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Commentary

Organic cation transporter OCT/SLC22A and H^+/organic cation antiporter MATE/SLC47A are key molecules for nephrotoxicity of platinum agents

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ABSTRACT

Platinum agents have been widely used in cancer chemotherapy for a long time. Cisplatin, carboplatin, oxaliplatin and nedaplatin have a common chemical structure consisting of platinum, carrier groups and leaving groups, and undergo the similar mechanism of cytotoxicity. However, each agent differs in its efficacy and adverse effects, although the molecular mechanism involved is unclear. Recently, it was reported that organic cation transporter OCT/SLC22A, and multidrug and toxin extrusion MATE/SLC47A play a role in the pharmacokinetics of platinum agents. Only cisplatin induces nephrotoxicity and the toxicity is kidney-specific. Kidney-specific OCT2 mediates the transport of cisplatin and is the determinant of cisplatin-induced nephrotoxicity. In addition, cisplatin and oxaliplatin are substrates for these transporters, but carboplatin and nedaplatin are not. Substrate specificity could regulate the features of platinum agents. In this commentary, we will discuss the characteristics of OCT and MATE, and demonstrate the recent topics about the relationship between the transport of platinum agents by organic cation transporters and their pharmacological characteristics.

1. Introduction

A platinum-based anticancer drug cis-diamminedichloroplatinum II (cisplatin) has been used clinically for over 30 years and continues to play an essential role in cancer chemotherapy against malignant solid tumors of the lung, bladder, colon, testis and brain. However, severe nephrotoxicity limits its clinical application. An increase in the serum creatinine concentration has been reported in 41% of patients treated with a high dose of cisplatin, although hydration was also carried out [1]. Renal injury from cisplatin was primarily found in proximal tubules [2]. Moreover, the tubular toxicity caused a decrease in the glomerular filtration rate, resulting in acute renal failure [3]. Therefore, it was suggested that cisplatin was toxic primarily to renal tubular epithelial cells. However, the molecular mechanisms of the kidney-specific toxicity of cisplatin have remained to be elucidated.

Cis-diammine-1,1-cyclobutanedicarboxylatoplatinum II (carboplatin) was developed as a less nephrotoxic platinum agent. Cis-diammineglycolatoplatinum (nedaplatin) is a similar type of cisplatin analogue, used in Japan. Platinum agents consist of platinum, leaving groups and carrier groups as shown in Fig. 1. The leaving groups of carboplatin and nedaplatin are different from that of cisplatin, while the carrier groups are the same. The leaving groups of platinum agents are replaced by water to produce an active agent in the cell during a non-enzymatic reaction [4]. After elimination of the leaving groups, cisplatin, carboplatin and nedaplatin produce the same active agent. Therefore, the extracellular mechanism could determine the cisplatin-specific nephrotoxicity.

The third generation platinum agent trans-L-1,2-diaminocyclohexaneoxalatoplatinum II (oxaliplatin) also has less nephrotoxicity. The carrier groups as well as leaving groups of oxaliplatin differ from those of cisplatin. Oxaliplatin exhibits a different pattern of sensitivity from cisplatin and carboplatin, owing to resistance to DNA repair proteins [5]. Diaminocyclohexane (DACH), which is a carrier group of oxaliplatin, plays an important role in the resistance. However, it has been unclear how oxaliplatin enters the cell.

These platinum agents have a similar mechanism of toxicity in the cell because of their common structural backbone (Fig. 1). However, they have different pharmacological characteristics (e.g. nephrotoxicity and anticancer effect) [5]. In this commentary, we will discuss the characteristics of organic cation transporter OCT/

Abbreviations: OCT, organic cation transporter; MATE, multidrug and toxin extrusion; Ctr1, copper transporter 1; DACH, diaminocyclohexane.

