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New Perspectives For The Treatment Of Cholestasis (Lessons from basic science applied clinically)

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Introduction

Cholestasis is a clinical syndrome that results from the disturbances in the formation of bile, a unique and vital property of the liver. The causes of cholestasis are broad and range from rare genetic diseases and disruption of the normal development of the bile excretory anatomy, to progressive, ultimately fatal diseases such as primary biliary cirrhosis and sclerosing cholangitis(1). Cholestasis may also develop from mechanical obstructions in the extrahepatic bile ducts or during the course of viral hepatitis or the administration of certain drugs and hormones. Whatever the cause, the syndrome is manifested by the hepatic retention of products normally excreted into bile, in particular bile salts. As the process progresses with time, jaundice and hypercholesterolemia may follow. The syndrome is almost always characterized by an elevation in serum alkaline phosphatase and if progressive, fibrosis, cirrhosis and clinical signs of liver failure ultimately develop.

During the past decade, as the molecular basis of bile formation has been clarified, the pathogenesis of many cholestatic disorders has also evolved resulting in the following paradigm.

> Determinants of bile secretion undergo an adaptive response during cholestasis which tend to minimize hepatic injury. This adaptation occurs by: (a) limiting hepatic uptake of bile acids and other organic solutes, (b) reducing bile acid synthesis, (c) accelerating bile acid detoxification and (d) up-regulating alternative pathways for excretion of bile salts and other solutes in liver, kidney and intestine

Much of this information has resulted from the study of animal models of cholestasis, which with some exceptions have been confirmed in patients with cholestasis (1–3). The molecular basis of this process, which underlies current efforts to intervene clinically, has resulted from 3 fundamental developments: 1) The cloning of transporters that are the determinants of hepatobiliary secretion (greatly advanced by the completion of the human genome project) (1). 2) The discovery that mutations in some of these transporters result in cholestatic liver disease in patients (thereby providing “proof of principle” for their function (4) and 3) The evolving field of nuclear receptors which now enable a partial understanding of how these critical transporter and metabolism genes are transcriptionally regulated (5;6) (Fig 1).

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It is obvious that were these adaptive responses more robust, progressive cholestatic liver diseases might not occur or at least might become more protracted over time. Therefore the central question is whether therapy can be devised that might augment these potentially beneficial adaptive responses in expression of transporters and metabolic pathways? This commentary reviews the molecular basis of bile formation and the adaptive responses that are known to occur in cholestatic liver injury. It follows with a summary of current as well as possible future therapies for jaundice and cholestasis that are mediated by nuclear receptor ligands.

Molecular Basis of Hepatic Bile formation and metabolism and their adaptive responses and regulation during cholestasis

Steps in bile formation and metabolism can be divided into 4 phases: Phase 0 (hepatic uptake); Phase I (hydroxylation); Phase II (conjugation) and Phase 3 (Excretion) of more water soluble conjugates into blood and bile)

Phase 0

The determinants of hepatic uptake of bile constituents include the sodium taurocholate co-transporting polypeptide (NTCP, SLC10A1) which is largely responsible for the first pass clearance of conjugated bile salts as they are returned to the liver in portal blood. Other unconjugated bile salts as well as bilirubin are variably taken up by one or more of 4 members of the solute carrier organic anion transporter family(SLC21), formally known as organic anion transporting polypeptides (OATPs) (7;8). For bilirubin this appears to be SLC21A6(9). These non-specific carriers also facilitate the uptake of many different organic anions, oligopeptides, and bulky organic cations. The transcription of NTCP is regulated by several different nuclear receptors including hepatocyte nuclear factor 1 (HNF1) and HNF4, the retinoic acid receptor α RARα and the short heterodimeric partner, SHP (NROB2), a nuclear receptor that is regulated by the farnesoid X receptor (FXR, NR1H4), and therefore bile acids, which are specific FXR ligands) (5;6;10). Small organic cations are taken up by another solute carrier, the organic cation transporter 1(OCT1), SLC22A1 (11).

All of these gene products are located on the basolateral membrane of hepatocytes. The expression of all of these uptake systems except OATP1A2 (OATP-A) are down-regulated during cholestasis (12;13). The later may reverse direction and function to facilitate efflux of substrates from the cholestatic hepatocytes. Since OATP1B3 (OATP-8) is directly regulated by FXR, its role as a bile acid efflux mechanisms also remains a possibility (14;15).

