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# Sepsis and cholestasis: basic findings in the sinusoid and bile canaliculus

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**Abstract** It is well known that the liver plays a major role in the clearance of systemic toxemia and is postulated as a regulational organ in the host-defense system. The well-controlled interaction between hepatic parenchymal cells and sinusoidal lining cells including macrophages and Kupffer cells can systematically regulate even critical infections. However, when patients are under the overload condition caused by severe infection, rejection of a transplanted liver and other hapatic dysfunction often are experienced following surgery. Among various signs and symptoms of hepatic dysfunction, progressive cholestasis is recognized as a polarized representation of the irreversible changes in hepatic constitutional cellular functions, especially in hepatic parenchymal cells. Bile canaliculi, the smallest components of the biliary tree, lie between the apical surfaces of adjacent hepatocytes. Septic cholestasis might be a result of disturbance of the total bile canalicular system, i.e., bile secretion, canalicular contraction, and so on. Recently, the molecular biology of the hepatocellular transport system has become better understood, and the pathophysiological condition of cholestasis can be explained as a representation of the intracellular molecular transcriptional system. Cellular changes in surgical cholestasis and molecular findings concerning the bile canaliculus are introduced in this article.

**Key words** Liver · Sepsis · Cholestasis · Bile canaliculus

## Introduction

The liver is increasingly recognized as a key organ in the initiation and the promotion of multiple organ failure during sepsis, because it performs the main regulational role in the cellular metabolism of functional epithelial cells and immune cells concerned with the host defense mechanisms. Moreover, under the overload condition in sepsis, the functional performance of the liver critically regulates many interrelated elements of the systemic inflammatory response. The liver plays an active role in the clearance of systemic endotoxins, bacteria, and the vasoactive byproducts of sepsis, and in the inactivation and detoxification of these compounds through interactions between liver macrophages (mainly Kupffer cells) and hepatocytes. These phenomena may be regulated by active or passive changes in sinusoidal lining cells (e.g., sinusoidal endothelial cells, polymorphonuclear cells, and platelets). In addition, the activated liver simultaneously produces and releases various cytokines, vasoactive lipids, and acute-phase proteins. It is of interest to examine the effects of these serial changes during sepsis on cholestasis.

## Today's knowledge of cholestasis

Hepatic dysfunction, a pathophysiologic condition in sepsis, is induced by both macro- and microcirculatory disturbances and by functional failure in intrahepatic cellular systems. The stereotypical response of the liver in the process of hepatic failure has been well reported. However, little is known of its mechanisms; for example, the developmental mechanism of cholestasis that is characteristic as a result of hepatic failure.[1] Cholestatic liver disease is one form of liver injury that promotes cirrhosis, either following extrahepatic bile duct obstruction or because of intrahepatic metabolic abnormalities.[2] The essential pathogenesis of cholestasis developing during sepsis arises from the latter condition, and is based on disturbance of the intra- and extracellular transportation system of bilirubin in hepatocytes, influenced by the responses of hepatic parenchymal cells and sinusoidal lining cells. It is well known that the structure of the liver sinusoid is characteristic

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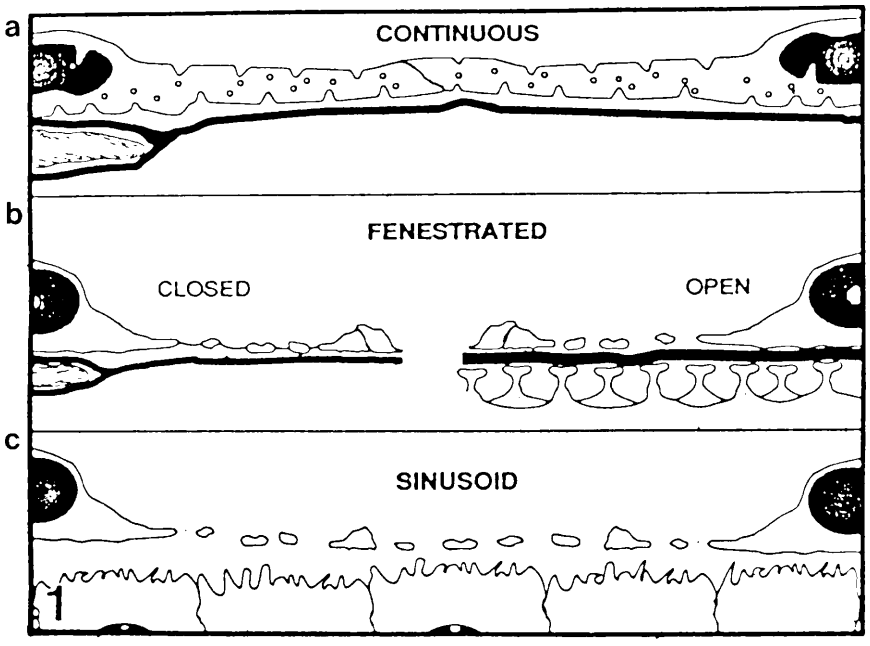


