Perivascular adipose tissue remodeling impairs vasoreactivity in thermoneutral-housed rats

Henckel, M.M.[1,2], Chun, J.H.[3], Knaub L.A. [1,2], Pott G. [1,2], James G.[4], Walker L.A.[5], Reusch J.E.B. [1,2], Keller A.C. [1,2]

[1]University of Colorado Anschutz Medical Campus Division of Endocrinology, Metabolism, & Diabetes;

[2]Rocky Mountain Regional VA Medical Center; [3]Microtek, Inc.; [4]Cornell College; [5]Division of Cardiology

University of Colorado Anschutz Medical Campus

U.S. Department of Veterans Affairs

Ludeman Family Center for Women's Health Research

UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Background

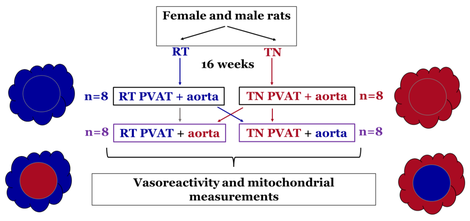
Cardiovascular disease (CVD) accounted for 32% of global deaths in 2019. CVD manifests as compromised vascular response, such as diminished vasodilation and mitochondrial function.

We show that 1) animals housed at thermoneutrality (TN) had dysfunctional vasoreactivity), and 2) perivascular adipose tissue (PVAT), a regulator of vasoreactivity, showed altered phenotype in animals housed at TN.

Hypothesis: **PVAT remodeling at thermoneutrality leads to diminished vasoreactivity and decreased mitochondrial respiration.**

Methods

- Male (M) and female (F) Wister rats were housed at either room temperature (RT, 24°C) or thermoneutrality (TN, 30°C) for 16 weeks.
- Aorta, with and without PVAT, was analyzed on OROBOROS O2k (respiration) and upright myograph (vasoreactivity).
- Paraffin-embedded PVAT was analyzed with H&E staining and UCP-1 florescent expression for PVAT phenotype identification.



Results

PVAT regulates vasoreactivity: sex differences

PVAT from RT animals rescues TN aorta

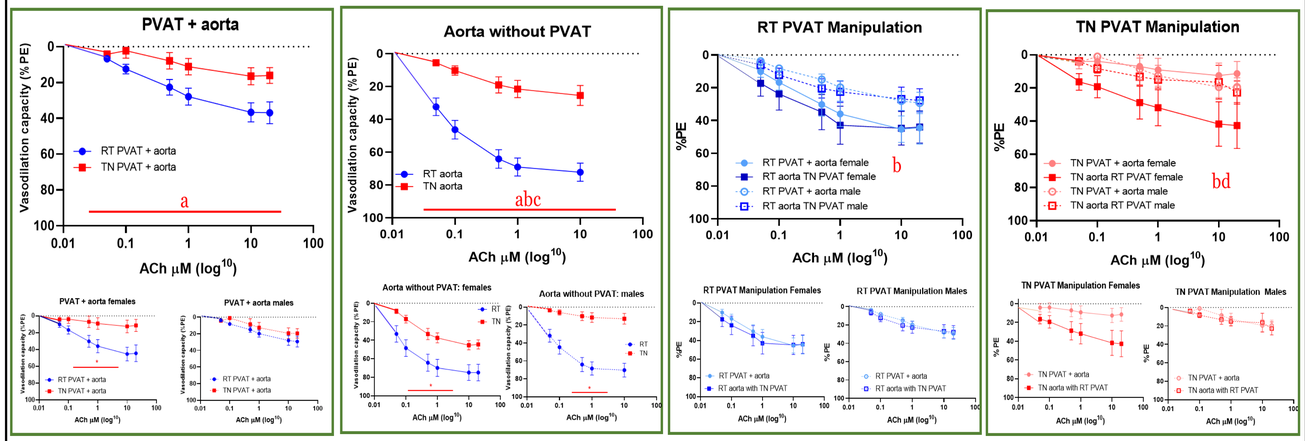


Figure 1. PVAT and aortic vascular reactivity. Aorta of RT or TN-housed animals were tested with PVAT or alone (left), or with PVAT switched to oppositely-housed animal aorta (right). Aorta were exposed to ACh (acetylcholine, dilation) and PE (phenylephrine, constriction) and tested for contractile response. [a]p<0.05 temperature, [b]dose x sex, [c]dose x sex x temperature, [d]p<0.05 sex, [e]dose x temperature, three-way ANOVA or *p<0.05 Student's t-test, sexes alone. Data are mean ± SEM.

