Borer Lecture - University of Michigan

September 2017

Exercise as a Regulator of Endocrine Dysfunction in Type 2 Diabetes

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Professor, Division of Kinesiology
Department of Movement Science
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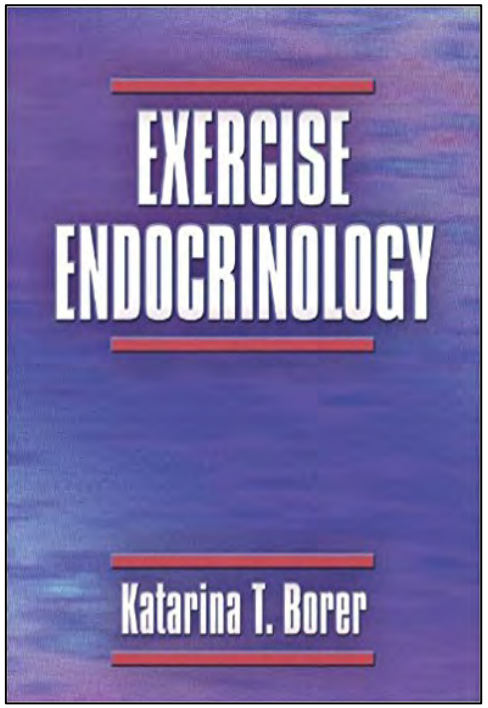
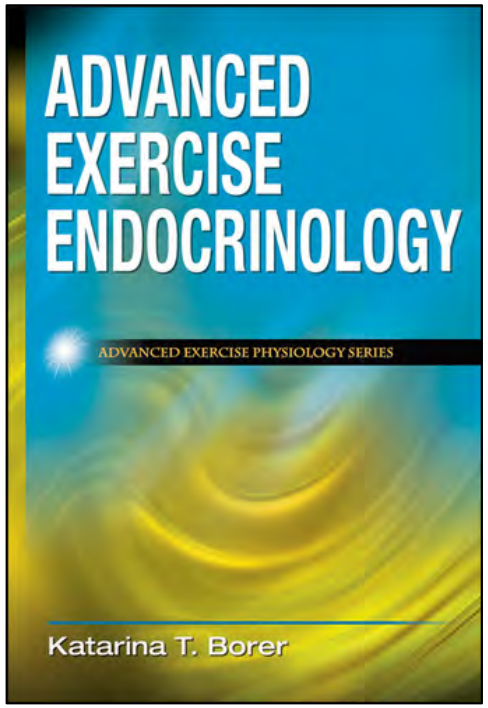
Seminal contributions to exercise, energy regulation, and bioenergetics



