Nitric Oxide Metabolites Change in Cisplatin-Induced Nephrotoxicity: The Effect of L-Arginine and Losartan

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Abstract: Cisplatin (CP) is an anticancer drug with the most common side effect of nephrotoxicity. CP also alters the level of nitric oxide (NO), and NO itself may promote CP-induced nephrotoxicity.

In this short report, we measured the serum levels of NO metabolites in an animal model of CP-induced nephrotoxicity, and tested the effect of two nephroprotectant agents; l-arginine and losartan on serum levels of NO metabolites.

The results indicated that CP increased the serum concentration of nitrite but not nitrate. However, l-arginine and losartan significantly decreased the serum level of nitrite.

It seems that l-arginine and losartan provide their nephroprotectant effect against CP-induced nephrotoxicity by reducing the serum level of nitrite.

Keywords: Cisplatin, Nitric oxide, L-arginine, Losartan, Nephrotoxicity.

INTRODUCTION

Cisplatin (CP) is a platinum compound used for solid tumors therapy. However, it has many side effects including nephrotoxicity. CP-induced nephrotoxicity (CPIN) is associated with decreasing in glomerular filtration rate (GFR); and increasing in blood urea nitrogen (BUN), serum level of creatinine, and tubular injury [1-4]. Some studies documented that administration of CP increase serum nitric oxide (NO) levels [5, 6], and increasing of NO may promote CPIN [5]. L-arginine as precursor of NO has protective role against CPIN [1]. There is one paradox here; CP increases NO [2, 3] and NO-donating agents attenuate CPIN [1, 3]. To answer this paradox, it needs to define which type of NO metabolites change during CP therapy.

NO is unstable and rapidly oxidized to nitrite (NO_2^-) and nitrate (NO_3^-), and NOx refers to sum of nitrite and nitrate concentrations [7]. Within the kidney, NO participates in control of renal hemodynamic, tubuloglomerular feedback, rennin release, and sodium and water excretion [8].

Losartan is an angiotensin-II receptor blocker, and its protective role against CPIN has been reported too [2]. We used l-arginine and losartan (rennin angiotensin receptor blocker) as two nephroprotectant supplementations in CPIN model to investigate the NO metabolite changes when these agents are accompanied with CP.

We attempted to find first, which metabolite; nitrite, nitrate, or NOx is disturbed by CP, and second, the nephroprotective role of losartan or l-arginine against CPIN accompanied by the changes of nitrite or nitrate.

METHODS AND MATERIALS

Fifty one male and female Wistar rats were randomly divided into four groups.

Group 1: the rats (male=6, female=6) received losartan (10 mg/kg/day, ip) for 9 days plus single dose of CP (Sigma) at day 3; Group 2: rats (male=5, female=6) received single dose of l-arginine (300 mg/kg) at day 1 plus single dose of CP at day 2. The doses of l-arginine and losartan were selected based on previous studies [1-4]; Group 3: rats (male=7, female=7) received CP alone (control); and Group 4: rats (male=7, female=7) received saline alone (sham).

One week after administration of a single dose of CP (7 mg/kg), blood samples were collected and the NO stable metabolites (nitrite/nitrate, and NO_x) were measured in serum by an ELISA assay kit (Cayman Chemical Co., USA) that involves the Griess reaction.

STATISTICAL ANALYSIS

Data are expressed as mean ± SEM. The groups were compared by one-way analysis of variance (ANOVA) with regard to the serum levels of NOx, nitrite, and nitrate. Post-hoc test was performed for

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inter-group comparisons using the least significant difference (LSD) test.

RESULTS

The serum concentrations of NOx and nitrite were higher in the control group than in the sham group. L-arginine significantly reduced the serum levels of NOx and nitrite when compared with the control group ($p<0.05$). No significant difference in serum levels of NOx and nitrite were detected between l-arginine (group 2) and the sham group (Figure **1**). Losartan had no effect on the serum level of NOx, but it reduced the nitrite level significantly ($p<0.05$) when in comparison with the control group. CP, l-arginine, or losartan did not alter the serum level of nitrate (Figure **1**).

