Al-Mukhtar Journal of Sciences 32 (1): 9-16, 2017

Antioxidant Activity of Lipoic Acid on Cyclosporine A-Induced Physiological Changes to the Kidneys in Male Albino Rats

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Received: 9 February 2017 / Accepted: 22 April 2017
Doi: https://doi.org/10.54172/mjsc.v32i1.89

Abstract: Cyclosporine A (CsA) is the most widely used immunosuppressive drug for preventing graft rejection and autoimmune disease. However, the therapeutic treatment induces several side effects such as nephrotoxicity, cardiotoxicity and hepatotoxicity. This study aimed to assess the protective role of lipoic acid (LA) on kidney toxicity of male albino rats induced by cyclosporine (CsA). Forty adult male rats were allocated into four groups: Group (I) served as a control group. Group (II); received treatments orally with CsA (25 mg/kg b.w.), daily for 3 weeks. Group III: (Recovery CsA group): treated orally with CsA (25 mg/kg b.w.), daily for 3 weeks, then recovered for another 3 weeks. Group IV (LA and CsA group): received LA (100 mg/kg b. w.) orally 1 h before treatment by CsA (25 mg/kg b. w.) daily for 3 weeks. The results indicated that treatment of CsA caused a significant elevation in the concentrations of serum urea, creatinine, and uric acid which indicate injury to the kidney function. Renal malondialdehyde (MDA) concentration was markedly increased reflecting increased lipid peroxidation, whereas, reduced glutathione (GSH) and superoxide dismutase (SOD) were significantly decreased. On the other hand, LA plus CsA dose-dependently inhibited activities of serum urea, creatinine, and uric acid. The administration of LA plus CsA exhibited significant reduction in lipid peroxidation while GSH content and SOD activity were enhanced significantly which reflect an improvement in renal toxicity. In conclusion, the results indicated a negative role of CsA on kidney function and oxidative stress in induction toxicity, suggested Thus, Lipoic acid play a positive role on toxicity of kidney induced by cyclosporine A.

Key Words: Lipoic acid, cyclosporine A, oxidative stress, renal toxicity.

INTRODUCTION

As a highly potent immunosuppressive drug, cyclosporine (CsA) remains largely used for the prevention of acute rejection in solid organ transplantation, and for the treatment of various auto-immune diseases. However, CsA can lead to a chronic form of renal damage characterized by a progressive and irreversible deterioration of renal function associated with interstitial fibrosis, tubular atrophy, arteriolar hyalinosis and glomerulosclerosis (Nankivell et al., 2004, Chapman and Nankivell 2006).

Alpha-lipoic acid (LA), or 1,2-dithiolane-3-pentanoic acid, is a naturally occurring dithiol compound synthesized enzymatically in the mitochondrion from octanoic acid. LA is a necessary cofactor for mitochondrial α-ketoacid dehydrogenases, and thus serves a critical role in mitochondrial energy metabolism. In addition to synthesis, LA is also absorbed intact from dietary sources, and it transiently accumulates in many tissues. There is growing evidence that orally supplied LA may not be used as a metabolic cofactor but instead, elicits a unique set of biochemical activities with potential pharmacotherapeutic value against a host of pathophysiologic insults. LA has a potent antioxidant, a detoxification agent and improve age-associated cardiovascular, cognitive, and

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neuromuscular deficits (Scott et al., 1994, Smith et al., 2004, Koh et al., 2005). This impressive array of cellular and molecular functions has piqued considerable interest among the lay public and the research community for the use of LA both as a nutritive supplement and as a pharmacotherapy. In light of this growing interest, we will attempt to provide an update on the biochemical, toxicological, and pharmacological mechanisms of LA. As many excellent reviews already exist that outline the metabolic role of LA as a covalently bound enzyme cofactor, only a brief summary of this particular aspect of LA function will be presented herein. Instead, a focus mainly on the cellular actions of orally supplied, nonprotein-bound LA will be presented. Pertinent clinical benefits of LA will also be discussed in light of this molecular mechanism(Liu et al., 2002, Shay et al., 2009).Therefore, this study investigated the modulating and antioxidant activity of lipoic acid on renal toxicity induced by cyclosporine A in male albino rats.

