Curcumin Attenuates Blood Pressure and Oxidative Stress in 2K-1C Renovascular Hypertensive Rats

Orachorn Boonla[1], Upa Kukongviriyapan.[1], Poungrat Pakdeechote[1], Veerapol Kukongviriyapan[2], Patchareewan Pannangpetch[2], Saowanee Nakmareong[3], Praphassorn Surawattanawan[4]

[1]Department of Physiology, [2] Pharmacology, Faculty of Medicine, [3]Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, 40002, Thailand

[4]Research and Development Institute, Government Pharmaceutical Organization, Rama 6 Road, Rajatevee, Bangkok, Thailand.

Background and Objective: Curcumin (CUR), is an active ingredient isolated from *Curcuma longa* Linn. Although CUR has been described as a strong antioxidant, its effect on renovascular hypertension has not been investigated. The objective of this study was to investigate the effect of CUR on the reduction of blood pressure and oxidative stress status in renovascular hypertensive rats.

Methods: Male Sprague-Dawley rats were underwent 2-kidney-1-clip (2K-1C) or sham operation. Three days after operation, 2K-1C and sham operated rats were recovered and divided into five groups (N=6/group). Group 1 and 2 are sham operated rats receiving propylene glycol (PG), a solvent of CUR, and CUR (100 mg/kg/day) continuously for six weeks, respectively, Group 3-5 are 2K-1C hypertensive rats receiving PG and CUR at doses of 50 and 100 mg/kg/day respectively, for six weeks. Blood pressure was measured weekly. Superoxide production in carotid arteries, plasma malondialdehyde (MDA) and plasma protein carbonyl were assessed at the end of experimental period.

Results: Chronic treatment with CUR significantly decreased blood pressure of the 2K-1C hypertensive rats ($p<0.05$). The levels of superoxide production and oxidative stress markers of hypertensive animals were also reduced after CUR treatment ($p<0.05$). All parameters studied were not affected after CUR treatment in normotensive animals.

Conclusion: Our data suggest that chronic treatment with CUR reduces blood pressure and oxidative stress in rats with renovascular hypertension. The plausible mechanisms might be attributable to the antioxidant property of CUR.

Keywords: curcumin, antioxidant, oxidative stress, 2K-1C renovascular hypertension

ศรีนครินทร์เวชสาร 2556;28 (supple) Srinagarind Med J 2013;28 (supple)

Introduction

The experimental two-kidney, one-clip hypertension (2K-1C) or Goldblatt renovascular hypertension[1] resembles human renovascular hypertension and is a widely used model of chronic hypertension. The renin angiotensin aldosterone system (RAAS) is activated in this model of hypertension, and increased angiotensin II is associated with increased oxidative stress. Angiotensin II enhanced superoxide generation via activation of vascular NAD(P)H oxidases. Increased superoxide production results in oxidative damage[2] and reduces nitric oxide (NO) bioavailability, consequently development of hypertension[3] .

Curcumin (CUR) (diferuloymethane), is an active compound and strong antioxidant isolated from *Curcuma longa* Linn. Previous study demonstrated that CUR reduced blood pressure and decreased oxidative stress in NO deficient rats[4]. However, no previous study has

examined the effect of CUR on alleviation of oxidative stress and blood pressure in the 2K-1C hypertension model.

Objectives

The objective of this study was to investigate the effect of CUR on reduction of blood pressure and oxidative stress status in renovascular hypertensive rats.

Methods

Animals and experimental procedures

Male Sprague-Dawley rats (160-180 g) obtained from National Laboratory Animal Center, Mahidol university, Salaya, Nakornpathom are used in this study. The animals were housed at the Northeast Laboratory Animal Center, Khon Kaen university, Thailand. All animals were maintained and kept on 12-hour light/dark cycle at 25± 2^0 C with free access to standard rat chow and water. All procedures were approved by the Institutional Animal Ethics Committee of Khon Kaen university (AEKKU 66/2555).

