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LABORATORY INVESTIGATION

Efficacy of α-Lipoic Acid Against Diabetic Cataract in Rat

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Abstract

Purpose: α-Lipoic acid (LA) is well known as a powerful antioxidant. The efficacy of dihydrolipoate-LA for oral administration against streptozotocin (STZ)-induced diabetic cataract in rat was investigated.

Methods: Rats were divided into three groups, control, diabetes mellitus (DM), and DM treated with LA (DM+LA). Diabetes was induced by intravenous injection of 50 mg/kg STZ. DM+LA rats were fed 30 mg/rat per day LA in their diet. Lens changes were assessed using Scheimpflug images (EAS-1000) and by measuring light-scattering intensity.

Results: Increase in lens light scattering was less ($P < 0.05$) in DM+LA rats than in DM rats 5 weeks after induction of diabetes. DM rats had the highest and control rats the lowest blood glucose levels at every measurement point up to 111 days ($P < 0.05$).

Conclusion: LA treatment delayed development and progression of cataract in rats with streptozotocin-induced diabetes. **Jpn J Ophthalmol** 2007;51:10–13 © Japanese Ophthalmological Society 2007

Key Words: antioxidant, diabetic cataract, α-lipoic acid, lipoic acid, rat

Introduction

α-Lipoic acid (LA) and its reduced form, dihydrolipoate (DHLA), are both powerful antioxidants. Both act not only directly, by radical quenching and metal chelation, but also indirectly, through the recycling of other antioxidants such as ascorbic acid, vitamin E, and glutathione.[1,2] LA and DHLA have received much attention because many diabetic complications are believed to be mediated by oxygen free-radical generation. LA has been shown to protect against cataractogenesis, a diabetic complication resulting from polyol accumulation, crystallin glycation, and oxidative insults,[3] in both in vivo and in vitro models.[4–10]

LA prevented cataract formation by increasing glutathione, ascorbate, and vitamin E levels, and restoring the activities of glutathione, peroxidase, catalase, and ascorbate free-radical reductase in the lenses of 60% of rats treated with L-buthionine sulfoximine, an inhibitor of glutathione synthesis.[4] Intraperitoneal injection of LA significantly reduced blood glucose levels, increased lenticular glutathione content, and inhibited cataractogenesis in a sand rat model of acute type 2 diabetes.[9] However, LA delivered by intubation had no effect on blood glucose levels and cataract development in sand rats fed a "medium-energy" diet (a chronic diabetic model), although glutathione levels increased.[9] In addition, it has been reported that LA might prevent protein glycation[11] and inhibit aldose reductase activity in lenses cultured under hyperglycemic conditions.[12]

Although several reports have shown that LA may prevent formation of experimentally induced cataract, it remains unclear whether LA can also prevent or delay cataract progression. Therefore, to investigate the effects of LA on cataract progression in streptozotocin-induced diabetic rats over a 10-month period, we periodically analyzed photographs of the lenses.

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Table 1. Blood glucose levels

Blood glucose (mg/dl)	Days after DM induction			
	3 days	41 days	80 days	111 days
CTL	80.7 ± 3.9*	82.6 ± 8.1	72.5 ± 2.1*	—
DM	381.1 ± 28.8	>500	686.2 ± 81.2	620.9 ± 111.2
DM+LA	347.8 ± 70.5	369.1 ± 72.4	531.4 ± 168.1*	514.8 ± 99.7*

CTL, control; DM, diabetes mellitus; LA, α-lipoic acid.
*$P < 0.05$ vs. DM.

Materials and Methods

Thirty-six 7-week-old female Brown Norway rats were used in this study. All animals were cared for and handled in accordance with Guidelines for Animal Experiments at Kanazawa Medical University and the ARVO Resolution on the Use of Animals in Research. Food and water were provided ad libitum.

Rats were divided into control (CTL, 8 rats), diabetes mellitus (DM, 14 rats), and DM with LA treatment groups (DM+LA, 14 rats). Diabetes was induced by intravenous injection of 50 mg/kg streptozotocin (STZ) (2% solution in 0.1 M citrate buffer, pH 4.6), and onset was confirmed in all rats 3 days later by blood glucose levels exceeding 200 mg/dl (11 mmol/l), as measured with a Glutest GT-1610 analyzer (Sanwa Kagaku Kenkyusho, Nagoya, Japan).