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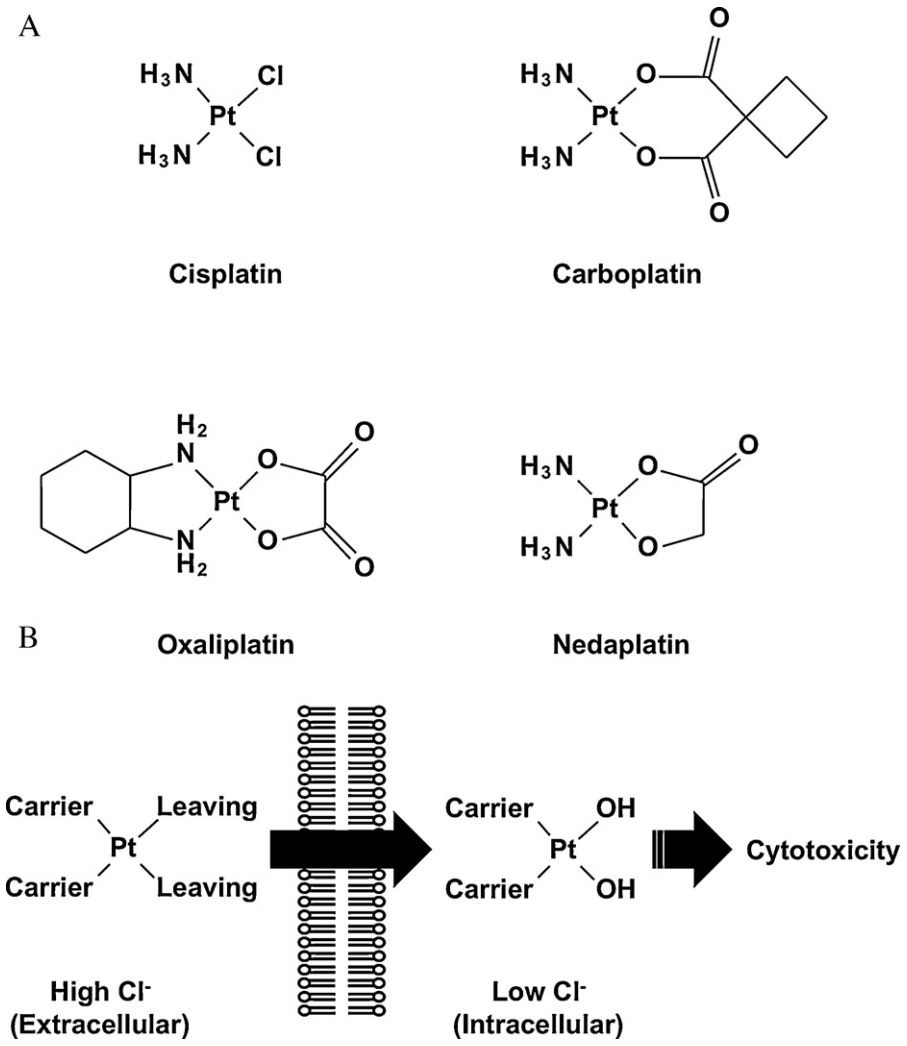

Fig. 1. Chemical structure (A) and conformation change of platinum agents (B). Platinum agents consist of platinum, carrier group and leaving group. Intracellularly, the leaving group(s) of platinum agents was replaced by water to produce an active agent in a non-enzymatic reaction. An active agent reacts with DNA or proteins, and induces cytotoxicity.

SLC22A and multidrug and toxin extrusion MATE/SLC47A, and demonstrate the recent topics about the relationship between the transport of platinum agents by organic cation transporters and their pharmacological characteristics.

2. Characteristics of organic cation transporters

In 1994, the first membrane potential-dependent organic cation transporter Oct1 was isolated from rat kidney [6]. In humans, OCT1/SLC22A1 is expressed in the sinusoidal membrane of the liver, but not in the kidney [7]. Subsequently, we identified rat Oct2, which is specifically expressed in the kidney [8]. Human OCT2/SLC22A2 is also expressed in the basolateral membrane of renal proximal tubules [9]. Using Oct1/2 knockout mice, it was clearly indicated that Oct1 and Oct2 are important for the renal excretion of a typical organic cation, tetraethylammonium [10]. Human OCT3/SLC22A3 is predominantly expressed in the placenta, but also widely expressed in other organs, including the kidney and intestine [11]. OCT1-3 transport cationic drugs, metformin, cimetidine and procainamide, with a membrane potential. OCTs play an important role in the uptake of cationic drugs into tissues [12,13].

