Effects of vitamin E on mercuric chloride-induced renal interstitial fibrosis in rats and the antioxidative mechanism

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Objective: To observe the effects of vitamin E (Vit E) on mercuric chloride (HgCl2)-induced renal interstitial fibrosis (RIF) in rats and discuss its antioxidative mechanism.

Methods: A total of 32 Sprague-Dawley rats were randomly assigned to three groups: normal group, model group and Vit E group. RIF was induced by oral administration of HgCl2 at a dose of 8 mg/kg body weight once a day for 9 weeks. Rats in Vit E group were administered with Vit E capsule at 100 mg/kg body weight, and rats in normal and model groups were treated with normal saline. At the end of the 9th week, rats were sacrificed and renal hydroxyproline (HyP) content was assayed by Jamall’s method and collagen deposition was visualized by hematoxylin and eosin (HE), Masson’s trichrome and periodic acid-silver methenamine (PASM) staining. The activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and contents of glutathione (GSH) and malondialdehyde (MDA) in kidney tissue were tested with commercial kits. The expressions of nuclear factor-κB (NF-κB), inhibitor-κB (IκB), phospho-IκB (p-IκB) and tumor necrosis factor-α (TNF-α) were determined by Western blot. The expression of α-smooth muscle actin (α-SMA) was assayed by Western blot and immunofluorescent staining.

Results: Renal HyP content, HE, Masson’s trichrome and PASM staining results and α-SMA expression confirmed development of HgCl2-induced RIF in rats. Oxidative stress markers GSH, GSH-Px and MDA confirmed oxidative stress in RIF rats. Compared with model rats, rats

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in Vit E group had lower kidney Hyp content ($P<0.01$). GSH and MDA contents decreased significantly in Vit E group compared with model group ($P<0.01$). The expressions of NF-$\kappa$B and IκB had no significant difference among all groups ($P>0.05$). In Vit E group, the expressions of p-IκB and TNF-$\alpha$ decreased significantly compared with model group ($P<0.01$). The expression of α-SMA in Vit E group was also decreased significantly compared with model group ($P<0.01$).

**Conclusion:** Vit E has a protective effect on experimental RIF induced by HgCl$_2$ in rats and it is related to inhibition of lipid peroxidation, which involves blocking of NF-$\kappa$B signaling pathway and the activation of cells producing extracellular matrix.

**Keywords:** vitamin E; renal interstitial fibrosis; mercuric chloride; lipid peroxidation; animal experimentation; rats

A growing body of evidence suggests that mercurial compounds, in particular, mercuric chloride (HgCl$_2$) are toxic to humans. Owing to the use of mercury pesticides in agriculture or as components of batteries or in fluorescent light bulbs, low levels of mercury exists in a wide variety of physical or chemical states, each of which has unique characteristics for target organ specificity$^{[1]}$. For example, exposure to mercury vapor or to organic mercury compounds specifically affects the central nervous system$^{[2]}$, while kidney, liver and gastrointestinal tract are mainly targeted by inorganic mercury compounds, such as HgCl$_2$$^{[1,3]}$.

HgCl$_2$ is one of the most common causes of acute chemical nephropathy and acute renal failure$^{[3]}$. Mercury poisoning can induce fibrogenic growth factors such as transforming growth factor-$\beta_1$ (TGF-$\beta_1$), connective tissue growth factor (CTGF) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and accumulation of extracellular matrix (ECM) proteins$^{[3]}$. The excessive deposition of interstitial matrix components was mainly due to an expansion of interstitial myofibroblast populations that are characterized by de novo activation of $\alpha$-smooth muscle actin ($\alpha$-SMA).