**Fig. 1.** Schema of the capillary structures in three kinds of tissues, i.e., peripheral capillary in general tissue (*a*), sinusoids of the adrenal gland (*b*), and sinusoids of the liver (*c*). The characteristics of hepatic sinusoids are absence of basement membrane and of smooth muscle cells; there are also many pores, arranged in sieve plates, in the hepatic sinusoidal endothelial cells

for exchange between the bloodstream and the organ's functional cells, compared with the structure of capillary vessels in other tissues or the sinusoid of the adrenal gland (Fig. 1). To investigate the pathogenesis of cholestasis under conditions of severe infection may contribute to the essential understanding of this condition, and to future therapy.

## Clinical causes of inflammation-induced cholestasis

Clinically, inflammation-induced cholestasis is caused by drug- and alcohol-induced liver injury, intra- and extrahepatic infections, total parenteral nutrition, and nonmetastatic neoplastic disorders (e.g., renal cell carcinoma and malignant lymphoma); it also occurs postoperatively (e.g., after major abdominal surgery).[1] At a glance, it seems that there are no relationships among these conditions. But these conditions have a common denominator in that they can induce proinflammatory cytokines, which are potent inhibitors of hepatocellular bile secretion.[2]

## Morphological observations in the liver of the patient with sepsis

In an early study, we showed that hepatic insufficiency in rats with endotoxemia was induced following the occurrence of significant changes in sinusoids.[3] In a recent report,[4] a group of patients with clinically defined sepsis was studied by light and electron microscopic procedures. Most of these patients had undergone hepatectomy or pancreatoduodenectomy and suffered from cholestasis induced by severe infection as a postoperative complication. In the hepatectomy group with severe infection, poor regeneration was characteristically proven by computed tomography (CT) imaging, with findings similar to those shown in patients with cirrhosis.[5]

This phenomenon led us to take an interest in the effect of pathophysiological sepsis on the well observed phenomenon of hepatic regeneration after hepatectomy in humans. Further research in this field will help us to understand the pathogenesis of this mechanism, and will, eventually, enable us control of hepatic regeneration.

### *Sinusoidal changes*

In sepsis, intracellular bile congestion is observed in hepatocytes, with sinusoidal dilatation and the appearance of increasing numbers of infiltrating cells in the sinusoid (Fig. 2A). These phenomena are thought to cause cell aggregations of sinusoidal lining cells, resulting in obstruction of the sinusoidal lumen. This obstruction was induced by the aggregation of Kupffer cells, polymorphonuclear cells, eosinocytes, platelets, exfoliated endothelial cells, and so on, with an interposing fibrin appearance (Fig. 2B), and there was detection of endotoxin-like materials on the Kupffer cell membrane (Fig. 2C). Such structural findings suggest hypoperfusion in sinusoids, which induces dilatation of Disse's space. The structure of the hepatocytic membrane microvilli facing Disse's space becomes irregular, but that on other sides does not. However, with clinical

