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Protective Effect of Beta Carotene Pretreatment on Renal Ischemia/Reperfusion Injury in Rat

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Abstract: Renal ischemia/reperfusion injury is a major cause of acute renal failure. The production of free radicals and reactive oxygen species are important factors contributing to ischemia/reperfusion injury. Thus, scavenging of the excess free radicals can be an important therapeutic approach. The present study examined the protective effect of beta carotene against renal ischemia/reperfusion injury in rat. Male adult Wistar rats (250-300 g) were exposed to 45 min of renal ischemia followed by 4 h of reperfusion. Beta carotene (10, 30 and 100 mg kg^{-1}) or vehicle was administered for 5 days prior to ischemia. Renal function was assessed by plasma and urinary analysis. Present results showed that ischemia/reperfusion injury increased ($p<0.05$-$p<0.001$) serum urea and creatinine levels, as well as urinary excretion of protein and calcium and fractional excretion of sodium, while decreased glomerular filtration rate and potassium excretion. However, alterations in these biochemical indices due to ischemia/reperfusion injury were attenuated by beta carotene pretreatment ($p<0.05$-$p<0.001$), although not by all doses. Since, beta carotene administration improved renal function, it seems that beta carotene protects renal tissue against ischemia/reperfusion-induced oxidative damage.

Key words: Beta carotene, ischemia/reperfusion, renal function, antioxidant, oxidative stress

INTRODUCTION

Renal ischemia and subsequent reperfusion (I/R) injury is encountered in a variety of clinical conditions such as renal transplantation, surgical revascularization of the renal artery and treatment of suprarenal aortic aneurysms (Bird *et al*., 1988). Renal ischemia is a major cause of acute renal failure (Star, 1998) which remains a major clinical problem with high prevalence and a mortality rate of up to 60% in critically ill patient (Leung and Yan, 2009).

I/R injury lead to the production of excess Reactive Oxygen Species (ROS) and reactive nitrogen species (RNS) (Li and Jackson, 2002). These species cause oxidative stress resulting in alterations in the level of mitochondrial oxidative phosphorylation, ATP depletion, increases in the intracellular calcium and activation of protein kinases, phosphatases, proteases, lipases and nucleases leading to a loss of cellular function and integrity (Sekhon *et al*., 2003).

A decreased efficiency of antioxidant defense mechanisms can exacerbate the extent of ROS-induced oxidative damage (Senthil *et al*., 2004). The organism has a complex network of the antioxidant defense system that comprises several enzymatic antioxidants such as superoxide dismutase, glutathione peroxidase and catalase and non-enzymatic antioxidants such as vitamin E (tocopherol), vitamin A, carotenoids (including beta carotene), vitamin C and glutathione (Sies, 1993).

Beta Carotene (BC) as a carotenoid pigment functions mainly as provitamin A in animals. It also scavenges free radicals powerfully (Sarada *et al*., 2002). It is known that BC is the most effective naturally occurring quencher of singlet oxygen and a strong scavenger of RNS (including nitrogen dioxide and peroxynitrite) in solution (Kikugawa *et al*., 1997). It is reported that BC inhibits the lipid peroxidation in hypoxic condition even better than vitamin E (Edes *et al*., 1989).

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Beneficial effects of carotenoid supplementation have been shown in many clinical conditions such as chronic renal failure (Yu and Paetau-Robinson, 2006), hepatic I/R injury (Codoner-Franch *et al*., 2008) and for the protection against cancer (Jeong *et al*., 2009).

Therefore, the goal of this study is to investigate the effects of beta carotene pretreatment on renal I/R injury in rat by biochemical analysis of renal function.

MATERIALS AND METHODS

Animals: Male Wistar rats weighing 250-300 g were used with free access to water and standard rat chow. All rats maintained at 22±1°C with a 12/12 h light/dark cycle. The experimental protocols were approved by the ethic committee of Ahwaz Jundishapur University of Medical Sciences.

