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# Gene expression and regulation of drug transporters in the intestine and kidney ☆

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ABSTRACT

Intestinal absorption and renal secretion of ionic drugs are controlled by a number of drug transporters expressed at the brush-border and basolateral membranes of epithelial cells. Over the last several years, considerable progress has been made regarding the molecular identification and functional characterization of drug transporters. Under some physiological and pathophysiological conditions, the expression and transport activity of drug transporters are changed, affecting the pharmacokinetics of substrate drugs. The regulation of transport activity in response to endogenous and exogenous signals can occur at various levels such as transcription, mRNA stability, translation, and posttranslational modification. Transcriptional regulation is of particular interest, because changes in transport activity are dynamically regulated by increases or decreases in levels of mRNA expression. The tissue-specific expression of drug transporters is also under transcriptional control, and recent studies using clinical samples from human tissues have revealed the expression profiles of drug transporters in the human body. The purpose of this research updates is to review the recent progress in the study of the gene expression and regulation of intestinal and renal drug transporters.

## 1. Introduction

Mucosal surfaces of tissues such as the intestine and kidney are lined by a single layer of epithelial cells. Epithelial cells function as a barrier to select essential (such as nutrients) and waste (such as toxic xenobiotics) compounds, being equipped with uptake and efflux transport systems. During the last decade, many kinds of nutrient and drug transporters in the intestine and kidney have been identified as uptake and efflux transport systems. Currently, various transporters have been classified as ATP-binding cassette (ABC) transporters and solute carriers (SLCs) based on sequence similarity by the Human Gene Nomenclature Committee.

In general, nutrient transporters in the intestine are tightly regulated by nutrient load [1]. Observed patterns of response for essential nutrients and/or nutrients that are toxic in excess, such as zinc and iron, are generally consistent with the maintenance of the body's nutrient status under conditions of

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*Abbreviations:* ABC, ATP-binding cassette; ATF, activating transcription factor; BCRP, breast cancer resistance protein; Cdx2, caudal-related homeobox protein; CRE, cAMP responsive element; CREB, CRE binding protein; EMSA, electrophoretic mobility shift assay; HNF-4α, hepatocyte nuclear factor-4α; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OCT, organic cation transporter; OCTN, novel organic cation transporter; PEPT, peptide transporter; Pgp, P-glycoprotein; PKA, protein kinase A; PPARα, peroxisome proliferator-activated receptor α; SLC, solute carrier

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variable intake. For example, expression of the divalent metal ion transporter (DMT1/SLC11A2), involved in iron absorption, is increased in the intestine by an iron-deficient diet [2]. Drug transporters are also regulated by many biochemical signalling pathways, and such regulation may influence the pharmacokinetics of substrate drugs. The regulation of transport activity in response to endogenous and exogenous signals may occur at various levels such as transcription, mRNA stability, translation, and posttranslational modification (Fig. 1). This diversity of regulatory mechanisms may be advantageous to correspond to various biological signals. In general, transcriptional regulation and posttranslational modification are believed to be responsible for long-term and short-term regulation, respectively. We are interested in the transcriptional regulation of drug transporters, because changes in transport activity are dynamically regulated by increases or decreases in levels of mRNA expression. The tissue-specific expression of drug transporters is also under transcriptional control, although there is little information about the mechanisms behind intestinal and renal-specific expression.

This research updates will focus on our current understanding of the expression and gene regulation of drug transporters in the intestine and kidney, concentrating on the control mechanisms governing the expression of each transporter. For SLC drug transporters, H$^+$/peptide transporters (PEPT) and organic ion transporters (OCT/OCTN/OAT) were selected as representative of transporters expressed in the intestine and kidney. The transporters mainly referred to here are listed in Table 1. On the other hand, only the expression profiles of ABC transporters are covered in this article. We do not refer to the gene regulation of ABC transporters, because several excellent reviews about gene regulation of ABC transporters have been already published [3–6].

## 2. Function and regulation of drug transporters

### 2.1. PEPT1 (SLC15A1)

#### 2.1.1. *General function and pharmacokinetic roles*

H$^+$/peptide cotransporter 1 (PEPT1, SLC15A) is localized at the brush-border membranes of intestinal epithelial cells and plays an important role for protein absorption to mediate the cellular uptake of di- and tripeptides digested from ingested food [7]. Because of its broad substrate specificity, PEPT1 recognizes various peptide-like drugs such as oral β-lactam antibiotics, which are structurally resemble to small peptides [8]. Intestinal PEPT1 can be utilized as a target for improving the intestinal absorption of poorly absorbed drugs such as nucleoside analogues [9,10]. Recently, mathematical models of H$^+$-coupled substrate transport mediated by PEPT1 were proposed to elucidate the transport characteristics of differently charged substrates [11,12].

