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Expression and Function of Renal Organic Anion Transporters in Cholestasis

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1. Introduction

Acute jaundice due to bile duct obstruction is defined as the retention of bile and bile components. Kidney and liver are largely responsible for inactivation and excretion of drugs, including organic anions, and other chemicals. In obstructive jaundice, adaptive mechanisms may permit urinary excretion of those potentially toxic compounds that could not be eliminated by the liver because biliary transport is impaired (Reichen & Simon, 1988; Klaassen & Aleksunes, 2010; Hagenbuch 2010).

A large and diverse number of organic, or weak organic acids that exist as anions at physiological pH, are secreted by mammalian renal tubules principally along the proximal portion of the nephron. Although this system secretes a number of endogenous compounds, it is generally accepted that is particularly important in secreting numerous exogenous compounds, including pharmacologically active substances, industrial and environmental toxins, and plant and animal toxins (Wright & Dantzler, 2004; G. Burckhardt & Pritchard, 2000). The renal organic anion transport plays a critical role, in protecting against the toxic effects of these anionic substances, by removing them from the blood principally via the organic anion transport mechanisms found in the apical and basolateral membrane of renal epithelial cells. Several carrier proteins have been cloned and are functionally characterized from both membrane domains of rat kidneys (El-Sheikh et al., 2008; Wright & Dantzler, 2004). Defining the modifications on the expression of these transporters is important, both to understand the cholestatic process and to identify potential therapeutic targets.

Cholestasis has been shown to alter the transport of bile salts and other organic anions (Denk et al., 2004; Klaassen & Aleksunes, 2010). The modulation in the expression of renal organic anion transporters constitutes a compensative mechanism to overcome the hepatic dysfunction in the elimination of organic anions.

This chapter reviews our current knowledge of the significant roles played by these transporters in organic anions elimination, focusing particularly in their renal expression and in the mechanisms involved in the regulation of their expression and function in extrahepatic cholestasis.

2. Organic anion transporters

The expression and function of several organic anion transporters in kidneys from rats with obstructive cholestasis will be reviewed. These transport proteins are listed below:

- Organic Anion Transporter 1 (Oat1)
- Organic Anion Transporter 3 (Oat3)
- Bilitranslocase (BTL)
- BSP/Bilirubin Binding Protein (BBBP)
- Sodium dependent Bile Salt Transporter (ASBT)
- Organic Anion Transporting Polipeptide 1 (Oatp1)
- Multidrug Resistance Protein 2 (Mrp2)

Oat1, Oat3, BTL and BBBP are expressed in the basolateral membranes. BBBP is also expressed in apical membrane, together with ASBT, Oatp1 and Mrp2. Their membrane localization is shown in Figure 1.

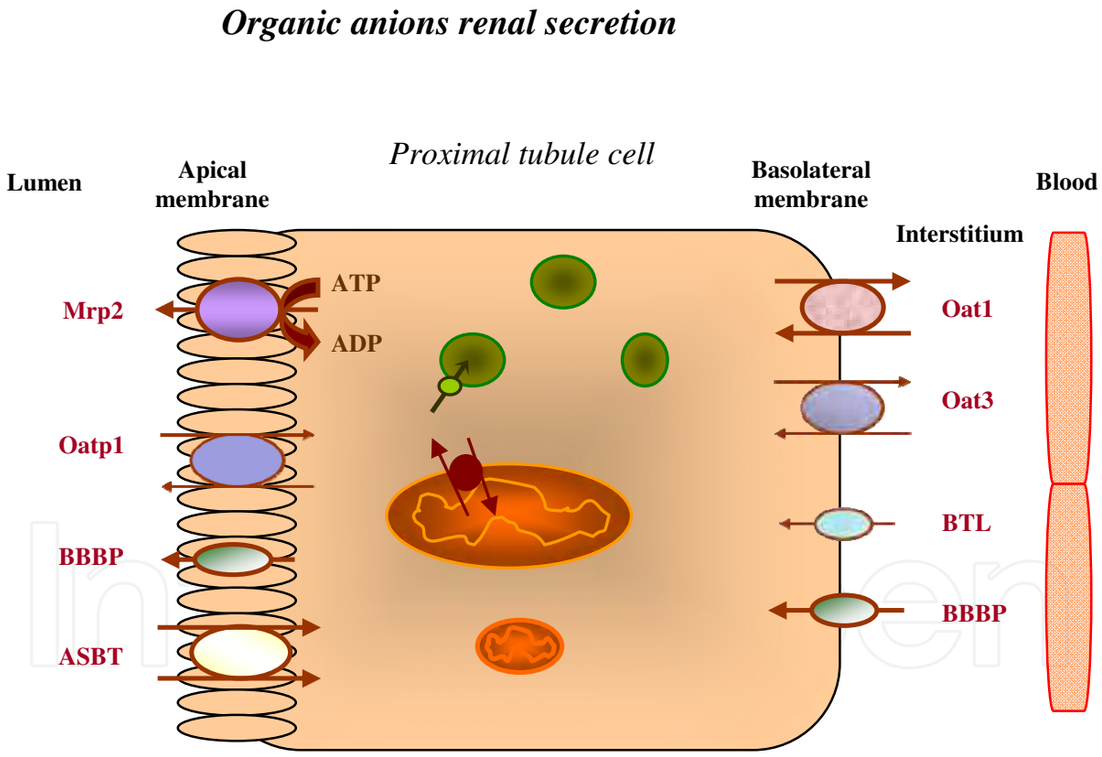


Fig. 1. Organic anion transporters in proximal renal tubule cell. For proteins abbreviations see the text.