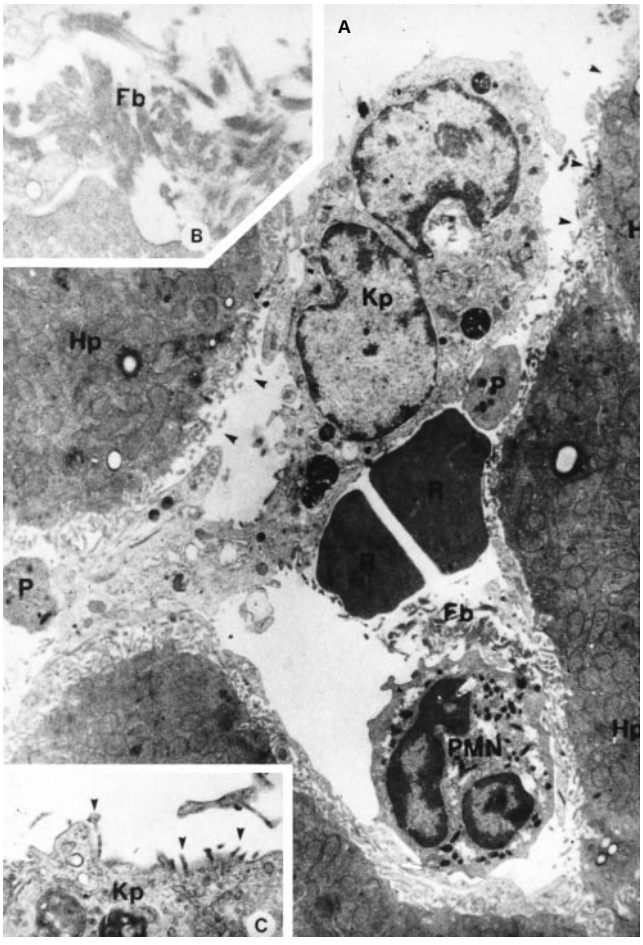


**Fig. 2A–C.** High magnification of hepatic sinusoids in sepsis. **A** Cell aggregations composed of Kupffer (*Kp*) cells, polymorphonuclear (*PMN*) cells, red cells, platelets (*P*), etc, with **B** the appearance of fibrin (*Fb*). **C** Particles recognized as bacterial endotoxin were observed on the surface of Kupffer cells. *Hp*, Hepatocytes. *Arrowheads* indicate the particles of endotoxins

cholestasis, the microvilli of the bile canaliculi mostly disappear, and dense materials are detected in the bile canaliculi. In areas with such sinusoidal changes, hepatocyte degeneration and/or apoptosis is observed. Sinusoidal endothelial cells present an irregular arrangement of sieves and pores on the cell surfaces, with cell swelling, and, rarely, there is complete exfoliation.

### *Kinetics of Kupffer cells*

The responsiveness of Kupffer cells to external stimulation (mechanical and/or infectious stimuli) has been recognized as a reaction to the host defense mechanism, paralleling the reactions of other macrophages in sinusoids. Finally, the Kupffer cells interact, in the manner of autocrine or paracrine systems, with hepatic parenchymal cells according to specific or nonspecific induction by external stimuli (Fig. 3). As the first morphological step in Kupffer cell activation, an increase in intracellular lysosomes and in cell size are characteristically found. Subsequently many regulatory signal transport phenomena follow in the Kupffer cells, and these phenomena occur repeatedly until the cell shows apoptosis or a resting condition. The interactions between Kupffer cells and other cells are regulated by signal transmission or autostimulation in each cell, under the control of gene determination. Regulation of protein levels, via the release of several signal molecules (e.g., interleukins, interferons, tumor necrosis factor, transforming growth factor, prostaglandins, thromboxane A2, prostacyclin, leucotriene B, and platelet activating factor), as well as inorganic molecules, participates in the processing of Kupffer cell reactions. As a result of the continuity of such phenomena, Kupffer cells are induced to regulate the structures of many kinds of liver cells, as shown in the schema in Fig. 3. Initial morphological changes occur as platelets surround activated Kupffer cells and are activated themselves. In these platelets, the characteristic original form disappears, because of, for example, the development of pseudopods and the disappearance of typical granules.

