Tetrahydrocurcumin prevents hypertension and reduces oxidative stress induced by cadmium

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Abstract

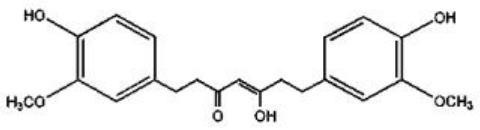
Tetrahydrocurcumin (THU), a compound-derived from curcumin, has been reported to possess strong antioxidant. The present study was aimed to investigate the protective effect of THU on cadmium-induced hypertension and oxidative stress in a mouse model exposed to Cd. Mice received $CdCl_2$ (100 mg/L) via drinking water for 8 weeks. Animals in the control groups received deionized water as drinking water and were orally administered with propylene glycol as the vehicle. THU was intragastrically administered at dose of 100 mg/kg body weight/day concurrently with or without Cd treatment. Results showed that Cd administration elevated arterial blood pressure and increased oxidative stress by enhancing superoxide production and elevating lipid peroxidation and protein oxidation. THU supplementation significantly decreased blood pressure (P<0.05), which is related to the suppression of oxidative stress. Overall findings provide evidence for a protective effect of THU on mice exposed to Cd. The present study suggests that THU might be used as a dietary supplement to protect hypertension and oxidative stress in Cd-induced toxicity.

Keyword: Tetrahydrocurcumin, Hypertension, Cadmium, Oxidative stress

1. Introduction

THU is one of the major metabolites of curcumin, the component of turmeric [1]. Recently, attention has been focused on THU, because this compound appears to exert greater antioxidant activity in various conditions [2]. THU also acts as a novel chemopreventive agent [3]. Previous studies have demonstrated that THU prevents oxidative stress, endothelial dysfunction, hypertension and diabetes in rats [4, 5].

Cadmium (Cd) is a serious industrial and environmental pollutant. It has been characterized as a "class I carcinogen" and identified as a major environmental contaminant and an occupational health hazard. A large amount of Cd has been released into the environment, including air, water and soils. Cd causes damages to various organs, such as cardiovascular, pulmonary, renal, musculoskeletal and endocrine systems [6]. Previous studies indicated that Cd exposure increases risk of hypertension [7, 8]. However, the mechanisms involved with hypertension remain unclear.



Tetrahydrocurcumin

Chemical Structures of tetrahydrocurcumin [2]

2. Objective

The aim of this study was to investigate whether THU could protect against hypertension and oxidative stress in mice exposed to Cd.

3. Materials and methods

3.1 Animals and experimental protocol

Procedures and experimental protocols were reviewed and approved by the Institutional Animal Ethics Committee of Khon Kaen University (AEKKU 42/2554). Male ICR mice (25-30 g) obtained from the Animal Care Unit of the Faculty of Medicine, Khon Khaen University, Khon Kaen, Thailand. Mice were maintained in a temperature controlled room with a 12 h light: 12 h dark cycle and free access to standard chow diet (Chareon Pokapan Co. Ltd., Thailand) and water.

After 1 week of acclimatization, mice were randomly divided into four experimental groups with 6-8 animals per group, consisting of (1) normal control group receiving deionized water (DI) as drinking water and orally administered with vehicle (propylene glycol); (2) THU control groups receiving deionized water (DI) as drinking water and THU at dose of 100 mg/kg BW; (3) Cd-treated group receiving $CdCl_2$ (100 mg/L) in drinking water and vehicle; and (4) THU-treated groups receiving $CdCl_2$ and THU at dose of 100 mg/kg BW. The animals were exposed to $CdCl_2$ (100 mg/L) and administered with THU (100 mg/kg BW) for 8 consecutive weeks.

3.2 Assessments of blood pressure and heart rate

Flowing 8 weeks of treatment, mice were anesthetized with ketamine/xylazine (100:2.5 mg/kg, i.p.), blood pressure and Heart rate were determined. A tracheotomy was performed and animal's body

temperature was kept constant at 37±2 ◦C by a heating pad. The carotid artery was cannulated and connected to a pressure transducer for monitoring arterial blood pressure using the Acqknowledge data acquisition and analysis software (Biopac System Inc., CA, USA). The left jugular vein was cannulated for infusion of vasoactive agents. At the end of the experiment, mice were sacrificed by overdose of anesthetic drugs, blood samples, thoracic aortas and hearts were collected subsequently for assays of oxidative stress makers.