DISCUSSION

In this short study, we found that CP increased the serum levels of NOx and nitrite but not nitrate. Moreover, losartan and l-arginine as nephroprotectant

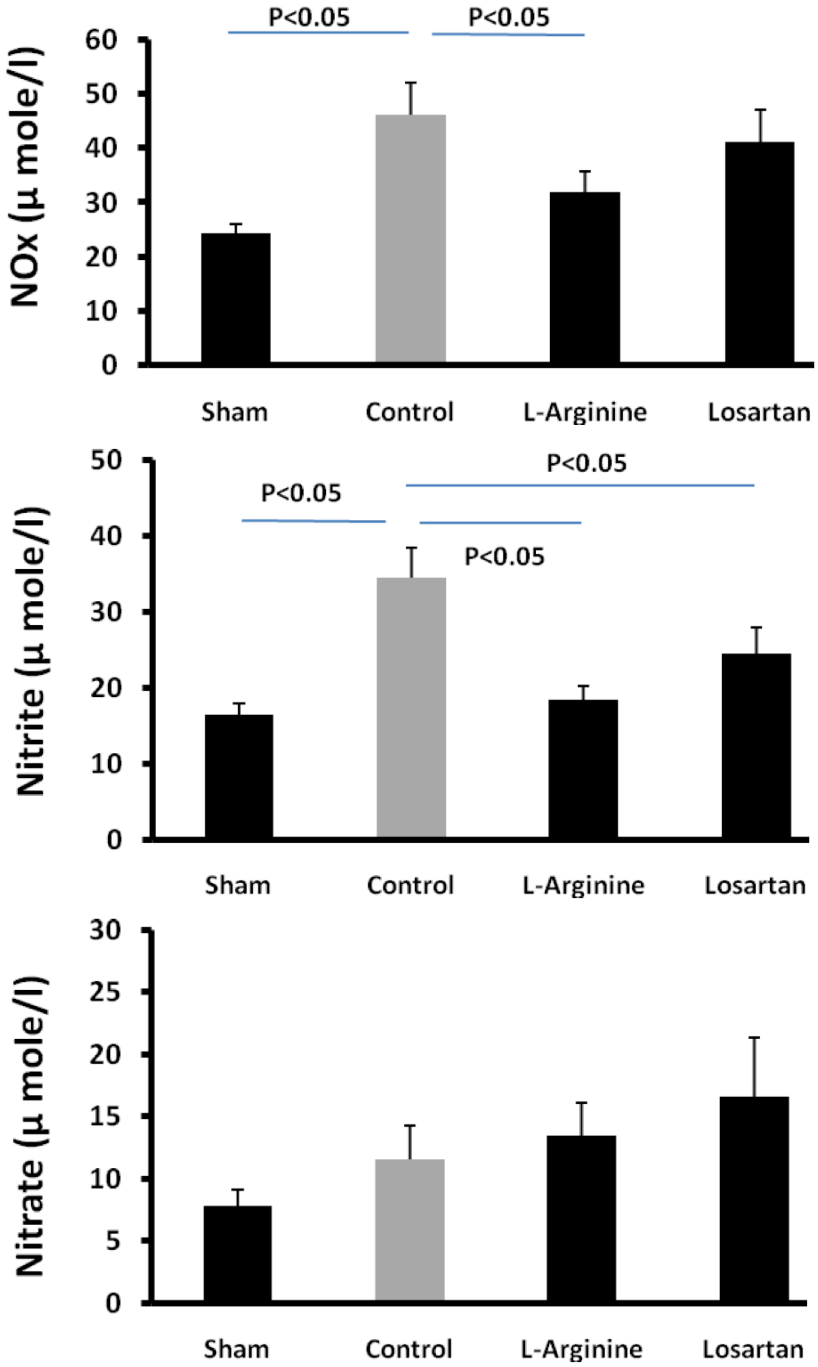

Figure 1: Serum levels of nitrite, nitrate, and NO_x in the groups.

agents did not affect the serum level of nitrate. It is reported that CP increases serum NO levels [5, 6], and increase in the NO level may promote CPIN [5]. NO-mediated cellular injury may arise by a variety of mechanisms and these mechanisms become significant only when high concentrations of NO are generated [9]. The effects of NO are related to its production site, duration of action, and the related NO synthase (NOS) isoform. The NOS isoforms are categorized into endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS) [10, 11]. iNOS, especially, may contribute to NO production in pathological conditions such as CPIN [12]. Selective inhibition of iNOS reduced CP-induced histological damage, renal dysfunction, oxidative stress, and nitrosative stress [12]. Therefore, the major source of increased NO in CPIN may not be related to eNOS. However, to avoid CPIN, control of NOx and nitrite levels seems to be necessary.

CONCLUSION

The present finding suggests that increase in serum level of NO; especially serum nitrite level, plays an important role in progression of CPIN; and nephroprotectant agents such as l-arginine and losartan may attenuate CPIN by reduction of serum levels of nitrite and NOx.

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