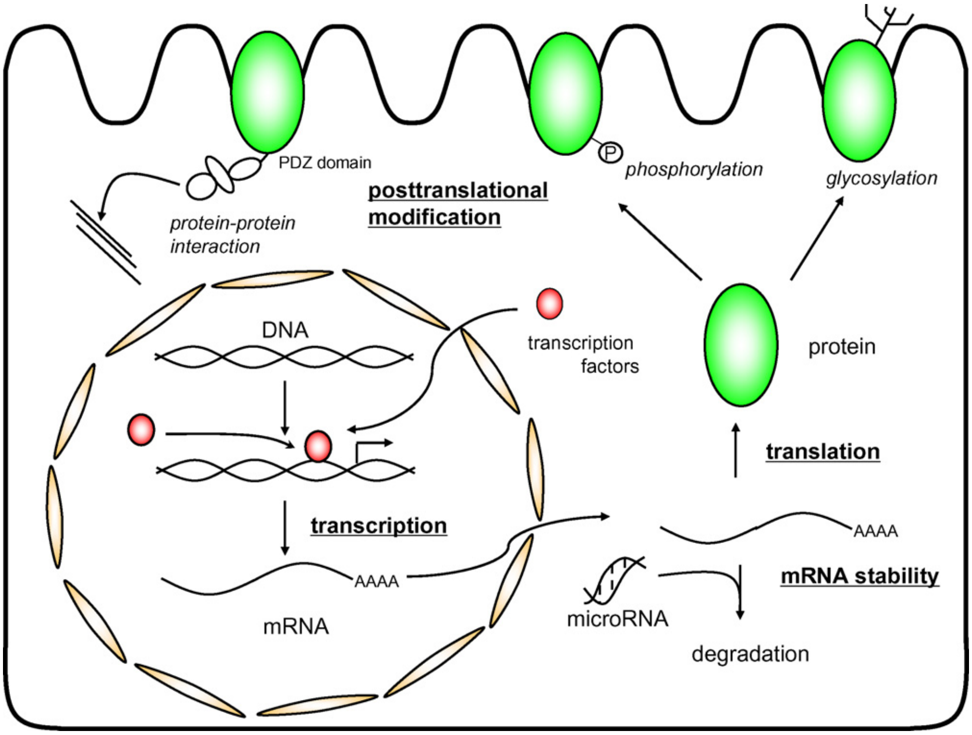

**Fig. 1 – Various factors influencing the expression of drug transporters. The activity of drug transporters may be regulated at various levels including transcription, mRNA stability, translation, and posttranslational modification. Posttranslational modification may involve glycosylation, phosphorylation, and protein–protein interaction. Moreover, transcriptional regulation is of particular interest, because many extra- and intracellular signals eventually alter the activity of transcription factors. In addition to the regulation of various signals, the tissue-specific expression of drug transporters is also under transcriptional control.**

**Table 1 – Major drug transporters expressed in the intestine and kidney**

| Transporter | Major pharmacokinetic/ physiological roles | Tissue distribution | Regulation/ diseases | Transcription factors | Reference |
|---|---|---|---|---|---|
| PEPT1 | Intestinal absorption, renal reabsorption | Small intestine, kidney | Fasting, diurnal rhythm | Sp1 | [35] |
| | | | | Cdx2 | [36] |
| | | | | PPARα | [37] |
| OCT1 | Hepatic uptake | Liver | Intrahepatic cholestasis | HNF-4α | [81] |
| OCT2 | Renal excretion | Kidney | Gender | Androgen receptor (Rat) | [75] |
| OCTN2 | Intestinal absorption, renal reabsorption | Intestine, kidney | Intestinal bowel diseases | Heat-shock transcription factor | [56] |
| OAT1 | Renal excretion | Kidney | Renal failure | Not identified | |
| OAT2 | Hepatic uptake | Liver | Gender | HNF-4α | [82] |
| OAT3 | Renal excretion | Kidney | Renal failure | HNF-1α/β | [79] |
| | | | | CREB-1 | [80] |
| | | | | ATF-1 | [80] |