Otsuka et al. [14] identified human multidrug and toxin extrusion 1 MATE1/SLC47A1 in 2005. It was expressed in the kidney, liver, muscle and several tissues. Its kidney-specific homologue MATE2-K/SLC47A2 was also cloned [15]. They are localized in the brush-border membrane of proximal tubules in the kidney, and mediate the transport of cationic drugs with an oppositely directed H^+ gradient as a driving force [16]. In mice only Mate1, not Mate2, is expressed in the kidney. Recently, we generated Mate1 knockout mice and demonstrated that Mate1 is a major efflux transporter mediating the tubular secretion of metformin and cephalexin [17,18].

Organic cation transport systems consist of OCT2, MATE1 and MATE2-K in human kidney and mediate tubular secretion of cationic drugs (Table 1) [12,13,19]. In vitro double-transfected OCT2/MATE1 epithelial cells were constructed and revealed the cooperation of OCT2 and MATE1 [20]. Their dysfunctional mutations were identified, and basal transcriptional mechanisms were clarified [13,19]. These factors could affect the interindividual variation in the transport activity and pharmacokinetics of cationic drugs.

3. Transport of platinum agents by OCT, MATE and Ctr1

3.1. OCT1-3/SLC22A1-3

In 2005, we and another group indicated that cisplatin was transported by OCT2, using in vitro expression systems [21,22].

Further studies showed that cisplatin was transported greatly by OCT2 and weakly by OCT1, and that oxaliplatin was transported potently by OCT2 and weakly by OCT3 [23], although the kinetic parameters are still not indicated. On the other hand, carboplatin and nedaplatin were not transported by organic cation transporters [23]. The results are summarized in Table 1.

It is worth noting the relationship between chemical structure and substrate specificity. The carrier group of cisplatin is the same as that of carboplatin and nedaplatin, while their leaving groups are different (Fig. 1). However, cisplatin was transported by OCT2, but carboplatin and nedaplatin were not. Therefore, the characteristics of the leaving groups rather than carrier groups would be important for the substrate specificity of OCT2 among platinum agents. On the other hand, the carrier and leaving groups of oxaliplatin were different from those of cisplatin, though both agents are substrates of OCT2. In addition, dichlorodiaminocyclohexaneplatinum (DACH-$PtCl_2$) was also a substrate of OCT2 [24]. One explanation is that the electronegativity of the leaving group (i.e. pK_a value of the leaving group) affects substrate specificity. Chloride, the leaving group of cisplatin, exhibits the lowest pK_a value among the leaving groups of platinum agents. Oxalate is the leaving group of oxaliplatin. The pK_a value of oxalate is lower than that of malate or acetate, a part of the leaving group of carboplatin or nedaplatin. It was suggested that the lower pK_a value of the leaving group could determine the substrate specificity of OCT2. Further study of the substrate specificity using other platinum agents is needed.

