

## Review

## Bile acids in physico-chemical host defence

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**Abstract**

The discovery of the physico-chemical host defence is closely connected with the endotoxin research. It is well known that the toxic effects of endotoxins under experimental conditions can be induced only when they are administered parenterally. However, in naturally occurring enterotoxemic diseases (e.g. septic and various shocks, etc.), the endotoxin is absorbed from the intestinal tract. The cause and mode of translocation have been unknown. The generally used experimental shock models differ from natural diseases only in the mode by which endotoxin enters the blood circulation. If the common bile duct of rats was chronically cannulated (bile-deprived animals) orally administered endotoxin was absorbed from the intestinal tract into blood circulation and provoked endotoxin shock. This translocation of endotoxins and the consequent shock can be prevented by sodium deoxycholate or natural biles. The bile acids split the endotoxin macromolecule into atoxic fragments. A similar detoxifying detergent action plays a significant role in host defence against infectious agents with outer lipoprotein structure (e.g. so-called ‘big’ viruses). This defence mechanism of macroorganisms based on the detergent activity of bile acids (end-products of the cholesterol metabolism) is called as physico-chemical defence system. Therefore, bile deficiency and the consequent endotoxemia are important components in the pathogenesis of certain diseases (e.g. sepsis, intestinal syndrome of radiation disease, hepato-renal syndrome, parvovirus infection, herpes, psoriasis, atherosclerosis, etc.). Bile acids may be used for the prevention and/or therapy of the above mentioned clinical conditions. © 2004 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Bile acids; Endotoxin; Lipopolysaccharides; Physico-chemical host defence

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**1. Introduction**

The discovery of the physico-chemical host defence – an important part of natural resistance – is in connection with endotoxin research as it is described earlier [1,2]. Numerous mechanisms contribute to host defence. One such mechanism is the detergent action exerted in the gut by hepatic bile acids. This was discovered during our studies on the absorption of endotoxins from the gastrointestinal tract. It is well known that endotoxins are capable of inducing a syndrome similar to septic shock when applied parenterally [3–6]. Therefore, experimentally induced endotoxin shock is based on an artificial situation, which differs from the natural disease with regard to the entry of endotoxin into the host organism. Under natural conditions, during the so-called entero-endotoxaemic

syndrome (e.g. various forms of shock) endotoxin will enter the circulation invariably from the gastrointestinal tract. It is known that endotoxin impairs the movement of intestinal villi [7], but the mechanism of its absorption was not known [8]. Intravenously or intraperitoneally injected endotoxin induces a shock syndrome in mammals, which is similar to the natural disease (entero-endotoxaemia) that occurs prior to death (diarrhoea, inactivity and circulatory disturbances). The pathological findings in animals that succumb to endotoxin shock are similar to those seen in animals that have died of natural disease (intestinal oedema and haemorrhages). There are major differences in the sensitivity of various species to parenterally given endotoxin, which shows correlation with phylogenetic development [9,10]. When given orally endotoxin is, however, not able to exert toxicity in the most sensitive animal species [3]. The reason for this has remained unknown for some time, because the intestinal enzymes do not affect the endotoxin molecule.

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In early experiments we found that orally given endotoxin was harmless when given to rats at doses that were 500–3000 times higher than the parenteral lethal dose. Moreover, such treatment was harmless even when the gut mucosa had been damaged by histamine release induced by compound 48/80 and the animals had been sensitized to LPS toxicity by the intravenous application of lead acetate. It was also observed that endotoxin given orally to rats could be re-isolated from gut content by the phenol–water extraction. No endotoxin absorption could be demonstrated even when the animals were made extremely susceptible to endotoxin by the use of lead acetate [3]. Although the intestinal syndrome during radiation disease is due to entero-endotoxemia, in irradiated animals endotoxin absorption can be demonstrated only on days 6 and 7 by sensitisation with lead acetate [11,12].

The above experiments did not clarify the mechanism of endotoxin absorption from the gastrointestinal tract. The reason for the extreme tolerance of healthy animals to orally given endotoxin could not be explained. Research was restricted to the study of animals/individuals with natural disease or, alternatively, of animals parenterally injected with endotoxin. There was little interest in the problem of endotoxin absorption, which is the prerequisite of the biological effect of endotoxin.

