

**Borer Lecture - University of Michigan
September 2017**

Exercise as a Regulator of Endocrine Dysfunction in Type 2 Diabetes

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Endocrinology and Metabolism Institute, Cleveland Clinic**

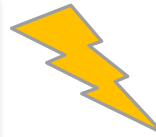
**Staff, Department of Pathobiology
Lerner Research Institute, Cleveland Clinic**

**Professor, Molecular Medicine
Lerner College of Medicine, Cleveland Clinic**

**Professor, Physiology
Case Western Reserve University**

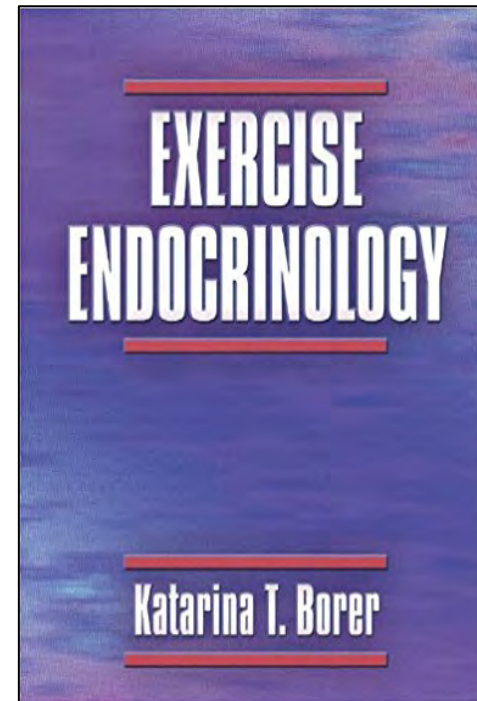


Katarina Borer, Ph.D.

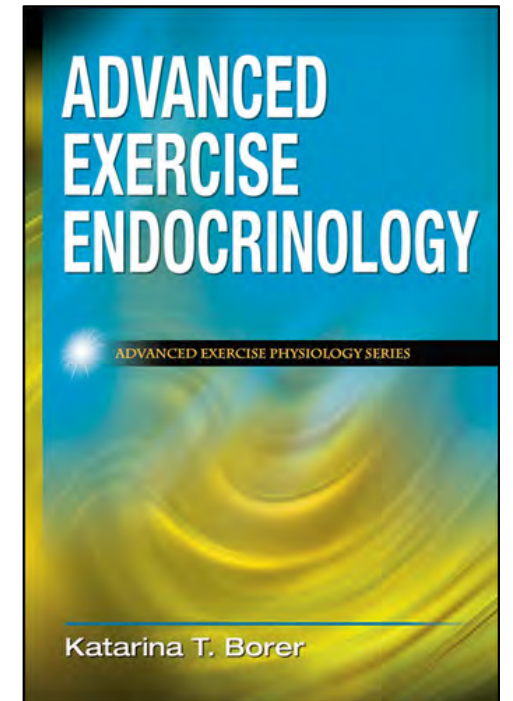


Seminal contributions
to exercise, energy
regulation, and
bioenergetics

Professor, Division of Kinesiology
Department of Movement Science
The University of Michigan, Ann Arbor



2003

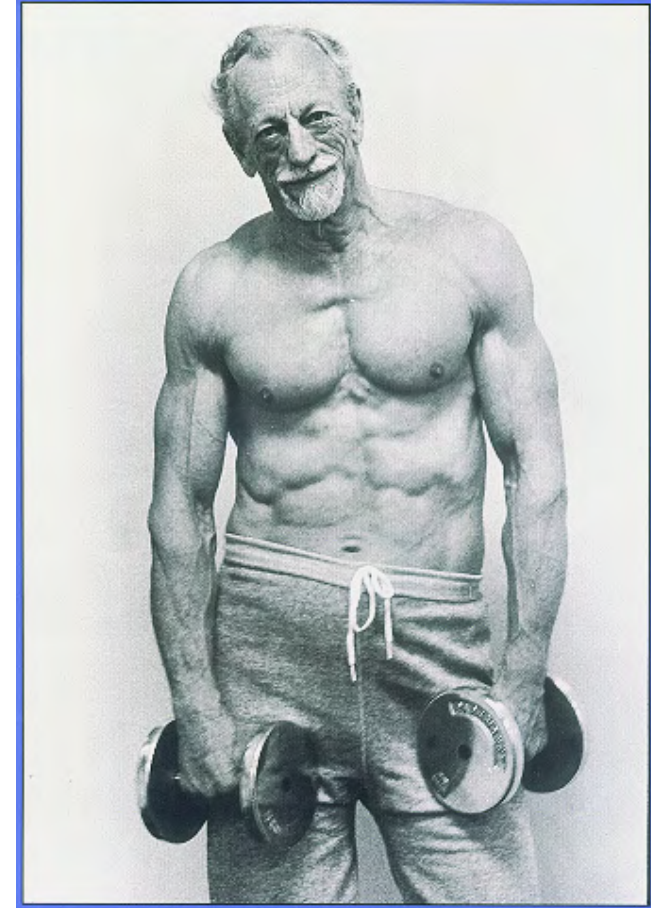


2013

OBJECTIVES TODAY

Provide a broad overview of exercise as it relates to the pathophysiology of type 2 diabetes

- Identify the effect of high intensity exercise on endocrine function in type 2 diabetes
- Describe a skeletal muscle contraction model and its use to interrogate insulin resistance
- Examine skeletal muscle mitochondrial dynamics and its role in insulin resistance



Diabetes Mellitus Prevalence

Type 2 Diabetes (T2D) >90%

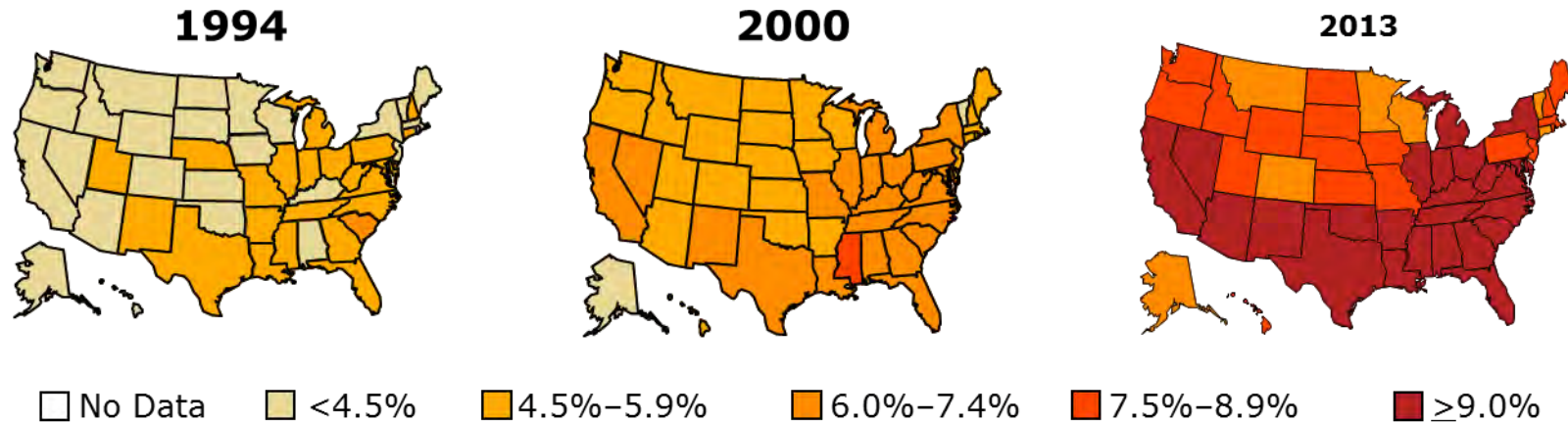
1980 - 108 million (4.7%) – Global

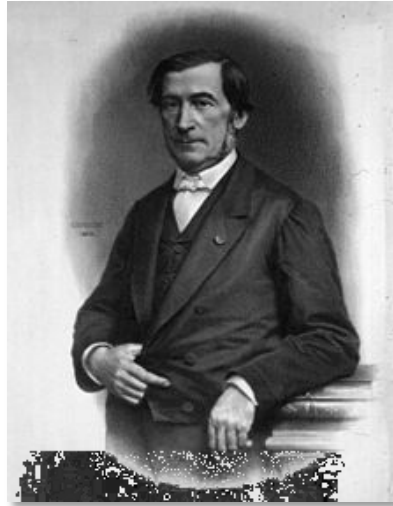
2014 – 422 million (8.5%) – Global

USA 2017 - 30.3 million (9.4%)

(WHO 2014, CDC 2017)

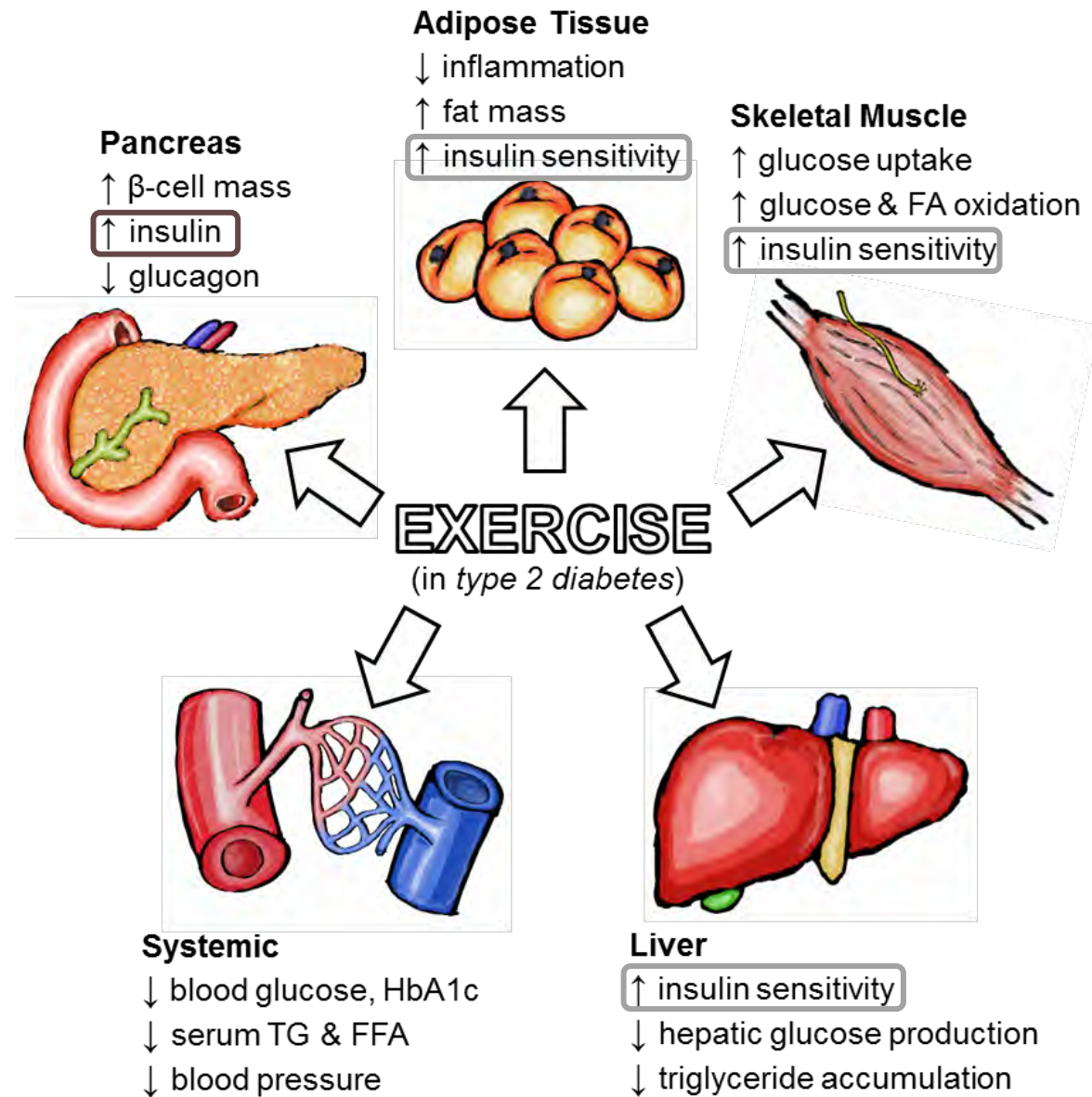
Diabetes



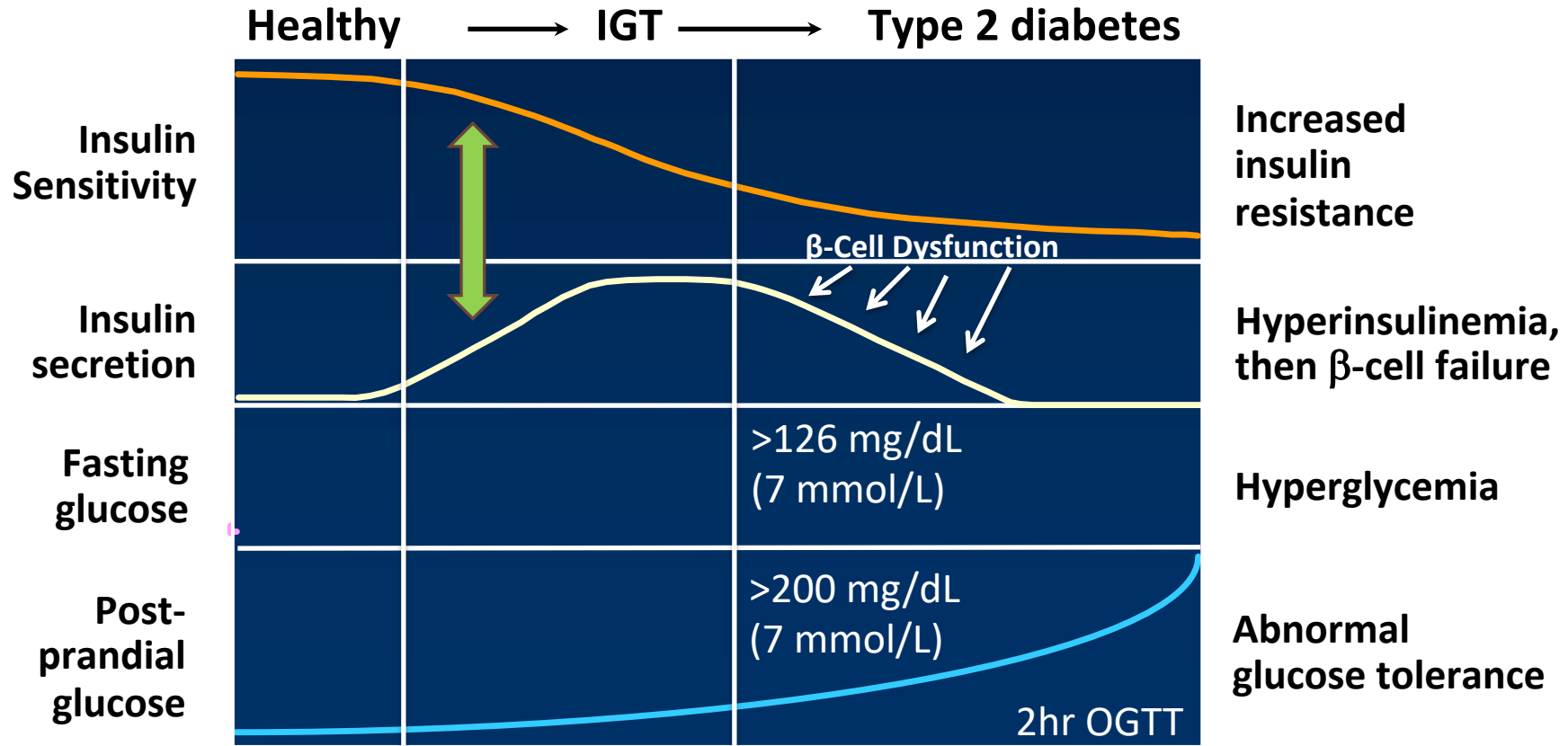


Apollinaire Bouchardat
(1809 – 1886)