There are some controversial results regarding the substrate specificity of OCT for platinum agents, which were summarized in a previous review [4]. Cisplatin was reported to be transported by OCT2 in several papers [21–29], while it was also reported in others that cisplatin was not transported by OCT2 [30,31]. In the case of organic cations, consistent results about substrate specificity were obtained in published articles [12,13,19]. It was assumed that the stability of platinum agents in solution affects the results. Cisplatin was relatively stable in a chloride-containing buffer, while the chloride of cisplatin was easily replaced by water in chloride-lowering conditions, such as intracellular conditions [32]. The half-life of cisplatin was 2.4 h in water [33]. On the other hand, the leaving group of oxaliplatin was replaced by chloride in chloride-containing conditions to produce DACH-$PtCl_2$, although the stability of oxaliplatin was greater than that of cisplatin [34]. Almost all reports indicated that oxaliplatin was a substrate of OCT2 [23–25,31], because oxaliplatin is more stable than cisplatin. In addition, platinum agents bind to proteins and chemicals by covalent bonds. The protein-binding ratio of cisplatin in plasma was increased in a time-dependent manner, and cisplatin was bound to protein with a half-life of 2 h in plasma [35]. Furthermore, a letter to editor published by the American Journal of Pathology [36], discussed the influence of the chemical interaction between cisplatin and cimetidine on experimental data. Therefore, after solubilization, careful and rapid use, and a combination of drugs should be considered to obtain correct results when using platinum agents.

3.2. MATE1,2-K/SLC47A1-2

The transport of platinum agents by MATEs has been investigated in only a few reports. The cellular uptake of cisplatin for 1 h was increased by the expression of hMATE1 and hMATE2-K without pre-treatment with ammonium chloride [23]. On the other hand, there was no significant stimulation of the intracellular accumulation of platinum in hMATE1 and hMATE2-K-expressing cells after incubation with cisplatin for 2 min under conditions of ammonium chloride-generated intracellular acidification [25]. Rat MATE1 also transported cisplatin [25]. An inhibitory effect of cisplatin on the transport of tetraethylammonium by hMATE1 and hMATE2-K was observed [23]. It is still unclear whether cisplatin is a substrate for human MATEs. Oxaliplatin was greatly transported by hMATE2-K [25]. In addition, it was also a substrate for hMATE1 and rat MATE1 [25].

The transport by H^+/organic cation antiporter MATE is bi-directional, depending on the direction of the H^+ gradient [37]. Therefore, uptake experiments were used to characterize H^+/organic cation antiporters with an artificial outward H^+ gradient. However, platinum agents are aquated to produce an active species in the cell in a non-enzymatic reaction. Therefore, further study is needed to clarify whether an active form of platinum agents was transported by MATEs.

3.3. Ctr1/SLC31

Human copper transporter Ctr1 was identified in 1997 and plays a role in the cellular uptake of copper [38]. It is expressed ubiquitously and is highly expressed in the liver and kidney, and is localized at the basolateral membrane of proximal tubules [39]. In 2002, Ishida et al. [40] found that Ctr1 transports cisplatin using yeast and mammalian cells. In addition, Ctr1 transports carboplatin and oxaliplatin as well as cisplatin [41]. Using several cell lines, it was shown that the cellular accumulation and sensitivity of cisplatin correlated with Ctr1 expression [42]. Therefore, Ctr1 is important for the anticancer effect of platinum agents.

Ctr1 was reported to be a channel-like transporter, based on its structure [43]. On the other hand, OCT is an active transporter, whose driving force is an inside-negative membrane potential [12,13]. Therefore, OCT-mediated cellular uptake is concentrative, while Ctr1-mediated transport is equilibrative. In addition, Ctr1 expression was down-regulated after the cisplatin treatment [44]. Because of their functional characteristics, OCT could have stronger activity than Ctr1.

3.4. Other transporters

Transport of platinum agents by other transporters than OCT, MATE and Ctr1 was also summarized in the previous reviews [4]. ATP7A and ATP7B are copper efflux transporters, and also mediate the efflux of cisplatin. The expression of these transporters lowered cellular accumulation and cytotoxicity of platinum agents.

Table 1
Characteristics of organic cation transporter OCT and H^+/organic cation antiporter MATE.