The lack of knowledge stimulated our interest in the problem of endotoxin absorption. The *in vitro* experiments showed that the treatment of endotoxin with a bile acid, sodium deoxycholate, resulted in the production of small atoxic units [13]. The toxicity was possible to revert if sodium deoxycholate was removed by dialysis. If protein was present in the system, the process became irreversible, because the endotoxin fractions were adsorbed to the protein. In this case it was necessary to extract the endotoxin (e.g. with phenol–water) to restore the molecule with some loss [13]. On the basis of these findings we considered the possibility that bile acids may play an important role *in vivo* in the detoxification of endotoxin. If indeed this was the case, it was possible to recover orally given endotoxin from the gastrointestinal tract by extraction even though it is present there in ‘fragmented’, atoxic form. This hypothesis was further supported by the pathological observation that feces of calves and piglets suffering from *Escherichia coli* diarrhea were deficient in bile acids and contained significant quantities of neutral fat [14]. We predicted that bile deficiency was present. This hypothesis was also supported by the pathological observation that in newborn animals that succumbed to *E. coli* diarrhea the gallbladders were fully loaded, indicating the lack of release into the intestinal lumen, this resulted in acholic feces [15]. We observed at autopsy edema and yellow color in the small intestine in mice parenterally injected with endotoxin, which suggests infiltration with bile acids. Perhaps parenterally given endotoxin triggered the release of bile acids into the small intestine as a defence reaction but in this case no protection could be achieved [16,17]. It is known that bacterial endotoxin is chemically a lipopolysaccharide

molecule, in which the toxic moiety has been identified as the lipid, a portion rich in fatty acids [18,19]. On the basis of the above observations one may suggest that bile acids detoxify endotoxin within the gastrointestinal tract.

On the other, hand it is well known that the natural or experimental endotoxemia causes an impaired biliary excretion of bile acids [20,21].

## 2. Bile-deprived rats

Because rats do not have gallbladders, it is possible to produce bile deficiency by the cannulation of the common bile duct. With this technique we successfully produced a chronic bile deficiency, which was suitable for the study of endotoxin absorption from the gastrointestinal tract. In healthy animals orally given endotoxin or the endotoxin released from Gram-negative bacteria within the gastrointestinal tract did not cause clinical symptoms because of bile acids. They are present in the gut on a permanent basis and will tear apart the endotoxin molecule due to the detergent action. Non-toxic small fractions are produced, which are adsorbed by protein molecules present in the gut. It was anticipated that bile deficiency was necessary for the development of entero-endotoxemia. This hypothesis was experimentally proven in rats [22,23]. Endotoxin labelled with tritium or radioactive chromium was not absorbed in normal animals after oral application [24]. No clinical symptoms were produced by such treatment. In contrast, if such endotoxin was given to rats having a bile fistula for 1–2 weeks, which led to bile acid deficiency, the animals succumbed to endotoxin shock. It was possible to detect radioactive endotoxin in the blood of these animals (by the measurement of  $^3\text{H}$  and  $^{51}\text{Cr}$  radioactivity). Such animals could further be sensitized to endotoxin by lead acetate treatment [12]. These experiments revealed that bile deficiency is required for the absorption of endotoxin from the gastrointestinal tract. In further experiments, we treated the endotoxin with sodium deoxycholate prior to oral application to rats having bile fistulas. Complete protection was observed, even when the rats had been sensitized to endotoxin by treatment with lead acetate. Identical results were obtained when bile was used from rats, pigs and cows for the restoration of missing bile acids. Such treatments prevented the development of endotoxin shock [9].

These experiments provided proof for the role of bile acids in host defence against endotoxin, and indicated that bile deficiency leads to the absorption of intestinal endotoxin, both of which have clinical significance. Other investigators confirmed our results in animal experiments and also in clinical situations (endotoxemia of patients suffering from bile duct occlusion and icterus) Bailey [25], Cahill [26] and later Gaffin [27]. It was found that the treatment of icteric patients with bile acids prior to surgery prevented the impairment of renal function and the development of renal deficiency [26–29]. It seems obvious that this beneficial effect of bile acids is based on the physico-chemical, surface-active

and detergent action. Our results support the hypothesis that the inactivation of endotoxin in the gastrointestinal tract by bile acids is due to the detergent action [30]. For this reason we studied the efficacy of other detergents in addition to sodium deoxycholate present in the bile of various animal species. Our goal was to find out whether or not they were capable to detoxify endotoxin by fractionation of the molecule.