2003

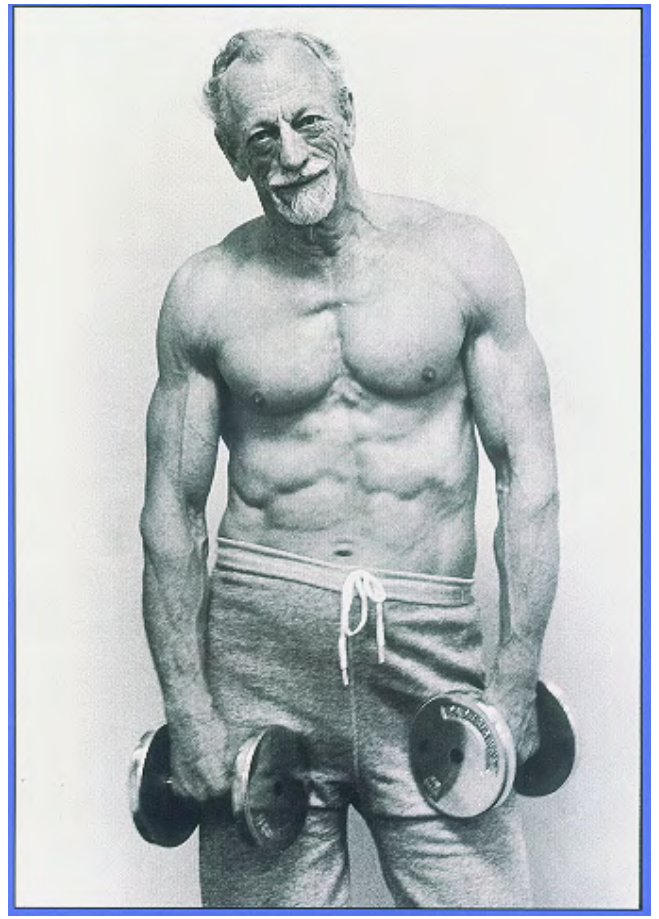


2013

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

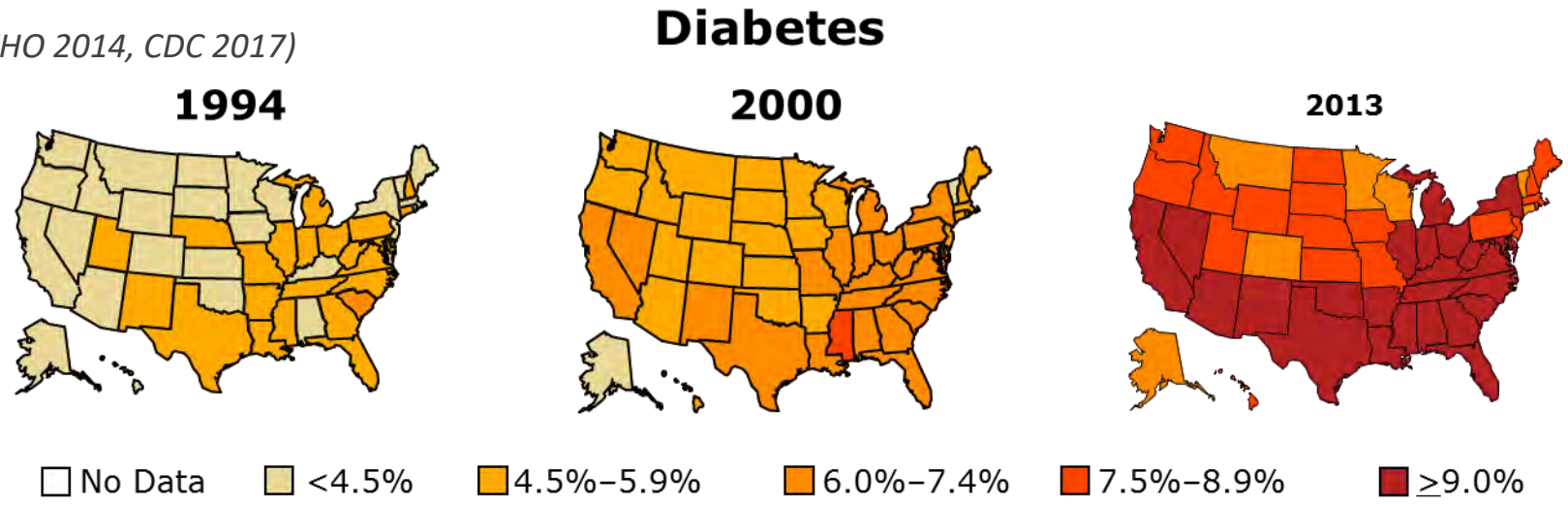
Type 2 Diabetes (T2D) >90%

1980 - 108 million (4.7%) – Global

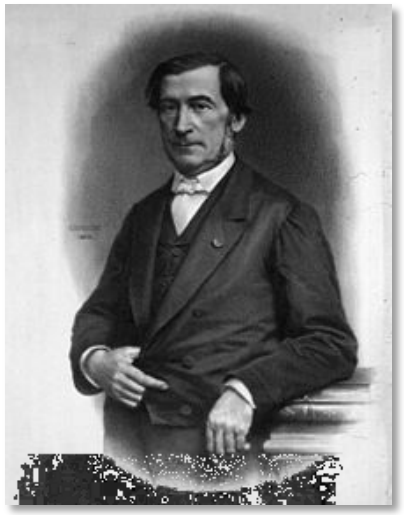
2014 – 422 million (8.5%) – Global

USA 2017 - 30.3 million (9.4%)

(WHO 2014, CDC 2017)

