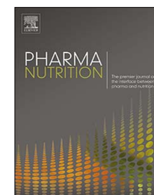
PharmaNutrition 5 (2017) 127–132

Contents lists available at ScienceDirect

PharmaNutrition

journal homepage: www.elsevier.com/locate/phanu



Protective effect of alpha-lipoic acid on progression of cataract formation in fructose-induced experimental cataract

Sajida Begum Khan, Rajesh Choudhary, Prabhat Kumar Vishwakarma, Amrita Singh, Jaya Shree, Surendra H. Bodakhe*

Department of Pharmacology, Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, C.G., 495009, India

A R T I C L E I N F O

Chemical Compounds studied in this article:
Alfa-lipoic acid (PubChem CID: 6112)
Fructose (PubChem CID: 5984)

Keywords:
Alpha-lipoic acid
Cataract
Fructose
Oxidative stress
Hypertension
Diabetes

A B S T R A C T

Cataract is the leading cause of ocular blindness worldwide and exacerbated by various systemic disorders, including diabetes and hypertension. The present study was designed to investigate the protective effects of alpha-lipoic acid (LA) against fructose-induced experimental cataract. Sprague-Dawley albino rats (150–180 g) were assigned to groups each containing six animals. Group I (normal) received 0.3% carboxymethyl cellulose (10 ml/kg/day, p.o.) by gavage. Group II (fructose control) received carboxymethyl cellulose by gavage and 10% (w/v) fructose solution in place of drinking water. Group III and IV received LA at two dose levels 20 and 40 mg/kg/day orally by gavage respectively, concurrent with fructose solution (10% w/v) for eight consecutive weeks. Mean arterial pressure, blood glucose level, and lenticular opacity were examined biweekly and pathophysiological parameters in eye lenses were evaluated after eight weeks of the experimental protocol. The eight weeks administration of LA (20 and 40 mg/kg) concurrent with fructose solution significantly reduced the mean arterial pressure and blood glucose level. Additionally, lipoic acid treatment led to significant alleviation in lens antioxidants (CAT, SOD, GPx, and GSH), total protein, and Ca^{2+} ATPase activity. Moreover, a significant reduction in lens MDA and Ca^{2+} was seen as compared to fructose control group. Ophthalmoscope observations indicated that LA treatment delayed the onset and progression of cataract against the fructose treatment. The results suggest that alpha-lipoic acid supplement play a beneficial role in the management of diabetes and hypertension associated cataractogenesis.

1. Introduction

Cataract is a multifactorial disease, characterized by cloudiness and opacification of the eye's lens mainly due to the formation of large protein aggregates in the lens. Cataract change the clarity of the natural lens inside the eye's that slowly degrade visual quality. It is a leading cause of visual disability and blindness all over the globe and the problem is acute in the developing countries. Million people suffer from cataract-related visual impairments. [1,2]. A number of etiological factors like diabetes, central obesity, older age, race, smoking, alcohol, and hypertension have been recognized as risk factors for cataract. The association between diabetes, hypertension, and cataract is well recognized, being identified as a risk factor in case-control and experimental studies [3–5]. Our previous studies demonstrated that nutrient supplements substantially delay the progression of cataract formation against hypertension and high fructose diet conditions [6,7].

Alpha-lipoic acid (LA) as a cofactor in multi enzyme dehydrogenase complexes associated with the citric acid cycle has been well known for the past fifty years. More recently it has been found as a powerful antioxidant and found effective in preventing or lessening the damage caused by reactive oxygen species (ROS) by scavenging ROS directly or stimulating the synthesis of other antioxidant such as glutathione [8]. It may also be effective in both prevention and treatment of oxidative stress in a number of models or clinical conditions, including ischemia-reperfusion injury, diabetes, HIV infection and neurodegenerative diseases [9–11]. Oxidative stress is implicated in etiology of cataractogenesis. Because of potent antioxidant properties of LA, Its preventive role was evaluated against fructose-induced experimental cataract.

2. Materials and methods

2.1. Drugs and solutions

DL-alpha-lipoic acid (DL-6,8-thioctic acid) and D-fructose were procured from Hi-Media chemicals, Mumbai, India. All other laboratory

* Corresponding author.
E-mail address: drbodakhe@gmail.com (S.H. Bodakhe).

http://dx.doi.org/10.1016/j.phanu.2017.10.001
Received 13 September 2017; Received in revised form 5 October 2017; Accepted 6 October 2017
Available online 07 October 2017
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chemicals and reagents used were of analytical grade. 10% (w/v) fructose solution were prepared by dissolving fructose in drinking water and fed to rats. LA was suspended in 0.3% carboxymethyl cellulose solution as the vehicle and administered orally by gavage.

2.2. Experimental animals

Male Sprague-Dawley albino rats (150–180 g) were selected for the present study. They were kept under standard environmental conditions (22 ± 2 °C, with 55 ± 5% humidity and 12 h light/dark cycle), according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Govt. of India. They were allowed free access to food and water *ad libitum*. The experimental protocols were approved by Institutional Animal Ethics Committee (IAEC, 994/GO/ERe/S/06/CPCSEA) of the Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G), India. The experimental procedures on animals were carried out in strict compliance with the ethical principles and guidelines of the CPCSEA, Govt. of India.

