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Multi-organ Protective Effects of Cerium Oxide Nanoparticle/Selenium in Diabetic Rats: Evidence for More Efficiency of Nanocerium in Comparison to Metal Form of Cerium

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ABSTRACT

Oxidative stress is involved in complications of diabetes. This study investigated the hypothesis that the cerium oxide nanoparticle/sodium selenite combination can synergistically improve oxidative stress indexes in vital organs (kidney, heart, brain and lung) of diabetic rats. Diabetes was induced in overnight-fasted male Wistar rats via a single dose of streptozotocin (STZ, 60 mg kg^{-1}). The effective doses of cerium oxide nanoparticle (60 mg/kg/day) and sodium selenite (5 μmol/kg/day) alone or in combination were administered for 14 days to diabetic rats. Rats with blood glucose of more than (300 mg dL^{-1}) were selected and divided into six groups including vehicle control, STZ control, cerium oxide nanoparticles, sodium selenite, combination of cerium oxide nanoparticles with sodium selenite and metal form of cerium oxide. At the end of 2 weeks, organ tissues including brain, heart, lung and kidney of animals were removed and then oxidative stress markers including cellular Lipid Peroxidation (LPO), Total Antioxidant Power (TAP), Total Thiol Molecules (TTM) and Reactive Oxygen Molecules (ROM) were evaluated. Combination of cerium oxide nanoparticles and sodium selenite significantly reduced ROM and LPO levels in all the organs. The results of TTM showed an increase in all tissues expect the lung. TAP increased in combination group in all studied tissues expect the lung. The beneficial effect of cerium oxide nanoparticles/sodium selenite in diabetic rats is mediated through control of oxidative stress mechanisms. These effects were more noticeable in kidney, brain and heart.

Key words: Cerium oxide nanoparticles, sodium selenite, oxidative stress, diabetes

INTRODUCTION

Oxidative stress processes have been suggested to be a contributory factor in complication of diabetes melhitus resulting from increased free radical production or reduced activity of antioxidant defenses or both (Rahimi *et al*., 2005). During diabetes disease, persistent hyperglycemia in all tissues causes increased production of free radicals, especially Receative Oxygen Molecules (ROM), from glucose auto-oxidation and protein glycosylation. These products have significant influence

in the beginning and developing of complications of chronic diabetes (Astaneie *et al*., 2005). Thus, one of the aims in decreasing of diabetes complication is to use of antioxidant agents (Mohammadirad *et al*., 2011; Mehri *et al*., 2010; Momtaz and Abdollahi, 2010).

Selenium as an essential trace element plays a key role in selenoproteins and selenoenzymes structures such as Glutathione Peroxidase (GPx), selenoprotein-P and thioredoxin reductase (Klein, 2004; Zeng and Combs, 2008) that produce antioxidant effects (Miroliaee *et al*., 2011). The cerium oxide nanoparticles has been recently found helpful in rat diabetes by reducing oxidative stress (Pourkhalili *et al*., 2011).

In the present study, the effects of cerium oxide nanoparticles was tested and compared with its metal form and the combination form of cerium oxide nanoparticles/sodium selenite on process of oxidative stress in various organs of diabetic rats including brain, heart, lung and kidney.

MATERIALS AND METHODS

Materials: Tris base, 1,1,3,3-tetraethoxypropane (MDA), 5,5'dithiobis-2-nitro benzoic acid (DTNB), methanol (high performance liquid chromatography [HPLC]-grade), trichloroacetic acid (TCA), diethyl ether, tetrabutylammonium hydroxide (TBAHS), n-butanol, 2-thiobarbituric acid (TBA), KH_2PO_4 (analytical grade), 2,4,6-tripyridyl-s-triazine (TPTZ), sodium selenite, ketamin, xylazin and PBS (phosphate buffer solution from Merck (Tehran), 2,7-dichlorodihydrofluorescein diacetate (DCFD) from Sigma-Aldrich (Taufkirchen, Germany), cerium oxide nanoparticles from Navarrean Nenoproducts Technology (Spain), streptozotocine (STZ) from Pharmacia and Upjohn (USA) were used in this study.

