Aldose Reductase Inhibition by AT-001 Prevents Diabetic Cardiomyopathy via Reducing Myocardial Fatty Acid Oxidation Rates

Poster 0024

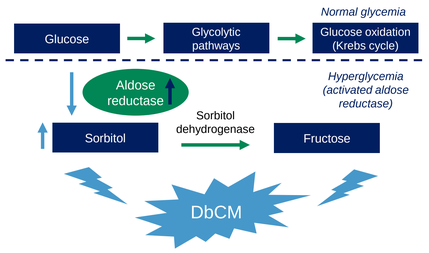
Keshav Gopal[1,2], **Qutuba G. Karwi**[1], **S. Amirhossein Tabatabaei-Dakhili**[1,2], **Cory S. Wagg**[1], **Riccardo Perfetti**[3], **Ravichandran Ramasamy**[4], **John R. Ussher**[1,2], **Gary D. Lopaschuk**[1]

[1]Cardiovascular Research Centre, University of Alberta, Edmonton, Canada; [2]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada; [3]Applied Therapeutics, New York, NY, USA; [4]Diabetes Research Program, New York University, New York, NY, USA

Introduction

- The number 1 cause of death in patients with type 2 diabetes (T2D) is cardiovascular disease.
- This includes diabetic cardiomyopathy (DbCM), which is cardiac dysfunction in the absence of underlying coronary artery disease and/or hypertension in diabetic individuals, and for which there are no approved therapies.[1]
- In T2D patients, compared with control subjects, LV diastolic function and myocardial glucose uptake are shown to be decreased, whereas myocardial non-esterified fatty acid uptake and oxidation are increased.[2]
- The expression of aldose reductase, the rate-limiting enzyme in the polyol pathway that converts glucose to sorbitol, is increased under hyperglycemic conditions.
- Studies have shown that increased aldose reductase activity can modulate myocardial glucose and fatty acid oxidation, while also promoting cardiac dysfunction.[3]
- It has been suggested that optimizing the altered cardiac energetics observed in T2D (i.e., impaired glucose oxidation rates and elevated fatty acid oxidations rates) via aldose reductase inhibition may be a novel strategy to prevent the progression of DbCM.[1]

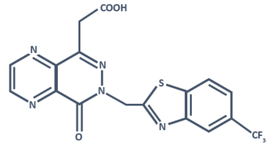
PATHOGENESIS OF DbCM & HYPERACTIVATED POLYOL PATHWAY[4]



- Myocardial glucose oxidation ↓
- Myocardial fatty acid oxidation ↑
- Diastolic with/without systolic dysfunction

Introduction (continued)

AT-001: NEXT GENERATION ALDOSE REDUCTASE INHIBITOR



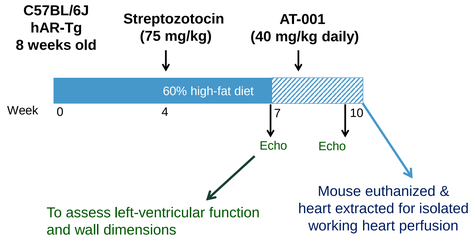
- ~1,000 times more potent than prior aldose reductase inhibitors
- No off-target inhibition of aldehyde reductase
- Broad exposure: cardiac and nerve tissue

Applied Therapeutics

Objectives

Our goal was to determine whether AT-001, a next generation aldose reductase inhibitor, could mitigate experimental DbCM, and whether the potential mechanisms of benefit involve alterations in myocardial glucose and/or fatty acid oxidation rates and cardiac efficiency.

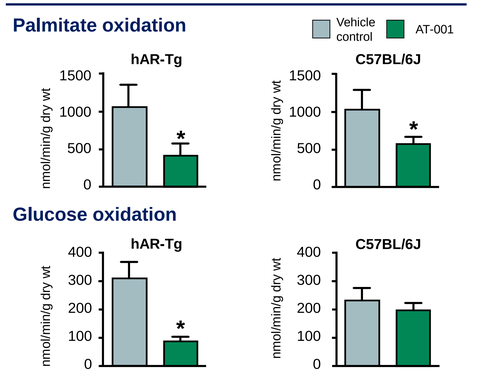
Methods & experimental design



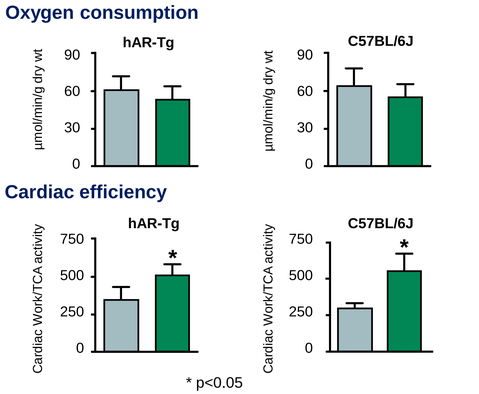
hAR-Tg: human aldose reductase overexpressing transgenic mice

Results

AT-001 CORRECTS ABNORMAL ENERGY METABOLISM IN A MOUSE MODEL OF DbCM



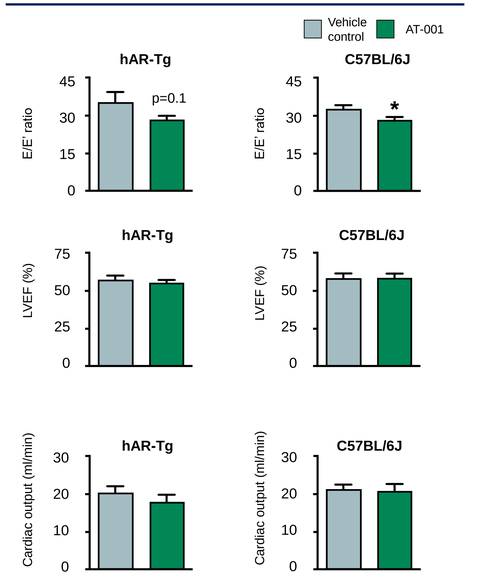
AT-001 IMPROVES OXYGEN CONSUMPTION AND CARDIAC EFFICIENCY IN A MOUSE MODEL OF DbCM



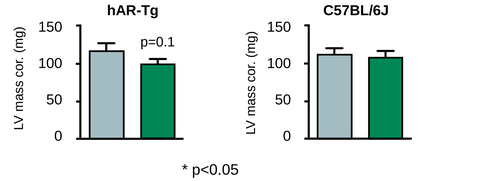
* p<0.05

Results (continued)

AT-001 PREVENTS DIASTOLIC DYSFUNCTION IN A MOUSE MODEL OF DbCM



AT-001 PREVENTS CARDIAC HYPERTROPHY IN A MOUSE MODEL OF DbCM



* p<0.05

Summary & conclusions

Aldose reductase inhibition by AT001 in DbCM:

- Improves diastolic function and decreases myocardial palmitate oxidation rates.
- Improves cardiac efficiency evident by increased cardiac work normalized to TCA activity (acetyl CoA production).
- Prevents cardiac structural and functional abnormalities in a mouse model of DbCM, and normalizes cardiac energetics by shifting cardiac metabolism towards a non-diabetic metabolic state.

Future directions

We will investigate the effect of AT-001 treatments on cardiac lipotoxicity and cardiac insulin sensitivity in DbCM

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APPLIED THERAPEUTICS

NYU Langone Health

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Disclosure

No conflict of interest to disclose for this presentation.