*“You shall earn your bread
by the sweat of your
brow.”*



Pathophysiology of Type 2 Diabetes



*IGT = impaired glucose tolerance

*OGTT = Oral Glucose Tolerance Test (75 gram)

Exercise Acutely Improves Insulin Sensitivity

A Single Session of Low-Intensity Exercise Is Sufficient to Enhance Insulin Sensitivity Into the Next Day in Obese Adults

SEAN A. NEWSOM, PHD
ALLISON C. EVERETT, BS

ALEXANDER HINKO, PHD
JEFFREY F. HOROWITZ, PHD

Diabetes Care 36:2516–2522, 2013

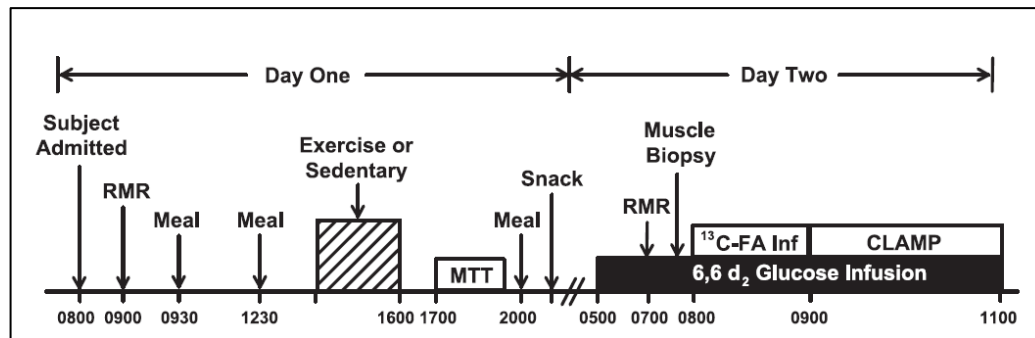


Figure 1. Study design.

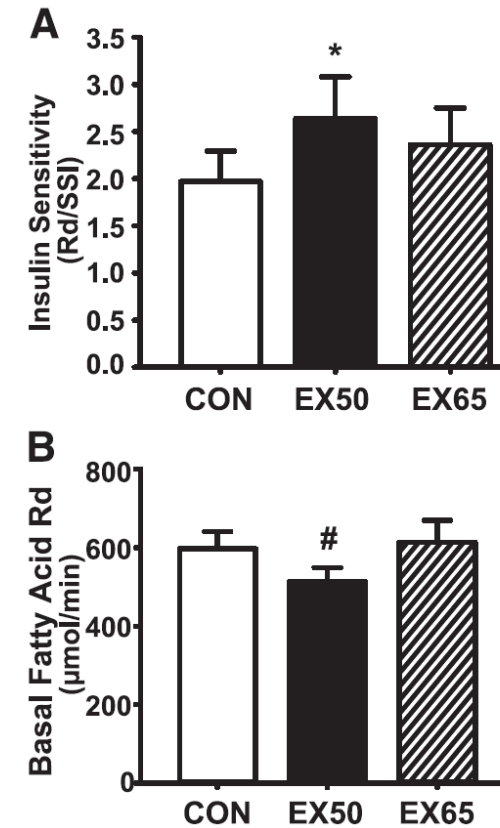


Figure 2. Changes in (A) insulin sensitivity and (B) fatty acid uptake after exercise at 50% (EX50) and 65% (EX65) of $\text{VO}_{2\text{MAX}}$.



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**Endocrinology and
Metabolism[®]**

Functional High Intensity Training Improves Pancreatic β -cell Function in Adults with Type 2 Diabetes

Stephan Nieuwoudt, Ciarán E Fealy, Julie A Foucher, Amanda R. Scelsi, Steven K. Malin, Mangesh R. Pagadala, Michael Rocco, Bartolome Burguera, John P. Kirwan

American Journal of Physiology - Endocrinology and Metabolism Published 16 May 2017 **Vol. no.**

DOI:10.1152/ajpendo.00407.2016

Physical training may enhance β -cell function in type 2 diabetes *

Flemming Dela,^{1,2} Michael E. von Linstow,^{3,4} Kári Joensen Mikines,^{1,5} and Henrik Galbo^{1,6}

¹Copenhagen Muscle Research Centre and ²Department of Medical Physiology, The Panum Institute, University of Copenhagen, 2200 Copenhagen N; ³Clinic for Spinal Cord Injuries and ⁴Department of Orthopedic Medicine T, Rigshospitalet, 2100 Copenhagen Ø; ⁵Department of Urology, Herlev University Hospital, DK 2730 Herlev; and ⁶Department of Rheumatology, Bispebjerg Hospital, Bispebjerg, 2400 Copenhagen NV, Denmark

Delineating Factor: Residual β -Cell Capacity

Aerobic Exercise (5 days/week)

- “lack of time” – *Korkiakangas et al., 2011*

High Intensity Training (HIT)



“It’s not easy fitting 60 minutes of exercise into my busy schedule. Today I took 360 ten-second walks.”

CrossFit® training

- Functional High Intensity Training (F-HIT)
- Constantly varied workouts (8-20 minutes)
- Structured, Accountability, Personal Trainer
- Introductory program: 3 days/week for 6 weeks
- **Great Lakes CrossFit Gym (Bedford, Ohio)**



How to measure β -cell function?



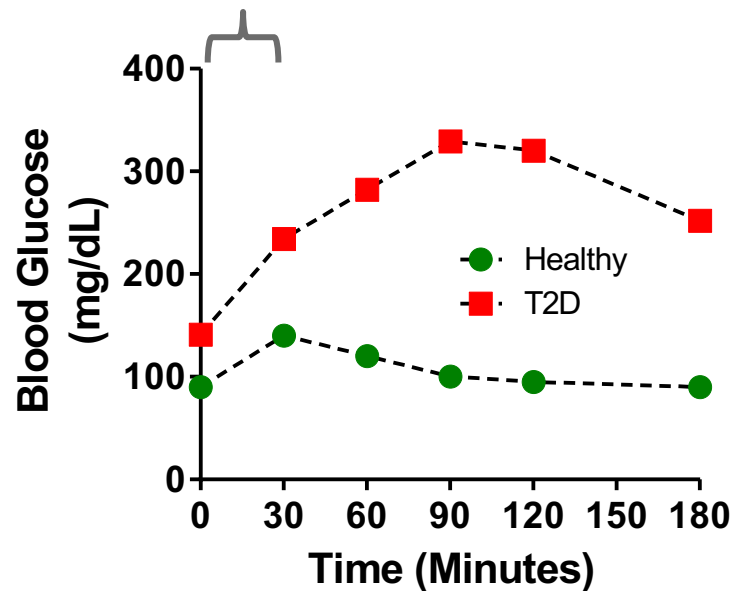
Insulin Secretion on the Background of Insulin Sensitivity

β -Cell Function = Insulin Secretion \times Insulin Sensitivity

- Disposition Index

Oral Glucose Tolerance Test (OGTT)

Early Phase

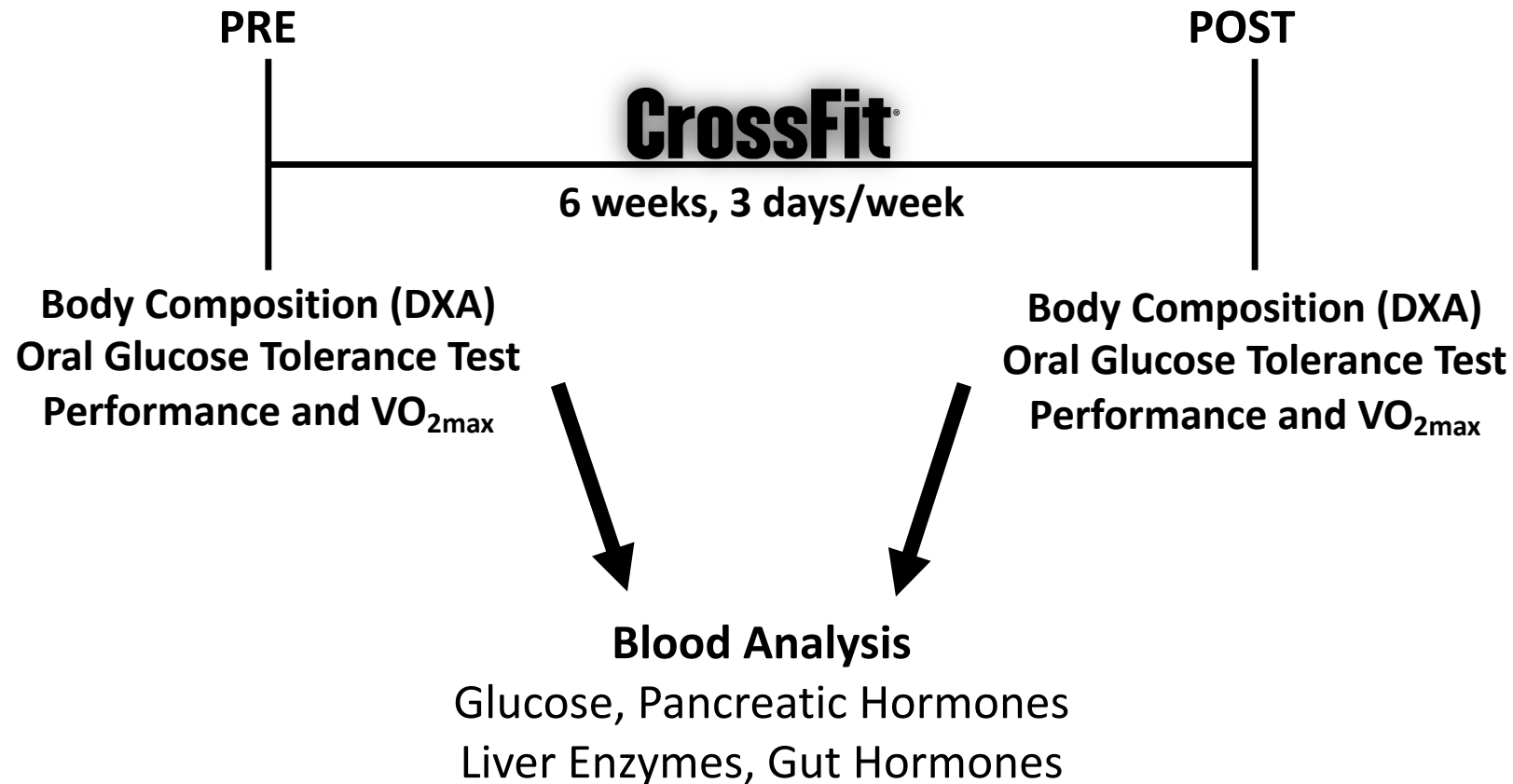


Secretion Index = Δ Insulin/ Δ Glucose
Glucose Stimulated Insulin Secretion

Insulin Sensitivity Index
Modified Stumvoll Equation

Study Participants Recruited:

- Adults Diagnosed with Type 2 Diabetes
 - (non-insulin dependent)
- Sedentary, Weight Stable

