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Physiological and pathophysiological factors affecting the expression and activity of the drug transporter MRP2 in intestine. Impact on its function as membrane barrier

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ABSTRACT

The gastrointestinal epithelium functions as a selective barrier to absorb nutrients, electrolytes and water, but at the same time restricts the passage into the systemic circulation of intraluminal potentially toxic compounds. This epithelium maintains its selective barrier function through the presence of very selective and complex intercellular junctions and the ability of the absorptive cells to reject those compounds. Accordingly, the enterocytes metabolize orally incorporated xenobiotics and secrete the hydrophilic metabolites back into the intestinal lumen through specific transporters localized apically. In the recent decades, there has been increasing recognition of the existence of the intestinal cellular barrier. In the present review we focus on the role of the multidrug resistance-associated protein 2 (MRP2, ABCC2) in the apical membrane of the enterocytes, as an important component of this intestinal barrier, as well as on its regulation. We provide a detailed compilation of significant contributions demonstrating that MRP2 expression and function vary under relevant physiological and pathophysiological conditions. Because MRP2 activity modulates the availability and pharmacokinetics of many therapeutic drugs administered orally, their therapeutic efficacy and safety may vary as well.

1. Introduction

1.1. Intestinal barrier and multidrug resistance-associated protein 2 (MRP2, ABCC2)

1.1.1. Intestinal barrier

The intestinal epithelium is the largest and most significant internal barrier against the external environment, acting selectively to allow absorption of nutrients, electrolytes and water, while maintaining an effective defense against the action of intraluminal xenobiotics potentially harmful [1]. This function is dependent on the integrity of complex intercellular junctions, which condition the paracellular route of entrance, and metabolizing enzymes and efflux transporters, which condition the transcellular route of entrance.

The paracellular pathway is defined by transport through the gap between enterocytes, which is regulated by intercellular complexes localized at the apical-lateral membrane junction and along the lateral membrane [2]. The junctional complexes consist of three components that can be identified at the ultrastructural level as desmosomes, adherens junctions and tight junctions [3].

Abbreviations: 5′UTR, 5′ untranslated region; ABC, ATP-binding cassette; AP-1, activator protein-1; ATF-2, activating transcription factor-2; BCRP, breast cancer resistance protein; BDL, bile duct ligation; BSEP, bile salt export pump; CAR, constitutive androstane receptor; CD, Crohn's disease; CDNB, 1-chloro-2,4-dinitrobenzene; CRC, colorectal cancer; CRE, cAMP response element; CYP, Cytochrome P450; db-cAMP, dibutyryl cyclic AMP; DNP-SG, dinitrophenyl-*S*-glutathione; ERM, ezrin/radixin/moesin; FRD, food responsive diarrhea; FXR, farnesoid X receptor; GLP-2, glucagon-like peptide 2; GST, glutathione S-transferase; HIV, human immunodeficiency virus; I/R, ischemia-reperfusion; IBD, inflammatory bowel disease; IL-1β, interleukin 1β; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LEC, Long-Evans Cinnamon; LPS, lipopolysaccharide; LXRα, liver X receptor α; MDR, multidrug resistance; MDR1, multidrug resistance protein-1; MRP, multidrug resistance-associated protein; MRP2, multidrug resistance-associated protein 2; hMRP2, human MRP2; rMrp2, rat Mrp2; mMrp2, mouse Mrp2; cMrp2, chicken Mrp2; dMrp2, dog Mrp2; OATP1A2, organic anion transporting polypeptide 1A2; OATP2B1, organic anion transporting polypeptide 2B1; OCTN1, carnitine/organic cation transporter 1; PDZ, PSD-95/*Drosophila* discs large/Zonula Occludens-1; PKA, cAMP dependent protein kinase A; PEPT1, peptide transporter 1; PXR, pregnane X receptor; RA, rheumatoid arthritis; RXRα, retinoid X receptor alpha; SNP, single nucleotide polymorphism; SULT, sulphotransferase; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis; UGT, UDP-glucuronosyltransferase; ZT, Zeitgeber Time.

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Regarding the transcellular pathway, the compounds orally ingested can be absorbed by passive diffusion or by specific transport systems. Among the influx transporters, peptide transporter 1 (PEPT1/SLC15A1), carnitine/organic cation transporter 1 (OCTN1/SLC22A4), organic anion transporting polypeptide 1A2 (OATP1A2/SLCO1A2) and organic anion transporting polypeptide 2B1 (OATP2B1/SLCO2B1), play a special role in intestinal xenobiotic absorption [4]. Once inside the intestinal epithelial cells (enterocytes), these compounds may be metabolized by phase I enzymes such as cytochrome P450 (CYP) members and/or phase II conjugating enzymes such as glutathione S-transferase (GST; EC 2.5.1.18), UDP-glucuronosyltransferase (UGT; EC 2.4.1.17), and sulphotransferase (SULT; EC 2.8.2.), in order to decrease compound hydrophobicity [5]. Original compounds and their metabolites can be further absorbed into the blood or lymph circulation with mediation of absorptive transporters, such as multidrug resistance-associated proteins (MRP) 1, 3, 4 and 5 (ABCC1, ABCC3, ABCC4, ABCC5 respectively), which are localized at the basolateral membrane of the enterocyte [6]. The action of these transporters is eventually counterbalanced by a concerted function of ATP-binding cassette (ABC) transporters expressed at the apical membrane, which return their substrates to the intestinal lumen [7]. The principal efflux transporters are P-glycoprotein or multidrug resistance protein-1 (MDR1/ABCB1), multidrug resistance-associated protein 2 (MRP2/ABCC2) and breast cancer resistance protein (BCRP/ABCG2) [6]. Thus, enzymes and apical membrane transporters acting in tandem represent an efficient barrier against xenobiotics absorption while providing a mechanism for compounds elimination from the body. This was already postulated by Benet's group [8] with reference to the interplay between CYP3A and MDR1 and experimentally demonstrated for cyclosporine. Similar to the interaction between CYP3A and MDR1, conjugating reactions products become MRP2 substrates for further secretion into the intestinal lumen. A generalization of these coordinated actions is illustrated in Fig. 1. This same figure also shows that drugs and their metabolites can be alternatively absorbed into the circulation. The balance between apical secretion and basolateral absorption is variable and probably dependent on the drug and the relative expression of apical vs. basolateral transporters.

What follows is an update on the regulation of one of the components of the intestinal barrier, MRP2, under physiological and pathophysiological conditions, with special emphasis in MRP2 expression as well as the underlying mechanisms and functional consequences, when available.

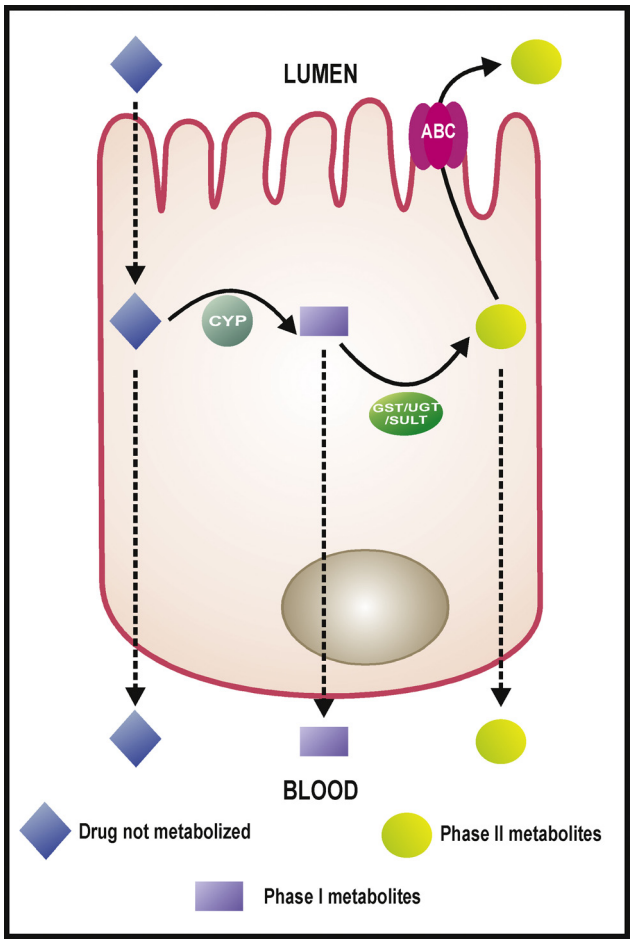

Fig. 1. Interplay between phase I/II metabolism and transport of drugs in the enterocyte. Hydrophobic drugs may freely access the cell by diffusion through the apical membrane of the enterocyte. Although some drugs could interact directly with ABC transporters to be extruded back into the lumen, they may also suffer metabolic phase I transformations by cytochrome P450 (CYP) and subsequent conjugation by phase II systems such as UDP-glucuronosyltransferase (UGT), glutathione S-transferase (GST) or sulphotransferase (SULT). Finally, the more hydrophilic metabolites may be actively secreted into intestinal lumen by ABC transporters. Alternatively, drugs and their metabolites can be absorbed into the circulation.

1.1.2. Intestinal multidrug resistance-associated protein 2

MRP2 is the second member identified in the now thirteen-member family of MRPs and serves as a prominent protective mechanism against intestinal absorption of xenobiotics. MRP2 is strategically localized at the apical membrane of enterocytes, anchored to the actin cytoskeleton through ezrin/radixin/moesin (ERM) family of proteins. MRP2 and ERM members can interact to each other directly or through PSD-95/*Drosophila* discs large/Zonula Occludens-1 (PDZ) proteins. This interaction appears to be crucial for MRP2 localization, stability and activity [9,10].

MRP2 shows maximal expression in the proximal small intestine, decreasing to the distal ileum. Its expression is concentrated at the tip of the intestinal villus, with lowest expression at the crypt level. The pattern of distribution of MRP2 is similar between rats [11] and humans [12] and coincides with the gradient of phosphorylated ezrin along the gastrointestinal tract in rats, which also decreases from the proximal to the distal regions of the intestine [13].

As mentioned in the previous section, MRP2 substrates are generated by specific biotransformation enzyme systems. Consistent with this, distribution of MRP2 along the small intestine, the primary site of absorption of orally ingested xenobiotics, agrees well with preferential phase II enzymes distribution. Even more, a gradient in the activities of UGT and GST was also demonstrated along the villus-crypt axis with the highest activities at the tip of the villus and the lowest at the crypt region [14,15]. Taken together, the evidence suggests that phase II enzymes and MRP2 work coordinately contributing to intestinal excretion of conjugated derivatives of potentially harmful compounds.

Intestinal MRP2 is active in regulating the pharmacokinetics, and consequently, the therapeutic efficacy of orally-administrated therapeutic agents [16]. The restriction imposed to intestinal drug absorption by MRP2 is part of the more universal feature of ABC transporters, known as multidrug resistance (MDR). Several strategies have been developed to revert MDR [17], like the use of protein inhibitors, monoclonal antibodies and antisense oligonucleotides or interfering RNA. Reversion of MDR targeting specifically MRP2 was not extensively studied, probably because most of the MRP2 substrates can also be transported by other ABC members, rendering this kind of therapy futile. Regarding strategies directed to overcome the restriction imposed by intestinal ABC transporters towards drug absorption, the few studies available are mainly directed to MDR1 [18,19]. However, in view of the clinical rele-

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vance of MDR, including participation of MRP2, further studies are warranted.

The expression and function of MRP2 can be regulated at transcriptional level, implying changes in mRNA synthesis rate due to an action on MRP2 promoter, or at post-transcriptional level, comprising complex regulatory processes with or without changes in MRP2 mRNA levels [20]. Irrespective of the mechanism, MRP2 regulation may be exerted by various endogenous and exogenous compounds, including drugs, nutrients and hormones, and may also occur under specific physiological and pathophysiological conditions [21].

1.2. MRP2 transcriptional regulation

This kind of regulation is frequently mediated by nuclear receptors activated by both *endo*- and xenobiotics that bind to response elements within MRP2 promoter. This leads to an increase in MRP2 mRNA synthesis, induction of MRP2 protrein synthesis and finally, higher MRP2 activity. Among nuclear receptors, the pregnane X receptor (PXR, NR1I2) plays a major role in MRP2 transcriptional regulation. It bears a promiscuous hydrophobic ligand binding pocket that allows the interaction with agonists of different molecular sizes and chemical structures, including drugs, environmental toxicants and dietary contaminants (reviewed in [22]). PXR acts as a heterodimer in combination with the retinoid X receptor alpha (RXRα, NR2B1) and binds to sequences characterized by direct or everted repetitions [23,24]. Under non-activating conditions (i.e. in the absence of an agonist) PXR mainly interacts with corepressor proteins, such as the silencing mediator of retinoid and thyroid hormone receptor [25] and the nuclear receptor corepressor proteins [26]. They mediate chromatin compaction and in consequence, gene repression. Upon agonist binding, corepressors dissociate from PXR allowing binding of coactivators like the steroid receptor coactivator 1 [22,27]. Coactivators favor chromatin decompaction and couple spatially to the promoter and the transcriptional machinery, ultimately leading to an increase in gene transcription. Besides PXR, the constitutive androstane receptor (CAR, NR1I3), the farnesoid X receptor (FXR, NR1H4) and the liver X receptor α (LXRα, NR1H3) have been shown to modulate MRP2 transcriptionally through binding to response elements similar to those of PXR [24,28]. CAR is activated by drugs like phenobarbital and valproic acid [29,30], FXR is activated by bile salts [24] and LXRα is activated by oxysterols [31,32].