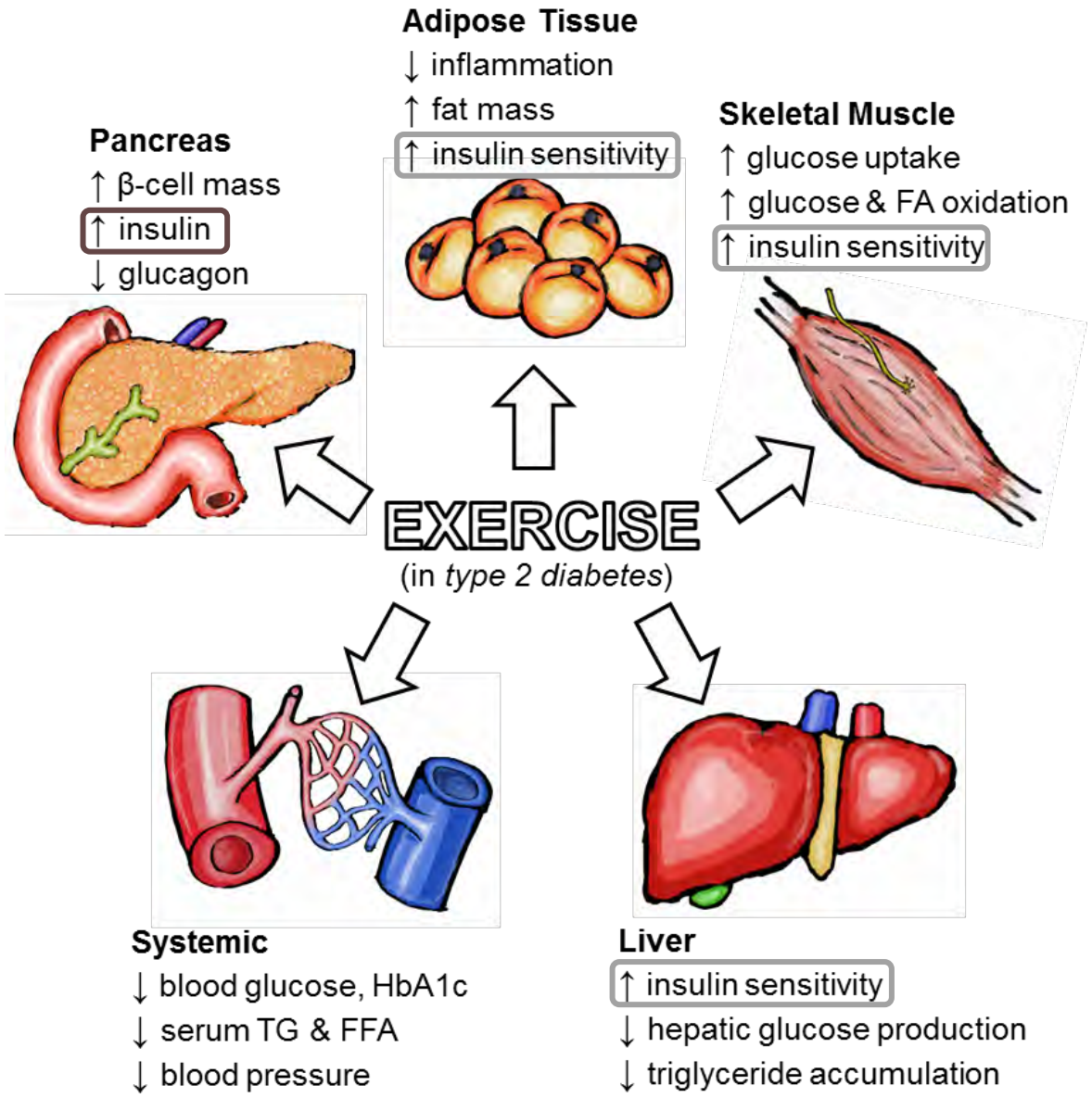


(CDC's Division of Diabetes Translation, National Diabetes Surveillance System)