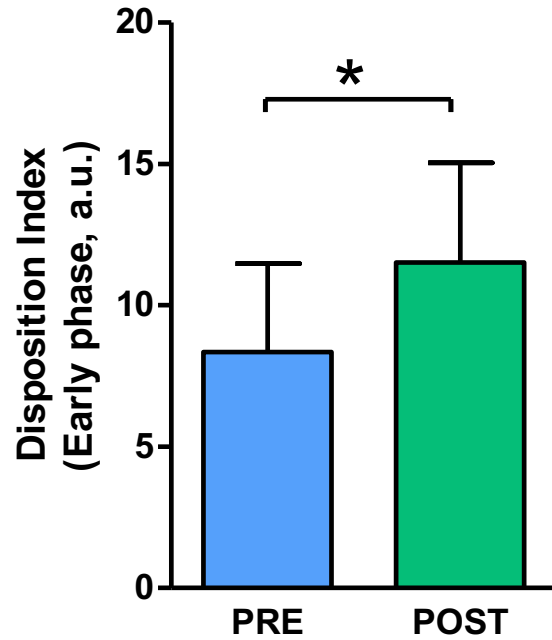


CrossFit Training Results

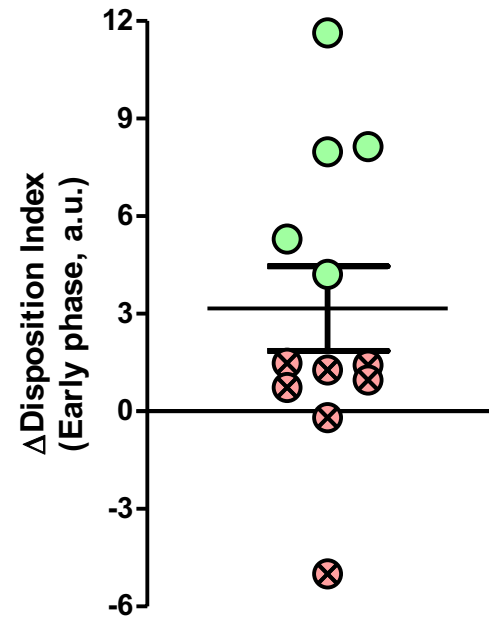
	PRE	POST	Δ	P-value
n (M/F)	12 (5/7)			
Age, years	54 \pm 2			
Body composition				
Body weight, kg	98.0 \pm 3.7	96.1 \pm 2.7	-1.8 \pm 1.0	0.09
Total fat, %	43.6 \pm 1.8	42.5 \pm 1.8	-1.1 \pm 0.3	0.002*
Abdominal fat,%	56.2 \pm 1.8	55.3 \pm 1.7	-0.9 \pm 0.7	0.22
Physical performance				
VO_{2max}/ L/min	2.43 \pm 0.12	2.81 \pm 0.15	0.38 \pm 0.08	0.001*
Session 2 (PRE) vs. 18 (POST), reps	223 \pm 12	282 \pm 11	59 \pm 8	<0.001*

CrossFit Training Results

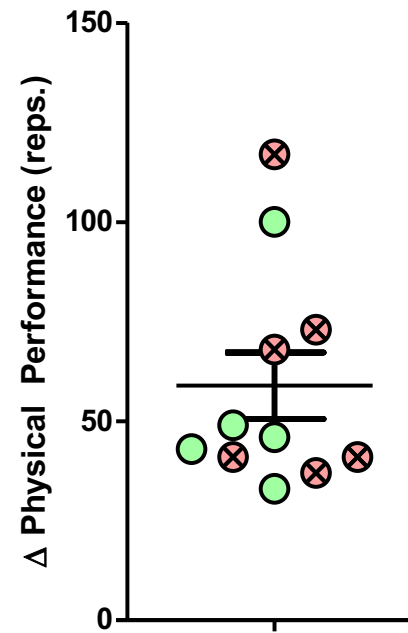
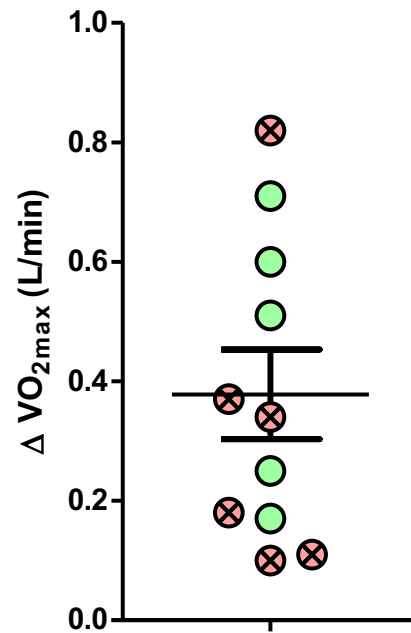
Disposition Index



Delta Disposition Index



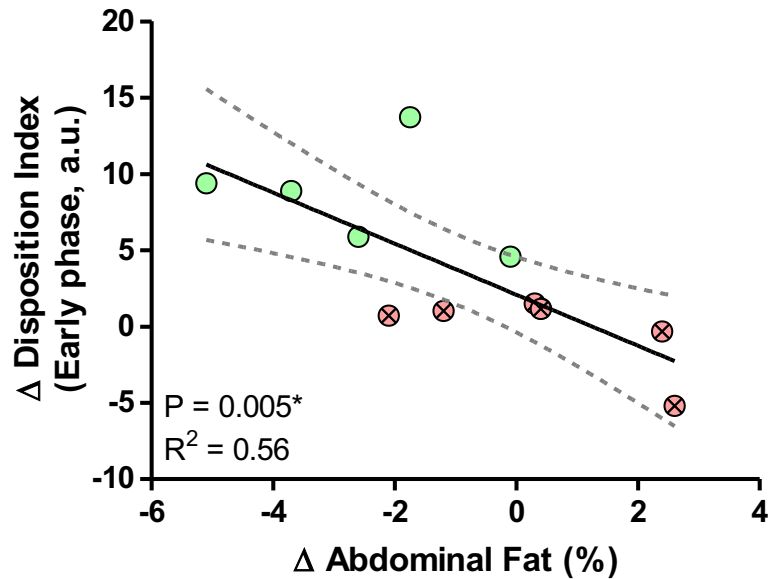
PRE-Intervention	Responders	Non-responders	P-value
Glucose Tolerance			
Glucose tAUC (0-180min), g/dL*min	33.6 ± 2.2	44.2 ± 4.1	0.05*
β-Cell Secretory Capacity			
C-peptide tAUC (0-180min), ng/mL*min	792 ± 54	551 ± 74	0.03*



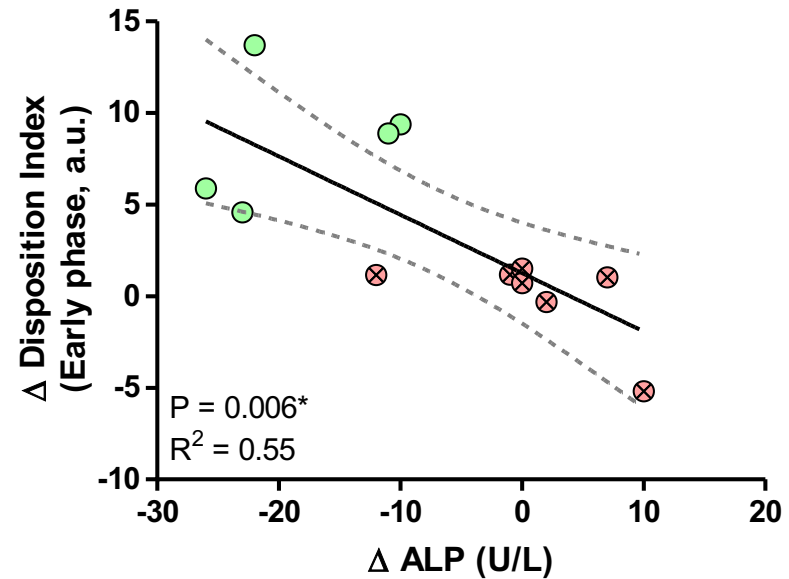
Correlations with β -Cell Function

Abdominal Fat %

Alkaline Phosphatase (ALP)



Adipose Tissue



Liver Function

F-HIT Increases β -cell function in adults with T2D*

Improvements are driven by increased insulin secretion, not sensitivity

Improvements in function correlate with reduced **Abdominal Fat** and **ALP**

*Responders vs. Non-responders

- Severity of Diabetes

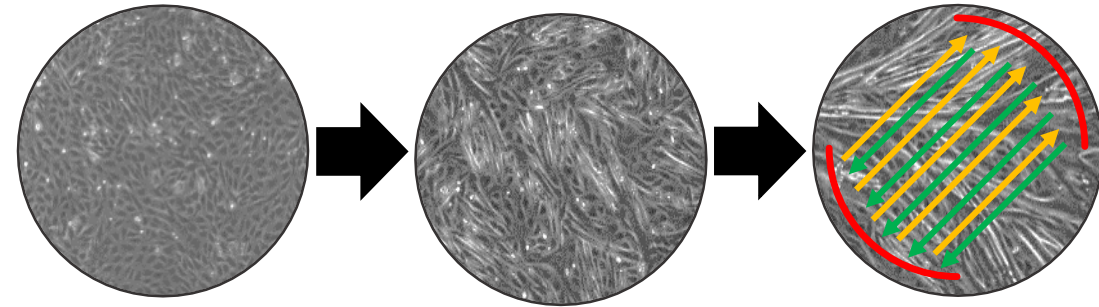
Limitations

- Molecular Mechanisms
- Isolate the function of exercise alone

Exercise in a Petri Dish Model

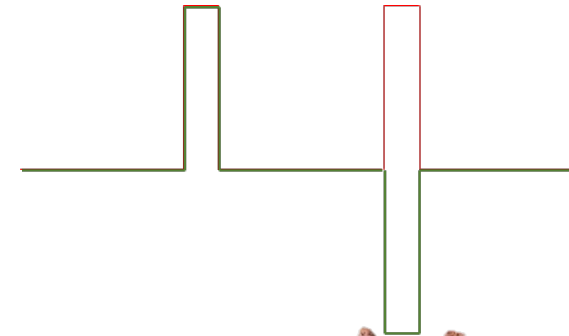
Muscle cells

- C2C12 myocytes
- Differentiation

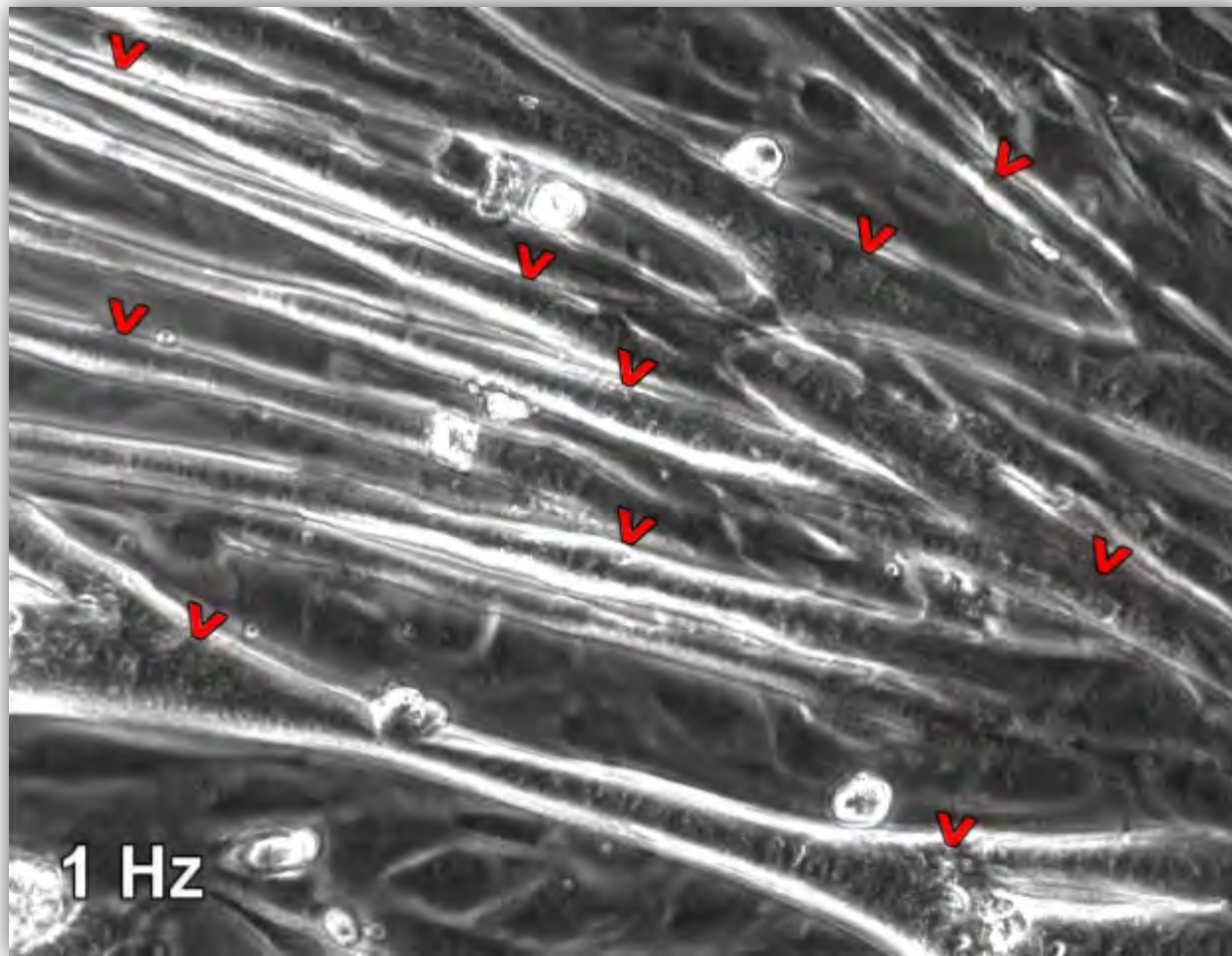


Electrical Pulse Stimulation (EPS)

- Electrodes (Platinum) → Electrical Field
- Electrophoresis
 - Polarity switching



