

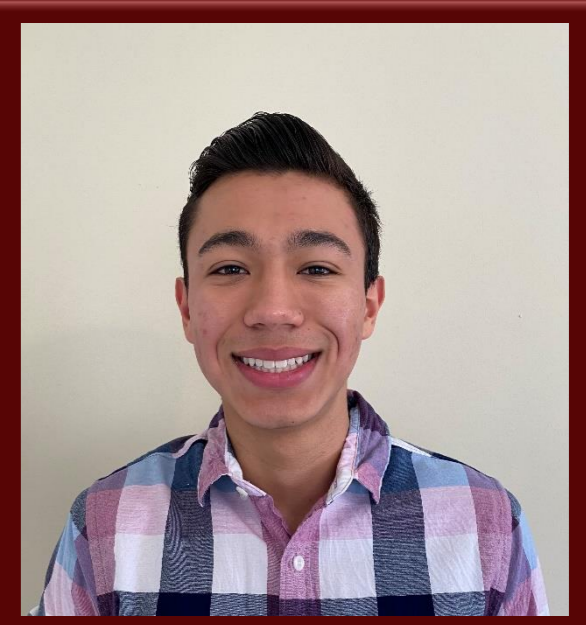


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Exercise Modulates Androgen Control of Lipolysis in White Adipose Tissue of Male and Female Pigs

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Introduction

Current knowledge regarding androgen control of lipolysis in white adipose tissue (WAT) has been largely restricted to experiments conducted in male subcutaneous (sc) WAT. However, vWAT has a higher endogenous lipolytic rate than scWAT. Furthermore, the metabolism of androgens to estrogens in WAT creates confusion about the direct effects of androgens on WAT lipolysis. While exercise is known to increase WAT lipolysis, the androgenic control of lipolysis under exercised conditions has not been explored. Dihydrotestosterone (DHT) is a minimally metabolized androgen whose steroid interconversion in WAT is limited to the alpha and beta stereoisomers of 3-androstenediol. Therefore, using DHT the receptor-specific effect of androgens on lipolysis can be ascertained. Female scWAT readily inactivates androgens. Therefore, ***we hypothesized that, regardless of exercise state, DHT would increase lipolytic glycerol production in scWAT and vWAT of males but increase lipolytic glycerol production only in vWAT of females.***

Materials & Methods

- Male (n=3) and Female (n=7) miniature Yucatan pigs (6-7 months of age) were left sedentary (normal pen activity) or given an exercise treatment.
- Exercised pigs underwent a treadmill running regimen for 13 weeks that progressively increased in duration and intensity each week.
- Pigs were euthanized after 13 weeks and scWAT and vWAT were collected and exposed to steroid treatments (**Table 1**).
- Intubation with the 10 nM of the beta adrenergic agonist, isoproterenol, was expected to increase glycerol release into the media.
- Glycerol content was determined with the Sigma Aldrich Glycerol Assay kit.

Table 1: Well Treatment Combinations

Well Treatment:	Contents: ^a
Control	Ethanol (0.085%) + DMSO (0.085%)
DHT	Dihydrotestosterone
ENZ	Enzalutamide
FULV	Fulvestrant
DHT/ENZ	Dihydrotestosterone + enzalutamide
DHT/FULV	Dihydrotestosterone + fulvestrant
DHT/ENZ/FULV	Dihydrotestosterone + enzalutamide + fulvestrant