Previous studies of renal impairment usually used animal model of acute renal failure with oral or intraperitoneal administration of HgCl$_2$$^{[4,5]}$. However, pathological process of acute mercury poisoning is different from clinical chronic renal diseases induced by mercuric poisoning. In our previous study, a rat model of renal interstitial fibrosis (RIF) was successfully established by oral administration of HgCl$_2$. It was characterized by obvious lipid peroxidation, activation of renal myofibroblasts, and over-production and deposition of ECM$^{[7,8]}$, which was a satisfactory RIF experimental model to test antifibrotic agents.

Alpha-tocopherol (vitamin E, Vit E), which is lipid-soluble and acts mainly within cell membranes, is the first line of defense against lipid peroxidation$^{[9]}$. Although Bennett et al$^{[10]}$ showed that vitamins A and E suppressed renal inflammation in pyelonephritis, there have been few studies examining the relationship between Vit E administration and pyelonephritis scarring since then. In this study, we aimed to investigate the mechanism of action of Vit E against RIF-related lipid peroxidation.

**1 Materials and methods**

1.1 Experimental animals A total of 32 male Sprague-Dawley rats weighing (120±10) g (specific pathogen free, Certificate No. SCXK 2003-0003) were supplied by the Shanghai Laboratory Animal Center, Shanghai Institute for Biological Sciences of Chinese Academy of Sciences. The animals were housed in an air-conditioned room at 25°C with a 12/12 h dark/light cycle. All animals received humane care during the study with unlimited access to chow and water.

1.2 Drugs and Reagents Vit E capsule (100 mg/capsule; batch number: 20040602) was purchased from Shanghai Sine Wanxiang Pharmaceutical Co., Ltd (Shanghai, China). HgCl$_2$ (powder, 500 g/bottle; batch number: 2000102) was purchased from Guizhou Tongren Chemical Reagent Factory (Guizhou Province, China). The kits for assessing lipid oxidation injury, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities and glutathione (GSH) and malondialdehyde (MDA) contents, were purchased from Nanjing Jiancheng Biotech Company (Jiangsu Province, China). Complete mini-plate inhibitor cocktail was purchased from Roche Company (Basel, Switzerland); mouse α-SMA antibody was purchased from Dako Company (Glostrup, Denmark); rabbit inhibitor-κB (IκB) antibody and rabbit TNF-α antibody were purchased from Boster Company (Wuhan, China); mouse anti-nuclear factor (NF)-κB p65 antibody and mouse anti-phospho-IκB (p-IκB) antibody were purchased from Transduction Laboratories (Lexington, Kentucky, USA); horseradish peroxidase-conjugated rabbit anti-mouse immunoglobulin and peroxidase-conjugated goat anti-rabbit immunoglobulin were purchased from Amersham Pharmacia Biotech Company (Buckinghamshire, England); Cy3-labeled goat anti-mouse IgG (H + L) was purchased from Invitrogen Company (Carlsbad, California, USA).

1.3 Grouping and HgCl$_2$-induced RIF The rats were allocated to three groups: normal group ($n=8$), model group ($n=12$) and Vit E treatment group (Vit E group, $n=12$). RIF was induced by using a method of Yuan et al$^{[17-18]}$. HgCl$_2$ being
dissolved in normal saline with the working concentration of 0.8 mg/mL, was given orally at a dose of 10 mL/kg body weight to rats of model group and Vit E group every morning for 9 weeks. The rats in normal group received the same volume of normal saline. Meanwhile, rats in Vit E group were administered intragastrically with Vit E at 10 mL/kg body weight (100 mg Vit E suspended in 10 mL normal saline, ensuring that Vit E is fully resuspended before and during the experiment by vortexing the suspension) once a day for 9 weeks from the first day of HgCl₂ administration. The rats in the normal and model groups received an equal volume of normal saline, respectively.