Electrical Pulse Stimulation of C2C12 Myotubes





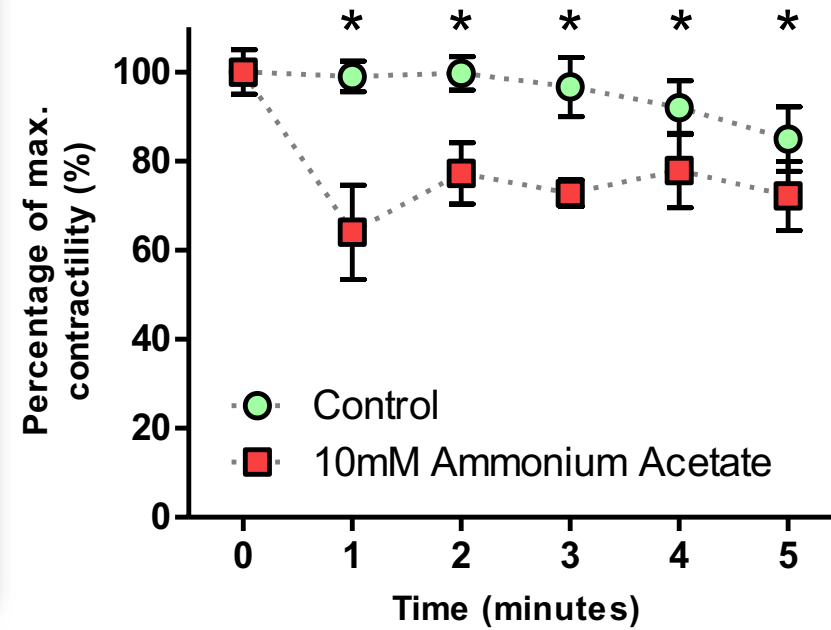
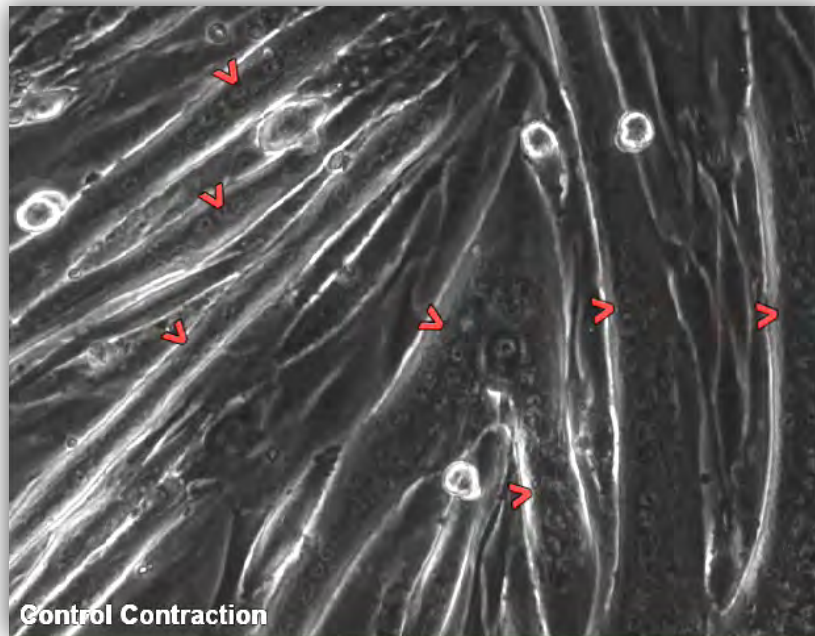
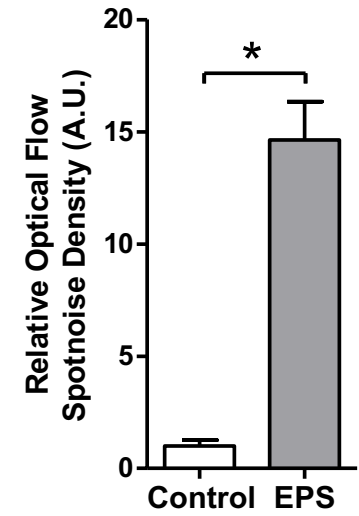
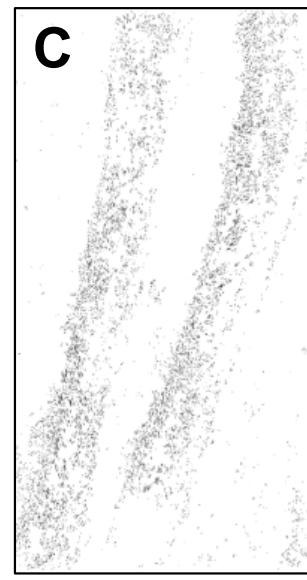
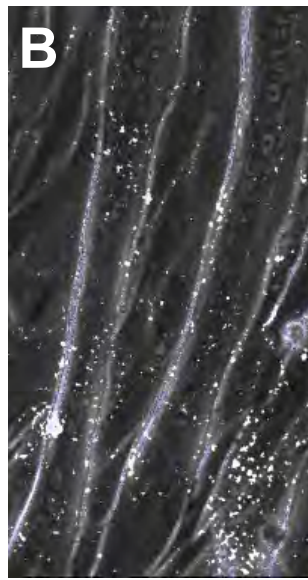
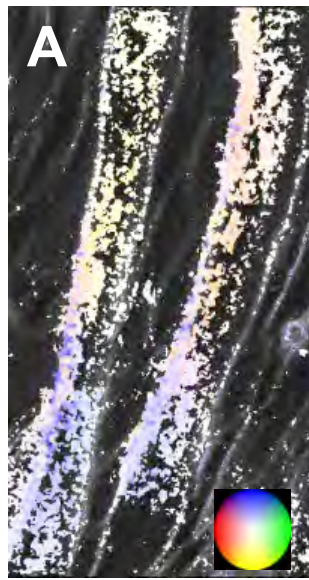
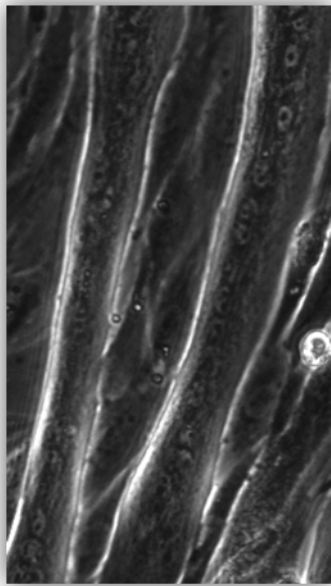
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Cell Physiology

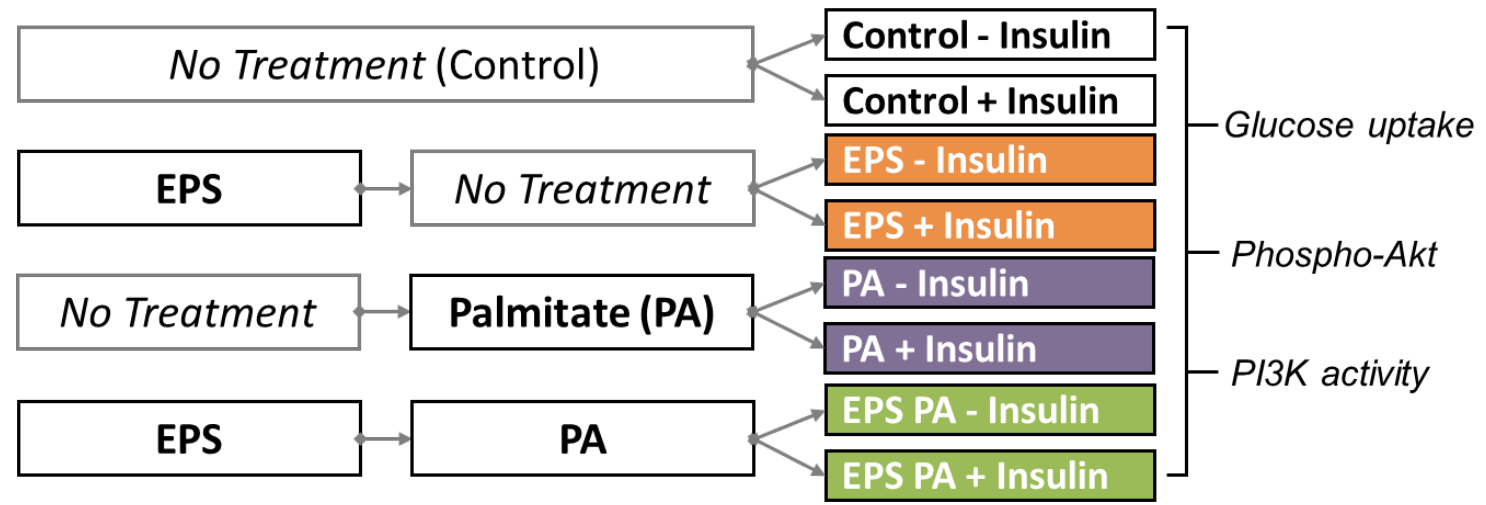
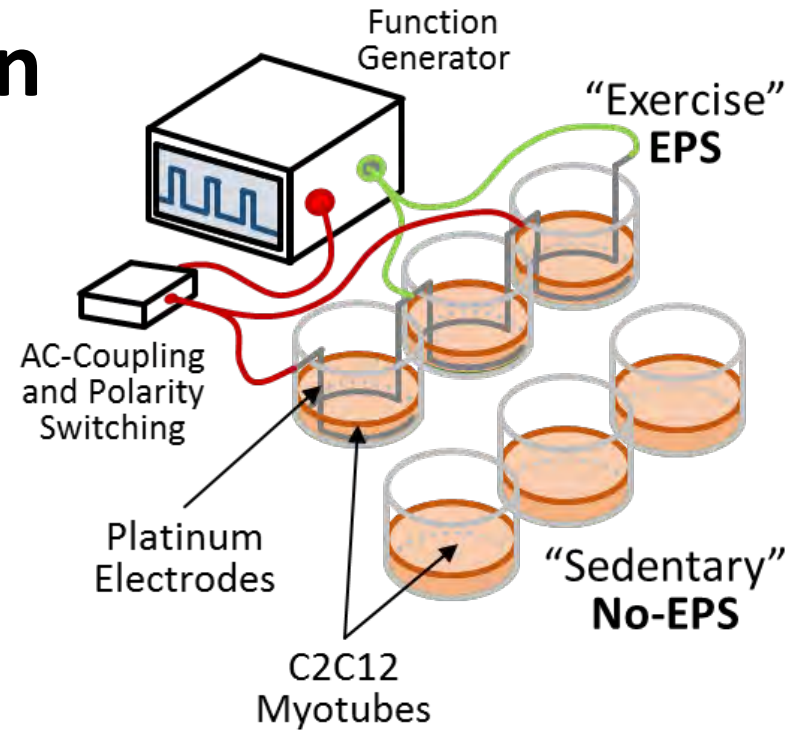
In vitro Contraction Protects Against Palmitate-Induced Insulin Resistance in C2C12 Myotubes

Stephan Nieuwoudt, Anny Mulya, Ciaran E. Fealy, Elizabeth Martelli, Srinivasan Dasarathy, Sathyamangla V. Naga Prasad, John P. Kirwan

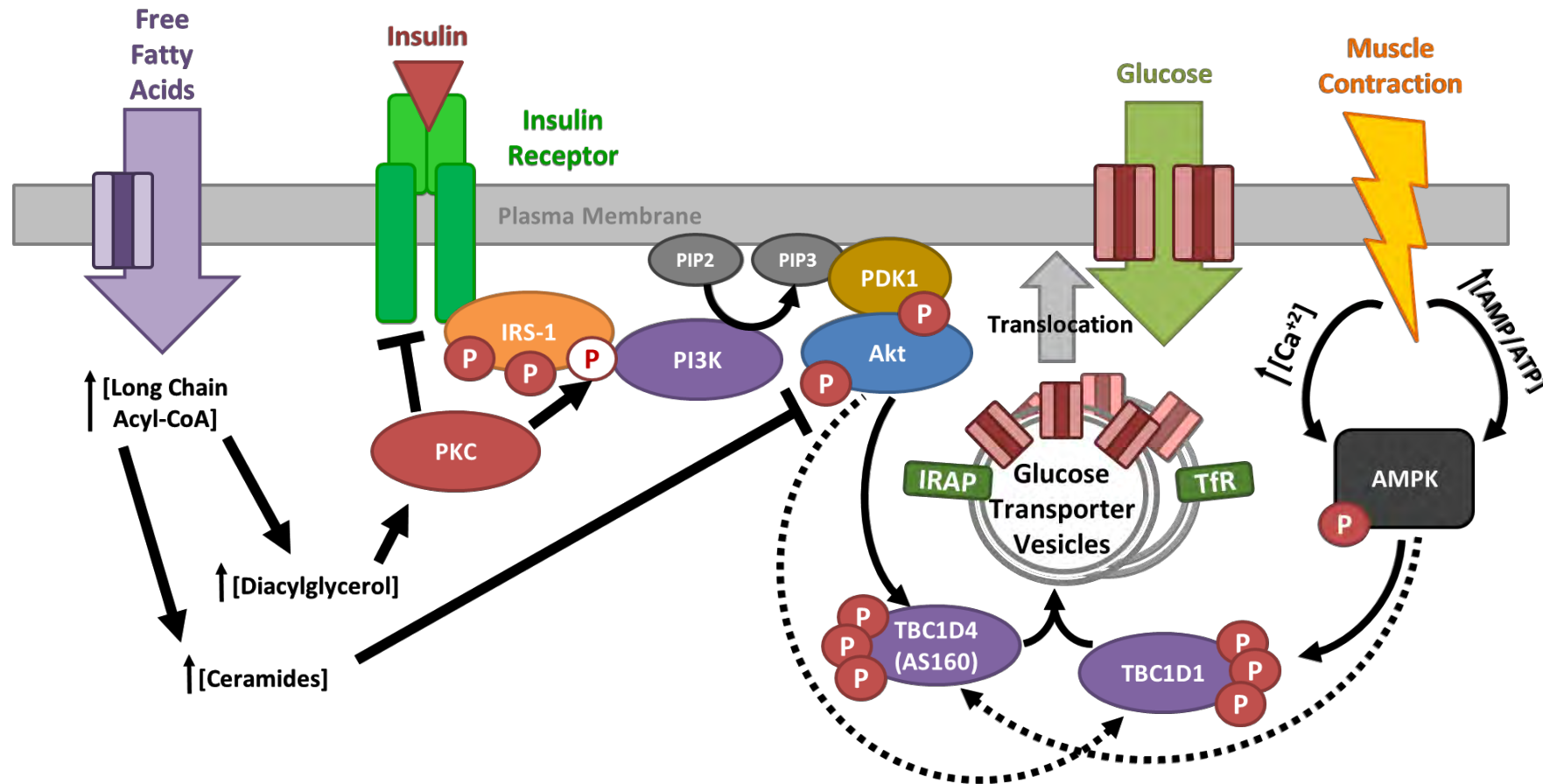
American Journal of Physiology - Cell Physiology Published 23 August 2017 Vol. no. , DOI: 10.1152/ajpcell.00123.2017