Surgery and experimental design: Animals were randomly divided into five groups (n = 7): Group 1, all surgical procedures were carried out except clamping of the renal pedicles (Sham); Group 2, animals received Tween-80 in physiologic saline (4 mL kg^{-1}, i.p.) for 5 days and then I/R was performed (I/R); Groups 3, 4 and 5 which received BC at 10, 30 and 100 mg kg^{-1} through i.p., respectively (as BC10+I/R; BC30+I/R; BC100+I/R) (Singh *et al*., 2002; Sarada *et al*., 2002; Manda and Bhatia, 2003a, b), for 5 days prior to I/R induction (Matos *et al*., 2006). In the day of experiment, animals were anaesthetized with a combination of xylazine (20 mg kg^{-1}, i.p.) and ketamine (100 mg kg^{-1}, i.p.). Anaesthesia was maintained by supplementary doses of anaesthetics. Body temperature was recorded rectally and maintained at 37°C by using a thermostatic blanket (Harvard apparatus, USA). Tracheostomy was performed to maintain airway patency and to facilitate spontaneous respiration. The right femoral artery was cannulated (PE-50) to measure mean arterial blood pressure (MAP) continuously (Powerlab system, ADInstruments, Australia). The right femoral vein was cannulated for anaesthetics administration and heparinized saline infusion at 2-6 mL kg^{-1} h^{-1}. A midline laparotomy was performed and the bladder was cannulated for urine collection. The renal pedicles, containing the artery, vein and nerve supply of each kidney were isolated. After 45 min stabilization period, I/R injury was induced by clamping both renal vascular pedicles for 45 min, followed by 4 h of reperfusion (Nesic *et al*., 2006). In all groups, urine was collected during reperfusion period. The blood sample was obtained by a heparinized syringe from heart at the end of reperfusion. Blood was immediately centrifuged at 3000 rpm for 5 min and plasma was collected. Plasma and urine samples were stored at -20°C until analysis.

Biochemical analysis: Blood Urea Nitrogen (BUN) and creatinine concentration of plasma and urine were measured spectrophotometrically (Ultrospec 3000, Pharmacia Biotech, USA) by using commercial kits (Darman Kave, Iran). Creatinine clearance was calculated to estimate the Glomerular Filtration Rate (GFR). Proteinuria and calciuria were assessed by measuring urinary protein and Ca^{2+} concentrations using appropriate kits (Pars Azmun, Iran). Plasma and urine Na^{+} concentrations were measured by flame photometry (Metrolab 315, Argentina) then fractional excretion of Na^{+} ($FENa^{+}$) was calculated. Urinary K^{+} concentration was also measured by the same flame photometer. Creatinine clearance and fractional excretion of sodium were calculated as follows (Langenberg *et al*., 2006):

$$(Creatinine_{urine}/Creatinine_{plasma} \times Urine_{volume/time})/body\ weight$$

$$Sodium_{urine}/Sodium_{plasma} \times Creatinine_{plasma}/Creatinine_{urine} \times 100$$

All experiments and assays were performed in physiology research center laboratory of Ahwaz Jundishapur University of Medical Sciences.

Statistics analysis: Results were presented as Mean±SEM. Data from different groups were compared by using one-way Analysis of Variance (ANOVA) followed by Dunnett's test. Differences were considered significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Mean arterial pressure was relatively constant throughout the experiments (data not shown).

Animals that underwent renal I/R exhibited significant increases in BUN compared to sham group ($p<0.001$). Administration of BC attenuated BUN elevation dose-dependently ($p<0.05$-$p<0.001$) so that BUN of the BC100+I/R group was not significantly different from sham group (Fig. 1).

According to the results renal I/R induced a significant increase in the creatinine level compared to the sham group ($p<0.05$). However, as shown in Fig. 2, pretreatment with BC at 30 and 100 mg kg^{-1} but not at 10 mg kg^{-1} prevented ($p<0.05$) the I/R induced elevation of creatinine. In addition BC30+I/R and BC100+I/R groups were not significantly different from sham group.