MATERIALS AND METHODS

Chemicals

Cyclosporine A (CsA) is presented in the form of ampoules under traditional name Sandimmune and provided by Novartis Pharma (Basel, Switzerland). It is presented as a clear, yellow liquid supplied in 1ml ampoules containing 50 mg/ml and was further diluted with olive oil. Alpha-Lipoic acid (LA) was purchased in the form of a yellow powder from Sigma chemical company (St Louis, Missouri, USA) and was suspended in sterile normal saline, before use.

Experimental animals

Male Wistar albino rats, each weighing 180 ± 20 g, were obtained from an animal house in Medical Research Center (MRC), Faculty of Medicine, Ain Shams University. The animals were acclimatized to the laboratory conditions for a period of 14 days. They were maintained at an ambient temperature of 25 ± 3°C, 50 ± 20% relative humidity and 12/12 h of light–dark cycle and were given a standard rat feed and water ad libitum. All experimental procedures were conducted according to the ethical standards approved by the Institutional Animal Ethics Committee guidelines for animal care and use, Ain Shams University, Cairo, Egypt.

Experimental protocol

The rats were randomly divided into four groups, each of eight rats as follows:

Group I (Control): received saline (2 ml/kg b. w.) and olive oil (2 ml/kg b. w.) orally for 21 days.

Group II (CsA-treated group): was treated orally by gastric gavage with CsA (25 mg/kg b.w.), daily for 21 days.

Group III (Recovery CsA-treated group): was treated orally by gastric gavage with CsA (25 mg/kg b.w.), daily for 21 days and recover for another 21 days.

Group IV (LA and CsA-treated group): received LA (100 mg/kg b. w.) orally (Jalali-Nadoushan and Roghani 2013) , 1 h before treatment by CsA (25 mg/kg b. w.) daily and concurrently for 21 days.

At the end of the experimental period, the animal groups were sacrificed after 24 hrs. of the last dose of different administrations and their blood were collected, by carotid bleeding, in centrifuge tubes and serum was obtained from the blood after centrifugation at 3000 rpm for 10 min. The kidney tissue was immediately excised, cleaned of adhering connective tissue, rinsed in physiological saline, weighed and stored at -20°C until analysis studies.

Methods of analysis

Serum urea, creatinine and uric acid were estimated by using the method of (Fawcett and Scott 1960, Seeling and Wust 1969, Barham and Trinder 1972, Scott et al., 1994) respectively. Renal glutathione (GSH) was spectrophotometrically assayed by the method of (Sedlak and Lindsay 1968). The activity of renal SOD was determined by assessing the inhibition of pyrogallol autoxidation (Marklund 1985). Malondialdehyde (MDA) was determined in kidney by using the method of (Uchiyama and Mihara 1978).

Statistical analysis

Statistical analyses of the resulted data were done using InStat version 2.0 (Graph Pad, ISI, Philadelphia, PA, USA, 1993) computer software. The results were expressed as means ±SE). Multiple comparisons were done using one-way ANOVA

ISSN: online 2617-2186 print 2617-2178

followed by Tukey-Kramer as a post-ANOVA test. Statistical significance was accepted at P< 0.001, P< 0.01, P< 0.05.

RESULTS

CsA administration caused a significant increase in serum urea, creatinine and uric acid concentrations (P<0.001) in the CsA treated groups compared to the control group I. These concentrations tended to be highly significant compared to the values of the control group I (Table 1).

Table (1): The effect of LA on CsA - induced changes on serum urea, creatinine and uric acid concentrations.