Induction of renal hypertension was carried out in rats according to the 2K-1C model originally described by Goldblatt[1]. 2K-1C hypertension was induced by clipping the left renal artery with a silver clip (0.2 mm internal diameter). Sham-operated rats underwent the same surgical procedure except for the placement of the renal artery clip. Rats were randomly divided into five experimental groups: group 1; sham-operated rats received propylene glycol (PG), a solvent of CUR, group 2; sham-operated rats received CUR 100 mg/kg/day, and groups 3-5; 2K-1C hypertensive rats received PG, CUR at doses of 50 and 100 mg/kg/day, respectively. Oral administration with PG, CUR 50 or 100 mg/kg/day was started 3 days after operation and maintained for 6 weeks. Body weight and systolic blood pressure (SBP) were assessed weekly throughout the experimental period by tail-cuff plethysmography (Blood pressure analyzer, model 179; IITC, Woodland Hills, California, USA).

At the end of the experiment, the animals were anesthetized with pentobarbital sodium (60 mg/kg, i.p.). Blood samples were collected from abdominal aorta for measurement of oxidative stress markers. The concentration of plasma MDA, a lipid peroxidation maker, was measured as thiobarbituric acid reactive substances by a spectrophotometric method as previously described[4]. Protein oxidation in plasma was assessed by the determination of carbonyl groups based on the reaction with DNPH following a previously described[5].

The carotid arteries were rapidly excised for assessment of superoxide production (O2•") by using lucigenin enhanced chemiluminescence method[4].

Statistical analysis

Data are presented as mean ฑ S.E.M. Statistical differences were evaluated by one-way analysis of variance (ANOVA) and followed by Student Newman–Keul's test to show specific group differences. All analysis was performed using Sigmastat software version 3.1. Statistical significance was determined at a level of $p< 0.05$.

Results

At the beginning of the experiments, baseline SBP and body weight were not different in all experimental groups (Fig. 1A and B). SBP progressively increased in 2K-1C hypertensive rats after the first week of surgery, and progressive increase in SBP was found until six weeks of experimental period. Interestingly, 2K-1C rats treated with CUR 50 or 100 mg/kg/day showed significantly reduction in blood pressure, however, the SBP of these rats was still higher than the normal control level (Fig. 1A). These results indicate that CUR possesses antihypertensive properties. There is no change in SBP of sham rats treated with UR at dose of 100 mg/kg.

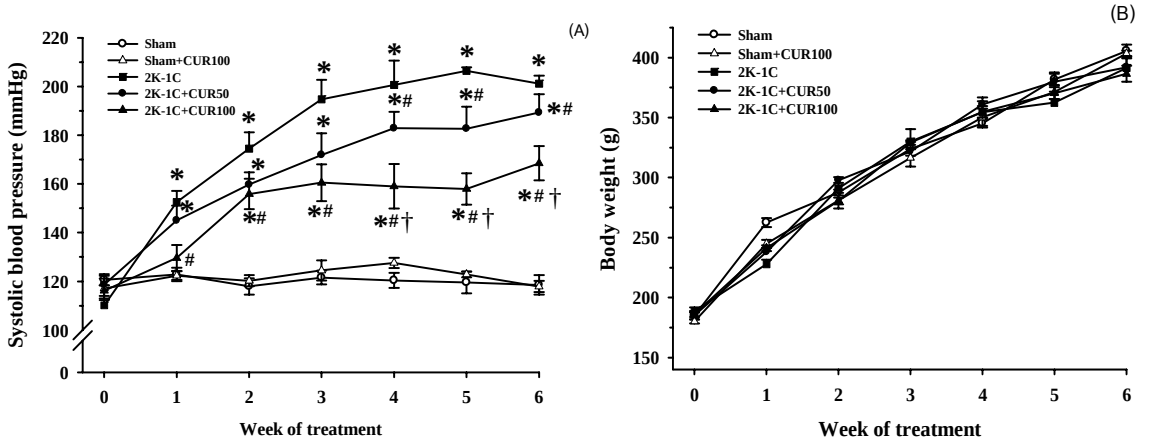

Figure 1 Effects of curcumin on systolic blood pressure as measured by tail-cuff method (A) and body weight (B) of rats in all experimental groups. Values are expressed as mean ± S.E.M. (n= 6 /group), *p< 0.05 vs. sham group, #p< 0.05 vs. 2K-1C group and □ p< 0.05 vs. 2K-1C+CUR50 group.

