ADX-103, a Novel Aldehyde Trap, Decreases Retinal Edema and Inflammation in a Rat Model of Diabetic Macular Edema

198-C0009

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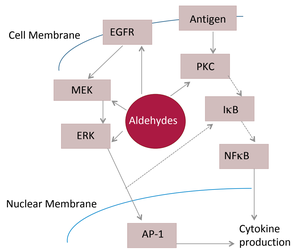
INTRODUCTION

Diabetic Macular Edema (DME) is a common cause of vision loss. Hyperglycemia leads to carbonyl stress in the retina, resulting in accumulation of toxic aldehydes such as glyoxal, methylglyoxal, malondialdehyde, and 4-hydroxy-trans-2-nonenal. Aldehydes bind covalently to amine and thiol residues on proteins, and initiate inflammatory signaling cascades (Figure 1). The ability of the novel aldehyde trap, ADX-103, to prevent ocular inflammation was tested in a rat streptozotocin (STZ)-induced model of DME.



Schematic depicting inflammation pathways initiated by aldehyde mediators.

MATERIALS and METHODS

Brown Norway rats were administered STZ for six weeks to induce diabetes. Single doses of 3.5 µL of 0.5% ADX-103 (n=10) or saline vehicle (n=12) were administered by intravitreal (IVT) injection to STZ-treated rats at Weeks 6 and 8. Non-diabetic rats (n=4) did not receive any treatment and served as a negative control.

Retinal thickness, vascularity, and function were monitored weekly by optical coherence tomography (OCT) and fundus angiography (FA), from Weeks 6 through 10; electroretinograms (ERG) were generated on Weeks 6, 8 and 10.

Rats were sacrificed at Week 10, and retinas were processed for histopathology. Six microscopic sections were examined for each eye, and retinas were assessed and scored by a pathologist for changes in retinal thickness, vascularity, and neutrophil infiltration.

RESULTS

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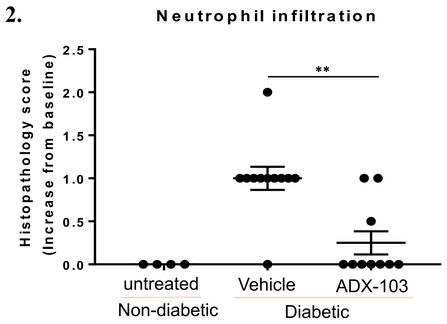

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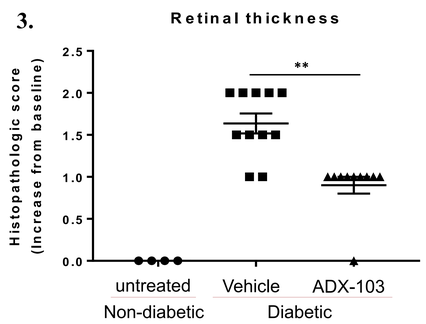

Treatment with ADX-103 significantly inhibited neutrophil infiltration in diabetic retinas. Microscopic sections of the retinas were assessed for changes in neutrophil infiltration. Reduction in neutrophil infiltration was observed in the diabetic rats treated with ADX-103 compared to vehicle-treated rats. Scoring: 0=normal, 1=minimal microscopically visible changes, 2=mild microscopically visible changes, 3=moderate microscopically visible changes. **p<0.01 Statistical analysis was performed by a non-parametric Dunn's multiple comparison followed by the Kruskal-Wallis test.