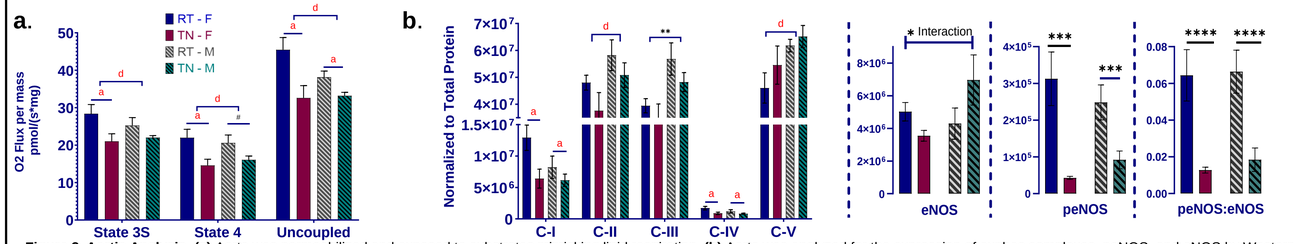


Figure 2. Aortic Analysis. (a) Aorta was permeabilized and exposed to substrates mimicking lipid respiration. **(b)** Aorta was analyzed for the expression of oxphos complexes, peNOS, and eNOS by Western blot. [a]p<0.05 temperature, [d]p<0.05 sex, *p<0.05 interaction, **p<0.005 , ***p<0.0005 , ****p<0.0001 , #p<0.08, 2-way ANOVA (n=7-8). Data are mean ±SEM.

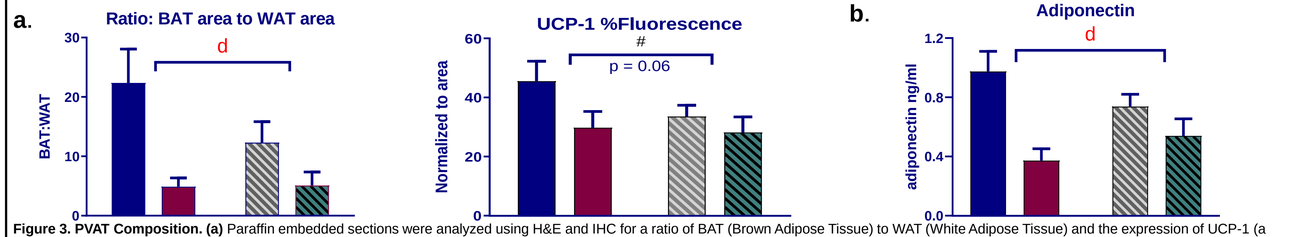
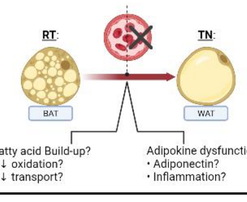


Figure 3. PVAT Composition. (a) Paraffin embedded sections were analyzed using H&E and IHC for a ratio of BAT (Brown Adipose Tissue) to WAT (White Adipose Tissue) and the expression of UCP-1 (a marker of beige/brown adipocytes). PVAT was analyzed for adiponectin concentrations with ELISA. [d]p<0.05 sex, #p<0.08, 2-way ANOVA (n=7-8). Data are mean ±SEM.

Summary

- PVAT regulates vasoreactivity in a sex-dependent manner and is remodeled in animals housed at TN.
- Mitochondrial lipid-dependent respiration decreased in TN-housed aorta.
- RT PVAT corrected diminished vasodilation and constriction in aorta from TN-housed female animals.



Conclusions

- Our study shows sex as an important factor in the PVAT regulation of vascular function; we also show the importance of lipid metabolism and cellular signaling in vascular health.
- We identify several possible therapeutic targets to treat CVD and expand the understanding of CVD pathology and sex differences therein.
- Sex as biological variable in CVD research and treatment is of paramount importance in bringing efficacious therapies for CVD to all people.

Disclosures

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