### 2.1.2. *Regulation of PEPT1*

Adibi [13] summarized the recent progress in the study of the regulation of intestinal PEPT1. He classified the regulation of intestinal PEPT1 as physiological, pathological, or pharmacological regulation. As physiological factors, oligopeptides [14], various hormones (thyroid hormone, insulin, leptin, etc.) [15–17], cytokines (interferon-γ and tumor necrosis factor-α) [18,19], development [20,21], and diurnal rhythm [22–24] regulated the expression of intestinal PEPT1. These regulatory mechanisms vary as follows. In the case of oligopeptides [14], thyroid hormone [17], diurnal rhythm [22–24], and development [20,21], parallel changes in gene expression are brought about by alterations of the transcription and/or stability of PEPT1 mRNA. In contrast, treatment with insulin [15] and leptin [16] did not induce any change in *PEPT1* gene expression, and the mechanism of increased protein expression appears to be increased trafficking from a preformed cytoplasmic pool to the apical membranes. Interferon-γ does not affect the expression of PEPT1 at the mRNA or protein level, but enhances the $H^+$-electrochemical gradient across the apical plasma membrane in model intestinal epithelial cells [18].

In rats under various nutritional and metabolic conditions (high-protein diet [25,26], fasting [23,25], diabetes [27]), the expression of Pept1 in the intestine was mainly regulated at the transcriptional level. Under the chronic renal failure, intestinal Pept1 expression was regulated at protein level [28]. In patients with intestinal diseases including ulcerative colitis [29], Crohn's disease [29], and short-bowel syndrome [30], PEPT1 expression is induced in the colon. Pharmacological studies have shown that the mRNA expression of PEPT1 can be up-regulated by agents such as pentazocine [31] and 5-fluorouracil [32,33].

### 2.1.3. *Transcriptional regulatory mechanisms of PEPT1*

Shiraga et al. [26] have revealed that the rat Pept1 promoter was transcriptionally regulated by certain amino acids *via* an amino acid-responsive element. In the mouse Pept1 promoter, essential promoter/enhancer sites were shown to be present within 1140 bp upstream of the transcription start site [34]. Nevertheless, the *cis*-elements and/or transcription factors critical for basal transcriptional regulation have not been identified. To address these issues, we have recently cloned the human PEPT1 promoter region and examined its promoter activity using a human intestinal cell line, Caco-2 [35]. Deletion analysis of the human PEPT1 promoter suggested that the region spanning −172 to −35 bp was essential for basal transcriptional activity. This region lacked a TATA-box but contained some GC-rich sites which supposedly bind with the transcription factor Sp1. Electrophoretic mobility shift assay (EMSA), mutational analysis, inhibition analysis, and overexpression analysis have demonstrated a significant role for Sp1 in the basal transcriptional regulation of PEPT1 [35].

Because Sp1 is ubiquitously expressed, it cannot be the factor responsible for the intestine-specific expression of PEPT1. We then clarified the mechanisms behind the intestinal expression of the *PEPT1* gene [36]. Among the transcription factors investigated, only caudal-related homeobox protein 2 (Cdx2) markedly trans-activated the PEPT1 promoter, although the promoter region responsible for this effect lacked a typical Cdx2-binding sequence, but possessed some Sp1-binding sites. Cdx2 was suggested to have a novel mode of action, namely binding with Sp1. This hypothesis was confirmed by the results of a reporter assay, an immunoprecipitation assay, and a chromatin immunoprecipitation assay. The significance of CDX2 *in vivo* for *PEPT1* regulation was shown by the determination of mRNA levels of CDX2 and PEPT1 in human tissue. In gastric samples, some with intestinal metaplasia, the levels of PEPT1 and CDX2 mRNA were highly correlated (Fig. 2A). These findings collectively suggest that Cdx2 plays a key role in the transcriptional regulation of the intestine-specific expression of PEPT1 through interaction with Sp1 [36] (Fig. 2B).

Starvation markedly increased the amount of mRNA and protein of PEPT1 in rats, leading to altered pharmacokinetics of the PEPT1 substrates [23,25], but the mechanisms underlying this augmentation have not been clarified. We recently examined the role of peroxisome proliferator-activated receptor α (PPARα) in the augmentation of PEPT1 expression by fasting [37], because PPARα plays a pivotal role in the adaptive response to fasting in the liver and other tissues. In 48-h fasted rats, the expression level of PPARα mRNA in the small intestine markedly increased, accompanied by an elevation in serum level of free fatty acids, which are endogenous PPARα ligands. Oral administration of a synthetic

PPARα ligand WY-14643 to fed rats increased the mRNA level of intestinal PEPT1. In the small intestine of PPARα null mice, augmentation of PEPT1 mRNA expression during fasting was completely abolished. To test the possibility that PPARα directly regulates the human PEPT1 promoter, we searched for the potential PPAR responsive element (PPRE) in the promoter region up to 10 kb upstream of the transcription start site and found several candidates. However, none of these sites enhanced basal promoter activity in response to WY-14643 treatment in Caco-2 cells. The functional PPRE and/or some other regulatory region related to PPARα may be located in more distal regions or intronic regions. Taken together, these results indicate that PPARα plays critical roles in fasting-induced intestinal PEPT1 expression [37].