Phase I

Once within the hepatocytes, lipid soluble constituents undergo hydroxylation reactions mediated by the cytochrome P-450 (CYP) enzyme system. Many specific CYP enzymes carry out this function in human hepatocytes although the majority of drugs are metabolized by CYP3A4. Bile acids are formed from cholesterol via CYP7A1 and CYP8B1(10) whose activity is inhibited by FXR via SHP. Many CYPs are regulated by the nuclear receptors PXR and CAR whose ligands or activators include many exogenous xenobiotics (16;17). During cholestasis bile acid metabolism is altered in a species specific manner such that less toxic compounds are formed and alternative pathways are selected (18;19).

Phase II

metabolism consists of conjugation reactions that confer greater aqueous solubility to bile acids and other lipophilic constituents. Newly synthesized bile acids are normally conjugated with taurine or glycine prior to excretion into bile by bile acid-CoA synthetase and bile acid-

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CoA:amino acid N-acetyltransferase. During cholestasis conjugation reactions favor the formation of bile acid glucuronides and sulfates which are substrates for the multidrug resistance associated protein 2 and 3 (MRP2, ABCC2 and MRP3, ABCC3). These enzymatic reactions are mediated by uridine glucuronyl transferases (UGT2B4) and sulfotransferases (SULT2A1)) respectively. Expression of these phase 11 enzymes increases during cholestasis mediated in part by the bile acid nuclear receptors PXR and FXR and possibly VDR (20;21). Bilirubin is normally conjugated with glucuronides prior to excretion and several steps in the clearance of bilirubin, including its uptake via OATP1B1, intracellular bind to glutathione S-transferase (GSTA1), another phase 11 enzyme), conjugation with UGT1A1 and excretion via MRP2 (and MRP3 during cholestasis (22)) appear to be regulated in part by the nuclear receptor CAR based on studies in the Car null mouse (23;24), whose activator in these circumstances may be bilirubin (25).

Phase 3

Finally these potentially toxic substances are normally excreted from the liver into bile. Bile salt dependent (BSDF) and bile salt independent (BSIF) bile flow are largely generated by the bile salt export pump (BSEP, ABCB11) and MRP2, respectively (1). BSEP and MRP2 are members of the ABC superfamily of ATP dependent transporters. While BSEP is relatively specific for the biliary transport of bile acids, MRP2 exports glutathione and numerous other organic anions into bile usually conjugated with glutathione, glucuronide or sulfate conjugates (26). Both of these transporters are located on the canalicular membrane of the hepatocytes. Mutations in *BSEP* result in a variable spectrum of cholestatic diseases ranging from Progressive Familial Intrahepatic cholestasis type 2 (PFIC-2) in infants to Benign Recurrent Intrahepatic Cholestasis (BRIC-2) and Intrahepatic Cholestasis of Pregnancy (ICP) in adults (1;4). Mutations in *MRP2* result in the Dubin-Johnson Syndrome manifested by direct reacting hyperbilirubinemia while polymorphisms in these transporters may predispose to drug induced cholestasis (27).

A third member of the ABC superfamily, the multidrug resistanace protein 3 (MDR3, ABCB4), is a phospholipid export pump, that functions to translocate phosphatidylcholine to the outer leaflet of the canalicular membrane, facilitating the excretion of this lipid into bile where it associates with bile salts and cholesterol in lipid micelles. Mutations in MDR3 result in deficiencies of phosphatidylcholine in bile, and variable forms of either PFIC type 3 or ICP. Cholestasis occurs presumably because bile salts are no longer able to form micelles in bile are free to exert their detergent properties on lipids lining the canalicular and biliary epithelium (28;29).

The expression of BSEP and MDR3 is highly regulated by the nuclear receptor FXR and thus tends to be maintained if not up-regulated at the canalicular membrane during cholestasis as bile acid concentrations in the liver rise (30;31).

Nevertheless, these adaptive changes are insufficient to prevent cholestasis from developing leading to up-regulation of several other transporters at the sinusoidal surface of the liver. These include MRP3 and MRP4 (ABCC4) and the heteromeric Organic Solute Transporter (OST) composed of two subunits, alpha and beta (OSTα/β) (32;33). Based on experiments in Mrp3 and Mrp4 knockout mice, the export of bilirubin conjugates is thought to be largely mediated by Mrp3 (and possible OATP1A1) whereas bile acid divalent conjugates (Sulfates and glucuronides) may be preferable substrates for Mrp4 (34;35). However in-vitro studies indicate that both human MRP3 and MRP4 transporters are capable of transporting bile acid conjugates (36;37) which can then be excreted via the urine according to animal studies, as a result of a combination of glomerular filtration, down regulation of, the sodium dependent apical bile acid transporter (Asbt) in the proximal tubule, and the up-regulation of renal Mrp2 and Mrp4 (6; 38).

