as reflux (see Fig. 3), which is considered a physiological phenomenon. Bile acids are usually present in this duodeno-gastric content and can even increase the incidence of these retro-propagated contractions. Numerous physiological studies indicate that bile acid may affect the secretory, motor, and absorptive processes by engaging neuro-hormonal mechanisms. The functional relationships among bile inflow into the duodenum, its motor activity, and pancreatic secretion were observed quite a long time ago [9]. It was found that the presence of bile or natural hydrophobic bile acids in the small bowel

![Diagram](image1.png)

**Fig. 2.** The effect of hydrophobic bile acids in the stomach and small intestine on digestive juice secretion [4, 6, 9, 13, 14, 17, 18, 20, 23, 24, 26, 29]

![Diagram](image2.png)

**Ryc. 2.** Wpływ hydrofobowych kwasów żółciowych obecnych w żołądku i jelcie cienkim na wydzielanie soków trawiennych [4, 6, 9, 13, 14, 17, 18, 20, 23, 24, 26, 29]

![Diagram](image3.png)

**Fig. 3.** The effect of hydrophobic bile acids present in the small bowel on the motor activity of the gastrointestinal tract and gallbladder [10, 11, 16, 19, 25–27]

**Ryc. 3.** Wpływ hydrofobowych kwasów żółciowych obecnych w jelcie cienkim na aktywność ruchową przewodu pokarmowego i pęcherzyka żółciowego [10, 11, 16, 19, 25–27]
results in the suppression of small-intestinal and gallbladder motility and determines the periodic appearance of the migrating motor complex, while diversion of bile from the duodenum causes the opposite effect [10]. It was also found that cholecystokinin, the main hormone regulating gallbladder motor function, may not contribute in the bile acid-induced alteration of gallbladder motility [12]. Bile acid infusion or depletion also affects gastric secretion, exocrine pancreatic secretion, pancreatic and gallbladder growth, as well as small-intestinal vasodilatation-related increase in intramural blood flow [13, 14]. The natural bile acids are able to modulate electrophysiological heart function [15]. Intraduodenal administration of more hydrophilic bile acids caused minimal effect on interdigestive gastrointestinal motility, while the inhibition of gallbladder motility was similar to the effect of hydrophobic bile acids [16]. Intraduodenal administration of ursodeoxycholic acid inhibited exocrine pancreatic secretion, this effect thus being opposite to that of taurodeoxycholic acid [16]. Interestingly, the intraduodenal infusion of taurocholate evoked a stronger effect on exocrine pancreatic secretion than intrajejunal infusion, while the secretion of pancreatic juice in response to the administration of taurocholate into the ileum remained unchanged [17].

The described differences in the influences of bile acids on digestive functions suggest a multiplicity of controlling mechanisms affected by bile acids.

There are relatively few reports concerning the direct effect of bile acids on afferent nerve endings of the gastrointestinal mucosa. Studies in cats and rodents revealed that the effects of hydrophobic bile acids on small-intestinal secretory and motor activities and mucosal permeability to some compounds are mediated by neural mechanisms related to the enteric nervous system [18, 19]. The inhibition of the effects of bile acids by hexamethonium administration indicates the involvement of cholinergic neurons. A number of studies suggest that bile acids can affect gastric and small-intestinal functions by means of muscarinic receptors [20]. Cholinergic mechanisms also participate in the stimulation of pancreatic enzyme secretion by bile acids present in the intestinal lumen [21]. These findings do not exclude the contribution of other neural mechanisms, which warrants further investigation. There also seem to be differences between the influences of hydrophilic and hydrophobic bile acids in their actions mediated by the nervous system. It was reported that taurocholate exhibited an effect similar to muscle contraction-blocking drugs [22] and the action of tauroursodeoxycholate, a nontoxic bile acid, was neuroprotective [23].

The possible effects of bile acids on digestive function via humoral mechanisms are multidirectional, since bile acids modulate some of the hormonal peptide release from endocrine gastric and small-intestinal mucosal cells. Furthermore, bile acids may affect peptidergic mechanisms.

