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Emerging Roles of Uremic Toxins and Inflammatory Cytokines in the Alteration of Hepatic Drug Disposition in Patients with Kidney Dysfunction

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ABSTRACT

Patients with kidney dysfunction exhibit distinct pharmacokinetic profiles compared to those with normal kidney function. Hence, it is desirable to monitor the drug efficacy and toxicity caused by fluctuations in plasma drug concentrations associated with kidney dysfunction. Recently, pharmacokinetic information of drugs excreted mainly through the urine of patients with kidney dysfunction has been reported via drug-labeling information. Pharmacokinetic changes in drugs mainly eliminated by the liver cannot be overlooked as drug metabolism and/or transport activity in the liver may also be altered in patients with kidney dysfunction; however, the underlying mechanisms remain unclear. To plan an appropriate dosage regimen, it is necessary to clarify the underlying processes of functional changes in pharmacokinetic proteins. In recent years, uremic toxins have been shown to reduce the activity and/or expression of renal and hepatic transporters. This inhibitory effect has been reported to be time-dependent. In addition, inflammatory cytokines, such as interleukin-6, released from immune cells activated by uremic toxins and/or kidney injury can reduce the expression levels of drug-metabolizing enzymes and transporters in human hepatocytes. In this mini-review, we have summarized the renal and hepatic pharmacokinetic changes as well as the potential underlying mechanisms in kidney dysfunction, such as the chronic kidney disease and acute kidney injury.

SIGNIFICANCE STATEMENT

Patients with kidney dysfunction exhibit distinct pharmacokinetic profiles compared to those with normal kidney function. Increased plasma concentrations of uremic toxins and inflammatory cytokines during kidney disease may potentially affect the activities and/or expression levels of drug-metabolizing enzymes and transporters in the liver and kidneys.

Introduction

Chronic kidney disease (CKD) is a growing public health problem, affecting approximately 10% of the global population (Collaboration, 2020). Kidneys play an essential role in homeostasis via the production of erythropoietin and vitamin D3, degradation of ammonia, and urinary excretion of xenobiotic compounds, including therapeutic agents. Therefore, changes in kidney function in patients with CKD may affect not only patient prognosis but also the dosage regimen in pharmacotherapy. Glomerular filtration rate (GFR) is generally used as an indicator of kidney function, which is suggested to correlate with renal drug clearance, including active secretion and reabsorption. Interestingly, recent studies have revealed that patients with kidney disease exhibit changes in renal active transport and hepatic drug metabolism and transport compared to those without organ damage (Yoshida et al., 2016; Miners et al., 2017; Tan et al., 2018; Fujita et al., 2019). As an opportunity to focus on pharmacokinetic changes in patients with kidney disease, the US Food and Drug Administration (FDA) assessed the pharmacokinetics in patients with impaired kidney function using approximately 94 small-molecule drugs approved over a 5-year duration (2003–2007) (Zhang et al., 2009). The survey results indicated that the pharmacokinetics of drugs that are predominantly eliminated by nonrenal processes can be affected by kidney disease. Evaluation of pharmacokinetics in patients with kidney disease is now a necessary requirement for drug development (https://www.fda.gov/media/78573/download), and such drug-labeling information can be obtained from pharmaceutical companies. However, the underlying mechanisms of these pharmacokinetic changes have not yet been elucidated. Functional changes in drug-metabolizing enzymes and transporters have been widely explained by the inhibitory effects of uremic toxins (Table 1), such as indoxyl sulfate, and inflammatory

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ABBREVIATIONS: AhR, arylhydrocarbon receptor; AKI, acute kidney injury; AUC, under the blood concentration curve; $AUC_{unbound}$, under the blood concentration curve for unbound drug; CKD, chronic kidney disease; CL_{UintH}, hepatic intrinsic clearance; FDA, Food and Drug Administration; fp, unbound fraction; GFR, glomerular filtration rate; IL, interleukin; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P450, cytochrome P450; UGT, UDP-glucuronosyltransferase.