1.4 Sampling harvesting At the end of the 9th week, all the rats were anesthetized with 40 mg/kg sodium pentobarbital. Blood samples were collected from interior vena cava and kept at 4 ℃ for 3 h, then centrifuged at 1 300 × g for 15 min at 4 ℃, and the serum was kept at −80 ℃ for renal function tests. All kidneys were cut sagittally into two separate tissue sections. One section was stored in 10% formaldehyde solution for observing macroscopically and evaluating histopathologically. After routine process, paraffin blocks were prepared for each kidney. An average of three sections in sagittal plane were obtained for each kidney (4 μm in thickness). The sections were stained with hematoxylin and cosin (HE), Masson’s trichrome and periodic acid-silver methenamine (PASM) and examined by light microscopy, respectively. The remain was snap-frozen in liquid nitrogen and stored at −80 ℃ for hydroxyproline (Hyp) content determination and protein extraction. All experimental procedures were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the guidelines of Shanghai University of Traditional Chinese Medicine Committee on Animals.

1.5 Renal function and lipid peroxidation and tissue Hyp content Blood serum creatinine (Cr) and blood urea nitrogen (BUN) levels were measured by the clinical laboratory of Shuguang Hospital. Levels of SOD, GSH, GSH-Px and MDA in the kidney tissue were tested according to the protocols of Nanjing Jianingcheng Institute of Biological Products. All these parameters were expressed by per gram of protein which was assayed with bicinchoninic acid (BCA) kit.

Renal Hyp content was assayed with Jamall’s method [22]. Briefly, kidney samples weighing 100 mg were homogenized and hydrolyzed in 6 mol/L HCl at 105 ℃ for 18 h. Hydrolysates were filtrated with 3 mm filter paper and dried at 40 ℃. The samples were then incubated with Ehrlich’s solution (25% (w/v) p-Dimethylaminobenzaldehyde and 27.3% (v/v) perchloric acid in isopropanol) for 90 min at 50 ℃ and measured absorbance at 558 nm (A₅₅₈). All results were normalized to wet kidney weight. The concentration of Hyp in each sample was determined by a standard.

1.6 Immunohistochemistry The 3 μm-thick sections were used for immunohistochemical examinations. These sections were digested with pepsin at 37 ℃ for 20 min, followed by incubation with 0.1% bovine serum albumin (BSA) in phosphate buffer saline (PBS) for 30 min, and then incubated again with primary antibodies against α-SMA (1:100) at 37 ℃ for 1 h. The sections were then incubated with Cy3-labeled secondary antibody at 37 ℃ for 1 h, and images were observed with a fluorescence microscope (Olympus, Japan).

1.7 Western blot for protein analysis Renal tissues were homogenized in lysis buffer (150 mmol/L NaCl, 1% nonidet P-40, 0.1% sodium dodecyl sulfate (SDS), 50 mmol/L Tris-HCl pH 7.4, 1 mmol/L ethylene diamine tetraacetic acid (EDTA), 1 mmol/L phenyl methane sulfonyl fluoride (PMSF), 1 × complete mini-protease inhibitor cocktail). The supernatants were collected after centrifugation at 10 000 × g at 4 ℃ for 15 min. Protein concentration was determined by using a BCA protein assay kit. Equal amount of proteins was separated by 10% SDS polyacrylamide gel electrophoresis (SDS-PAGE) under denaturing and reducing condition, and then transferred to nitrocellulose membrane. Thereafter, the membrane was blocked with 5% skimmed milk in tris-buffered saline tween-20 (TBST) at room temperature for 1 h, and incubated with primary antibody against NF-κB/p-IκB, TNF-α/IκB and α-SMA (1:200 dilution) at 4 ℃ overnight. After washing in TBST, the blots were incubated with horseradish-coupled secondary antibody. The signals were visualized by using enhanced chemical luminescence. All targeted bands were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

1.8 Statistical analysis Values were expressed as X ± s. Statistical analyses were performed by using analysis of variance (ANOVA) followed by the least significant difference (LSD)-t test. P < 0.05 was considered significant.