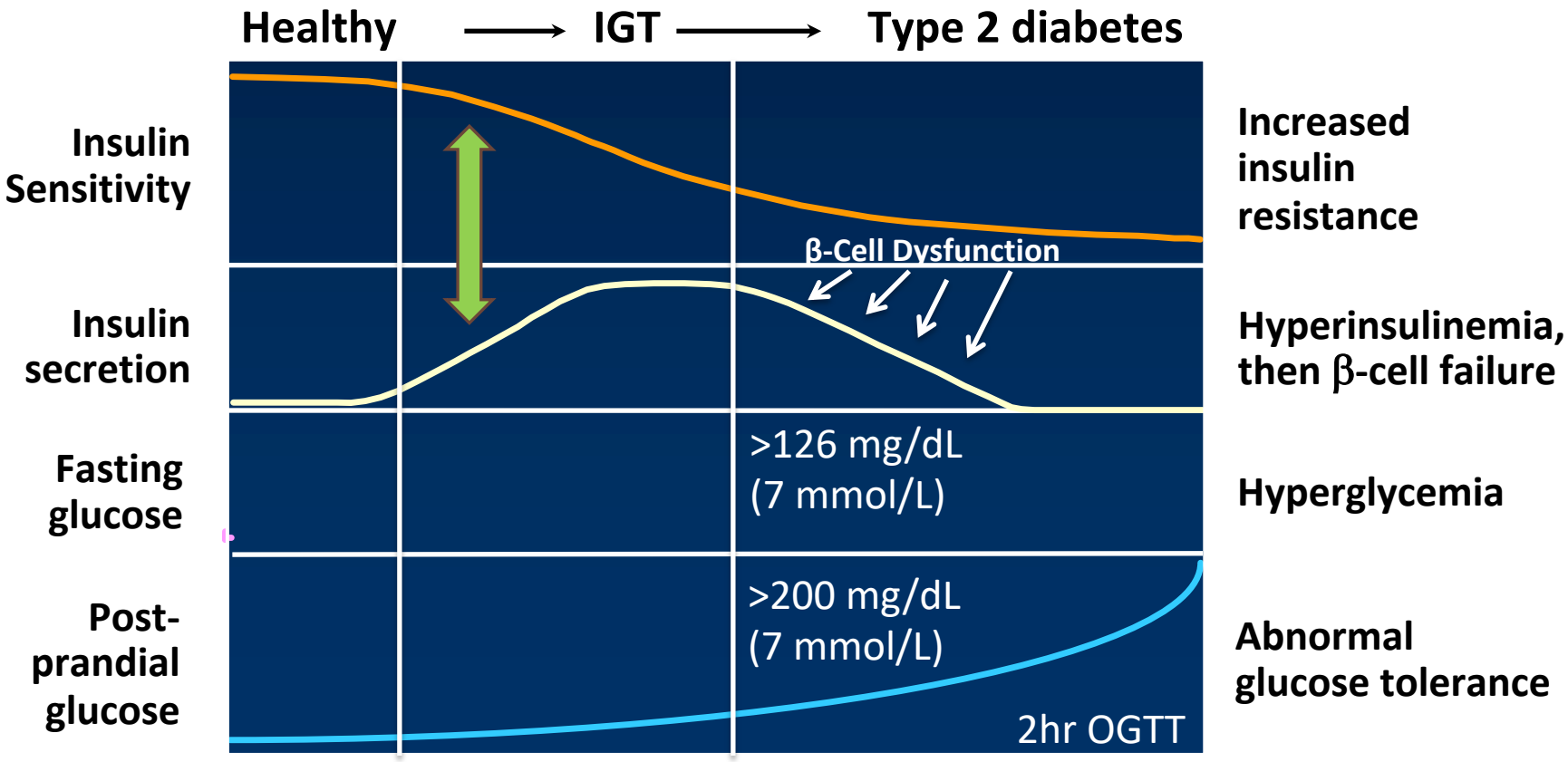
Apollinaire Bouchardat
(1809 – 1886)

"You shall earn your bread by the sweat of your brow."



(Kirwan et al., 2017)

Pathophyisology 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

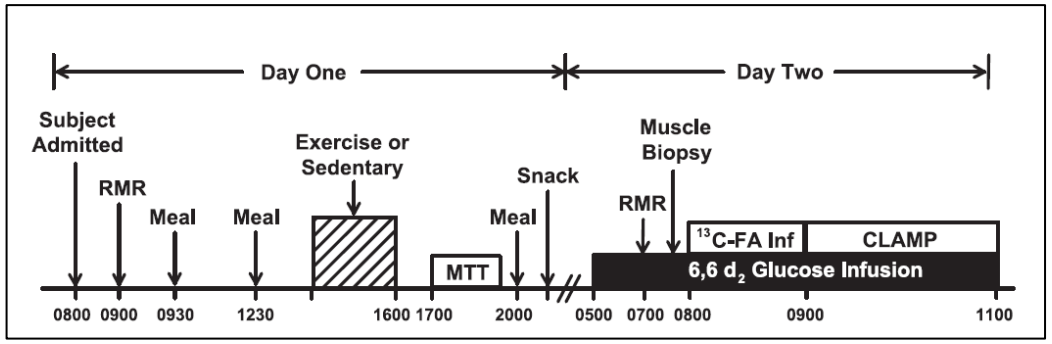


Figure 1. Study design.