3.3 Assay of superoxide production

Superoxide ($O_2^{\bullet-}$) production was determined by using lucigenin enhanced chemiluminescence method [9]. In brief, a vessel segment was carefully cleaned and incubated in 450 µl oxygenated Krebs-Ringer bicarbonate solution at 37°C for 30 minutes. The chemiluminescence signal was measured after the addition of lucigenin (30 µM), and counted in a luminometer (Turner Biosystems, CA, USA).

3.4 Assay of malondialdehyde

Malondialdehyde (MDA) is the main degradative product of lipid peroxidation and is used as an indicator of cellular damage caused by reactive oxygen species (ROS). MDA in plasma and heart tissues were analyzed by using thiobarbituric acid as previously described [9]. The level of MDA in the tissues was normalized against the protein concentration. Protein was determined by the Bradford dye binding method.

3.5 Assay of protein carbonyl

Protein oxidation in plasma and heart tissues were assessed by the determination of carbonyl groups based on the reaction with dinitrophenyl hydrazine (DNPH) as previously described [2] with modifications [9]. The protein carbonyl content was determined by a spectrophotometric method. The protein amount was assayed by Bradford dye binding method.

3.6 Statistical Analysis

Results were expressed as mean ± S.E.M. Differences among treatment groups were analyzed by one-way analysis of variance (ANOVA) followed by post hoc comparison test. A *p*-value of less than 0.05 was considered significant.

4. Results

4.1 Effect of THU on blood pressure and heart rate

Data of blood pressure (BP) and heart rate (HR) of all experimental groups are shown in Figure 1. Cd-treated mice showed a significant increase in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) when compared with controls (Figure 1A, 1B and 1C). Mice receiving THU 100 mg/kg/day together with Cd showed a significant decrease in BP when compared with mice receiving Cd alone. There were no significant differences in heart rate among all of experimental groups (Figure 1D).

4.2 Effect of THU on superoxide production

Exposure to Cd for 8 weeks induced a marked $O_2^{\bullet-}$ production in thoracic aorta compared to those of normal controls (Figure 2). THU at dose of 100 mg/kg significantly reduced the rate of $O_2^{\bullet-}$ production in the thoracic aorta as compared to mice treated with Cd alone.

4.3 Effect of THU on lipid peroxidation

The results show that exposure to Cd for 8 weeks induced a remarkable increase of MDA levels in plasma and heart tissues (Figure 3A and 3B). Treatment with THU significantly alleviated the oxidative stress by decreasing the MDA levels in plasma and heart tissues. In addition, administration of THU 100 mg/kg did not change the normal levels of MDA as shown in the control groups (Figure 3).

4.4 Effect of THU on protein oxidation

Cd also causes damage to protein, as there was an elevation in plasma and heart protein carbonyl in Cd-treated mice (Figure 4). However, THU at tested dose significantly suppressed protein oxidation (Figure 4A and 4B).