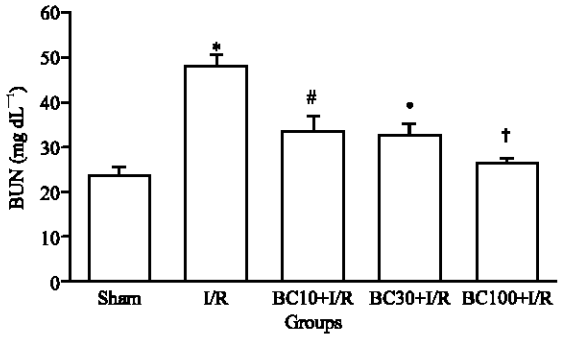

Fig. 1: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on BUN (Mean±SEM) in rat. Using one-way ANOVA followed by Dunnett's test. *Significant difference vs. sham group ($p<0.001$). #, • and † significant difference vs. I/R group, $p<0.05$, $p<0.01$ and $p<0.001$, respectively

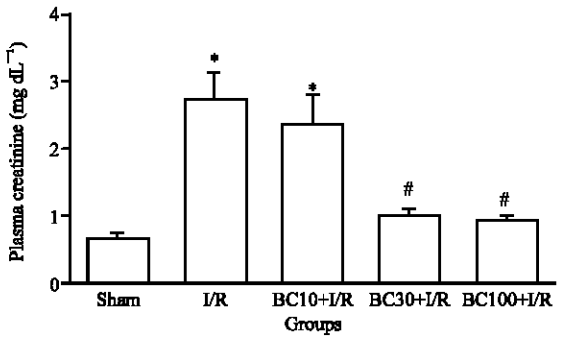

Fig. 2: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on plasma creatinine concentration (Mean±SEM) in rat. Using one-way ANOVA followed by Dunnett's test. *Significant difference vs. sham group ($p<0.05$). #Significant difference vs. I/R group ($p<0.05$)

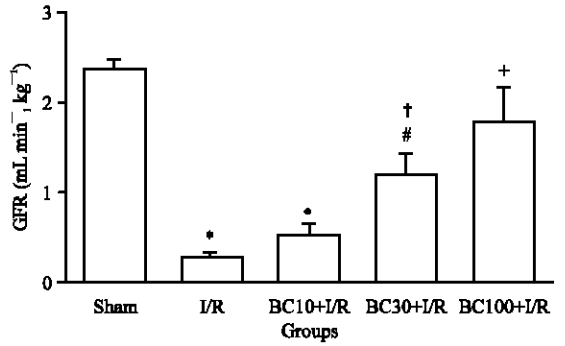

Fig. 3: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on GFR (Mean±SEM). Using one way ANOVA followed by Dunnett's test. *, • and † significant difference vs. sham group, ($p<0.001$, $p<0.01$ and $p<0.05$, respectively). # and + significant difference vs. I/R group, ($p<0.05$ and $p<0.01$, respectively)

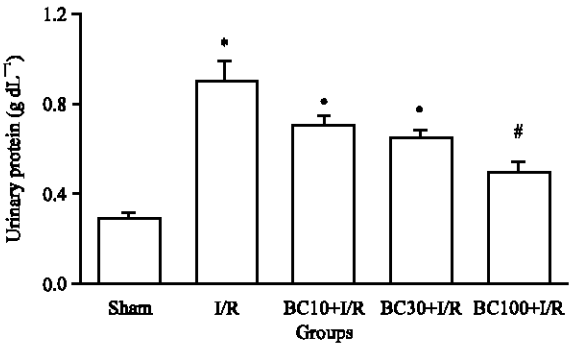

Fig. 4: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on urinary protein concentration (Mean±SEM) in rat. Using one way ANOVA followed by Dunnett's test. * and • significant difference vs. sham group ($p<0.01$ and $p<0.05$, respectively). #Significant difference vs. I/R group ($p<0.05$)

After I/R induction the GFR was decreased significantly compared to the sham group (Fig. 3), but it improved in all BC treated groups, especially in the BC30+I/R and BC100+I/R groups compared to the I/R group ($p<0.05$), as no considerable difference was observed between BC100+I/R and sham group.

Renal ischemia reperfusion induced proteinuria in rats ($p<0.05$) as compared to the sham group. Pretreatment with beta carotene at the dose of 100 mg kg^{-1}, however significantly reduced proteinuria ($p<0.05$), as shown in Fig. 4. The difference between sham and BC100+I/R groups was not remarkable.

