

# Preclinical efficacy of 2-Deoxyglucose to sustain mitochondrial metabolic function and delay progression of Alzheimer's pathology

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## Abstract

### Learning Objectives:

- 1) To investigate the impact of 2-DG on mitochondrial bioenergetics in female 3xTgAD mouse model
- 2) To determine the therapeutic efficacy of 2-DG to delay Alzheimer's Pathology in female 3xTgAD model
- 3) To investigate the mechanism of 2-DG induced neuroprotective benefits against Alzheimer's disease

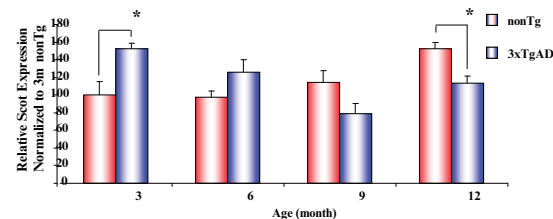
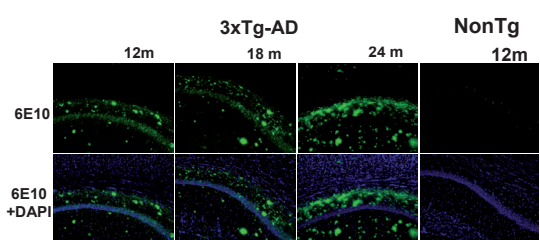
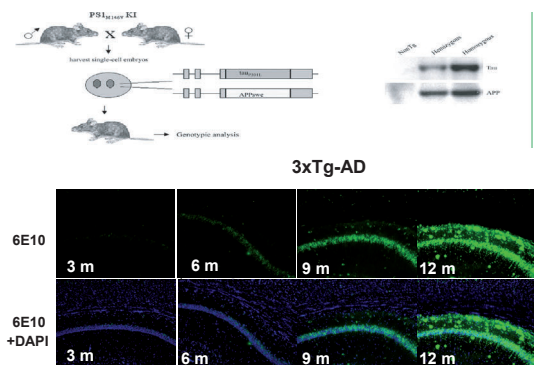
**Background:** Both basic science and clinical studies have indicated the critical role of mitochondrial bioenergetics in the pathogenesis of AD. Previously, we demonstrated that mitochondrial bioenergetic deficits preceded Alzheimer's disease (AD) pathology in the female triple transgenic AD (3xTg-AD) mouse model. To compensate for decline in glucose metabolism, activation of an alternative ketogenic fuel pathway occurred. Yet, the compensatory activation of alternative fuel source is temporary and diminishes with disease progression.

**Methods:** To determine the efficacy of 2-Deoxyglucose (2-DG) to rescue mitochondrial bioenergetic deficits and delay the progression of Alzheimer's pathology, 3xTgAD female mice at 6 months were fed with either regular diet (AIN-93G) or diet containing 0.04% 2-DG for 7 weeks. Both mitochondrial bioenergetic parameters and AD pathological markers were analyzed upon completion of the treatment.

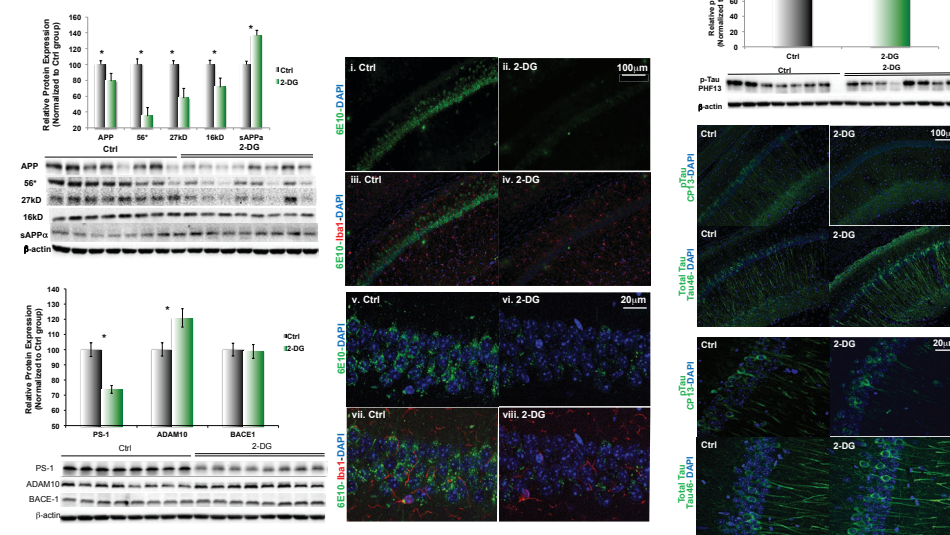
**Results:** 2-DG diet significantly induced ketogenesis as indicated by increased serum ketone body levels. In addition, compared to the control group, 2-DG increased the expression of enzymes involved in fatty acid metabolism, ketone body utilization, and oxidative phosphorylation. More importantly, 2-DG diet induced significant reduction of AD like amyloid pathology. 2-DG diet reduced both amyloid precursor protein (APP) and amyloid beta (Aβ) oligomer. In parallel with the reduction in Aβ pathology, 2-DG also induced reduction in oxidative stress. Mechanistically, 2-DG induced activation of the α-secretase pathway, indicating a switching towards non-amyloidogenic pathways by 2-DG. Gene expression analyses indicate that 2-DG induced an increase in Aβ clearance pathways, including Aβ degradation, sequestering, and transportation.