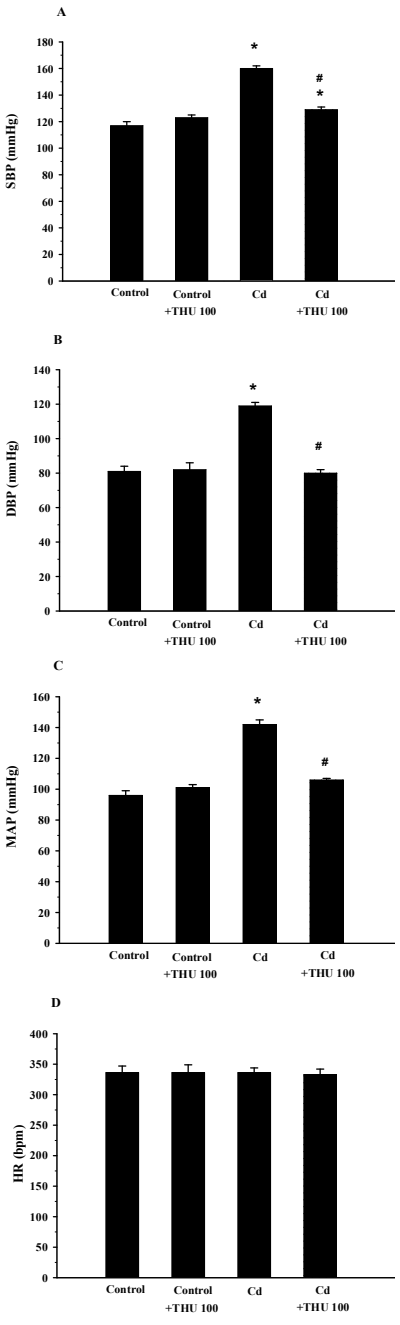


Figure 1. Changes in blood pressure and heart rate in all studied animals, (SBP, systolic blood pressure (A); DBP, diastolic blood pressure (B); MAP, mean arterial pressure (C); HR, heart rate (D)). Data are expressed as mean ± S.E., n=6-8/group; $^{*}P < 0.05$ compared with normal control group; $^{\#}P < 0.05$ compared with Cd control group.

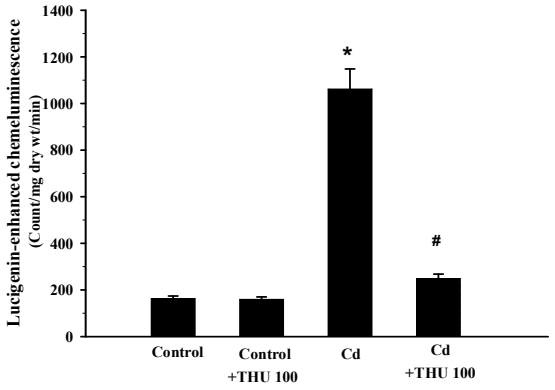
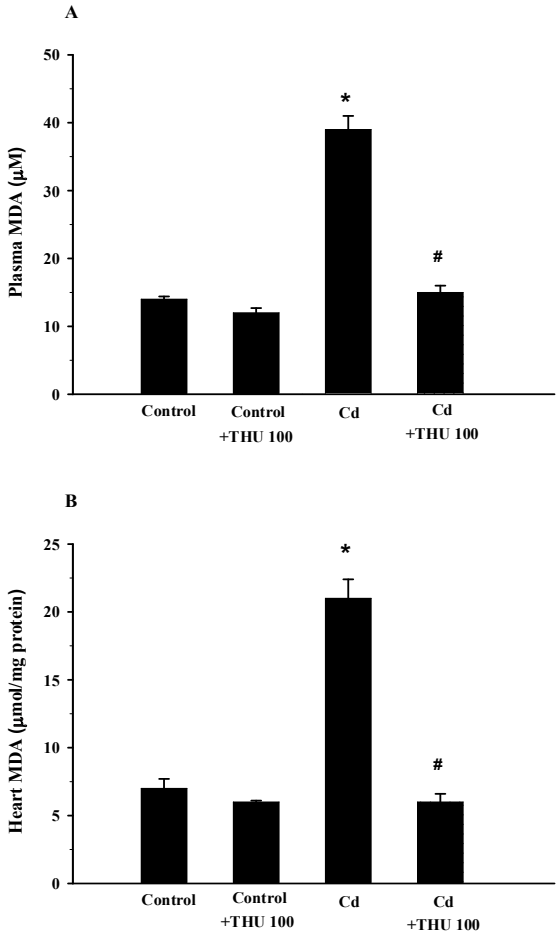


Figure 2. Effect of THU on $O_2^{\bullet-}$ production in mice exposed to Cd. Data are expressed as mean ± S.E., n=6-8/group; $^{*}P < 0.05$ compared with normal control group; $^{\#}P < 0.05$ compared with Cd control group.