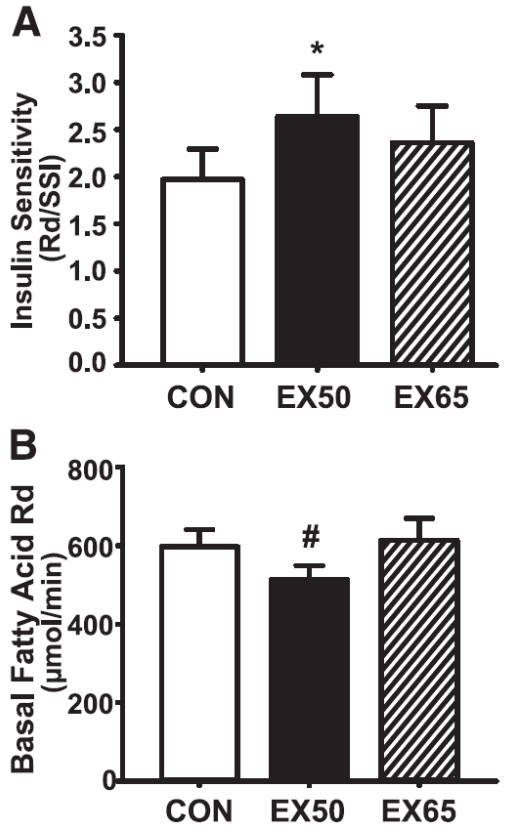
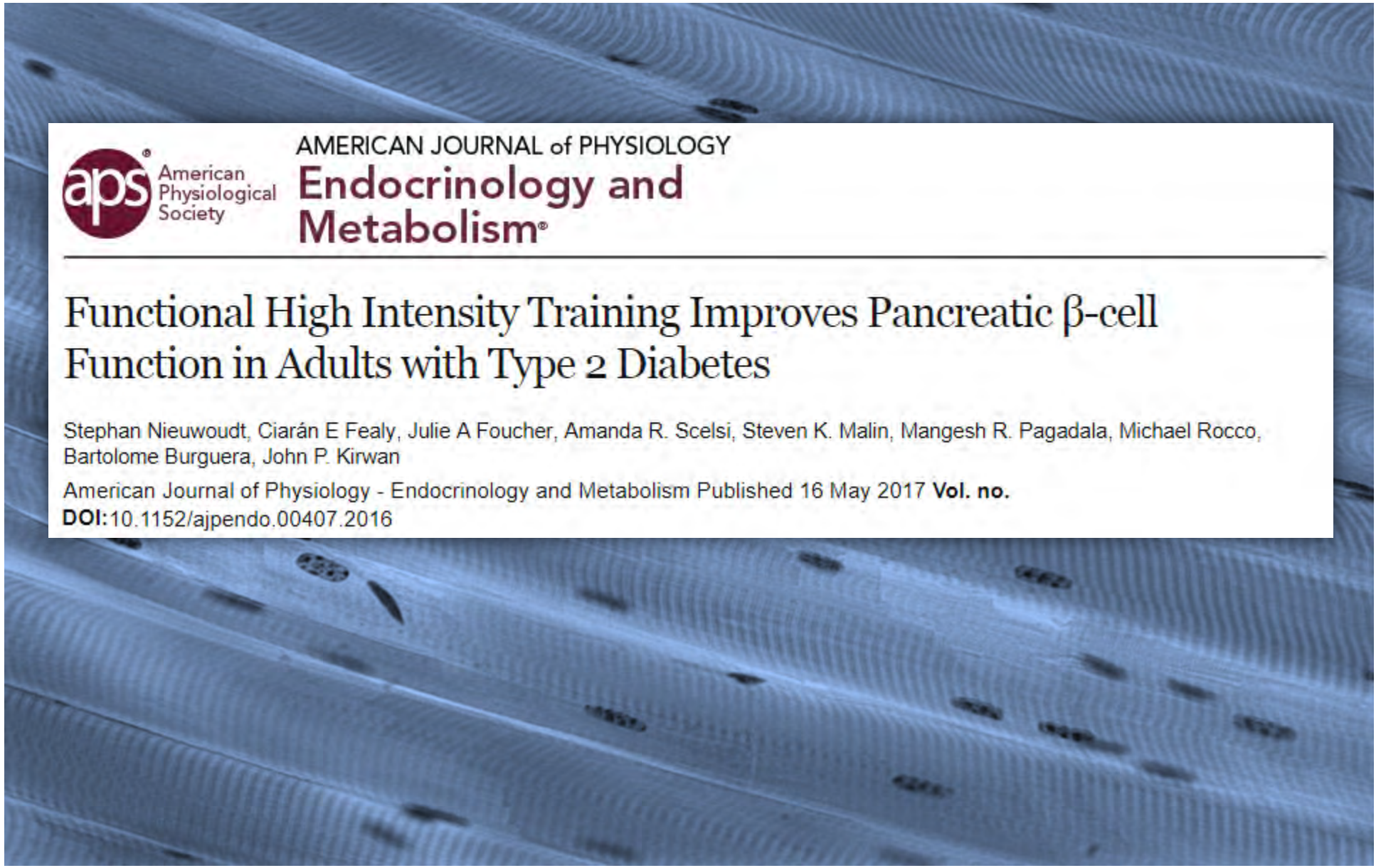