**Conclusions:** Collectively, the data suggest that 2-DG treatment induced ketogenesis, increased fatty acid oxidation, sustained mitochondrial bioenergetics and reduced AD like pathology. Findings from this study provided pre-clinical evidence for 2-DG as a potential therapeutic strategy to delay AD progression. Data further suggest a clinical strategy to use 2-DG or other metabolic modulators to sustain mitochondrial bioenergetics, prevent further alteration of brain metabolic profile and hence delay the progression of Alzheimer's disease.

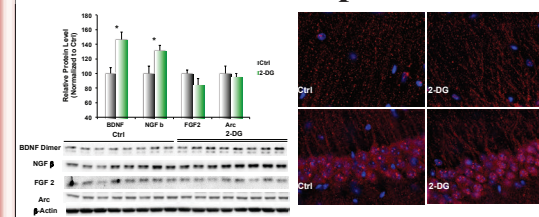
## Basics of 3xTg-AD Mice



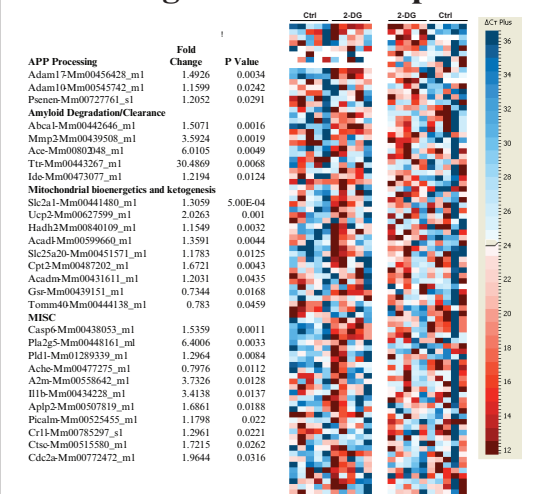
## 2-DG Induced Reduction in Amyloid Pathology Activation of α-Secretase Pathway