TABLE 1

Effects of uremic toxins on renal and hepatic transporters

Uremic toxins	Total C_{max}	Unbound C_{max}	OAT1 IC_{50}	OAT3 IC_{50}	OATP1B1 IC_{50}
2-Nonenal[a]	727 μM (Duranton et al., 2012)	0.7 μM (Hsueh et al., 2016)	IC_{50}: 19 μM for 6-CF uptake (Hsueh et al., 2016)	60 μM for 6-CF uptake (Hsueh et al., 2016)	N/A
4-Decenal[a]	650 μM (Duranton et al., 2012)	0.7 μM (Hsueh et al., 2016)	IC_{50}: 38 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 53 μM for 6-CF uptake (Hsueh et al., 2016)	N/A
3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF)	81.1 μM (Fujita et al., 2014)	N/A	IC_{50}: 79 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 28 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 158 μM for SN38 uptake (Fujita et al., 2014)
Creatinine	N/A	1.2 mM (Hsueh et al., 2016)	IC_{50}: 14 mM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 40 mM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: > 10 mM for E_1 3S uptake (Sato et al., 2014)
Hippuric acid	398 μM (Duranton et al., 2012)	231 (Duranton et al., 2012)	IC_{50}: 31 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 41 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 6.71 mM for SN38 uptake (Fujita et al., 2014)
6-Hydroxyindole	0.227 μM (Masuo et al., 2020)	N/A	N/A	N/A	IC_{50}: 16.7 (coincubation) IC_{50}: 12.1 (pre- and coincubation) (Masuo et al., 2020)
Indole 3-acetic acid	11.6 μM (Duranton et al., 2012)	2.11 (Duranton et al., 2012)	IC_{50}: 140 μM for 6-CF uptake (Hsueh et al., 2016)	38% inhibition for 6-CF uptake by 250 μM (Hsueh et al., 2016)	>3 mM for SN38 uptake (Fujita et al., 2014) 194 μM for SN38 uptake (Katsube et al., 2017)
Indoxyl sulfate	109 μM (Duranton et al., 2012)	15.1 μM (Duranton et al., 2012)	IC_{50}: 110 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 270 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 2.29 mM for SN38 uptake (Fujita et al., 2014)
Indoxyl-β-D-glucuronide[a]	9.49 μM (Duranton et al., 2012)	N/A	N/A	IC_{50}: 670 μM for 6-CF uptake (Hsueh et al., 2016)	N/A
Kynurenic acid[a]	0.799 μM (Duranton et al., 2012)	N/A	IC_{50}: 34 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 23 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 180 μM for $E_1$3S uptake (Sato et al., 2014)
N2,N2-Dimethylguanosine	N/A	1.3 μM (Hsueh et al., 2016)	no inhibition for 6-CF uptake by 140 μM (Hsueh et al., 2016)	IC_{50}: 140 μM for 6-CF uptake (Hsueh et al., 2016)	N/A
Nonanal	0.485 μM (Duranton et al., 2012)	0.5 μM (Hsueh et al., 2016)	IC_{50}: 22 μM for 6-CF uptake (Hsueh et al., 2016)	42% inhibition for 6-CF uptake by 50 μM (Hsueh et al., 2016)	N/A
p-Cresol	N/A	N/A	N/A	N/A	IC_{50}: 4.6 mM for $E_1$3S uptake (Sato et al., 2014)
p-Cresyl sulfate	N/A	211 μM (Hsueh et al., 2016)	IC_{50}: 210 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 200 μM for 6-CF uptake (Hsueh et al., 2016)	47% inhibition by 1 mM (Masuo et al., 2020)
Phenol	59 μM (Hsueh et al., 2016)	N/A	31% Inhibition for 6-CF uptake by 6.4 mM (Hsueh et al., 2016)	IC_{50}: 3.1 mM for 6-CF uptake (Hsueh et al., 2016)	N/A
Phenylacetic acid	N/A	3.5 mM (Hsueh et al., 2016)	IC_{50}: 540 μM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 1.3 mM for 6-CF uptake (Hsueh et al., 2016)	N/A
Uric acid	383 μM (Duranton et al., 2012)	500 μM (Hsueh et al., 2016)	IC_{50}: 2.2 mM for 6-CF uptake (Hsueh et al., 2016)	IC_{50}: 670 μM for 6-CF uptake (Hsueh et al., 2016)	N/A

6-CF, 6-carboxyfluorescein; E3S, estrone-3-sulfate; N/A, not available.
[a]Highest concentrations of C_{max} and unbound C_{max} for uremic toxins.

cytokines have been suggested to affect their expression and function (Table 2). Although the pharmacokinetic changes during kidney disease have been mostly reported in patients with CKD, the extrarenal inflammatory reaction is characteristic of acute kidney injury (AKI). The mini-review have summarized the renal and hepatic pharmacokinetic changes as well as the potential underlying mechanisms in kidney diseases such as CKD and AKI.