Animals: A total of 36 adult male Wistar rats were obtained from Animal House of Faculty of Pharmacy, Tehran University of Medical Science (TUMS). Rats weighing 250-300 g were housed in polypropylene cages under standard conditions of temperature (25°C), relative humidity (50-55%), with free access to drinking water and food and 12 h light/dark cycle. All experiments were performed according to the animal welfare rules approved by TUMS Ethics Committee.

Experimental protocol and groups: Following 12 h of fasting, experimental diabetes was induced by intraperitoneal (ip) injection of dissolved STZ in citrate buffer (0.1 M, pH 4.5) at the single dose of 60 mg kg^{-1}. Blood glucose of rats were measured by a glucometer three days after injection of STZ and rats with blood glucose of more than (300 mg dL^{-1}) were selected and randomly divided into five groups with six rats in each group. The animals were treated for two consecutive weeks by ip injection as follows: Group 1 diabetic rats received saline (ip), group 2 diabetic rats received metal form of cerium oxide (60 mg kg^{-1}), group 3 diabetic rats received cerium oxide nanoparticles (60 mg kg^{-1}), group 4 diabetic rats received sodium selenite (5 μmol/kg/day), group 5 diabetic rats received combination of cerium oxide nanoparticles (60 mg kg^{-1}) and sodium selenite (5 μmol/kg/day). Effective doses of compounds were selected from earlier study (Pourkhahli *et al*., 2011). Moreover, one group including six rats was studied as the vehicle control group that received only ip injection of saline. Treatments were continued up to 2 weeks and animals were weighed daily and their blood glucose was measured using a glucometer. Then animals were anesthetized with ip injection of ketamine (4 mg/100 g) and xylazine (1 mg/100 g) mixture and then immediately, brain, heart, lung and kidney were removed, weighed and stored in -80°C. In the next stage, 100 mg of these tissues were homogenized in PBS (50 mM, pH 7) under ice cooling and then centrifuged at 3000 g for 30 min at 4°C. The supernatant was used to assay oxidative stress markers.

Measurement of reactive oxygen molecules (ROM): 2,7-Dichlorodihydrofluorescein diacetate (DcFD) was used to measure ROM production as previously set up in the lab and described in details (Momtaz *et al*., 2010). The sample was incubated with 5 μM DCFD at 37°C for 30 min in the dark. Then, fluorescence was read with 488 nm excitation and 525 nm emission using a fluorometer.

Measurement of lipid peroxidation (LPO): LPO in brain, heart, lung and kidney samples was determined by the reaction of TBA with lipid peroxides. Brain, heart, lung or kidney samples were mixed with trichloroacetic acid (20%) and the precipitate was dispersed into H_2SO_4 (0.05 M). TBA (0.2% in 2 M sodium sulfate) was added and heated for 30 min in boiling water bath. LPO adducts were extracted by n-butanol and absorbance was measured at 532 nm.

Measurement of total antioxidant power (TAP): TAP was determined by measuring its abiity to reduce Fe^{3+} to Fe^{2+} established as the ferric-reducing antioxidant power (FRAP) test. The reagents included 300 mM acetate buffer (pH 3.6) with 16 mL acetic acid per liter of buffer solution, 10 mM TPTZ in 40 mM HCl and 20 mM $FeCl_3$. Working FRAP reagent was prepared as required by mixing 25 mL acetate buffer, 2.5 mL TPTZ solution and 2.5 mL $FeCl_3$ solution. Ten μL of H_2O diluted sample was then added to 300 mL freshly prepared reagent warmed at 37°C. The complex between Fe^{2+} and TPTZ gives a blue color with absorbance at 593 nm.

Measurement of total thiol molecules (TTM): A volume of homogenate (0.2 mL) was mixed with 0.6 mL of Tris-EDTA buffer (Tris base [0.25 M], EDTA [20 mM], pH 8.2) in a 10 mL test tube and then mixed with 40 mL of DTNB (10 mM) in methanol. The final volume was made up to 4.0 mL by adding 3.16 mL of methanol. The test tube, after capping, was centrifuged at 3000 g for 10 min at ambient temperature. After 15-20 min the color appeared. The absorbance of the supernatant was measured at 412 nm.