## 2.2. PEPT2 (SLC15A2)

### 2.2.1. General function and pharmacokinetic roles

PEPT2 (SLC15A2), mainly expressed in the kidney, shows about 50% amino acid identity with PEPT1, and has higher affinity for substrates than PEPT1 [8]. PEPT2 is also expressed in a variety of tissues such as lung, mammary gland and choroids plexus [8], and recent study revealed that PEPT2 function as an uptake system for peptides fragments from neuropeptide metabolism in the enteric nervous system [38]. This transporter mediates the renal reabsorption of di- and tripeptides and peptide-like drugs through glomerular filtration. Pept2$^{-/-}$ mice were viable and without obvious abnormalities of the kidney [39,40], and detailed *in vivo* analyses using these mice demonstrated that Pept2 is the predominant oligopeptide transporter in the kidney [41]. When Pept2$^{-/-}$ mice were fed diets of different protein contents, Pept2$^{-/-}$ mice adapted food intake to dietary protein content with higher consumption rates on low protein and reduced food intake rates on the high-protein diet [42].

### 2.2.2. Regulation of PEPT2

Little data is available on the regulation of PEPT2 compared with PEPT1. Using a cell culture model, it was found that Pept2 was regulated by intracellular Ca [43] and epidermal growth factor [44]. Hypothyroidism [45] and thyroidectomy [46] of rats resulted in an increased level of renal PEPT2 expression, suggesting that amino acid homeostasis and drug pharmacokinetics are regulated in states of altered thyroid function. Using 5/6 nephrectomized rats, we found that the renal expression of Pept2, not Pept1, was selectively up-regulated 2 weeks after surgery [47], but levels of both Pept1 and Pept2 were markedly decreased 16 weeks post-surgery [48]. As described above, rat intestinal Pept1 expression showed a

