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Angiotensin 1-7 and losartan worsen the cisplatin induced nephrotoxicity in female rats

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ABSTRACT

Introduction: Cisplatin (CP) is an anti-cancer drug with the most common side effects of nephrotoxicity. Losartan, an angiotensin II type 1 receptor (AT1R) antagonist and angiotensin 1-7 (Ang1-7) protects the kidney against CP administration in males Moreover, the activity of the renin angiotensin system (RAS) and the incidence of CP induced nephrotoxicity are gender related.
Objectives: The role of Ang1-7 and losartan against CP induced nephrotoxicity in female rats was examined.
Methods: Thirty-two female Wistar rats in five experimental groups were treated with vehicle, single dose of CP (7.5 mg/kg), CP+losartan (10), CP+Ang1-7 (30 µg/kg/d) or CP+Ang1-7+A779 (Mas receptor antagonist, 100 µg/kg/d). The biochemical and histology measurements were conducted one week later.
Results: The levels of serum creatinine (Cr) and blood urea nitrogen (BUN) in serum increased insignificantly by CP alone administration. However co-treatment of CP with losartan, Ang1-7, or Ang1-7 plus A779 showed an increase of the serum levels of BUN and Cr, and kidney tissue damage score (KTDS) ($P<0.05$) when compared with control groups.
Conclusion: The AT1R and Mas receptor (MasR) antagonists and Ang1-7 administration promote the CP induced damage of kidney in female rats, and special attention is needed during CP therapy in hypertensive patients who are treating with anti-hypertensive drug of losartan.

Implication for health policy/practice/research/medical education:
Prescribing losartan in females may have the opposite effect to protect the kidney against cisplatin-induced nephrotoxicity.
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Original

Introduction

Losartan as a well-known antihypertensive drug is widely used in clinical settings to control blood pressure. It is an antagonized angiotensin II (AngII) type 1 receptor (AT1R), and AngII, the most important active component of renin angiotensin system (RAS) exerts its vasodepressor action via AT1R. On the contrary, this peptide exerts its vasopressor effect through AngII type 2 receptor (AT2R). The expressions of these two receptors in male and female kidneys are founded to be originally different, while AT2R expression in females is more than males (1, 2). RAS includes two important arms; vasodepressor pathways include angiotensin converting enzyme 1 (ACE1), AngII and AT1R, and vasopressors pathways include angiotensin 1-7 (Ang1-7), Mas receptor (MasR) and AT2R (3, 4).

Cisplatin (CP) is known as an anticancer drug for solid tumor therapy in clinical settings, however its major side effect is nephrotoxicity. CP may affect RAS components, and it is reported that AT1R antagonist has a protective role against CP induced nephrotoxicity by increasing glomerular filtration rate (GFR) and renal blood flow (RBF) (5-8). Ang1-7 also potentially may increase RBF (9).

It seems that the inhibition of vasopressor pathways of RAS protects the kidney after CP therapy in male rats (6), while CP itself alters the blood pressure response to AngII. On the other hand, CP induced nephrotoxicity is gender dependent, and AT1R antagonist does not protect the kidney in females. Accordingly, one question is raised. What is the role of RAS vasopressor components

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(AT1R antagonist, Ang1-7 and MasR) against CP induced nephrotoxicity in females? To answer this question, female rats were subjected to CP induced nephrotoxicity and simultaneously treated with AT1R antagonist (losartan), Ang1-7 alone, or Ang1-7 accompanied by MasR antagonist (A779).

Objectives

The role of Ang 1-7 and losartan against CP induced nephrotoxicity in female rats was investigated.