### *Kinetics of sinusoidal endothelial cells*[5]

The hepatic microcirculation can be best recognized in terms of the lobule, the basic anatomical unit of the liver. The bloodstream in the lobule starts at its periphery via the hepatic artery and the portal vein. It enters the sinusoids, the specialized capillaries of the liver, and flows into the central vein located in the center of the lobule. As the blood circulates through the sinusoids, the removal of nutritional elements, oxygen consumption, and several metabolic processes are constantly repeated. These unique functions depend mainly on the characteristic sinusoidal structure, which, mainly, consists of sinusoidal endothelial cells. In contrast to the walls of capillaries in other tissues, the hepatic sinusoidal endothelial walls have no basement membrane, and there are no muscle cells beneath the endothelial cells; these cells possess pores approximately 0.1 μm in diameter, which are arranged in clusters of sieve plates (Fig. 1). Through these fenestrations, the endothelial cells influence the filtration of particles from the blood to parenchymal cells and vice versa. Recent investigations have suggested that the sizes of sieve plates and/or pores are influenced by the cytokines in the sinusoid and in Disse's space, or by the direct contact of intrasinusoidal macrophages with endothelial cells. By such regulation, selective exchanges of nutritional substances between the sinusoid and the space of Disse are controlled. However, such selective autoregulation, paralleling the function of the defense system, is easily

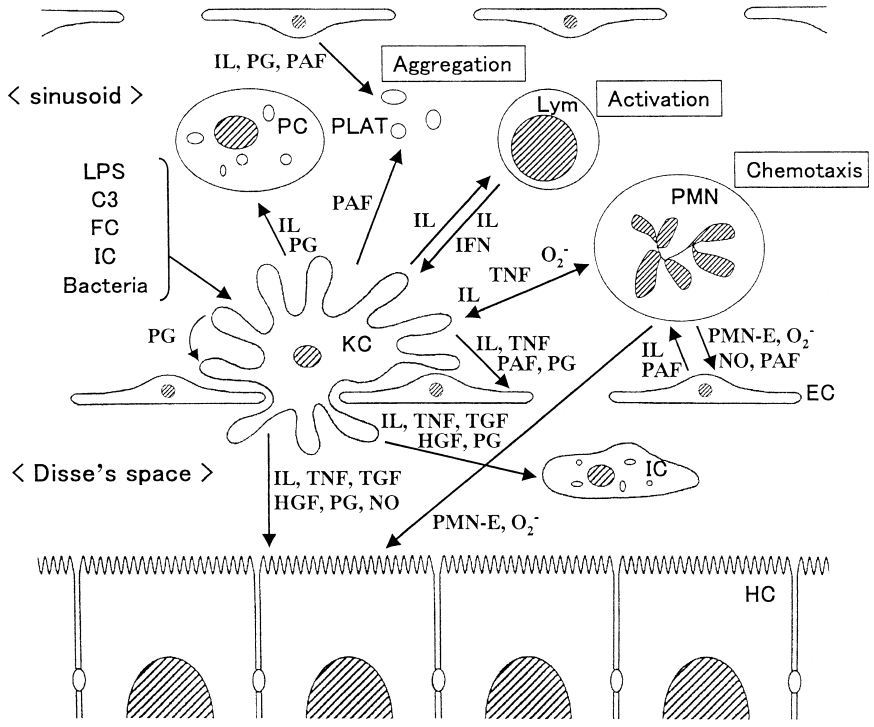


**Fig. 3.** Schema of cell-cell interactions in regard to cytokines and chemical modulators in sinusoids and Disse's space. Kupffer cells (*KC*) are activated by various stimulants, such as lipopolysaccharide (*LPS*), complement, immune complex (*IC*), and bacteria. Kupffer cells secrete various cytokines and chemical modulators, and stimulate sinusoidal lining cells, such as endothelial cells (*EC*), polymorphonuclear cells (*PMN*), lymphocytes (*Lym*), platelets (*PLAT*), pit cells (*PC*), Ito cells (*IC*), and others. Cytokines and chemical modulators are further secreted from these cells and they cause sinusoidal changes and injuries to hepatocytes (*HC*) and endothelial cells (*EC*). *IL*, Interleukin; *PG*, prostoglandin; *PAF*, platelet activating factor; *IFN*, interferon; *TNF*, tumor necrosis factor; *TGF*, transforming growth factor; *HGF*, hepatocyte growth factor; *PMN-E*, PMN-polymorphonuclear cells; *Fc*, fragment c; *NO*, nitric oxide

