

PROTECTIVE EFFECT OF CAPTOPRIL AGAINST CISPLATIN-INDUCED NEPHROTOXICITY IN RATS

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ABSTRACT

This study has been initiated to determine whether captopril, an angiotensin-converting enzyme (ACE) inhibitor containing sulfhydryl (-SH) group can protect against cisplatin-induced nephrotoxicity in rats. A single dose of cisplatin (7.5mg/kg bwt) injected i.p. caused a significant increase in blood urea nitrogen (BUN) and creatinine levels amounting to 402% and 573%, respectively with a marked elevation in lipid peroxides measured as malondialdehyde (MDA) content (54%), accompanied by a significant decrease in reduced glutathione (GSH) content (27%) of kidney tissue as compared to control group. In addition, there were marked increases in kidney tissue content of nitric oxide (NO) (43%) and plasma endothelin-1(ET-1) (37%). On the other hand, administration of captopril (60mg/kg bwt, i.p.) 1 h before cisplatin protected the kidney as indicated by restoration of BUN, creatinine, MDA, GSH, NO and ET-1. These results indicate that captopril, an ACEI, has a protective effect against cisplatin-induced damage to kidney. This reflects the beneficial role of captopril in treatment of renovascular hypertension and congestive heart failure; an effect that may be related to its free radicals scavenging and antioxidant effects which are sulfhydryl dependent.

Keywords: Cisplatin, captopril, malondialdehyde, glutathione, nitric oxide, endothelin.

INTRODUCTION

Cisplatin, a widely used anti-neoplastic agent, is primarily used in the treatment of a variety of solid tumors (Meyer and Medias, 1994). However, the clinical usefulness of cisplatin has been seriously restricted because of its nephrotoxic side effects (Garnick *et al.*, 1988; Taguchi *et al.*, 2005). The major site of renal injury is the S3 segment of the proximal tubule in the outer medulla of the kidney. The toxicity in epithelial cells is morphologically characterized by tubular necrosis, loss of microvilli, alterations in number and size of lysosomes, and mitochondrial vacuolization. These structural alterations are accompanied by functional disturbance of various cell organelles (Kuhlmann *et al.*, 1997).

The mechanism by which cisplatin kills tumor cells is distinct from the mechanism by which it selectively kills the proximal tubule cells (Townsend *et al.*, 2003). Several investigators have suggested different mechanisms by which cisplatin selectively kills the proximal tubule cells. It was hypothesized that cisplatin is activated in the kidney to toxic metabolite through a platinum-glutathione conjugate, then to a cysteinyl-glycine-platinum-conjugate, which is further processed to a cysteine conjugate which is a metabolically reactive thiol (Salahudeen *et al.*, 1998). In addition, two distinct pathophysiological mechanisms have been recognized as promoters of cellular damage, i.e. inhibition of protein synthesis (Leibbrandt *et al.*, 1995; Rosenberg and Sato, 1993) and glutathione

depletion (Bompart, 1989; Zhang and Lindup, 1993). Moreover, many evidences have been accumulated that this side effect is closely related to reactive oxygen species (ROS) which cause mitochondrial damage, inhibition of membrane transport proteins and lipid peroxidation (Kuhlmann *et al.*, 1997; Baliga *et al.*, 1998; Matsushima *et al.*, 1998).

Nitric oxide (NO) originally identified as the endothelium-derived relaxing factor is known to be a critical intra-and intercellular signal molecule that plays a fundamental role in regulation of a wide variety of biologic functions (Turpaev, 1998). NO is a small lipophilic molecule that has a very short half-life. *In vivo* it is produced in the vascular endothelium, and by epithelial cells, nerve cells, smooth muscle cells, and inflammatory cells such as macrophages [Belvisi *et al.*, 1992; Guo *et al.*, 1995]. NO is synthesized in the vasculature by nitric oxide synthases (NOS), a family of enzymes that includes neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS). It can travel freely through cell membranes and can therefore act on neighboring target cells. Substrate flux through eNOS results in the production of nanomolar concentrations of NO; it is generally associated with the cytoprotective effects of NO and those actions that maintain vascular homeostasis. Substrate flux through iNOS results in the production of micromolar concentrations of NO; it is generally associated with the cytotoxic effects of NO and those actions that promote vascular pathology (Schwarz *et*

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al., 1999). In addition to its important physiologic function, NO is involved in various pathologic processes that lead to cytotoxicity (Hogg and Kalyanaraman, 1999; Murphy, 1999).