Figure 2. Changes in (A) insulin sensitivity and (B) fatty acid uptake after exercise at 50% (EX50) and 65% (EX65) of VO_{2MAX}.



AMERICAN JOURNAL of PHYSIOLOGY
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

Am J Physiol Endocrinol Metab 287: E1024–E1031, 2004.
First published July 13, 2004; doi:10.1152/ajpendo.00056.2004.

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]

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

P90X®

INSANITY™

orangetheory® FITNESS

CrossFit®

"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)**

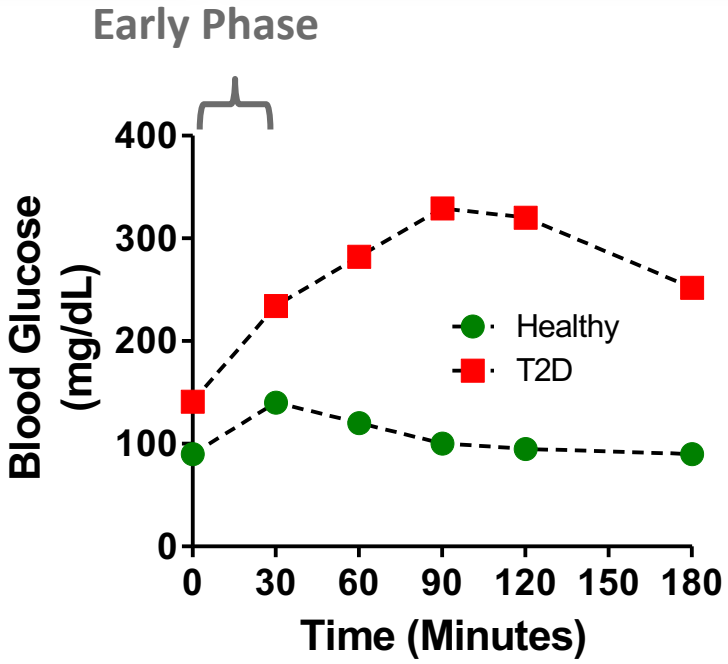
How to measure β-cell function?

Insulin Secretion on the Background of Insulin Sensitivity

β-Cell Function = **Insulin Secretion** x **Insulin Sensitivity**

- Disposition Index

Oral Glucose Tolerance Test (OGTT)



Secretion Index = ΔInsulin/ΔGlucose
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

PRE — **POST**

CrossFit®

6 weeks, 3 days/week

Body Composition (DXA)
Oral Glucose Tolerance Test
Performance and VO_{2max}

Body Composition (DXA)
Oral Glucose Tolerance Test
Performance and VO_{2max}

Blood Analysis

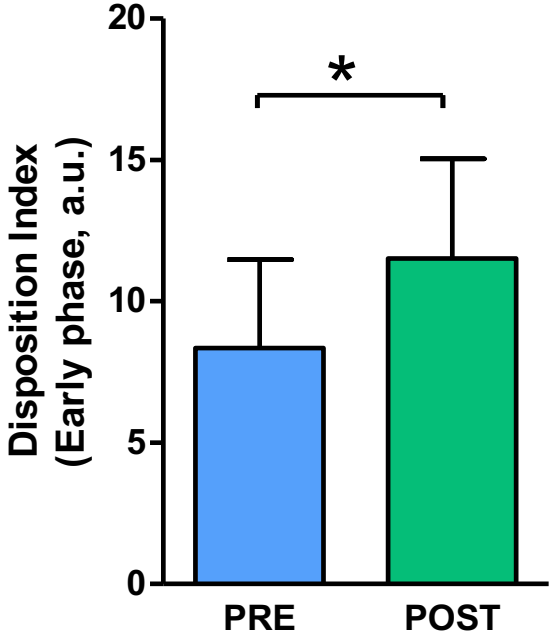
Glucose, Pancreatic Hormones
Liver Enzymes, Gut Hormones