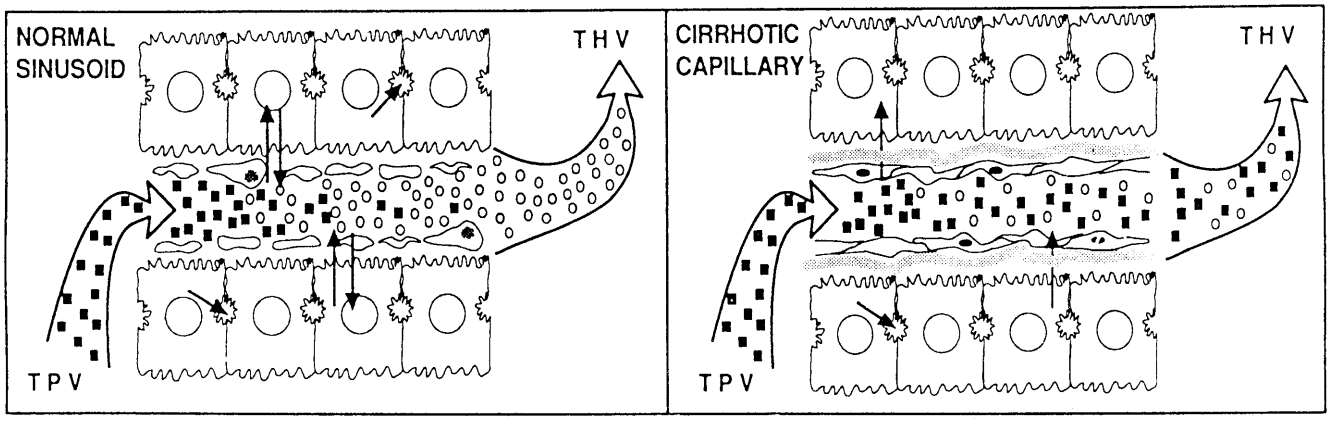


**Fig. 4.** Proposed effect of capillarization on hepatic sinusoids. Significant decreases in pores and sieve plates in sinusoidal endothelial cells, and the appearance of deposits just beneath the endothelial cells are observed. These changes are recognized as "sinusoid capillarization". *TPV*, Total portal vein; *THV*, total hepatic vein

disturbed by, for example, molecular changes on the endothelial cell surface. Thus, the sinusoidal endothelial cells have important roles in facilitating exchange and transport from and into the bloodstream and also in the maintenance of sinusoidal wall elasticity and blood viscosity. These factors strongly influence the condition of the hepatic microcirculation, which determines the exact hepatic functions. However, it is well known that the capillarization of hepatic sinusoids, characterized by deposits just beneath the endothelial cell basal lumen, influences the auto-regulatory system in cirrhotic liver (Fig. 4).

## Bile canaliculi

Bile canaliculi, the smallest components of the biliary tree, lie between the apical surfaces of adjacent hepatocytes (Fig. 5). Collections of bile canaliculi finally form the biliary ducts in the interlobular space. The biliary duct is regulated by the bloodstream of the peribiliary plexus arising from the hepatic artery flow and the portal vein flow. The peribiliary plexus forms a regular network in normal liver, but significant irregular changes of vessel arrangement are observed in cirrhotic liver (data not shown). Such a distored peribiliary