It is well known that the presence of bile in the duodenum releases secretin, although this mechanism is not always efficient [24]. Bile acids are directly responsible for this effect as they influence the duodenal S cells belonging to the APUD cell group [21, 24]. There is also no doubt as to the stimulating effect of bile and pancreatic juice upon motilin release, although the precise mechanism of this action has not been clarified [25]. Bile acids are also responsible for these actions [26]. There is no consensus as to the effect of bile and bile acids on pancreatic polypeptide and cholecystokinin release. While it was once reported that bile acids stimulate pancreatic polypeptide release, other authors found the opposite or lack of such effect [21, 26]. It was reported that cholecystokinin release from the gut is inhibited by bile [27], but others did not confirm this, suggesting that pure bile acids are able to induce such an effect [28]. There is also some controversy as to the data concerning the effect of bile on vasoactive intestinal peptide release. While one group of authors suggested a positive effect, other authors did not confirm this in the dog [29]. There is no controversy regarding the stimulatory effect of bile and bile acids on somatostatin release and its plasma concentration, as studied both in man and dog [21, 29]. Moreover, it was found that bile and bile acids may act on the release of gastric inhibitory polypeptide, enteropeptide, gastrin, PYY, and neurotensin from the stomach and small intestine [27, 30, 31]. These hormones and peptides obviously play marked roles in the regulation of digestive functions. This makes the role of luminal bile and bile acids in this regulation even more important.

The Role of Bile Acids in the Large Intestine

The magnitude of the bile acid pool in the large intestine is less stable than in the small intestine because there are more factors influencing the amount of bile acids present there (the hindgut factors are superimposed upon the small-intestinal and biliary factors). Furthermore, the relatively smaller disturbances in bile acid content in the hindgut than in the small bowel may express the proportionally greater functional consequences in the body. This question thus seems to be of greater importance in pathophysiology than in physiology.
Several disturbances observed in this area confirm this view [32]. However, only physiological aspects will be described in this section, although not too many data are available.

The Effect of Bile Acids on Secretion and Absorption in the Large Bowel

In the large intestine, bile acids are present in considerably smaller concentrations than in the small bowel, but they remain in the lumen much longer because of the much longer transit time. Therefore, in this intestinal region, the time for bile acid retention in the lumen is sufficient for their effective bacterial biotransformation [8]. When the large intestinal transit time is further delayed, the bacterial bile acid biotransformation process will be more pronounced and more deoxycholic acid will be synthesized there at the expense of cholic acid [33]. Thus bile-acid hydrophobicity increases in the hindgut, affecting its function. At the same time, more deoxycholic acid is absorbed into the blood and is transported into the liver and bile and may alter the physiological processes in other digestive organs. It was shown that bile acids inhibit the growth of anaerobic bacteria in the gut [34]. Therefore it can be assumed that there is a certain balance between luminal bile acid concentration and the amount of bacteria in the gut.

In the large bowel, the hydrophobic bile acids reverse the principal direction of water and electrolyte transmucosal transport from the absorptive to the secretory type, i.e. directing their inflow from the blood towards the intestinal lumen [6]. These changes are also accompanied by increased mucosal permeability in the large intestine. Enteric nervous system neurons and nitric oxide are among the main regulators of this process. Additionally, bile acids stimulate mucous secretion in the hindgut, most probably as a consequence of direct influence upon the intestinal mucosa [36].

The Effect of Bile Acids on the Motor Activity of the Hindgut

The effect of bile acids on the motor activity of the large intestine has not been sufficiently clarified. This is due to the relatively small importance of this question (low bile acid concentration in the large intestinal content and the predominating role of other biochemical processes) and by difficulties in performing studies imitating natural conditions. The biotransformation of bile acids and the variability of the bacterial content are the most changeable parameters in the large bowel [8]. Bile acids administered into the large intestinal lumen stimulate its motor activity. This comprises an enhancement of contractility and an increased incidence of spike bursts, including the migrating spike bursts. However, no alterations in the slow waves and in colonic pressure were reported [37, 38]. Furthermore, it was suggested that bile acids initiate defection by stimulating rectal motor activity and relaxing the anal sphincter [39]. A principally similar effect of bile acids, i.e. stimulation of colonic motor activity, was observed in in vitro studies [40]. The hydrophobic bile acids, especially deoxycholic acid, exerted a stronger excitatory effect on large intestinal motility than the more hydrophilic bile acids, including chenodeoxycholic acid and cholic acid [40]. However, changes in the migration velocity and direction of large intestinal content might modulate the magnitude of the bile acid pool, with successive physiological and pathophysiological consequences of this effect [41]. The mechanisms mediating these effects of bile acid have not been worked out in detail. However, it appears that the bile acid-dependent modulation of the release of some gut hormones, such as vasoactive intestinal peptide or PYY, occurring mostly in the small bowel, and the direct activation of neurons of the enteric nervous system by bile acids may exert certain effects upon large-bowel motility [18, 22, 29].

References


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