^a - Concentration of all treatment ingredients were 1.0 nM

Results

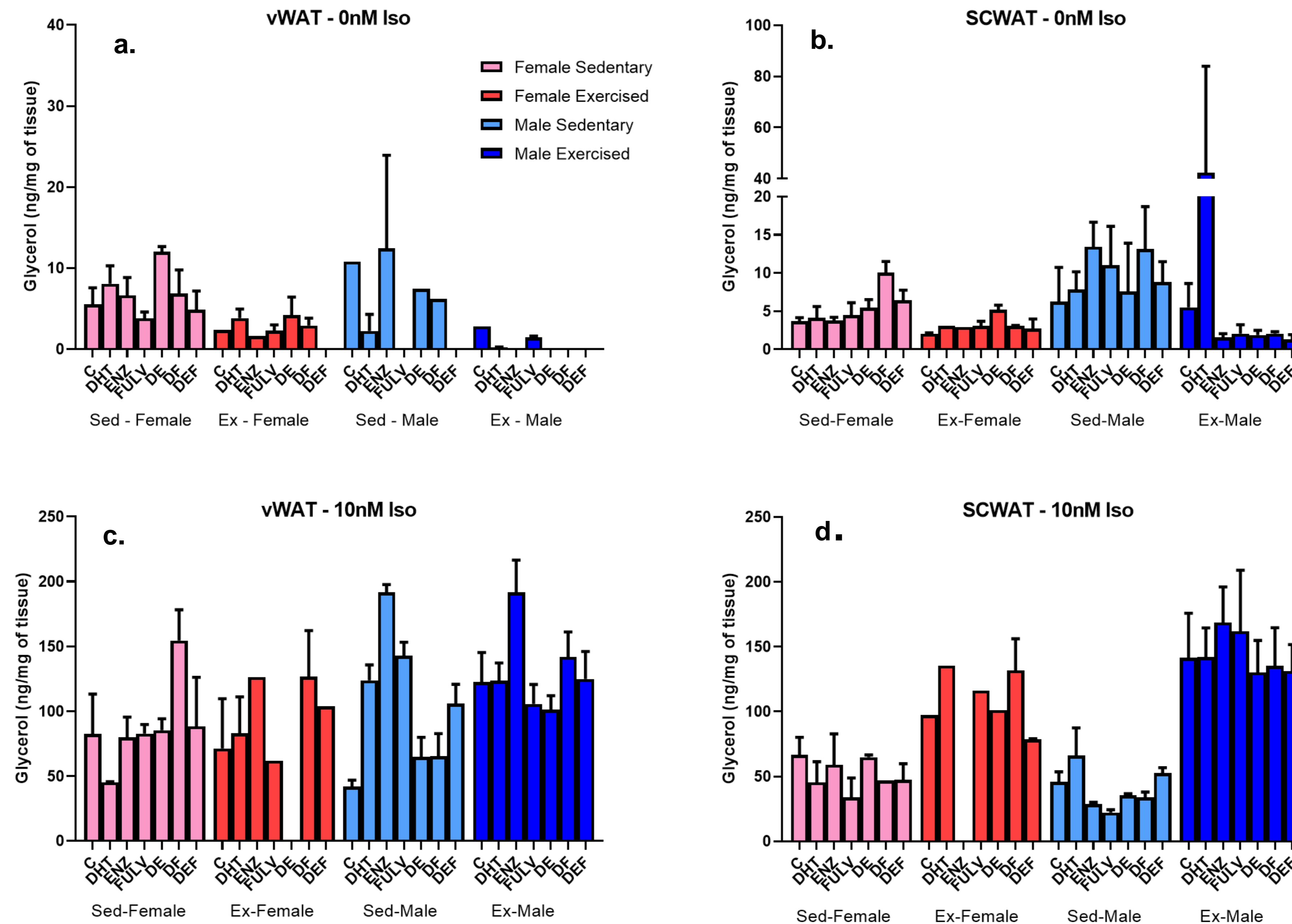


Fig.1

Fig.1 Glycerol release from white adipose tissue explants in male and female pigs.

vWAT= visceral white adipose tissue. scWAT= subcutaneous adipose tissue. Basal levels of lipolysis between sex and exercise treatments are similar in vWAT. However, in scWAT both sedentary and exercised males have higher levels of glycerol release into the media. By contrast, under stimulation with isoproterenol, the response of males and females and different exercise groups is similar between treatment groups. Given that we have only conducted this experiment on three males to date, we were unable to run statistics on our data. Iso=isoproterenol.

