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Mechanisms of Bile Formation and Cholestasis: Clinical Significance of Recent Experimental Work

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INTRODUCTION

The last decade has been witness to an exponential increase in our understanding of the fundamental mechanisms involved in hepatic bile formation and intrahepatic cholestasis, defined herein as impaired formation of canalicular bile. This review will provide a summary of recent experimental work, with particular reference to the clinical implications of this information. For further in-depth discussions of this subject, interested readers are referred to several recent reviews (1–6).

Bile formation, believed to be an osmotic process resulting from the active secretion of solutes followed by passive water movement, has long been conceptually divided into bile acid-dependent and bile acid independent (BAIBF) components (Fig. 1). Bile acid-dependent bile flow is conventionally defined as the slope of the line relating canalicular bile flow to bile acid output (1, 3), and BAIBF as the extrapolated y-intercept of this line. While useful for discussion purposes, the limitations of this approach to studies of bile formation are readily apparent (1, 3) and it is best to consider the mechanisms responsible for the formation of these two components interrelated.

HEPATIC UPTAKE MECHANISMS

Recent studies have indicated that transhepatocytic movement of taurocholate, as a representative bile acid, from sinusoid to canaliculus is driven by the transmembrane gradient for sodium across the sinusoidal membrane and by the negative intracellular potential difference across the canalicular membrane (7, 8). The activity of sinusoidal Na^+,K^+-ATPase (9) is believed to be critical in the maintenance of these two driving forces (see Fig. 2). Several studies have addressed the binding properties of bile acids to specific membrane sites (10, 11) and a putative bile acid membrane transport protein has been recently characterized (12–14). Of clinical import, photolabile derivatives of phalloidin, the bicyclic toxic heptapeptide from the poisonous mushroom Amanita phalloides (15), and antamanide, a derivative from the same toadstool, also bind to this same protein (16). These findings provide an explanation not only for the hepatotropism exhibited by phallotoxins, but also for the protective effect of antamanide (17) and other organic anions, such as penicillin, that may compete for the same carrier protein.

INTRACELLULAR TRANSPORT

In contrast to hepatic uptake mechanisms, the steps involved in intracellular transport of bile acids and other organic anions are not well established. Cytosolic glutathione-S-transferases (18) and other recently identified proteins (19) appear to be the major intracellular binders of bile acids and other organic anions. Vesicular transport of bile acids, similar to that described for IgA (20), has been suggested by ultrastructural studies of hepatocytes during bile acid-induced choleresis (21). Further support for this hypothesis has resulted from recent studies examining the mechanisms of bile acid transport in subcellular fractions of rat liver (22). Identification of the steps involved continues to be an active area of research, since intracellular transport and canalicular secretion, rather than sinusoidal uptake, appear to be rate-determining steps for bile acid transport (23, 24). Based on ultrastructural observations, the Golgi apparatus has been postulated to be the site of the defect in bile secretion that accounts for the cholestasis observed in arteriohepatic dyplasia (25).

ELECTROLYTE TRANSPORT MECHANISMS

The importance of electrolyte transport processes on the plasma membrane in the elaboration of bile has also been the focus of recent work (see Refs. 3 and 6). Earlier work consistent with a role of bicarbonate in bile formation (26–28) led, in part, to the identification and characterization of a canalicular chloride:bicarbonate (29) and a sinusoidal sodium:proton exchanger (30, 31), that may be functionally "coupled" to generate an osmotic driving force for BAIBF (6, 29, 30). Indirect observations supporting this view include: 1) the cholestasis, observed with the estrogen, ethinyl estradiol, is associated with diminished sodium:proton exchange activity (32); 2) glucocorticoids and thyroid hormone, both shown to stimulate BAIBF (33, 34), also result in enhanced sodium:proton exchange (35, 36); 3) urso-

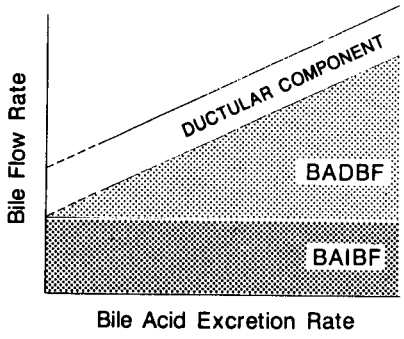

FIG. 1. Schematic representation of bile acid-dependent (BADBF), BAIBF, and ductular components of bile flow.

