DOI:10.21276/ijprhs.2018.04.02

CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Review Article

Mechanisms Underlying Cisplatin Induced Nephrotoxicity- A Review

Manickam Kalappan Vanitha [1,*], Pandi Anandakumar [2]
[1]Department of Medical Biochemistry, Dr. ALMPGIBMS, University of Madras, Taramani campus, Chennai, India
[2] Biochemistry Unit, Department of Biomedical Sciences, College of Health Sciences,
Arsi University, Asella, Ethiopia.

ARTICLE INFO | ABSTRACT

Received:30 Jun 2018
Accepted:12 July 2018

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.

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

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, adrenocorticol carcinoma etc. [1]. Cisplatin-based chemotherapy is used with radiation therapy in the treatment of esophageal cancer, localized cervical cancer and head and neck cancer [2]. 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 [3].

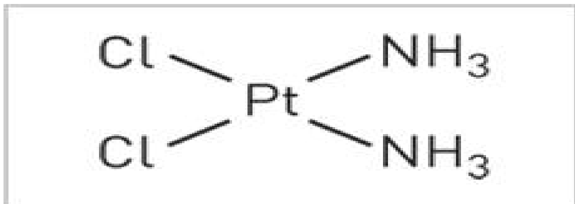

Fig 1: Structure of cisplatin

Its dose-limiting toxicities have prompted the development of the non-nephrotoxic derivative carboplatin and other platinum-based drugs. The therapeutic efficacy of cisplatin for certain cancer types is remarkably high. For example, the cure rate of testicular cancer with cisplatin is over 90%. As a result, for over a half century, cisplatin and related platinium derivatives have been a backbone in chemotherapy of cancer. However, cisplatin is also well-known for its side effects. Particularly, renal disorder has been noted since the initial use of cisplatin in patients. The adversarial effect of cisplatin on renal cells, called cisplatin nephrotoxicity, is showed clinically as lower glomerular filtration rate, decreased serum magnesium and potassium levels [1–3]. It is estimated that about a quarter to one-third of patients undergoing cisplatin treatment experience cisplatin nephrotoxicity [4, 5].

Regardless of years of research, the mechanism underlying cisplatin nephrotoxicity remains uncertain and effective renal protective approaches during chemotherapy are still not available. In this review, we briefly summarize the different mechanisms that can lead to cisplatin induced nephrotoxicity.

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 [6]. Years of research have identified two different membrane transporters capable of transporting cisplatin into cells: Ctr1 and OCT2. Ctr1 is a copper transporter which was also shown to mediate cisplatin uptake into mammalian cells [6], including ovarian cancer cells [7]. Adult kidney has a high expression of Ctr1 and the Ctr1 localizes to the basolateral membrane of the proximal tubule. Both cisplatin uptake and cytotoxicity was found to be reduced during the down regulation of Ctr1 in renal cells, indicating that Ctr1 is an essentialt cisplatin uptake mechanism in kidney cells [8, 9]. 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 [10]. 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 [11].

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 [12-15]. Cisplatin arrests DNA synthesis and replication in quickly proliferating cells by the formation of inter- and intrastrand cross-links with the genetic material, DNA [16]. 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 [17].

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 [18]. 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 [19]. 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 [20].

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 [21].

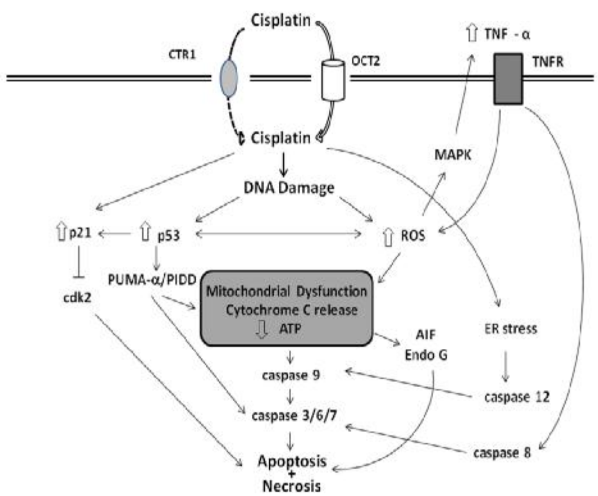

Fig 2: Mitochondrial dysregulation in cisplatin nephrotototoxicity [32]

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 [22-23]. 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 [24-26]. 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 [27-29]. 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 cysteinse-S-conjugate beta-lyase in order to produce highly reactive thiols [30]. 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 [31].