In addition to hydrophobic compounds which bind to nuclear receptors, other xenobiotics act predominantly through binding to membrane receptors or interaction with membrane proteins. In these cases, the signal pathway may be associated to an increase in adenylyl cyclase activity and thus results in increased intracellular cAMP levels. The effect of sustained increases in intracellular cAMP on intestinal hMRP2 expression was demonstrated by Arana et al., [33]. In this study, differentiated Caco-2 cells, a cell line derived from colon cancer, were used to mimic the human enterocyte behavior. Increased intracellular cAMP levels were first achieved through incubation with the membrane permeable analogue dibutyryl cyclic AMP (db-cAMP). Under these conditions a significant induction in hMRP2 protein and mRNA expression was observed. The result was corroborated when cAMP was endogenously generated through incubation with the adenylyl cyclase activator forskolin. hMRP2 induction resulted in increased chemoresistance to 1-chloro-2,4-dinitrobenzene (CDNB) and increased efflux of dinitrophenyl-*S*-glutathione (DNP-SG), a model substrate of MRP2 formed by of CDNB glutathione conjugation. Reporter gene and chromatin immunoprecipitation assays demonstrated an increased binding of the transcription factors c-JUN and activating transcription factor-2 (ATF-2) to a regulatory cluster containing activator protein-1 (AP-1) and cAMP response element (CRE) binding sites within the hMRP2 promoter. This particular example of regulation of hMRP2 gene transcription by an endogenous molecule is illustrated in Fig. 2.

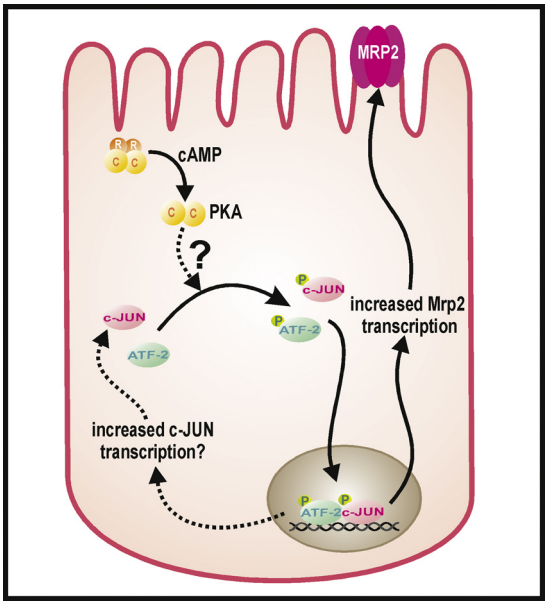

Fig. 2. Transcriptional regulation of hMRP2 gene by cAMP. Intracellular levels of cAMP may increase in response to a variety of signals, which in turn leads to up-regulation of hMRP2 protein in the apical membrane of the enterocyte. First, cAMP activates cAMP dependent protein kinase A (PKA), releasing the catalytic subunits (C) from the regulatory subunits (R). PKA is then able to phosphorylate and activate transcription factors, like c-JUN and ATF-2. Whether this activation is direct or indirectly remains unknown. Phosphorylated c-JUN and ATF-2 then interact with each other and the complex is recruited to the promoter region of hMRP2 gene. hMRP2 transcription is enhanced and hMRP2 protein expression in the apical membrane is increased. c-JUN/ATF-2 complex may also induce the expression of c-JUN, thus enhancing the formation of the complex.

Besides the above described transcriptional mechanisms, the study of hMRP2 promoter revealed binding sites for other transcription factors like the nuclear factor erythroid 2- related factor 2, the peroxisome proliferator activated receptor alpha, CCAAT/enhancer-binding protein-β and hepatic nuclear factors among others [34,35]. Although most of the transcription factors and nuclear and membrane receptors mentioned in this section were initially described in liver, a role of these factors in the mediation of intestinal hMRP2 regulation by exogenous compounds cannot be ruled out as they are constitutively expressed in intestinal tissue [36].

1.3. MRP2 post-transcriptional regulation

MRP2 protein expression and activity can be regulated without a concomitant modulation of the transcription rate. This could be due to different mechanisms, namely post-transcriptional (modifications in transport or processing of mRNA), translational (modulation of protein synthesis) or post-translational (changes in protein stability or localization, or substrate affinity). As an example of post-transcriptional regulation, mRNA splicing has been shown to be one of the causes underlying Dubin-Johnson syndrome, characterized by a truncated or non-functional protein [37,38]. Regarding translational regulation, Jones et al. [39] described an increased hepatic rMrp2 protein expression by pregnenolone-16α-carbonitrile treatment or a decrease in pregnant rats, both situations without changes in mRNA levels. Further works from the same group demonstrated the presence of several rMrp2 transcription initiation sites. The alternative use of these sites leads to several 5′UTR (5′ untranslated region) in rMrp2 mRNA with

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differential translational efficiency [40,41]. A possible explanation could be the differential presence or absence of miRNA target sites in the different 5′UTR fragments. For instance, the presence of a miRNA target site in a particular 5′UTR could result in an increased susceptibility to this miRNA and thus in reduced transational efficiency. On the contrary, the absence of the miRNA target site in an alternative 5′UTR may result in a reduced susceptibility to the miRNA and increased translational efficiency. In addition, Werk et al. [42] described the presence of single nucleotide polymorphisms in hMRP2 5′UTR which lead to differential suppression of hMRP2 expression by the miRNA-379. Finally, as an axample of post-translational regulation, modifications in hMRP2 localization, e.g from the apical membrane to sub-apical compartments and vice-versa, impact directly on hMRP2 transport activity. Crocenzi et al. [43] widely described this process in the liver, particularly in different physiological and pathophysiological conditions. Information about post-translational regulation of intestinal MRP2 is scarce and restricted to a report by Nakano et al. [44] showing internalization of rMrp2 in response to classic protein kinase C activation and with participation of ezrin dephosphorylation.

2. Regulation of intestinal MRP2 under physiological conditions

2.1. Diurnal rhythmicity

Stearns et al. [45] studied the diurnal rhythmicity of rMrp2 expression, among several other transporters, in rat jejunum. They harvested jejunal mucosa at first time point denominated "Zeitgeber Time 0" (ZT0 = lights-on at 7 am) and subsequently at 3-h intervals over a 24-h period (ZT24) and performed quantitative PCR. Rhythmicity was assessed with the cosinor procedure (Cosinor Periodicity, downloaded from www.circadian.org) assuming a period of 24 ± 0.1 h [46]. As result, they observed that rMrp2 mRNA varies along the day, with the peak expression time (acrophase) at ZT12. The variation between maximum and minimum levels was 2.5-fold, estimated from the cosinor amplitude. According to these results, they concluded that rMrp2 and many drug transporters display profound diurnal rhythms in transcription, which may underlie diurnal rhythms in drug pharmacokinetics and have a significant impact on diurnal changes in intestinal absorptive and efflux capacity. However, they only studied expression at transcriptional level rather than at protein or functional level. Thus, additional studies describing potential changes on the protein expression and activity of rMrp2 are required to more properly elucidate the impact on intestinal barrier function.

2.2. Gender and hormonal regulation

Despite its relevance, there is very little information about the influence of gender or sex hormones on intestinal MRP2 expression and function. However, important sex steroid hormones, such as estradiol and its derivative estradiol-17β-D-glucuronide, ethinyl estradiol and testosterone, which were shown to affect the expression and/or function of hepatic rMrp2 [47–49], could also be important factors influencing the expression of intestinal MRP2.

With reference to gender-related differences, only MacLean et al. [50] quantified the rMrp2 mRNA and protein expression by 3-cm segmentation of the whole intestine from male and female rats. They demonstrated that rMrp2 expression decreased along the intestinal axis from proximal to distal parts in both genders, as was also initially described by Mottino whenever for female rats [11]. Additionally, westernblotting detection of rMrp2 in the different regions was of similar magnitude between genders, suggesting a similar efficiency in the handling of rMrp2 substrates along the intestine. Respect to humans, there are several articles reporting also a gradient of hMRP2 expression along the intestine [51–53]. They included the assessment of hMRP2 content in samples from both genders, though the whole data were systematically grouped and none of them looked for potential differences between genders.

During pregnancy and lactation stages important hormonal changes are noted which mainly involve increased levels of estrogens, progestogens and lactogenic factors, such as prolactin. Their action on detoxification systems could produce a variety of effects which may have important physiological, pharmacological and toxicological consequences. On this regard, we have demonstrated that expression of rMrp2 protein as well as mRNA is preserved in small intestine of pregnant rats with respect to control animals [54]. In the same study we analyzed the capacity of enterocytes to secrete DNP-SG through the apical membrane, a process that was postulated to be mainly mediated by rMrp2 [55]. We analyzed DNP-SG secretion in the proximal small intestine using the everted intestinal sac model, where we added CDNB and detected its derivative DNP-SG in the mucosal compartment. Using this model we have demonstrated that secretion of DNP-SG from the cell to the mucosal compartment was the rate-limiting step of the overall process, which did not differ between pregnant and controls rats, consistent with preserved expression of rMrp2. Because metabolizing enzymes and rMrp2 are down-regulated in liver during pregnancy, secretion of conjugated derivatives across the apical membrane of the proximal intestinal cells may represent an alternative pathway to prevent toxicity of xenobiotics, particularly those entering the body orally. These data clearly indicate a differential regulation of rMrp2 expression between liver and intestine. Posible explanations are a different exposition to hormones such as estrogens between the liver and the intestine or different tissue sensitivity to same regulatory factors.

Food intake is greatly increased in post-partum rats (2–4 fold) with respect to normal females, particularly at the latter stage of lactation (14–21 days after delivery) [56,57]. This implies adaptation of the intestinal tract to satisfy the increased need for absorption of nutrients, e.g. by increasing the mucosal surface. The absorption by diffusion or mediated by uptake transporters of dietary xenobiotics is also expected to increase resulting in increased interaction with intestinal cells. A parallel increase in rMrp2 expression may represent a compensatory mechanism to deal with increased exposition and consequent risk of toxicity. Interestingly, the study of intestinal rMrp2 in post-partum period demonstrated a significant increase in rMrp2 protein and mRNA levels with respect to controls, being maximal at the latter stage of lactation, in agreement with the maximal increase in food intake and intestinal hypertrophy [56–58]. Analysis of CDNB metabolism and transport in the everted sac model revealed that rMrp2-mediated secretion of DNP-SG into the mucosal compartment was also increased in jejunum from lactating rats in agreement with the increased expression of rMrp2. In additional experiments using the same model, we analyzed whether DNP-SG added to the mucosal compartment is transported to the serosal compartment in intestinal sacs from jejunum, ileum and colon of control, pregnant and post-partum rats. This study could bring information about whether DNP-SG, once secreted into the lumen, may be reabsorbed, thus decreasing the efficiency of the secretory process. The data indicated that transport of DNP-SG was indeed significantly decreased in jejunum from post-partum animals. It is possible that the increased expression of rMrp2 in the proximal region of the intestine in lactating rats contributes not only to facilitate secretion but also to prevent reabsorption of the conjugated derivative of CDNB from the lumen. In an attempt to elucidate the mechanism responsible for the increased expression of rMrp2 post-partum, we administered ovine prolactin to ovariectomized rats following

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a similar protocol that demonstrated to be efficient in increasing hepatic transport of bile acids [59] and to induce expression of the Na^+-taurocholate cotransport polypeptide [60] and hepatic and intestinal phase II enzymes [61–63]. We failed to demonstrate any effect of ovine prolactin on rMrp2 expression and morphology of the small intestine [54].

Alternatively, a possible candidate is glucagon like peptide 2 (GLP-2), whose plasma levels are also increased during lactation [64]. This enterotrophic hormone can modulate morphology, function and integrity of the intestine [65] via its specific receptor, GLP-2R. GLP-2R is a transmembrane receptor protein belonging to the G protein-coupled receptor family. GLP-2R is expressed mainly in the proximal small intestine decreasing towards the distal small intestine. This expression pattern concides with that of rMrp2 and some conjugating enzymes. A potential mechanism of action of GLP-2 consists in GLP-2R activation, increased cAMP levels, cAMP-dependent protein kinase (PKA) activation and increased CRE- and AP-1-dependent transcription [66–68].