Protein measurements: Protein level was measured in tissues according to Bradford method. Briefly, homogenate samples mixed with Bradford reagent dye and after 5 min, the absorbance were determined at 595 nm using the spectrophotometer. Bovine Serum Albumin (BSA) was used as standard. Stress oxidative markers were presented per milligram protein of tissue homogenate.

Statistical analysis: Data were expressed as Means±SE and compared using one way analysis of variance (ANOVA) followed by Tukey multiple comparisons test. The significance level was tested at $p<0.05$.

RESULTS

Blood glucose and animal's tissue weight: As data are shown in Table 1, the weight of diabetic rats (BW) remarkably decreased ($p<0.05$) and their blood glucose significantly raised as compared with controls ($p<0.001$). After use of cerium oxide nanoparticles/sodium selenite combination and also cerium oxide nanoparticles alone, an increase in animal's weight ($p<0.01$ and $p<0.05$, respectively) was observed in comparison to diabetic rats. Also, a remarkable decrease in blood glucose ($p<0.05$) was shown only in the combination of sodium selenite and cerium oxide nanoparticles, when compared to diabetic rats. No significant change in animal weight was observed when using sodium selenite and the metal form of cerium oxide. The body weight/kidney weight index (BW/KW) in diabetic rats remarkably decreased ($p<0.01$) as compared with control

Table 1: Effects of various treatments on body weight (BW) and plasma glucose

	BW (g)		
Animal groups	Initial	Final	Plasma glucose (mg dL^{-1})
Control	183.35±3.39	199.80±5.87	141.03±4.37
Diabetic control	189.24±2.80	177.90±5.46^{a}	455.60±18.31^{aaa}
Metal form of cerium oxide	196.65±5.54	182.60±4.70^{c}	454.15±19.05^{aaac}
Cerium oxide nanoparticles	194.00±4.56	203.30±2.01^{b}	446.77±19.24^{aaac}
Sodium selenite	190.89±6.80	196.30±6.38	445.73±21.06^{aaac}
Cerium oxide nanoparticles/sodium selenite	197.32±6.30	210.50±3.57^{bb}	372.18±12.15^{aaab}

Data are Mean±SE of six animals in each group, Significantly different from control at $^{aaa}p<0.001$, $^{a}p<0.05$, Significantly different from diabetic control at $^{bb}p<0.01$, $^{b}p<0.05$, Significantly different from cerium oxide nanoparticle/sodium selenite combination at $^{c}p<0.05$

Table 2: Effects of various treatments on BW/KW (Body weight/Kidney weight), BW/BRW (Body weight/Brain weight) index

Animal groups	KW (g)	BW/KW	BRW (g)	BW/BRW
Control	1.58±0.03	133.17±072	2.15±0.04	130.74±3.31
Diabetic control	1.75±0.04	104.62±0.43^{aa}	1.62±0.07^{aaa}	98.38±3.92^{aa}
Metal form of cerium oxide	1.57±0.02	111.22±3.81^{a,ccc}	1.70±0.05^{aaa}	107.69±6.64
Cerium oxide nanoparticles	1.60±0.03	157.04±4.70^{a,bbb}	1.78±0.04^{aaa}	121.14±2.01
Sodium selenite	1,60±0.05	124.13±6.65^{cc}	1.82±0.02^{aaa}	115.10±3.94
Cerium oxide nanoparticles/sodium selenite	1.45±0.07^{bb}	150.94±4.75^{bbb}	1.90±0.03^{a,bb}	127.38±7.66^{b}

Data are Mean±SE of six animals in each group, Significantly different from control group at $^{aaa}p<0.001$, $^{aa}p<0.01$, $^{a}p<0.05$, Significantly different from diabetic control group at $^{bbb}p<0.001$, $^{bb}p<0.01$, $^{b}p<0.05$, Significantly different from cerium oxide nanoparticle/sodium selenite at $^{ccc}p<0.001$, $^{cc}p<0.01$

animals. No significant change in this index was observed by use of metal form of cerium oxide and sodium selenite. Following administration of cerium oxide nanoparticles and a combination of cerium oxide nanoparticles/ sodium selenite, an increase in this index ($p<0.001$, $p<0.001$, respectively) was observed in comparison to diabetic rats. Also, BW/BRW in diabetic rats significantly decreased ($p<0.01$) as compared to control animals. Only, administration of cerium oxide nanoparticle/sodium selenite combination reversed this index ($p<0.05$) in diabetic rats (Table 2). The similar results were seen in BW/HW. This index in diabetic rats significantly decreased ($p<0.001$) as compared to control animals. Only, administration of cerium oxide nanoparticle/sodium selenite combination reversed this index (BW/HW) in diabetic rats ($p<0.01$). No significant change in body weight/lung weight index (BW/LW) was observed in diabetic rats and the other groups as compared to control rats (Table 3).