CrossFit Training Results

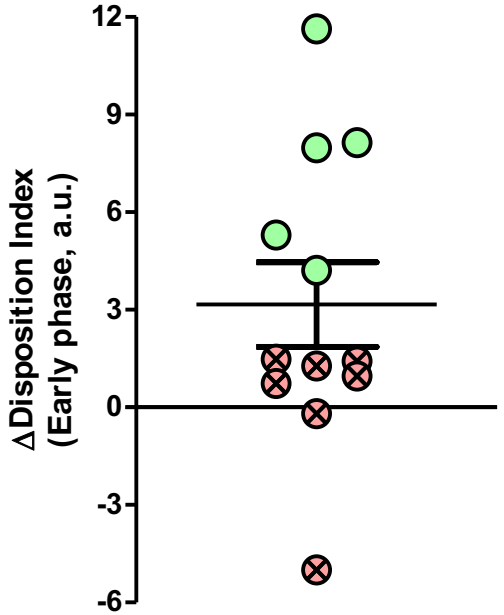
	PRE	POST	Δ	P-value
n (M/F)	12 (5/7)			
Age, years	54 ± 2			
Body composition				
Body weight, kg	98.0 ± 3.7	96.1 ± 2.7	-1.8 ± 1.0	0.09
Total fat, %	43.6 ± 1.8	42.5 ± 1.8	-1.1 ± 0.3	0.002*
Abdominal fat,%	56.2 ± 1.8	55.3 ± 1.7	-0.9 ± 0.7	0.22
Physical performance				
VO_{2max}, L/min	2.43 ± 0.12	2.81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