2.1 Oat1

Organic anion transporter 1 (Oat1) is a key organic anions/α-ketoglutarate exchanger in the energetically linked basolateral entry of organic anions into the proximal tubule cells of the kidneys (Tojo et al., 1999; Kojima et al., 2002). Its substrate selectivity is markedly broad.

Oat1 is expressed predominantly in the kidneys and weakly in the brain. Oat1 couples organic anions entry to dicarboxylate exit (Sweet, 2005; Torres et al., 2008; Brandoni & Torres, 2010; G. Burckhardt & B.C. Burckhardt, 2011). This protein has been immunolocalized to the basolateral surface of the proximal tubule. Oat1 mediates the transport of many compounds (dicarboxylates, nucleotides, prostaglandins, antivirals, loop and thiazide diuretics, β-lactam antibiotics, non-steroidal anti-inflammatory drugs, including the prototypical substrate of the classical pathway, para-aminohippurate (PAH) (Brandoni & Torres, 2010; G. Burckhardt & B.C. Burckhardt, 2011). This has been demonstrated *in vitro* by its heterologously expression following microinjection of Oat1 cRNA into *Xenopus* oocytes or transfection of Oat1 cDNA into epithelial cell lines (B.C. Burckhardt & G. Burckhardt, 2003; Russel et al., 2002; Van Wert et al., 2010). Eraly *et al.* (2006) have generated a colony of Oat1 knockout mice, permitting the elucidation of the role of Oat1 in the context of other potentially functional redundant transporters. They found that the knockout mice manifest a profound loss of organic anion transport (e.g. PAH) both *ex vivo* (in isolated renal slices) as well as *in vivo* (as indicated by loss of renal secretion). In the case of the organic anion, furosemide, loss of renal secretion in knockout animals resulted in impaired diuretic responsiveness to this drug (Eraly et al., 2006). These results indicate an important role for Oat1 transporter in the handling of organic anions by the classical pathway.

Connected to this, we have reported an up regulation of Oat1 protein expression in rats with an early phase of acute obstructive cholestasis which might explain the increased renal elimination of the well-known organic anions, PAH and furosemide (FS) (Brandoni et al., 2006a). Performing bile duct ligation (BDL) as a well-established model of cholestasis (Brandoni & Torres, 2009a), we have determined an increase in the systemic clearance of PAH associated to an increase in the abundance of Oat1 in renal cortex homogenates in rats at 21 h after bile duct ligation (early phase of acute extrahepatic cholestasis) (Brandoni et al., 2003a).

FS is a well-known loop diuretic secreted through the organic anion transport system. The capacity of the organic anion transport system to secrete a diuretic determines its intraluminal concentration, which is critical for a diuretic activity. Oat1 and Oat3 are involved in the renal tubular secretion of FS and are thereby responsible for their delivery to the site of action in effective amounts (Hasannejad et al., 2004; G. Burckhardt & B.C. Burckhardt, 2011). The protein expression of Oat1 was significantly increased both in cortical homogenates and in basolateral membranes from kidneys after 21 hours of BDL (Brandoni et al., 2006a; Brandoni et al., 2003a). This Oat1 up regulation might lead to a higher elimination of its transported compounds. In fact, we found that systemic clearance and urinary excretion of PAH were both higher in BDL rats. Connected to this, PAH uptake rate (Brandoni et al., 2006a) was increased in basolateral membranes vesicles from BDL rats showing a higher Vmax than Sham animals and no difference in Km. Moreover, Oat1 up-regulation was associated with a concomitant increase of systemic and renal FS clearance.

Similar studies were performed by Brandoni *et al.* (Brandoni et al., 2006b) after 3 days of bile duct ligation (the peak of elevation of serum bile acids and bilirubin). After this time, BDL rats displayed a reduction in the renal elimination of PAH. Oat1 protein expression in kidney homogenates was not modified, but decreased in basolateral membranes. This study demonstrated, once more, the key role of Oat1 expression in the impaired elimination of

PAH after 3 days of obstructive cholestasis. So, the evolution time of obstructive cholestasis has an important impact in the regulation of Oat1.

It has been described that protein kinase C (PKC) induces Oat1 down-regulation through carrier retrieval from the cell membrane. Various humoral factors induced by 3 days of bile duct ligation may probably lead to the activation of PKC. Moreover, bile acids and high bilirubin levels can activate PKC (G. Burckhardt & B.C. Burckhardt, 2011; Hirohata et al., 2002). It has been demonstrated that 3 days of bile duct ligation is the period in which serum bile acids and bilirubin levels reach the peak of elevation. We therefore postulate that the peak of elevation of bile acids and bilirubin can also trigger PKC activation. This PKC activation may cause the phosphorylation of caveolin-2, which may induce internalization of caveolae with Oat1 protein anchored with caveolin as has been recently suggested by Kwak *et. al*. (2005).