Methods and Materials

Thirty-two female Wistar rats (194 ± 4 g) were allocated to five groups. The first group (n = 7) received vehicle (saline). The second group (n = 7) was treated with CP (7.5 mg/kg, Mylan Drug Company, Athens, Greece) as a single dose. The third group (n = 6) received a single dose of CP plus a daily injection of losartan (10 mg/kg/d). The fourth group (n = 6) was similar to group 3 but Ang1-7 (30 µg/kg/d.ip) instead of losartan. Finally, the fifth group (n = 6) received single dose of CP plus daily injection of Ang1-7 [30 µg/kg/d intraperitoneal injection (IP)] and Mas receptor (MasR) antagonist (A779, 100 µg/kg/d IP). The duration of the experiment was one week, and on the 8th day blood samples were obtained, and finally, the animals were sacrificed humanly, and hematoxylin and eosin staining on the kidney tissue was performed. Based on the tissue damage intensity, the damage was scored from 0 to 4 using kidney tissue damage score (KTDS).

The diagnostic kits (Pars Azmoon, Iran) were used to measure the serum levels of blood urea nitrogen (BUN) and creatinine (Cr) using RA-1000 auto-analyzer (Technicon, Ireland).

Statistical analysis

The quantitative data (BUN, serum Cr, kidney and body weight) were shown as mean ± SEM and analyzed by the analysis of variance (ANOVA) test and LSD as post hoc to determine the difference between the groups. The qualitative data (KTDS) was analyzed by Kruskal–Wallis and Mann–Whitney U t*ests*. The *P* values less than 0.05 were considered statistically significant.

Results

The administration of CP increased the serum levels of BUN and Cr insignificantly (Figure 1). However, these markers were increased ($P < 0.05$) when losartan, Ang1-7 or a combination of Ang1-7 and A779 were accompanied by CP (Figure 1). The CP administration reduced the body weight (BW) significantly when compared with the vehicle treated group ($P < 0.05$), while the weight loss in CP + Ang1-7 + A779 group was also significantly different from CP alone treated group ($P < 0.05$; Figure 1).

The normalized kidney weight in CP treated groups were increased significantly ($P < 0.05$) (Figure 1). However, the kidney weight in CP+losartan or CP+Ang1-7+A779 treated groups were also increased significantly ($P < 0.05$) compared to the CP alone treated group ($P < 0.05$). The KTDS was not different significantly between vehicle and CP alone treated groups, however all the supplements (losartan, Ang1-7 or Ang1-7+A779) increased the KTDS significantly ($P < 0.05$, Figure 1). The staining tissue sample is demonstrated in Figure 2.

Discussion

Two major findings must be considered. First CP increased the BUN and Cr levels, and KTDS in female rats but the elevation was not statistically meaningful. CP may not accompany with side effect of nephrotoxicity in female rats, while in male animal the CP induced nephrotoxicity were documented. CP-induced nephrotoxicity is gender dependent, and the exact mechanism is not well understood, but sex hormone may be involved.

Second; losartan, Ang1-7 and Ang1-7 +A779 act as risk factors, and they promote the renal toxicity when they are accompanied by CP. Losartan increases the RBF (10), and this phenomenon maybe more intense in female because the AT2R expression in females is more than males (1, 2). Therefore, the vasodilatory effects of losartan cause more blood and CP transport to the kidneys, and as a result, the undesirable effects of CP in the kidney will be increased. The same interpretation for Ang1-7 may be valid. Ang1-7 reduces renal AT1R (11) and increase RBF (9). On the other hand, the impact of MasR in renal hemodynamics is gender related with greater effect in females. Collectively, Ang 1-7 possibly facilitated renal circulation in female than male rats, and more CP transport to the kidney and possibly more tissue damage will be performed. Finally, when MasR was blocked by A779, the effect of Ang1-7 against CP induced nephrotoxicity was not change significantly. Although MasR is the specific receptor of Ang1-7 (12), other results suggested that Ang1-7 may exert its vasodilatation action through other pathways.

Conclusion

Losartan and Ang1-7 (with and without MasR blockade) may increase RBF in female compared to male rats. This increase in blood flow increases the amount of drug into the kidney and the probability of the adverse effects on tubular system is more pronounced. As a suggestion, special attention is needed by chemotherapist's clinician to the patients who are being treated simultaneously with losartan as a anti-hypertensive drug.