NO, as a free radical, has the ability to modify the redox environment of vascular cells. NO has opposing, dose-dependent effects on the intracellular redox environment; low levels of NO reduce the presence of intracellular reactive oxygen species (Garg and Hassid, 1990), but high levels of NO, through the formation of peroxynitrite (ONOO⁻), may promote oxidative damage (Radi *et al.*, 1991; Bonini and Augusto, 2001; Pfeiffer *et al.*, 2000). The role of nitric oxide (NO) and endothelins in the pathophysiology of acute renal failure has been discussed by Bruzzi *et al.* (1997) and Goligorsky *et al.* (2002).

In this regard, interaction of NO with ROS leads to generation of highly reactive and cytotoxic byproducts, such as peroxynitrite, which can attack on DNA, lipids and proteins (Beckman and Koppenol, 1996). Moreover, Knotek *et al.* (1996) reported that endothelins regulated blood flow, glomerular hemodynamics and sodium and water homeostasis in the kidney. Endothelins have been implicated in the pathophysiology of acute ischemic renal failure and nephrotoxicity induced by cyclosporine and cisplatin (Masereeuw *et al.*, 2000).

There is a great interest in expanding the clinical usefulness of cisplatin by developing new agents in order to reduce its nephrotoxicity (Kadikoylu *et al.*, 2004). Therefore, administration of various agents with cisplatin has been reported. Angiotensin-converting enzyme inhibitors (ACEIs) are widely prescribed for the treatment of hypertension and congestive heart failure. They also delay the progression of chronic renal failure and diabetic nephropathy (Omata *et al.*, 1996). Captopril, an ACEI containing sulfhydryl (-SH) group is widely used for such disorders (Jones *et al.*, 1992).

The aim of the present study is to examine the role of captopril in the protection of cisplatin-induced nephrotoxicity in rats besides its effects on kidney tissue MDA, GSH and NO as well as plasma ET-1.

MATERIALS AND METHODS

Animals

Adult male Wistar albino rats weighing 120-150 g were obtained from the animal facility of the National Cancer Institute (NCI), Cairo University and were kept in the animal facility of the Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt, one week for adaptation. They were fed standard diet pellets (El-Nasr Chemical Company, Abu-Zaabal, Egypt) and water was given *ad libitum*.

Materials

Lyophilized cisplatin (Cisplatyl 50, Laboratoire Roger Bellon, France) and captopril (Sigma-Aldrich Chemical Co., St. Louis, MO, USA) were dissolved in normal saline and given i.p. in doses of 7.5 mg/kg bwt (Al-Majed *et al.*, 2003; Uehara *et al.*, 2005; Mansour *et al.*, 2006) and 60 mg/kg bwt (Mansour *et al.*, 1999), respectively. All other chemicals were of the highest available commercial grade.

Experimental design

Forty adult male Wistar albino rats were divided into 4 groups (each of 10 animals) as follows:

- Group I: received 0.5 ml saline, injected i.p. and served as a control group.
- Group II: received a single dose of captopril (60 mg/kg bwt), injected i.p.
- Group III: injected with a single dose of cisplatin (7.5 mg/kg bwt), i.p.
- Group IV: injected i.p. with captopril (60 mg/kg bwt) 1 h prior to a single i.p. injection of cisplatin (7.5 mg/kg bwt).

Methods

Seven days after treatment, the animals were anesthetized with ether. Blood samples were withdrawn by heart puncture, centrifuged and plasma was separated. Plasma urea nitrogen and creatinine were determined according to the methods of Hallet and Cook (1971) and Bonsenes and Taussky (1945), respectively. Plasma ET-1 was measured through radioimmunoassay using an antibody specific for ET-1 (RAS 6901, Peninsula Laboratories), following method of Brunner *et al.* (1994).

Kidneys were removed and washed with ice cold saline, freed from surrounding fats, blotted with a piece of filter paper, weighed and homogenized in ice cold 0.15M KCl. GSH and MDA contents were estimated in kidney homogenate using Beutler *et al.* (1963) and Yoshioka *et al.* (1979) methods, respectively. NO level was determined in kidney tissues according to the method of Ignarro *et al.* (1987).