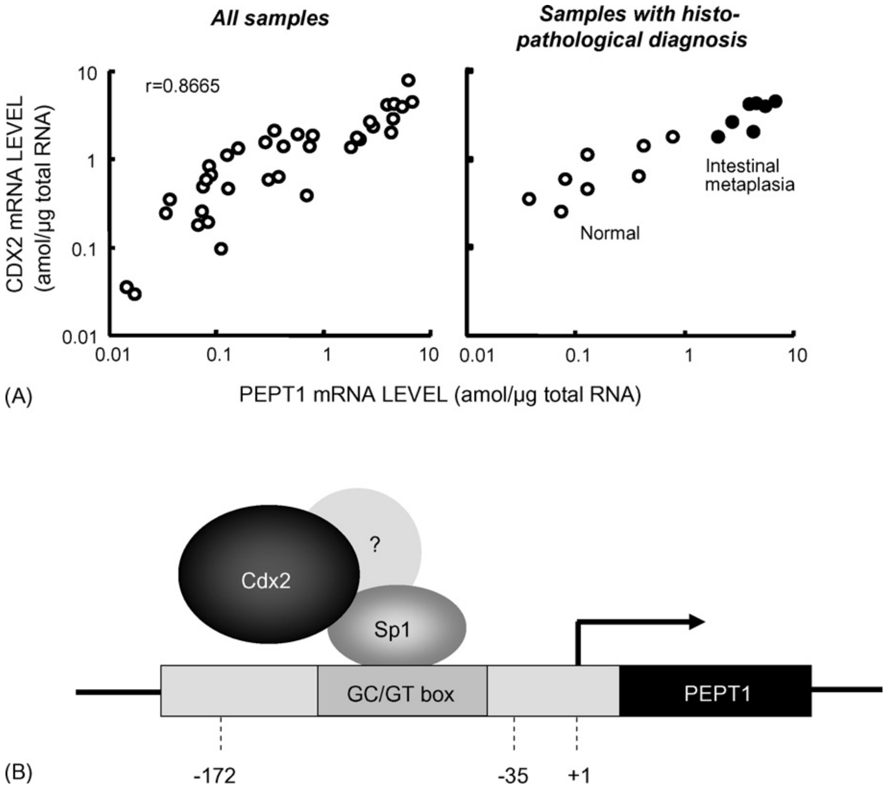

**Fig. 2 – Transcriptional regulation of intestinal PEPT1. (A) Correlation between PEPT1 and CDX2 mRNA levels in human gastric tissue samples. The mRNA levels of PEPT1 and CDX2 were quantified with the real-time PCR method in the gastric mucosal samples. Some of these tissue samples were examined by a pathologist who made a diagnosis of intestinal metaplasia. All samples were plotted (left panel). The samples examined by the pathologist were plotted (right panel). Open and closed symbols indicate the normal samples and the samples proved to be case of intestinal metaplasia, respectively [36]. (B) PEPT1 promoter activity is regulated by Cdx2 and Sp1. A reporter assay, immunoprecipitation assay, and chromatin immunoprecipitation assay demonstrated that Cdx2 plays a key role in the transcriptional regulation of the intestine-specific expression of PEPT1 through interaction with Sp1 [35,36].**

diurnal rhythm, but renal Pept2 and renal Pept1 expression did not [22]. These findings suggest that the regulatory mechanisms for peptide transporters differ between isoforms and tissues (intestine and kidney).

### 2.2.3. *Transcriptional regulatory mechanisms of PEPT2*

There is little information available about the transcriptional regulatory mechanisms of PEPT2 except for one report [49]. The mouse *Pept2* gene possesses a TATA-less promoter, and its core promoter was located between 432 and 286 bp upstream from the translation start site.

## 2.3. *Organic ion transporters (OCT/OCTN/OAT)*

### 2.3.1. *General function and pharmacokinetic roles*

The organic ion transporter family (SLC22A) consists of organic cation transporters (OCTs), zwitterion/cation transporters (OCTNs) and organic anion transporters (OATs) [50]. This family plays important roles in the renal secretion and hepatic uptake of various compounds including drugs, toxins and endogenous metabolites (OCTs and OATs) [51,52], and in the intestinal and renal absorption of carnitine (OCTN2) [53]. Mutations of transporters for the SLC22 family are responsible for specific diseases such as "primary systemic carnitine deficiency" (OCTN2) [54], and are linked with rheumatoid arthritis (OCTN1) [55] and Crohn's disease (OCTN2) [56].

### 2.3.2. *Regulation of organic ion transporters*

Not only the functional characteristics but also the regulational aspects of OCTs have been investigated. Ciarimboli and Schlatter [57] recently summarized how the transport of organic cations is regulated in the short and long term. The short-term regulation is mainly caused by the phosphorylation/dephosphorylation of OCT proteins, which induced a change in substrate affinity or membrane trafficking [57]. In the long-term, the regulation of development [58], hormones [59], chronic renal failure [60], and diabetes [61] were demonstrated to affect the expression of Octs in the kidney. The sex hormonal regulation of rat Oct2 in the kidney has been extensively investigated. Namely, the expression level of rat Oct2, but not Oct1 or Oct3, in the kidney was much higher in males than females [62]. The treatment of male and female rats with testosterone significantly increased rat Oct2 expression in the kidney [59,60], suggesting that testosterone plays a pivotal role in the transcriptional regulation of the rat *Oct2* gene. This gender difference in renal Oct2 expression was also observed in rabbits [63] and mice [64], but not clear in humans. In the liver, it was reported that rat hepatic Oct1, not renal Oct1, is down-regulated by obstructive cholestasis [65]. Mouse hepatic Oct1 is demonstrated to be regulated by peroxisome proliferator agonist receptor-$\alpha$ and -$\gamma$ [66].

The regulation of OATs, in addition to OCTs, has been well studied. Terlouw et al. [67] have summarized the regulation of renal organic anion transporters under various conditions. Using isolated proximal tubules of rabbit kidney and renal cultured cell lines such as OK, the regulation of Oats by various protein kinases and the signal molecules have been investigated, mainly focusing on the short-term regulation [68–70]. It was demonstrated that Oat1 and/or Oat3 in the rat kidney were regulated by development [58], hyperuricemia [71], bilateral ureteral obstruction [72] and acute biliary obstruction [73]. Human OAT1 is also down-regulated by renal failure [74].

### 2.3.3. *Transcriptional regulatory mechanisms of organic ion transporters*

As described above, there are various reports about the regulation of OCTs and OATs, but most reports do not address the molecular mechanisms behind the alteration of mRNA expression. To understand the role of testosterone in the gender differences in the expression of renal Oct2 in rats, we performed functional reporter analyses of rat *Oct1–3* genes coexpressed with the androgen receptor [75]. It was found that a physiological concentration of testosterone ($\sim$10 nM) specifically enhanced transcription of the *Oct2* gene, but not of the *Oct1* or *Oct3* gene, and that androgen response element (ARE)-1 ($-2975$ to $-2960$) and ARE-3 ($-1340$ to $-1325$) in the rat Oct2 promoter region would play important roles in the enhanced transcription of *Oct2*.