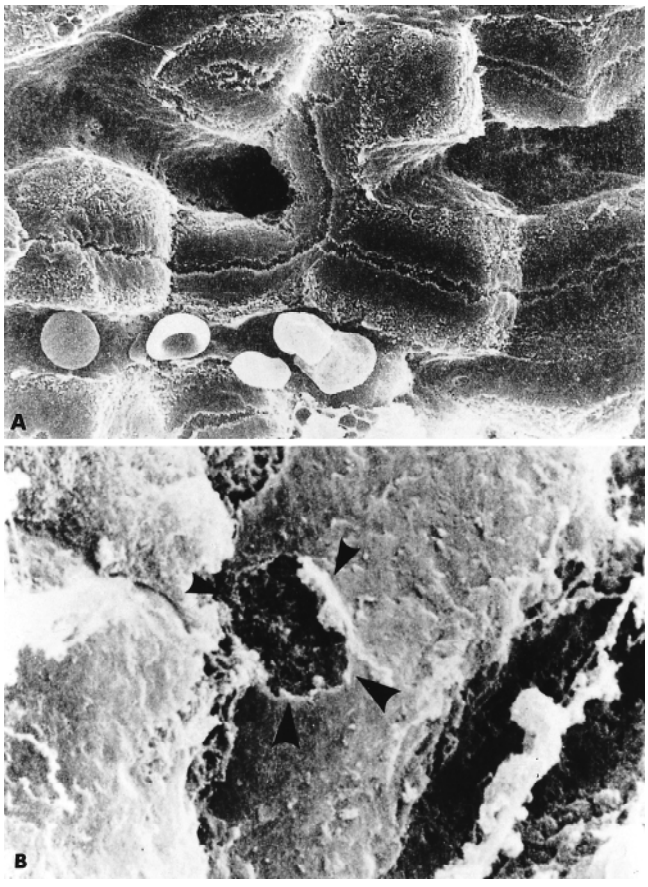


**Fig. 5A,B.** Scanning electron-micrographs of **A** normal liver and **B** hepatic failure. Regular arrangement of the bile canaliculus between two hepatocytes in normal liver, and abnormally dilated bile canaliculus with diminished microvilli on its lumen side, which looks uncontractable, are clearly observed. A definite difference in bile canaliculus condition between **A** and **B** is recognized. **A** ×2700; **B** ×5100

plexus may have a detrimental effect on the function of biliary duct cells and on the local defense.

Bile canaliculi are surrounded by actin and myosin microfilaments and possess contractile activity, which has a major role in facilitating the transport of bile through the canalicular route (Fig. 6). Treatment of rats with drugs that impair the polymerization and depolymerization of actin results in bile secretory failure and defective bile canalicular contraction. The control mechanism, via upstream regulation, depends on the prompt formation of inositol 1,2,4-triphoshate ($IP_3$) by the activation of phospholipase C, which opens $Ca^{2+}$ channels and induces the release of $Ca^{2+}$ into the hepatocytic cytoplasm. The increase of cytoplasmic $Ca^{2+}$ activates myosin light chain kinase, leading to contraction. The detailed mechanism of the impairment of prompt formation of $IP_3$ has been partially elucidated. The main extrahepatocytic effects of this impairment are a disturbance in sinusoidal blood flow[3] and the diffusion of NO or CO produced in neutrophils or endothelial cells,[6] as well as the diffusion of some interleukins.

## Mediators of inflammation-induced cholestasis

Regardless of its etiology, inflammation-induced cholestasis is mediated by the cholestatic effects of endotoxins (e.g., lipopolysaccharide [LPS] in the outer membrane of Gram-negative bacteria) and/or by LPS-induced proinflammatory cytokines.[1] Endotoxins stimulate Kupffer cells to produce proinflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, interleukins (IL)-1, -6, and -8), and these cytokines directly affect hepatocyte function.[2,7] Endotoxins may be derived from intestinal translocation promoted by various factors, such as alcohol, drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]), and total parenteral nutrition (TPN).[8–11] Plasma endotoxin concentrations are increased in patients with chronic hepatitis C,[13] and serum/plasma concentrations of proinflammatory cytokines (e.g., TNF-α and IL-6) are elevated in patients with chronic hepatitis B or C.[13]

## Cholestatic effects of endotoxin and inflammatory cytokines

Cholestasis is a side-effect of cytokine therapy with TNF-α[14] and IL-2[15] in humans. Parenteral administration (intravenous or intraperitoneal) of LPS to rats produces cholestasis, as has been demonstrated in the isolated perfused liver,[16–18] and in isolated and isolated hepatocytes.[19,20] Some studies have suggested that TNF-α inhibits bile flow and bile salt uptake in the rat.[21,22]

## Molecular changes in inflammation-induced cholestasis

The hepatocyte is a polarized epithelial cell with distinct features in its basolateral (sinusoidal) and apical (canalicular) plasma membrane domains. Some hepatocellular membrane transporters play an important part in the excretion of bile salts. Two major sinusoidal bile salt uptake systems have been cloned (Fig. 7): an $Na^+$-dependent $Na^+$/taurocholate cotransporter (Ntcp) and an $Na^+$-independent organic anion transporting protein (Oatp1).