Statistical analysis of data

Statistical analyses were performed using InStat version 2.0 (GraphPad, ISI software, Philadelphia, PA, USA, 1993) computer program. Data are expressed as means $\pm$ standard error (SEM). Multiple comparisons were done using one way ANOVA followed by Tukey-Kramer as a post ANOVA test. The 0.05 level of probability was chosen as a criterion for significance.

RESULTS

Table 1 shows that injection of cisplatin (i.p.) in a dose of 7.5 mg/kg bwt caused significant increases in the levels of

Table 1: Effect of captopril treatment on cisplatin-induced increases in plasma urea and creatinine of male albino rats

Parameters Animal groups	Urea (mg/dl)	Creatinine (mg/dl)
Control	48 ± 3.84	0.52 ± 0.03
Captopril	45 ± 3.10	0.54 ± 0.04
Cisplatin	241 ± 18.30*	3.50 ± 0.45*
Cisplatin + captopril	60 ± 4.60 [#]	0.61 ± 0.12 [#]

Data are expressed as mean values ± SEM (n=10). Captopril was administered i.p. in a single dose of 60 mg / kg bwt, 1h before a single dose of cisplatin (7.5 mg / kg bwt, i.p.).

Multiple comparisons were done using one way ANOVA followed by Tukey-Kramer as a post-ANOVA test.

* Significantly different from control group at $p \leq 0.05$.

[#] Significantly different from cisplatin-treated group at $p \leq 0.05$.

Table 2: Effect of captopril treatment on cisplatin-induced changes in MDA and GSH contents in kidney tissue of male albino rats

Parameters Animal groups	MDA (nmol/g tissue)	GSH (μmol/g tissue)
Control	171.13 ± 14.75	2.18 ± 0.20
Captopril	149.13 ± 13.42	2.10 ± 0.20
Cisplatin	263.70 ± 10.64*	1.30 ± 0.10*
Cisplatin+Captopril	187.70 ± 16.27 [#]	3.20 ± 0.30 [#]

Data are expressed as mean values ± SEM (n=10). Captopril was administered i.p. in a single dose of 60 mg / kg bwt, 1h before a single dose of cisplatin (7.5 mg / kg bwt, i.p.).

Multiple comparisons were done using one way ANOVA followed by Tukey-Kramer as a post-ANOVA test.

* Significantly different from control group at $p \leq 0.05$.

[#] Significantly different from cisplatin-treated group at $p \leq 0.05$.

plasma urea nitrogen and creatinine amounted to 402% and 573%, respectively after seven days of treatment as compared to control group. On the other hand, pretreatment of animals with captopril significantly reduced the elevated levels of urea and creatinine in plasma by 75% and 83%, respectively (in comparison with cisplatin-treated group), which returned to the normal value.

Moreover, cisplatin (7.5 mg/kg) produced a significant increase (54%) and significant decrease (27%) in MDA and GSH content of kidney tissue, respectively, as compared with control group, while administration of captopril (60 mg/kg) before cisplatin decreased MDA level by 29% and increased GSH content by 146% in comparison with cisplatin-treated group (table 2).

Fig. 1 reveals that tissue NO level was significantly increased by 43% after cisplatin treatment as compared to control group. Pretreatment with captopril decreased NO production by 20% compared to cisplatin group.

Fig. 2 shows that plasma ET-1 level was significantly increased by 37% 7 days after injection of cisplatin in comparison to control group. However, administration of captopril before cisplatin reduced significantly the level of plasma ET-1 (as compared with cisplatin-treated group) which returned to the normal value.