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In human liver, bile acid efflux across the basolateral membrane of hepatocytes and cholangiocytes is also facilitated by OSTα/β which is up-regulated in human cholestatic disorders, particularly primary biliary cirrhosis (33). Efflux is driven by the rise in bile acid concentrations in the liver. OSTα/β is highly regulated by FXR with 2 identified FXR response elements in the human OSTα promoter and one in OSTβ (39).

Cholangiocytes proliferate in many cholestatic disorders and thus also play a role in the adaptive response to cholestasis by continuing to express ASBT on the luminal surface and MRP3, MRP4 and OSTα/β on their basolateral surface. Thus bile acids that accumulate within obstructed bile ducts may return in part to the circulation and follow similar paths to the urine.

Nuclear receptor medicine in patients with jaundice and cholestatic disorders

Since none of these adaptive responses described briefly above is capable of preventing chronic cholestatic disorders from ultimately progressing, attention is directed to potential mechanisms for augmenting this response. Clinical experience suggests that this is a rational approach.

Constitutive androstane receptor, CAR (NR1I3) activators

Recent studies have demonstrated that Yin Shi Huang, an herbal medicine containing Yin Chin (Artemisia capillairis) and several other plants, and used in Asia to treat neonatal jaundice, is a potent activator of the nuclear receptor CAR (24). Treatment with either Yin Shi Huang or Yin Chin in humanized CAR mice but not in CAR null mice stimulate the expression of all of the critical steps in hepatic bilirubin clearance including SLC1A6 (OATP-C), the presumptive bilirubin uptake transporter, GSTA1 and A2, the cytosolic binding proteins, UGT1A1, the bilirubin conjugating enzyme and MRP2, the bilirubin conjugate export pump. This treatment also enhanced the clearance of bilirubin infusions. 6,7-dimethylesculetin, a compound present in Yin Chin, activated CAR in primary hepatocytes, suggesting that this may be the primary ingredient.

Inchin-ko-to is another herbal medicine also used for treatment of jaundice in Japan and China. Inchin-ko-to is a potent choleretic and a known inducer of Mrp2 (40).

Phenobarbital is also a strong CAR activator, and stimulates the translocation of CAR from the cytoplasm to the nucleus where CAR exerts its broad effects on nuclear transcription (41). Phenobarbital has been used to treat patients with primary biliary cirrhosis and results in a decrease in serum bilirubin and bile acids, a change in the serum chenodeoxycholic:cholic acid ratio and some amelioration of symptoms of pruritus (42). Side effects including mild sedation and formation of inactive vitamin D metabolites, precluded its adoption in clinical practice. One study compared Phenobarbital with Rifampicin in PBC but found the later drug more effective (43)

Pregnane X receptor, PXR (NR1I2) agonists

Rifampicin, a strong PXR ligand, has been used successfully to treat pruritus in children and adults and has also led to improvement in liver function tests in patients with PBC (44–46). Rifampicin is a strong inhibitor of human CYP7A and thus should block bile acid synthesis (47). Previous studies in healthy volunteers noted increased bile acid glucuronide excretion in urine with rifampin and speculated that that bile acid 6-alpha hydroxylation was mediated by stimulating CYP3A4 followed by glucuronidation (48).

Further studies demonstrated that a two week treatment in gallstone patients prior to surgery indeed results in up-regulation of mRNAs for CYP3A4, UGT1A1 and MRP2, all regulated presumably by PXR (5;49). Side effects of rifampicin include drug induced hepatitis, although the drug is well tolerated in most patients.

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Ursodoxycholic acid is currently accepted as the standard of care for treatment of primary biliary cirrhosis and is often used in other cholestatic disorders with variable beneficial effects (50;51). Long term studies in PBC indicate that UDCA therapy normalizes life expectancy in patients with early stage 1 or 2 disease on liver biopsies and delays progression of fibrosis (51). While the mechanism of this beneficial effect is undoubtedly complex, UDCA is a relatively strong PXR agonist and a weaker FXR agonist. Animal studies suggest that PXR and CAR deficiency in mice predisposes these null mice to more significant cholestatic liver injury and thus agonists of these nuclear receptors might be therapeutic (52). Thus it seems possible that some of UDCA's beneficial effects might be mediated via PXR. Indeed studies in FXR null mice indicate that UDCA increases bile acid hydroxylation and Mrp4 expression independently of FXR (53;54). However other in-vitro studies indicate that UDCA can also increase BSEP mRNA as well as FXR protein in human hepatoma cells (55). Treatment of gallstone patients for two weeks with UDCA has led to an increase in expression of BSEP, MDR3, and MRP4 (49) so that it is likely that these effects of UDCA are mediated via FXR for induction of BSEP and MDR3 and via PXR for induction of MRP4. PXR is transcriptionally active in stellate cells which inhibit transformation and proliferation so that it is possible that the antifibrotic effects of UDCA are also mediated via PXR (56). However, in contrast to rifampicin, UDCA induction of CYP3A metabolism has not been demonstrated in patients with Primary Biliary Cirrhosis or healthy volunteers (57).