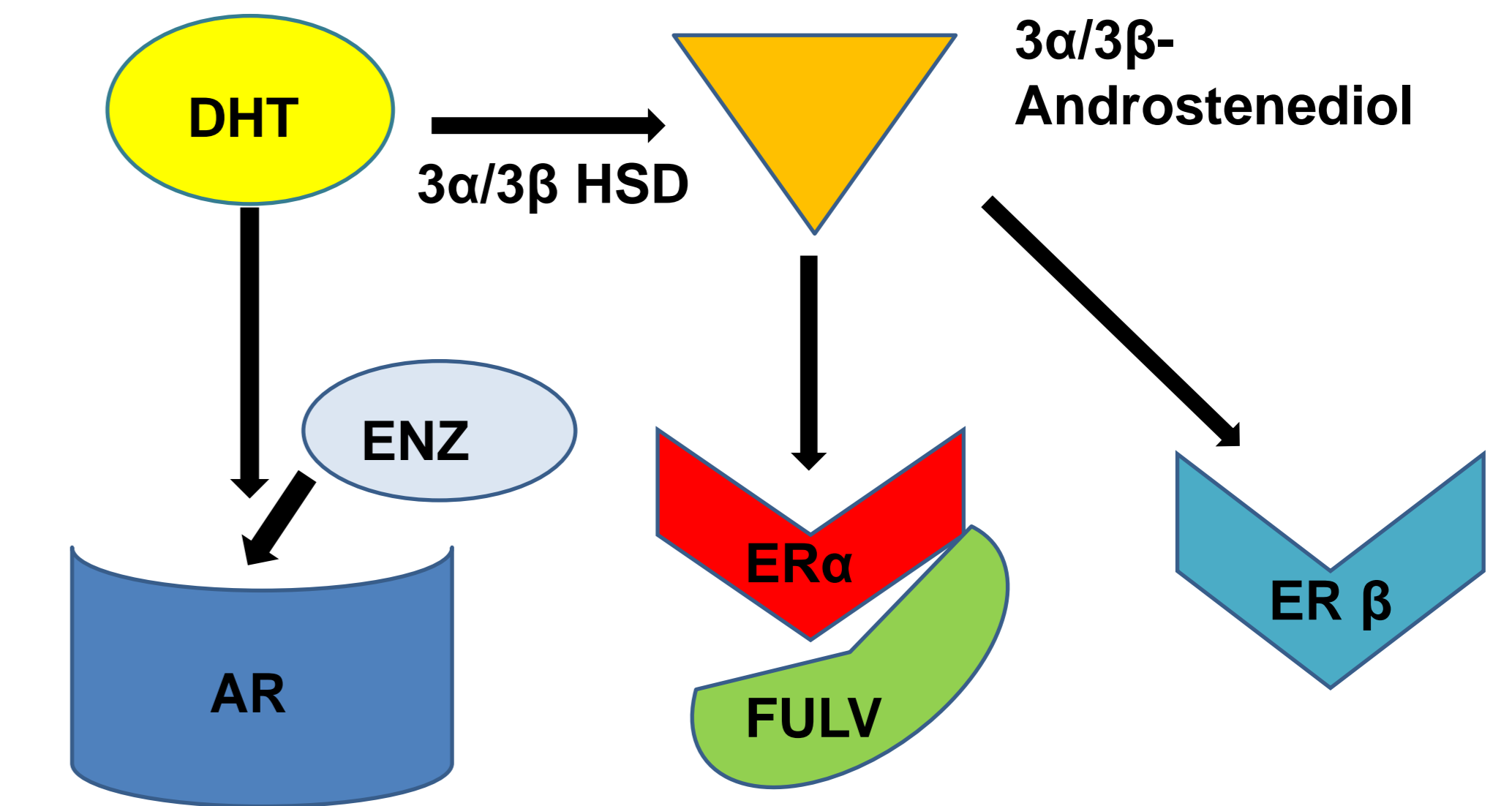


Fig.2 Diagram of DHT and its metabolites and receptor antagonists interacting with steroid receptors.

Enzalutamide (ENZ) is an androgen receptor antagonist and fulvestrant (FULV) is an estrogen receptor alpha degrader (ERα).

Conclusions

The effects of DHT on WAT lipolytic rate as measured by glycerol in the media are more pronounced when explants are incubated with 10nM isoproterenol, particularly in exercised males. This data suggests that exercise modulates the sensitivity of WAT to lipolytic effects of DHT especially in vWAT.

Increasing the number of subjects, especially male pigs, could provide further insight into the relationships found between DHT, exercise, sex, and modulation of the lipolytic rate of WAT. Further experiments with more subjects will decrease the between-pig variability and strengthen the findings of this project.

Acknowledgments

- Dr. Newell-Fugate for letting me take charge of this portion of the project and present this data.
- Kadden Kothmann for his help with experimental procedures, interpreting data, and guidance.
- Dr. Cristine Heaps for her lab's collaboration with this project.
- Funding: Texas A&M President's Excellence Fund – Triads for Transformation Round 4 (Newell-Fugate); NIH R01HL139903 (Heaps)