Levels of ROM in tissues: There was a significant increase ($p<0.001$) in ROM in all of the diabetic rat tissues as compared with the normal rat tissues (Table 4). Treatment of diabetic animals with cerium oxide nanoparticles decreased ROM in kidney and lung ($p<0.01$ and $p<0.05$, respectively) as compared to diabetic group. Administration of sodium selenite alone decreased ROM in kidney ($p<0.05$). Combination of cerium oxide nanoparticles/sodium selenite significantly decreased ROM in all tissues in comparison to diabetic group ($p<0.001$ in kidney and lung; $p<0.01$ in heart and brain) and reached close to normal values in all tissues expect the lung. No significant change was detected by administration of metal form of cerium oxide.

Table 3: Effects of various treatments on BW/HW (Body weight/Heart weight) and BW/LW (Body weight/Lung weight) index

Animal groups	HW (g)	BW/HW	LW (g)	BW/LW
Control	0.88±0.07	227.20±2.11	1.33±0.02	151.28±1.25
Diabetic control	1.20±0.06^{a}	149.50±6.72^{aaa}	1.20±0.02^{aa}	149.37±1.20
Metal form of cerium oxide	1.32±0.03^{aa,c}	143.98±11.98^{aaa,ccc}	1.21±0.03^{a}	152.09±0.80
Cerium oxide nanoparticles	1.06±0.04	176.99±11.04^{a}	1.24±0.01	160.58±3.47
Sodium selenite	1.09±0.06	182.32±4.39^{a}	1.23±0.01	159.50±2.23
Cerium oxide nanoparticles/sodium selenite	0.98±0.03	216.37±8.85^{bb}	1.26±0.01	159.17±3.66

Data are Mean±SE of six animals in each group, Significantly different from control group at $^{aaa}p<0.001$, $^{aa}p<0.01$, $^{a}p<0.05$, Significantly different from diabetic control at $^{bb}p<0.01$, Significantly different from cerium oxide nanoparticle/sodium selenite combination at $^{ccc}p<0.001$, $^{c}p<0.05$

Table 4: Effects of various treatments on production of ROM in kidney, heart, brain and lung

	ROM (umol mg^{-1} protein)			
Animal groups	Kidney	Heart	Brain	Lung
Control	0.15±0.03	0.12±0.02	0.08±0.01	0.09±0.01
Diabetic control	0.35±0.02^{aaa}	0.35±0.03^{aaa}	0.31±0.02^{aaa}	0.29±0.02^{aaa}
Metal form of cerium oxide	0.28±0.01^{a,c}	0.33±0.03^{aaa,c}	0.33±0.03^{aaa,ccc}	0.24±0.01^{aaa,cc}
Cerium oxide nanoparticles	0.18±0.03^{bb}	0.25±0.02^{a}	0.27±0.01^{aaa,c}	0.22±0.01^{aaa,b}
Sodium selenite	0.22±0.03^{b}	0.29±0.03^{aa}	0.31±0.01^{aaa,cc}	0.25±0.01^{aaa,cc}
Cerium oxide nanoparticles/sodium selenite	0.15±0.01^{bbb}	0.20±0.02^{bb}	0.16±0.02^{bb}	0.16±0.01^{a,bbb}

Data are mean±SE of six animals in each group, Significantly different from control group at $^{aaa}p<0.001$, $^{aa}p<0.01$, $^{a}p<0.05$, Significantly different from diabetic control at $^{bbb}p<0.001$, $^{bb}p<0.01$, $^{b}p<0.05$, Significantly different from cerium oxide nanoparticle/sodium selenite at $^{ccc}p<0.001$, $^{cc}p<0.01$, $^{c}p<0.05$

