“Fit Fat” in the Race Against Metabolic Dysfunction

Effects of Nutrition and Exercise on Adipose Tissue Metabolic Health

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How did we get here?
Obesity → Inflamed Fat → Metabolic Disease

Insulin resistance

TNFα

Recruited Macrophages

Fatty acids

Inflammation

Interleukins

Resident Macrophage

Lean

Obese

How does exercise affect adipose tissue?
Menopause and Metabolic Disease: 
*Mitigating Role of Exercise*
Postmenopausal Obesity Results from Reduced Physical Activity

• **MONET study** (102 women followed for 5 years from pre-post menopause) found:
  1. Calories burned over time ↓ due to ↓ Physical Activity
  2. Time spent in **moderate physical activity** ↓ and 
     sedentary time ↑

“spontaneous physical activity = SPA”


Rodent Ovariotomy (OVX) Models Human Menopause

Ovarian hormones (*17β-estradiol* = most important)
We assess spontaneous physical activity in rodents using metabolic cages
OVX Reduces SPA

* P<0.05

Vieira-Potter VJ et al. 2012 *Endocrinology*
Vieira-Potter VJ et al. 2014 *AJP Reg*
Are women less *motivated* to exercise after menopause?
We measure *motivated* physical activity in rodents by giving them access to a running wheel.

Does OVX decrease motivation for wheel running in rats?
(Yes!) OVX reduces motivated wheel running in rats

![Graph showing averaged running distance (km/wk) for SHM, OVX, HCR, and LCR for Highly Active and Inactive Rats. The graph indicates a significant reduction in running distance in OVX rats compared to SHM, with P < 0.001.](image)
Reduced running associates with dysregulated dopamine signaling

Park et al. Physiology and Behavior 2016.

Nucleus Accumbens brain region
RE-CAP:

- Obesity $\rightarrow$ Dysfunctional Fat $\rightarrow$ Disease
- Menopause $\rightarrow$ Inactivity $\rightarrow$ Obesity/Disease
- Menopause in women, and OVX in rodents, reduces physical activity, which predicts weight gain and metabolic dysfunction.

Are Rats Selectively Bred for High Motivation for Physical Activity Protected Against Metabolic Dysfunction Following OVX?
The HCR/LCR Rat: A Model of Intrinsic Aerobic Fitness

HCR Rats Love to Run!

Our lab has been using this model to study how fitness protects against ovarian hormone loss-mediated metabolic dysfunction...
HIGHFIT (HCR) Rats Are Protected From OVX-Associated Metabolic Dysfunction

What about Insulin Resistance?

Line x OVX, P<0.05
* Line main effect, P<0.05
Total N=43 (7-13/grp)

Vieira-Potter VJ et al. 2015 AJP Reg
Although OVX impairs skeletal muscle insulin sensitivity in both lines HCR maintain better insulin sensitivity than LCR.

Fitness Improves AT Function!
HIGH FIT HCR Rats Have FIT FAT!

HCR Adipose Tissue Has ➤ Immune Cell Infiltration

Mitochondrial CS Activity

Mitochondria

CD3+SVCs
CD4+SVCs
CD11c+SVCs

% of total SVC fraction

HCR Adipose Tissue Has ➤ Immune Cell Infiltration

Mitochondria

Mitochondrial CS Activity

Mitochondria

HCR Adipose Tissue Has ➤ Immune Cell Infiltration

Mitochondria

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HCR Adipose Tissue Has ➤ Immune Cell Infiltration

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Does “Fit Fat” protect HCR Rats from OVX and HFD-associated Metabolic Dysfunction?
When we challenge OVX HCR and LCR rats with High Fat Diet (HFD), both groups gain weight.


# Diet main effect, P<0.05

* Line main effect, P<0.05
Despite weight gain, fitness is still protective against OVX+HFD-induced IR!

* Line main effect, P<0.05
★ Line x Diet effect, P<0.05

Park et al. OVX high-fit rats are protected against diet-induced IR, MSSE 2016; Jul;48(7):1259-69.
HCR rats compensate for HFD-induced IR by increasing SPA!

What if we increase total physical activity in LCR rats... might this protect them from OVX-associated metabolic dysfunction??

If you give a rat a running wheel...

HCR run ~5 X more than LCR!

We were able to increase **total physical activity** in LCR rats...

**Impact on metabolic health??**

Exercise Normalizes Body Weight in LOW-FIT LCR Rats

Weight Gain

End Body Weight

Body Fat %

Lean Mass


Impact on IR??
Increasing Physical Activity Rescues IR!

Does increasing total physical activity in LCR rats make their fat more ‘fit’??

* EX main effect, P < 0.05

Park et al. Voluntary Running Attenuates Metabolic Dysfunction in Ovariectomized Low-Fit Rats, MSSE 2016.
Wheel Running Reduces Adipose Tissue Inflammatory Gene Expression in OVX LCR Rats
Menopause and Metabolic Disease: What About Diet?
Soy isoflavones are *phytoestrogens*

- Soy isoflavone = *phytoestrogen* (plant derived compounds with estrogen-like biologic activity)

*Can soy isoflavones rescue adverse metabolic effects associated with OVX?*
**SOY Rescues OVX-Associated Metabolic Dysfunction**

A. % Body Fat

- **SHM-CON**
- **SHM-SOY**
- **OVX-CON**
- **OVX-SOY**

B. Total Lean Mass (g)

- **SHM-CON**
- **SHM-SOY**
- **OVX-CON**
- **OVX-SOY**

* SOY main effect, P < 0.05
† OVX main effect, P < 0.05

(IN LCR RATS)
Rodent *Ovariectomy* (OVX) Models Human Menopause

Does the MECHANISM by which SOY improves metabolism require ER alpha or ER beta?

Estrogens $\rightarrow$ **17β-estradiol** (most important) progesterone

**OVX**

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Does the MECHANISM by which SOY improves metabolism require ER alpha or ER beta?
Adiposity Increase Post-OVX *Due to loss of ERα*

**% Fat Mass**

- ERα KO
- ERαKO OVX/CON

**% Lean Mass**

- ERα KO
- ERαKO OVX/CON

*ns*

WEEKS POST-OVX

- 1
- 2
- 3

- 0
- 7
- 12
SOY Improves Body Composition Via ERα

**ERα KO – effect of SOY**

**Erβ KO – effect of SOY**

*ERα is REQUIRED for SOY’s improvement!*

WEEKS POST-OVX
SOY’s ability to ‣ OVX-Associated Insulin Resistance also requires ERα

**SOY does not improve IR in ERαKO**

**SOY improves IR in OVX ERα+- mice**

![Graph showing glucose levels](image1)

- ERαKO OVX/CON
- ERαKO OVX/SOY

*NS*  

![Graph showing glucose levels](image2)

- ERWT OVX/CON
- ERWT OVX/SOY

*P<0.05*
Conclusions

• High fit HCR rats have “fit fat”
  – ↓ inflamed and appears to have ↑ mitochondrial function
  – more sensitive to insulin

• High fit HCR rats are protected from weight gain and IR post-OVX
  – The mechanism may involve a compensatory ↑ in Spontaneous Physical Activity (SPA)

• Exercise ↓IR, ↑SPA, and improves adipose tissue immunometabolism.

• Similar to exercise, SOY is protective against metabolic dysfunction following OVX
  – Mechanism involves estrogen receptor alpha

• Ongoing work aims to determine if synergistic effects between SOY and exercise exist to improve postmenopausal metabolic dysfunction.
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