We further evaluated the effects of GLP-2 exogenous administration on intestinal rMrp2 chemical barrier function and demonstrated for the first time that GLP-2 administration up-regulates rMrp2 expression [69]. Consistent with this, transport activity was increased by GLP-2. These findings are of particular relevance considering that GLP-2 exhibits trophic action and may be critical to provide protection to the increased intestinal surface against xenobiotic exposure and also in conditions of increased food intake as occur with the post-partum period. Whether GLP-2 may play an additional role in prevention of cell toxicity and chemical injury under conditions of intestinal damage needs further exploration. During development, GLP-2 is involved in the regulation of growth and absortive functions of the intestine [65]. So it is possible to speculate that GLP-2 may also regulate MRP2 during development.

2.3. Human genetic polymorphisms

hMRP2 was reported [70] to show genetic polymorphism, an additional factor that can affect expression under physiological conditions. Moriya et al. [71] examined whether single nucleotide polymorphisms (SNPs) in the ABC transporter genes, including hMRP2, were associated with their respective mRNA expression levels in duodenal enterocytes of 13 healthy Japanese volunteers. In this study, 5 mutations were analyzed: G1249A, C2302T, C2366T, G4348A and C-24T. Among these mutations, only C-24T was detected in the 13 subjects. However, there was no remarkable effect on the relative concentration of hMRP2 mRNA. The authors concluded that known polymorphic mutations in the hMRP2 gene unlikely condition gene expression.

However, it is not possible to rule out an impact on hMRP2 function. Bernsdorf et al. [72] confirmed that C-24T polymorphism was neither of relevance for the expression of hMRP2 nor affected the intestinal absortion of talinolol, a recognized MRP2 substrate, after its oral administration. Trdan Lušin et al. [73] studied the effects of several efflux transporter genetic polymorphisms in women with osteoporosis, on both pharmacokinetic and pharmacodynamic parameters of raloxifene, whose glucuronide derivatives are known MRP2 sustrates. In the case of hMRP2, the polymorphism studied was T3972C and the data obtained indicated no effect on serum concentrations of raloxifene metabolites.

Haenisch et al. [74] investigated the allele frequency of the hMRP2 SNPs C-24T, A-23G, G1249A, C1446G, C1457T, C2302T, C2366T, G3542T, G3561A, T3563A, C3972T, G4348A, and G4544A in 374 German healthy volunteers and evaluated the effect on duodenal hMRP2 expression (mRNA and protein) and function. They found that the allele frequencies were 18.3% (−24T), 21.1% (1249A), 1.4% (1446G), 0.1% (3542T), 4.5% (3563A), 34.2% (3972T), and 4.4% (4544A). The authors demonstrated that none of the SNPs investigated affected significantly duodenal hMRP2 mRNA and protein content, except for C-24T which was weakly related with lower protein content of hMRP2. Functional studies, evaluated by the disposition of intravenously and orally administered talinolol, demonstrated that only G1249A was possibly associated with higher activity of intestinal hMRP2. In spite of the reported data, the true impact of hMRP2 SNPs on its expression and transport function remains to better established.

3. Regulation of intestinal MRP2 under pathophysiological conditions

3.1. Immunological and inflammatory diseases

Inflammation is a complex immunological reaction that can be initiated by different stimuli, such as infection, trauma, malignant growth or ischemia. An acute inflammatory response leads to the release of pro-inflammatory cytokines either locally or systemically, in particular the tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6), which are the major pro-inflammatory cytokines in all animal species [75]. In mammals, the increased expression of these cytokines is accompanied by a down-regulation of nuclear receptors, such as FXR, PXR and CAR. These nuclear receptors are involved in the regulation of biotransformation enzymes and ABC transporters at the transcriptional level [76,77]. Many reports have demonstrated that inflammation alters the expression of several drug ABC transporters in the liver, including rMrp2/mMrp2 [78–82]. This regulation depends on inflammatory cytokines, particularly IL-6 and IL-1β [80], possibly involving PXR [24].

The inflammatory response is likely a shared component of a variety of diseases. The first inflammation model assayed for expression of intestinal MRP2, consisted in endotoxin-treated rats [83]. After 24 h, inflammation was confirmed by measuring IL-6 mRNA levels, which were highly increased in jejunum sections. In these same sections rMrp2 and PXR mRNA levels were significantly diminished; similar results were previously reported in the liver [78–81]. Consistent with expression results, the authors found that rMrp2 activity was diminished as well. The addition of MK571 (MRP specific inhibitor) in transport assays failed reduce rMrp2-mediated transport. Considering that rMrp2 mRNA expression was not completely suppressed, the authors conclude that another type of regulation is likely involved, probably post-translational. Tomita et al. [84] tested the same model of lipopolysaccharide-induced inflammation in rats, although in this case the measurements were made 8 h after the treatment. Inflammation state was confirmed by elevated IL-1β mRNA levels. As observed before [85,86], these results agree with the notion that the intestinal mucosa exhibits an acute phase response as shown for the liver. The results obtained by Tomita et al. [84] regarding regulation of intestinal rMrp2 mRNA and activity were in agreement with those of Kalitsky-Szirtes and colleagues [83].

Haritova et al. [87] studied the expression of ABC transporters in a pathogen exposure inflammation model, by infecting chickens with *Escherichia coli*. The authors observed that cMrp2 mRNA distribution in healthy chickens is similar to that in mammalian species and that infected chickens showed no significant change in intestinal cMrp2 mRNA expression. Pazos et al. [88] also studied the expression of hMRP2 in an inflammation model of infection. In this case, intestinal epithelial cells were exposed to *Salmonella enterica* serotype Typhimurium and hMRP2 protein expression and activity showed a significant increase. In addition, Pazos et al. [88] assayed the model *in vivo* by infecting mice with the same bacteria. Inmunohistochemistry of proximal colon sections suggested

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that mMrp2 expression changes in the same manner as in their *in vitro* model.The differences in the regulation of expression of MRP2 reported by Haritova et al. [87] and Pazos et al. [88] are due to the presence of pathogenicity factors in *S. Thyphimurium* that up-regulate MRP2 expression and not due to the inflammation process itself.

Iida et al. [89] assayed a model of inflammation triggered by indomethacin. Indomethacin is known to stimulate the synthesis of inducible nitric oxide synthase (iNOS) and IL-1β in the liver [90]. In this model, intestinal iNOS mRNA levels (jejunum and ileum) tended to increase but showed no statistical significance. rMrp2 mRNA expression was significantly down-regulated at the two higher doses tested (5 and 7.5 mg/Kg) with no changes at the lowest dose of indomethacin (1 mg/Kg), indicating dependence with dose [89].

Rheumatoid arthritis (RA) is a chronic disorder that primarily affects joints and manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff. RA may also result in low red blood cell count and inflammation around the lungs and heart. Rats treated with adjuvant manifest systemic inflammation with increased levels of inflammatory cytokines after the acute phase [91], thus representing a fairly good model for human RA. Uno et al. [92] and Kawase et al. [93] studied intestinal ABC transporters expression in RA inflammation model at 7 days for the acute phase and 21 days for the chronic phase. Uno et al. [92] measured mRNA levels and observed that jejunum rMrp2 mRNA was significantly diminished after 7 days but not at 21 days. Similar time-dependent alterations were observed for PXR mRNA, but not for CAR mRNA, suggesting that PXR might be associated with rMrp2 regulation in this model. Kawase et al. [93] found that rMrp2 protein expression in membrane fractions of small intestine was slightly increased 7 days after adjuvant treatment and a significantly decreased after 21 days. Taken together, these reports show a clear dissociation between intestinal rMrp2 mRNA and protein levels in response to adjuvant injection. The reason for such dissociation is unknown, but taking into account that activity is closely associated to protein content, an impairment in rMrp2 transport activity in this particular inflammatory condition is expected.

3.2. Hepatic diseases

3.2.1. Cholestasis

Cholestasis consists in bile flow impairment and consecuent accumulation of bile acids and bilirubin in the hepatocytes. Down-regulation of activity of main canalicular ABC transporters was found to be involved [94], including MRP2 and the bile salt export pump (BSEP/ABCB11). To ameliorate the impact of bile salt accumulation, sinusoidal transporters associated with the uptake process are down-regulated, whereas MRP3, associated with basolateral secretion, is up-regulated [95]. Cholestatic diseases have origin in different causes, namely, intrahepatic (like acute hepatitis, alcoholic liver disease and primary biliary cirrhosis) or extrahepatic (gallstone formation, bile duct cancer, pancreatic cancer and pancreatitis). Several animal models, mainly murine, resemble human cholestatic liver injury. Examples are lipopolysaccharide-treated rats (cholestasis of sepsis), estrogen-treated rats and bile duct ligation also in rats. These experimental models were initially applied to the study of drug transporters in the liver. Interestingly, in all cases a down-regulation of rMrp2 was shown [96–98]. In contrast, an up-regulation of renal rMrp2 was observed in some of these cases [99–102]. Intestinal rMrp2 expression during cholestasis was first studied in the bile duct ligation (BDL) model by Dietrich et al. [103], Kamisako and Ogawa [104], and Villanueva et al. [102]. All these groups found a decrease in rMrp2 intestinal expression. Dietrich and colleagues [103] evaluated intestinal rMrp2 protein and mRNA expression in rats 3 and 7 days after BDL surgery and found a decline at both levels. The reduction observed for protein levels was faster and more pronounced than that of mRNA levels. Therefore the authors hypothesized that intestinal rMrp2 expression was regulated during obstructive cholestasis, not only by a slow transcriptional down-regulation, but also by a rapid down-regulation, presumably mediated by post-transcriptional mechanisms. Dietrich et al. [103] also evaluated intestinal hMRP2 expression in patients with obstructive cholestasis. As observed in rat studies, cholestasis in humans led to down-regulation of hMRP2 protein in the proximal intestine. Nevertheless, mRNA levels of hMRP2 in the same patients did not show any differences, suggesting a different mechanism of regulation than in rats. This species-related difference was also reported for liver, as obstructive cholestasis decreased MRP2 mRNA in rats [96] but not in humans [105], whereas protein content was significantly reduced in both species. Dietrich et al. [103] also identified IL-1β as the central mediator for transcriptional regulation of intestinal rMrp2 during bile duct obstruction and discarded a role for accumulation of biliary components in serum as responsible for such regulation.

Similar observations were made by Villanueva et al. [102], who evaluated rMrp2 protein levels in rats 1, 7 and 14 days after BDL surgery. One day after BDL the attenuation of rMrp2 protein levels was not detected, however a significant reduction was observed 7 days after BDL, which was maintained for 14 days. rMrp2 function as a membrane barrier was also determined and found to be significantly reduced. In contrast, Kamisako and Ogawa [104] observed that intestinal rMrp2 mRNA expression remarkably decreased 1 day after BDL and recovered to control values 3 days after BDL. They did not explore the mechanism or provide an explanation respect to the differences with the study by Dietrich et al. [103]. The different strain of rats or chow used to feed them could be potential explanations.

Estrogens can cause reversible intrahepatic cholestasis in humans and animals, attributed to decreased expression and activity of the canalicular BSEP and MRP2 [96,106] and concomitant impairment of bile flow formation [94,107]. This pathology could be associated with pregnancy and oral-contraceptive use, but can also be induced by estrogen antagonists (e.g., tamoxifen), androgenic anabolic steroids and estrogens in men receiving prostatic cancer treatment [94]. Administration of the synthetic estrogen ethinyl estradiol to rats constitutes a model of estrogen-induced cholestasis [94]. Alternatively endogenous estrogen metabolites such as estradiol-17β-D-glucuronide can also exert cholestatic effects [108,109]. Kamisako and Ogawa [104] assayed a model of estrogen-induced cholestasis, treating rats with ethinyl estradiol for 5 days, and found no difference in rMrp2 mRNA levels in the liver or the intestine. In addition, Arias et al. [110] used this same model and measured not only mRNA levels but also protein levels and activity of intestinal rMrp2. They showed that rMrp2 mRNA levels did not change after ethinyl estradiol treatment, but protein levels were considerably diminished. These results indicate that this regulation probably occurs at the post-transcriptional level. Studies of immunofluorescence confocal microscopy also showed a decrease in rMrp2 without changes in its apical localization. Accordingly, rMrp2 activity measured by DNP-SG transport was substantially decreased, whereas intestinal absorption of DNP-SG, inversely associated with MRP2 function, was largely increased after ethinyl estradiol treatment.

Taken together, the reports found in the literature on cholestasis coincide in demonstrating down-regulation of protein expression and activity of intestinal MRP2, independently of the disease or the species analyzed. This is not the case for mRNA expression, since obstructive cholestasis seems to regulate MRP2 at the transcriptional level in rats but at the post-transcriptional level in humans. Finally, the effect of ethinyl estradiol was only evaluated in rats and

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demonstrated that the down-regulation of intestinal rMrp2 occurs at the post-transcriptional level.

