Mechanisms Underlying Cisplatin Induced Nephrotoxicity- A Review

Manickam Kalappan Vanitha 1,* , Pandi Anandakumar 2

1Department of Medical Biochemistry, Dr. ALMPGIBMS, University of Madras, Taramani campus, Chennai, India
2Biochemistry Unit, Department of Biomedical Sciences, College of Health Sciences, Arsi University, Asella, Ethiopia.

ARTICLE INFO

Cisplatin is one of the most frequently used chemotherapeutic agents for the treatment of different types of cancers including testicular, head and neck, ovarian, cervical and non-small cell lung carcinoma. Cisplatin induced nephrotoxicity is a challenging side effect during chemotherapy. In kidneys, cisplatin preferentially accumulates in renal tubular cells causing tubular cell injury and death, resulting in acute kidney injury. Pathologically, cisplatin nephrotoxicity is characterized by cell injury and death in renal tubules. Although the effect of cisplatin is dependent on its dose, the major risk of nephrotoxicity commonly thwarts the use of higher doses to maximize its antineoplastic effects. This review focuses on different molecular mechanisms underlying cisplatin induced nephrotoxicity in a brief manner.

Keywords: Cisplatin; nephrotoxicity; DNA damage; mitochondrial dysfunction.

1. INTRODUCTION

Among the anti-tumor drugs, Cisplatin occupies a very important place. Cisplatin-based blended chemotherapy regimens are presently used as a significant therapy in the treatment of testicular cancer, ovarian germ cell tumors, epithelial ovarian cancer, head and neck cancer, advanced cervical cancer, bladder cancer, mesothelioma, endometrial cancer, non-small cell lung cancer, malignant melanoma, carcinoids, penile cancer, adrenocortical carcinoma etc. 1. Cisplatin-based chemotherapy is used with radiation therapy

---

*Corresponding author
Dr Manickam Kalappan Vanitha
Department of Medical Biochemistry,
Dr. ALMPGIBMS,
University of Madras, Taramani campus
Chennai-600 113.
Tamil Nadu, India
E-mail: vanithakalappan@gmail.com
in the treatment of esophageal cancer, localized cervical cancer and head and neck cancer. It is used as consolidation therapy for many types of solid tumors that have failed standard treatment regimens. The therapeutic effects of cisplatin are pointedly enhanced by dose acceleration. However, high-dose therapy with cisplatin is limited by its collective nephrotoxicity and neurotoxic side effects.

2. MECHANISMS OF CISPLATIN NEPHROTOXICITY

2.1 Cisplatin accumulation in renal cells

Glomerular filtration and tubular secretion of the kidney play a vibrant role in clearing cisplatin. Years of research have identified two different membrane transporters capable of transporting cisplatin into cells: Ctrl1 and OCT2. Ctrl1 is a copper transporter which was also shown to mediate cisplatin uptake into mammalian cells, including ovarian cancer cells. Adult kidney has a high expression of Ctrl1 and the Ctrl1 localizes to the basolateral membrane of the proximal tubule. Both cisplatin uptake and cytotoxicity was found to be reduced during the down regulation of Ctrl1 in renal cells, indicating that Ctrl1 is an essential cisplatin uptake mechanism in kidney cells. The uptake of OCT2 substrates was inhibited by cisplatin as well. Similarly, cimetidine, an OCT2 substrate, decreased cisplatin uptake and cytotoxicity in vitro and cisplatin nephrotoxicity in vivo. The function of OCT2 in regulating renal cisplatin uptake and toxicity has been reported. The knockout of the OCT2 gene remarkably reduced urinary cisplatin excretion and nephrotoxicity; and also a single-nucleotide polymorphism (SNP) in the OCT2 gene (RS316019) was related with reduced cisplatin-induced nephrotoxicity in several patients.

2.2 Cytotoxic effects of Cisplatin

Most important cause of cisplatin mediating its toxic effects are believed to be its close interaction with DNA molecules. In a hydrophilic environment, the chloride ligands of cisplatin are replaced by water molecules generating a positively charged electrophile. This electrophile that is formed, highly reacts with nucleophilic sites on intracellular macromolecules to form adducts of DNA, RNA, and protein. Cisplatin arrests DNA synthesis and replication in quickly proliferating cells by the formation of inter- and intrastrand cross-links with the genetic material, DNA. Substantial evidence also suggests that those cells that lack DNA repair mechanisms are more susceptible to cisplatin-induced cell death, this is in line with the concept that cisplatin mediates its anti-tumor effects through DNA damage.