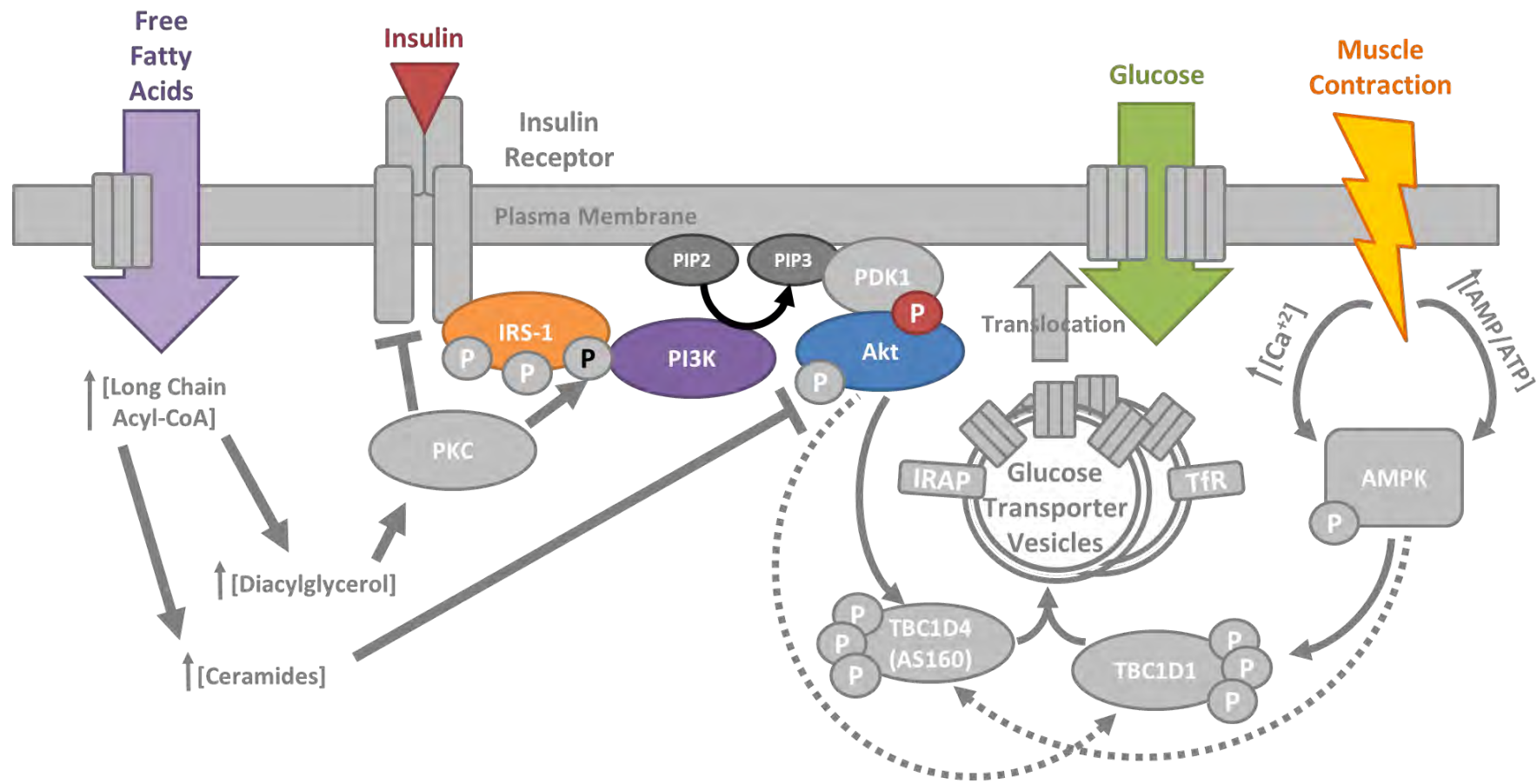


Experimental Design



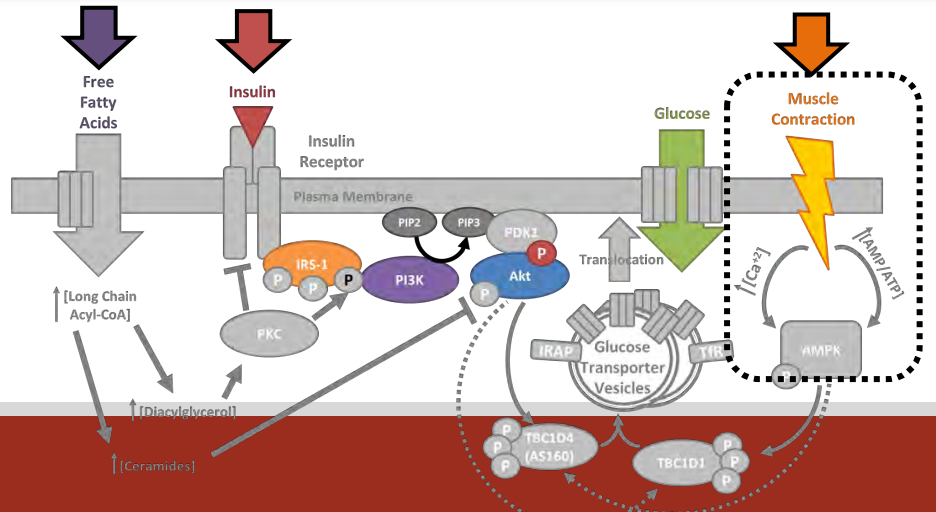
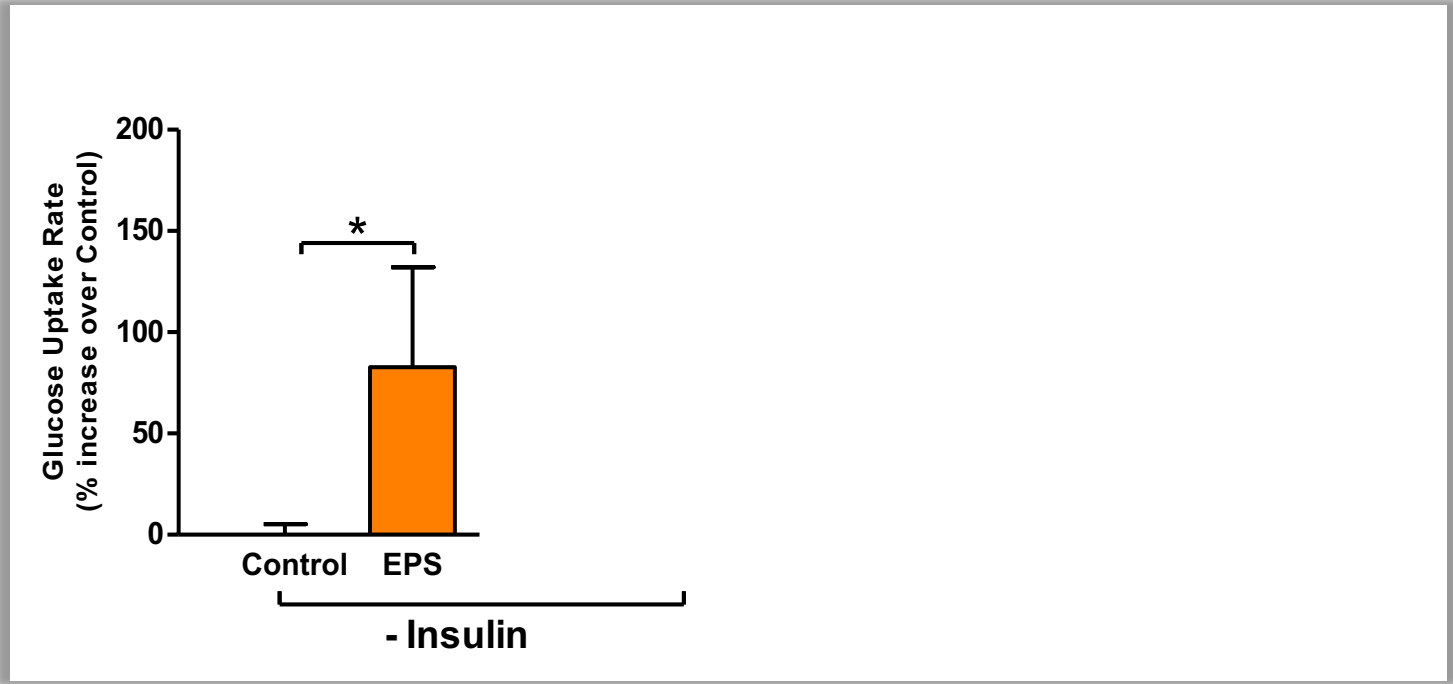
How Does Insulin Regulate Glucose Uptake



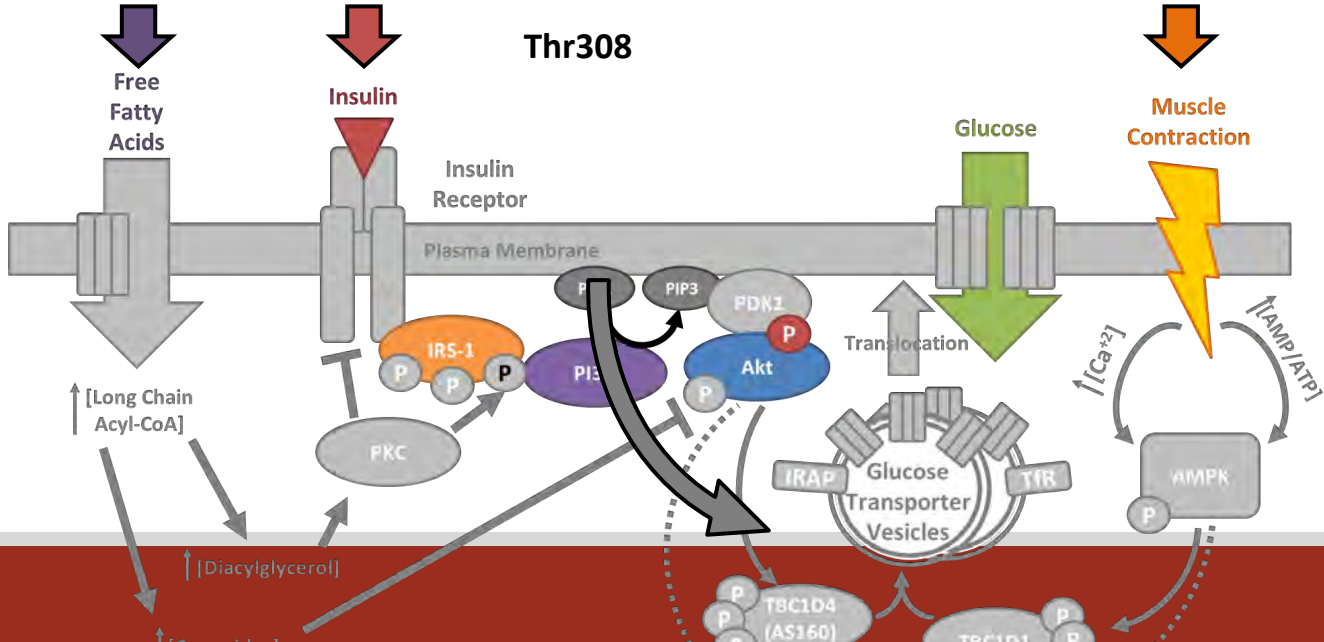
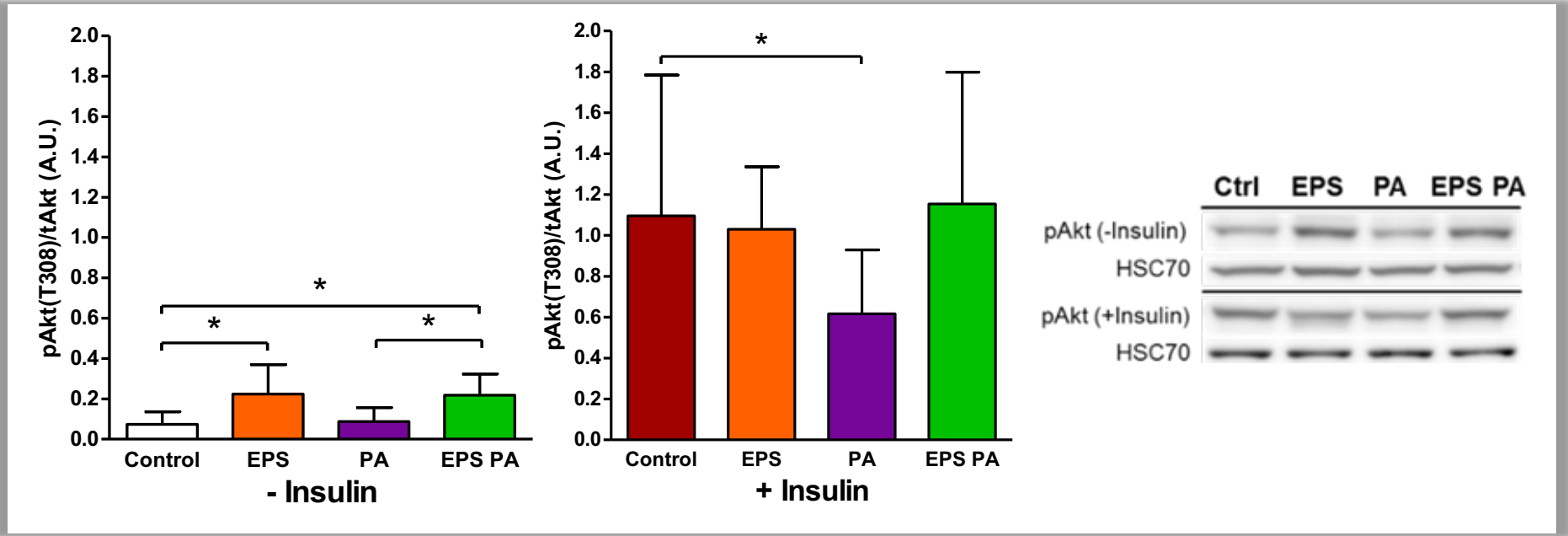