Rats subjected to renal I/R injury demonstrated significantly ($p<0.01$) increased $FENa^+$ compared to sham group (Fig. 5). Although, BC in BC30+I/R and BC100+I/R groups could obviously decrease $FENa^+$ ($p<0.05$), but there is still a significant difference between BC30+I/R, BC100+I/R groups and sham group ($p<0.05$).

Urinary excretion of calcium increased remarkably ($p<0.001$) in I/R group compared to the sham group (Fig. 6). Following BC administration there was a reduction of calcium excretion only in the BC100+I/R group ($p<0.05$). BC100+I/R group had also significant difference with sham group ($p<0.05$).

As data show renal I/R significantly ($p<0.001$) increased urinary potassium excretion (Fig. 7) while pretreatment with BC decreased it in both BC30+I/R and BC100+I/R groups compared to the I/R group.

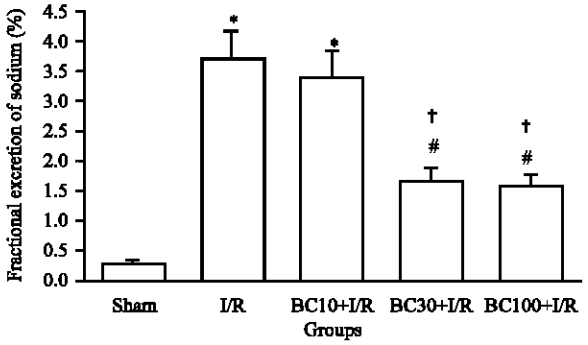

Fig. 5: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on fractional excretion of Na^+ (Mean±SEM). Using one way ANOVA followed by Dunnett's test. * and † significant difference vs. sham group ($p<0.01$ and $p<0.05$, respectively). #Significant difference vs. I/R group ($p<0.05$)

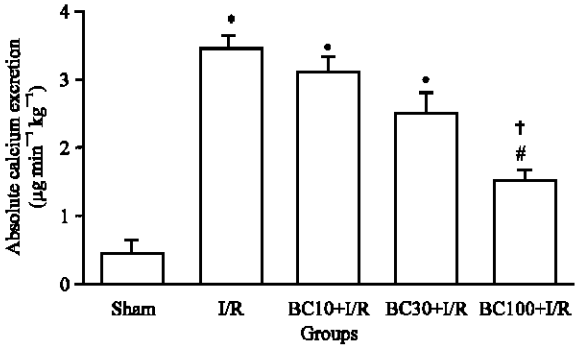

Fig. 6: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on absolute calcium excretion (Mean±SEM) in rat. Using one way ANOVA followed by Dunnett's test. *, • and † significant difference vs. sham group, ($p<0.001$, $p<0.01$ and $p<0.05$, respectively). #Significant difference vs. I/R group ($p<0.05$)

However, potassium excretion of all BC treated groups were higher than that of sham group ($p<0.05$, $p<0.01$).

Renal I/R injury causes both glomerular and tubular dysfunction (Chatterjee *et al*., 2002). Present results indicated that renal ischemia reperfusion causes elevation in BUN, creatinine and subsequent reduction in GFR which show impairment of glomerular function. Renal I/R also caused a large increase in $FENa^+$, potassium and calcium excretion, suggesting impairment of tubular function. I/R injury of the kidney by considerable proteinuria was seen in I/R group. This result is in accordance with previous study (Rabb *et al*., 1997) which notified I/R injury of the kidney enhances vascular permeability to the plasma proteins.

