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Short Communication

Liarozole, an Inhibitor of Retinoic Acid Metabolism, Retarded Atherogenesis in *LDLR-/-*Mice

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Abstract

Liarozole is a Retinoic Acid Metabolism Blocking Agent (RAMBA). As retinoic acid (RA) and its precursor, beta-carotene (BC), have been shown to inhibit atherosclerosis development in mouse models, in the present study we investigated whether liarozolecan mimic the anti-atherogenic effect of RA. We demonstrate, by using the LDL receptor-knockout mouse model fed a high-fat diet, that liarozole significantly reduces by 50% the aortic sinusatherosclerotic lesion area.

Keywords: Liarozole; Atherosclerosis; Mice

1.Introduction

Liarozole is a retinoic acid metabolism blocking agent (RAMBA). It inhibits several cytochrome P-450 enzymes, among them4-hydroxylase (Cyp-26),which metabolizes retinoic acid.Therefore, treatment with liarozole increases cellular retinoic acid (RA) levels. RAMBAs were originally developed to treat skin diseases and cancer, and there are no reports on their effect on atherosclerosis.

Several findings suggest RA has beneficial effects on atherosclerosis. It ameliorated high-fat, diet-induced atherosclerosis in rabbits [1] and increased the anti-atherogenic process of reverse cholesterol transport in macrophages [2]. We also showed that a vitamin A-deficient diet accelerated atherogenesis in a mouse model [3] and that treatment with retinoic acid or with its precursor, beta-carotene, significantly inhibits atherogenesis. These studies motivated us to investigate whether inhibition of RA catabolism by liarozole would retard atherosclerosis similar to a BC-fortification regime.

2. Material and Methods

Twelve-week-old, male LDL receptor-deficient mice (LDLR-/-) of the C57BL6 genetic background (Jackson Laboratories) were used. The mice were housed in plastic cages on a 12-hour light/12-hour dark cycle with free access toa high-fat diet (17.3% protein, 21.2% fat, 0.15% cholesterol; TD88137, Harlan Teklad) and water. The Animal Care and Use committee of Sheba Medical Center, Tel-Hashomer, approved all animal protocols (approval No. 682/11). Liarozole hydrochloride (Tocris) was dissolved in ethanol to prepare a 100mM solution. The liarozole in ethanol solution was diluted in saline to 1.6 mg/ml. Mice were allocated into three groups (15 animals per group) with similar body-weight, plasma cholesterol, and TG levels at baseline. The "control" group was injected with saline alone. The "BC" group was fed a high-fat diet fortified with the alga *Dunaliella* (80g *Dunaliella* powder, containing 6% beta-carotene, mixed with 1 Kg feed, total 4.8 g beta-carotene/Kg feed) and injected with saline. The "liarozole" group was treated with liarozole. Mice were injected (10µl

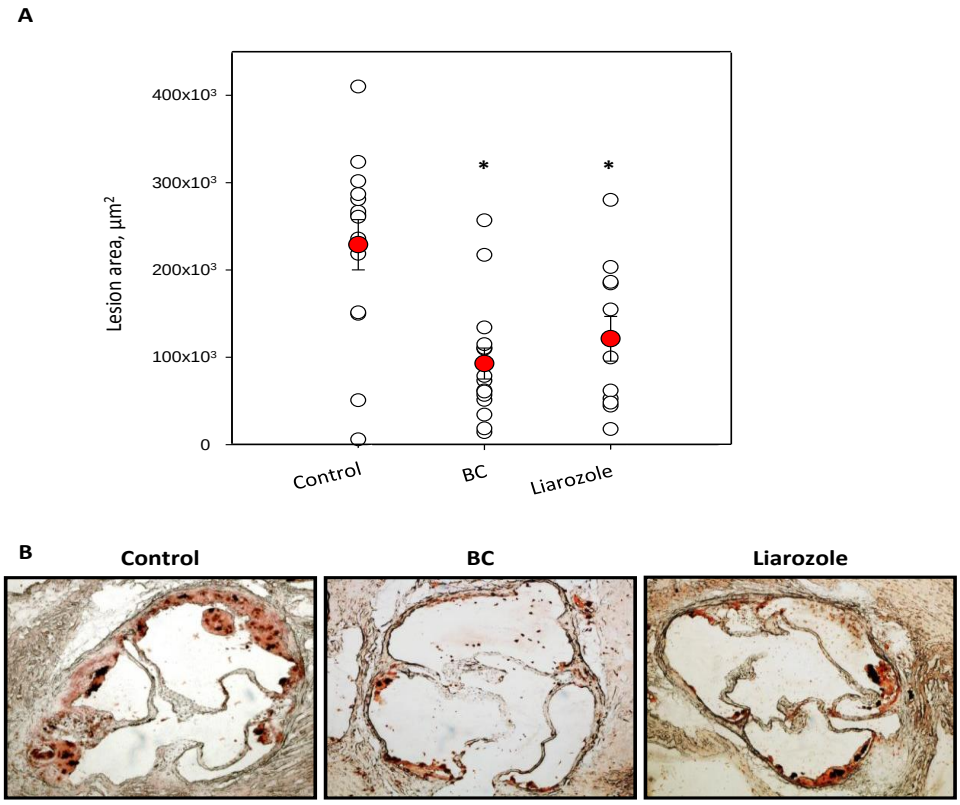
solution, 16µg liarozole) subcutaneously every other day and were killed after 10 weeks of treatment.

3. Result and Discussion

A trend towards lower body-weight gain was noted in the liarozole-treated mice; however, this trend was not statistically significant. Liarozole did not affect plasma cholesterol or triglyceride levels. In addition, cholesterol and triglyceride distribution in plasma lipoproteins (measured following FPLC separation) were not affected by liarozole. At the end the experiment, the aortic sinus lesion area was measured after Oil Red O staining (Figure 1). The results show that similar to beta-carotene treatment, liarozole inhibited atherogenesis significantly as indicated by the 50% lower aorticsinus atherosclerotic lesion area compared to the control group.

This study demonstrates for the first time that inhibition of RA catabolism with RAMBA inhibits atherosclerosis development in an animal model. Although plasma cholesterol and plasma triglyceride levels were not significantly affected by liarozole, the aortic sinus lesion area was significantly reduced compared to the control group. In the present study, the anti-atherogenic effect of liarozole was comparable to the effect of beta-carotene fortification of the diet and similar to the anti-atherogenic effect of RA in our previous work. The results suggest liarozole and other RAMBAs can be considered as anti-atherogenic agents.

Figure 1: Liarozole reduces the aortic sinus atherosclerotic lesion area in LDLR-/- mice
Lesions were quantified after 10 weeks of treatment. (A) Values are means±SE, (B) One representative aortic sinus lesion section is shown for each treatment group. n=13-15.*****p<0.05 compared to control. Open symbol=lesion of individual mouse. Red symbol=group mean.



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