Pharmacological Inhibition of Aldose Reductase by AT-001 Prevents Abnormal Cardiac Energy Metabolism and Improves Heart Function in an Animal Model of Diabetic Cardiomyopathy

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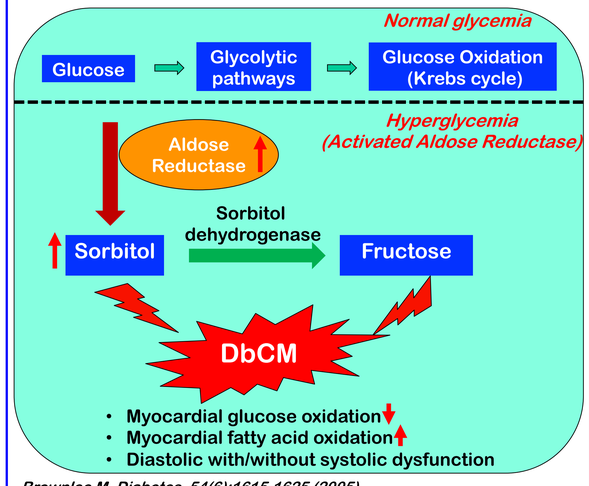
INTRODUCTION

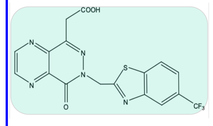
- The number 1 cause of death in patients with type 2 diabetes (T2D) is cardiovascular disease.
- This includes diabetic cardiomyopathy (DbCM), which is cardiac dysfunction in the absence of underlying coronary artery disease and/or hypertension in diabetic individuals, and of which there are no approved therapies [1].
- In T2D patients, compared with control subjects, LV diastolic function and myocardial glucose uptake were shown to be decreased, whereas myocardial non-esterified fatty acid uptake and oxidation were increased [2].
- The expression of aldose reductase, an important enzyme in the Polyol pathway that converts glucose to sorbitol, is increased under hyperglycemic conditions.
- Studies have shown that increased aldose reductase 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



Brownlee M. Diabetes. 54(6):1615-1625 (2005)

AT-001: Next Generation Aldose Reductase Inhibitor



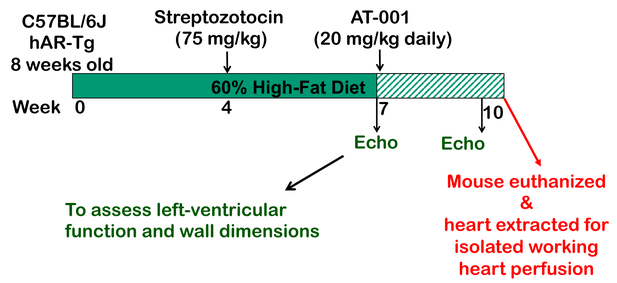
- ~1,000X more potent than prior aldose reductase inhibitors
- No off-target inhibition of aldehyde reductase
- Broad exposure: cardiac and nerve tissue

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 fat oxidation rates and cardiac efficiency.

