Available online at www.sciencedirect.com

SciVerse ScienceDirect

Procedia Environmental Sciences 8 (2011) 629 – 632

Procedia Environmental Sciences

ICESB 2011: 25-26 November 2011, Maldives

The Ameliorate Effect of Endomorphin 1 on the Mice Nephrotoxicity Induced by Cadmium

Pin Gong[a] , Fuxin Chen[b] , Rui Wang [c,*]

[a.] *College of Life Science and Engineering ,Shaanxi University of Science and Technology,Xi'an, 710021,China*
[b.] *Department of Chemistry and Chemical Engineering ,Xi'an University of Science and Technology, , Xi'an, 710054,China,*
[c.] *School of Basic Medical Sciences,Lanzhou University,Lanzhou 730000, China*

Abstract

To wonder whether endomorphin 1(EM1), the antioxidative peptide, can protect against the renal toxicology of cadmium (Cd), which probably related to the oxidative injury. Methods: In vivo assays have been designed and performed, such as the measurement of oxidative damage parameters and the index of antioxidative system. Result: Data from our study demonstrated the effect of EM1 could ameliorate the increased concentration of lipid peroxidation products and protein carboxylatio and increase the content of antioxidative system, the antioxidant capacity of EM1 probably relate to its structure. Conclusion: Our study first demonstrated the nephrotoxicity induced by Cd can be suppressed by the treatment of EM1.

Selection and/or peer_review under responsibility of the Asia Pacific Chemical Biological & Environmental Engineering Society (APCBEES)

Keywords : cadmium; endomorphin 1; kidney;oxidative stress;antioxidant

1. Introduction

Cadmium (Cd) was widely used in industrial fields, however, Cd has been reported as an important environmental pollutant because of its extremely long half-life and classified as human carcinogen [1]. Sources of human exposure to this metal include food, water, air contaminations as well as cigarette smoke, and alcoholic beverages [2]. Several animal studies have shown that Cd accumulates preferentially in the hepatic and renal tissues leading to distinct pathological changes and physiological disorders to the liver and the kidney [3-4]. Many evidences that exposure to Cd leading to the renal

* Corresponding author. Tel.: 13772196479
Email: angel198303@163.com

Selection and/or peer-review under responsibility of the Asia-Pacific Chemical, Biological & Environmental Engineering Society (APCBEES)
doi:10.1016/j.proenv.2011.10.097

damage can be ameliorated by the antioxidant therapy support the proposal that oxidative strss play an important role in the Cd-induced nephrotoxicity [5], and inspired the further explore for the potential therapy using antioxidant for Cd-related diseases.

Endomorphin 1(EM1,Tyr-Pro-Trp-Phe-NH_2) and endomorphin 2 (Tyr-Pro-Phe-Phe-NH_2), the endogenous μ-opioid receptor agonists, were shown to be strong analgesics on acute pain[6-7]. Our group have firstly found that EMs directly scavenge galvinoxyl radicals and AAPH-derived alkyl peroxyl radicals, inhibit lipid peroxidation (LPO), DNA and protein oxidative damage [8], and that EMs inhibit the oxidation of human low density lipoprotein induced by Cu^{2+} and AAPH in a concentration dependent manner, due to their free radical scavenging activities[9]. We also demonstrated that EMs can effectively protect brain mitochondria oxidative stress induced by in vitro anoxia-reoxygenation [10]. More recently, our study revealed that EM1 can protect the oxidative damage of mice liver induced by the intoxication of Cd and act as an antioxidant [11]. Our data also proved that EM1 can ameliorate the toxicity effect of Cd on rat heart (unpublished data). To wonder about whether EM1can play a role in the protection of kidney damaged by Cd, in vivo assays have been designed and the oxidative damage markers and the antioxidative enzyme systems have been investigated to reveal the possible pathway to suppress the renal toxicity of mice induced by Cd.

2. Results And Discussion

The increasing evidences revealed the widely existence of Cd in our daily life and the toxicity of Cd upon the health of human[1].The detailed mechanism of Cd toxicity and the possible therapy for prevention and cure of Cd intoxication attract great attentions.