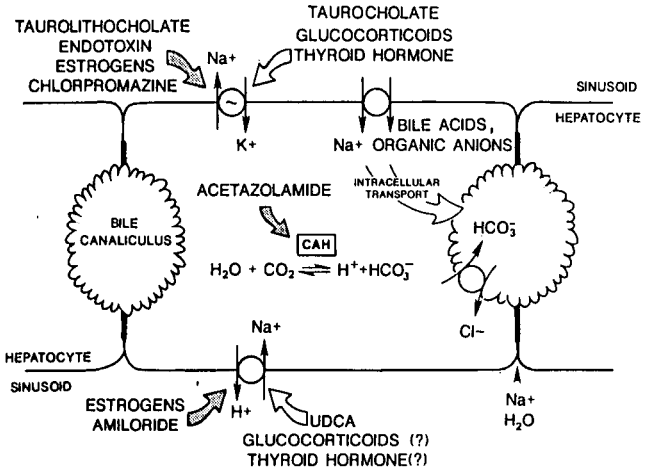

FIG. 2. Proposed model of bile formation that incorporates membrane transport processes and inhibitors (*shaded arrows*) and stimulants (*open arrows*) of these processes. *CAH*, carbonic anhydrase; *UDCA*, ursodeoxycholate; ⇅, primary active transport process (*e.g.*, Na^+,K^+-ATPase); ⇄, exchange mechanism (or antiport); →, secondary active transport process (*e.g.*, Na^+-coupled bile acid transport).

deoxycholate, a dihydroxy bile acid, associated with enhanced canalicular bicarbonate secretion (37), appears to act via the sodium:proton antiport (38, 39); and 4) acetazolamide, an inhibitor of carbonic anhydrase, necessary, in part, for the intracellular generation of bicarbonate, causes a reduction in bile flow under ursodeoxycholate-stimulated conditions (40).

These findings provide an alternative model (see Fig. 2) to previous concepts of bile formation that attempted to directly correlate bile flow to Na^+,K^+-ATPase activity. Thus, whereas a number of experimental agents have been shown to increase (thyroid hormone, taurocholate) or decrease (ethinyl estradiol, chlorpromazine) Na^+,K^+-ATPase activity, a consistent relationship between enzyme activity and bile flow has not always been observed (41).

CANALICULAR CONTRACTION

The role that canalicular contraction plays in bile formation remains unclear. Nevertheless, coordinated contractions of canalicular microfilaments have been observed in isolated rat hepatocytes (42, 43) and primary monolayer cultures (44), that are sensitive to intracellular calcium (45, 46) as well as bile salt concentration (47). Norethandrolone-induced cholestasis may be related to altered microfilament function (48). The phenothiazine, chlorpromazine, induces cholestatic jaundice in 1–2% of treated patients (49) and asymtomatic liver function abnormalities in up to 50% of patients (50). Chlorpromazine and its metabolites affect the polymerization of actin to its filamentous form (51), and ultrastructural changes observed during chlorpromazine-induced cholestasis resemble those induced by microfilament inhibitors (52). Work with microtubule inhibitors, such as colchicine, suggests that this component of the cytoskeleton may also play a role in bile formation (53, 54). Drug-induced cholestasis, such as observed with chlorpromazine, had been considered largely nonfatal until reports of hepatic injury with benoxaprofen, a nonsteroidal antiinflammatory drug, began to circulate (55, 56). The mechanism of this unusual cholestatic reaction remains to be elucidated, hampered by the scanty information contained in case reports, but alteration of biliary contractility and/or direct injury to the canalicular membrane has been proposed to explain the unique ductular concretions manifested histologically.

DUCTULAR MODIFICATIONS

Somatostatin has been shown to exert an anticholeretic effect in dogs, unrelated to hemodynamic effects (57, 58), that is thought to be mediated by a local effect on the bile ductular cells (57). If clinically significant, somatostatin-induced concentration of bile, the result of either increased ductular reabsorption or suppressed ductular secretion, might lead to decreased susceptibility to cholesterol precipitation and subsequent gallstone formation (57).

MEMBRANE FLUIDITY

The microviscosity of the hepatocyte membrane may also be a factor in bile formation. Ethinyl estradiol decreases hepatocyte plasma membrane fluidity (by increasing the cholesterol/phospholipid ratio in the membrane) with a concomitant reduction in Na^+,K^+-ATPase activity (59). Nonionic detergents, such as Triton WR-1339, have been shown to reverse the decreased membrane fluidity associated with estrogen administration and return bile flow and bile excretion to normal values (60). Chlorpromazine-induced cholestasis also may result, in part, from an alteration in membrane fluidity (61). On the other hand, cortisol and thyroid hormone, agents associated with choleresis, increase membrane fluidity and Na^+,K^+-ATPase activity (62). However, the exact relationship between mem-

brane fluidity and bile secretion remains unclear. Thus, cholestasis can be induced with ethinyl estradiol without an observable change in membrane fluidity (63), and canrenoate, a congener of the active metabolite of spironolactone, decreases membrane fluidity without a concomitant decrease in bile formation (64). Spironolactone, itself, has been shown to increase BAIBF (65).