3.2.2. Hepatic failure

Liver injury can result from infection (viral hepatitis), surgical resection or exposure to toxic compounds. Partial hepatectomy in rats constitutes a fitting model for the study of liver injury since the substantial loss of liver mass is associated with impairment in the overall metabolic and secretory function even if cell function is preserved. It was reported that hepatic rMrp2 expression remains unaltered after two-third hepatectomy [111,112]. In contrast, rMrp2 activity in proximal jejunum increased significantly one day after partial hepatectomy and returned to control values 7 days after the surgery [113]. Surprisingly, protein expression and localization of rMrp2 remained unchanged [113]. This discrepancy may be explained considering that, as a result of the reduced liver mass, an augmented proportion of CDNB available systemically probably reaches extrahepatic tissues. Additionally, CDNB conjugation is increased as a result of increased GST activity [113]. The evidence indicates that as a consequence of decreased liver mass there is more MRP2 substrate (DNP-SG) available to be transported by intestinal rMrp2.

Acute hepatic failure can be induced experimentally by CCl_4 resulting in hyperbilirubinemia [114–116]. Yokooji and colleagues [117] examined the effect of bilirubin treatment on intestinal transport of DNP-SG in an *in vitro* model. Bilirubin addition significantly decreased the DNP-SG efflux in rat jejunum. The suppression of DNP-SG efflux in jejunum was also observed after intravenous administration of bilirubin in an *in vivo* model [117,118]. These results suggested that diseases accompanied by hyperbilirubinemia might modulate the intestinal rMrp2 function *in vivo*. Yokooji et al. [119] examined the effect of CCl_4-induced acute hepatic failure on the intestinal expression and function of rMrp2 in the intestine. After 24 h rMrp2 protein expression and function in jejunum was significantly decreased, whereas after 48 and 120 h it was partially and almost completely recovered, respectively.

3.2.3. Wilsonsís disease

The hepatolenticular degeneration commonly known as Wilson's disease, is a hereditary, autosomal recessive disorder which occurs to about one of every 40,000 people [120,121]. The Long-Evans Cinnamon (LEC) rats are deficient in the Wilson's disease gene, ATP7B, and show biochemical features that are very similar to those found in human [122,123]. Chiba et al. [124] investigated the expression of intestinal ABC transporters in LEC rats. rMrp2 expression was decreased in jejunum at mRNA and protein levels when compared to Wistar rats considered as controls. However, rMrp2-mediated efflux of pravastatin did not change in LEC rats in spite of decreased rMrp2 expression. Serosal-to-mucosal permeation of mannitol across the jejunum was significantly higher in LEC rats. The authors speculated that this is probably caused by the smaller thickness of the muscle layers. This would also affect pravastatin permeation and would compensate its decreased rMrp2-mediated efflux, so that no changes were observed in serosal-to-mucosal pravastatin permeation between groups. However, it is not expected that the thickness of muscle layer influences drug permeation and in consequence, the reasons for dissociation between expression and efflux activity in LEC rats remain unexplained.

3.3. Intestinal diseases

3.3.1. Colorectal cancer

Colorectal cancer (CRC) represents the third most commonly diagnosed cancer and one of the main causes of cancer-related death in Western countries [125]. ABC transporters are often up-regulated in various tumor types and result in increased drug efflux, generating resistance to some anticancer chemotherapeutic agents [126]. Several articles report on ABC transporters expression in colorectal carcinoma tissues from patients. Regarding hMRP2, Hinoshita et al. [127] and Hlavata et al. [128] measured the mRNA levels in CRC biopsies from patients and compared them with noncancerous regions from the same patients. Although normal colorectal mucosa showed very low or no hMRP2 mRNA expression both articles agree that hMRP2 is significantly up-regulated in CRC tissue. Andersen et al. [129] corroborated these previous findings and further demonstrated that not only CRC tissues presented higher levels of hMRP2 mRNA than noncancerous region from the same individual but also from healthy patients. In contrast, Nakamura et al. [130] and Ballestero et al. [131] reported that hMRP2 mRNA levels were barely detected either in CRC biopsies or in its surrounding normal tissue. In spite of these latter studies, most of the evidence supports the idea of increased expression of hMRP2 mRNA in CRC with respect to the normal situation.

Andersen et al. [129] also assessed the levels of hMRP2 mRNA in patients with adenomas presenting mild or severe dysplasia. No statistically significant differences were observed for hMRP2 mRNA levels between adenomas and samples from healthy patients. This is in accordance with the data reported by Ballestero et al. [131] who found low and similar hMRP2 mRNA levels between normal and polyp tissues. Regarding hMRP2 protein expression, Dietrich et al. [132] found low hMRP2 levels in biopsies obtained from patients with adenoma, which were similar to the levels detected in its surrounding normal tissue. Similar findings were reported in murine models.

3.3.2. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of inflammatory autoimmune diseases that involve the gastrointestinal tract. Crohn's disease and ulcerative colitis are the principal types of inflammatory bowel disease. Ulcerative colitis (UC) is a relapsing non-transmural inflammatory disease that is restricted to the colon [133]. Crohn's disease (CD) is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa that typically involves discontinuous portions of the entire gastrointestinal tract and the development of complications like strictures, abscesses, or fistulas [133]. Langmann et al. [134] studied the expression of ABC transporters in non-inflamed mucosa samples from terminal ileum and colon transversum belonging to patients with UC or CD. hMRP2 mRNA expression was decreased with respect to healthy patients. Nuclear receptor PXR was strongly reduced and even absent in some patients with UC. Englund et al. [135] analyzed samples from the colon and rectum of patients with UC, which showed increased levels of IL-1β and IL-6 mRNA. hMRP2 mRNA expression levels showed no difference respect to healthy patients. It should be kept in mind that the intestinal sections used in both reports represent regions where MRP2 expression is normally low. In contrast, Pazos et al. [88] examined colonic sections from patients with UC and CD by immunohistochemistry and observed an increase in hMRP2 apical expression. This would be consistent with data of up-regulation under conditions of inflammation due to bacterial infection.

Greger et al. [136] studied inflammatory chronic diseases common in dogs, called inflammatory bowel disease and food responsive diarrhea [137]. Samples for measurements of mRNA levels were taken from duodenum and colon, and both diseases showed an increase in dMrp2 expression.

Based on the scarce information found in the literature it is not possible to generalize on the effects of bowel inflammatory diseases since no changes, or even opposite variations, were found depending on where the samples were taken from and, more importantly, on the etiology of the disease.

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3.3.3. Ischemia-Reperfusion conditions

Intestinal ischemia-reperfusion (I/R) is a common clinical complication during small bowel transplantation, circulatory shock, and strangulation of the ileum. Ischemia is a restriction in blood supply to tissues, causing a shortage of oxygen and glucose, resulting in damage or dysfunction of the tissue. Reperfusion consists in the return of the blood circulation to the tissue after ischemia. This can cause inflammation and oxidative stress, resulting in reperfusion injury. Ogura et al. [138] observed that rMrp2 mRNA and protein levels were decreased 6 h after I/R in the jejunum, but were not significantly altered in the ileum at any time. The authors also investigated serum levels of IL-6, TNF-α and IL-1β. IL-6 was significantly increased 6 h after I/R likely causing the decreased in jejunal rMrp2 expression. Conversely, the serum level of TNF-α was not increased after I/R and only a trace amount of serum IL-1β was detected at any time.

3.4. Renal diseases

Kidneys are vital in maintaining metabolic homeostasis via transporter-mediated active secretion and/or reabsorption of numerous endobiotics and xenobiotics. Renal failure causes a loss of metabolic homeostasis, affecting not only kidney but also liver and intestine [139–141]. An effective murine model of renal failure consists in a two-stage five-sixth nephrectomy. Naud et al. [142] assayed this model to study intestinal ABC transporters regulation. Intestinal rMrp2 protein levels decreased significantly after nephrectomy, while rMrp2 mRNA remained unaltered. Because the protein distribution is not uniform along the vertical axis of the villus, it is possible that the use of mature enterocytes precludes the demonstration of a difference in the synthesis of the transporter. The authors further studied the intestinal profile of rMrp2 mRNA expression by *in situ* hybridization and observed that mRNA for rMrp2 is mostly expressed in crypt cells in rat intestine irrespective of treatment and that there was no major difference in localization between both groups. Thus, it seems that the down-regulation of intestinal rMrp2 in renal failure depends on post-translational mechanisms, though a more direct demonstration is necessary. rMrp2 activity was also decreased correlating well with protein levels. Assessment of the clearance of creatinine demonstrated a correlation with the extent of impairment in rMrp2 expression and function, suggesting that the decrease in transporter expression and activity is more pronounced when the renal failure is more severe. A variety of molecules accumulate during renal failure making them candidates for intestinal rMrp2 regulation. In addition, several studies have demonstrated that renal failure is associated with a chronic activation of inflammatory response [143–148]. Thus, some specific cytokines that are increased in renal failure also constitute potential mediators. In order to evaluate this possibility, Naud et al. [142] incubated serum from renal failure rats with Caco-2 cells. As a result, they demonstrated that a serum mediator is indeed responsible for the decrease in hMRP2 intestinal expression. However they did not identify the specific mediator.

Chronic renal failure show gender-associated differences, female patients and animals progress slower to end stages than males [149–151]. Lu and Klaassen [152] studied rMrp2 mRNA expression after two-stage five-sixth nephrectomy in male and female rats. The authors observed that mRNA levels of rMrp2 in jejunum were low in both genders and that after nephrectomy these levels tended to increase but did not reach significance. Although protein expression was not determined, the previous study by Naud et al. showing dissociation between protein and mRNA suggests post-transcriptional regulation of rMrp2 in chronic renal failure.

3.5. Diabetes

Diabetes is a chronic disease that presents elevated blood glucose levels and may be originated by two major causes. Type 1 diabetes is caused by the autoimmune destruction of the insulin-producing beta cells in the pancreas, while type 2 diabetes is more common and associated with the generation of resistance to insulin function. In order to evaluate intestinal rMrp2 expression in diabetes two murine models were assayed (alloxan- and streptozotocin-induced diabetes in rats). Alloxan and streptozotocin both destroy pancreatic beta cells and generate diabetes in rodents similar to type 1 diabetes in humans. Alloxan produced an impairment in gliclazide ABC-dependent transport in the distal ileum, which suggests a suppression of the expression or activity of ABC transporters, including rMrp2 [153]. In contrast, streptozotocin augmented protein level and activity of intestinal rMrp2 [154]. It is not unusual to find controversial results regarding regulation of rMrp2 in different models of diabetes. Similar differential regulations of rMrp2 were already reported for liver and kidney [155–162].

3.6. HIV infection

The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome [163] a condition in humans in which cell-mediated immunity is lost and allows life-threatening opportunistic infections and cancers to thrive. The use of antiretroviral drugs in HIV uninfected individuals is becoming the most promising strategy for prevention of HIV [164]. The bioavailability of the antiretroviral drugs depends not only on drug metabolism but also on drug transport processes that involve membrane-associated transport proteins [165–167]. De Rosa et al. [168] studied the expression of some ABC drug transporters in recto-sigmoid colon samples from HIV-infected patients and normal subjects. hMRP2 mRNA and protein expression were detected in all the cases. While mRNA levels were not different between groups, expression of hMRP2 protein was significantly reduced in the HIV-infected group compared to the normal group. The authors also evaluated the expression of PXR mRNA and found no significant differences between groups.

4. Conclusions

The concept of “intestinal biochemistry barrier” emerged from the recent advances in the knowledge of the intestinal physiology. It is associated with the cellular metabolism followed by excretion of drug metabolites into the intestinal lumen. Apical efflux transporters are involved in the latter process, MDR1, BCRP and MRP2 being major examples. Usually, their substrates present overlapping specificity towards the different transporters, which together with a differential and complementary distribution of these same transporters along the intestine provide an efficient mechanism to protect the body from xenobiotic toxicity.

MRP2, one of the major components of the intestinal transcellular barrier presents specificity for amphiphilic compounds, particularly organic anions conjugated with glucuronic acid, glutathione or sulphate. MRP2 expression and activity vary under multiple physiological and pathophysiological conditions. These regulations are expected to affect bioavailability or toxicity of its substrates, namely drugs of therapeutic use and contaminants, ultimately leading to drug–drug or drug-toxic interactions. Unfortunately, only a few studies are available in the literature demonstrating such effects. Clinical studies are needed to confirm predictions based on experiments performed *in vitro* or *in vivo* in animal models and to further demonstrate the impact on the phar-

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Table 1
Summary of the regulation of intestinal Mrp2 under pathophysiological conditions.