	Tissue distribution	Membrane localization	Driving force	Preferred platinum agents	Other substrates
OCT1/SLC22A1	Liver	Basolateral membrane	Membrane potential	Cisplatin (weak)	Cimetidine, TEA, metformin,
OCT2/SLC22A2	Kidney	Basolateral membrane	Membrane potential	Cisplatin, oxaliplatin	MPP, etc.
OCT3/SLC22A3	Ubiquitous	Basolateral membrane	Membrane potential	Oxaliplatin (weak)	
MATE1/SLC47A1	Kidney, liver, etc.	Brush-border membrane	Opposite H^+ gradient	Cisplatin (weak), oxaliplatin	
MATE2-K/SLC47A2	Kidney	Brush-border membrane	Opposite H^+ gradient	Oxaliplatin	
Ctr1/SLC31A1	Ubiquitous	Basolateral membrane	Channel-like	Cisplatin, carboplatin, oxaliplatin, etc.	Copper

OCT, organic cation transporter; MATE, multidrug and toxin extrusion; TEA, tetraethylammonium; MPP, 1-methyl-4-phenylpyridinium.

However, their roles in nephrotoxicity of platinum agents are unclear. Multidrug resistance-associated proteins MRPs play a role in the efflux of glutathione-conjugated platinum agents, but are scarcely related with the toxicity of platinum agents. Moreover, P-glycoprotein did not transport cisplatin. Therefore, in this commentary, we focused on organic cation transporters and CTR1 in renal handling and nephrotoxicity of platinum agents.

4. Renal handling and nephrotoxicity of platinum agents

4.1. Nephrotoxicity of cisplatin

Toxicity of cisplatin is found specifically in the kidney, but rarely in the liver or blood. In addition, pharmacokinetic studies showed that the accumulation of cisplatin was higher in the kidney than in other tissues or plasma [45]. Furthermore, it was reported that renal injury from cisplatin was primarily found in proximal tubules [2]. These reports suggested that kidney-specific transporters in the proximal tubule were involved in the nephrotoxicity of cisplatin.

Renal tubular epithelial cells consist of brush-border membranes and basolateral membranes. Using polarized renal epithelial cells, it was showed that treatment with cisplatin from the basal side resulted in stronger cytotoxicity than that from the apical side [46,47]. The accumulation of cisplatin from the basal was also greater, compared with the apical. Therefore, there were specific mechanisms mediating cisplatin uptake at the basolateral membranes of renal epithelial cells. As described above, OCT2 is kidney-specific basolateral cation transporter. The features of cisplatin-induced nephrotoxicity corresponded to the characteristics of OCT2. Further studies clearly indicated that suppression of OCT2, using OCT2 inhibitors or Oct2 knockout mice, ameliorated cisplatin-induced nephrotoxicity [21,27–29]. Furthermore, Filipski et al. [27] reported that a nonsynonymous single-nucleotide polymorphism in OCT2/SLC22A2 was associated with reduced cisplatin-induced nephrotoxicity in patients. These recent reports strongly indicated that OCT2 should mediate the renal uptake of cisplatin and be a determinant of cisplatin-induced nephrotoxicity (Fig. 2).

Ctr1 is also expressed in the kidney and mediates the cellular uptake of cisplatin [38,40]. The contribution of Ctr1 to cisplatin-induced nephrotoxicity is obscure. Pabla et al. [39] recently reported that Ctr1 was localized in the basolateral membrane of proximal tubules and that siRNA for Ctr1 reduced cisplatin-induced cytotoxicity in Human Embryonic Kidney 293 cells. The authors discussed that Ctr1 plays an important role in the tubular uptake of cisplatin during nephrotoxicity. However, the tissue distribution of Ctr1 is not kidney-specific but ubiquitous [38], while that of OCT2 is kidney-specific [7]. Moreover, the expression level of Ctr1 was higher in the liver than in other tissues. In addition, OCTs were not expressed in Human Embryonic Kidney 293 cells, which were used as a renal epithelial cell model in this report [39]. Therefore, it is clear that the kidney-specific toxicity of cisplatin is determined not by Ctr1, but by OCT2.