Among the OCT and OAT families, OAT3 showed the most abundant expression in the human kidney [76], and plays important roles in the renal secretion of anionic cephalosporins [74,77,78]. Recently, Kikuchi et al. [79] and we [80] characterized the basal transcriptional activity of the human *OAT3* gene. The minimal promoter region of human *OAT3* was identified to be located approximately 300 bp upstream of the transcription start site, where there are a canonical TATA box ($-32$ to $-27$), a hepatocyte nuclear factor-1 (HNF-1)-binding site ($-65$ to $-53$), and a cAMP responsive element (CRE) ($-87$ to $-80$). Kikuchi et al. [79] demonstrated that HNF-1$\alpha$/1$\beta$ were involved in the basal expression of human OAT3 through the interaction of the HNF-1-binding site using intestinal Caco-2 and hepatic HepG2 cells. On the other hand, using the renal proximal tubular cell line OK, we demonstrated that CRE-binding protein (CREB)-1 and activating transcription factor (ATF)-1 were responsible for basal promoter activity by binding to CRE [80]. Furthermore, the activity of the OAT3 promoter was increased through the phosphorylation of CREB-1 and ATF-1 by treatment with 8-bromoadenosine 3′,5′-cyclic monophosphate, a protein kinase A (PKA) activator [80]. These findings indicate that HNF-1$\alpha$/1$\beta$, CREB-1, and ATF-1 function as constitutive regulators of the human OAT3 gene, and that PKA further stimulated OAT3 gene expression by the phosphorylation of CREB-1 and ATF-1 (Fig. 3).

In contrast to OAT3, other SLC22A members such as OCT1 and OAT2 were primarily expressed in the liver. Although the basal transcriptional mechanism of neither transporter has been clarified, liver-specific transcriptional mechanisms were recently demonstrated. Namely, the human *OCT1* [81] and human *OAT2* [82] genes in the liver are activated by a liver-enriched homodimeric nuclear receptor, hepatocyte nuclear factor-4$\alpha$ (HNF-4$\alpha$) and suppressed by a bile acid-inducible transcriptional repressor, a small heterodimer partner. The hepatic uptake of OCT1 and OAT2 substrates may be decreased in individuals with diseases associated with elevated intracellular levels of bile acids.

Pharmacogenomic analyses have also found the transcription factors involved in the gene expression of OCTN1 and OCTN2. Namely, single nucleotide polymorphisms (SNP)s in the promoter region (regulatory SNPs; rSNPs) of both transporters are suggested to be associated with chronic inflammatory diseases, and promoter regions including rSNPs were demonstrated to be functional binding sites of transcription factors, RUNX1 for OCTN1 [55] and heat-shock transcription factor for OCTN2 [56].

## 3. Expression profile of human intestinal and renal drug transporters

The development of quantitative real-time PCR techniques has meant that expression levels of drug transporters can be quantitatively determined using a very small amount of tissue sample. Recently, based on these techniques, expression profiles of various genes including those for human drug transporters have been determined using surplus tissue specimens collected during surgery or biopsy.

### 3.1. *Expression profile of intestinal drug transporters*

For SLC drug transporters, the expression profiles of PEPT1 and organic ion transporters along the human digestive tract were determined using normal portions of mucosal samples from cancer patients treated surgically [83]. PEPT1 mRNA was highly expressed in the small intestine (duodenum > jejunum > ileum) compared to other tissues, and some patients showed a significant level of expression in the stomach. The expressional pattern of PEPT1 in the stomach and histological diagnosis indicated that gastric PEPT1 originated from the intestinal metaplasia. This ectopic expression of PEPT1 is induced by the intestine-specific transcription factor CDX2 as described in Section 2.1.3. There was little expression of organic ion transporters except for OCTN2, which showed similar levels to PEPT1 [83]. Using *Oct1* knockout mice, it was demonstrated that Oct1 plays important roles in the intestinal excretion of cationic drugs [84]. However, in the human intestine, there is little expression of OCT1.