2.3 Mitochondrial changes in cisplatin nephrotoxicity

Varieties of research on cisplatin indicate that mitochondrial DNA, or other mitochondrial targets, could be more important than nuclear DNA damage in mediating cisplatin-induced cell death. It is understood that Cisplatin is hydrolyzed to generate a positively charged metabolite which specially accumulates within the negatively charged mitochondria. Thus, the sensitivity of cells to cisplatin appears to correlate with both the density of mitochondria and the mitochondrial membrane potential. This observation may explain the particular sensitivity of the renal proximal tubule to cisplatin toxicity, as this segment exhibits one of the highest densities of mitochondria in the kidney. This was supported by a study which stated that comparison of cisplatin-sensitive and cisplatin-resistant ovarian cancer cells exhibited a lower mitochondrial membrane potential as well as less damage to mitochondrial DNA in the latter. Mitochondria generate ATP via oxidative phosphorylation. However, during oxidative phosphorylation, the leakage of electrons from the mitochondrial respiratory chain is an intracellular source of free radical generation. Damage of mitochondria results in the leakage of electrons which ultimately affects the flow of electrons across the electron transport chain. Under such circumstances, large amount of free radicals in the form of reactive oxygen species (ROS) are produced from mitochondria, which may lead to cell injury and death. Disruption of mitochondrial respiratory chain as well as calcium accumulation has been noted in a study.
IIIIII
© International Journal of Pharma Research and Health Sciences. All rights reserved

Fig 2: Mitochondrial dysregulation in cisplatin nephrotoxicity

Along with the above study, it is also described that cisplatin nephrotoxicity affects the activity of the terminal enzyme of electron transport chain called cytochrome C oxidase and a decrease in complex IV protein expression. These problems lead to the abnormal function of the respiratory chain in mitochondria leading further to the accumulation of reactive oxygen species.

It is also reported that cisplatin toxicity may reduce the activity of mitochondrial MnSOD, coupled with decrease in cellular glutathione levels in turn declining the cellular antioxidant levels. All of these disturbances created by cisplatin in mitochondria results in the decrease in mitochondrial mass, distortion of mitochondrial cristae leading to mitochondrial swelling in the later stages which ultimately affects the energy currencies of the cell, namely ATP.

Therefore, these studies apparently reveal the hand of oxidative stress as a major factor for mitochondrial pathology in nephrotoxicity induced by cisplatin.

2.4 Biotransformation of cisplatin – a major mechanism for induction of nephrotoxicity

Biotransformation of cisplatin to an effective toxin is considered to be one of the key mechanisms in the induction of nephrotoxicity caused by cisplatin. The process of conversion starts with the formation of glutathione conjugates in the circulation, expected to be mediated by the critical enzyme glutathione-S-transferase. When the glutathione-conjugates pass through the kidney, they are cleaved to cysteinyl-glycine-conjugates by gamma glutamyl transpeptidase (GGT) expressed on the surface of the proximal tubule cells. With the help of enzymes called amino dipeptidases, these cysteinyl-glycine-conjugates are further metabolized to cysteine-conjugates that are also expressed on the surface of the proximal tubule cells. Later, these cysteine-conjugates are acted on by enzyme called cysteine-S-conjugate beta-lyase in order to produce highly reactive thiols. The conjugated thiols have been reported to induce either apoptosis or necrosis in LLC-PK1 cells depending on the chemical nature of the compound and the antioxidant status of the cell.

3. CONCLUSION

To conclude, this review pinpoints the different possible mechanisms that can lead to cisplatin induced nephrotoxicity. This will further provide way for understanding the mechanisms underlying nephrotoxicity induced by cisplatin in a detailed manner.

4. REFERENCES


29. Tristão VR, Pessoa EA, Nakamichi R, Reis LA, Batista MC, Durão Junior Mde S, Monte JC. Synergistic effect

© International Journal of Pharma Research and Health Sciences. All rights reserved


Conflict of Interest: None

Source of Funding: Nil