Renal Pharmacokinetics in Patients with Kidney Disease

Renal clearance of a drug is affected by the binding to plasma proteins such as albumin and α1-acid glycoprotein, and their concentrations fluctuate due to kidney dysfunction in disorders such as CKD and nephrotic syndrome. Sayama et al. (2014) compared the pharmacokinetic changes in 151 drugs in patients with moderate (GFR: 30–59 mL/min per 1.73 m^2) and severe (GFR: 15–29 mL/min per 1.73 m^2) chronic kidney disease to those in healthy controls using a literature survey. The unbound fraction (fp) of drugs with acidic and neutral charges tended to increase as the degree of kidney damage increased, leading to an increase in renal clearance. On the other hand, a decrease in renal clearance for drugs undergoing either secretion or reabsorption in the kidney tubules was observed with a reduction of the GFR. This result suggests that the renal excretion of drugs is reduced due to the func-

tional decline of the entire nephron associated with kidney injury. In addition, active renal transport mediated by organic anion transporter (OAT)-1 and OAT3, which are expressed on the basolateral membrane of the proximal tubular epithelial cells, has been reported to be reduced in patients with CKD (Chapron et al., 2017; Pradhan et al., 2019; Takita et al., 2020; Tan et al., 2022).

Several reports have proposed an underlying mechanism for the decline in renal excretion capacity via inhibition of renal transporters (Table 1). During CKD, the plasma concentrations of cytotoxic uremic toxins increase (Duranton et al., 2012), which inhibits transporter-mediated renal tubular secretion mediated by OATs and organic cation transporters (OCTs). Hsueh et al. (2016) evaluated the efficacies of 72 uremic toxins in inhibiting OAT1 and OAT3 expression. They reported that 12 and 13 uremic toxins inhibited OAT1- and OAT3- mediated transport, respectively, at clinically relevant unbound plasma concentrations. Among these toxins, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, hippuric acid, indoxyl sulfate, *p*-cresyl sulfate, phenylacetic acid, and uric acid reduced OAT1- and/or OAT3-mediated substrate uptake at clinically relevant unbound concentrations. Moreover, renal clearance of various kinds of OAT or OCT substrate drugs, such as famotidine, has been reported to be reduced more than the reduction in GFR (decrease in the secretory process) in patients with stage 4 CKD compared with that in healthy control patients. OAT1 and OAT3 are suggested to be involved in the urinary excretion of uremic toxins via their uptake into cells (Deguchi et al., 2004). These results can be explained by the fact that increased levels of uremic toxins in patients with CKD reduce their renal excretion and that of other drugs via transporter inhibition (Fig. 1). In contrast, the renal secretion process involves not only uptake by basolateral membranes but also excretion into tubular ducts across the apical membranes of tubular epithelial cells, with multidrug resistance proteins 2 and 4 for organic anionic drugs and solute carrier family 47 members 1 and 2 (*SLC47A1/2*, also known as MATE1/2K) for organic cationic compounds playing important roles in this process. However, detailed information on changes in the expression levels of these drug transporters in patients with kidney dysfunction is lacking. Therefore, further studies are required to measure the protein expression levels in patients with kidney disease.

Changes in Drug Disposition in Extrarenal Organs During Kidney Disease

Alteration in the plasma unbound fraction is a hepatic pharmacokinetic change caused by kidney dysfunction. Reynolds et al. (1976) reported that the plasma concentrations of phenytoin in epileptic patients with CKD were lower than those in patients with normal kidney function; the unbound fraction was 2.1-fold higher in patients with kidney dysfunction, and the unbound concentration was comparable between them. When hepatically eliminated drugs are orally administered, the area under the blood concentration curve (AUC) is generally inversely proportional to the product of fp and hepatic intrinsic clearance (CL_{UintH} If there is no change in Fa•Fg (product of fraction of absorption and intestinal availability) and CL_{UintH}, the AUC decreases depending on the fp value, whereas the AUC for unbound drug ($AUC_{unbound}$) related to the efficacy and side effects of the drug is not affected. Therefore, if the dose is increased based on the low blood concentration in patients, $AUC_{unbound}$ may become higher in patients with kidney dysfunction than in those with normal kidney function. Fujita et al. (2011) reported severe myelosuppression and increased levels of the active metabolite SN-38 in patients with severe kidney failure (creatinine clearance ≤20 ml/min) who were receiving hemodialysis and the anticancer drug irinotecan. Pharmacokinetic analysis revealed a 2.6-fold increase in the fp value of SN-38 and a 4.4-fold increase in its $AUC_{unbound}$ in patients (Fujita et al., 2016). The major elimination pathway of SN38 is glucuronidation via UDP-glucuronosyltransferase (UGT)-1A1 in the liver, and this increase may be explained by a reduction in hepatic uptake via organic anion-transporting polypeptide (OATP)-1Bs rather than the metabolic processes in the liver (Fujita et al., 2014). In this case, CL_{UintH} for SN38 may be largely decreased due to kidney failure, resulting in a significant increase in $AUC_{unbound}$, but the change in AUC by a 1.7-fold increase is masked by the increase in the fp value. Although only the total drug concentration is generally measured in clinical situations, alterations in $AUC_{unbound}$ may be overlooked if CL_{UintH} and fp are inversely correlated.