2 Results
2.1 Histological changes in rats’ kidneys In this study, no histological abnormalities were observed in the kidneys of normal group. However, massive inflammatory cells infiltration, interstitial edema, coexistence of tubular dilatation and atrophy, basement membrane of tubuli and glomeruli thickening, glomerular atrophy and glomerular sclerosis and accumulation of ECM in renal interstitium were found in all rats of model group, and renal Hyp content of model rats increased significantly compared with normal rats. These findings confirmed our model as a consistent and reliable experimental model of RIF. Masson staining confirmed the accumulation of collagen proteins in renal inter-
sternal space of HgCl₂-induced model, while less collagen deposition was observed in rats of Vit E group (Figure 1).

2.2 Effects of Vit E in reducing α-SMA expression in rats’ kidneys In normal rats, α-SMA-positive renal fibroblasts were weakly stained and were detected in tubuli and glomeruli. Along with HgCl₂-intoxication, the number of α-SMA-positive renal fibroblasts increased gradually and reached peak at the 9th week in fibrotic kidneys. In Vit E group, number of α-SMA-positive renal fibroblasts was significantly reduced (Figure 2A).

Levels of α-SMA protein increased dramatically in model group compared with normal group (P<0.01). In Vit E group, α-SMA protein expression decreased remarkably (P<0.01) compared with model group. The results were also confirmed by immunoblotting (Figure 2B and 2C).

**Figure 1. Effects of vitamin E on histological changes in rat kidneys tested by HE, Masson’s trichrome and PASM staining (Light microscopy, ×200)**

Normal: normal kidney; Model: atrophy tubule, thickened membrane, and widened intersitial space, more inflammatory cells infiltration and more myofibroblasts were observed; Vit E: less inflammatory cells infiltration and some dilated tubules were found, with no atrophy and less renal interstitial fibrosis. HE: hematoxylin and eosin; PASM: periodic acid-silver methenamine.

**Figure 2. Effects of vitamin E on α-SMA expression in rat kidneys**

A. Immunofluorescence staining of α-SMA in rat kidneys (Fluorescence microscopy, ×200). Normal: α-SMA-positive renal fibroblasts (red, as shown by the green arrow) were weakly stained and were detected in tubuli and glomeruli. Model: massive α-SMA-positive renal fibroblasts were found in fibrotic kidneys compared with normal rats. Vit E: α-SMA-positive renal fibroblasts decreased remarkably. B: Western blot showed that α-SMA expression in normal rats was little, whereas it increased significantly in model rats. In Vit E group, the expression of α-SMA decreased significantly. C: Graphic presentation of the relative expression of α-SMA. The values are expressed as the density of α-SMA to GAPDH (%). **P<0.01, vs normal group; *P<0.01, vs model group. α-SMA: α-smooth muscle actin; GAPDH: glyceraldehyde 3-phosphate dehydrogenase.
2.3 Effects of Vit E in alleviating lipid peroxidation injury in rats’ kidney During HgCl₂ administration process, two rats died in model group and Vit E group, respectively. Rats in model group had higher kidney to body weight ratio, elevated levels of BUN, Cr and lipid peroxidation injury (by measuring GSH-Px activity and GSH and MDA contents) compared with rats in normal group received no HgCl₂. These changes were attenuated by Vit E therapy. Vit E significantly decreased the ratio of kidney to body weight, serum BUN and Cr levels and renal tissue MDA content, and increased GSH content. Renal tissue SOD and GSH-Px activities were not significantly different in rats of model and Vit E groups (Table 1 and Table 2).

2.4 Effects of Vit E on activation of NF-κB signal pathway in rats’ kidney Western blot showed that there was no significant difference of NF-κB and IκB expressions in kidneys among all groups. However the expressions of TNF-α and p-IκB in model rats were increased significantly, Vit E treatment significantly inhibited the up-regulation of TNF-α and p-IκB (Figure 3).