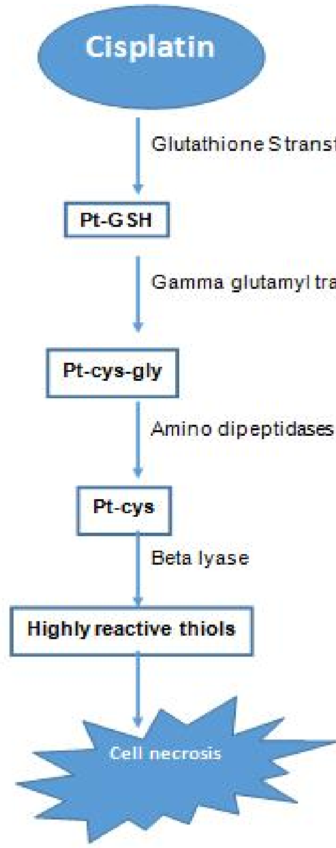

Fig 3: Mechanism that shows the biotransformation of cisplatin to reactive thiols

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

1. Shi M, McMillan KL, Wu J, Gillings N, Flores B, Moe OW, Hu MC. Cisplatin nephrotoxicity as a model of chronic kidney disease. Lab Invest. 2018 (In press).
2. Mercantepe F, Mercantepe T, Topcu A, Yılmaz A, Tumkaya L. Protective effects of amifostine, curcumin, and melatonin against cisplatin-induced acute kidney injury. Naunyn Schmiedebergs Arch Pharmacol. 2018 (In press)
3. Wang SW, Xu Y, Weng YY, Fan XY, Bai YF, Zheng XY, Lou LJ, Zhang F. Astilbin ameliorates cisplatin-induced nephrotoxicity through reducing oxidative stress and inflammation. Food Chem Toxicol. 2018 ; 114:227-236.