In summary, in this experimental model during an early phase of acute extrahepatic cholestasis where no evident renal cell injury exists yet, an Oat1 up regulation connected with an increase in renal organic anion elimination was demonstrated. The protein expression of Oat1 was significantly increased both in cortical homogenates and in basolateral membranes from kidneys after 21 hours of BDL, which might suggest an increase in the synthesis or a decrease in the degradation of this membrane transporter. In this model, Oat1 up regulation might be found in order to enhance renal secretion of toxic compounds that may be harmful in the presence of the pathological state. Connected to this, Tanaka *et al*. (2002) found that bilirubin ditaurate, sulfate conjugated bile acids, and some components of the human bile up regulate the expression of Mrp2 in human renal tubular cells. On the other hand, we found an increased ^{3}H-PAH uptake by S2 cells expressing Oat1 in the presence of bilirubin ditaurate (Brandoni et al., 2006c).

Contrary to what has been observed during an early phase of acute extrahepatic cholestasis, Oat1 expression significantly decreased in the basolateral membranes from kidneys after 3 days of bile duct ligation (Brandoni et al., 2006b). It has been suggested an internalization of membrane transporters or an inhibition in the recruitment of preformed transporters into the membranes. This study stressed, once more, the critical role of Oat1 renal expression in the excretion of PAH, in a model of extrahepatic cholestasis in rats.

2.2 Oat3

Oat3 is mainly expressed in kidneys, and to a lesser extent in brain and liver. The human Oat3 gene is paired with that of Oat1 and located on chromosome 11q12.3. Inmunohistochemistry revealed the location of Oat3 at the basolateral membrane of renal proximal tubules (Cha et al., 2001; Kojima et al., 2002). In rats, Oat3 was also found in several other nephron segments including the thick ascending limb of Henle's loop, distal convoluted tubule and collecting ducts. Oat3 is the predominant organic anion transporter in the human kidney. Oat3 has a broad spectrum of substrates, and it mediates the transport of PAH, ochratoxin A, estrone sulfate (ES), cimetidine, benzylpenicillin, cephaloridine and glutarate. The selectivity of Oat3 overlaps that of Oat1, but affinities for several substrates appear to permit discrimination between both transporters. For example, Oat3 displays a moderately high affinity for ES, whereas Oat1 interacts little with ES (Sweet, 2005; Brandoni & Torres, 2010; Torres et al., 2008; Burckhardt & Burckhardt, 2011). Consequently, ES has

been frequently used as a test substrate for Oat3 activity. Oat3 can operate as an organic anion/dicarboxylate exchanger (Sweet et al., 2003, Bakhiya et al., 2003). Recent experiments with tissue from Oat3 knockout mice show reduced uptake of PAH, ES, and taurocholate in renal cortical slices and nearly complete inhibition of transport of the fluorescent organic anion fluorescein in intact choroid plexus (Sweet et al., 2002).

Brandoni *et al* (2003a, 2006a) have studied the cortical renal expression of Oat3 in association with the pharmacokinetics and renal excretion of PAH and FS in rats with acute extrahepatic cholestasis. Male Wistar rats underwent bile duct ligation (BDL rats). All studies were carried out 21 h after surgery. The systemic and renal clearance of both PAH and FS increased in BDL rats. In kidneys from BDL rats, immunoblotting showed a significant increase in the abundance of both Oat1 (as described above) and Oat3 in homogenates from renal cortex. In basolateral membranes from the kidney cortex of BDL rats, Oat1 abundance was also increased and Oat3 abundance was not modified. Immunohistochemical techniques confirmed these results. Acute obstructive jaundice is associated with an upregulation of Oat1 and Oat3, which might explain, at least in part, the increased systemic and renal elimination of PAH and FS. In this connection, extrahepatic cholestasis is associated with the production of various cytokines and growth factors that may affect gene transcription (Plebani et al., 1999).