Contraction Model Validation

Glucose Uptake

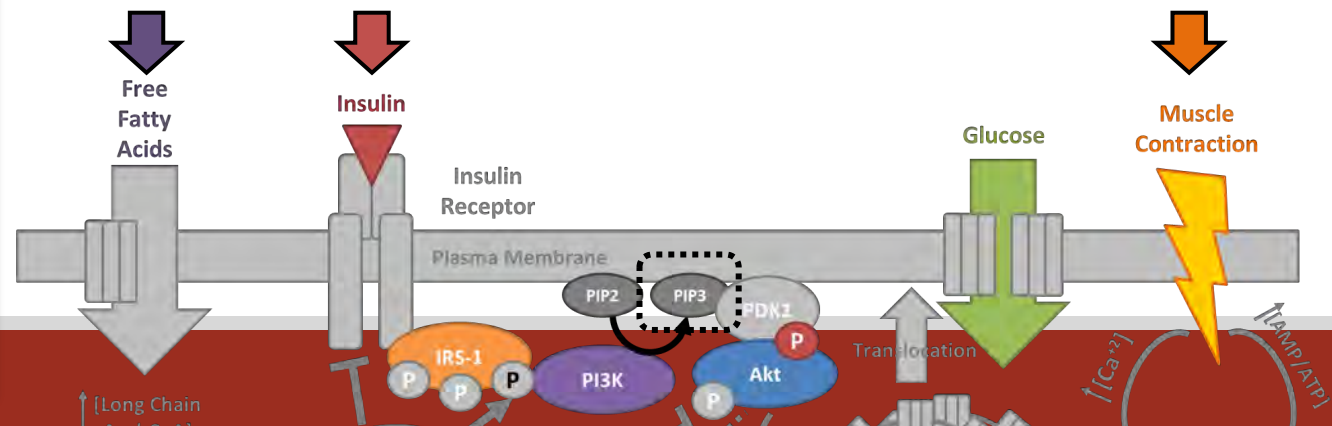
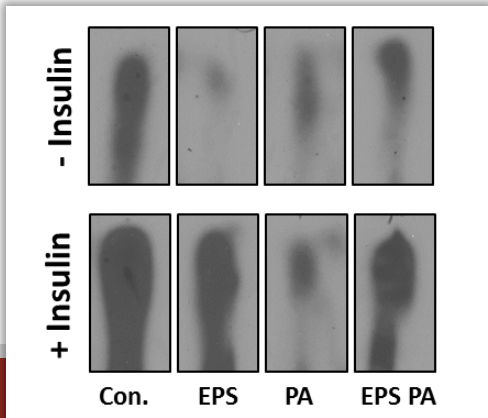
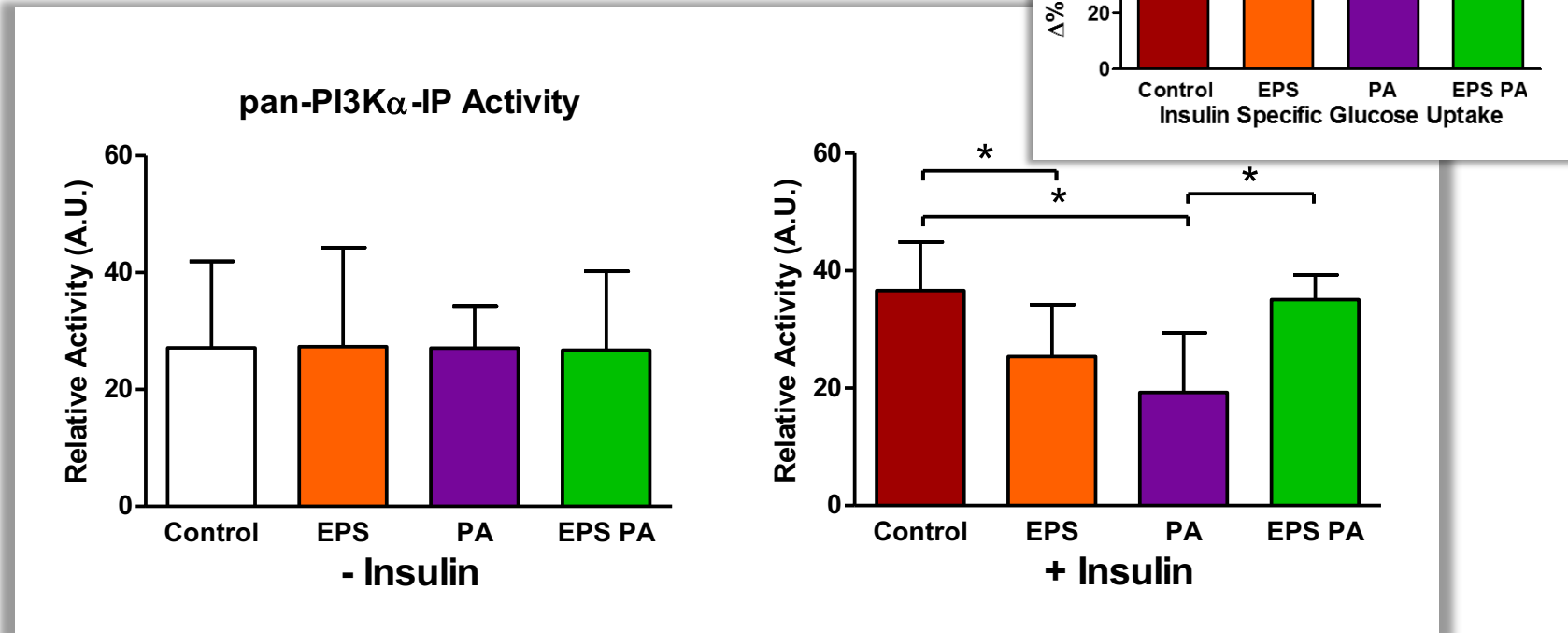


Contraction Model Validation - Akt Phosphorylation



Contraction Model Validation

Whole-cell PI3K activity



Conclusions

Model is validated by a known phenomenon

Contraction alone can provide protection against lipid-induced insulin resistance

Protective mechanism is evident within the canonical insulin signaling pathway

Non-canonical activation of PI3K may also mediate protective effect

What is Mitochondrial Dynamics?

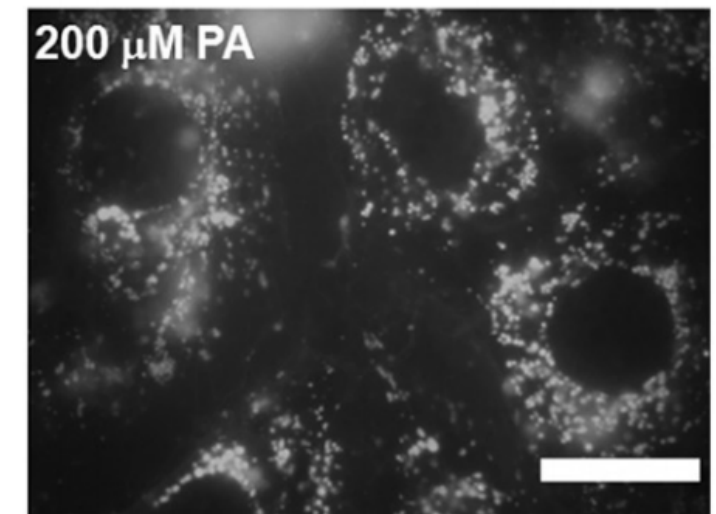
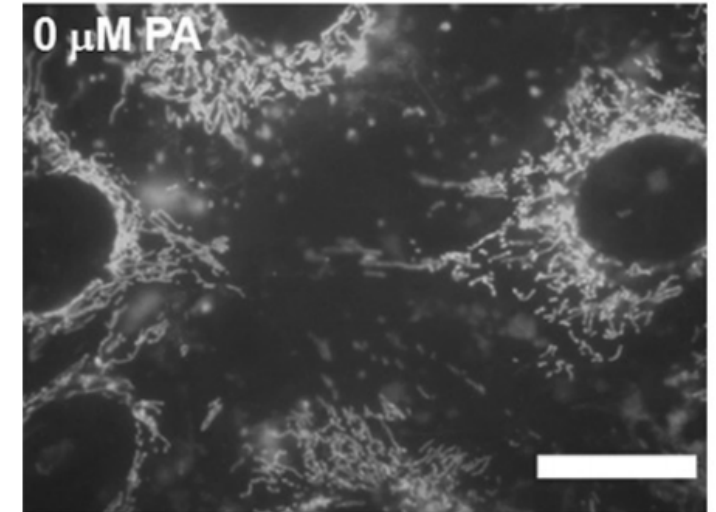
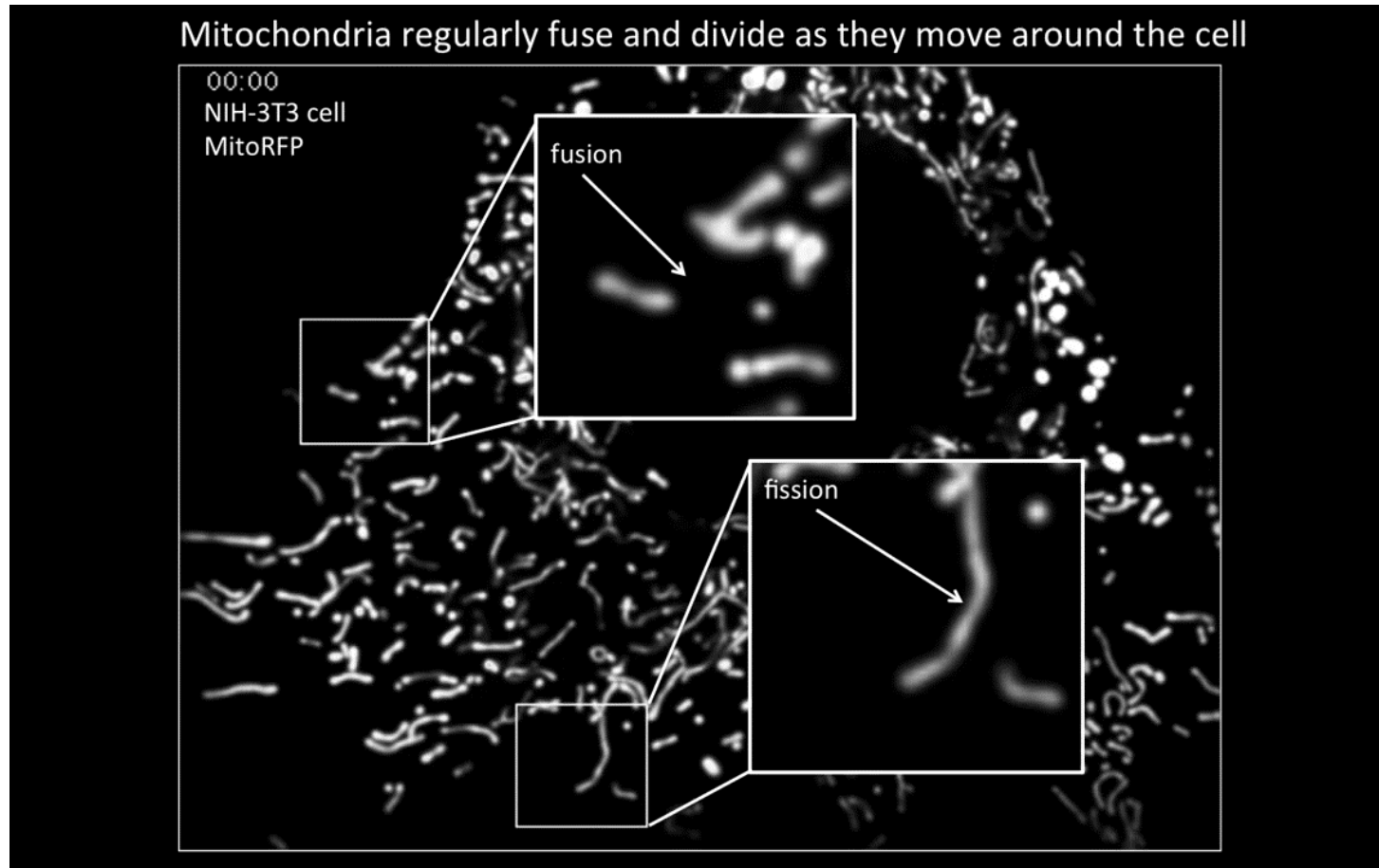
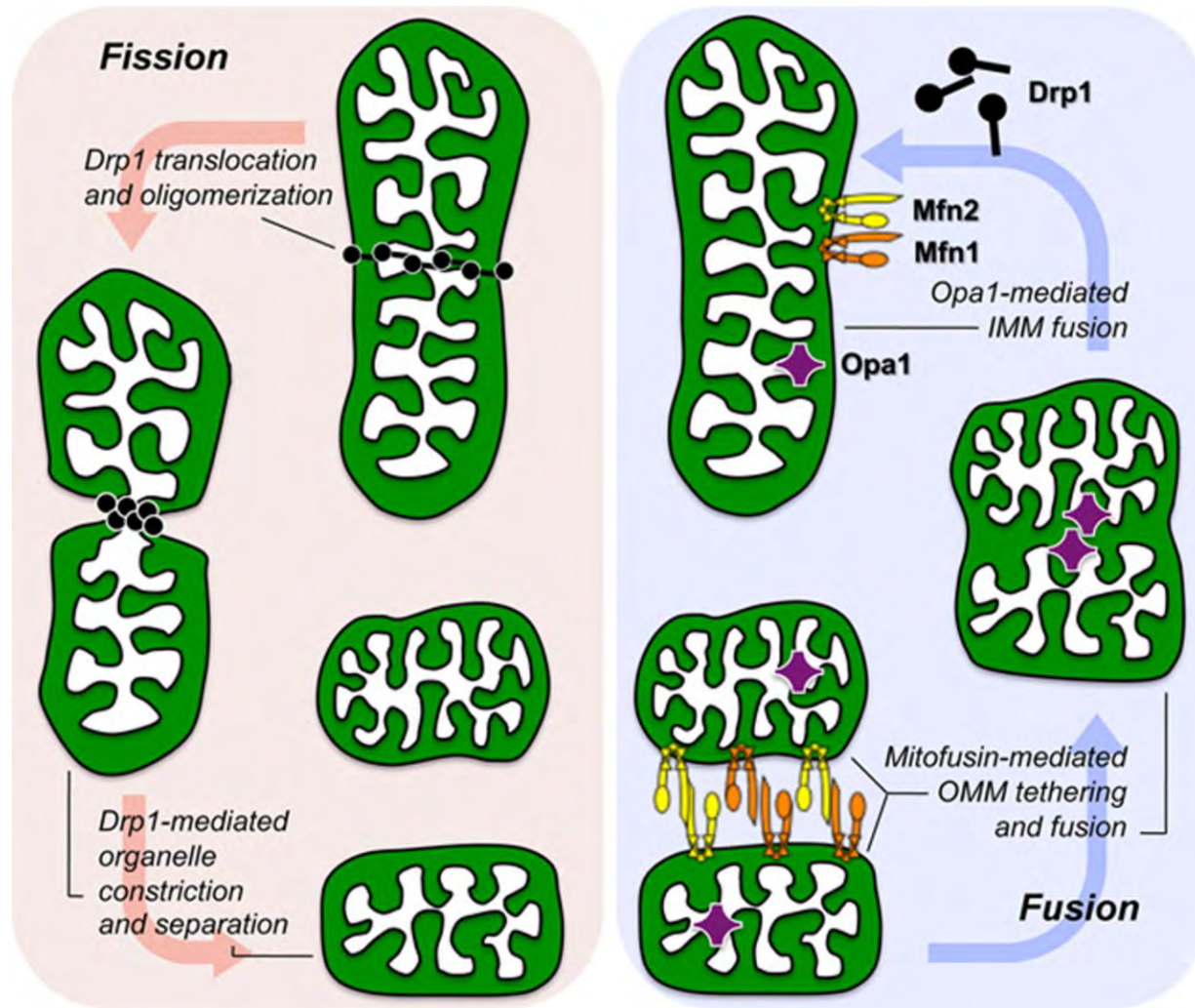