Table 5: Effects of various treatments on LPO in kidney, heart, brain and lung

	LPO (umol mg^{-1} protein)			
Animal groups	Kidney	Heart	Brain	Lung
Control	1.43±0.38	2.18±0.33	1.77±0.12	2.68±0.13
Diabetic control	5.95±0.18^{aaa}	6.13±0.28^{aaa}	5.10±0.21^{aaa}	6.45±0.23^{aaa}
Metal form of cerium oxide	5.48±0.53^{aaa,ccc}	6.64±0.28^{aaa,ccc}	5.44±0.29^{aaa,ccc}	6.84±0.18^{aaa,ccc}
Cerium oxide nanoparticles	3.60±0.36^{aa,bb}	4.40±0.61^{aa,b}	3.57±0.26^{aa,bb,c}	6.10±0.21^{aaa,cc}
Sodium selenite	4.35±0.26^{aaa,cc}	4.23±0.29^{aa,bb}	3.45±0.33^{aa,bb,c}	5.79±0.33^{aaa,c}
Cerium oxide nanoparticles/sodium selenite	2.37±0.31^{bbb}	3.14±0.26^{bbb}	2.28±0.15^{bbb}	4.71±0.26^{aaa,bbb}

Data are Mean±SE of six animals in each group, Significantly different from control group at $^{aaa}p<0.001$, $^{aa}p< 0.01$, Significantly different from diabetic control at $^{bbb}p<0.001$, $^{bb}p<0.01$, $^{b}p<0.05$, Significantly different from cerium oxide nanoparticle/sodium selenite at $^{ccc}p<0.001$, $^{cc}p<0.01$, $^{c}p<0.05$

Levels of LPO in tissues: There was a significant elevation ($p<0.001$) in LPO in all diabetic rat tissues as compared with normal rats. Treatment of diabetic animals with cerium oxide nanoparticle decreased LPO in kidney, heart and brain ($p<0.01$, $p<0.05$ and $p<0.01$, respectively) as compared to diabetic group. Administration of sodium selenite alone decreased LPO in heart and brain ($p<0.01$ and $p<0.01$, respectively). Combination of cerium oxide nanoparticles and sodium selenite significantly ($p<0.001$) decreased LPO in all tissues as compared with diabetic rats. No significant change was detected by administration of metal form of cerium oxide (Table 5).

Levels of TAP in tissues: There was a significant decrease ($p<0.001$) in TAP in all diabetic rat tissues as compared with normal group. Treatment of diabetic animals with cerium oxide

Table 6: Effects of various treatments on TAP in kidney, heart, brain and lung

	TAP (umol mg^{-1} protein)			
Animal groups	Kidney	Heart	Brain	Lung
Control	5.63±0.66	6.74±0.30	6.26±0.53	5.97±0.58
Diabetic control	1.27±0.26^{aaa}	1.51±0.22^{aaa}	1.46±0.26^{aaa}	1.67±0.20^{aaa}
Metal form of cerium oxide	1.42±0.24^{aaa,cc}	1.57±0.17^{aaa,ccc}	1.77±0.34^{aaa,ccc}	1.46±0.17^{aaa}
Cerium oxide nanoparticles	3.08±0.18^{aa,b}	3.11±0.33^{aaa,bb}	3.31±0.26^{aaa}	3.06±0.43^{aaa}
Sodium selenite	2.91±0.33^{aa}	2.39±0.20^{aaa,c}	3.31±0.46^{aaa}	2.68±0.33^{aaa}
Cerium oxide nanoparticles/sodium selenite	4.23±0.15^{bbb}	4.02±0.35^{aaa,bbb}	4.68±0.45^{bbb}	2.70±0.47^{aaa}

Data are Means±SE of six animals in each group, Significantly different from control group at $^{aaa}p<0.001$, $^{aa}p<0.01$, Significantly different from diabetic control at $^{bbb}p<0.001$, $^{bb}p<0.01$, $^{b}p<0.05$, Significantly different from cerium oxide nanoparticle/sodium selenite combination at $^{ccc}p<0.001$, $^{cc}p<0.01$, $^{c}p<0.05$