Three days of BDL is the period in which serum bile acids and bilirubin levels reach the peak of elevation (Tanaka et al., 2002; Lee et al., 2001; Pei et al., 2002). Brandoni *et al* (2006b) have studied Oat1 as previously described and also Oat3 function and expression after 3 days of BDL. After this time, BDL rats displayed a reduction in the renal elimination of PAH. Oat1 protein expression in kidney homogenates was not modified, but it decreased in the basolateral membranes. On the contrary, Oat3 expression increased both in homogenates and basolateral membranes from kidneys after three days of BDL. Oat3 is found in various cells and in all parts of the nephron, whereas Oat1 is confined to proximal tubules (Kojima et al., 2002). The human and rat Oat3 transport PAH with relatively high affinity (87 µmol/L and 65 µmol/L respectively) (Wright & Dantzler, 2004; Anzai et al., 2006; Rizwan & Burckhardt, 2007; Cha et al., 2002), similarly to Oat1. On the contrary, ES, cholate, and taurocholate are substrates for Oat3 and not for Oat1 using *in vivo* and *in vitro* methodologies (Wright & Dantzler, 2004; Anzai et al., 2006; Rizwan & Burckhardt, 2007; Eraly et al., 2006; Cha et al., 2002; Sweet et al., 2002). The over-expression of Oat3 does not compensate for the down-regulation of Oat1 regarding PAH transport because in this disease the high plasma levels of bile acids compete with PAH for Oat3 transport (Brandoni et al., 2006 b; Torres, 2008). Moreover, bile acids regulate the expression of several genes involved in bile salt transport (Rost et al., 2003; Boyer et al., 2006). It is possible that high bile acid levels up-regulate Oat3 expression without affecting Oat1 expression; being this another example of substrate specific regulation.

Chen et al. (2008) have demonstrated that Oat3 is responsible for renal secretion of bile acids during cholestasis and that the pharmacokinetic profile of Oat3 substrates may be affected by cholestasis. In obstructive cholestasis, the main route to excrete bile acids is urinary excretion. It has been demonstrated that Oat3 protein expression level is increased in Eisai hyperbilirubinemic rats (EHBR). EHBR are mutant without multidrug resistance-associated protein 2 that show higher serum and urinary concentration of bile acids, compared with Sprague-Dawley (SD) rats (wild type). On the contrary, the expression of Oat1 was

unchanged. Moreover, the transport activities of rat and human Oat3, but not Oat1 were markedly inhibited by various bile acids such as chenodeoxycholic acid and cholic acid. Cholic acid, glycocholic acid and taurocholic acid, which mainly increased during cholestasis are transported by Oat3 (Chen et al., 2008; Burckhardt and Burckhardt, 2011). These authors also demonstrated that the plasma concentration of cefotiam, a specific substrate for Oat3, was more increased in EHBR than in SD rats despite upregulation of Oat3 ·. This may be due to the competitive inhibition of cefotiam transport by bile acids via Oat3. These results suggested that renal Oat3 but not Oat1 plays critical roles in the adaptative responses to the renal handling of bile acids in cholestasis.

In summary, these findings indicate that Oat3 plays an important pathophysiological role in protecting tissues from cholestatic injury by stimulating the renal secretion of bile acids. From a pharmacokinetic standpoint, it is possible that increased serum bile acids and/or administration of ursodeoxycholic acid (UDCA), recently introduced for cholestatic liver disease therapy (Paumgartner & Beuers, 2004) could influence the tubular secretion of anionic drugs via Oat3 as was demonstrated for cefotiam. So, in this situation, more attention should be paid to prevent the occurrence of drug interaction or drug-induced toxicity.

2.3 BTL

The membrane protein bilitranslocase (BTL) is not a bile acid transporter, but rather a bile pigment transporter that was originally isolated from rat livers (Tiribelli et al, 1978; Passamonti et al. 2009). Bilitranslocase has been indicated as the protein responsible for the electrogenic hepatic uptake of cholephilic organic anions, such as bromosulfophtalein (BSP) and thymol blue, the tetrapyrrole bilirubin, and flavonoids (the anthocyanin malvidin 3-glucoside and the flavonol quercetin) (Passamonti et al. 2009). Bilitranslocase has also been detected in basolateral plasma membranes from kidney cells and it has been demonstrated to be involved in the renal transport of BSP, bilirubin and anthocyanins (Elías et al., 1990; Vanzo et al., 2008). In this way, bilitranslocase contributes to the hepatic and renal elimination of exogenous organic anions (such as BSP), endogenous metabolites (such as bilirubin) and anthocyanins (flavonoid-based pigments that are present in many fruits and vegetables in the human diet, which have been reported to be positively implicated in human health (Vanzo et al., 2008; Passamonti et al. 2009)).

To evaluate the functional activity of bilitranslocase, we measured BSP electrogenic uptake in liver plasma membrane and in renal basolateral membrane vesicles prepared from sham and BDL rats (Brandoni et al., 2010). No modifications were observed in bilitranslocase activity and in the abundance in liver plasma membrane vesicles from BDL rats. On the contrary, extrahepatic cholestasis resulted in a marked increase of renal BSP uptake and this was due to an important increase in V_{max} (capacity). The capacity of a transfer is principally determined by the total number of active carriers presented in renal basolateral membrane vesicles. The difference in V_{max} indicates that a higher number of functional carrier units exists in renal basolateral membrane vesicles from BDL rats, which is in agreement with the higher expression of bilitranslocase in basolateral membranes. The observation that BDL rats have a higher renal expression of bilitranslocase at the basolateral membranes despite no change in this protein abundance in kidney homogenates suggests an alteration in bilitranslocase trafficking that might be caused by an increased recruitment of preformed

transporters into the membranes or an inhibition in the internalization of membrane transporters.