4. Hosseinian S, Hadjzadeh MA, Roshan NM, Khazaei M, Shahraki S, Mohebbati R, Rad AK. Renoprotective effect of *Nigella sativa* against cisplatin-induced nephrotoxicity and oxidative stress in rat. Saudi J Kidney Dis Transpl. 2018;29(1):19-29
5. Alabi QK, Akomolafe RO, Olukiran OS, Nafiu AO, Adefisayo MA, Owotomo OI, Omole JG, Olamilosoye KP. Combined Administration of l-Carnitine and Ascorbic Acid Ameliorates Cisplatin-Induced Nephrotoxicity in Rats. J Am Coll Nutr. 2018;37(5):387-398.
6. Konishi H, Fujiwara H, Itoh H, Shiozaki A, Arita T, Kosuga T, Morimura R, Komatsu S, Ichikawa D, Okamoto K, Otsuji E. Influence of magnesium and parathyroid hormone on cisplatin-induced nephrotoxicity in esophageal squamous cell carcinoma. Oncol Lett. 2018 ;15(1):658-664.
7. Zhou L, Wei XH, Pan CS, Yan L, Gu YY, Sun K, Liu YY, Wang CS, Fan JY, Han JY. QiShenYiQi Pills, a Compound Chinese Medicine, Prevented Cisplatin Induced Acute Kidney Injury via Regulating Mitochondrial Function. Front Physiol. 2017 21;8:1090.
8. Sharma S, Joshi A, Hemalatha S. Protective Effect of *Withania coagulans* Fruit Extract on Cisplatin-induced Nephrotoxicity in Rats. Pharmacognosy Res. 2017;9(4):354-361.
9. Townsend DM, Deng M, Zhang L, Lapus MG, Hanigan MH. Metabolism of cisplatin to a nephrotoxin in proximal tubule cells. J Am Soc Nephrol 2003;14:1–10.
10. Brady HR, Kone BC, Stromski ME, Zeidel ML, Giebisch G, Gullans SR. Mitochondrial injury: an early event in cisplatin toxicity to renal proximal tubules. Am J Physiol 1990;258:F1181–F1187.
11. Chen G, Hutter KJ, Zeller WJ. Positive correlation between cellular glutathione and acquired cisplatin resistance in human ovarian cancer cells. Cell Biol Toxicol 1995;11:273–281.
12. Fink, D.; Howell, SB. How does cisplatin kill cells? In: Kelland, LR.; Favilli, F., editors. Platinum-based Drugs in Cancer Therapy. Humana Press; Totowa, New Jersey: 2000; 149-167.
13. Hanigan MH, Gallagher BC, Townsend DM, Gabarra V. Gamma-glutamyl transpeptidase accelerates tumor growth and increases the resistance of tumors to cisplatin in vivo. Carcinogenesis 1999;20:553–559.
14. Tsunekawa M, Wang S, Kato T, Yamashita T, Ma N. Taurine administration mitigates cisplatin induced nephrotoxicity by decreasing DNA damage and inflammation: An immunocytochemical study. Adv Exp Med Biol. 2017;975:703-716
15. Meng H, Fu G, Shen J, Shen K, Xu Z, Wang Y, Jin B, Pan H. Ameliorative effect of Diadzin on cisplatin-induced nephrotoxicity in mice via modulation of inflammation, oxidative stress, and cell death. Oxid Med Cell Longev. 2017;2017:3140680.
16. Cummings BS, Schnellmann RG. Cisplatin-induced renal cell apoptosis: caspase 3-dependent and -independent pathways. J Pharmacol Exp Ther 2002; 302: 8–17.
17. Hu J, Wu TM, Li HZ, Zuo ZP, Zhao YL, Yang L. The synthesis, structure-toxicity relationship of cisplatin derivatives for the mechanism research of cisplatin-induced nephrotoxicity. Bioorg Med Chem Lett. 2017; 27(15):3591-3594.
18. Fink, D.; Howell, SB. How does cisplatin kill cells?. In: Kelland, LR.; Favilli, F., editors. Platinum-based Drugs in Cancer Therapy. Humana Press; Totowa, New Jersey: 2000; 149-167.
19. Gemba M, Fukuishi N. Amelioration by ascorbic acid of cisplatin-induced injury in cultured renal epithelial cells. Contrib Nephrol 1991;95:138–142.
20. El-Arabey AA. Dual function of OCT2 and MATE1 in cisplatin induced nephrotoxicity. Pharmacol Res. 2017;119:493.
21. Ishida S, Lee J, Thiele DJ, Herskowitz I. Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals. Proc Natl Acad Sci U S A 2002;99:14298–14302.
22. Jamshidzadeh A, Heidari R, Golzar T, Derakhshanfar A. Effect of Eisenia foetida Extract against Cisplatin-Induced Kidney Injury in Rats. J Diet Suppl. 2016;13(5):551-9
23. Jung K, Lee D, Yu JS, Namgung H, Kang KS, Kim KH. Protective effect and mechanism of action of saponins isolated from the seeds of gac (Momordica cochinchinensis Spreng.) against cisplatin-induced damage in LLC-PK1 kidney cells. Bioorg Med Chem Lett. 2016;26(5):1466-70.
24. Bolisetty S, Traylor A, Joseph R, Zarjou A, Agarwal A. Proximal tubule-targeted heme oxygenase-1 in cisplatin-induced acute kidney injury. Am J Physiol Renal Physiol. 2016;310(5):F385-94.
25. Derungs A. Drug-induced acute kidney injury. Ther Umsch. 2015;72(11-12):717-27
26. Morsy MA, Heeba GH. Nebivolol Ameliorates Cisplatin-Induced Nephrotoxicity in Rats. Basic Clin Pharmacol Toxicol. 2016 Jun;118(6):449-55.
27. Zhu S, Pabla N, Tang C, He L, Dong Z. DNA damage response in cisplatin-induced nephrotoxicity. Arch Toxicol. 2015;89(12):2197-205.
28. Helmy MM, Helmy MW, El-Mas MM. Additive Renoprotection by Pioglitazone and Fenofibrate against Inflammatory, Oxidative and Apoptotic Manifestations of Cisplatin Nephrotoxicity: Modulation by PPARs. PLoS One. 2015;10(11):e0142303
29. Tristão VR, Pessoa EA, Nakamichi R, Reis LA, Batista MC, Durão Junior Mde S, Monte JC. Synergistic effect

of apoptosis and necroptosis inhibitors in cisplatin-induced nephrotoxicity. Synergistic effect of apoptosis and necroptosis inhibitors in cisplatin-induced nephrotoxicity. Apoptosis. 2016; 21(1):51-9.

30. Karakoc HT, Altintas R, Parlakpinar H, Polat A, Samdanci E, Sagir M, Duran ZR. Protective Effects of Molsidomine Against Cisplatin-Induced Nephrotoxicity. Adv Clin Exp Med. 2015; 24(4):585-93.
31. Hassan HA, Edrees GM, El-Gamel EM, El-Sayed EA. Proanthocyanidin and fish oil potent activity against cisplatin-induced renal cell cycle arrest and apoptosis in rats. Ren Fail. 2015;37(8):1356-62.
32. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins.2010;2(11):2490-2518.

Conflict of Interest: None
Source of Funding: Nil