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Are Mice and Rats Good Experimental Models to Explore Novel Compounds against Cisplatin Induced Nephrotoxicity?

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Animal models are indispensable tools in biomedical research. Mice and rats are the most commonly used animal models since the early days of scientific discovery and they continue to be the premier mammalian models utilized to explore the functions of individual genes, the pathophysiological mechanisms of various diseases, and the effectiveness and the toxicities of drugs [1]. Among the many advantages to using the mice or rats as model organisms is their striking similarity to humans in anatomy, physiology, and genetics. The genomes of mice and rats have been sequenced and many genes have been found to be conserved between mice or rats and human [2]. Scientists from all the spectrum of biomedical fields have gravitated to these animal models because of their close genetic and physiological similarities to humans, as well as the ease, particularly mice, with which its genome can be manipulated and analyzed. Despite the fact that rodents models (mice and rats) have contributed significantly to our understanding of pathophysiology of human diseases and the development of new treatments and diagnostic tools, these models are not always reliable preclinical models for the preclinical pharmacological research. Indeed, there are many examples of scientific data which are generated from mice and rats but turned out to be ineffective in clinical trials on humans. These failures cost the pharmaceutical industry millions of dollars.

Cisplatin (CP) is an inorganic platinum-based chemotherapeutic agent that is widely used in the treatment of a variety of solid malignant tumors such as head and neck, lung, testis, ovarian and bladder cancers [3]. There are various significant side effects of CP such as myelosuppression, peripheral neuropathy, ototoxicity, anaphylaxis [4] and nephrotoxicity which is the main dose-limiting side effect of CP [5]. CP nephrotoxicity is an ideal model to study the early pathophysiological features of all types of acute kidney injury [4]. In the mammalian kidney, transport of endogenous and xenobiotic organic compounds is mediated by multispecific organic anion/cation transporters, which are localized in the apical and basolateral cell membrane domains of the specific nephron segments.These transporters are also responsible for drug resistance, drug-drug interactions, and drug-induced nephrotoxicity [6]. In rat and mouse proximal tubules, a number of these transporters exhibit a significant sex and species differences in their expression. The expression and activity of organic anion/cation transporters is influenced by several conditions, including transcriptional regulation, gender-dependent regulation and genetic variation.Gender and species (rat versus mouse) differences in ions transporters expression are well recognized [1].

Cisplatin induced renal tubular cell injury may be related to CP uptake by basolateral organic cation transporters (OCTs) [7]. Moreover, it has been demonstrated that *OCT2* is the critical OCT isoform which is responsible for CP uptake in the kidney. Over expression of OCT2 in Human Embryonic Kidney (HEK293) cells increases CP uptake and cellular sensitivity to CP toxicity [8]. Furthermore, a recent study confirmed that CP-induced nephrotoxicity is a gender dependent; greater intensity of damage in male than female [9]. Gender differences of CP-induced nephrotoxicity may be related to CP uptake by *OCT2*. In addition, CP uptake was increased by *OCT2* overexpression in male rats and was associated with increased cellular sensitivity to CP toxicity [10,11]. Interestingly, a recent study by Kim et al. [12] concluded that administration of glutamine might represent a new strategy for the treatment of CP-induced nephrotoxicity through reduced the CP-induced expression of *OCT2* and CP accumulation [12].

The expression of renal *OCT2* in different species has been studied in more detail at both mRNA and protein level. The expression of *OCT2* mRNA in rats, mice and rabbits exhibits the male-dominant pattern, but at the protein level this basolateral transporter in proximal tubule segments is clearly stronger in male than female rats and mice, but sex-independent in rabbits and humans [1].

Multidrug and Toxin Extrusion Protein 1 (MATE1) mediates secretion of CP in urine. Mice with genetic deletion of MATE1 are more sensitive to CP nephrotoxicity [13]. Moreover, the potent inhibition of MATEs by ondansetron enhances the nephrotoxicity associated with CP treatment in mice [14]. Some inhibitors of *OCT2* such as cimetidine and ondansetron interact with higher potency with MATE1, blocking CP efflux from the cells and potentially increasing CP renal toxicity [15]. The *MATE1* is localized to the proximal tubules, brush-border membrane and male-dominant in both mRNA and protein expression. However, mice exhibit higher expression of mRNA in male, but the protein was detected in the apical membrane of various tubule segments with unknown levels of expression in male and female. The *MATE1* is present also in the rabbit and human kidneys but the mRNA and protein expression levels of *MATE1* in male and female has been poorly investigated [1]. Therefore, (A) Sex and species differences in the renal expression of *OCT2* and *MATE1* transporters at the levels of mRNA and/or protein may not be relevant to the situation in humans, (B) Previous differences should be taken in our consideration, when we explore novel compounds against CP-induced nephrotoxicity by using mice or rat as model and (C) *OCT2* and MATE1 transporters represent as an ideal approach to protect CP nephrotoxicity.

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