Disease	Source	Regulation level			Reference
		mRNA	Protein	Activity	
Inflammation	LPS-treated rats	Down-regulated	–	Reduced	[80,81]
	E. coli infected chickens	No change	–	–	[84]
	S. Typhimurium infected intestinal epithelial cells	–	Up-regulated	Increased	[85]
	S. Typhimurium infected mice	–	Up-regulated	–	
	Indomethacin induced rats	Down-regulated	–	–	[86]
Rheumatoid arthritis	Adjuvant-induced arthritis in rats	Down-regulated	Down-regulated	–	[89,90]
Cholestasis	BDL in rats	Down-regulated	Down-regulated	Reduced	[99–101]
	Bile obstruction in humans	No change	Down-regulated	–	[100]
	Estrogen-induced	No change	Down-regulated	Reduced	[101,107]
Hepatic failure	Partial hepatectomy in rats	–	No change	Increased	[110]
	CCl_4-induced	–	Down-regulated	Reduced	[116]
Wilson's disease	LEC rats	Down-regulated	Down-regulated	No change	[121]
Colorectal cancer	Tumor biopsies in humans	Up-regulated	–	–	[124–126]
	Tumor biopsies in humans	Undetected	–	–	[127,129]
	Adenoma biopsies in humans	No change	No change	–	[126–128]
	Adenoma biopsies in mice	–	No change	–	[128]
Inflammatory bowel disease	Uninflammed ileum or colon from UC or CD patients	Down-regulated	–	–	[131]
	Inflammed colon or rectum from UC patients	No change	No change	–	[132]
	Inflammed colon from UC or CD patients	–	Up-regulated	–	[85]
	Inflammed duodenum or colon from IBD or FRD dogs	Up-regulated	–	–	[133]
Intestinal ischemia-reperfusion	Intestinal ischemia-reperfusion in rats	Down-regulated	Down-regulated	–	[135]
Renal diseases	Two-stage five-sixth nephrectomy in rats	No change	Down-regulated	Reduced	[139,149]
Diabetes	Alloxan-induced diabetes in rats	–	–	Reduced	[150]
	Streptozotocin-induced diabetes in rats	–	Up-regulated	Increased	[151]
HIV infection	Recto-sigmoid colon from HIV-infected patients	No change	Down-regulated	–	[166]

(–): information is not available; LPS: lipopolysaccharide; BDL: Bile duct ligation; LEC: Long-Evans Cinnamon; CD: Crohn's disease; UC: Ulcerative colitis; IBD: inflammatory bowel disease; FRD: Food responsive diarrhea.

macokinetics or toxicity of drugs under specific physiological or pathophysiological conditions.

Regarding physiological regulations, diurnal variations were reported in rats, with a maximal increase in mRNA levels detected at 7 p.m (ZT12), though its functional relevance was not explored. Several studies focused on potential variations in the expression and activity of intestinal hMRP2 due to genetic polymorphisms in humans showing only minor variations. In rats, expression seems not to be influenced by gender whereas a significant increase in both expression and activity was described in lactating mothers. The intestinal trophic factor glucagon-like peptide 2 was likely involved in the up-regulation of rMrp2 described for lactating rats.

Table 1 summarizes the pathophysiological situations currently reviewed that affect the expression and function of intestinal MRP2. In particular, processes involving an inflammatory response have led to a reduction of the expression of MRP2 at the transcriptional level with concomitant decreased activity. The mechanism of regulation presumably involves an inflammatory cytokine and reduction of the expression of nuclear receptors like PXR, but the molecular mechanisms following participation of cytokines remain uncertain. During *S. Typhimurium* infection, intestinal mMrp2 is up-regulated and depends on specific bacterial factors not related to the inflammation response. Cholestatic disease involves inflammation and increases of inflammatory cytokines in the case of BDL in rodents, suggesting a transcriptional regulation. Human obstructive cholestasis and estrogen-induced cholestasis in rats seem to be regulated in a post-transcriptional manner. A post-transcriptional regulation is also involved in the impairment of protein expression and activity observed under renal failure conditions. The mechanisms explaining these post-transcriptional regulations remains unexplored, but could involve changes in mRNA processing or stability, protein degradation or localization. IBD shows wide variability regarding MRP2 expression and depends on the model assayed, making it difficult to generalize. The effects of experimental diabetes on intestinal rMrp2 regulation have shown controversial results depending on the model analyzed. Particularly, type I diabetes induced by alloxan or streptozotocin have shown opposite regulations on intestinal rMrp2 even when they are models for the same type of diabetes. Unfortunately, studies on intestinal hMRP2 regulation in patients are not available. Colorectal cancer shows high interindividual variability in human with regard to hMRP2 expression. In general, tumor samples tend to show an increase while adenoma samples show no difference in hMRP2 expression. Up-regulation of MRP2 has been highly associated with development of multidrug resistance. Finally, MRP2 protein is down-regulated during Wilsonís disease and HIV infection, though the mechanisms remain unknown. Other pathophysiological conditions, implicating directly or indirectly the intestine, still remain to be explored, and more importantly, further clinical studies are required to establish their impact in humans.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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References

[1] K.R. Groschwitz, S.P. Hogan, Intestinal barrier function: molecular regulation and disease pathogenesis, J. Allergy Clin. Immunol. 124 (1) (2009) 3–20.
[2] C.M. Van Itallie, J.M. Anderson, Claudins and epithelial paracellular transport, Annu. Rev. Physiol. 68 (2006) 403–429.
[3] M.G. Farquher, G.E. Palade, Junctional complexes in various epithelia, J. Cell. Biol. 17 (1963) 375–412.
[4] P. Zakeri-Milani, H. Valizadeh, Intestinal transporters: enhanced absorption through P-glycoprotein-related drug interactions, Expert. Opin. Drug Metab. Toxicol. 10 (6) (2014) 859–871.
[5] L.S. Kaminsky, Q.Y. Zhang, The small intestine as a xenobiotic metabolizing organ, Drug. Metab. Dispos. 31 (2003) 1520–1525.
[6] M. Estudante, J.G. Morais, G. Soveral, L.Z. Benet, Intestinal drug transporters: an overview, Adv. Drug Deliv. Rev. 65 (10) (2013) 1340–1356.
[7] C.G. Dietrich, A. Geier, R.P. Oude Elferink, ABC of oral bioavailability: transporters as gatekeepers in the gut, Gut 52 (12) (2003) 1788–1795.
[8] L.Z. Benet, The drug transporter-metabolism alliance: uncovering and defining the interplay, Mol. Pharm. 6 (6) (2009) 1631–1643.
[9] S. Kikuchi, M. Hata, K. Fukumoto, Y. Yamane, T. Matsui, A. Tamura, S. Yonemura, H. Yamagishi, D. Keppler, S. Tsukita, S. Tsukita, Radixin deficiency causes conjugated hyperbilirubinemia with loss of Mrp2 from bile canalicular membranes, Nat. Genet. 31 (3) (2002) 320–325.
[10] M.S. Anwer, Role of protein kinase C isoforms in bile formation and cholestasis, Hepatology 60 (3) (2014) 1090–1097.
[11] A.D. Mottino, T. Hoffman, L. Jennes, M. Vore, Expression and localization of Multidrug resistant protein Mrp2 in rat small intestine, J. Pharm. Exp. Ther. 293 (2000) 717–723.
[12] X. Cao, S.T. Gibbs, L. Fang, H.A. Miller, C.P. Landowski, H.C. Shin, H. Lennernas, Y. Zhong, G.L. Amidon, L.X. Yu, D. Sun, Why is it challenging to predict intestinal drug absorption and oral bioavailability in human using rat model, Pharm. Res. 23 (8) (2006) 1675–1686.
[13] T. Nakano, S. Sekine, K. Ito, T. Horie, Ezrin regulates the expression of Mrp2/Abcc2 and Mdr1/Abcb1 along the rat small intestinal tract, Am. J. Physiol. Gastrointest. Liver Physiol. 305 (2013) G807–G817.
[14] L.M. Pinkus, J.N. Ketley, W.B. Jakoby, The glutathione S-transferases as a possible detoxification system of rat intestinal epithelium, Biochem. Pharmacol. 26 (1977) 2359–2363.
[15] J.R. Chowdhury, P.M. Novikoff, N.R. Chowdhury, A.B. Novikoff, Distribution of UDP-glucuronosyltransferase in rat tissue, Proc. Natl. Acad. Sci. USA 82 (1985) 2990–2994.
[16] K.M. Giacomini, S.M. Huang, D.J. Tweedie, L.Z. Benet, K.L. Brouwer, X. Chu, A. Dahlin, R. Evers, V. Fischer, K.M. Hillgren, K.A. Hoffmaster, T. Ishikawa, D. Keppler, R.B. Kim, C.A. Lee, M. Niemi, J.W. Polli, Y. Sugiyama, P.W. Swaan, J.A. Ware, S.H. Wright, S.W. Yee, M.J. Zamek-Gliszczynski, L. Zhang, Membrane transporters in drug development, Nat. Rev. Drug Discov. 9 (2010) 215–236.
[17] S. Kapse-Mistry, T. Govender, R. Srivastava, M. Yergeri, Nanodrug delivery in reversing multidrug resistance in cancer cells, Front. Pharmacol. 5 (159) (2014) 1–22.
[18] U. Stein, W. Walther, Reversal of ABC transporter-dependent multidrug resistance in cancer a realistic option? Am. J. Cancer 5 (5) (2006) 285–297.
[19] C.M.F. Kruijtzer, J.H. Beijnen, J.H.M. Schellens, Improvement of oral drug treatment by temporary inhibition of drug transporters and/or cytochrome P450 in the gastrointestinal tract and liver: an overview, Oncologist 7 (2002) 516–530.
[20] P.M. Gerk, M. Vore, Regulation of expression of the multidrug resistance-associated protein 2 (MRP2) and its role in drug disposition, J. Pharmacol. Exp. Ther. 302 (2) (2002) 407–415.
[21] L. Payen, L. Sparfel, L. Courtois a Vernhet, O. Guillouzo a Fardel, The drug efflux pump MRP2: regulation of expression in physiopathological situations and by endogenous and exogenous compounds, Cell Biol. Toxicol. 18 (4) (2002) 221–233.
[22] A. Di Masi, E. Marinis, P. De Ascenzi, M. Marino, Nuclear receptors CAR and PXR: molecular, functional, and biomedical aspects, Mol. Asp. Med. 30 (5) (2009) 297–343.
[23] A. Geick, M. Eichelbaum, O. Burk, Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin, J. Biol. Chem. 276 (18) (2001) 14581–14587.
[24] H.R. Kast, B. Goodwin, P.T. Tarr, S.A. Jones, A.M. Anisfeld, C.M. Stoltz, P.A. Tontonoz, S. Kliewer, T.M. Willson, P.A. Edwards, Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor, J. Biol Chem. 277 (4) (2002) 2908–2915.
[25] D.R. Johnson, C.-W. Li, L.-Y. Chen, J.C. Ghosh, J.D. Chen, Regulation and binding of pregnane x receptor by nuclear receptor corepressor silencing mediator of retinoid and thyroid hormone receptors (SMRT), Mol. Pharmacol. 69 (1) (2006) 99–108.
[26] X. Ding, J.L. Staudinger, Repression of PXR-Mediated induction of hepatic CYP3A gene expression by protein kinase C, Biochem. Pharmacol. 69 (5) (2005) 867–873.
[27] D. Sharma, A.J. Lau, M.A. Sherman, T.K.H. Chang, Agonism of human pregnane X receptor by rilpivirine and etravirine: comparison with first generation non-nucleoside reverse transcriptase inhibitors, Biochem. Pharmacol. 85 (11) (2013) 1700–1711.
[28] I. Chisaki, M. Kobayashi, S. Itagaki, T. Hirano, K. Iseki, Liver x receptor regulates expression of MRP2 but not that of MDR1 and BCRP in the liver, Biochim. Biophys. Acta 1788 (11) (2009) 2396–2403.
[29] T. Kawamoto, T. Sueyoshi, I. Zelko, R. Moore, K. Washburn, M. Negishi, Phenobarbital-Responsive nuclear translocation of the receptor CAR in induction of the CYP2B gene, Mol. Cell. Biol. 19 (9) (1999) 6318–6322.
[30] L. Cerveny, L. Svecova, E. Anzenbacherova, R. Vrzal, F. Staud, Z. Dvorak, J. Ulrichova, P. Anzenbacher, P. Pavek, Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane x receptor pathways, Drug Metab. Dispos. 35 (7) (2007) 1032–1041.
[31] C. Traversari, S. Sozzani, K.R. Steffensen, V. Russo, LXR-Dependent and −Independent effects of oxysterols on immunity and tumor growth, Eur. J. Immunol. 44 (7) (2014) 1896–1903.
[32] V. Vollrath, A.M. Wielandt, M. Iruretagoyena, J. Chianale, Role of Nrf2 in the regulation of the Mrp2 (ABCC2) gene, Biochem. J. 395 (3) (2006) 599–609.
[33] M.R. Arana, G.N. Tocchetti, P. Domizi, A. Arias, J.P. Rigalli, M.L. Ruiz, M.G. Luquita, C. Banchio, A.D. Mottino, S.S.M. Villanueva, Coordinated induction of GST and MRP2 by cAMP in caco-2Cells: role of protein kinase a signaling pathway and toxicological relevance, Toxicol. Appl. Pharmacol. 287 (2) (2015) 178–190.
[34] T. Tanaka, T. Uchiumi, E. Hinoshita, S. Inokuchi a Toh, M. Wada, H. Takano, K. Kohno, M. Kuwano, The human multidrug resistance protein 2 gene: functional characterization of the 5′-Flanking region and expression in hepatic cells, Hepatology 30 (6) (1999) 1507–1512.
[35] B. Stöckel, J. König, T. Nies a, Y. Cui, M. Brom, D. Keppler, Characterization of the 5′-Flanking region of the human multidrug resistance protein 2 (MRP2) gene and its regulation in comparison withthe multidrug resistance protein 3 (MRP3) gene, Eur. J. Biochem. 267 (2000) 1347–1358.
[36] G. Pang, J. Xie, Q. Chen, Z. Hu, How functional foods play critical roles in human health, Food Sci. Hum. Wellness 1 (1) (2012) 26–60.
[37] G. Tate, M. Li, T. Suzuki, T. Mitsuya, A new mutation of the ATP-Binding cassette, sub-family C, member 2 (ABCC2) gene in a Japanese patient with Dubin-Johnson syndrome, Genes Genet. Syst. 77 (2) (2002) 117–121.
[38] R. Mor-Cohen, N. Zivelin a Rosenberg, I. Goldberg, U. Seligsohn, A novel ancestral splicing mutation in the multidrug resistance protein 2 gene causes Dubin-Johnson syndrome in Ashkenazi Jewish patients, Hepatol. Res. 31 (2) (2005) 104–111.
[39] B.R. Jones, W. Li, J. Cao, T.A. Hoffman, P.M. Gerk, M. Vore, The role of protein synthesis and degradation in the post- transcriptional regulation of rat multidrug resistance- associated protein 2 (Mrp2, abcc2), Mol. Pharmacol. 68 (3) (2005) 701–710.
[40] Y. Zhang, W. Li, M. Vore, Translational regulation of rat multidrug resistance- associated protein 2 expression is mediated by upstream open reading frames in the 5J untranslated region, Mol. Pharmacol. 71 (1) (2007) 377–383.
[41] Y. Zhang, T. Zhao, W. Li, M. Vore, The 5′-Untranslated region of multidrug resistance associated protein 2 (MRP2; ABCC2) regulates downstream open reading frame expression through translational regulation, Mol. Pharmacol. 77 (2) (2010) 237–246.
[42] A.N. Werk, H. Bruckmueller, S. Haenisch, I. Cascorbi, Genetic variants may play an important role in mRNA–miRNA interaction, Pharmacogenet. Genom. 24 (6) (2014) 283–291.
[43] F.A. Crocenzi, A.E. Zucchetti, A.C. Boaglio, I.R. Barosso, E.J. Sanchez Pozzi, A.D. Mottino, M.G. Roma, Localization status of hepatocellular transporters in cholestasis, Front. Biosci. 1 (17) (2012) 1201–1218.
[44] T. Nakano, S. Sekine, K. Ito, T. Horie, Correlation between apical localization of Abcc2/Mrp2 and phosphorylation status of ezrin in rat intestine, Drug Metab. Dispos. 37 (7) (2009) 1521–1527.
[45] A.T. Stearns, A. Balakrishnan, D.B. Rhoads, S.W. Ashley, A. Tavakkolizadeh, Diurnal rhythmicity in the transcription of jejunal drug transporters, J. Pharmacol. Sci. 108 (1) (2008) 144–148.
[46] W. Nelson, Y.L. Tong, J.K. Lee, F. Halberg, Methods for cosinor-rhythmometry, Chronobiologia 6 (4) (1979) 305–323.
[47] A.D. Mottino, J. Cao, L.M. Veggi, F. Crocenzi, M.G. Roma, M. Vore, Altered localization and activity of canalicular Mrp2 in estradiol-17beta-D-glucuronide-induced cholestasis, Hepatology 35 (6) (2002) 1409–1419.
[48] F.R. Simon, M. Iwahashi, L.J. Hu, I. Qadri, I.M. Arias, D. Ortiz, R. Dahl, E. Sutherland, Hormonal regulation of hepatic multidrug resistance associated protein 2 (Abcc2) primarily involves the pattern of growth hormone secretion, Am. J. Physiol. Gastrointest. Liver Physiol. 290 (2006) G595–G608.
[49] T. Suzuki, Y.L. Zhao, M. Nadai, K. Naruhashi, A. Shimizu, K. Takagi, K. Takagi, T. Hasegawa, Gender-related differences in expression and function of hepatic P-glycoprotein and multidrug resistance-associated protein (Mrp2) in rats, Life Sci. 79 (2006) 455–461.
[50] C. MacLean, U. Moenning, A. Reichel, G. Fricker, Closing the gaps: a full scan of the intestinal expression of p-glycoprotein, breast cancer resistance