4.2. No nephrotoxicity of other platinum agents

Other platinum agents, carboplatin, oxaliplatin and nedaplatin, did not induce nephrotoxicity. Carboplatin and nedaplatin were not transported by organic cation transporters including OCT2 [23]. In addition, their renal accumulation was lower than that of cisplatin [25]. Because carboplatin and nedaplatin were not transported by OCT2, they were not highly accumulated in the kidney and did not induce nephrotoxicity. On the other hand, oxaliplatin was transported by OCT2 [23,31], although it did not induce nephrotoxicity. The renal accumulation of oxaliplatin was lower than that of cisplatin in rats after an intraperioneal administration [25]. An in vitro uptake study showed that

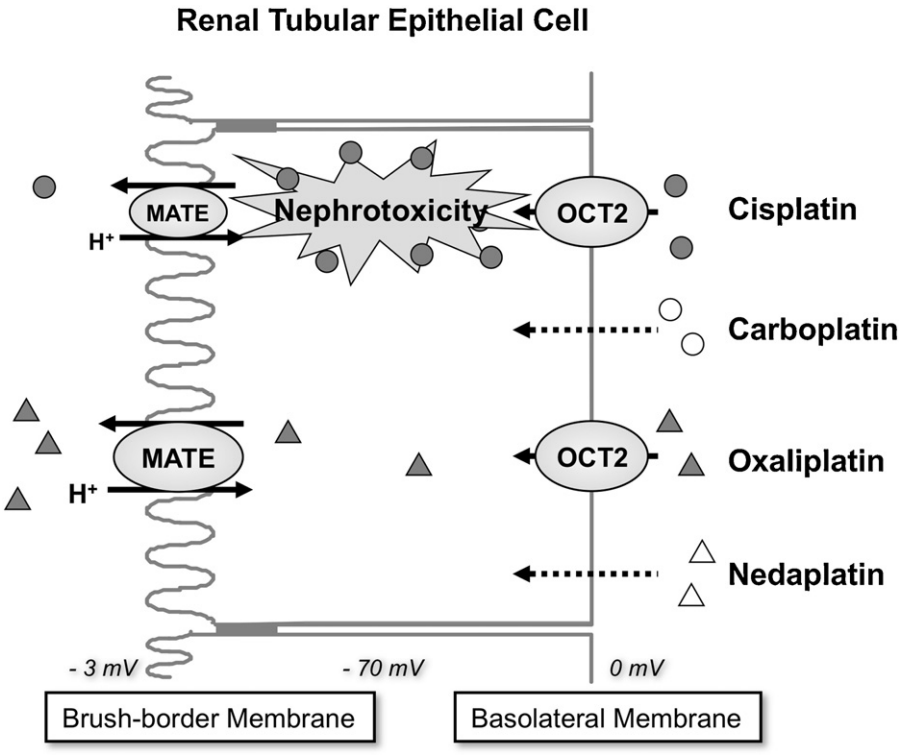

Fig. 2. Renal handling of platinum agents via organic cation transporters, OCT2 and MATE. Cisplatin was transported by OCT2 and weakly by MATE. The renal accumulation of cisplatin was higher than those of other platinum agents, and cisplatin caused nephrotoxicity. Carboplatin and nedaplatin were not transported by OCT and MATE. Oxaliplatin was a substrate for OCT2 and MATE, and was not nephrotoxic. Cisplatin and oxaliplatin were excreted into urine by tubular secretion as well as glomerular filtration.

oxaliplatin is transported greatly by MATE2-K and slightly by MATE1 [25]. It was suggested that the MATE-mediated efflux of oxaliplatin from tubular cells protects against the nephrotoxicity of oxaliplatin. However, oxaliplatin did not induce nephrotoxicity at a high dose in animal studies or in any clinical studies. Therefore, the pharmacological characteristics of oxaliplatin, different from those of cisplatin, would also be a major reason for the low nephrotoxicity.