Changes in hepatic clearance of various drugs have been investigated in CKD patients. Sayama et al. (2014) searched for changes in CL_{UintH} for 151 drugs and found that CL_{UintH} values of cytochrome P450 (P450) and UGT substrate drugs were decreased by 30%–40% in CKD patients compared with those in healthy subjects. They found no clear differences between moderate (GFR: 30 to 59 mL/min per 1.73 m^2) and severe (GFR: 15 to 29 mL/min per 1.73 m^2) kidney failure. Moreover, Miners et al. (2017) revealed that the elimination of most substrate drugs for CYP1A2, CYP2C9, CYP2C19, and CYP3A4 tended to be reduced in patients with kidney disease compared with that in healthy subjects, whereas that of some drugs was unaffected. Yoshida et al. (2016) and Tan et al. (2018) conducted literature surveys on changes in the pharmacokinetics of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, CYP2D6, and OATP substrate drugs in patients with kidney disease. They found that elimination of substrate drugs for CYP2D6 and OATP1B was generally reduced as kidney function declined. Tan et al. (2019) evaluated the effects of CKD on CYP2C8 and OATP1B levels using substrates of CYP2C8 (rosiglitazone and pioglitazone), OATP1B (pitavastatin), or both proteins (repaglinide) due to the overlap between OATP1B and CYP2C8 substrates in their previous survey. OATP1B activity was estimated to decrease by 60% in severe CKD, whereas CYP2C8 activity showed no significant change. Sun et al. (2010) measured the blood concentration profiles and fp values of intravenously and orally administered erythromycin, which is a substrate of both OATP1B1 and CYP3A4, in healthy subjects and patients with kidney failure receiving hemodialysis and reported reduced hepatic clearance of unbound erythromycin ($CL_{unbound}$) by 31%, whereas Yoshida et al. (2016) reported that the effect of kidney dysfunction on $CL_{unbound}$ for CYP3A4 substrate drugs was variable. Since the pharmacokinetics of erythromycin correlate with OATP1B1 activity, which was supported by the observation that erythromycin metabolism declined in the patients with the OATP1B1 c.521C substitution (Lancaster et al., 2012), OATP1B1 function may be affected by kidney dysfunction. Furthermore, one notable observation reported was that oral clearance of OATP1B1 substrate fexofenadine, which is minimally metabolized and mainly eliminated from bile, was reduced by 63% in patients with kidney failure receiving hemodialysis compared with the healthy control subjects (Nolin et al., 2009). The reduced elimination process of fexofenadine in patients with kidney failure may further reinforce the hypothesis that OATP1B1 activity in the liver is decreased in CKD patients. These analyses are consistent with reports that the mRNA expression levels of OATP1B1 in human hepatocytes are decreased in the presence of plasma from patients with kidney failure (Fujita et al., 2014; Masuo et al., 2020). In addition to the typical substrates of drug-metabolizing enzymes and transporters, Fujita et al. (2019) summarized the changes in pharmacokinetics and clinical responses of 10 cytotoxic anticancer drugs and 15 tyrosine kinase inhibitors. In this report, an increase in systemic exposure to cyclophosphamide, eribulin, paclitaxel, afatinib, and vandetanib was observed in patients with kidney dysfunction compared to those with normal kidney function. Among of them, both paclitaxel and vandetanib are known as OATP1B1 substrates (Svoboda et al., 2011; Koide et al., 2018). Although there is currently no clinical

TABLE 2

Effects of inflammatory cytokines on the expression levels of drug-metabolizing enzymes and transporters in primary cultured human hepatocytes