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protein, and multidrug resistance-associated protein 2 in male and female rats, Drug Metab. Dispos. 36 (7) (2008) 1249–1254.
[51] C. Zimmermann, H. Gutmann, P. Hruz, J.P. Gutzwiller, C. Beglinger, J. Drewe, Mapping of multidrug resistance gene 1 and multidrug resistance-associated protein isoform 1–5 mRNA expression along the human intestinal tract, Drug Metab. Dispos. 33 (2) (2005) 219–224.
[52] S. Berggren, C. Gall, N. Wollnitz, M. Ekelund, U. Karlbom, J. Hoogstraate, D. Schrenk, H. Lennernäs, Gene and protein expression of P-glycoprotein: mRP1, MRP2, and CYP3A4 in the small and large human intestine, Mol. Pharm. 4 (2) (2007) 252–257.
[53] G. Englund, F. Rorsman, A. Rönnblom, U. Karlbom, L. Lazorova, J. Gråsjö, A. Kindmark, P. Artursson, Regional levels of drug transporters along the human intestinal tract: co-expression of ABC and SLC transporters and comparison with Caco-2 cells, Eur. J. Pharm. Sci. 29 (3–4) (2006) 269–277.
[54] A.D. Mottino, T. Hoffman, L. Jennes, M. Cao Jingsong Vore, Expression of multidrug resistant protein Mrp2 in small intestine from pregnant and post-partum rats, Am. J. Physiol. 280 (6) (2001) G1261–G1273.
[55] Y. Gotoh, H. Suzuki, S. Kinoshita, T. Hirohashi, Y. Kato, Y. Sugiyama, Involvement of an organic anion transporter (canalicular multispecific organic anion transporter/multidrug resistance-associated protein 2) in gastrointestinal secretion of glutathione conjugates in rats, J. Pharmacol. Exp. Ther. 292 (2000) 433–439.
[56] A.W. Cripps, V.J. Williams, The effect of pregnancy and lactation on food intake, gastrointestinal anatomy and the absorptive capacity of the small intestine in the albino rat, Br. J. Nutr. 33 (1975) 17–32.
[57] E. Elias, R.H. Dowling, The mechanism of small-bowel adaptation in lactating rats, Clin. Sci. Mol. Med. 51 (1976) 427–433.
[58] B.F. Fell, K.A. Smith, R. Campbell, Hypertrophic and hyperplastic changes in the alimentary canal of the lactating rat, J. Path. Bact. 85 (1963) 179–188.
[59] Y. Liu, J.F. Hyde, M. Vore, Prolactin regulates maternal bile secretory function post partum, J. Pharmacol. Exp. Ther. 261 (1992) 560–566.
[60] Y. Liu, T. Ganguly, J.F. Hyde, M. Vore, Prolactin increases mRNA encoding Na^+-TC cotransport, Am. J. Physiol. 268 (1995) 11–17.
[61] M.G. Luquita, V.A. Catania, E.J. Sánchez Pozzi, A.D. Mottino, Ovine prolactin increases hepatic UDP-glucuronosyltransferase activity in ovariectomized rats, J. Pharmacol. Exp. Ther. 278 (1996) 921–925.
[62] M.G. Luquita, V.A. Catania, E.J. Sánchez Pozzi, M. Vore, A.D. Mottino, Prolactin increases the hepatic content of Mu class subunits of glutathione S-Transferase in the rat, Drug Metab. Dispos. 27 (1999) 122–124.
[63] M.G. Luquita, V.A. Catania, E.J. Sánchez Pozzi, M. Vore, L.M. Veggi, J.M. Pellegrino, A.D. Mottino, Induction of phase II biotransformation reactions in rat jejunum during lactation: possible involvement of prolactin, Biochim. Biophys. Acta 1472 (1999) 82–92.
[64] L.R. Jacobs, S.R. Bloom, R.H. Dowling, Response of plasma and tissue levels of enteroglucagon immunoreactivity to intestinal resection, lactation and hyperphagia, Life Sci. 29 (1981) 2003–2007.
[65] D.J. Drucker, Biological actions and therapeutic potential of the glucagon-like peptides, Gastroenterology 122 (2002) 531–544.
[66] D.G. Munroe, A.K. Gupta, F. Kooshesh, T.B. Vyas, G. Rizkalla, H. Wang, L. Demchyshyn, Z.J. Yang, R.K. Kamboj, H. Chen, K. McCallum, M. Sumner-Smith, D.J. Drucker, A. Crivici, Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 1569–1573.
[67] B. Yusta, R. Somwar, F. Wang, D. Munroe, S. Grinstein, A. Klip, D.J. Drucker, Identification of glucagon-like peptide-2 (GLP-2)-activated signaling pathways in baby hamster kidney fibroblasts expressing the rat GLP-2 receptor, J. Biol. Chem. 274 (1999) 30459–30467.
[68] R.P. Boushey, B. Yusta, D.J. Drucker, Glucagon-like peptide (GLP)-2 reduces chemotherapy-associated mortality and enhances cell survival in cells expressing a transfected GLP-2 receptor, Cancer Res. 61 (2001) 687–693.
[69] S.S. Villanueva, A. Arias, M.L. Ruiz, J.P. Rigalli, J.M. Pellegrino, M. Vore, V.A. Catania, A.D. Mottino, Induction of intestinal multidrug resistance-associated protein 2 by glucagon-like peptide 2 in the rat, J. Pharmacol. Exp. Ther. 335 (2010) 332–341.
[70] S. Ito, I. Ieiri, M. Tanabe, A. Suzuki, S. Higuchi, K. Otsubo, Polymorphism of the ABC transporter genes, MDR1 MRP1 and MRP2/cMOAT, in healthy Japanese subjects, Pharmacogenetics 11 (2) (2001) 175–184.
[71] Y. Moriya, T. Nakamura, M. Horinouchi, T. Sakaeda, T. Tamura, N. Aoyama, T. Shirakawa, A. Gotoh, S. Fujimoto, M. Matsuo, M. Kasuga, K. Okumura, Effects of polymorphisms of MDR1: MRP1, and MRP2 genes on their mRNA expression levels in duodenal enterocytes of healthy Japanese subjects, Biol. Pharm. Bull. 25 (10) (2002) 1356–1359.
[72] A. Bernsdorf, T. Giessmann, C. Modess, D. Wegner, S. Igelbrink, U. Hecker, S. Haenisch, I. Cascorbi, B. Terhaag, W. Siegmund, Simvastatin does not influence the intestinal P-glycoprotein and MPR2: and the disposition of talinolol after chronic medication in healthy subjects genotyped for the ABCB1, ABCC2 and SLCO1B1 polymorphisms, Br. J. Clin Pharmacol. 61 (4) (2006) 440–450.
[73] T. Trdan Lušin, A. Mrhar, B. Stieger, G.A. Kullak-Ublick, J. Marc, B. Ostanek, A. Zavratnik, A. Kristl, K. Berginc, K. Delić, J. Trontelj, Influence of hepatic and intestinal efflux transporters and their genetic variants on the pharmacokinetics and pharmacodynamics of raloxifene in osteoporosis treatment, Transl. Res. 160 (4) (2012) 298–308.
[74] S. Haenisch, K. May, D. Wegner, A. Caliebe, I. Cascorbi, W. Siegmund, Influence of genetic polymorphisms on intestinal expression and rifampicin-type induction of ABCC2 and on bioavailability of talinolol, Pharmacogenet. Genomics 18 (4) (2008) 357–365.
[75] T.V. Leshchinsky, K.C. Klasing, Divergence of the inflammatory response in two types of chickens, Dev. Comp. Immunol. 25 (2001) 629–638.
[76] A.P. Beigneux, A.H. Moser, J.K. Shigenaga, C. Grunfeld, K.R. Feingold, Reduction in cytochrome P-450 enzyme expression is associated with repression of CAR (constitutive androstane receptor) and PXR (pregnane X receptor) in mouse liver during the acute phase response, Biochem. Biophys. Res. 293 (2002) 145–149.
[77] R. Stienstra, E. Lichtenauer-Kaligis, M. Muller, Stress- (and diet-) related regulation of hepatic nuclear receptors and its relevance for ABC-transporter functions, Drug Metab. Rev. 36 (2004) 391–406.
[78] K.B. Goralski, G. Hartmann, M. Piquette-Miller, K.W. Renton, Downregulation of mdr1a expression in the brain and liver during CNS inflammation alters the in vivo disposition of digoxin, Br. J. Pharmacol. 139 (2003) 35–48.
[79] G. Hartmann, H. Kim, M. Piquette-Miller, Regulation of the hepatic multidrug resistance gene expression by endotoxin and inflammatory cytokines in mice, Int. Immunopharmacol. 1 (2001) 189–199.
[80] G. Hartmann, A. Cheung, M. Piquette-Miller, Inflammatory cytokines, but not bile acids, regulate expression of murine hepatic anion transporters in endotoxemia, J. Pharmacol. Exp. Ther. 303 (2002) 273–281.
[81] M. Piquette-Miller, A. Pak, H. Kim, R. Anari, A. Shahzamani, Decreased expression and activity of P-glycoprotein in rat liver during acute inflammation, Pharm. Res. 15 (1998) 706–711.
[82] W. Tang, C. Yi, J. Kalitsky, M. Piquette-Miller, Endotoxin downregulates hepatic expression of P-glycoprotein and MRP2 in 2-acetylaminofluorene-treated rats, Mol. Cell Biol. Res. Commun. 4 (2000) 90–97.
[83] J. Kalitsky-Szirtes, A. Shayeganpour, D.R. Brocks, M. Piquette-Miller, Suppression of drug-metabolizing enzymes and efflux transporters in the intestine of endotoxin-treated rats, Drug Metab. Dispos. 32 (2004) 20–27.
[84] M. Tomita, Y. Takizawa, A. Kanbayashi, H. Murata, A. Tanaka, M. Nakaike, M. Hatanaka, T. Kai, M. Hayashi, Suppression of efflux transporters in the intestines of endotoxin-treated rats, Int. J. Pharm. 428 (2012) 33–38.
[85] E.P. Molmenti, T. Ziambaras, D.H. Perlmutter, Evidence for an acute phase response in human intestinal epithelial cells, J. Biol. Chem. 268 (1993) 14116–14124.
[86] Q. Wang, J. Wang, S. Boyce, J. Fischer, P. Hasselgren, Endotoxemia and IL-1β stimulate mucosal IL-6 production in different parts of the gastrointestinal tract, J. Surg. Res. 76 (1998) 27–31.
[87] A.M. Haritova, N.V. Rusenova, A.G. Rusenov, J. Schrickx, L.D. Lashev, J. Fink-Gremmels, Effects of fluoroquinolone treatment on MDR1 and MRP2 mRNA expression in *Escherichia coli*-infected chickens, Avian Pathol. 37 (5) (2008) 465–470.
[88] M. Pazos, D. Siccardi, K.L. Mumy, J.D. Bien, S. Louie, H.N. Shi, K. Gronert, R.J. Mrsny, B.A. McCormick, Multi-drug resistance transporter 2 regulates mucosal inflammation by facilitating the synthesis of hepoxilin A3, J. Immunol. 181 (11) (2008) 8044–8052.
[89] A. Iida, S. Ouchi, T. Oda, J. Aketagawa, Y. Ito, Y. Takizawa, M. Tomita, M. Hayashi, Changes of absorptive and secretory transporting system of (1 → 3) β-D-glucan based on efflux transporter in indomethacin-induced rat, Eur. J. Drug Metab. Pharmacokinet. 40 (2015) 29–38.
[90] J. Nandi, B. Saud, M.J. Zinkievich, Z. Yang, A.R. Levine, TNF-a modulates iNOS expression in an experimental rat model of indomethacin-induced jejunoileitis, Mol. Cell Biochem. 336 (2010) 12–24.
[91] X. Cai, Y.F. Wong, H. Zhou, Y. Xie, Z.Q. Liu, Z.H. Jiang, Z.X. Bian, H.X. Xu, L. Liu, The comparative study of Sprague-Dawley and Lewis rats in adjuvant-induced arthritis, Naunyn Schmiedebergs Arch. Pharmacol. 373 (2006) 140–147.
[92] S. Uno, M. Uraki, A. Ito, Y. Shinozaki, A. Yamada, A. Kawase, M. Iwakia, Changes in mRNA expression of ABC and SLC transporters in liver and intestines of the adjuvant-induced arthritis rat, Biopharm. Drug Dispos. 30 (2009) 49–54.
[93] A. Kawase, S. Norikane, A. Okada, M. Adachi, Y. Kato, M. Iwaki, Distinct alterations in ATP-binding cassette transporter expression in liver, kidney, small intestine, and brain in adjuvant-induced arthritic rats, J. Pharm. Sci. 103 (2014) 2556–2564.
[94] M. Trauner, P.J. Meies, J.L. Boyer, Molecular regulation of hepatocellular transport systems in cholestasis, J. Hepatol. 31 (1999) 165–178.
[95] J. Koeig, D. Rost, Y. Cui, D. Keppler, Characterization of the human multidrug resistance protein isoform MRP3 localized to the basolateral hepatocyte membrane, Hepatology 29 (1999) 1156–1163.
[96] M. Trauner, M. Arrese, C.J. Soroka, M. Ananthanarayanan, T.A. Koeppel, S.F. Schlosser, F.J. Suchy, D. Keppler, J.L. Boyer, The rat canalicular conjugate export pump (Mrp2) is down-regulated in intrahepatic and obstructive cholestasis, Gastroenterology 113 (1) (1997) 255–264.
[97] T.A. Vos, G.J. Hooiveld, H. Koning, S. Childs, D.K. Meijer, H. Moshage, P.L. Jansen, M. Müller, Up-regulation of the multidrug resistance genes, Mrp1 and Mdr1b, and down-regulation of the organic anion transporter, Mrp2, and the bile salt transporter, Spgp, in endotoxemic rat liver, Hepatology 28 (6) (1998) 1637–1644.
[98] D. Rost, J. Kartenbeck, D. Keppler, Changes in the localization of the rat canalicular conjugate export pump mrp2 in phalloidin-induced cholestasis, Hepatology 29 (1999) 814–821.
[99] S. Heemskerk, A. van Koppen, L. van den Broek, G.J.M. Poelen, A.C. Wouterse, H.B.P.M. Dijkman, F.G.M. Russel, R. Masereeuw, Nitric oxide differentially