Groups	Parameters		
	Urea mg/dl	creatinine mg/dl	Uric acid mg/dl
G I (Control)	15.81± 0.22	0.73 ± 0.020	5.57 ± 0.025
G II: (CsA)	44.45 ±0.43a'	1.90 ±0.02a**	8.45 ±0.04a**
G III: (Recov.)	33.76 ±0.291 ab**	1.51 ±0.035 ab**	6.69 ±0.045 ab**
GIV (LA &CsA)	21.47 ±0.153 ab**	0.87 ±0.015 ab**	5.86 ±0.19 ab**

Data are expressed as means ± S.E. (n = 6 in each group).
a: Significant change at p< 0.05 with respect to control group I.
b: Significant change at p< 0.05 with respect to group II.
*Highly significant change at p < 0.01. **Very highly significant change at p < 0.001.N.S: Non-significant change.

The present data showed a significant elevation in the level of renal MDA (P<0.001), while a significant reduction in renal GSH and SOD activity (P<0.001) was observed in CsA treated group compared to the control group I (Table 2).On the other hand, treatment with LA plus CsA caused a highly significant decrease in serum urea, creatinine and uric acid concentrations (P<0.001) in the LA plus CsA treated group IV compared to the CsA group II (Table 1).Renal MDA was restored significantly (P<0.001), also renal GSH content and SOD activity were attenuated in the LA plus CsA treated group IV as compared to the CsA group II (Table 2).

Table (2): The effect of LA on CsA – induced changes on renal GSH, SOD and MDA levels.

Groups	Parameters		
	Renal		
	MDA U/g wet tissue	GSH U/g wet tissue	SOD U/g wet tissue
G I (Control)	30.34 ± 0.071	28.45 ± 0.115	81.31 ± 0.083
G II: (CsA)	56.20 ± 0.049a**	56.14 ± 0.044a**	63.28±0.057 a**
G III: (Recov.)	30.32 ± 0.062	28.41± 0.093	81.38 ± 0.0859
GIV(LA and CsA)	38.28 ± 0.058 ab**	76.39 ± 0.076 ab**	40.20 ± 0.049 ab**

Data are expressed as means ± S.E. (n = 6 in each group).
a: Significant change at p< 0.05 with respect to control group I.
b: Significant change at p< 0.05 with respect to group II.
*Highly significant change at p < 0.01.
**Very highly significant change at p < 0.001.
N.S: Non-significant change.

DISCUSSION

Deciphering new biological pathways that contribute to CsA renal toxicity is of great importance because they may lead to the development of early biomarkers of kidney injury. A significant elevation in serum urea, uric acid and creatinine concentrations were observed in CsA treated rats as compared with control (group I). These results are in agreement with(Tirkey et al., 2005) who showed that chronic administration of CsA caused a marked impairment of renal function along with significant oxidative stress in the kidneys. Oxidative stress promote the formation of a variety of vasoactive mediators that can affect on renal function directly by causing renal vasoconstriction or decreasing the glomerular capillary ultrafiltration coefficient and thus reducing glomerular filtration rate (Garcia-Cohen et al., 2000, Burdmann et al., 2003). CsA inhibits mitochondrial mediated apoptosis but also induces mitochondrial apoptotic cell death in the kidney (Pallet et al., 2008) caused ischemia induced up-regulation of endothelin receptors, support the potential for an important role for up-regulation of endothelin receptors in pathophysiologic mechanisms of CsA-induced glomerular dysfunction(Fogo et al., 1992).In this study, CsA treated rats (group II) showed a

ISSN: online 2617-2186 print 2617-2178

significant increase in the levels of renal MDA with excess production of hydrogen peroxide in living cells, accompanied with a significant decrease in GSH and SOD that leads to decline in the activity of the antioxidant enzymes depletion of both the GSH and protein thiols. Similar biochemical changes were previously reported in other studies(Khan et al., 2006, Ajala et al., 2008) which then give rise to increased hydroxyl radical formation. The effects of reactive oxygen species (ROS) on cellular and extracellular components of organisms have been investigated extensively in recent years. CsA promotes the formation of reactive oxygen species (ROS) such as hydrogen peroxides. These ROS enhance the peroxides and reactive hydroxyl radicals. These lipid peroxides and hydroxyl radical may cause cell membrane damage and thus destroy the cell. It also inhibits the activities of free radical quenching enzymes such as catalase, superoxide dismutase and glutathione peroxidase. The role of CsA in ROS production was observed in the present study by increased amount of renal and hepatic lipid peroxides (LPO). The intracellular generation of hydrogen peroxides (H2O2) could be involved in the initiation of CsA toxicity in rats, caused cell membrane damage like lipid peroxidation which leads to the imbalance between synthesis and degradation of enzyme protein.