These results suggest that the complex series of hormonal changes induced in kidneys by extrahepatic cholestasis (Sheen et al., 2010) might influence the regulation of bilitranslocase and Oatp1 in a similar way. The characteristic accumulation of bile acids, bilirubin, and other potential toxins in cholestasis may affect transcriptional and posttranscriptional regulatory mechanisms (Donner et al., 2007; Geier et al., 2007). In this connection, as it has been mentioned earlier, bilirubin, sulfate-conjugated bile acid and human bile up regulated the expression of Mrp2 in renal tubular cells but not in liver cells (Tanaka et al., 2002).

In summary, the higher renal expression and function of bilitranslocase in renal basolateral membranes from rats with obstructive cholestasis might also contribute to the dramatic increase in BSP renal excretion observed in this experimental model. This would be another compensation mechanism to overcome the hepatic dysfunction in the elimination of organic anions.

2.4 BBBP

BSP/Bilirubin binding protein (BBBP) is a protein isolated from rat liver located on the sinusoidal membrane of the liver and described as a transport protein involved in the well known sodium-independent hepatic uptake of BSP and bilirubin (Stremmel & Berk, 1986; Stremmel et al., 1986; Torres et al., 1993; Torres, 1997). The transport of this protein is electroneutral as indicated by experiments in liver plasma membrane vesicles. BBBP is an organic anion carrier protein expressed in both apical and basolateral membranes from rat kidney cells, which accounts at least in part, for the renal tubular transport of PAH (Torres et al. 2003).

Brandoni et al. (2003b; 2004a; 2004b) have described an increment in BBBP expression in homogenates and in basolateral membranes from kidney cortex after 21 h of obstructive cholestasis without modifications in its apical membrane expression. The increase in BBBP homogenate expression suggests an increment in its synthesis or a decrease in its degradation, while the traffic protein is preferably directed to the basolateral domain. The higher basolateral membrane expression of BBBP could contribute to the higher BSP and PAH renal excretion described in this experimental model of acute cholestasis (Brandoni et al., 2003b; Brandoni et al., 2004a; Brandoni et al., 2004b).

In summary, modifications in hepatic excretion of organic anions have been demonstrated in rats with extrahepatic cholestasis. We have evaluated, in rats with acute bile duct ligation, the urinary excretion of two different organic anions, PAH mainly excreted by the kidneys and BSP mainly excreted by the liver.

The higher abundance of the organic anions carrier BBBP, detected in rats with obstructive jaundice might explain, at least in part, the higher renal capacity to eliminate distinct negatively charge compounds in this group of rats. These results suggest a relevant role of this kind of transporters in renal elimination of those organic anions excreted mainly by liver, in the presence of the obstructive cholestasis.

2.5 ASBT

The sodium dependent bile salt transporter (ASBT) is expressed in the ileum, the apical membrane of cholangiocytes and in the brush border membrane of proximal tubular cells (Christie et al., 1996; Lazaridis et al., 1997; Wilson et al. 1981; Burckhardt et al. 1987).

Bile acids, after secretion with the bile into the small intestine, are nearly completely reabsorbed in the terminal ileum. They return with the portal venous blood to the liver where they are taken up and resecreted into the bile. Some 10-50 % of the reabsorbed bile acids (depending on the bile acid species) escape hepatic uptake and spill over in the peripheral circulation. About 10-30 % of the bile acids, presents in the blood plasma, is not protein-bound and hence is subject to glomerular filtration (Rudman & Kendall, 1957). However, urinary excretion of bile acids is much smaller than the amount filtered due to a nearly complete tubular reabsorption of the filtered bile acids (Weiner et al., 1964; Barnes et al. 1977). Thus, the kidneys also take part in the recirculation process and aid to conserve bile acids. Tubular reabsorption of bile acids is accomplished by ASBT (Wilson et al. 1981; Burckhardt et al. 1987).

After a 14 day bile duct obstruction, a decreased taurocholate transport of brush border membrane vesicles derived from rat kidneys has been found by Lee et al. (2001). The reduced taurocholate uptake was associated with a reduction of renal ABST protein expression in membrane-rich microsomal fractions prepared from rat kidneys.

Schlattjan et al. (2003) have demonstrated that as early as 1 day after induction of an obstructive cholestasis a reduced taurocholate transport of proximal tubular cells can occur without a change in the amount of the transport protein in these cells. The diminished taurocholate transport in this early phase of cholestasis may be mediated by a change of the phosphorylation status and hence activity of ASBT and/or by a redistribution of the transporter between the plasma membrane and intracellular compartments of the proximal tubular cells.

In summary, these studies have demonstrated that there is a functional adaptive down regulation of renal tubular bile acid transport enhancing renal clearance of bile acids during the early phase of an obstructive cholestasis.

2.6 Oatp1

Organic anion-transporting polypeptides (Oatp) are a group of membrane solute carriers with a wide spectrum of amphipathic transport substrates. Several members of the Oatp family are located in the apical membrane of proximal tubules, and have been suggested to play a role in the secretion/reabsorption of selected anionic substrates (Hagenbuch & Meier, 2003; Kalliokoski & Niemi, 2009; Hagenbuch 2010).