Taipalensuu et al. [85] determined mRNA levels of 10 ABC drug transporters in the human jejunum, and found that multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein (BCRP) are more extensively expressed than multidrug resistance protein 1 (MDR1). In contrast, Zimmermann et al. [86] demonstrated that MRP3 among MRP1-5 and MDR1 was the most abundantly expressed in the duodenum and all segments of the colon, and that MDR1 showed the highest level of expression in the terminal ileum. The differences between these two reports may be due to the segment of the human intestine sampled. For the distribution of ABC transporters in the intestine, it was reported that MDR1 mRNA [83] and Pgp [87] levels gradually increased from the duodenum to ileum. MRP2 showed significant expression in the small intestine but hardly any expression in colonic segments [86]. BCRP mRNA expression was maximal in the duodenum and decreased continuously down to the rectum [88]. This expression profile contrasts to that of MDR1 mRNA, suggesting that BCRP and MDR1 complement the transport function of each other along the digestive tract as the substrate specificity of the two transporters overlaps.

### 3.2. *Expression profile of renal drug transporters*

We also reported expression levels of organic ion transporters in normal sections of renal tissue obtained from seven surgically nephrectomized patients with renal cell carcinoma

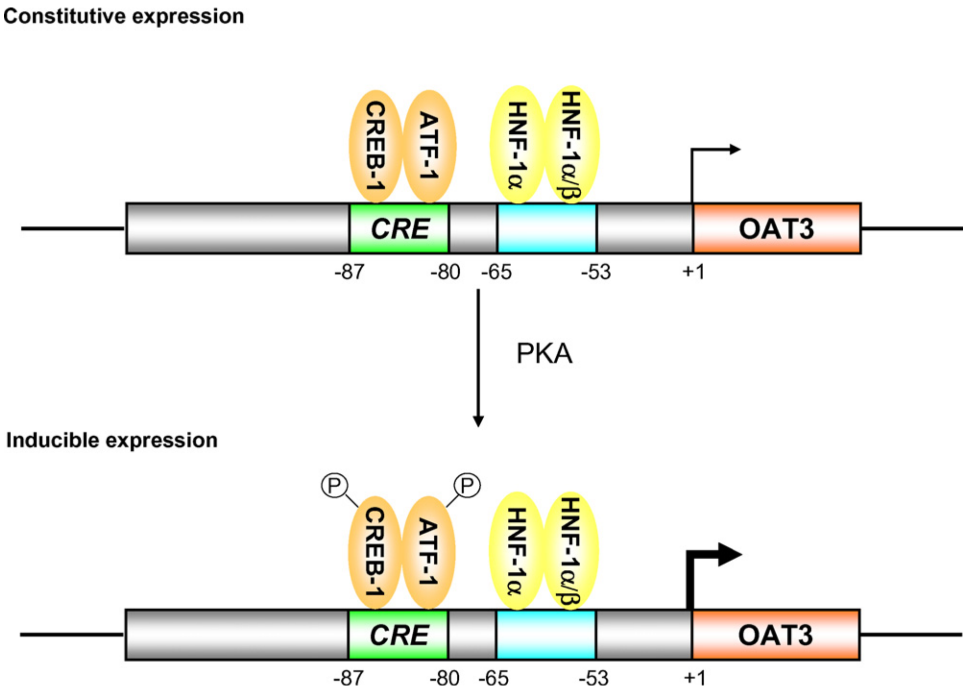

**Fig. 3 – Schematic model of transcriptional regulation of the human OAT3 gene. CREB-1 and ATF-1 bind to CRE, and HNF1α/β bind to the HNF1-binding site, and these transcription factors activate the transcription of the OAT3 gene (constitutive expression) [79,80]. PKA further stimulates the transcriptional activity of the OAT3 gene through phosphorylation of both CREB-1 and ATF-1 (inducible expression) [80].**