The excess production of ROS may be due to its ability to produce alteration in mitochondria by blocking the permeability transition pore .Reactive oxygen metabolites are generated by specialized phagocytic cells (neutrophils) as cytotoxic agents to fight invading micro-organism, a process known as the respiratory or oxidative burst. Therefore, phagocytes use the membrane bound NADPH oxidase complex which catalyzes one electron, reduction of O2 into O-2. The ROMs are generated in a biological system via several enzymatic and non-enzymatic pathways(Morel et al., 1991, Agar et al., 2011).On the other hand, the present results illustrated that the antioxidant LA administration had an ameliorating effect on the changes of the biochemical parameters associated with CsA challenge. This effect was indicated by improvement of serum urea, uric acid and creatinine concentrations. These results are in agreement with (Sivaprasad et al., 2004) who found that administration of LA one hour after CsA offered marked protection against nephrotoxicity. This protection was manifested as a significant reduction in serum levels of urea, uric acid, creatinine and amelioration of apoptotic markers (Forbes et al., 2008) Voltage-dependent anion channels (VDAC), known as mitochondrial porins, are membrane proteins encoded by nuclear gene and synthesized in ribosome.

VDAC plays crucial roles in the physiological and pathologic processes, including energy metabolism and cell apoptosis. VDAC was actually more sensitive to oxidative stress-induced cell death (Wang et al., 2013). In addition, free radical scavengers may also be helpful in prolonging survival time of dopaminergic neurons (Chen and Le 2006). In this respect, LA could attenuate neuronal damage and loss through counteracting oxidative stress, possibly via regulating antioxidant defense system as well as inhibition of free radical generation(Connell and Saleh 2012). LA and its reduced form dihydrolipoic acid are present in all prokaryotic and eukaryotic cells and considered a vitamin, and can be synthesized in human cells. LA is involved in the regulation of carbohydrate and lipid metabolism in converting blood glucose into energy(Malinska and Winiarska 2005), improving glycemic control.In the present study, administration of LA prior to CsA treatment markedly ameliorated LPO in the rat kidney as manifested by decreased MDA level accompanied by increased GSH content and SOD activity. In agreement with the present findings, (Wollin and Jones 2003) mentioned that LA is a naturally occurring cofactor within pyruvate dehydrogenase and α-keto-glutarate dehydrogenase. Also, Free LA has the ability to scavenge superoxide, hydrogen peroxide, hydroxyl radicals, and peroxynitrite, and can also recycle glutathione (GSH), α-tocopherol and ascorbic acid. In vitro, α-lipoic acid decreased plasma susceptibility to oxidation(Marangon et al., 1999), and were protective against haemolysis of human erythrocytes induced by peroxyl radicals (Constantinescu et al., 1994) and increased GSH synthesis in isolated human erythrocytes (Han et al., 1997). Also, α-lipoic acid attenuated superoxide generation and kidney

ISSN: online 2617-2186 print 2617-2178

expression of NADPH oxidase in diabetic rats, and it was concluded that α-lipoic acid improves pathology in diabetes by reducing oxidative stress (Lexis et al., 2006). Thus, LA has been shown to reduce oxidative stress both in vivo and in vitro studies. Reduction of renal GSH, SOD activity in CsA-treated rats was observed in this study, which was similar to the previous studies (Mohamadin et al., 2005). LA has proved to possess lipid lowering, anti-lipo peroxidative and antioxidant properties (Amudha et al., 2006).