The first member of the Oatp gene family of membrane transporters, Oatp1, has been isolated from rat liver and shown to mediate Na^+-independent saturable transport of BSP (Hagenbuch & Meier, 2003). Oatp1 is also localized, in addition to the basolateral plasma membrane of hepatocytes, at the apical membranes of kidney proximal tubule (S3 segment). Thus, this transporter could be responsible for reabsorption of organic compounds that are freely filtered, such as estradiol-17β-glucuronide, or important for the secretion of certain organic compounds that are taken up into proximal tubular cells across the basolateral

membrane (Gotoh et al., 2002; Obadait et al., 2012). However, it is surprising that BSP, a known substrate for the Oatp1 transport, is normally secreted negligibly by the kidney in non-pathological conditions.

Regulation of Oatp1 expression and function occurs at transcriptional and post-transcriptional levels and is, at least in part, tissue-specific. Thus, while in the kidney Oatp1 expression is stimulated by testosterone and inhibited by estrogens, hepatic Oatp1 expression is not influenced by sex hormones (Gotoh et al., 2002; Wood et al., 2005; Rost et al., 2005). Functional down regulation of Oatp1 has been demonstrated via serine phosphorylation by extracellular ATP (Hagenbuch & Meier, 2004). In addition, protein kinase C activation leads to decreased transport of estrone-3-sulfate in Oatp1 expressing *X. laevis* oocytes (Geier et al., 2007; Planchamp et al, 2007).

In rats with cholestasis due to bile duct ligation, the hepatic expression of Oatp1 is down regulated (Geier et al., 2007). This transporter mediates hepatic uptake of numerous organic anions from the systemic circulation. This observation may also be an adaptive change because BDL rats need to restrict excess uptake of various organic anions into hepatocytes. Renal Oatp1 mediates urinary excretion and re-uptake of organic anions at apical (brush border) membrane. It is worth noting that differential processing and trafficking of this transporter in liver and kidney may have important functional and regulatory consequences.

Our data showed that BDL rats have a higher renal expression of Oatp1 protein at apical membranes despite no change in Oatp1 abundance in kidney homogenates (Brandoni et al., 2009b). These observations suggest an alteration in Oatp1 trafficking that might be caused by an increased recruitment of preformed transporters into the membranes or an inhibition in the internalization of membrane transporters. The results of this study have shown that the kidneys are able to adapt rapidly to obstructive cholestasis because BSP renal elimination had increased nearly 30-fold during the first day after induction of bile duct obstruction. This study has shown evidence that this renal adaptation to cholestasis involves an up regulation of the transport capacity of the proximal tubular organic anion-transporting polypeptide 1, Oatp1. This increase in Oatp1 protein units at the apical membrane of renal cells may be a compensatory mechanism for reducing injury to hepatocytes or renal epithelia from cytotoxic materials that may occur in rats with obstructive cholestasis.

Extrahepatic cholestasis induces a complex series of hormonal changes in kidneys (Sheen et al., 2010), which might influence the regulation of Oatp1. Likely several local and systemic factors are produced at the same time, and the role of such factors in the regulation of channels and transporters, in renal cells, in the presence of BDL is still unknown. Probably, the accumulation of bilirubin, bile acids and other potential toxics existing in this cholestatic model may affect transcriptional regulatory mechanisms (e.g. fetal transcription factor, pregnene X receptor) and post-transcriptional regulations (Cheng et al., 2005).

In summary, we present evidence that cholestasis induced by common BDL in the rat induces a redistribution in renal Oatp1 protein units into apical membranes from renal cells (Brandoni et al., 2009b). Moreover, this likely adaptation to hepatic injury, specifically in biliary components elimination, present in this model might explain, at least in part, the huge increase in BSP renal excretion observed in this experimental model.

2.7 Mrp2

This transporter is a primary-active ATP-dependent pump, identified as multidrug resistance-associated protein 2 (Mrp2) (Klaassen & Aleksunes, 2010; Keppler, 2011). As in hepatocytes, renal proximal tubular cells and jejunal cells also exhibit constitutive expression of Mrp2 at the apical membrane (Schaub et al., 1997).

Mrp2 is involved in the organic anion transport of a wide variety of potentially toxic endo- and xenobiotics incluiding bilirubin, drugs, and carcinogens, e.g. in the form of amphiphilic anionic conjugates. In addition, Mrp2 mediates the transport of BSP-conjugated derivates (Nies & Keppler, 2007; Passamonti et al. 2009). It has also been described that Mrp2 mediates PAH transport in kidneys (Van Aubel et al., 2000; Leier et al., 2000).

In obstructive jaundice, adaptive mechanisms may permit the liver adapts to the higher load of biliary constituents in part by altering the expression of hepatobiliary transporters. In fact, studies of the regulation of the canalicular Mrp2 transporter have described reduced levels of mRNA and protein in rats after bile duct ligation (Denson et al., 2002; Dietrich et al., 2004).