4.3. Mechanism for urinary excretion of platinum agents

The pharmacokinetics of cisplatin was investigated a long time ago. Cisplatin was mainly excreted into urine. The half-life of alpha-phase is around 20 min [48,49]. The unbound form of cisplatin is rapidly eliminated from blood. The half-life of beta phase was longer than 30 h [48,49], because cisplatin attaches to proteins by a covalent bond. The renal clearance of free cisplatin exceeded creatinine clearance in humans and rats [49–52]. Therefore, it was suggested that cisplatin was secreted into urine via organic cation transport systems consisting of OCT2 and MATEs in renal tubular cells. On the other hand, carboplatin was not excreted via renal tubular secretion [53,54]. Siddik et al. [52] clearly demonstrated that cisplatin, but not carboplatin, was excreted by an active renal secretory mechanism. It corresponded with the substrate specificity of organic cation transporters. Oxaliplatin was also a substrate of OCT and MATE, and its excretion was also mediated by tubular secretion [55,56]. These reports suggested that platinum agents, which are substrates for OCT and MATE, were excreted into urine via tubular secretion by organic cation transport systems in addition to glomerular filtration (Fig. 2).

5. Clinical application

Hydration, more than 4000 mL/day, is usually used to prevent severe nephrotoxicity of cisplatin. Although the protective mechanisms of hydration are uncertain, it is considered that hydration may increase the excretion of cisplatin, prevent the dissociation of the chlorides from cisplatin or modify the sensitivity of tubular cells by the osmotic stress [57]. The continuous diuresis reduces the patients' quality-of-life. Moreover, hydration cannot completely prevent nephrotoxicity, especially in cases of high doses [1]. OCT2 mediates the renal uptake of cisplatin. In vivo studies successfully showed that OCT2 inhibitors, imatinib and cimetidine, suppressed cisplatin-induced nephrotoxicity [27–29]. Therefore, coadministration of an OCT2 inhibitor is one of the strategies for preventing cisplatin-induced nephrotoxicity.

We recently found that MATE inhibition potentiated cisplatin-induced nephrotoxicity, using Mate1 knockout mice and a specific inhibitor pyrimethamine [58]. The substrate specificity of OCT2 and MATE is almost the same, as organic cations are secreted across the renal epithelial cell via OCT2 and MATEs [12,13,19]. Therefore, OCT2 inhibitors possibly inhibit MATEs and potentiate cisplatin-induced nephrotoxicity. Notably, cimetidine was indicated to be a potent MATE inhibitor rather than OCT2, as previously reported and discussed [59,60]. The IC_{50} values for MATE1 and OCT2 are 1.1 μM and 8.6–73 μM, respectively [59]. It was reported that an excess of cimetidine inhibited cisplatin-induced nephrotoxicity [29]. However, a clinical dose of cimetidine may actually enhance nephrotoxicity. The IC_{50} values of imatinib for OCT2 and MATEs are similar, and a clinical level of imatinib decreased the renal accumulation of cisplatin and ameliorated cisplatin-induced nephrotoxicity [28]. Therefore, the coadministration of imatinib may prevent cisplatin-induced nephrotoxicity in clinical conditions. Inhibitory potency for OCT2 and MATEs, blood concentration and renal concentration of OCT2 inhibitors should be considered, when applied as a renoprotective agent against cisplatin-induced nephrotoxicity.

6. Conclusion

Platinum agents, cisplatin, carboplatin, oxaliplatin and nedaplatin, exhibit individual characteristics, although they have a similar chemical structure and a common cytotoxic mechanism in the cell. The kidney-specific toxicity of cisplatin is determined by the kidney-specific transporter OCT2. Carboplatin and nedaplatin are not substrates of OCT2 and do not induce nephrotoxicity. However, oxaliplatin did not show nephrotoxicity although it was transported by OCT2. Efflux transporter MATEs would contribute to the protection from oxaliplatin, or the pharmacological characteristics of oxaliplatin would also be a major cause of low nephrotoxicity. Recent findings indicate that organic cation transporters are key to the nephrotoxicity of platinum agents. Not only intracellular signaling, but also pharmacokinetics mediated by drug transporters could play an essential role in the therapeutic efficacy and adverse effects of platinum agents.

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