EM1, the in vitro free radical scavenger and in vivo antioxidant, has been shown so far to protect against the toxicity of Cd on various tissues, including the liver and the heart. In this study, we continue to demonstrate the protect effect of EM1 on the renal damage induced by Cd (1mg/kg, intraperitoneal (i.p), 6 days). From the data shown in Figure 1 and 2, we can learn that the effect of Cd significantly cause damage to lipid and protein and lead to the increased LPO ($p<0.05$) and protein carboxylation(PCO)($p<0.05$). However, EM1(50 μ M/kg, i.p.6days) could markedly ameliorate the increased LPO and PCO,($p<0.05$) possibly by scavenging the overproduction of free radicals and reduced the oxidative pressure. Moreover, it is also shown that Cd can decrease the concentration of superoxide dismutase (SOD)($p<0.01$), catalase (CAT)($p<0.05$), glutathione (GSH) ($p<0.05$) probably owing to the damage to the antioxidant system because of the toxicology of Cd, which in consistent with our previous study. The co-administration of EM1 can increase the levels of the SOD ($p<0.05$) and GSH ($p<0.05$), probably because of the protection effect acting by EM1 against the intoxication of Cd. However, the treatment of EM1 has no effect on the concentration of CAT, revealing the possible different mediation mechanism of CAT.

According to the proposal arising from our above studies [11], we suggested that the antioxidant capacity in vivo and free radical scavenging effect of $EM1_3$in vitro, at least part related to the structure of EM1. It is suggested that both the indole ring on the Trp_3 and the side chain on the indole nucleus are essential for the antioxidant activity of EM1. H-10 on the Trp_3 is the most active allylic hydrogen of EM1, which can be easily abstracted by free radicals. In addition, conjugation with –NH on the indole would further weaken the C–H-10 bond [8]. The Tyr1 could react with reactive oxygen radicals, forming a long-lived tyrosyl radical attributed to the action of phenolic hydroxyl. The tyrosyl radical may react with another tyrosyl radical, acquiring a stable dityrosine structure [12]. Hence, the structure features confer the ability of scavenging reactive oxygen radicals to EM1 molecule directly.

In conclusion, our study provided suggestive evidence for the prolonged Cd exposure causing renal damage can be suppressed by treatment with EM1, indicating that oxidative stress plays a critical role in

Cd-induced nephrotoxicity.

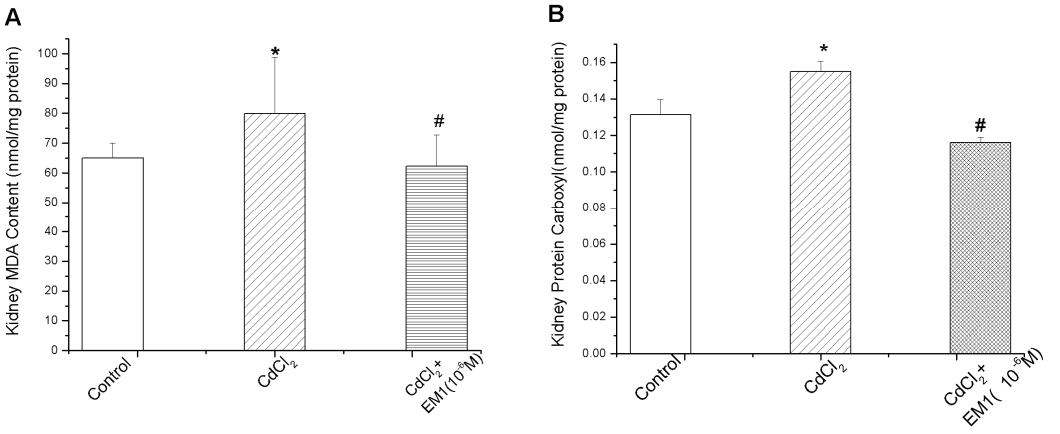

Fig. 1. TheThe effects of EM1 on the renal MDA (A) and PCO (B) level in Cd(II)-exposed mice. Results are expressed as mean ± S.E.M.; n = 6–8 animals per group (*p < 0.05 vs. Control group and #p < 0.05 vs. Cd(II) group).

.