It has been demonstrated to play an important role in regulating antioxidative capacity by increasing SOD, GSH and catalase activities by upregulating the gene expression of SOD, GSH and catalase (Hagar *et al.,* 2006). Reduced glutathione together with GPx is important in maintaining the structure of mitochondrial and cell membranes. In addition, (Huong and Ide 2008) reported that a-lipoic acid reduced the activities and mRNA levels of various lipogenic enzymes together with the mRNA levels of various proteins. As that Alpha-lipoic acid (α-LA), a naturally occurring dithiol compound, has long been known as an essential cofactor for mitochondrial bioenergetic enzymes. As an antioxidant, α-LA directly terminates free radicals, chelates transition metal ions, increases cytosolic glutathione, vitamin C, E levels and prevents toxicities associated with their loss (Singh and Jialal 2008).In conclusion, LA is a main active component for immuno-modulating and antioxidant activities, differ greatly in the chemical composition and physical properties, show the same basic multivitamins and protect the immune cells from oxidative damage. Thus, LA has a potential protective effect against CsA toxicity and is improving the renal function by decreasing the kidney tissue damage of CsA-induced nephrotoxicity in rats.

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ISSN: online 2617-2186 print 2617-2178

النشاط المضاد للأكسدة لحمض الليبويك على التغيرات الفسيولوجية للكلى الناجمة عن التعرض للسيكلوسبورين-أ في ذكور الجرذان البيضاء

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تاريخ الاستلام:9 فبراير 2017 / تاريخ القبول : 22 أبريل 2017.

Doi:https://doi.org/10.54172/mjsc.v32i1.89

المستخلص : استخدم البحث 40 من ذكور الجرذان البالغة والتي قسمت إلى 4 مجاميع، المجموعة الأولى: تمثل المجموعة الضابطة. وتم تجريع المجموعة الثانية بعقار السيكلوسبورين-أ (25 ملجم/كجم) عن طريق الفم يومياً لمدة 3 أسابيع. وتم تجريع المجموعة الثالثة السيكلوسبورين- أ (25 ملجم/كجم) عن طريق الفم يومياً لمدة 3 أسابيع ثم تركت فترة تعافٍ لمدة 3 أسابيع أخرى. والمجموعة الرابعة تم تجريعها بحمض الليبويك (100 ملجم/كجم) عن طريق الفم قبل ساعة من المعاملة بعقار السيكلوسبورين-أ (25 ملجم/كجم) يومياً لمدة 3 أسابيع، وتشير النتائج إلى أن المعاملة بعقار السيكلوسبورين-أ قد تسببت في ارتفاع ذي دلالة معنوية لتركيز كل من اليوريا والكرياتينين وحمض البوليك في الدم، مما أدى إلى ضعف في وظائف الكلىK وقد لوحظ أيضاً ارتفاع مالونداي الدهيد (MDA) الكلوي بشكل ملحوظ مما يعكس زيادة الدهون البيروكسيدية، في حين انخفض كل من الجلوتاثيون، (GSH) وفوق أكسيد الدسموتيز (SOD). من ناحية أخرى فأن المعاملة بحمض الليبويك مع السيكلوسبورين-أ أدت إلى خفض مستوى اليوريا والكرياتينين وحمض البوليك في الدم لتصبح أقرب للمجموعة الضابطة، فضلاً عن انخفاض كبير في الدهون البيروكسيدية (MDA) وتحسن في كلٍّ من محتوى GSH. ونشاط SOD بشكل ملحوظ يعكس مدى تحسن تسمم الكلى، من هذه الدراسة نستنتج الدور السلبي لعقار السيكلوسبورين-أ على وظائف الكلى من خلال رفع مستوى الإجهاد التأكسدي واسحثاث التسمم الكلوي، في حين يقوم حمض الليبويك بدور إيجابي في تقليل تسمم الكلى الناجم عن عقار السيكلوسبورين-أ.

الكلمات المفتاحية: حمض الليبويك، سيكلوسبورين-أ، الإجهاد التأكسدي، التسمم الكلوي.

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