Authors' contribution

SK, ZP, FK, ZL and SC performed animal experiments. AT collected the pathology findings and the analysis. MN designed, supervised and performed the data analysis and prepared the final version of the manuscript.

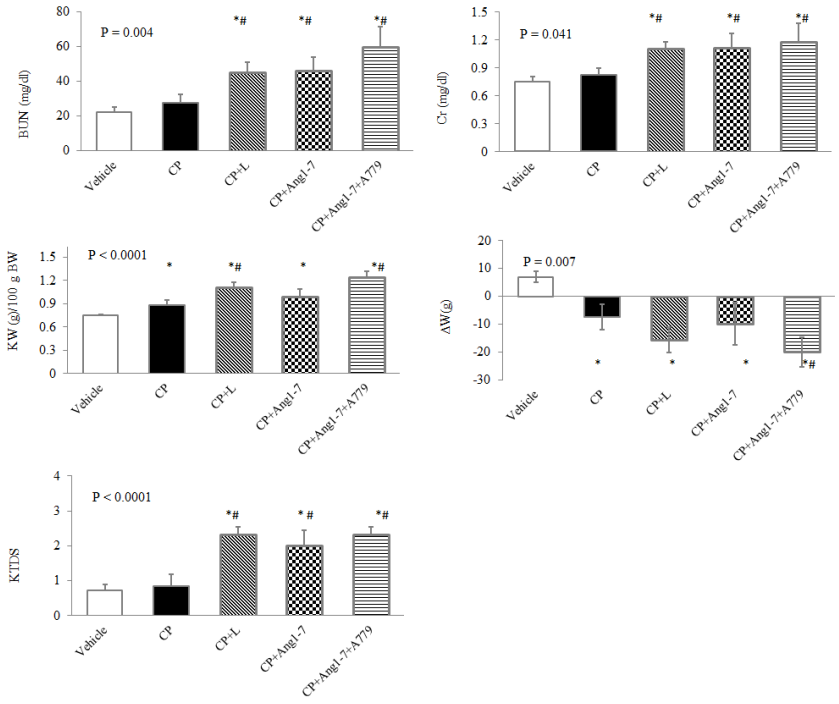

Figure 1. BUN and Cr levels, and body weight change (ΔW), KW and KTDS in the vehicle, cisplatin (CP), CP + losartan (L), CP + angiotensin 1-7 (Ang1-7) and CP+Ang1-7+A779 treated groups. The symbols (* or #) indicate statistical differences (P<0.05) from vehicle or CP alone treated groups.

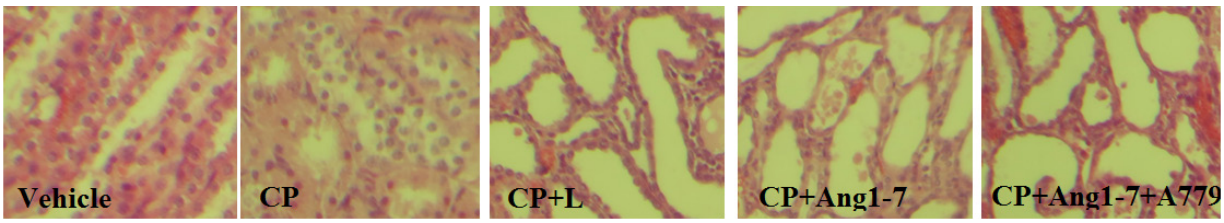

Figure 2. The samples of tissues images. More damages were seen in the CP+L, CP+Ang1-7 and CP+Ang1-7+A779 groups when compared with control groups.

Conflicts of interest

Authors declare that they have no conflict of interest.

Ethical issues

This experimental protocol was performed according to the regulations of the research ethics committee of Iranian ethical guidelines for the use of animals in research. Additionally, all animal experiments were in accordance with protocols approved by the United States National Institutes of Health (NIH, 1978). This study protocol was confirmed by Local Ethics Committee of Isfahan University of Medical Sciences. (Code # IR.MUI.REC.1397.2.055). Moreover, the authors observed the ethical issues including plagiarism, data fabrication and publication duplication.

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