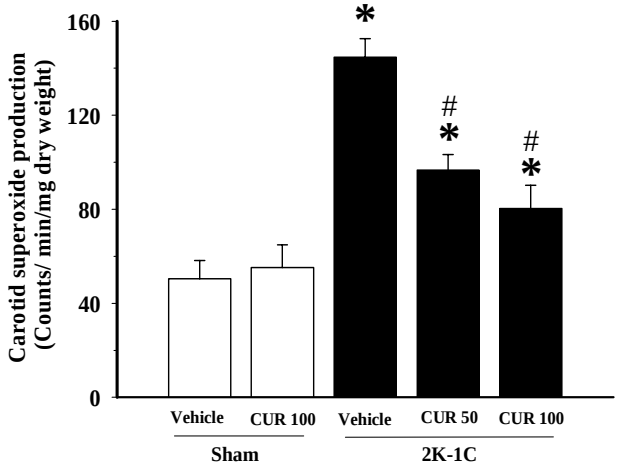

Figure 2 Effect of curcumin on superoxide production in the carotid arteries of rats in all experimental groups. Values are expressed as means ±S.E.M. (n= 6 /group), *p< 0.05 vs. sham group and #p< 0.05 vs. 2K-1C group.

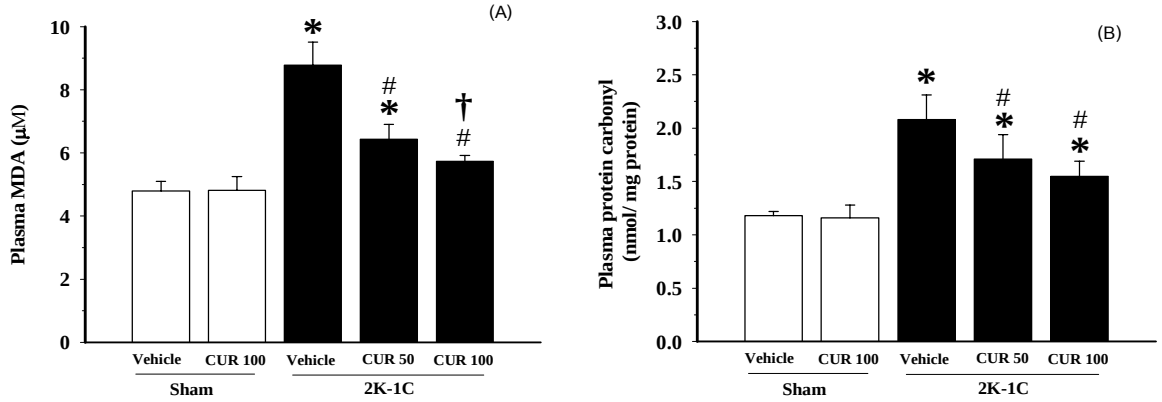

Figure 3 Effects of curcumin on plasma MDA (A) and plasma protein carbonyl contents (B) of rats in all experimental groups. Values are expressed as means ± S.E.M. (n= 6 /group), *p< 0.05 vs. sham group, #p< 0.05 vs. 2K-1C group and □ p< 0.05 vs. 2K-1C+CUR50 group.

Proceeding

The levels of O2•- production in carotid arteries, plasma MDA and protein carbonyl were significantly increased in 2K-1C hypertensive rats when compared to the sham controls ($p< 0.05$; Fig. 2 and 3), indicating that oxidative stress was occurred in rats with renovascular hypertension. 2K-1C rats with chronic administration with CUR (50 and 100 mg/kg/day) alleviated oxidative stress by suppressing the amount of vascular O2•" production and decreasing plasma MDA and protein carbonyl concentrations (Fig. 3A and B). The reduction in oxidative stress after CUR administration was associated with a decrease in SBP of 2K-1C hypertensive rats. It is found that all parameters studied were not affected after CUR treatment in sham (normotensive) animals.

Conclusion

The data in this study demonstrated that chronic treatment with CUR reduces the development of hypertension and oxidative stress in rats with renovascular hypertension. The involved mechanisms might be the antioxidant property of CUR.

Acknowledgments

This study was fund by grants from the Invitation Research grant (No.I55228), Faculty of Medicine, Khon Kaen University. Orachorn Boonla was supported by the Royal Golden Jubilee Ph.D. program, The Thailand Research Fund.

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Proceeding