### 3. Chemical detergents in endotoxin detoxification in vivo

Studies were done also with some commonly used detergents (e.g. sodium lauryl sulphate, cetylammmonium bromide, polyoxyethylene stearate, Tween 20 and benzalkonium chloride). Two rapid methods were developed for the determination of their activity. One approach was to inject a mixture of a lethal dose of endotoxin and a tolerated concentration of the detergent intraperitoneally to animals. If the detergent applied could detoxify endotoxin, the mortality of the animals was decreased. According to the second procedure the animals were sensitized to endotoxin by lead acetate. In this case microgram quantities of endotoxin could be used, mixed with detergent and given intravenously. Here it was also necessary to titrate detergent toxicity prior to its use. Again, a decrease in mortality indicated the anti-endotoxic effect of the detergent investigated. These experiments indicated that sodium deoxycholate and bile obtained from various animals (cow, pig, rat and rabbit) showed 100% efficacy in protection, whereas sodium lauryl sulphate gave 80%, cetylammmonium bromide 60%, and benzalkonium chloride 20% protection against the lethal dose of endotoxin, and Tween 20 was ineffective. The best results were thus obtained with bile acids or with natural bile [31].

The experimental results made it possible to explain the pathomechanism of entero-endotoxemia in newborn babies, which occurred frequently some time ago but lately decreased in number because of improved hygienic conditions in hospitals. However, this disease still has veterinary significance because 10–15% of newborn calves and piglets will fall victims to entero-endotoxaemia. It is likely that in a proportion of newborn animals bile production (probably because of disturbed liver function) or bile secretion into the small intestine (probably because of the lack of cholecystokinin) does not coincide with parturition, which leads to bile deficiency. There is a rapid penetration of Gram-negative bacteria into the gastrointestinal tract of newborn animals, which release endotoxins that would absorb in bile-deficient animals and cause disease and death. The situation is analogous to rats having a bile fistula and receiving endotoxin by the oral route. It follows that such newborn animals would be protected if given after parturition detergent preparations, optimally bile acids that would prevent disease. Such treatment would restore the bile content in the gut which would enter the enterohepatic circulation, stimulate the production of bile acids and their

secretion into the gut, in other words initiate the function of this fundamental host defence mechanism [15,30].

### 4. Bile acids in protection against endotoxin shock

On the basis of the above experiments, therapeutic preparations of bile acids have been produced, which seem to be beneficial for the treatment of entero-endotoxemia in newborns [32]. Comparative pathological studies conducted during these therapeutic trials demonstrated that these preparations were able to decrease mortality due to *E. coli* diarrhoea. For instance, in a cattle herd 195 calves received conventional treatment and 23 of them died, whereas after the treatment of 234 calves with the bile acid preparation only 6 were lost because of *E. coli* diarrhea. Essentially similar results were obtained during the trial in other herds. The results were similar though inferior in a pig farm, where 120 piglets were lost out of 2027 untreated animals, whereas 68 died of 1803 bile acid treated animals due to *E. coli* diarrhoea [15,32].

The experience gained during several decades has shown that the treatment of entero-endotoxemic newborn animals with drugs or vaccines is of limited value. Vaccines provide protection only against specific strains that have been used for its production and become useless against other strains that frequently occur in a given population. This is a serious limitation, as approximately 150 different *E. coli* strains are known simply on the basis of O serotypes. For this reason the induction of specific immunity seems impossible. Perhaps the new, so-called pilus antigen vaccines or the use of DNA vaccines will improve the situation [33]. The problem is similar when antibacterial agents (antibiotics, sulphonamides) are used for treatment. Resistance will occur within a short period of time, which renders these drugs ineffective. One may hope, on the basis of our results, that this disease could be prevented by the restoration of bile acid deficiency. Current evidence indicates that in *E. coli* diarrhea the so-called enterotoxins [34] could facilitate the translocation of endotoxin by causing damage to the gut mucosa. Such damage would inhibit or prevent the secretion of cholecystokinin, which in turn will lead to bile retention and allow the absorption of endotoxin into the bloodstream, resulting in endotoxemia and shock. This explanation is compatible with those views that emphasise the fundamental pathogenic role of endotoxin in these conditions.

The above examples of animal disease have comparative pathological significance and serve as models for human conditions. It is well known that a significant proportion of the human population suffers from problems of bile secretion and of gallbladder function [35]. It is possible that the use of bile acid preparations would be beneficial to such patients.

### 5. Physico-chemical host defence

The pathophysiological significance of findings reported above may be summarized as follows: a unique host defence

mechanism has been discovered, the significance of which is likely to lie way beyond protection against bacterial endotoxins. We call this mechanism the physico-chemical defence of the organism. The basis of this defence mechanism is the detergent effect of bile acids [1,30,35]. One may pose the question whether or not the protection based on detergent action provides defence against enterotoxemia only or perhaps there are other situations in which endotoxin plays a role.