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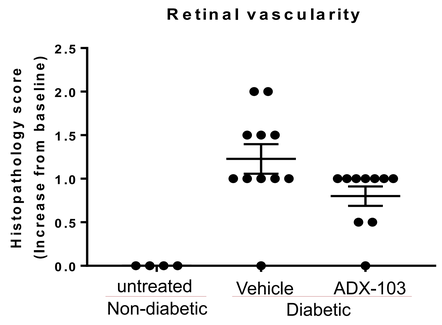
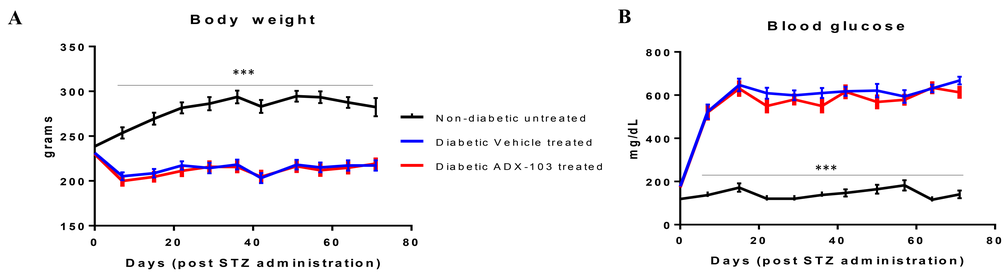


Treatment with ADX-103 resulted in a statically significant decrease in retinal thickness. Microscopic sections of the retinas were assessed for changes retinal thickness. Reduction in retinal thickness was observed in the diabetic rats treated with ADX-103 compared to vehicle treated rats. Scoring: 0=normal, 1=minimal microscopically visible changes; 2=mild microscopically visible changes; 3=moderate microscopically visible changes. **p<0.01 Statistical analysis was performed by a non-parametric Dunn's multiple comparison followed by the Kruskal-Wallis test.

Treatment with ADX-103 inhibited diabetes-induced retinal vascular changes. Microscopic sections of the retinas were assessed for vascular leakage. Compared to vehicle, reduction in retinal vascularity was observed in ADX-103-treated rats but was not statistically significant. Scoring: 0=normal, 1=minimal microscopically visible changes, 2=mild microscopically visible changes, 3=moderate microscopically visible changes.



Metabolic parameters. Body weight is significantly decreased and blood glucose is significantly increased in animals administered STZ. Body weight **(A)** and **(B)** non-fasting blood glucose were measured prior to STZ administration and weekly thereafter. ***p<0.001 from non-diabetic group. Statistical analysis was performed using Dunnett's test (compared to diabetic Vehicle treated group) following ANOVA.

SUMMARY

Diabetic retinopathy was successfully induced in STZ-treated rats. The diabetic animals lost approximately 10% of body weight in the first week post STZ administration, and maintained the weight until the end of study. Non-fasting glucose blood levels were significantly elevated in the diabetic rats compared to non-diabetic rats.

Increases in retinal thickness, vascularity, and neutrophil infiltration were observed in the vehicle-treated diabetic rats compared to the non-diabetic rats. ADX-103 treatment decreased retinal inflammation, as measured by statistically significant decreases in retinal thickness, neutrophil infiltration, and retinal vascular changes.

A decrease in vascular leakage was observed between the diabetic ADX-103-treated group and the vehicle-treated group, but the decrease did not reach statistical significance.

Although significant histopathological improvements were observed following treatment with ADX-103, ERG, OCT, or FFA did not show statistically significant effects following treatment with ADX-103.

CONCLUSIONS

Increasing evidence points to inflammation being one of the key contributors to the pathophysiology of diabetic retinopathy.

In the present DME study, histopathologic scoring showed statistically significant reductions in severities of retinopathy lesions, including neutrophil infiltration and retinal thickness, in diabetic rats treated with ADX-103 compared to vehicle.

Accumulation of intraretinal fluid, increase in cytokines, infiltration of leukocytes, neutrophils, and monocytes are early signs of disease progression[1].The data suggest that sequestration of aldehydes represents a novel therapeutic approach for the treatment of the ophthalmic inflammatory sequelae of diabetes.

1.Rübsam, A.; Parikh, S.; Fort, P.E. Role of Inflammation in Diabetic Retinopathy. *Int. J. Mol. Sci.* **2018**, *19*, 942

Disclosures: Halilovic (E), Brady (E), Macdonald (E)