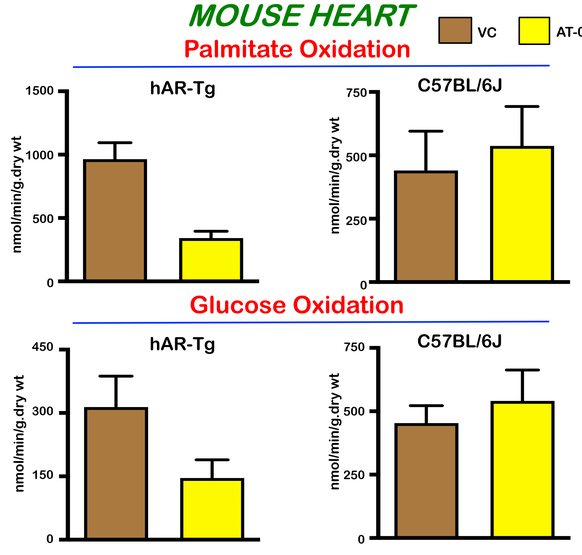
METHODS & EXPERIMENTAL DESIGN



hAR-Tg: human Aldose Reductase overexpressing transgenic mice

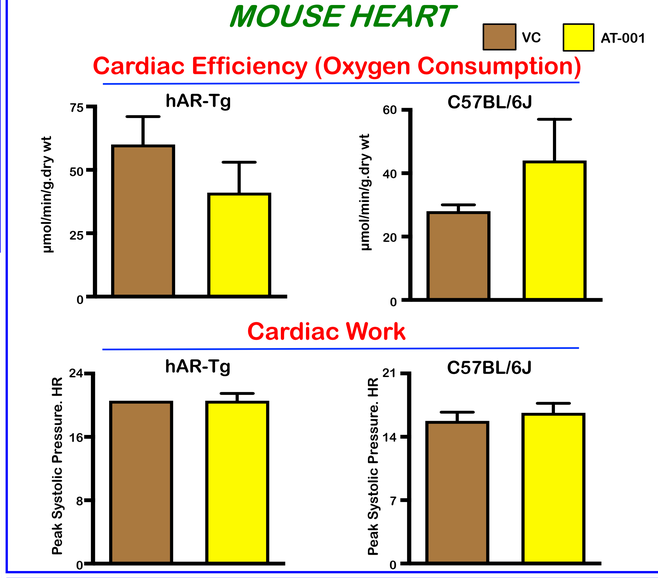
RESULTS

EFFECT OF AT-001 INHIBITION OF ALDOSE REDUCTASE ON FATTY ACID AND GLUCOSE OXIDATION RATES IN THE hAR-Tg T2D MOUSE HEART

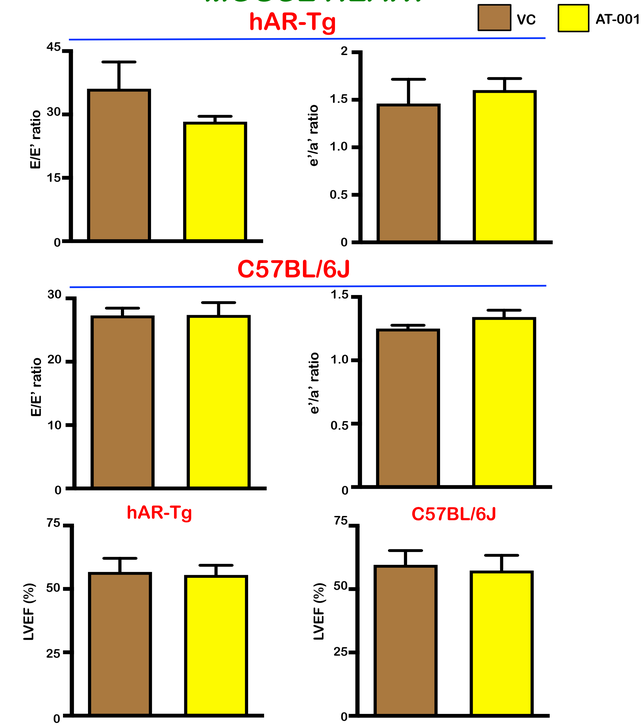


VC: Vehicle Control

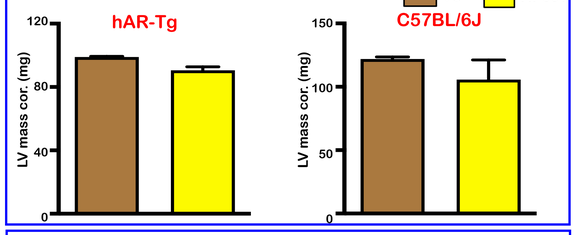
EFFECT OF AT-001 INHIBITION OF ALDOSE REDUCTASE ON CARDIAC EFFICIENCY AND CARDIAC WORK OF THE hAR-Tg T2D MOUSE HEART



EFFECT OF AT-001 INHIBITION OF ALDOSE REDUCTASE ON DIASTOLIC AND SYSTOLIC FUNCTION OF THE hAR-Tg T2D MOUSE HEART



EFFECT OF AT-001 INHIBITION OF ALDOSE REDUCTASE ON HYPERTROPHY OF THE hAR-Tg T2D MOUSE HEART



SUMMARY & CONCLUSIONS

Aldose reductase inhibition by AT001 in DbCM:

- Improves diastolic function and decreased myocardial palmitate oxidation rates
- Improves cardiac efficiency evident by decreased myocardial oxygen consumption
- 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.

ACKNOWLEDGEMENTS

UNIVERSITY OF ALBERTA CARDIOVASCULAR RESEARCH CENTRE
UNIVERSITY OF ALBERTA FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES
APPLIED THERAPEUTICS
NYU Langone Health

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DISCLOSURE

No conflict of interest to disclose for this presentation.