The canalicular membrane has two kinds of transport systems — adenosine triphosphate (ATP)-dependent transport (e.g., the multidrug export pump [Mdr 1a, b], the phospholipid export pump [Mdr 2], the canalicular conjugate export pump [Mrp 2], and the canalicular bile

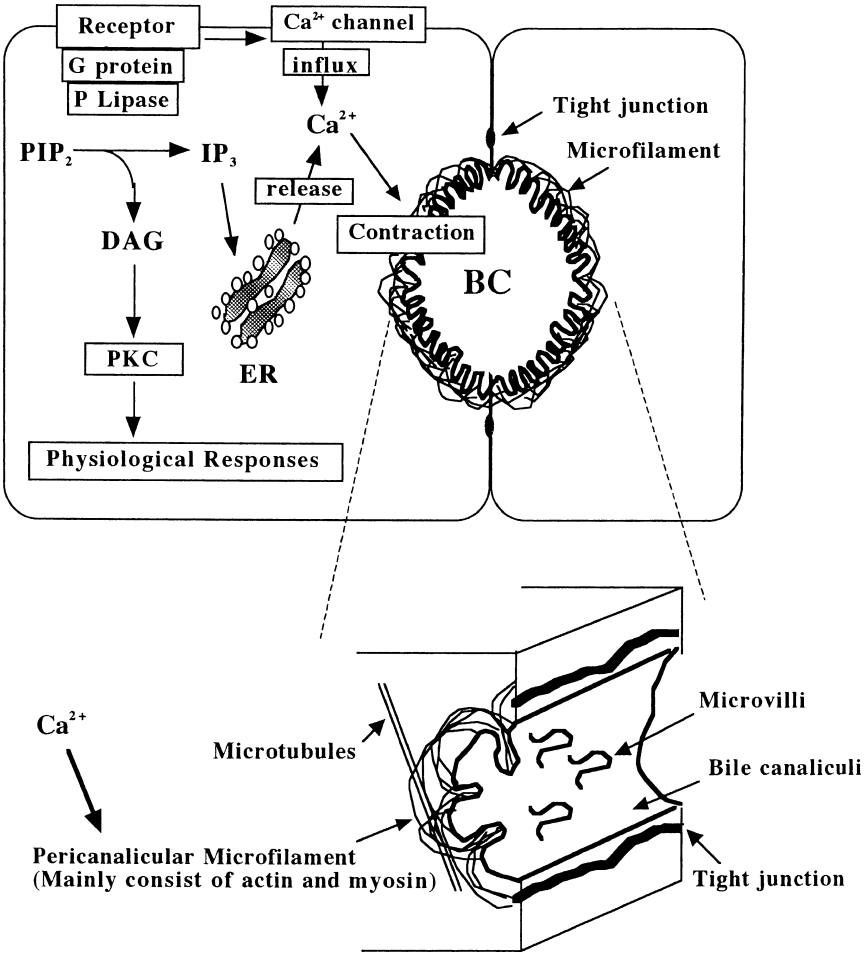


**Fig. 6.** Mechanisms of bile canalicular (*BC*) contraction. Receptor-mediated conversion of phosphatidyl inositol bisphosphate ($PIP_2$) into diacyl glycerol (*DAG*) and inositol trisphosphate ($IP_3$) leads to the activation of protein kinase C (*PKC*) and increased cytosolic $CA^{2+}$. Cytosolic $Ca^{2+}$ is increased by both the influx of extracellular $Ca^{2+}$ (through receptor-coupled $Ca^{2+}$ channels) and the release of $IP_3$-sensitive endogenous stores. Increased cytosolic $Ca^{2+}$ results in the contraction of pericanalicular microfilaments. *ER*, endoplasmic reticulum