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regulates renal ATP-binding cassette transporters during endotoxemia, Pflugers Arch.—Eur. J. Physiol. 454 (2007) 321–334.
[100] Y. Tanaka, Y. Kobayashi, E.C. Gabazza, K. Higuchi, T. Kamisako, M. Kuroda, K. Takeuchi, M. Iwasa, M. Kaito, Y. Adachi, Increased renal expression of bilirubin glucuronide transporters in a rat model of obstructive jaundice, Am. J. Physiol.Gastrointest. Liver Physiol. 282 (2002) G656–G662.
[101] J. Lee, F. Azzaroli, L. Wang, C.J. Soroka, A. Gigliozzi, K.D.R. Setchell, W. Kramer, J.L. Boyer, Adaptive regulation of bile salt transporters in kidney and liver in obstructive cholestasis in the rat, Gastroenterology 121 (2001) 1473–1484.
[102] S.S.M. Villanueva, M.L. Ruiz, C.J. Soroka, S.Y. Cai, M.G. Luquita, A.M. Torres, E.J. Sanchez Pozzi, J.M. Pellegrino, J.L. Boyer, V.A. Catania, A.D. Mottino, Hepatic and extrahepatic synthesis and disposition of dinitrophenyl-sglutathione in bile duct-ligated rats, Drug Metab. Dispos. 34 (8) (2006) 1301–1309.
[103] C.G. Dietrich, A. Geier, N. Salein, F. Lammert, F. Roeb, R.P.J. Oude Elferink, S. Matern, C. Gartung, Consequences of bile duct obstruction on intestinal expression and function of multidrug resistance-associated protein 2, Gastroenterology 126 (2004) 1044–1053.
[104] T. Kamisako, H. Ogawa, Alteration of the expression of adenosine triphosphate-binding cassette transporters associated with bile acid and colesterol transport in the rat liver and intestine during cholestasis, J. Gastroenterol. Hepatol. 20 (2005) 1429–1434.
[105] G. Zollner, P. Fickert, R. Zenz, A. Fuchsbichler, C. Stumptner, L. Kenner, P. Ferenci, R.E. Stauber, G.J. Krejs, H. Denk, K. Zatloukal, M. Trauner, Hepatobiliary transporter expression in percutaneous liver biopsies of patients with cholestatic liver diseases, Hepatology 33 (3) (2001) 633–646.
[106] J.M. Lee, M. Trauner, C.J. Soroka, B. Stieger, P.J. Meier, J.L. Boyer, Expression of the bile salt export pump is maintained after chronic cholestasis in the rat, Gastroenterology 118 (2000) 163–172.
[107] R. Bossard, B. Stieger, B. O'Neill, G. Fricker, P.J. Meier, Ethinylestradiol treatment induces multiple canalicular membrane transport alterations in rat liver, J. Clin. Invest. 91 (1993) 2714–2720.
[108] M. Meyers, W. Slikker, G. Pascoe, M. Vore, Characterization of cholestasis induced by estradiol-17 beta-D-glucuronide in the rat, J. Pharmacol. Exp. Ther. 214 (1) (1980) 87–93.
[109] F.A. Crocenzi, J.M. Pellegrino, V.A. Catania, M.G. Luquita, M.G. Roma, A.D. Mottino, E.J. Pozzi, Galactosamine prevents ethinylestradiol-induced cholestasis, Drug Metab. Dispos. 34 (2006) 993–997.
[110] A. Arias, S.S.M. Villanueva, M.L. Ruiz, M.G. Luquita, L.M. Veggi, J.M. Pellegrino, M. Vore, V.A. Catania, A.D. Mottino, Regulation of expression and activity of rat intestinal multidrug resistance-associated protein 2 by cholestatic estrogens, Drug Metab. Dispos. 37 (6) (2009) 1277–1285.
[111] T. Gerloff, A. Geier, B. Stieger, B. Hagenbuch, P.J. Meier, S. Matern, C. Gartung, Differential expression of basolateral and canalicular organic anion transporters during regeneration of rat liver, Gastroenterology 117 (1999) 1408–1415.
[112] T.A. Vos, J.E. Ros, R. Havinga, H. Moshage, F. Kuipers, P.L. Jansen, M. Muller, Regulation of hepatic transport systems involved in bile secretion during liver regeneration in rats, Hepatology 29 (1999) 1833–1839.
[113] S.S.M. Villanueva, M.L. Ruiz, M.G. Luquita, E.J. Sanchez Pozzi, V.A. Catania, A.D. Mottino, Involvement of mrp2 in hepatic and intestinal disposition of dinitrophenyl-s-glutathione in partially hepatectomized rats, Toxicol. Sci. 84 (2005) 4–11.
[114] M. Ogeturk, I. Kus, A. Kavakli, I. Zararsiz, N. Ilhan, M. Sarsilmaz, Effects of melatonin on carbon tetrachloride-induced changes in rat serum, J. Physiol. Biochem. 60 (2004) 205–210.
[115] S. Tada, N. Nakamoto, K. Kameyama, S. Tsunematsu, N. Kumagai, H. Saito, H. Ishii, Clinical usefulness of edaravone for acute liver injury, J. Gastroenterol. Hepatol. 18 (2003) 851–857.
[116] L.B. Zavodnik, I.B. Zavodnik, E.A. Lapshina, E.B. Belonovskaya, D.I. Martinchik, R.I. Kravchuk, M. Bryszewska, R.J. Reiter, Protective effects of melatonin against carbon tetrachloride hepatotoxicity in rats, Cell Biochem. Funct. 23 (2005) 353–359.
[117] T. Yokooji, T. Murakami, K. Ogawa, R. Yumoto, J. Nagai, M. Takano, Modulation of intestinal transport of 2,4-dinitrophenyl-S-glutathione, a multidrug resistance-associated protein 2 substrate, by bilirubin treatment in rats, J. Pharm. Pharmacol. 57 (5) (2005) 579–585.
[118] T. Yokooji, N. Mori, T. Murakami, Modulated function of tissue efflux transporters under hyperbilirubinemia in rats, Eur. J. Pharmacol. 636 (2010) 166–172.
[119] T. Yokooji, T. Murakami, R. Yumoto, J. Nagai, M. Takano, Function of multidrug resistance-associated protein 2 in acute hepatic failure rats, Eur. J. Pharmacol. 546 (2006) 152–160.
[120] S.A.K. Wilson, Progressive lenticular degeneration; a family nervous disease associated with cirrhosis of the liver, Brain 34 (1912) 295–309.
[121] G.J. Brewer, Recognition, diagnosis, and management of Wilson's disease, Proc. Soc. Exp. Biol. Med. 223 (2002) 39–46.
[122] P.C. Bull, G.R. Thomas, J.M. Rommens, J.R. Forbes, D.W. Cox, The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene, Nat. Genet. 5 (1993) 327–337.
[123] Y. Yamaguchi, M.E. Heiny, N. Shimizu, T. Aoki, J.D. Gitlin, Expression of the Wilson disease gene is deficient in the Long-Evans Cinnamon rat, Biochem. J. 301 (1994) 1–4.
[124] M. Chiba, S. Itagaki, M. Kobayashi, T. Hirano, K. Iseki, Characterization of hepatobiliary organic anion transporters in Long-Evans Cinnamon rats, Drug Metab. Pharmacokinet. 221 (2007) 387–390.
[125] R. Siegel, C. Desantis, A. Jemal, Colorectal cancer statistics, CA Cancer J. Clin. 64 (2) (2014) 104–117.
[126] Z. Chen, T. Shi, L. Zhang, M. Deng, C. Huang, T. Hu, L. Jiang, J. Li, Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: a review of the past decade, Cancer Lett. 370 (1) (2016) 153–164.
[127] E. Hinoshita, T. Uchiumi, K. Taguchi, N. Kinukawa, M. Tsuneyoshi, Y. Maehara, K. Sugimachi, M. Kuwano, Increased expression of an ATP-binding cassette superfamily transporter, multidrug resistance protein 2, in human colorectal carcinomas, Clin. Cancer Res. 6 (2000) 2401–2407.
[128] I. Hlavata, B. Mohelnikova-Duchonova, R. Vaclavikova, V. Liska, P. Pitule, P. Novak, J. Bruha, O. Vycital, L. Holubec, V. Treska, P. Vodicka, P. Soucek, The role of ABC transporters in progression and clinical outcome of colorectal cancer, Mutagenesis 27 (2012) 187–196.
[129] V. Andersen, L.K. Vogel, T.I. Kopp, M. Sæbø, A.W. Nonboe, J. Hamfjord, E.H. Kure, U. Vogel, High ABCC2 and low ABCG2 gene expression are early events in the colorectal adenoma-carcinoma sequence, PLoS One 10 (3) (2015) 1–13.
[130] T. Nakamura, T. Sakaeda, N. Ohmoto, T. Tamura, N. Aoyama, T. Shirakawa, T. Kamigaki, T. Nakamura, K.I. Kim, S.R. Kim, Y. Kuroda, M. Matsuo, M. Kasuga, K. Okumura, Real-time quantitative polymerase chain reaction for MDR1: MRP1, MRP2, and CYP3A-mRNA levels in Caco-2 cell lines, human duodenal enterocytes, normal colorectal tissues, and colorectal adenocarcinomas, Drug Metab. Dispos. 30 (1) (2002) 4–6.
[131] M. Ballestero, M.J. Monte, O. Briz, F. Jimenez, F. Gonzalez-San Martin, J.J.G. Marin, Expression of transporters potentially involved in the targeting of cytostatic bile acid derivatives to colon cancer and polyps, Biochem. Pharmacol. 72 (2006) 729–738.
[132] C.G. Dietrich, A.K. Vehr, I.V. Martin, N. Gassler, T. Rath, E. Roeb, J. Schmitt, C. Trautwein, A. Geier, Downregulation of breast cancer resistance protein in colon adenomas reduces cellular xenobiotic resistance and leads to accumulation of a food-derived carcinogen, Int. J. Cancer 129 (2011) 546–552.
[133] D.C. Baumgart, W.J. Sandborn, Inflammatory bowel disease: clinical aspects and established and evolving therapies, Gastroenterology 2 369 (2007) 1641–1657.
[134] T. Langmann, C. Moehle, R. Mauerer, M. Scharl, G. Liebisch, A. Zahn, W. Stremmel, G. Schmitz, Loss of detoxification in inflammatory bowel disease: dysregulation of pregnane X receptor target genes, Gastroenterology 127 (2004) 26–40.
[135] G. Englund, A. Jacobson, F. Rorsman, P. Artursson, A. Kindmark, A. Rönnblom, Efflux transporters in ulcerative colitis: decreased expression of BCRP (ABCG2) and Pgp (ABCB1), Inflamm. Bowel Dis. 13 (3) (2007) 291–297.
[136] D.L. Greger, F. Gropp, C. Morel, S. Sauter, J.W. Blum, Nuclear receptor and target gene mRNA abundance in duodenum and colon of dogs with chronic enteropathies, Domest. Anim. Endocrinol. 31 (2006) 327–339.
[137] K. Allenspach, Clinical immunology and immunopathology of the canine and feline intestine, Vet. Clin. North Am. Small Anim. Pract. 41 (2) (2011) 345–360.
[138] J. Ogura, M. Kobayashi, S. Itagaki, T. Hirano, K. Iseki, Alteration of Mrp2 and P-gp expression, including expression in remote organs, after intestinal ischemia-reperfusion, Life Sci. 82 (2008) 1242–1248.
[139] C. Guevin, J. Michaud, J. Naud, F.A. Leblond, V. Pichette, Down-regulation of hepatic cytochrome P450 in chronic renal failure: role of uremic mediators, Br. J. Pharmacol. 137 (2002) 1039–1046.
[140] F.A. Leblond, M. Petrucci, P. Dube, G. Bernier, A. Bonnardeaux, V. Pichette, Downregulation of intestinal cytochrome P450 in chronic renal failure, J. Am. Soc. Nephrol. 13 (2002) 1579–1585.
[141] T.D. Nolin, R.F. Frye, G.R. Matzke, Hepatic drug metabolism and transport in patients with kidney disease, Am. J. Kidney Dis. 42 (2003) 906–925.
[142] J. Naud, J. Michaud, C. Boisvert, K. Desbiens, F.A. Leblond, A. Mitchell, C. Jones, A. Bonnardeaux, V. Pichette, Down-regulation of intestinal drug transporters in chronic renal failure in rats, J. Pharmacol. Exp. Ther. 320 (2007) 978–985.
[143] C.W. Oettinger, L.A. Bland, J.C. Oliver, M.J. Arduino, S.K. McAllister, M.S. Favero, The effect of uremia on tumor necrosis factor-alpha release after an in vitro whole-blood endotoxin challenge, J. Am. Soc. Nephrol. 4 (1994) 1890–1895.
[144] R. Ziesche, M. Roth, E. Papakonstantinou, M. Nauck, W.H. Horl, M. Kashgarian, L.H. Block, A granulocyte inhibitory protein overexpressed in chronic renal disease regulates expression of interleukin 6 and interleukin 8, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 301–305.
[145] T. Akahoshi, N. Kobayashi, S. Hosaka, N. Sekiyama, C. Wada, H. Kondo, In-vivo induction of monocyte chemotactic and activating factor in patients with chronic renal failure, Nephrol. Dial Transplant. 10 (1995) 2244–2249.
[146] T. Higuchi, C. Yamamoto, T. Kuno, M. Mizuno, S. Takahashi, K. Kanmatsuse, Increased production of interleukin-1beta and interleukin-1 receptor antagonist by peripheral blood mononuclear cells in undialyzed chronic renal failure, Nephron 76 (1997) 26–31.
[147] P. Stenvinkel, O. Heimburger, F. Paultre, U. Diczfalusy, T. Wang, L. Berglund, T. Jogestrand, Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure, Kidney Int. 55 (1999) 1899–1911.