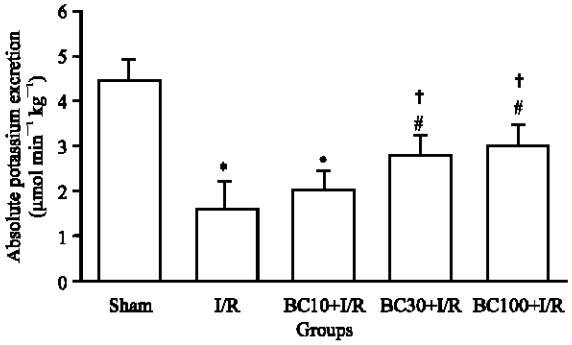

Fig. 7: Effect of I/R (ischemia reperfusion) and beta carotene pretreatment at 10, 30 and 100 mg kg^{-1} on absolute potassium excretion (Mean±SEM) in rat. Using one way ANOVA followed by Dunnett's test. *, • and † significant difference vs. sham group, ($p<0.001$, $p<0.01$ and $p<0.05$ respectively). #Significant difference vs. I/R group ($p<0.05$)

I/R injury is a major cause of acute renal failure (Liano and Pascual, 1996). The mechanisms underlying renal I/R injury are multifactorial and interdependent involving hypoxia, inflammatory responses and free radical damage (Williams *et al*., 1997). It is postulated that generation of free radicals and ROS are important factors contributing to I/R injury (Chander and Chopra, 2005). Animals with a favorable balance of oxidant production vs. oxidant removal show resistance to renal I/R injury (Nilakantan *et al*., 2007). Thus, scavenging of the excess free radicals can be an important therapeutic approach (Hearse, 1991). It has been shown that antioxidant enzymes, organic antioxidants or agents that inhibit the production of oxygen free radicals, decrease I/R injury (Inal *et al*., 2002; Yoneya *et al*., 2002; Di *et al*., 2006; Aktoz *et al*., 2007).

Among the various defense strategies, carotenoids (such as beta carotene) are most likely involved in the scavenging of two reactive oxygen species, singlet molecular oxygen ($O^{\bullet}_2$) and peroxyl radicals (Truscott, 1990; Young and Lowe, 2001; Schafer *et al*., 2002). BC by its strong ability in free radical scavenging (Kikugawa *et al*., 1997) can inhibit lipid peroxidation and consequent cell injury (Edes *et al*., 1989). It has been shown that BC also acts as an immune modulator at a low partial oxygen pressure (Wang and Russell, 1999).

Previous studies have reported that BC protects hepatocytes against both cellular necrosis and apoptosis in vitro by preventing bile acid-induced oxidative stress and mitochondrial perturbations (Gumpricht *et al*., 2004) and inhibits peroxynitrite induced damage in DNA (Muzandu *et al*., 2006). On the other hand, BC enhances antioxidant enzymes such as tissue glutathione

(Kheir-Eldin *et al*., 2001) and blood glutathione peroxidase (Sarada *et al*., 2002). BC therapy in diabetic rats prevents/reverses some parameter of oxidative stress (Maritim *et al*., 2002).

The results of this study revealed that BC administration could reduce I/R injury, as evidenced by decreased plasma creatinine and BUN, enhancement of GFR, decrease in $FENa^+$ and lower excretion of calcium and protein, as well as improvement in the potassium excretion compared to the control (I/R) group.

It is reported that BC also induces beneficial effect in chronic renal failure by decreasing oxidative stress (Yu and Paetau-Robinson, 2006). The protective effect of BC administration against oxidative stress was reported in other tissues such as brain (Kheir-Eldin *et al*., 2001) and gastric mucosa (Singh *et al*., 2002). BC supplementation in combination with alpha-tocopherol improves the antioxidant and energetic state of liver after ischemia and reperfusion injury (Codoner-Franch *et al*., 2008).

Findings of this study revealed that BC pretreatment at 100 mg kg^{-1} was more effective than 10 or 30 mg kg^{-1} in ameliorating of renal I/R injury. Comparison of different marker of renal I/R injury in this study showed that BC was more effective in ameliorating of glomerular dysfunction than tubular dysfunction, suggested by changes in creatinine and BUN versus $FENa^+$. It seems that some of this variation is due to different sampling methods of blood and urine, as blood samples were obtained at the end of reperfusion and urine samples were collected during reperfusion period.

In conclusion, the findings of this study indicate that pre-administration of beta carotene has a protective role in I/R damage of the kidney and the highest dose of antioxidant in this research was more effective.

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