	IL-1β	IL-2	IL-6	IFNγ	TGFβ	TNFα
NTCP	↓ (mRNA) (Le Vee et al., 2008) ↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA, protein) (Le Vee et al., 2009) ↓ (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		↓ (mRNA, protein) (Le Vee et al., 2009)
OAT2	→ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Le Vee et al., 2009) → (mRNA) (Nguyen et al., 2015)	→ (mRNA) (Le Vee et al., 2011)		↓ (mRNA) (Le Vee et al., 2009)
OATP1B1	↓ (mRNA, protein) (Le Vee et al., 2008) ↓ (mRNA, protein) (Le Vee et al., 2009) ↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA, protein) (Le Vee et al., 2009) → (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		↓ (mRNA, protein) (Le Vee et al., 2009)
OATP1B3	↓ (mRNA) (Le Vee et al., 2008) ↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Le Vee et al., 2009) ↓ (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		↓ (mRNA) (Le Vee et al., 2009)
OATP2B1	↓ (mRNA) (Le Vee et al., 2008) ↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Le Vee et al., 2009) → (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		↓ (mRNA) (Le Vee et al., 2009)
OCT1	↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Le Vee et al., 2009) ↓ (mRNA) (Nguyen et al., 2015)	→ (mRNA) (Le Vee et al., 2011)		↓ (mRNA) (Le Vee et al., 2009)
MRP2	↓ (mRNA) (Le Vee et al., 2008) ↓ (mRNA, protein) (Diao et al., 2010)		↓ (mRNA, protein) (Le Vee et al., 2009) ↓ (mRNA, protein) (Diao et al., 2010) → (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		→ (mRNA) (Le Vee et al., 2009) ↓ (mRNA, protein) (Diao et al., 2010)
MRP3	↓ (mRNA) (Le Vee et al., 2008) → (mRNA) (Nguyen et al., 2015)		↓ (mRNA), ↑ (protein) (Le Vee et al., 2009) → (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		→ (mRNA), ↑ (protein) (Le Vee et al., 2009)
MRP4	↓ (mRNA) (Le Vee et al., 2008)		↓ (mRNA) (Le Vee et al., 2009)			→ (mRNA) (Le Vee et al., 2009)
BCRP	↓ (mRNA) (Le Vee et al., 2008)		↓ (mRNA, protein) (Le Vee et al., 2009)	↓ (mRNA) (Le Vee et al., 2011)		→ (mRNA), ↑ (protein) (Le Vee et al., 2009)
BSEP	↓ (mRNA) (Le Vee et al., 2008) ↓ (mRNA), ↑ (protein) (Diao et al., 2010) ↓ (mRNA) (Nguyen et al., 2015)		→ (mRNA) (Le Vee et al., 2009) ↓ (mRNA), ↑ (protein) (Diao et al., 2010) ↓ (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		↓ (mRNA) (Le Vee et al., 2009) ↓ (mRNA), → (protein) (Diao et al., 2010)
P-gp	→ (mRNA) (Nguyen et al., 2015)		↓ (mRNA), → (protein) (Le Vee et al., 2009) → (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Le Vee et al., 2011)		→ (mRNA, protein) (Le Vee et al., 2009)
CYP1A2	↓ (mRNA, protein) (Muntané-Relat et al., 1995)	↓ (protein) (Elkahwaji et al., 1999)	↓ (mRNA, protein) (Muntané-Relat et al., 1995)			↓ (mRNA, protein) (Muntané-Relat et al., 1995)

TABLE 2 *continued*

	IL-1β	IL-2	IL-6	IFNγ	TGFβ	TNFα
	↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Dickmann et al., 2011) ↓ (mRNA) (Nguyen et al., 2015)			
CYP2A6			→ (mRNA) (Kleine et al., 2008)			
CYP2B6	→ (mRNA), ↓ (protein) (Aitken and Morgan, 2007) → (mRNA) (Nguyen et al., 2015)		↓ (mRNA, protein) (Aitken and Morgan, 2007) ↓ (mRNA) (Dickmann et al., 2011) ↓ (mRNA) (Nguyen et al., 2015)	↓ (mRNA), ↓/→ (protein) (Aitken and Morgan, 2007)	↑ (mRNA), ↓ (protein) (Aitken and Morgan, 2007)	→ (mRNA), ↓ (protein) (Aitken and Morgan, 2007)
CYP2C8	↓ (mRNA) (Aitken and Morgan, 2007) ↓ (mRNA) (Nguyen et al., 2015)	↓ (protein as CYP2C) (Elkahwaji et al., 1999)	↓ (mRNA) (Kleine et al., 2008) ↓ (mRNA) (Aitken and Morgan, 2007) ↓ (mRNA) (Dickmann et al., 2011) ↓ (mRNA) (Nguyen et al., 2015)	↓ (mRNA) (Aitken and Morgan, 2007)	↓ (mRNA) (Aitken and Morgan, 2007)	↓ (mRNA) (Aitken and Morgan, 2007)
CYP2C9	→ (mRNA), ↓/→ (protein) (Aitken and Morgan, 2007) → (mRNA) (Nguyen et al., 2015)	↓ (protein as CYP2C) (Elkahwaji et al., 1999)	↓ (mRNA, protein) (Aitken and Morgan, 2007) ↓ (mRNA) (Nguyen et al., 2015)	→ (mRNA) (Aitken and Morgan, 2007)	↓ (mRNA), ↓/→ (protein) (Aitken and Morgan, 2007)	→ (mRNA), ↓ (protein) (Aitken and Morgan, 2007)
CYP2C19	↓ (mRNA) (Aitken and Morgan, 2007)	↓ (protein as CYP2C) (Elkahwaji et al., 1999)	→ (mRNA) (Aitken and Morgan, 2007) ↓ (mRNA) (Dickmann et al., 2011) → (mRNA) (Nguyen et al., 2015)	→ (mRNA) (Aitken and Morgan, 2007)	↓ (mRNA) (Aitken and Morgan, 2007)	→ (mRNA) (Aitken and Morgan, 2007)
CYP2D6	→ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Dickmann et al., 2011) → (mRNA) (Nguyen et al., 2015)			
CYP2E1	→ (mRNA) (Nguyen et al., 2015)	↓ (protein) (Elkahwaji et al., 1999)	→ (mRNA) (Nguyen et al., 2015)			
CYP3A4	↓ (mRNA, protein) (Muntané-Relat et al., 1995) ↓ (mRNA, protein) (Aitken and Morgan, 2007) → (mRNA) (Nguyen et al., 2015)	↓ (protein) (Elkahwaji et al., 1999)	↓ (mRNA, protein) (Muntané-Relat et al., 1995) ↓ (mRNA) (Kleine et al., 2008) ↓ (mRNA, protein) (Aitken and Morgan, 2007) ↓ (mRNA) (Dickmann et al., 2011) ↓ (mRNA) (Nguyen et al., 2015)	↓ (mRNA, protein) (Aitken and Morgan, 2007)	↓ (mRNA, protein) (Aitken and Morgan, 2007)	↓ (mRNA, protein) (Muntané-Relat et al., 1995) ↓ (mRNA, protein) (Aitken and Morgan, 2007)
UGT1A1	↓ (mRNA) (Nguyen et al., 2015)		↓ (mRNA) (Nguyen et al., 2015)			