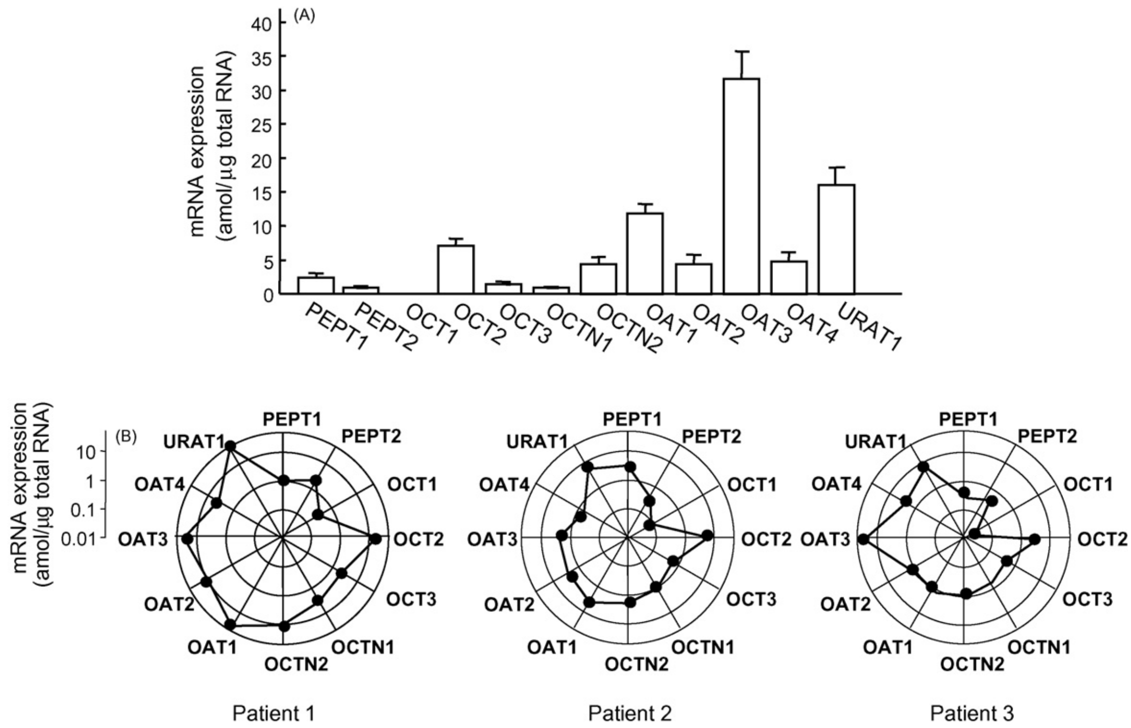

**Fig. 4 – Expression profiles of organic ion transporters and peptide transporters in the human kidney cortex. (A) Average expression levels. Each transporter's expression level was determined by the real-time PCR method using a portion of normal human kidney cortex from nephrectomized patients ($N = 82$). (B) Individual patients' expression profiles (typical patients). Patient 1 shows high levels of OAT1-4 and URAT1, whereas patient 2 exhibits low levels of these transporters, although the expression level of OCT2 was comparable between the two. Patient 3 shows a high level of OAT3, but low levels of other transporters.**

in 2002 [76]. Since then, the number of patients has increased to 82, and PEPT1, PEPT2, and an urate transporter (URAT1) have been included in current analyses (Fig. 4A). The mRNA expression level of OAT3 was the highest among the OAT family, followed by that of URAT1, OAT1. The OCT2 mRNA level was the highest in the OCT family, and OCT1 mRNA was rarely expressed. Among the OCTN family, OCTN2 showed the highest expression, but its level was lower than those of OAT1, OAT3, and OCT2. The expression levels of PEPT1 and PEPT2 were not so high as compared to levels of organic ion transporters, and PEPT1 expression was higher than PEPT2 expression. Fig. 4B shows the expression profile of drug transporters for typical individual patients. The expression pattern of drug transporters varied among patients. For example, patient 1 showed high levels of OAT1-4 and URAT1, whereas patient 2 exhibited low levels of these transporters. Regarding the expression of peptide transporters, PEPT1 < PEPT2 for patient 1, PEPT1 > PEPT2 for patient 2, and PEPT1 ≈ PEPT2 for patient 3. Patient 3 showed a high level of OAT3, but low expression levels of other transporters.

## 4. Conclusions and future perspectives

In these research updates, we addressed recent advances in the study of the gene regulation and expression of drug transporters in the intestine and kidney. Among drug transporters, MDR1 has been well studied in terms of its gene regulation, and many transcription factors for *MDR1* gene have been identified [3,4]. On the other hand, the history of gene regulation for intestinal and renal drug transporters is very short. For example, the transcription factors Sp1, Cdx2 and PPAR$\alpha$ were just proven to be responsible for the expression and regulation of intestinal PEPT1, but other transcriptional regulatory mechanisms triggered by various stimuli have not been clarified yet. Information about transcription factors specific to the kidney, especially the proximal tubular cells, is also limited, perhaps due to the absence of an appropriate model of human renal proximal tubular cell lines. Some drug transporters show species differences in renal expression. For example, rat Oct1, but not human OCT1, is expressed in the kidney. The identification of kidney-specific transcription factors should help us to understand not only the molecular mechanisms of such species differences but also the gene regulation of renal drug transporters in various physiological and pathophysiological conditions.

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