## 6. Bile acids and intestinal ischaemia

The intestinal ischaemia is aggravated by bile deficiency [36,37]. Moreover, it was found that bile production is decreased under these conditions [38]. This was further supported by the observation that the administration of bile acids (500 mg pulverized and radiation-sterilized pig bile) to dogs with intestinal ischaemia prevented death in 70% of the animals [39]. The protective value of bile acids was also indicated in rats suffering from 'strangulation ileus', where endotoxin plays a fundamental role in the pathogenesis. Bile acids given into the intestinal lumen (20 mg pulverized and radiation-sterilized pig bile) prolonged the survival of the animals by 7 h (50%) [40]. These results indicate that, the use of proper bile acid preparations will provide new opportunities for the treatment of patients with acute abdominal conditions.

## 7. Bile acids and virus defence

One may ask the question whether or not the protective effect of bile acid detergents is limited to bacterial endotoxins. Theiler observed that the yellow fever virus and other 'arthropod-borne' viruses (belonging to Toga group) are inactivated by bile or sodium deoxycholate. In contrast, the poliovirus, the virus of mouse encephalitis and endocarditis and Cocksackie viruses resist such treatments [41]. This observation served as a basic principle for the classification of viruses according to which two groups, sodium deoxycholate sensitive ('big viruses') and resistant ('small viruses') could be distinguished. It is interesting that nobody, including Theiler, recognized the pathological significance of these observations despite the fact that, Theiler was actually working with the yellow fever virus when he discovered the antiviral effect of bile. If we compare the bile acid sensitive and resistant viruses, it becomes clear that the viruses having lipoprotein capsule/peplon are sensitive and those that do not possess such a capsule are resistant. It follows that bile acids would affect *in vivo* all the viruses that possess lipoprotein 'capsule' (peplon). Those without capsules are all resistant. Therefore, it is logical to assume that the detergent effect of bile acids would act *in vivo* on all those viruses that have lipoprotein capsules and that this fact could be used for protection against such viruses. In model experiment using Aujeszky's disease virus, a herpesvirus, we demonstrated the protective effects

of bile acids. It was found in rats that bile-deficient animals contracted disease after the oral administration of Aujeszky's disease virus, whereas intact rats were resistant [35]. It is possible that temporary or partial bile acid deficiency plays an important role in infections with herpes viruses that may occur after alimentary overloads (e.g. weddings and other feasts).

The importance of bile acids is further emphasized by the observation that the symptom of acute parvovirus infection, which causes severe intestinal haemorrhage in dogs, closely resembles experimental endotoxin shock. During autopsy the characteristic finding is a dilated, tightly filled gallbladder. Endotoxin could be detected in the serum of such dogs using lead acetate sensitized rats [12,42]. These observations suggest that parvovirus induced mucosal damage in the small intestine, which leads to hemorrhage, is likely to inhibit cholecystokinin (CCK) synthesis and CCK deficiency leads to bile retention. Partial bile acid deficiency occurs in the gut, which makes the absorption of endotoxin possible. It is likely that the sick dogs die of endotoxin shock [42].

## 8. Bile acids and psoriasis

In our view, psoriasis, a condition considered to be inherited in a polygenic manner [43], is also associated with bile or bile acid deficiency, as in most cases supplementation of the usual treatment with bile acids will diminish the severity of the clinical signs within a short period. On the basis of clinical observations (digestive disorders, ultrasonographically confirmed gallbladder changes, etc.) it may be assumed that the deficiency of bile acids can indeed play a role in the pathogenesis of psoriasis [44]. In bile acid deficiency the absorption ('translocation') of endotoxins becomes possible [35,45], and this will trigger the release of inflammatory cytokines in the skin of individuals having a hereditary predisposition. If the absorption of endotoxins is prevented by bile acid supplementation, the release of inflammatory cytokines can be blocked. Probably this is the mechanism that explains the success of our treatment approach. Thus, the effect that cytokines have been recognized to exert in the pathogenesis of psoriasis suggests the indirect role of bacterial endotoxins. However, this effect probably occurs only if bile production or excretion is deficient (cholecystokinin deficiency, disturbance of cholesterol metabolism and bile production). Thus, the treatment of psoriasis with bile acids should actually be regarded as supplementation of a physiological substance rather than a medicinal therapy. In our view, its effectiveness, safety, simplicity and low cost make this treatment modality suitable for a wider use in the therapy of psoriasis [44]. The successful treatment of psoriasis with bile acids is an example demonstrating that the recognition of physico-chemical defence has practical importance. Thus, recognition of the role of bile acids enables us to provide casual treatment to psoriatics, who have mostly been given only symptomatic treatment so far.