## 2-DG Induced Increase in Neurotrophin



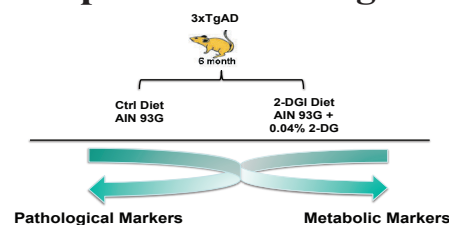
## 2-DG Regulated Gene Expression



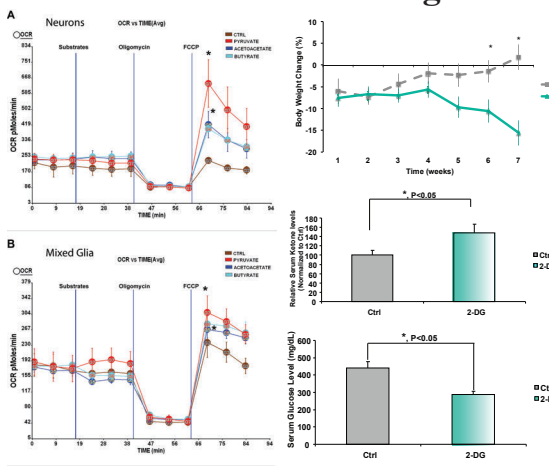
## Introduction

We have previously shown that mitochondrial bioenergetic deficits play a critical role in AD pathogenesis (Yao et al, 2009). Further, mitochondrial function deteriorates with AD progression (Lustbader et al, 2004; Takuma et al, 2005). The trajectory of the decline in mitochondrial bioenergetics provides a potential therapeutic strategy to partially compensate the energy loss and hence delay disease progression. Ketone body has been demonstrated as an alternative substrate other than glucose for brain. The clinical neuroprotective benefit of ketone bodies largely came from large scale epidemiology studies (Gasior et al, 2006; Guzman and Blazquez, 2004). 2-deoxyglucose (2-DG) is a glucose analog with the 2-hydroxyl group replaced by hydrogen. Due to the structural similarity between 2-DG and glucose, it is uptaken by glucose transporters of the cell. With no 2-hydroxyl group, 2-DG cannot be phosphorylated by hexokinase and therefore cannot undergo further glycolysis. 2-DG has been broadly used as a ketogenic compound. Diet containing a range of different 2-DG doses has been demonstrated to increase ketone body levels.

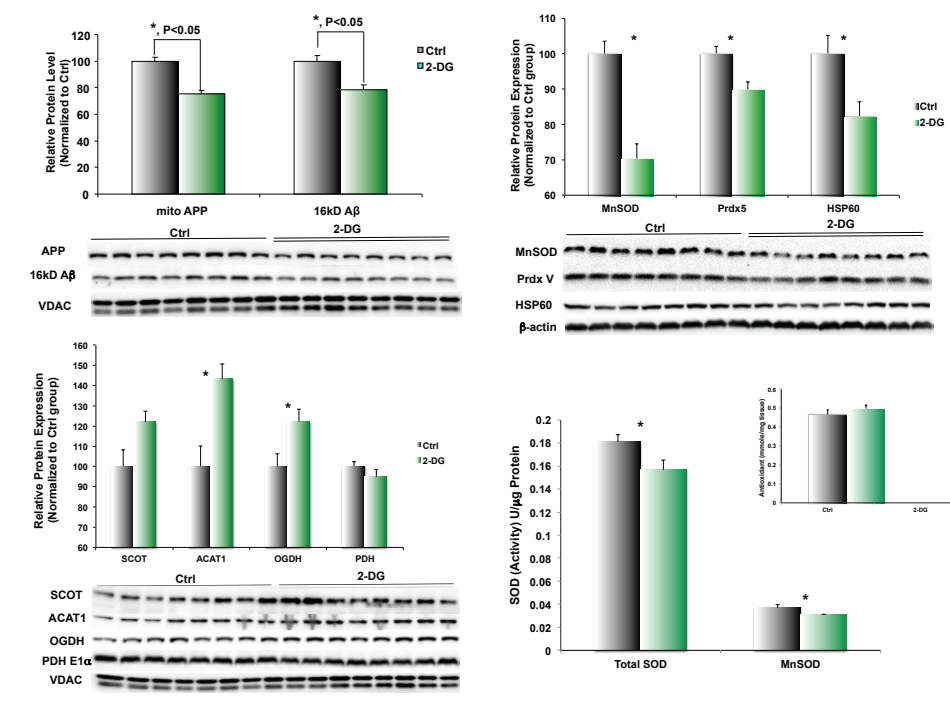
## Experiment Paradigm



## Ketones as Alternative Fuel 2-DG Induced Ketogenesis



## 2-DG Induced Sustainment of Mitochondrial Function



## Conclusions

- 3xTg-AD mice have decreased glucose metabolism and increased compensatory ketogenesis early in AD progression.
- Both neurons and mixed glia could utilize alternative substrates, such as ketones, other than glucose.
- 2-DG diet induced ketogenesis in 3xTgAD mice.
- 2-DG diet reduced AD like pathology in 3xTg-AD mice. The decrease in amyloid pathology is likely due to increased non-amyloidogenic pathway (α secretase).
- 2-DG diet also activated ketogenic pathways and enhanced mitochondrial bioenergetic capacity.
- 2-DG differentially regulated expression of genes involved in Alzheimer's disease.

## Acknowledgement

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