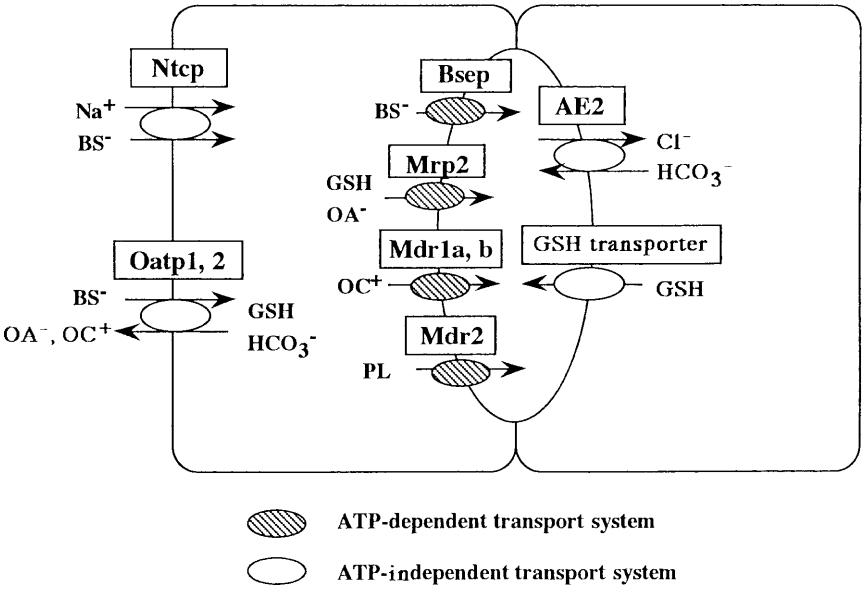


**Fig. 7.** Hepatocellular transport system. Both an $Na^+$-dependent $Na^+$/taurocholate cotransporter (*Ntcp*) and an $Na^+$-independent organic anion transporting protein (*Oatp 1*) transport bile salt ($BS^-$), organic anions ($OA^-$), and organic cations ($OC^+$). Bile salts are excreted into bile via a canalicular bile salt export pump (*Bsep*). Organic anions (e.g., conjugated bilirubin) and reduced glutathione (*GSH*) are excreted via a canalicular conjugate export pump (*Mrp 2*). The multidrug export pump (*Mdr 1a, b*) mediates the canalicular excretion of bulky lipophilic cations (e.g., anticancer drugs). The phospholipid export pump (*Mdr 2*) mediates the canalicular excretion of phosphatidyl choline. The canalicular membrane also contains several adenosine triphosphate (*ATP*)-independent transport systems, including a $Cl^-/HCO_3^-$ anion exchanger (*AE2*) for bicarbonate secretion and a canalicular GSH transporter. Biliary excretion of GSH (via Mrp2) and $HCO_3^-$ (via AE 2) are the major determinants of bile salt-independent bile flow. *PL*, Phospholipid

salt export pump [Bsep]), ATP-independent transport (e.g., a $Cl^-/HCO_3^-$ anion exchanger [AE 2] and the reduced glutathione [GSH] transporter). Gene expression of these transport systems reflects hepatocellular uptake capacity and the canalicular excretion of bile salts and other organic anions (e.g., bilirubin diglucuronide). Administration of a nonlethal dose of LPS to rats results in a marked reduction in the mRNA and protein levels of Ntcp[20,22,23] and Oatp 1,[24] as well as canalicular Mrp 2[25–28] and Bsep.[26,28] Administration of TNF-α or IL-1β also produces a time-dependent decrease in Ntcp mRNA levels,[23] and IL-6 reduces the $Na^+$-$K^+$-ATPase activity of hepatocytes.[29]

## Summary

Severe inflammatory conditions such as sepsis are usually associated with prominent mediator production, which often leads to shock. Regardless of its etiology, inflammation-induced cholestasis results from the downregulation of hepatocellular transport systems by inflammatory cytokines that have been activated by various infections (e.g., bacteria and viruses) and non-infectious stimuli (e.g., drugs and ischemia/reperfusion).[1]

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