SELECTED CLINICAL CORRELATES

The pathogenesis of total parenteral nutrition (TPN)-associated cholestasis is unknown. The cholestatic bile acid, lithocholate, formed by bacterial 7-α-dehydroxylation of chenodeoxycholate in the intestinal tract (66), has recently been implicated (67). The contribution of lithocholate to the total bile acid pool of duodenal bile obtained by duodenal drainage increased in five of 15 patients with inflammatory bowel disease on TPN and correlated with liver function abnormalities (67). In support of these findings, antibiotic administration to patients with inflammatory bowel disease on TPN, to reduce intestinal bacterial production of lithocholate, prevented hepatic abnormalities in comparison to control patients (68). Abnormal bile acid metabolism leading to increased levels of lithocholate may also play an etiological role in Byler's disease, an autosomal recessive form of fatal intrahepatic cholestasis (69, 70).

A reduction in bile acid-independent bile flow, possibly via a reduction in Na^+,K^+-ATPase activity, is considered to be a possible explanation for lithocholate-induced intrahepatic cholestasis (71). Alternatively, changes in canalicular membrane structure, specifically an increase in the cholesterol to phospholipid ratio, leading to altered permeability, may be involved (72). Recently, the ability of cholestatic bile acids to bind calcium was postulated to be related, in part, to the pathogenesis of lithocholate-induced cholestasis (73). This interaction of lithocholate and its derivatives with calcium, by inducing histamine release by tissue mast cells, has also been implicated in the disabling pruritus that affects some patients with cholestasis (74).

Amino acids have also been associated with hepatic dysfunction and cholestasis during TPN administration (75), and with reductions in bile acid independent bile flow (76). The intriguing possibility that this may be the result of amino acid inhibition of sodium-dependent bile acid transport, via a dissipation of the transmembrane sodium gradient, has been the focus of recent studies (77, 78).

In addition, the observation that *Escherichia coli* endotoxin causes a dimunition in bile flow (79), associated with a decrease in Na^+,K^+-ATPase activity (80), may offer an explanation for the intrahepatic cholestasis seen during severe bacterial infections (81). A case report of jaundice associated with an extrahepatic gram-positive infection was attributed to an endotoxin-like activity of circulating free teichoic acid (82).

Despite advances in our understanding of the mechanisms of bile formation and cholestasis, application of this information to the therapy of cholestatic liver injury remains limited. The cholestasis and lithogenic bile secretion associated with estrogen use may be regarded as a notable exception. While the actual incidence of estrogen-induced cholestasis is not known, groups at increased risk include Scandinavians (83), Chileans (84), and women with the Dubin-Johnson syndrome (85) or with a history of intrahepatic cholestasis of pregnancy (86), a syndrome believed to be the result of an abnormal reaction of the maternal liver to endogenous estrogen (87, 88). Experimental work has attributed estrogen-induced cholestasis primarily to alterations in liver plasma membrane lipid structure or Na^+,K^+-ATPase activity (59, 60) although this does not fully account for the wide differences in individual susceptibility to the cholestatic effect. Administration of the methyl donor, S-adenosyl-L-methionine (SAMe), leads to reversal of estrogen-induced impairment of bile flow in rats (89). This protective effect of SAMe may be due, in part, to alterations in membrane lipid fluidity and Na^+,K^+-ATPase activity (63). Alternatively enhanced formation of methyl-derivatives of estrogen (89), preventing binding of estrogen to hepatic microsomal proteins (90), may be involved. In a randomized, single-blind clinical study, SAMe administration (800 mg iv/day) was shown to be effective in the treatment of intrahepatic cholestasis of pregnancy (91). The relevance of these findings to other forms of intrahepatic cholestasis is the basis of current investigations. Pertinent in this regard are preliminary observations that demonstrate that SAMe confers a hepatocytoprotective effect and increases bile acid secretory rate maximum in taurolithocholate-induced cholestasis (92).

Clearly, much more remains to be understood regarding the mechanisms involved in bile formation. Effective management of disease processes has always been contingent on a thorough understanding of normal as well as pathophysiological mechanisms. Nevertheless, several new findings and areas of research have been discussed herein that promise to bring us closer to an understanding with potential therapeutic implications.

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