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[148] Q. Yao, J. Axelsson, P. Stenvinkel, B. Lindholm, Chronic systemic inflammation in dialysis patients: an update on causes and consequences, ASAIO J. 50 (6) (2004) LII–LVII.
[149] I. Ishikawa, Y. Saito, M. Nakamura, K. Takada, H. Ishii, T. Nakazawa, Y. Fukuda, M. Asaka, N. Tomosugi, T. Yuri, Fifteen-year follow-up of acquired renal cystic disease—agender difference, Nephron 75 (1997) 315–320.
[150] C.H. Coggins, J. Breyer Lewis, A.W. Caggiula, L.S. Castaldo, S. Klahr, S.R. Wang, Differences between women and men with chronic renal disease, Nephrol. Dial. Transplant. 13 (1) (1998) 430–1437.
[151] S.R. Silbiger, J. Neugarten, The role of gender in the progression of renal disease, Adv. Ren. Replace Ther. 10 (2003) 3–14.
[152] W. Lu, C. Klassen, Gender differences in mrna expression of ATP-binding cassette efflux and bile acid transporters in kidney, liver, and intestine of 5/6 nephrectomized Rats, J. Pharmacol. Exp. Therapeutic 36 (1) (2008) 16–23.
[153] H. Al-Salami, G. Butt, I. Tucker, M. Mikov, Influence of the semisynthetic bile acid (MKC) on the ileal permeation of gliclazide in healthy and diabetic rats, Pharmacol. Rep. 60 (2008) 531–542.
[154] D. Mei, J. Li, H. Liu, L. Liu, X. Wang, H. Guo, C. Liu, R. Duan, X. Liu, Induction of multidrug resistance-associated protein 2 in liver, intestine and kidney of streptozotocin-induced diabetic rats, Xenobiotica 42 (8) (2012) 709–718.
[155] M.T. Nowicki, L.M. Aleksunes, S.P. Sawant, A.V. Dnyanmote, H.M. Mehendale, J.E. Manautou, Renal and hepatic transporter expression in type 2 diabetic rats, Drug Metab. Lett. 2 (2008) 11–17.
[156] Q. Cheng, L.M. Aleksunes, J.E. Manautou, N.J. Cherrington, G.L. Scheffer, H. Yamasaki, A.L. Slitt, Drug-metabolizing enzyme and transporter expression in a mouse model of diabetes and obesity, Mol. Pharm. 5 (2008) 77–91.
[157] G.J. Anger, L. Magomedova, M. Piquette-Miller, Impact of acute streptozotocin-induced diabetes on ABC transporter expression in rats, Chem. Biodivers. 6 (2009) 1943–1959.
[158] N. Kameyama, S. Arisawa, J. Ueyama, S. Kagota, K. Shinozuka, A. Hattori, Y. Tatsumi, H. Hayashi, K. Takagi, S. Wakusawa, Increase in P-glycoprotein accompanied by activation of protein kinase Calpha and NF-kappaB p65 in the livers of rats with streptozotocininduced diabetes, Biochim. Biophys. Acta 1782 (2008) 355–360.
[159] Y. Hasegawa, S. Kishimoto, N. Shibatani, N. Inotsume, Y. Takeuchi, S. Fukushima, The disposition of pravastatin in a rat model of streptozotocin-induced diabetes and organic anion transporting polypeptide 2 and multidrug resistance-associated protein 2 expression in the liver, Biol. Pharm. Bull. 33 (2010) 153–156.
[160] Y. Hasegawa, S. Kishimoto, N. Shibatani, H. Nomura, Y. Ishii, M. Onishi, N. Inotsume, Y. Takeuchi, S. Fukushima, The pharmacokinetics of morphine and its glucuronide conjugate in a rat model of streptozotocin-induced diabetes and the expression of MRP2, MRP3 and UGT2B1 in the liver, J. Pharm. Pharmacol. 62 (2010) 310–314.
[161] D. Xu, F. Li, M. Zhang, J. Zhang, C. Liu, M.Y. Hu, Z.Y. Zhong, L.L. Jia, D.W. Wang, J. Wu, L. Liu, X.D. Liu, Decreased exposure of simvastatin and simvastatin acid in a rat model of type 2 diabetes, Acta Pharmacol. Sin. 35 (9) (2014) 1215–1225.
[162] T. Zhai, J. Wang, L. Sun, Y. Chen, The effect of streptozotocin and alloxan on the mRNA expression of rat hepatic transporters in vivo, AAPS Pharm. Sci. Tech. 16 (4) (2015) 767–770.
[163] R.A. Weiss, How does HIV cause AIDS? Science 260 (5112) (1993) 1273–1279.
[164] P.J. Klasse, R. Shattock, J.P. Moore, Antiretroviral drug-based microbicides to prevent HIV-1 sexual transmission, Annu. Rev. Med. 59 (2008) 455–471.
[165] K.C. Brown, S. Paul, A.D. Kashuba, Drug interactions with new and investigational antiretrovirals, Clin. Pharmacokinet. 48 (4) (2009) 211–241.
[166] O. Kis, K. Robillard, G.N. Chan, R. Bendayan, The complexities of antiretroviral drug–drug interactions: role of ABC and SLC transporters, Trends Pharmacol. Sci. 31 (1) (2010) 22–35.
[167] J. Weiss, W.E. Haefeli, Impact of ATP-binding cassette transporters on human immunodeficiency virus therapy, Int. Rev. Cell Mol. Biol. 280 (2010) 219–279.
[168] M.F. De Rosa, K.R. Robillard, C.J. Kim, T. Hoque, G. Kandel, C. Kovacs, R. Kaul, R. Bendayan, Expression of membrane drug efflux transporters in the sigmoid colon of HIV-Infected and uninfected men, J. Clin. Pharmacol. 53 (9) (2013) 934–945.

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