Scarce data is available reporting the role of extrahepatic tissues in Mrp2 substrate disposition under conditions of deficient biliary secretory function. Lee et al. (2001) have reported that the up regulation in Mrp2 protein in kidney occurred as early as one day after BDL. On the other hand, Tanaka et al. (2002) have evaluated renal Mrp2 function by PAH clearance in rats with obstructive jaundice. PAH clearance was significantly increased after BDL. They also found an increased in mRNA and protein expression of Mrp2 in BDL animals. In this work, the effect of conjugated bilirubin, unconjugated bilirubin, human bile, and sulfate-conjugated bile acid on Mrp2 gene expression was also evaluated in human renal proximal tubular epithelial cells. They have described that the mRNA expression of Mrp2 increased in these renal cells after treatment with conjugated bilirubin, sulfate-conjugated bile acid or human bile. These results suggest that increased renal Mrp2 is functionally active during obstructive jaundice and the increased Mrp2 expression in the kidneys may provide an alternative pathway for accelerating excretion of bilirubin conjugates during obstructive jaundice.

It has been demonstrated a minor role of the intestine in compensating for altered liver Mrp2 mediated secretory function. In fact, Dietrich *et al*. (2004) have indicated that the expression of Mrp2 in the intestine was down regulated in rats with obstructive cholestasis. A role for increased levels of interleukin-1β was implicated in down-regulation of Mrp2 in both liver and intestine from rats undergoing extrahepatic cholestasis. It was demonstrated that decreased binding of RARα:RXRα nuclear receptor dimer to the promoter region of Mrp2 in BDL rats, due to increased levels of interleukin-1β, accounts for Mrp2 down-regulation in liver. In contrast, renal cortex exhibits up-regulation of expression and function of Mrp2 in BDL rats, which likely results from preserved levels of RARα:RXRα dimer in this tissue. Additionally, it was shown increased renal tubular conversion of 1-chloro-2,4-dinitrobenzene (CDNB) to its glutathione conjugate dinitrophenyl-S-glutathione (DNP-SG) followed by subsequent Mrp2-mediated secretion into urine that partially compensates for altered liver function in experimental obstructive cholestasis (Villanueva et al., 2006). It is worth noting that these results might also explain the increase in BSP and PAH excreted load seen in BDL rats (Brandoni & Torres, 2009; Brandoni et al., 2010; Brandoni et al., 2003a).

In summary, these results confirm that the up regulation of the apical transporter Mrp2 in kidneys is involved in the higher secretion into urine of organic anions, such as BSP, PAH and DNP-SG. The current data demonstrate the relevance of the renal elimination, particularly under conditions of impaired biliary secretory function, as occurs in obstructive cholestasis that partially compensates for altered liver function in this pathology.

3. Conclusions

The higher expression of Oat1 and BBBP at the basolateral domain of renal tubular cells together with the increased expression of Mrp2 at apical membrane could justify the increased excretion of PAH and FS described after 21 h of obstructive jaundice (Brandoni et al., 2003a; Brandoni et al., 2006; Brandoni et al., 2003b; Brandoni et al., 2004a; Brandoni et al., 2004b; Tanaka et al., 2002; Villanueva et al., 2006).

As it has been already mentioned, BSP is an organic anion mainly excreted by the liver, which is a substrate for several carrier proteins such as Oat3, Oatp1, Mrp2 and bilitranslocase. We have demonstrated an increase in BSP urinary excretion in rats with extrahepatic cholestasis associated with a higher expression of Oatp1 in apical membranes and an unchanged expression of Oat3 in basolateral membranes from kidneys (Brandoni et al, 2003a; Brandoni et al., 2006; Brandoni & Torres, 2009b). Moreover, Mrp2 up regulation in kidneys from BDL rats has been described (Tanaka et al., 2002; Villanueva et al., 2006).

The increase in Oat1, bilitranslocase and BBBP protein units at renal basolateral membrane together with the increased expression of Oatp1 and Mrp2, and the fall in ABST function, at the apical domain of renal cells may be a compensatory mechanism for protecting hepatocytes or kidney cells from cytotoxic substances that accumulate in the presence of obstructive cholestasis. The upregulation observed in BTL, BBBP, Oatp1 and Mrp2 might explain the dramatic increase in BSP renal elimination displayed in this pathology (Brandoni et al., 2009b; Brandoni et al., 2010).

On the other hand, it has also been found that urinary excretion of bile acids is markedly increased in obstructive liver diseases (Ostrow, 1993). The increase in bile acids urinary excretion may be a consequence of the fact that the amount of filtered bile acids in cholestasis exceeds the maximum capacity for tubular reabsorption. But it may also involve adaptive mechanisms of the kidneys, such as a decline of tubular apical reabsorption of bile acids and an enhanced tubular basolateral uptake.

Mrp2 and the sodium-dependent bile salt transporter ABST are two renal apical bile acids carriers; Mrp2 mediates the exit of bile acids from the cells and ABST is involved in their reabsorption. As was previously mentioned, Mrp2 is upregulated (Tanaka et al., 2002) and there is a fall in the function of ABST (Schlattjan et al., 2003) in the presence of acute extrahepatic cholestasis. Both mechanisms may also contribute to the increased excretion of bile acids in the presence of this pathology. On behalf of the basolateral domain, Oat3 transports bile acids from the blood into the cells. As it has been mentioned earlier, its expression at the basolateral membrane does not change in this experimental model of 21 h of acute extrahepatic cholestasis in rats (Brandoni et al., 2006a).