## 9. Bile deficiency in radiation-induced intestinal syndrome

It is clear that the intestinal syndrome associated with radiation disease is caused by bacterial endotoxins. Because bile acids are capable of endotoxin detoxification and bile deficiency permits the absorption of endotoxins into the bloodstream ('translocation'), one may ask the question whether or not bile deficiency would play a role in radiation disease. For this reason we studied in rats the effect of experimental bile deficiency on the development of radiation-induced intestinal syndrome. It was observed that the rats having bile fistulas died within 5 days in radiation disease, whereas the control irradiated and sham-operated irradiated animals survived for 11 days. Apparently bile deficiency accelerated the development of endotoxaemia in this case [46].

## 10. Bile acids in endotoxin sensitive and resistant species

In relation to the importance of bile acids in host defence against endotoxins, one may ask the question whether or not bile composition plays a role in the endotoxin sensitivity/resistance of various species [47]. There are major differences in bile acid composition of bile obtained from sensitive (e.g. man, cow and guinea pig) and resistant species (e.g. birds and fish) [35,38]. It is interesting to note that there is a direct correlation between endotoxin sensitivity and radiation sensitivity of various species. Perhaps the ontogeny of the production of bile acids in the chickens bears relevance to the fact that chicken embryos show endotoxin sensitivity up to 11 days of age, which is the time of the initiation of bile acid synthesis in the liver. Older chicks or mature animals can only be made susceptible to endotoxin by lead acetate treatment. It is likely that bile acids function not only in the gut, but also in the liver in addition to acyl-oxyacyl hydrolase enzyme discovered in 1989 in the detoxification of bacterial endotoxins [35,48].

## 11. Endotoxin inactivation by liver/bile acids

Liver homogenates from healthy rats are capable of inactivating small (microgram) quantities of endotoxins. In contrast, if the rats received lead acetate intravenously prior to the preparation of liver homogenates, no endotoxin inactivation was observed [35]. Similar results were obtained if we incubated natural bile fluid with lead acetate. Such bile solutions lost their capacity to detoxify endotoxin. It is likely that lead acetate damages the side chains that play an important role in the detergent effect of bile acids, and for this reason the modified bile acids are unable to detoxify endotoxin. This phenomenon may play a role in the lead acetate induced endotoxin sensitivity *in vivo* [35].

After the dissociation of endotoxin by bile acids to its basic units the detoxified material maintains the capacity to induce endotoxin tolerance [35]. It is possible that this observation will lead to the isolation of nontoxic endotoxin subunits, which will be able to stimulate natural resistance without toxic side effects [35,49].

## 12. Conclusion

In conclusion, general physico-chemical defence based on the detergent action of bile acids protects the body against bacterial endotoxins and other agents (e.g. viruses) that possess lipoprotein or lipid structures. This novel mechanism contributes to the other known defence mechanisms. This mechanism is strengthened by the entero-hepatic circulation. Bile acids, the products of cholesterol metabolism, are reusable end-products. It is possible that bile acids play also a role in the pathophysiology of endocrine and reproductive abnormalities, which remains to be elucidated [49].

It is possible that deficient bile production or secretion leads to the absorption of minute amounts of endotoxin, which may play a role in the induction of atherosclerosis [50–61]. At least in cholesterol-treated rabbits endotoxin significantly increases the development of atherosclerosis [35,54,55,59]. Partial or temporary bile acid deficiency may occur for several reasons (CCK deficiency, disturbance of bile secretion and deficient bile production due to liver damage), which leads to endotoxin absorption. In turn, the absorbed endotoxin will act on sessile phagocytes fixed to the wall of blood vessels via e.g. endotoxin-binding protein and CD14 endotoxin receptor, which increases the production of cytokines and other active biologicals. These mediators, in conjunction with elevated cholesterol levels, could precipitate a plaque formation. On this basis one may suggest that the systematic investigation of bile production and secretion would be of great value in general pathophysiology.

It is clear from the facts presented here that, bile acids and endotoxins play a significant role in many more pathological conditions than it was reasonably anticipated (Table 1). It is likely that further investigation of these questions and the

Table 1

Proven and presumed roles of bile acids and endotoxins in certain pathological processes (2)

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| Intestinal infections                           |
| Surgical/septic shock                           |
| Intestinal ischemic shock                       |
| Tourniquet shock                                |
| Gastro-intestinal syndrome of radiation disease |
| Hepato-renal syndrome                           |
| Enteroviral infections (e.g. parvovirus)        |
| Herpes viral infections                         |
| Psoriasis                                       |
| Atherosclerosis                                 |
| Endocrine disorders                             |

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application of experimental results to patients will lead to new approaches in clinical medicine.

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