Table 7: Effects of various treatments on TTM in kidney, heart, brain and lung

	TTM (umol mg^{-1} protein)			
Animal groups	Kidney	Heart	Brain	Lung
Control	11.64±0.49	11.23±0.46	12.23±0.62	10.90±0.26
Diabetic control	7.66±0.27^{aaa}	7.48±0.26^{aa}	8.07±0.41^{aaa}	7.48±0.26^{aa}
Metal form of cerium oxide	7.63±0.34^{aaa,c}	7.63±0.34^{aa,c}	7.63±0.34^{aaa,cc}	7.23±0.47^{aa}
Cerium oxide nanoparticles	7.66±0.45^{aaa,cc}	7.70±0.75^{aa,c}	9.10±0.26^{aaa}	7.95±0.65^{a}
Sodium selenite	7.82±0.47^{aaa,c}	7.72±0.62^{aa,c}	9.23±0.22^{aa}	7.92±0.54^{aa}
Cerium oxide nanoparticles/sodium selenite	9.95±0.41^{bb}	10.43±0.23^{b}	10.43±0.23^{a,bb}	8.57±0.58

Data are Mean±SE of six animals in each group, Significantly different from control group at $^{aaa}p<0.001$, $^{aa}p<0.01$, $^{a}p<0.05$, Significantly different from diabetic control at $^{bb}p<0.01$, $^{b}p<0.05$, Significantly different from cerium oxide nanoparticle/sodium selenite at $^{cc}p<0.01$, $^{c}p<0.05$

nanoparticle increased TAP in heart and kidney as compared to that of diabetic group ($p<0.01$ and $p<0.05$, respectively) (Table 6). Administration of cerium oxide nanoparticle/sodium selenite combination significantly increased ($p<0.001$) TAP in all tissues expect the lung. No significant change was observed by administration of sodium selenite and metal form of cerium oxide in diabetic rats.

Levels of TTM in tissues: As data are shown in Table 7, the TTM level in all tissues considerably decreased in diabetic group when compared to normal group ($p<0.001$ in kidney and brain; $p<0.01$ in heart and lung).

Combination of cerium oxide nanoparticle/sodium selenite increased TTM in all tissues expect the lung as compared with diabetic group ($p<0.01$ in kidney and brain; $p<0.05$ in heart). No significant change was observed by administration of cerium oxide nanoparticles, sodium selenite, and metal form of cerium oxide.

DISCUSSION

The results show that induction of diabetes by STZ results in increasing the LPO, ROM and depletion of TAP that is in good agreement with previous knowledge. Diabetic animals treated with cerium oxide nanoparticles showed a significant reduction in LPO of the heart, kidney and brain. Similarly, a reduction of ROM in kidney and lung was observed; however, reduction in brain and

heart ROM was not significant. Cerium oxide nanoparticles amplified antioxidant capacity of kidney and heart. In spite of impressive effects of cerium oxide nanoparticles, the metal form of cerium oxide did not cause significant benefit in oxidative stress markers that is supported by recent study (Pourkhalili *et al.*, 2011). According to these results, it seems that antioxidant potential of cerium oxide nanoparticles comes from nano structure of cerium. Cerium nanoparticles are known to offer many active sites for free radical scavenging because of its large surface/volume ratio and also the mixed valence states for unique redox chemistry (Heckert *et al.*, 2008). In contrast, the metal form of cerium oxide is a monodisperse particle with single crystals, few twin boundaries with no significant antioxidant properties (Zhang *et al.*, 2002). Also, more distribution of cerium oxide nanoparticles than that of metal form is important in the present results because antioxidant activity depends on size, composition and particle surface area (Mohammad *et al.*, 2008; Singh *et al.*, 2008).

On the other hand, present results showed that treatment of diabetic animals with sodium selenite caused a significant reduction in LPO of the heart and brain and reduced kidney ROM. Selenium acting as an essential component of the antioxidant system can normalize the antioxidant status (Bajpai *et al.*, 2011; Miroliaee *et al.*, 2011). As reported, supplementing of rats with selenium improves antioxidant capacity of tissues exposed to static magnetic field (Ghodbane *et al.*, 2011). Conclusively, the present findings prove that combination of nanocerium and sodium selenite acts synergistically in normalizing oxidative stress markers in kidney, heart and brain of diabetic rats but lung did not respond noticeably.

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