IFNγ, interferon-γ; P-gp, P-glycoprotein; TGFβ, transforming growth factor-β; TNFα, tumor necrosis factor-α.

report indicating involvement of OATP1B1 in the hepatic disposition of these drugs, it has been reported that Oatp1b2-mediated transport was involved in the uptake of paclitaxel into the murine hepatocytes (Nieuweboer et al., 2014). Tatosian et al. (2021) performed a microdose cocktail study in patients with kidney dysfunction and found an increase in AUC and C_{max} values of dabigatran, an active form of P-glycoprotein substrate dabigatran etexilate, in CKD patients, suggesting a possible reduction in the intestinal efflux activity of this transporter. However, this pharmacokinetic change may also be caused by reduced urinary excretion in CKD patients, which is a major elimination pathway of dabigatran. This result needs to be confirmed by further analyses (Tatosian et al., 2021). On the other hand, several studies investigating the effects of CKD on expression and functional changes of drug-metabolizing enzymes and transporters in the liver using rodent models were reported (Leblond et al., 2000; Leblond et al., 2001; Guévin et al., 2002; Michaud et al., 2006; Naud et al., 2008; Dani et al., 2010). However, these studies showed a pronounced decrease in the expression and function of P450s and transporters, suggesting that there is a species difference in the effect of CKD on these pharmacokinetic proteins in the liver between human and rodents.

Mechanisms Underlying the Functional Changes in Hepatic Proteins During Kidney Disease