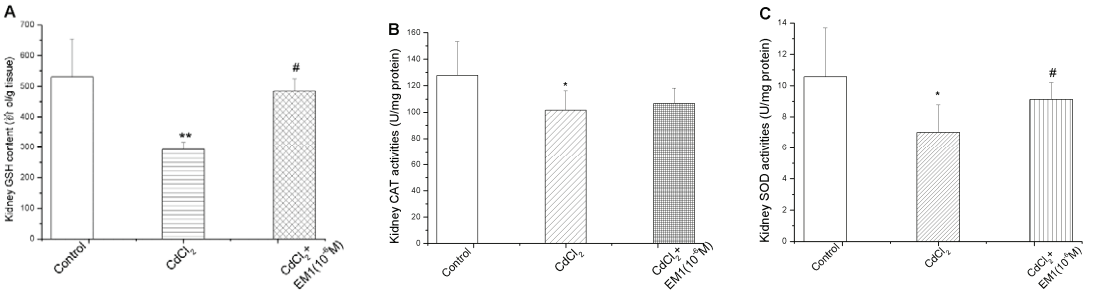

Fig. 2 The effects of EM1 on the renal GSH (A),CAT(B) and SOD (C) level in Cd(II)-exposed mice. Results are expressed as mean±S.E.M.; n = 6–8 animals per group (**p<0.01,*p < 0.05 vs. Control group and #p < 0.05 vs. Cd(II) group).

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No20772052) and grants from the Starting Funds for Doctors in Shaanxi University of Science and Technology (No.BJ10-13).

References

[1] Nordberg FG. Cadmium and health in the 21st century-historical remarks and trends for the future. *BioMetals* 2004;**17**: 485–9.

[2] Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure: a review of the literature and a risk estimate. *Scand. J. Work Environ. Health* 1998; **24**:1-51.

[3] Koyu A, Gokcimen A, Ozguner F, Bayram DS, Kocak A. Evaluation of the effects of cadmium on rat liver. *Mol. Cell. Biochem*. 2006;**284**(1–2):81–5.

[4] Thijssen S, Maringwa J, Faes C, Lambrichts I, Van Kerkhove E. Chronic exposure of mice to environmentally relevant, low cadmium leads to early renal damage, not predicted by blood or urine cadmium levels. *Toxicology* 2007;**229**:145–156.

[5] El-Demerdash FM, Yousef MI, Kedwany FS, Baghdadi HH. Cadmium-induced changes in lipid peroxidation, blood hematology, biochemical parameters and semen quality of male rats: protective role of Vitamin E and beta-carotene. *Food Chem. Toxicol* 2004;**42**:1563–71.

[6] Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selective endogenous agonist for the mu-opiate receptor. *Nature* 1997;**386**:499–502.

[7] Tseng LF, Narita M, Suganuma C, Mizoguchi H, Ohsawa M, Nagase H, et al. Differential antinociceptive effects of endomorphin-1 and endomorphin-2 in the mouse. *J. Pharmacol. Exp. Ther* 2000; **292**:576–83.

[8] Lin X, Yang DJ, Cai WQ, Zhao QY, Gao YF, Chen Q, et al. Endomorphins,endogenous opioid peptides, provide antioxidant defense in the brain against free radical-induced damage. *Biochim. Biophys. Acta* 2003;**1639**:195–202.

[9] Lin X, Xue LY, Wang R, Zhao QY, Chen Q. Protective effects of endomorphins,endogenous opioid peptides in the brain, on human low density lip oprotein oxidation. *FEBS J*. 2006;**273**:1275–84.

[10] Feng Y, Lu YW, Lin X, Gao YF, Zhao QY, Li W, et al. Endomorphins and morphine limit anoxia–reoxygenation-induced brain mitochondrial dysfunction in the mouse. *Life Sci.* 2008;**82**:752–63.

[11] Gong P, Chen FX, Ma GF, Feng Y, Zhao QY, Wang R. Endomorphin 1 effectively protects cadmium chloride-induced hepatic damage in mice. *Toxicology* 2008;**251**:35–44.

[12] Giulivi C, Davies KJ. Dityrosine: a marker for oxidatively modified proteins and selective proteolysis. *Methods Enzymol* 1994;**233**:363–71.