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<tr>
<th>Table 1</th>
<th>Effects of vitamin E on renal function and Hyp content in kidney tissues (x±s)</th>
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<td>Group</td>
<td>Kidney to body weight ratio (％)</td>
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<tr>
<td>Model</td>
<td>10</td>
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<td>Vitamin E</td>
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* P<0.05, vs normal group; △ P<0.05, vs model group. Hyp: hydroxyproline; Cr: creatinine; BUN: blood urea nitrogen.

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<th>Table 2</th>
<th>Effects of vitamin E on contents of SOD, GSH, GSH-Px and MDA in kidney tissues (x±s)</th>
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<tr>
<td>Group</td>
<td>SOD (NU/g kidney tissue)</td>
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<td>Normal</td>
<td>8</td>
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<td>Model</td>
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<tr>
<td>Vitamin E</td>
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* P<0.05, ** P<0.01, vs normal group; △ P<0.05, △△ P<0.01, vs model group. SOD: superoxide dismutase; GSH: glutathione; GSH-Px: glutathione peroxidase; MDA: malondialdehyde.

![Figure 3 Effects of vitamin E on activation of NF-κB signal pathway](image)

The values are expressed as the density of TNF-α (p-IκB) to GAPDH (％). ** P<0.01, vs normal group; △ P<0.05, vs model group. NF-κB: nuclear factor-κB; IκB: inhibitor-κB; p-IκB: phospho-IκB; TNF-α: tumor necrosis factor-α; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

3 Discussion

RIF is characterized by the destruction of renal tubules and interstitial capillaries as well as by the accumulation of ECM proteins[13]. Progressive interstitial fibrosis is considered as a common final pathway of nearly all forms of chronic kidney diseases[14, 15]. Therefore, prevention and reversal of interstitial fibrosis is one of the key strategies for the treatment of progressive renal diseases[13].

Among metals, mercury is unique in that it is found in the environment in several physical and chemical forms. All forms of mercury could induce toxic effects in a number of tissues and organs. The kidney is the primary target organ. HgCl₂ is a well-known human and animal nephrotoxicant[16]. It is reported that the renal GSH content is an important factor in the progression of HgCl₂ nephrotoxicity.
since depletion of renal GSH markedly enhanced renal damage induced by HgCl₂. Furthermore, inorganic mercury is able to change between different oxidation steps, HgCl₂ is a potential stimulator of the peroxidative chain reaction, and has been shown to enhance renal lipid peroxidation in rats.

In the present study, oral administration of HgCl₂ caused toxic response in the kidney of the experimental animals and this damage was associated with the increases in the ratio of kidney to body weight, BUN, Cr and renal TNF-α as well as lipid peroxides. In addition, significant reductions were observed in renal GSH content and GSH-Px activity. HgCl₂ administration resulted in severe damages in kidney as revealed from histological studies, including renal interstitial edema, basement membrane of tubuli and glomeruli thickening, glomerular atrophy and glomerular sclerosis, accumulation of ECM in interstitium.

Vit E is a lipid-soluble antioxidant that stops the production of reactive oxygen species (ROS), and formed when fat undergoes oxidation. Scientists are investigating whether, by limiting free radical production and possibly through other mechanisms, Vit E might help prevent or delay the chronic diseases associated with free radicals. Vit E is found naturally in some foods and it is available as a dietary supplement.

In this study, we demonstrated that Vit E could prevent RIF induced by HgCl₂, evidenced by that Vit E could improve kidney function, attenuate ECM deposition and decrease collagen specific amino acid — Hyp contents in HgCl₂-toxicated fibrotic kidney. More importantly, we found that Vit E could restore the levels of the enzymes of GSH and decreased MDA content in fibrotic kidney. It indicates that Vit E has potential effect against oxidative stress and lipid peroxidation.

