



Acarbose ameliorates western diet-induced metabolic and cognitive impairments in the 3xTg mouse model of Alzheimer's disease



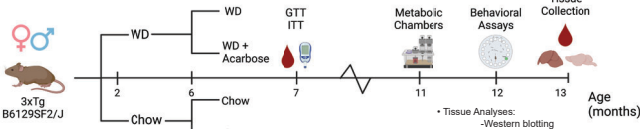
Michelle M Sonsalla, MS^{1,2,3}, Reji Babygirija, MS^{1,2}, Madeline Johnson^{1,2}, Samuel Cai^{1,2}, Chung-Yang Yeh, PhD^{1,2}, Mariah Calubag^{1,2}, Michaela Trautman, RD, CD^{1,2}, Isaac Grunow^{1,2}, and Dudley Lamming, PhD^{1,2,3}

¹ University of Wisconsin-Madison, Madison, WI, USA, ² William S. Middleton Memorial Veterans Hospital, Madison, WI, USA, and ³ Comparative Biomedical Science Graduate Program, University of Wisconsin-Madison, Madison, WI, USA

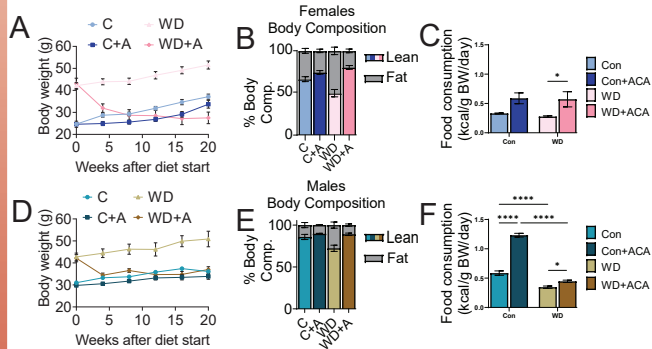
Introduction

- Alzheimer's disease (AD), a neurodegenerative disease in which patients exhibit impaired memory, motor function, and language due to neuronal damage, is rapidly growing in prevalence as the population ages.
- AD is a disease of aging, and other diseases of aging including diabetes and obesity are risk factors for AD.
- As such, geroprotective interventions may be of use in the prevention and treatment of AD.
- Here, we report our investigation into the effects of acarbose, a geroprotector used to treat type 2 diabetes, on cognition and disease pathology in the 3xTg-AD mouse model of AD in the presence or absence of a western diet.

Methods



Acarbose reduces body weight in both chow and WD-fed mice, despite increased food intake.

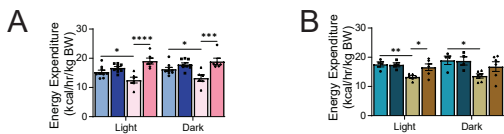


A,D) Western diet (WD) dramatically increased body weight in both female (A) and male (D) mice. Acarbose decreased body weight, particularly in WD-fed diet-induced obese mice after only 4 weeks on WD+A. B,E) WD led to a high percent fat mass, which was greatly ameliorated by acarbose in both females (B) and males (E).

C,F) Acarbose increased food consumption in both female (C) and male (F) mice.

** = $p < 0.01$, **** = $p < 0.0001$; $n = 8-14$

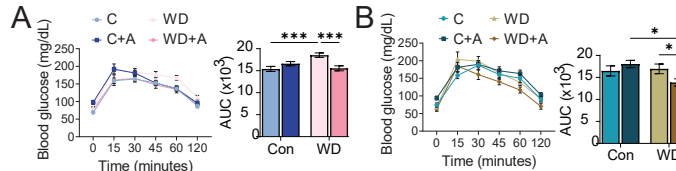
Acarbose increases energy expenditure in WD-fed mice.



Energy expenditure was measured using a Columbus Instruments Comprehensive Laboratory Animal Monitoring System (CLAMS). In both females (A) and males (B), mice on Western diet exhibited decreased energy expenditure, consistent with increased weight gain in these mice. Acarbose treatment increased energy expenditure, which helps to explain the decrease in weight and adiposity despite increased food consumption.