The mechanisms involved in decreased hepatic elimination during kidney disease have not yet been fully elucidated. In patients with CKD, there is an increase in the plasma concentrations of uremic toxins, which can potentially inhibit OATP1B1, P450s, and UGTs (Barnes et al., 2014; Fujita et al., 2014; Volpe et al., 2014). Masuo et al. (2020) showed that 6-hydroxyindole, a uremic toxin, had a long-lasting inhibitory effect on OATP1B1. Moreover, 3-indoxyl sulfate can induce mRNA expression of CYP1A2 via the activation of the arylhydrocarbon receptor (AhR) (Schroeder et al., 2010), whereas there has been no report of decreased CYP1A2 activity in patients with kidney disease. Moreover, Santana Machado et al. (2018) reported that indoxyl sulfate increased mRNA and protein expression of P-glycoprotein in human hepatocarcinoma HepG2 cells via activation of AhR and that higher doses of P-glycoprotein substrate cyclosporin A were needed to achieve the efficient blood target concentration in heart or kidney transplant recipients with CKD. Interestingly, the dose escalation of cyclosporin A was associated with increased plasma concentration of indoxyl sulfate. These observations suggest that uremic toxins such as indoxyl sulfate may increase the expression of P-glycoprotein and CYP1A2 via activation of AhR in the liver of CKD patients. In addition to its direct effect on pharmacokinetic proteins, the uremic toxin 3-indoxyl sulfate induces inflammation in endothelial cells (Ito et al., 2010) and promotes proinflammatory macrophage activation (Nakano et al., 2019), resulting in the release of inflammatory cytokines. Experiments using primary cultured hepatocytes have reported that inflammatory cytokines, such as interleukin (IL)-1β, IL-6, interferon-γ, transforming growth factor-β, and tumor necrosis factor-α, reduce the expression levels of P450s in a transcriptional manner (Table 2) (Abdel-Razzak et al., 1993; Muntané-Relat et al., 1995; Aitken and Morgan, 2007). Exposure of hepatic cell line HepaRG cells to IL-6 and lipopolysaccharides has been reported to suppress the mRNA expression of CYP1A2, CYP2B6, and CYP3A4 as well as their metabolic capacities (Rubin et al., 2015). Furthermore, protein expression of CYP2B6 has been reported to be downregulated by nitric oxide signaling in human and rat hepatocytes (Aitken et al., 2008). These cytokines also affect the expression levels of drug transporters (Table 2) (Le Vee et al., 2008; Le Vee et al., 2009; Diao et al., 2010; Le Vee et al., 2011). Inflammatory cytokines secreted during AKI can induce hepatic injury (Dixon et al., 2014). Therefore, uremic toxins may alter hepatic pharmacokinetics not only via direct inhibitory effects on drug-metabolizing enzymes and transporters but also via the downregulation of their expression mediated by inflammatory cytokines. Kirwan et al. (2009) reported increased plasma concentrations of midazolam in patients with AKI compared with those in patients with normal kidney function. On the other hand, clinical pharmacokinetic change of midazolam in CKD patients compared with healthy control subjects was either not observed or slightly reduced according to several clinical investigations (Nolin et al., 2009; Thomson et al., 2015; Rattanacheeworn et al., 2021), suggesting that hepatic CYP3A4 activity is reduced by AKI-specific mechanism such as acute inflammatory responses. Though clinical circulating cytokine levels in patients are lacking, blood levels of IL-6 have been reported to be increased in murine ischemic kidney injury (Kielar et al., 2005). Recently, inflammatory cytokines and pharmaceutical agents have been clinically used for their functional regulation, and a reduction in drug metabolism activity has been clinically reported in patients treated with such therapeutic proteins (Lee et al., 2010). Interactions among inflammatory cytokines, P450s, and drug transporters pose a challenge, which drove the FDA to issue guidance on drug-drug interaction assessment methods for therapeutic proteins in 2020 (https://www.fda.gov/media/140909/download).

Biomarkers for Hepatic Drug-Metabolizing Enzymes and Transporters

In clinical settings, biomarkers for monitoring drug-metabolizing enzymes and transporters are useful for designing appropriate dosage

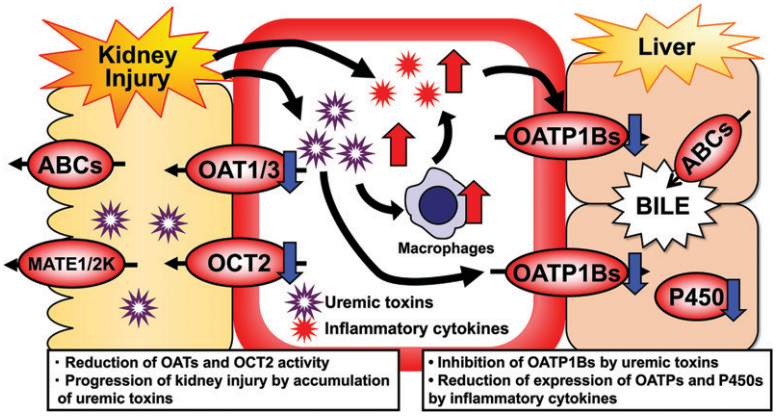

Fig. 1. Alterations in hepatic drug disposition in patients with kidney disease. Plasma concentrations of uremic toxins and inflammatory cytokines are elevated in kidney dysfunction. Uremic toxins can inhibit the expression of OATs and OCT2 in the kidneys. Uremic toxins can also inhibit and downregulate hepatic pharmacokinetic proteins, including OATP1B and cytochrome P450, in the liver. Uremic toxins can activate macrophages, resulting in the release of inflammatory cytokines that can modulate the hepatic pharmacokinetic proteins. ABC, ATP-binding cassette.

regimens and evaluating the drug-drug interactions (Chu et al., 2018). However, the application of such biomarkers to kidney disease patients may require careful discussion since not only enzymes and/or transporters but also biosynthesis of the biomarkers may be changed in kidney disease conditions. Takita et al. (2022) performed a pharmacokinetic modeling approach for both an endogenous biomarker and a probe drug for OATP1Bs and proposed a reduction in both biosynthesis and hepatic elimination of an OATP1Bs biomarker compound. Such an approach may be useful to carefully understand changes in transporter activity in kidney disease patients. Moreover, endogenous substrates for pharmacokinetic proteins may be recognized not only by target proteins but also by other proteins. Therefore, changes in plasma concentrations may not necessarily confirm target protein-mediated activity. In addition, as the kinetics of tissue distribution and elimination of endogenous substrates cannot be directly estimated in clinical studies, analyzing the pharmacokinetics of proteins using such endogenous biomarkers alone is challenging.