Oxidative stress not only causes kidney inflammation, but also leads to RIF through NF-κB pathway, which is now believed to play a key role in the inflammation-fibrosis-cancer axis. NF-κB is an important transcript factor that is often activated by oxygen stress. Its activation resulted in many inflammatory and fibrotic cytokines release, such as TNF-α and TGF-β1, which may ultimately result in fibrosis. NF-κB, a family of dimeric transcription factors, is sequestered in the cytoplasm by IκB proteins. Upon stimulation, IκB becomes phosphorylated and is subjected to degradation by the ubiquitin-proteasome pathway, then it liberates free NF-κB, which will translocate into nucleus and bind κB sequences to regulate expressions of more than 20 target genes. ROS can trigger activation of NF-κB by activating cytoplasmic IκB kinase (IKK) complex, which is the upstream mediator of IκB and can catalyze IκB phosphorylation. The biological responses are diversely depending on cell-specific and physiopathological state, but commonly include cellular proliferation, apoptosis prevention and so on. In our study, renal fibrotic rats had a higher TNF-α expression, the reason may be that TNF-α is NF-κB’s regulative gene. In the model rats, NF-κB activity and IκB phosphorylation level are higher than those in normal rats, however, Vit E could restore p-IκB level, and inhibit TNF-α expression. The results suggest that oxidative stress may cause RIF through up-regulating NF-κB activity in the model rats. Vit E could counteract oxidative stress-stimulated NF-κB pathway through inhibiting IκB phosphorylation in kidney, then inhibit myofibroblast activation and exert its pharmacological action against RIF.

4 Conclusion

Vit E could improve oxidative injury in HgCl₂-induced interstitial fibrotic kidney, and antagonize oxidative stress-stimulated NF-κB activity through inhibition of IκB phosphorylation, these effects importantly contribute to Vit E action mechanism against RIF.

5 Acknowledgement

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6 Conflict of interest statement

The authors declare that there are no conflicts of interest.

REFERENCES


维生素E抑制氯化汞诱导大鼠肾间质纤维化的抗氧化作用机制

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目的：观察维生素E对氯化汞诱导的大鼠肾间质纤维化的作用并探讨其抗氧化机制。

方法：32只大鼠随机分为正常组、模型组与维生素E组。除正常组外，其余大鼠以8 mg/kg氯化汞(mercuric chloride, HgCl2)灌胃，每天1次，共9周。维生素E组同时以维生素E100 mg/kg灌胃，正常组与模型组灌胃等量生理盐水。9周后处死大鼠，取眼检样品检测肾组织羟脯氨酸(hydroxyproline, Hyp)含量，苏木精伊红染色、Masson染色与过碘酸六胺银染色观察肾组织病理形态与胶原沉积；试剂盒方法检测肾组织过氧化物歧化酶(superoxide dismutase, SOD)和谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)活性与谷胱甘肽(glutathione, GSH)和丙二醛(malondialdehyde, MDA)含量；蛋白印迹法检测核因子κB(nuclear factor-κB, NF-κB)信号途径的κB抑制蛋白(inhibitor κB, IκB)、磷酸化IκB(phospho-IκB, p-IκB)以及肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)的表达；蛋白印迹法与免疫荧光法观察平滑肌肌动蛋白(α-smooth muscle actin, a-SMA)的表达。

结果：与正常组比较，肾组织Hyp含量、Masson染色与过碘酸六胺银染色及肾组织a-SMA的含量证实肾间质纤维化模型造模成功；GSH-Px活性与GSH、MDA含量变化提示肾间质纤维化模型存在氧化应激损伤。与模型组比较，维生素E组大鼠肾组织Hyp含量降低(P<0.01)，肾间质纤维化减轻，GSH与MDA含量降低(P<0.01)；维生素E组p-IκB、TNF-α、a-SMA蛋白表达明显降低，各组中IκB蛋白表达无明显变化。

结论：维生素E抗氧化作用诱导大鼠肾间质纤维化的作用机制在于抗脂质过氧化损伤，与抑制NF-κB信号传递及细胞外基质产生细胞活化有关。

关键词：维生素E；肾间质纤维化；升汞；脂质过氧化反应；动物实验；大鼠