DISCUSSION

This study shows that single injection of cisplatin in rats resulted in deterioration of renal function as indicated by elevation in plasma creatinine and blood urea nitrogen. These results are consistent with the previous studies on cisplatin-induced nephrotoxicity in experimental animals (Jones *et al.*, 1992; Miyaji *et al.*, 2001 and Behling *et al.*, 2006) and human beings (Weiner and Jacobs, 1983). The results reveal that creatinine and blood urea nitrogen returned approximately to the normal control levels when animals were injected with captopril 1h before cisplatin. This indicates that captopril has a protective potential on cisplatin-induced nephrotoxicity. Lipid peroxidation was

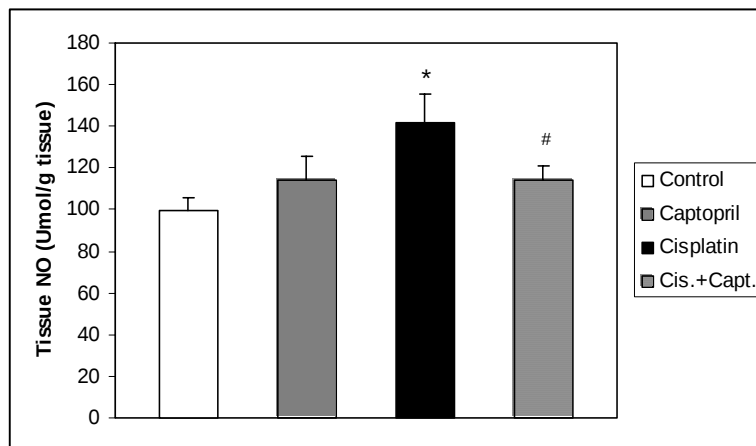


Fig. 1: Effect of captopril treatment on cisplatin - induced elevation in kidney tissue NO of male albino rats.

Data are expressed as mean values $\pm$ SEM (n=10). Captopril was administered i.p. in a single dose of 60 mg / kg bwt, 1h before a single dose of cisplatin (7.5 mg / kg bwt,i.p.).

Multiple comparisons were done using one way ANOVA followed by Tukey-Kramer as a post-ANOVA test

*Significantly different from control group at $p \leq 0.05$.

#Significantly different from cisplatin-treated group at $p \leq 0.05$.

Cis indicates cisplatin and capt indicates captopril.

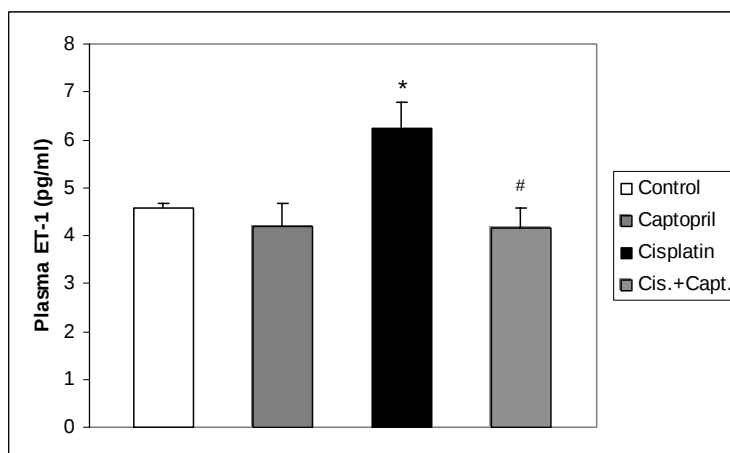


Fig. 2: Effect of captopril treatment on cisplatin - induced increase in plasma ET-1 of male albino rats.

Data are expressed as mean values $\pm$ SEM (n=10).Captopril was administered i.p. in a single dose of 60 mg/kg bwt,1h before a single dose of cisplatin(7.5 mg / kg bwt, i.p.).

Multiple comparisons were done using one way ANOVA followed by Tukey-Kramer as a post-ANOVA test

*Significantly different from control group at $p \leq 0.05$.

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monitored by measuring MDA resulting from free radical damage to membrane components of the cells. A moderate increase in the MDA concentration was observed in the kidney tissue of rats treated with cisplatin alone. Previous studies indicate an important role of ROS in the pathogenesis of the nephrotoxicity by cisplatin (Baliga *et al.*, 1998; Behling *et al.*, 2006 and Cetin *et al.*, 2006). Cisplatin induced free radical production causing oxidative renal damage. Various free radical scavengers have been shown to be effective in protection against cisplatin-induced nephrotoxicity (Weickert-Jacobsen *et al.*, 1999). Captopril significantly attenuated the increase

of MDA concentration in kidney tissue. This is probably due to free radicals scavenging and antioxidant properties which are sulfhydryl dependent (Chopra *et al.*, 1992 and Mansour *et al.*, 1999).