The function of OATs and OCTs in the proximal tubules are reduced in patients with kidney dysfunction, as described above (check *Renal Pharmacokinetics in Patients with Kidney Disease*). As there is individual variance in each patient, evaluation of the activities of OCT2 and OAT1/3 in individual patients using their biomarkers may aid in the design of an appropriate dosage regimen. Creatinine is mainly excreted into the urine via glomerular filtration and partly secreted by OCT2 and MATE1/2K (Chu et al., 2016), which accounts for 10%–40% of total creatinine clearance in the body (Levey et al., 1988). Therefore, OCT2 activity can be evaluated by estimating the secretory clearance of creatinine. As these OCTs are inhibited by nephrotoxic drugs, including tyrosine kinase inhibitors, at clinically relevant concentrations (Arakawa et al., 2017; Omote et al., 2018), it is necessary to distinguish between effects caused by drug interactions and those caused by actual kidney injury. To monitor the activities of OAT1 and OAT3, taurine (OAT1), 6β-hydroxycortisol (OAT3), and glycochenodeoxycholate-3-sulfate (OAT3) have been suggested as potential endogenous biomarkers. To date, there have been no reports on the monitoring of plasma concentrations of these markers in patients with CKD. Secretion and reabsorption processes in the renal kinetics of these biomarkers by transporters other than OAT1/3 have been suggested, but their clinical relevance has not yet been reported.

The most established endogenous marker for monitoring OATP1B activity in the liver is coproporphyrin I, an intermediate in heme synthesis. Eighty-five percent of coproporphyrin I is eliminated via bile (Barnett et al., 2018). The plasma concentration of coproporphyrin I is affected by the OATP1B inhibitor rifampicin and the c.521 T>C genotype of OATP1B1 (Barnett et al., 2018). Takita et al. (2022) suggested that monitoring the plasma concentrations of coproporphyrin I can help in the estimation of the functional changes in hepatic OATP1B levels in healthy subjects and patients with CKD using a physiology-based pharmacokinetic model. Blood levels of albumin to which coproporphyrin I binds are decreased in CKD, which adversely affects their binding rate. In this study, the fp value of coproporphyrin I in patients with CKD was predicted based on the fp value in healthy subjects and measured plasma albumin levels in patients with CKD (Takita et al., 2022).

Identification and validation of endogenous biomarkers for drug-metabolizing enzymes remain challenging. For CYP3A4, 4β-hydroxycholesterol has been suggested as a possible endogenous biomarker (Kasichayanula et al., 2014). The plasma concentrations of 4β-hydroxycholesterol in patients with stage 3–5 CKD (GFR <60 mL/min per 1.73 m^2) were 1.3-times higher than those in healthy volunteers and comparable between patients with stage 5D CKD (GFR <15 mL/min per 1.73 m^2) and healthy volunteers (Suzuki et al., 2022). This result suggests that the functional change in CYP3A4 in patients with CKD is not significant, consistent with the report that there is no apparent relationship between the severity of CKD and CYP3A4/5-mediated drug clearance (Yoshida et al., 2016).

Future Directions

Functional reduction in OAT1/3 levels in the kidneys and CYP2D6 and OATP1B levels in the liver can be observed in patients with kidney dysfunction compared with those in healthy subjects. This information is estimated based on changes in the plasma concentrations of parental drugs and their metabolites. The guidance issued by the FDA for determining the "Pharmacokinetics in Patients with Impaired Renal Function" mainly focuses on evaluating the drugs primarily excreted via renal mechanisms (https://www.fda.gov/media/78573/download). However, the effects of kidney dysfunction on pharmacokinetics in the gut and liver remain to be elucidated. To accurately evaluate the pharmacokinetic changes in patients with CKD, measuring the protein levels of drug-metabolizing enzymes and transporters in the kidneys and other organs during kidney disease may be necessary. This information will enable detailed pharmacokinetic prediction of each substrate of drug transporters and metabolizing enzymes in renal dysfunction patients based on physiologically based pharmacokinetic modeling, leading to the planning of an appropriate dosage regimen. Identification of biomarkers for pharmacokinetic proteins can be useful for detecting the functional changes in proteins in affected patients. In addition, Achour et al. (2021) reported that the abundance of hepatic drug enzymes and transporters in the liver can be quantified by liquid biopsy approach. In this research, they found that gene expression of 12 key drug-metabolizing enzymes and four drug transporters, including CYP2D6, CYP3A4, and OATP1B1, in plasma exosomes isolated from individual blood samples was well correlated with their protein expression in the liver. This novel technology may overcome the difficulties of limited access to tissue biopsies and has the potential to characterize the expression levels of pharmacokinetic proteins in various organs in patients with kidney dysfunction.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Arakawa, Kato.

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