UDCA also has post-transcriptional effects that may be beneficial in cholestasis including stimulating the apical targeting of Bsep and Mrp2 to the apical membrane from sub-membranous compartments as well as anti-apoptotic effects when induced by more toxic bile acids (58).

Farnesoid X receptor, FXR (NR1H4) agonists

All of the major transport steps in the enterohepatic circulation of bile acids are regulated by FXR (59) This includes 1) down regulation of NTCP indirectly via FXR activation of SHP. SHP suppresses HNF-4 which in turn leads to repression of HNF-1, a major activator of NTCP); 2) FXR activation of expression of BSEP, MDR3, and OSTα/β. FXR ligands should also inhibit bile acid synthesis since CYP7A1 and CYP8B1 are inhibited by SHP via activation of FXR (19). Bile acid conjugation with taurine and glycine is activated by targets of FXR (bile acid-CoA synthetase and bile acid-CoA :amino acid N-acetyltransferase (60). Therefore beneficial adaptive responses in these enzymes and transport steps might be enhanced by drugs designed as FXR ligands. This knowledge has led to the development of several potent FXR ligands, particularly GW4064 (61) and 6-Ethyl chenodeoxycholic acid (6-ECDCA), each of which have binding affinities for the ligand binding domain of FXR that are significantly greater than CDCA, the most potent endogenous FXR ligand (62). Studies in experimental animal models of cholestasis including common bile duct obstruction in the rat and mouse, lithocholic acid administration and ethinyl estradiol administration in rats all demonstrate that co-administration of these synthetic FXR ligands attenuates the cholestatic injury in these short term experiments, thus providing proof of principle (63;64). Other studies also demonstrate an anti-fibrotic role for 6-ECDCA (65;66). Therefore Clinical trials of these novel FXR agonists in cholestatic patients will be of interest.

Vitamin D receptor, VDR (NR1I1) agonists

Lithocholic acid, the most hydrophobic and cholestatic bile acid is a potent ligand for VDR (67). VDR is one of the activators of CYP3A4 and SULT2A1 (68), two enzymes that are needed to detoxify lithocholic acid through hydroxylation (phase 1) and subsequent sulfation (phase 11) reactions.

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Conclusions

Based on current knowledge of the diverse effects of nuclear receptor ligands and activators on bile acid metabolism and bile acid transporters in the enterohepatic circulation and kidney summarized here primarily for humans (and recently elsewhere (6;59;69–71), nuclear receptor medicine is already being used to treat certain patients with cholestatic liver disease.

The central role of FXR in the regulation of bile acid transporters and bile acid synthesis suggest that clinical trials with potent FXR ligands should proceed in selected patients with chronic cholestasis. However, they will need to proceed carefully. Recent studies also indicate that FXR is a regulator of lipid and glucose metabolism (72–76). In-vitro studies and findings in FXR null mice suggest that FXR has an anti-atherogenic role (77). Older clinical trials that assessed the effect of CDCA on gallstone dissolution in patients observed parallel declines in plasma triglyceride levels consistent with these more recent findings (78;79). Studies of FXR effects on carbohydrate metabolism are less clear and will require close monitoring once FXR agonists enter clinical practice.

Also, as this field evolves, it is important to recognize that observations of beneficial effects of nuclear receptor ligands, activators and antagonists in animal models of cholestasis may not necessarily extrapolate to humans. In cholestatic mice, bile acids are converted into more hydrophilic and therefore less toxic bile acid metabolites than are seen in man. Thus results concerning therapeutic benefit may lead to inappropriate conclusions. One such example is a recent study in FXR null mice following bile duct obstruction that suggests that FXR antagonists, rather than agonists may be beneficial in obstructive cholestatic disease (80).