Reduced glutathione has a multiple role as an antioxidant agent. It functions as a scavenger of ROS, including hydroxyl radicals, singlet oxygen, nitric oxide and peroxynitrite (Halliwell and Gutteridge, 1989). Data of our study indicate that GSH increased when animals were injected with captopril before cisplatin administration. It has been found that captopril increased GSH content in

erythrocytes and brain (deCavanagh *et al.*, 2000). Our data of the antioxidant effects of captopril against cisplatin-induced nephrotoxicity are in agreement with Kalia *et al.* (2007), who observed a significant valuable effect of captopril on hepatic oxidative stress induced by arsenite in rats. Moreover, our results are consistent with Mansour *et al.* (1999) who revealed the promising protective effect of captopril against doxorubicin-induced nephrotoxicity.

Captopril is an angiotensin-converting enzyme inhibitor (ACEI) which is prescribed for the treatment of hypertension and congestive heart failure. ACEIs, also delay the progression of chronic renal failure and of diabetic nephropathy (Omata *et al.*, 1996). The mechanisms underlying these pharmacological effects of ACEIs are not fully understood. Various experimental evidences support the involvement of hemodynamic effects and/or the stimulation of cytoprotective prostaglandins (Van Gilst *et al.*, 1986). The potentiation of free radical scavenging action by ACEIs has also been postulated (Chopra *et al.*, 1992). Captopril was found to increase antioxidant enzymes and non- enzymatic antioxidant defenses in several mouse tissues (deCavanagh *et al.*, 1995 and 1997).

The role of NO in the pathophysiology of acute renal failure has been discussed (Goligorsky *et al.*, 2002). Increasing evidences suggest that NO has an important role in modulating oxidative stress and tissue damage. Peresleni *et al.* (1996) demonstrated that oxidative stress to the epithelial cell caused an increase in NO synthase, which results in an elevation in NO release, nitrite production, and decreased cell viability. It has been hypothesized that cytotoxic effect of NO production depends on redox state of the cell and its ability to generate peroxynitrite (ONOO⁻) anion. Peroxynitrite, a highly reactive oxidant formed during the interaction between NO and O₂⁻, can attack a wide variety of biological targets. The present study indicates the marked elevation in NO level in the damaged kidney tissue of the cisplatin-treated rats and captopril significantly attenuated this elevation. This elevation of NO generation in the renal tissue of cisplatin-treated rats supports the above mentioned mechanism relating generation of NO caused by free radicals under oxidative stress (Gossmann *et al.*, 2001). Deng *et al.* (2001) reported that captopril attenuates oxidative stress, ROS-NO interaction and NO production by decreasing angiotensin II that regulates nicotinamide-adenine dinucleotide phosphate oxidase which is thought to be a major source of ROS (Jones *et al.*, 1996).

Cisplatin induced significant increase in plasma ET-1. Cisplatin was found to increase serum angiotensin converting enzyme (ACE) and plasma angiotensin II (Ang II) levels in beagle dogs (Cubeddu *et al.*, 1990).

Ang II-induced endothelial dysfunction (Marvaala *et al.*, 2001) is associated with increased circulating and tissue ET-1 levels (Ruschitzka *et al.*, 1999). Cell culture studies have revealed that Ang II is a powerful stimulator of ET-1 synthesis and release in vascular smooth muscle and endothelial cells (Marvaala *et al.*, 2001). Takeda *et al.* (1994) observed an increase in urinary ET-1/ creatinine level one week after cisplatin treatment. On the other hand, our results revealed that captopril significantly reduced cisplatin-induced elevation in plasma ET-1. This is in agreement with Lapointe *et al.* (2002) who illustrated that captopril significantly reduced circulating Ang II and ET-1 in rats, although they thought that ACEIs exerted their beneficial effects exclusively by reducing the synthesis of Ang II. There is now mounting evidence that ACEIs exert at least some of their beneficial effects by inhibition of the degradation of the endogenous vasodilator bradykinin as well (Yang *et al.*, 2001).

In conclusion, captopril, an ACEI could have a protective effect against cisplatin-induced nephrotoxicity. This reflects the beneficial role of captopril in treatment of renovascular hypertension and congestive heart failure; an effect that may be related to its free radicals scavenging and antioxidant effects which are sulfhydryl dependent.

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