Figure 1. Treatment with PA induces mitochondrial fragmentation in C2C12 cells. Jheng et al. (2011)

Mitochondrial Dynamics: A Primer



Mitochondrial Fission:

DRP1 (Cytosol)
MFF (OMM)
Mid49 (OMM)
Mid51 (OMM)

Mitochondrial Fusion:

MFN1 (OMM)
MFN2 (OMM)
OPA1 (IMM)

Mitophagy:

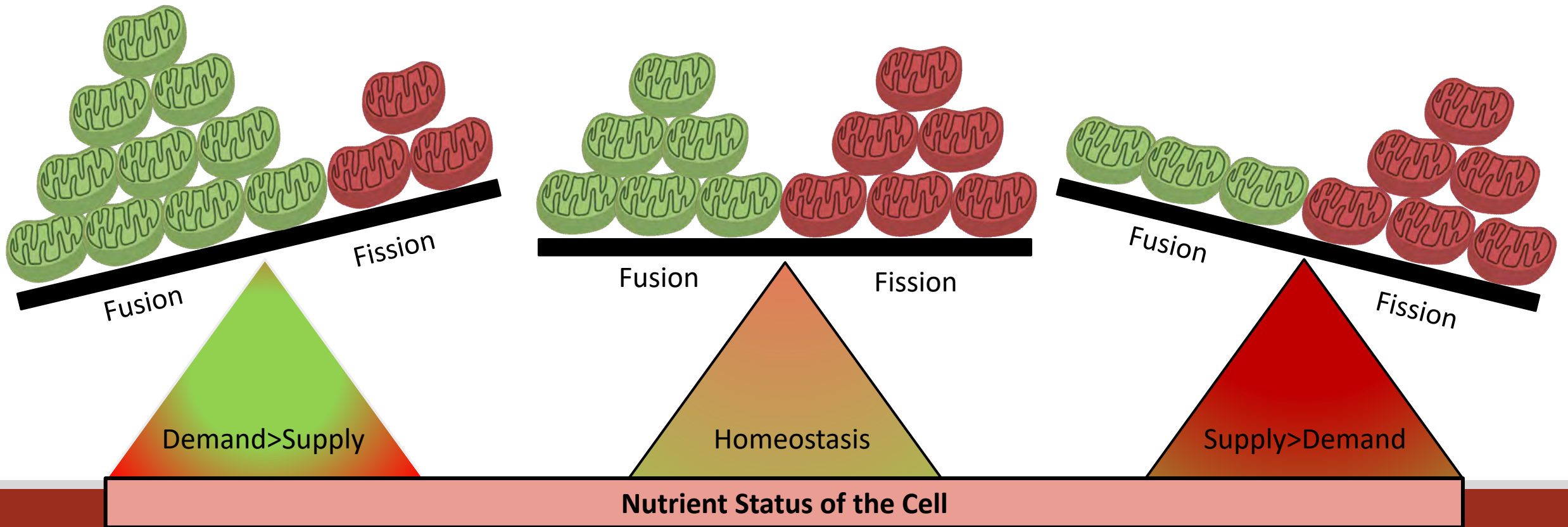
PINK1 (Cytosol/OMM/IMM)
Parkin (OMM)

Mitochondrial Dynamics and Metabolic Disease

Starvation; Exercise

Normal

Cardiometabolic; Neurological;
Pulmonary; Alzheimer's



Mitochondrial Fission and Insulin Resistance

Nutrient oversupply leads to:

- Opening of the permeability transition pore (mPTP)
 - Inhibits insulin-stimulated glucose uptake
- Loss of mitochondrial membrane potential ($\Delta\psi_m$)
- Fragmentation of the mitochondrial network
- Loss of mitochondrial function
 - Impaired O₂ consumption rates
 - Uncoupled respiration
 - Slowed ATP synthesis

Hyperinsulinemia results in order to accommodate inadequate energy production

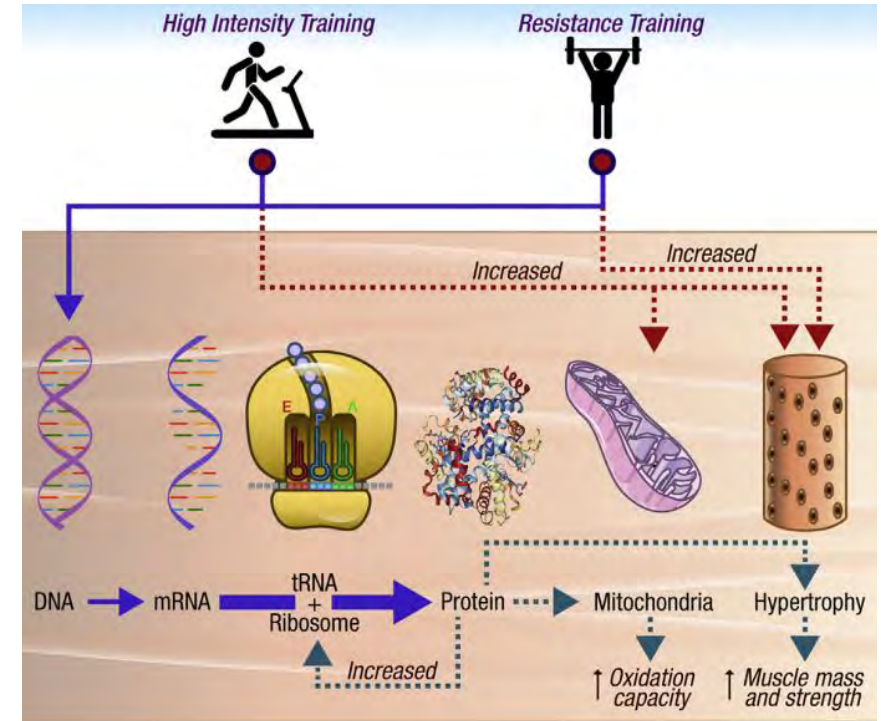
With continual overload on the mitochondria, insulin action worsens

Exercise as Molecular Medicine

Aerobic exercise leads to number adaptations in the mitochondria

- Number (mtDNA copies, biogenesis)
- Size (network & individual mitochondrion)
- Density (product of size and number)
- Function (ATP synthesis, Respiratory chain, ROS scavenging)

The effect of exercise training on mitochondrial dynamics is currently unknown



Does exercise training restore mitochondrial dynamics in insulin resistant individuals?

Hypothesis 1:

Exercise training will alter the mitochondrial phenotype such that there will be **enhanced fusion** and **reduced fission**

Hypothesis 2:

Metabolic improvements from exercise training related to changes in mitochondrial dynamics.

Study Design



Hyperinsulinemic-Euglycemic Clamp Study

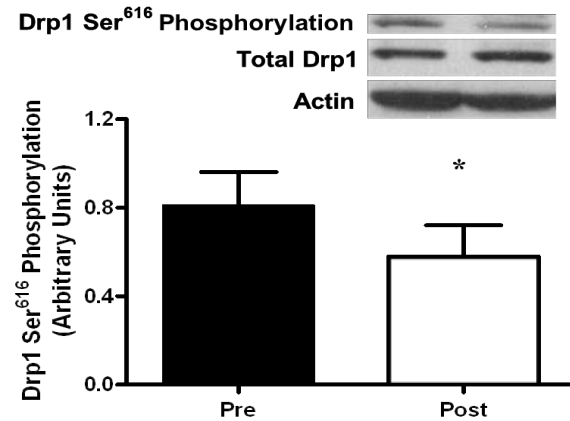


Exercise Training Improves Metabolic Phenotype

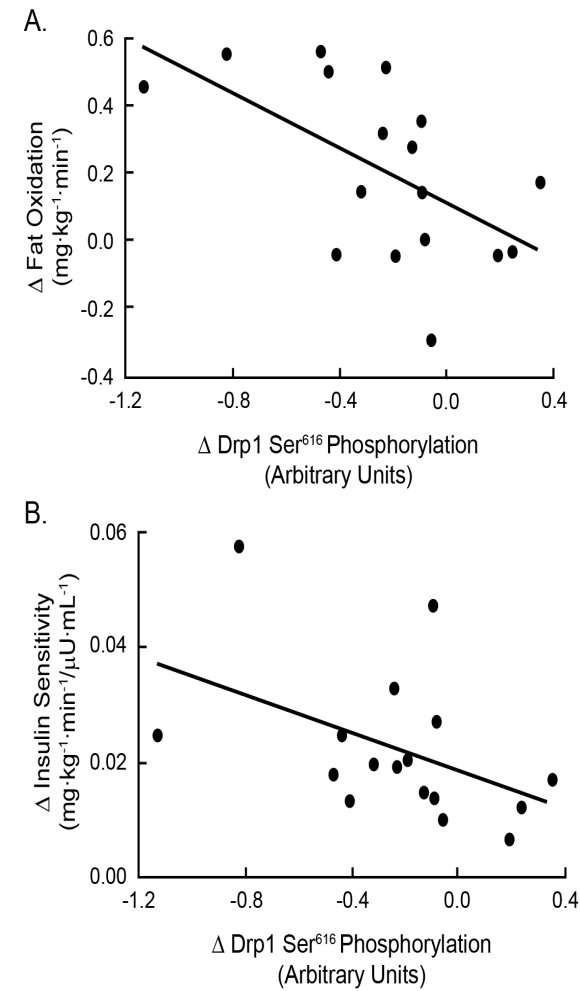
Table 1. Changes in subject characteristics after 12 weeks of exercise training

Characteristic	<i>M</i>	<i>SD</i>	p-value (2-tailed)
Age (yrs)	66.3	4.8	-
Δ Weight (kg)	-13.20	3.7	<0.001
Δ BMI (kg/m ²)	-4.23	1.3	<0.001
Δ Body Fat %	-6.80	3.4	0.001
Δ VO ₂ MAX (ml/kg/min)	8.13	3.9	<0.001
Δ FPG (mg/dL)	-4.03	4.3	0.020
Δ FPI (μU/mL)	-2.83	3.4	0.033
Δ Triglycerides (mg/dL)	-57.80	64.6	0.025
Δ Cholesterol (mg/dL)	-35.30	25.6	0.003
Δ HDL (mg/dL)	2.00	5.8	0.329
Δ VLDL (mg/dL)	-11.70	12.2	0.019
Δ LDL (mg/dL)	-25.60	21.6	0.006
Δ GDR (mg/kg/min)	2.32	1.2	<0.001
Δ NOGD (mg/kg/min)	2.05	1.1	<0.0001
Δ HOMA	-0.80	0.8	0.019
% Δ M/I	1.24	0.9	<0.001