The same volume of citrate buffer without STZ was injected into the CTL rats. LA (Wako Pure Chemical, Osaka, Japan, 30 mg/rat per day) was mixed with powdered food and given as a daily diet supplement to the DM+LA group starting 3 days after diabetes induction. The mixture rate of the LA in the food had been properly changed from the food intake the day before. Lenses were photographed weekly using an anterior eye segment system (EAS-1000, NIDEK, Gamagori, Japan). Light-scattering intensities at 0.08, 0.13, 0.18, and 0.23 mm from the center of the anterior capsule were measured to evaluate the extent of lens opacification as described by Kojima and Sasaki.[13] Blood glucose levels were measured at 3 and 41 days after diabetes induction with a glucose measurement kit (Glutest Sensor, Sanwa), 80 and 111 days after diabetes induction (Glucose Test, Wako). Food consumption and body weight were measured daily. The data are expressed as means ± SD. Differences between groups were assessed using the Student *t* test, and *P* values less than 0.05 were considered to be significant.

Results

In the CTL group, mean body weight increased from 100 to 180 g during the first 3 months, and then gradually leveled off at 200 g at 5 months. In contrast, mean body weight did not change in the DM or DM+LA groups, remaining at around 100 g. There were differences ($P < 0.01$) in body weight between the CTL and DM groups, and also between the CTL and DM+LA groups from the fourth day onward. Treating DM rats with LA had no significant effect (DM vs. DM+LA) on weight gain. The average food consumption was highest in the DM group (13.4 g/rat per day) followed by the CTL (11.4 g/rat per day) and DM+LA groups (9.8 g/rat per day). Significant differences were found among the groups ($P < 0.05$). Blood glucose levels were highest in the DM group at every measurement point, and an inhibitory effect on elevation of blood glucose was observed in the DM+LA group (Table 1). Significant differences in blood glucose levels were observed between CTL and DM groups, and between CTL and DM+LA groups at some measurement points ($P < 0.05$ in both cases). Blood glucose levels on day 80 and 111 were significantly lower ($P < 0.05$, $P < 0.01$ respectively) in the DM+LA groups than in the DM group.

Figure 1 shows representative Scheimpflug slit images for each group. A slight increase in opacity in the anterior subcapsular region was first observed 3 weeks after diabetes induction in the DM group, and the opacity subsequently became denser and spread over a larger area. In the DM+LA group, the development and progression of the opacity was much slower. Figure 2 shows changes in light-scattering intensity with time at a depth of 0.08 mm from the center of the anterior capsule. A rapid increase in light-scattering intensity was observed in the DM group starting from 3 weeks after the experimental induction of diabetes. Although the DM+LA group showed the same pattern of change as the DM group, the pace of the increase in the DM+LA group was much more gradual. Significant differences were found between the DM and CTL groups and also between the DM and DM+LA groups from 3 weeks. A significant difference between the CTL and DM+LA groups was found from 5 weeks. Increases in light-scattering intensity measured at deeper points (0.13, 0.18, and 0.23 mm depth from the anterior capsule) were detected later than increases at shallower points (data not shown).

During the process of cataract development in STZ-induced diabetic rats, initial signs of lens opacification have been reported to appear in the anterior subcapsular region, followed by the anterior deep cortex, exhibiting a diffused cloudiness that can be distinguished from the relatively transparent superficial cortex. This can explain the decrease of lens light-scattering intensity in both the DM and DM+LA groups at a depth of 0.08 mm at 9 weeks and thereafter.