2.3. Experimental protocol

The animals were randomly selected that were normal regarding the ocular examination and blood pressure at the baseline after an acclimatization period of seven days, and assigned to four groups (n = 6). Group I (normal) received a suspension of 0.3% carboxymethyl cellulose (10 ml/kg/day, p.o.) orally by gavage for eight weeks. Group II (fructose control) received 0.3% carboxymethyl cellulose orally by gavage and 10% (w/v) fructose solution in their drinking water (equivalent to a diet containing 48% − 57% fructose) for eight weeks [7]. Group III and IV received LA at two dose levels 20 and 40 mg/kg/day orally by gavage respectively, concurrent with fructose solution (10% w/v) for eight consecutive weeks.

Blood pressure in terms of mean arterial pressure (MAP), blood glucose level and ocular opacity were examined biweekly. After the completion of the experimental protocol (eight weeks), animals were sacrificed and their eyeballs were removed. Lenses were dissected via a posterior approach, washed with cold distilled water and stored at −20 °C until analysis.

2.4. Measurement of mean arterial pressure (MAP)

MAP was monitored biweekly at 10:00 to 11:00 a.m. by using a non-invasive blood pressure system (NIBP; CODA-08 Channel, Kent scientific, USA).

2.5. Measurement of blood glucose level

Blood glucose was monitored biweekly at 11:00 to 12:00 a.m. by using the glucose-monitoring device (One Touch Select, Johnson & Johnson Private Ltd., India).

2.6. Visual examination of the eyes

Eyes were examined biweekly using a panoptic ophthalmoscope (Welch Allyn, USA) on dilated pupil. Pupils of animals were dilated by topical administration of 1% tropicamide solution and lenticular opacity of the eye lenses was examined. Initiation and progression of the cataract formation were graded into five categories as follow: stage 0, clear and normal lens; stage 1, vacuoles cover approximately one-half of the anterior pole surface; stage 2, cortical opacity; stage 3, a hazy cortex with nuclear opacity; stage 4, mature cataract [12]. Percent cataract incidence was calculated as:

% cataract incidence = (no. of eyes in each stage/total no. of eyes) × 100

2.7. Estimation of oxidative stress markers

Different oxidative stress markers in the lens homogenate (10% w/v in 0.1 M potassium phosphate buffer, pH 7) were determined by spectrophotometric methods using UV–vis spectrophotometer (UV-1800, Shimadzu, Japan). The catalase (CAT) was assessed based on the ability of the enzyme to break down hydrogen peroxide into water and expressed as millimoles of hydrogen peroxide consumed per min in per mg of lens tissue [13]. Superoxide dismutase (SOD) was measured via nitroblue tetrazolium reduction assay. One unit (U) of SOD activity is defined as the amount of enzyme required to cause 50% inhibition of the nitro blue tetrazolium photoreduction rate [14]. Glutathione peroxidase (GPx) was assayed by using the methods of Tappel (1978) and expressed as micromoles of glutathione oxidized per min in per mg of lens tissue [15]. Reduced glutathione (GSH) was estimated by using Ellman's reagent [16]. The malondialdehyde (MDA), a lipid peroxidation marker, was estimated by using thiobarbituric acid reacting substances [17].

2.8. Estimation of lens protein contents

Total and soluble protein contents were assayed in the lens homogenate by using alkaline copper solution and phenol reagents. The liberated colored product was monitored at 610 nm. Bovine serum albumin was used as a standard for establishing the calibration curve [18].

2.9. Estimation of lens Ca^{2+} ATPase activity and Ca^{2+}

The Ca^{2+} ATPase activity in the lens homogenate was estimated using the method of Manikandan et al., 2010. The liberated phosphorous was measured at 640 nm by the spectrophotometric method [19]. Ca^{2+} in lens homogenates was estimated spectrophotometrically by using the diagnostic kit (Labcare diagnostic Pvt. Ltd., India).

2.10. Statistical analysis

The results were expressed as mean ± standard error of mean (SEM). The significant difference ($P < 0.05$) was statistically analyzed by using analysis of variance (ANOVA). Tests were performed using Graph Pad Prism 5.0 (GraphPad Software, Inc, USA).

3. Results

3.1. Effect of LA on MAP

The results are depicted in Fig. 1. The results showed that chronic administration of fructose solution to the animals of fructose control group led to significant ($P < 0.001$) induction of hypertension (MAP) from four weeks to eight weeks as compared to the normal group. Whereas, the eight weeks administration of LA concurrently with fructose solution significantly reduced the MAP at both dose levels 20 mg/kg ($P < 0.01$) and 40 mg/kg ($P < 0.001$) as compared to fructose control group. The results indicate that LA at 40 mg/kg dose level had better antihypertensive action than LA at 20 mg/kg dose level

3.2. Effect of LA on blood glucose level

Fig. 2 shows the result of blood glucose level in different experimental groups. Fructose control group showed significant elevation in blood glucose level in time-dependent manner from the fourth week ($P < 0.01$) to eighth week ($P < 0.01$) as compared to the normal group. The eight weeks oral administration of LA (20 and 40 mg/kg) significantly ($P < 0.01, P < 0.001$) reduced the blood glucose level in group III and IV as compared to fructose control group. The results

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