FigFigure 3. Effect of THU on MDA levels in plasma (A) and heart tissues (B) of mice exposed to Cd. Data are expressed as mean ± S.E., n=6-8/group; $^{*}P < 0.05$ compared with normal control group; $^{\#}P < 0.05$ compared with Cd control group.

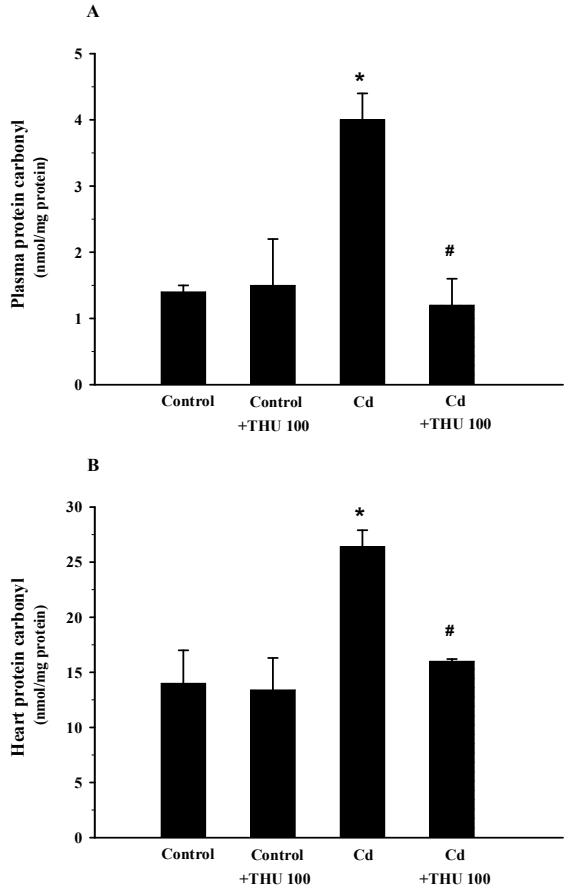


Figure 4. Effect of THU on protein carbonyl levels in plasma (A) and heart tissues (B) of mice exposed to Cd. Data are expressed as mean ± S.E., n=6-8/group; $^{*}P < 0.05$ compared with normal control group; $^{\#}P < 0.05$ compared with Cd control group.

5. Discussion

In this study, the beneficial effect of THU on subchronic Cd-induced oxidative stress and hypertension has been demonstrated. THU prevents development of blood pressure, and this effect was related to the ability of THU to suppress oxidant formation as indicated by the reduction in $O_2^{\bullet-}$ production, MDA and protein carbonyl in Cd-treated mice.

Previous studies found that long-term exposure to Cd increased blood pressure [10, 11]. Evidently, oxidative stress and free radicals can lead to cellular injury in the form of damaged DNA, lipids and proteins, which are often implicated in Cd toxicity [12]. It has been proposed that Cd induces ROS formation resulting in vascular dysfunction which finally leads to hypertension [13]. Previous studies reported the significant antioxidant effects of the THU. THU protects against oxidative stress by decreasing serum and tissues lipid peroxidation in streptozotocin-nicotinamide-induced diabetic rats [14]. THU also inhibited the oxidative modification of LDL in cholesterol-fed rabbits [15]. Pari and Amali have reported that THU exerts significant protection against chloroquine induced toxicity by its ability to ameliorate the lipid peroxidation through the free radicals scavenging activity, which enhanced the levels of antioxidant defense system [16]. The mechanism of antioxidant action of THU on the basis of the molecular structure might be explained by beta-diketone moiety of THU. It exhibits antioxidant activity by cleavage of the C-C bond at the active methylene carbon between two carbonyls in the beta-diketone moiety [17].

6. Conclusions

The present study demonstrated that subchronic exposure to Cd in mice causes an increase in blood pressure and oxidative stress. Supplementation with THU to these animals can ameliorate these deteriorate conditions. The protective effect of THU may be due to a marked decrease in oxidative stress. Further exploration on cellular mechanisms contributing to its vascular protective effect is required. Collectively, these findings suggest that dietary supplementation of THU may be useful to prevent oxidative stress, and hypertension during Cd intoxication.

7. Acknowledgments

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8. References

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