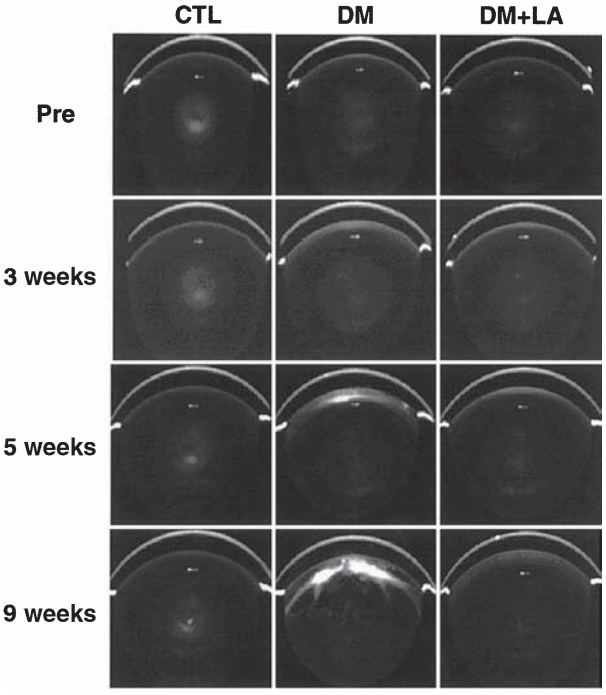

Figure 1. Scheimpflug slit images for each group. Slight changes around the anterior subcapsular region were observed 3 weeks after diabetes induction in the diabetes mellitus (DM) group. The opacities in the DM group rapidly enlarged and increased in density, while those in the DM with α-lipoic acid treatment (DM+LA) group progressed more slowly.

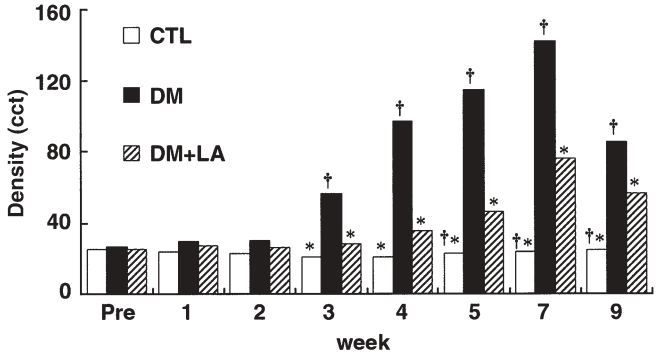

Figure 2. Changes in light scattering intensity at a depth of 0.08 mm. Light-scattering intensity in the DM group increased rapidly with time. Although the DM+LA group also showed an increase in light-scattering intensity, the change was much smaller than in the DM group. *cct*, computer compatible tape; □ *CTL*, control; ■ *DM*, diabetes mellitus; ▨ *DM+LA*, DM with α-lipoic acid group. **P* < 0.05 versus DM. †*P* < 0.05 versus DM+LA.

Discussion

Although LA has been reported to prevent cataract development in rats treated with L-buthionine sulfoximine[4] and in a sand rat model of acute type 2 diabetes,[9] it has not been reported whether LA can prevent or delay cataract progression. The present study investigated the preventive effect of LA on the development and progression of cataract in streptozotocin-induced diabetic rats during a 10-month period. Light-scattering measurements indicated that dietary LA is effective in delaying not only cataract development but also its progression. LA may be able to do this by preventing protein glycation[12] and reducing oxidative stress,[1,3,7] two of the three putative mechanisms of diabetic cataractogenesis;[3] LA is ineffective in reducing polyol pathway activity,[3,14] the third mechanism.

Swamy-Mruthinti et al.[15] measured progressive changes in lens opacification by Scheimpflug densimetric analysis and correlated them with protein glycation in the STZ-induced diabetic rat, and reported that crystallin glycation, rather than plasma glucose level, was strongly correlated with lens opacification. Suzuki et al.[11] also showed that LA significantly prevented BSA glycation and modification. Although we have not measured glycation in lens crystallin, it is possible that glycation in the DM+LA group may have been prevented by LA.

In the present study, LA showed an inhibitory effect on elevation of blood glucose at 80 and 111 days (Table 1). However, our results agree with those of previous studies.[9,16] In some other studies,[9,14,17–20] however, LA did not significantly lower blood glucose in diabetic conditions. This discrepancy may be due to (1) differences in the dosing and delivery of LA, (2) differences in animal models, or (3) differences in blood glucose sampling times. In fact, our results showed significantly lower blood glucose in DM+LA rats than in untreated DM rats only at 80 and 111 days. Khamaisi et al.[16] suggested that short-term administration of LA at high dosage to fasting normal or STZ-induced diabetic rats caused inhibition of systemic glucose production. The hypoglycemic effect of LA observed in our study may result from the above-mentioned mechanisms, and this effect may have partially contributed to ameliorating diabetic conditions. However, even when blood glucose levels were significantly lower in the DM+LA group than in the DM group, in agreement with a previous study,[9] the levels were still far above the normoglycemic range. Therefore, the LA inhibitory effect on blood glucose elevation does not appear to be the main mechanism of prevention of diabetic cataract formation.

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