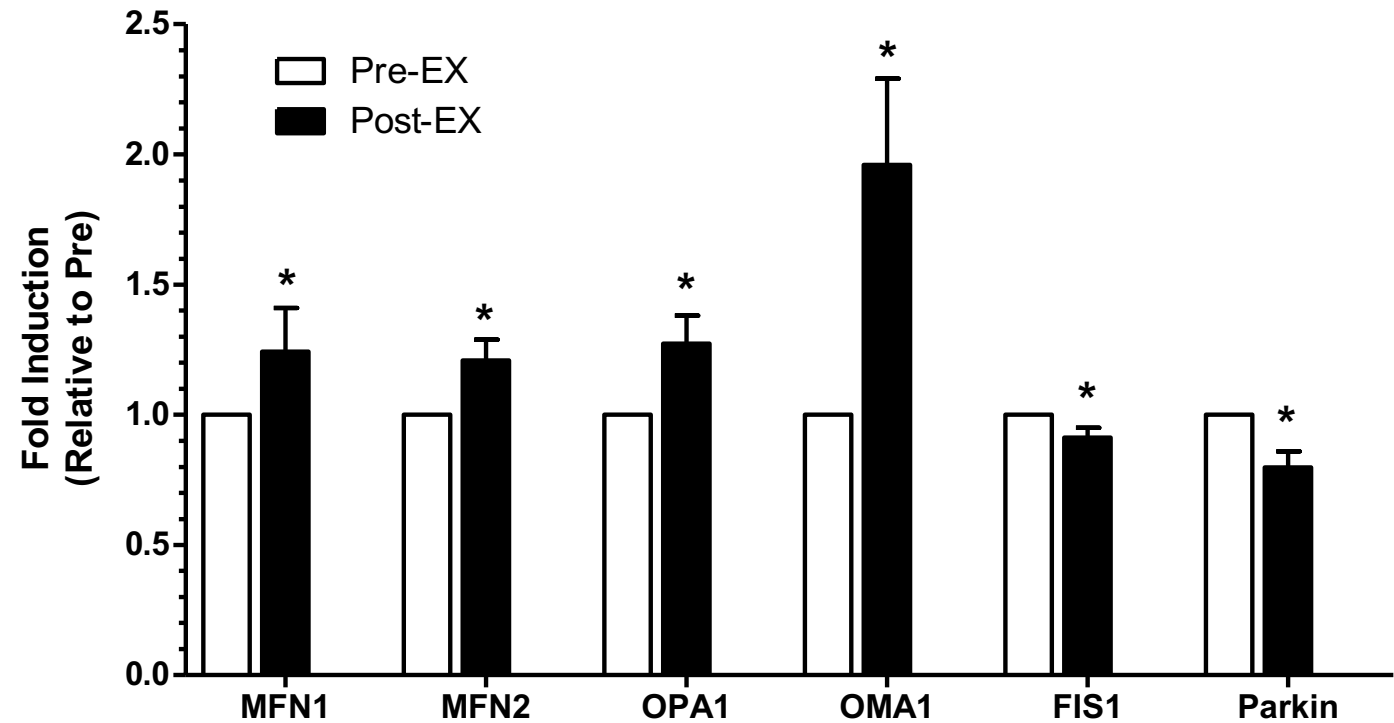
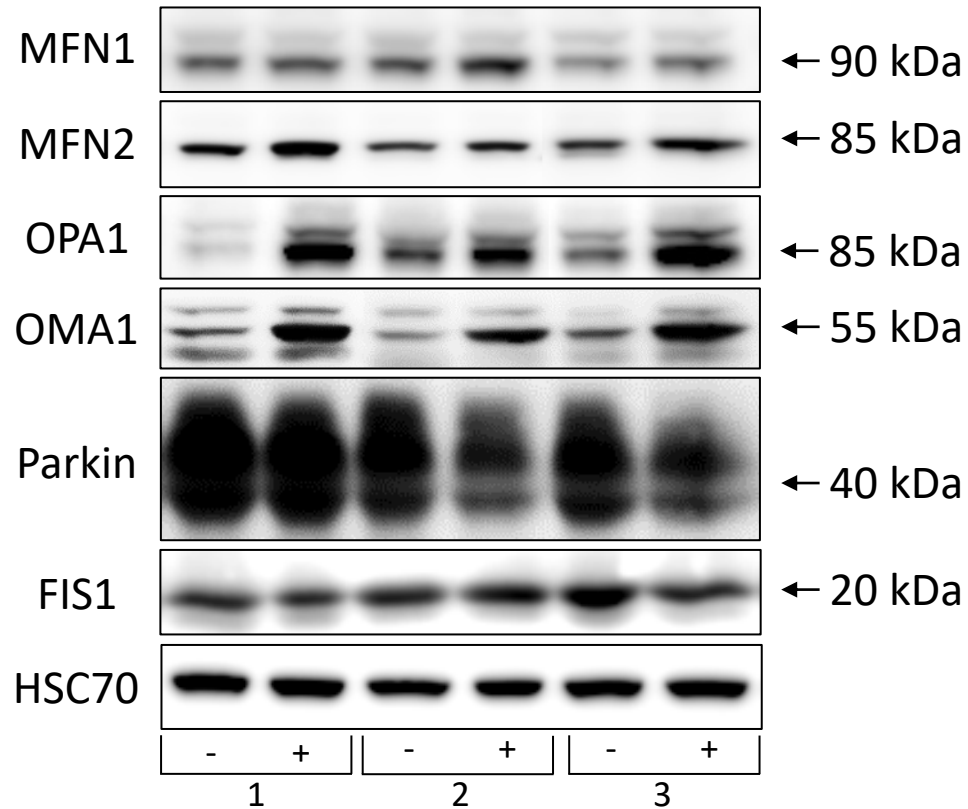
Exercise training restores Mitochondrial Dynamics in Insulin Resistant Individuals



- Reductions in Drp1 phosphorylation in association with improved insulin resistance and fat oxidation supports the hypothesis that Drp1 mediated mitochondrial fission may link mitochondrial function with insulin sensitivity

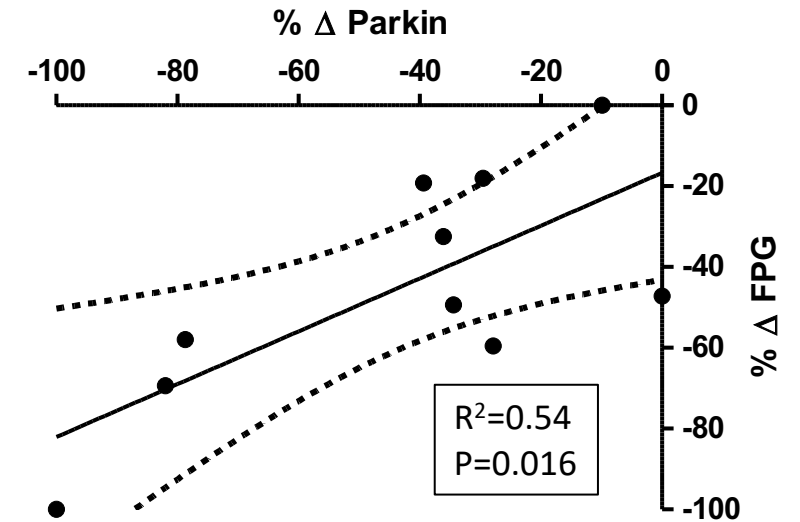
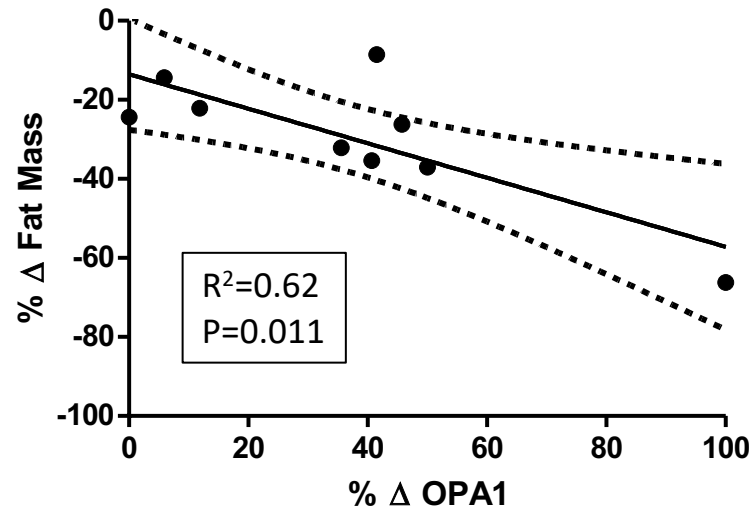
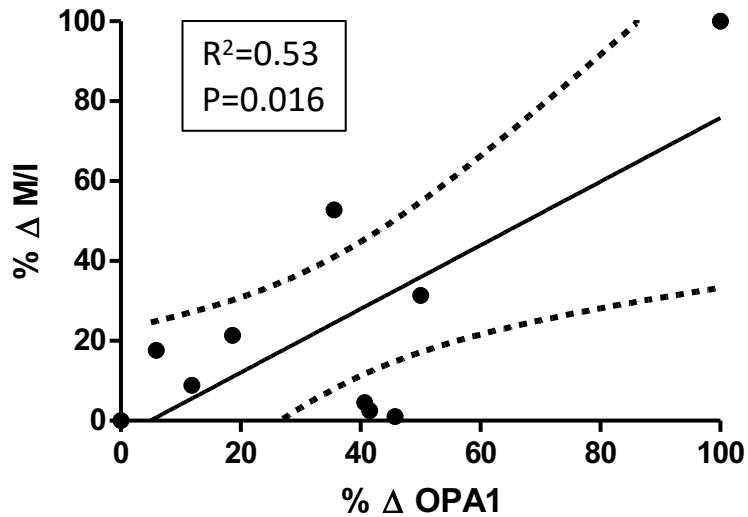


Exercise Training Improves Mitochondrial Dynamics

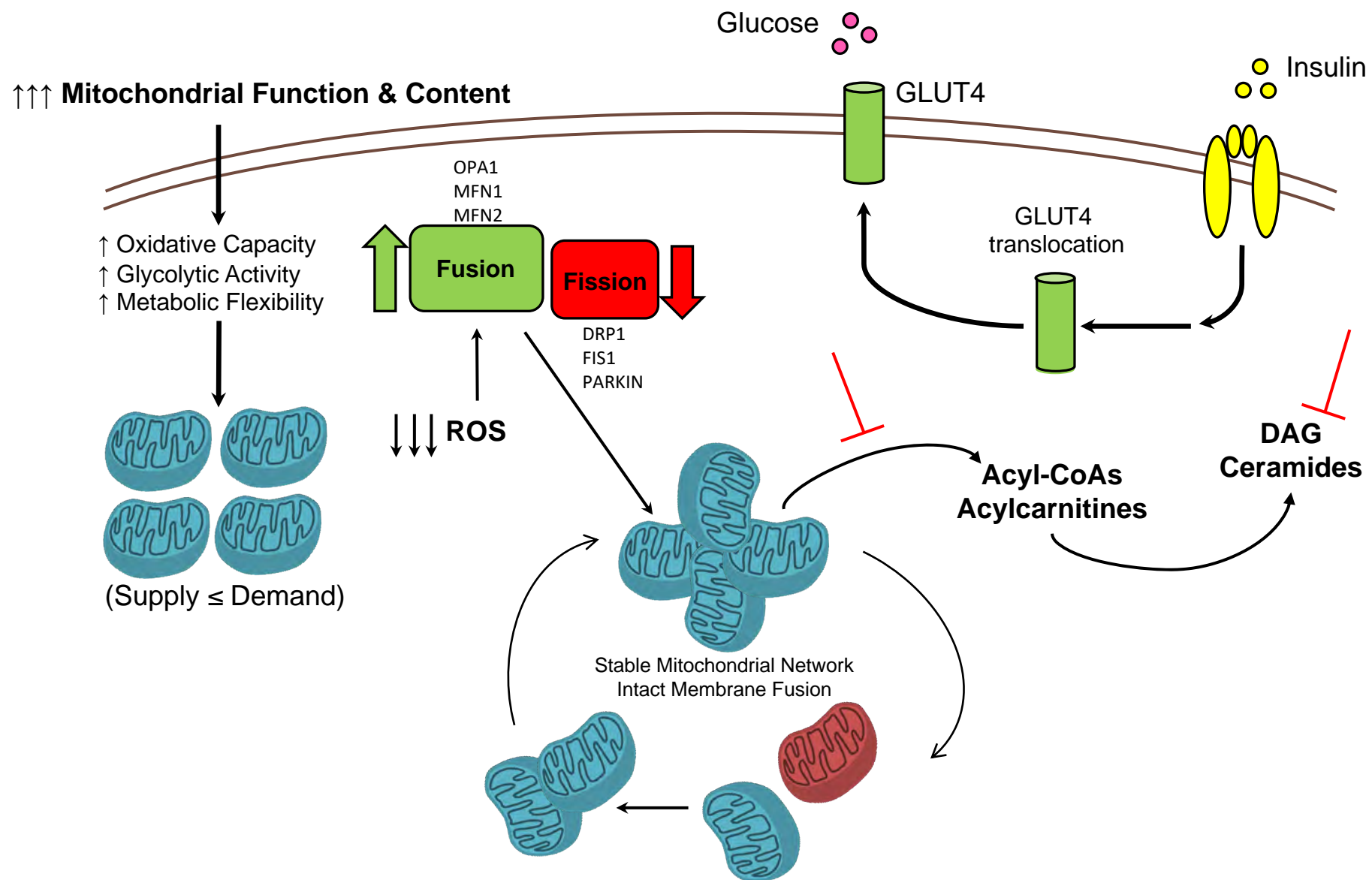


Representative immunoblots of regulators of mitochondrial dynamics from human skeletal muscle tissue. ± indicates either pre (-) or post (+) exercise training. Quantification of protein expression expressed as fold induction relative to pre-intervention corrected to loading control (HSC70).

Mitochondrial Dynamics & Insulin Sensitivity



Exercise Energetics and Type 2 Diabetes: Possible Mechanism



Implications

Targeting of novel proteins and pathways regulating glucose metabolism

- Development of pharmacologic interventions
- Development of therapeutic treatments



Kirwan Lab Research Team

Staff Scientists/Fellows/Grad Students/Residents

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Anny Mulya, Ph.D.

Gustavo Heresi, M.D.

Takhar Kasumov, Ph.D.

Mangesh Pagadela, M.D.

Juan Pablo del Rincon, M.D.

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Hanna Huang, CWRU Ph.D. Student

Adithya Hari, CWRU Ph.D. Student

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Thomas Solomon, Ph.D.

Jacob Haus, Ph.D.

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Emily Louis, Ph.D.

Steve Malin, Ph.D.

Melissa Erickson, Ph.D.

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Emily Huang - Lead Technologist

Debbie Paul- Research Assistant

CTSA Clinical Research Unit Team

CTSA Core Labs and Metabolic Kitchen



Key Collaborators

Art McCullough, Digestive Disease Institute, CCF, Cleveland

Chris Flask, Radiology, CWRU, Cleveland

Phil Schauer - Bariatric Metabolic Institute, CCF, Cleveland

Sangeeta Kashyap - Endocrinology Institute, CCF, Cleveland

Stacy Brethauer - Bariatric Metabolic Institute, CCF, Cleveland

Alastair Ross – Nestle Research Center, Lausanne

Jean-Philippe Godin – Nestle Research Center, Lausanne

Hope Barkoukis - Nutrition, CWRU, Cleveland

Richard Watanabe - Preventive Medicine, USC, Los Angeles

Patrick Catalano - Reproductive Biology, MHMC/CWRU, Cleveland

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