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$; $n = 4-9$

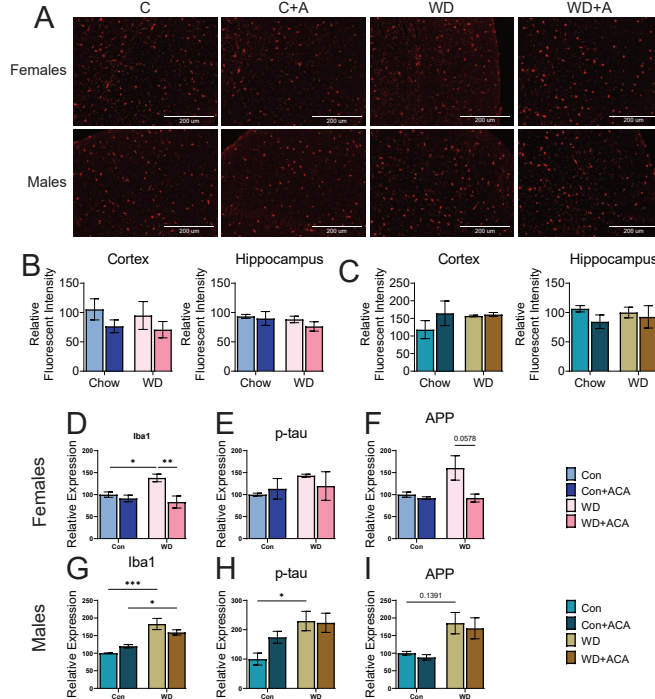
Acarbose-treated DIO mice had minor improvements in glucose homeostasis.



Female (A) mice exhibited impaired glucose tolerance when exposed to a Western diet, which was ameliorated by acarbose. In contrast, male (B) mice did not exhibit worsened glucose tolerance in response to Western diet but did show improvements with the administration of acarbose in conjunction with a Western diet.

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; $n = 8-10$

Acarbose-treated DIO mice exhibited a small decrease in microgliosis and AD pathology, particularly in female mice.



A-C) Brains were paraffin-embedded then sectioned (5 μ m sections) and stained for Iba1, a marker for microglia. No significant differences were seen but acarbose may decrease microgliosis mildly in the cortex of female 3xTg mice.

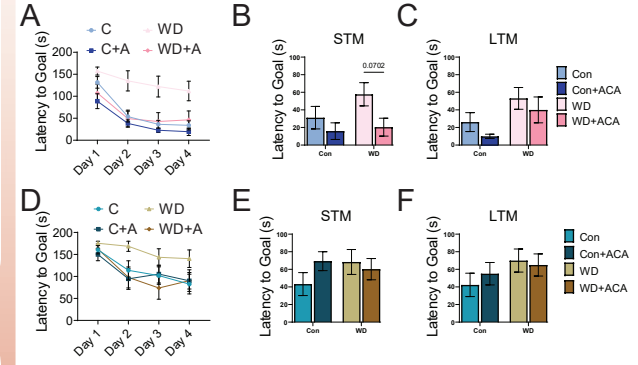
A) Representative images for cortex sections.

B-C) Quantification of relative fluorescent intensity of Iba1 in cortex (B) and hippocampus (C).

D-I) Western blots were performed on brain samples to measure Iba1, p-tau, and APP as metrics of AD pathology. No changes were shown for p-tau (E) levels in female brains. Western diet increased levels of Iba1 (D, G) and APP (F, I) in both males and females, which was ameliorated by acarbose in females only. Males also exhibited an increase in p-tau (H), which was not impacted by acarbose.

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; $n = 2-3$

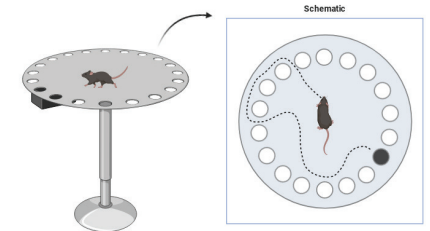
Western diet exacerbates cognitive deficit which is ameliorated by acarbose.



Barnes maze was utilized to measure spatial learning and memory. Mice were trained 4 times a day for 4 days then mice were subjected to a short-term memory test on day 5 and a long-term memory test on day 12.

A-C) Female mice exhibited worsened learning (A) on days 1-4 when on Western diet. This was completely reversed by acarbose. Similarly, Western diet exacerbated memory deficit in both STM (B) and LTM (C), which was ameliorated by acarbose only in STM. D-F) Western diet worsened learning (D) on days 1-4 in male mice, which was ameliorated by acarbose. Neither Western diet nor acarbose effected STM (E) and LTM (F).

$n = 5-10$



Conclusions

Western diet led to metabolic impairments and exacerbated AD pathology in the 3xTg mouse model of AD.

Specifically, Western diet had the following effects:

- Increased body and fat mass
- Decreased energy expenditure
- Reduced glucose tolerance in female mice
- Increased Iba1, p-tau, and APP levels
- Significant cognitive impairments

Acarbose ameliorated many of the Western diet-induced impairments, including:

- Body and fat mass
- Energy expenditure
- Glucose tolerance
- Iba1 and APP levels
- Cognitive deficits

Acknowledgements

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