Figure 2 shows a summary of expression modifications in organic anion transporters detected after acute extrahepatic cholestasis and table 1 shows their consequences in urinary excretions of BSP, PAH and FS.

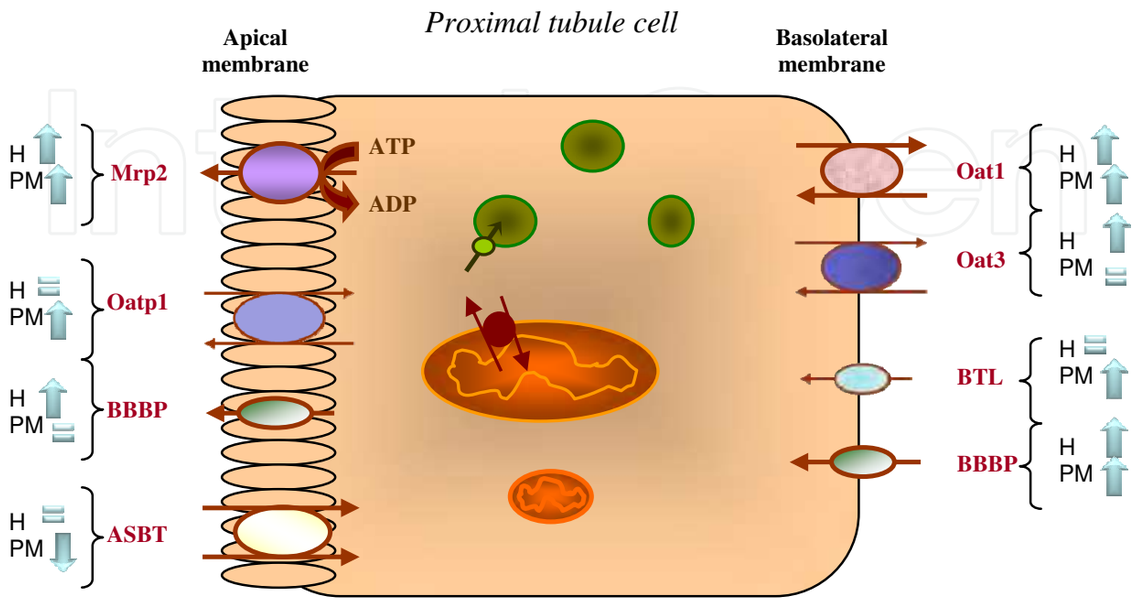


Fig. 2. Expression of the organic anion transporters in proximal renal tubule cell during extrahepatic cholestasis in the rat. For proteins abbreviations see the text. H: homogenate; PM: plasma membrane.

	Renal excreted loads		
Protein abundance	PAH	FS	BSP
Oat1 ↑	↑	↑	
BTL ↑			↑
BBBP[a] ↑	↑		↑
Oatp1 ↑			↑
Mrp2 ↑	↑		↑

([a])Apical expression of BBBP was not changed compared to sham animals while basolateral expression was increased as indicated in the table.

Table 1. Renal organic anions transporters: basolateral and apical membrane proteins in proximal tubule cell. The table summarizes our results about the renal excretion of the organic anions, PAH, FS and BSP and their relationship with renal expression of the organic anion transporters studied in rats after 21 h of BDL.

To sum up, as a consequence of the hepatic function impairment, alterations in the renal elimination of organic anions were observed. The higher abundances of the organic anions carriers detected in rats with extrahepatic cholestasis might explain the higher renal capacity to eliminate distinct negatively charge compounds in this group of rats. These results suggest a relevant role of these transporters in renal elimination of those organic anions excreted mainly by liver, in the presence of the obstructive cholestasis.

The knowledge of how these transporters are regulated in the presence of pathological states, such as extrahepatic cholestasis, will help to design optimal therapeutics regimens for the most correct use of negatively charged organic drugs.

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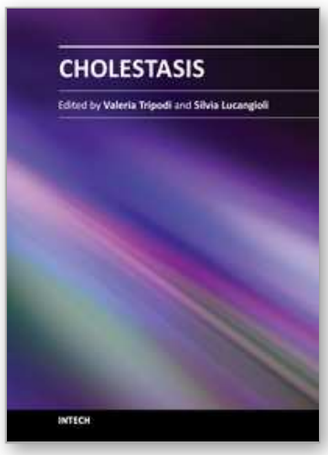
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This book covers different aspects on the understanding of mechanisms, effects, and management of cholestasis. This unique compendium contains important citations, an invaluable amount of research work, and many applications, which are outstanding resources for clinicians, pharmacists, biochemists, upper-level undergraduate, graduate, and continuing-education students who are dedicated to discovering new knowledge on cholestasis.

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