Finally, it is likely that combinations of small molecules that act as nuclear receptor ligands or activators may provide more promising results in patients with cholestasis then monotherapy, particularly if administered early in the course of the disease before maximum endogenous adaptive responses have already occurred. Since Rifampicin and UDCA induce different groups of transporters, one might predict that combination therapy with Rifampicin and UDCA and possibly other nuclear receptor ligands, including the more potent FXR agonists might be of even greater clinical benefit. It is an exciting time for this field when discoveries in basic science are shedding light on the mechanisms of old empiric therapies for cholestatic liver disease while at the same time provide novel insights for new treatment opportunities.

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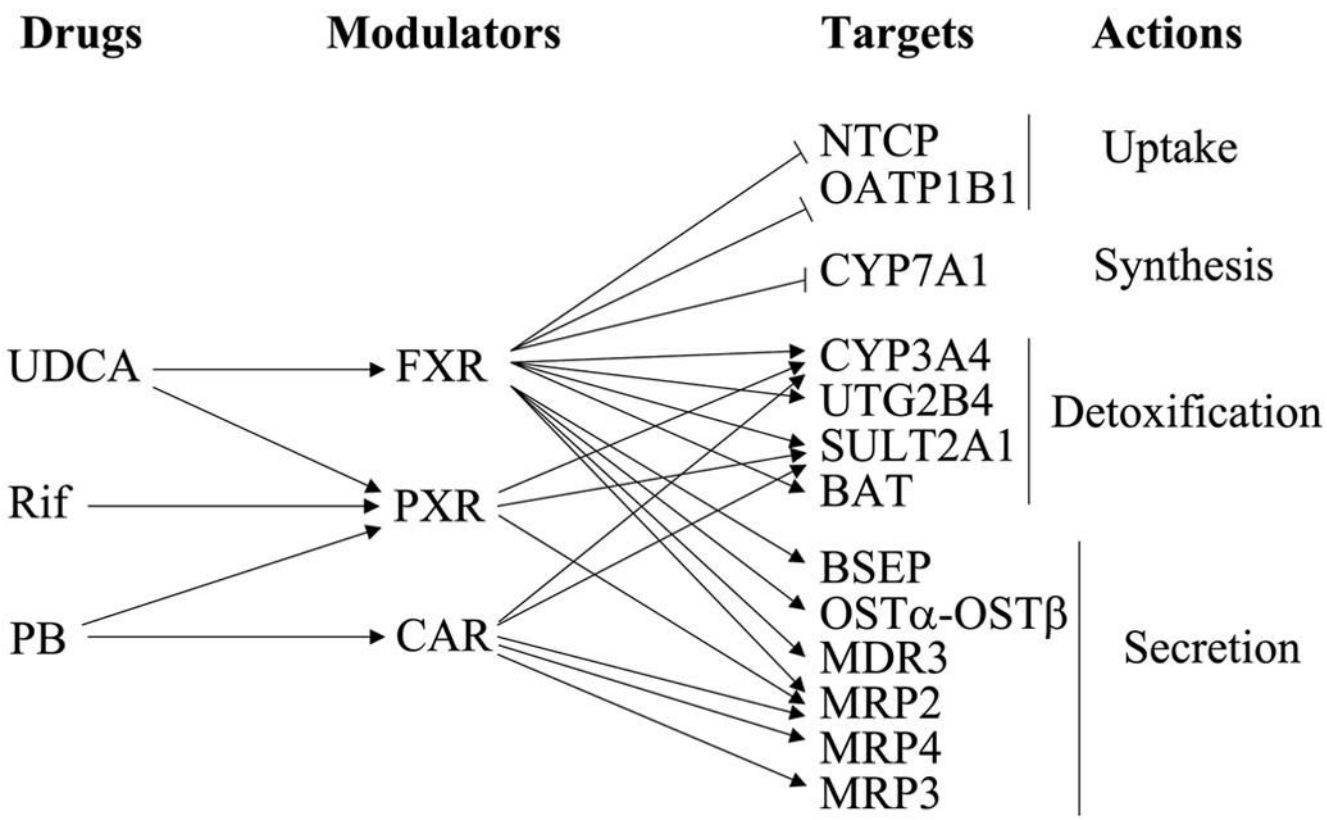

Fig 1.

Drugs that regulate hepatic bile acid and other organic solute uptake, synthesis, detoxification and secretion. The figure illustrates their action as nuclear receptor ligands that inhibit or stimulate transcription of key transporters and enzymes in this pathway. UDCA = ursodeoxycholic acid; Rif = Rifampicin; PB = phenobarbital