CrossFit Training Results

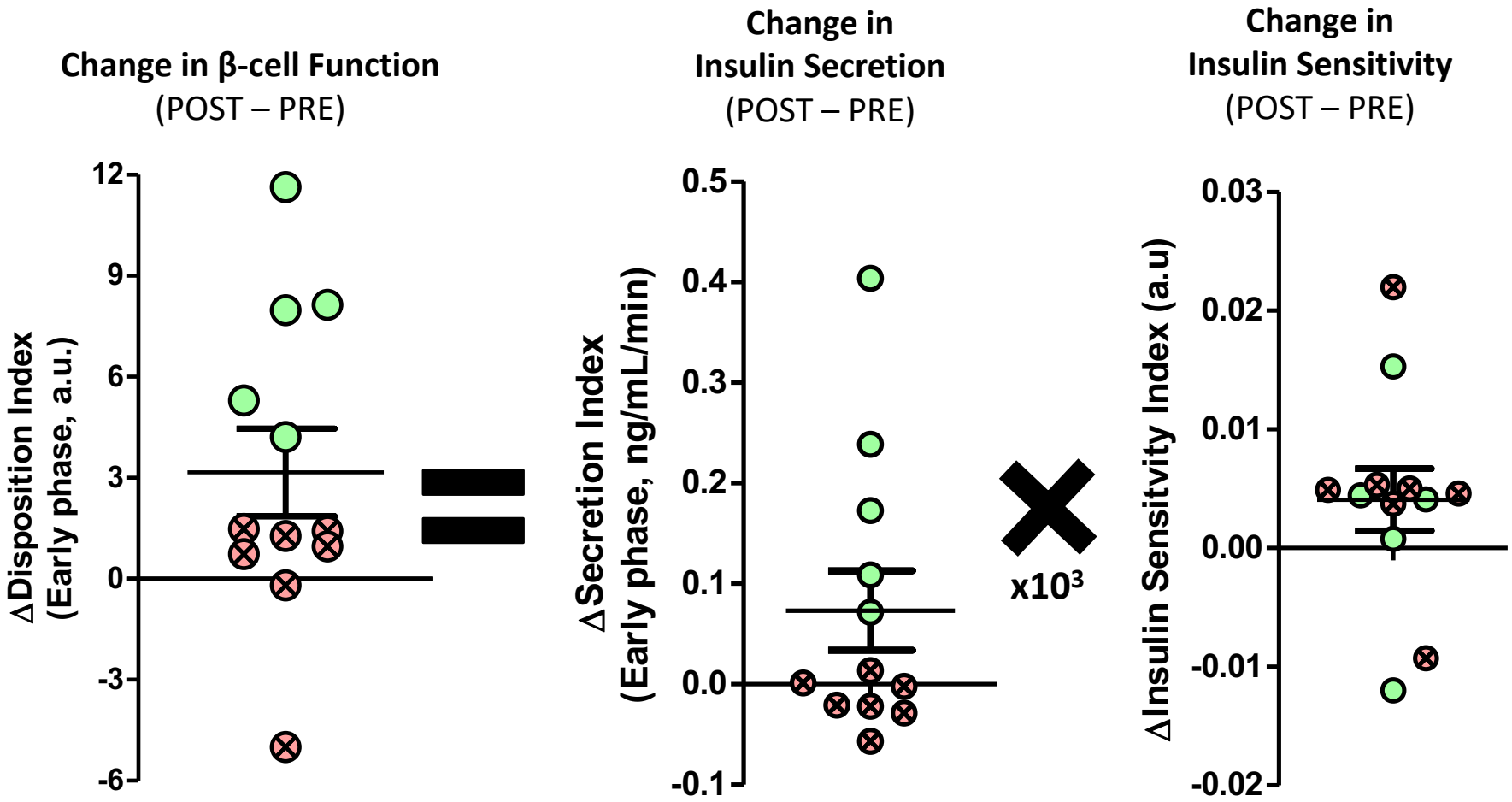
Disposition Index



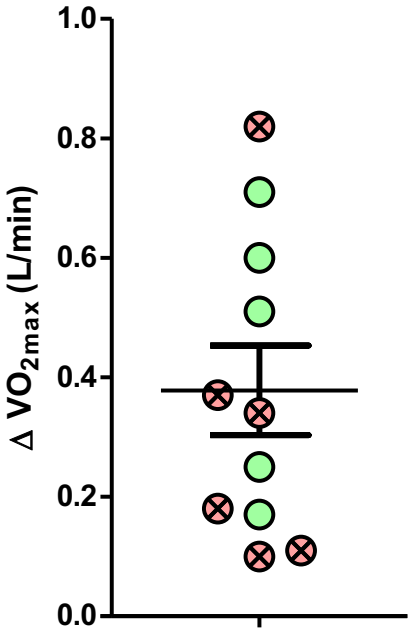
Delta Disposition Index

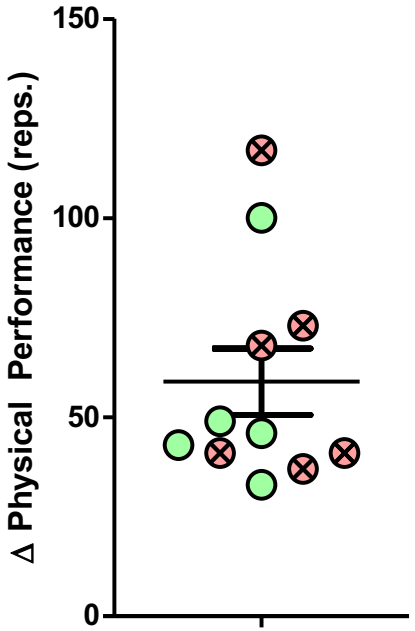


CrossFit Training Results



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*

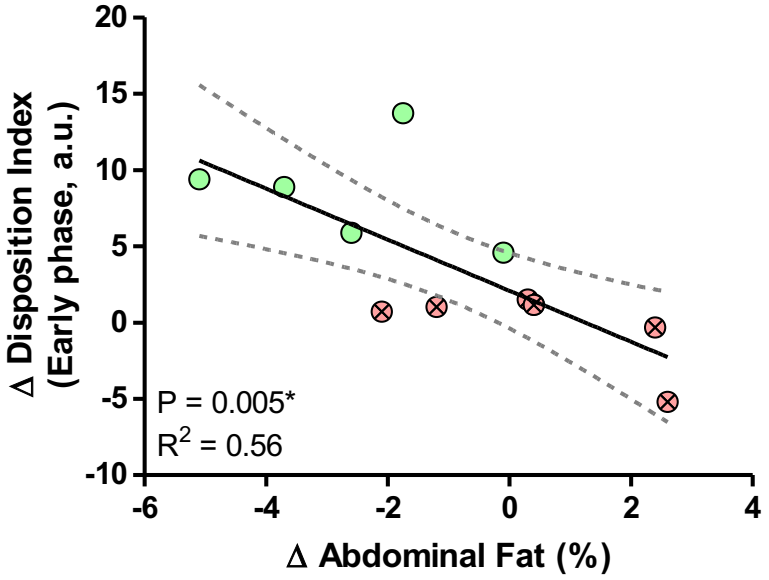




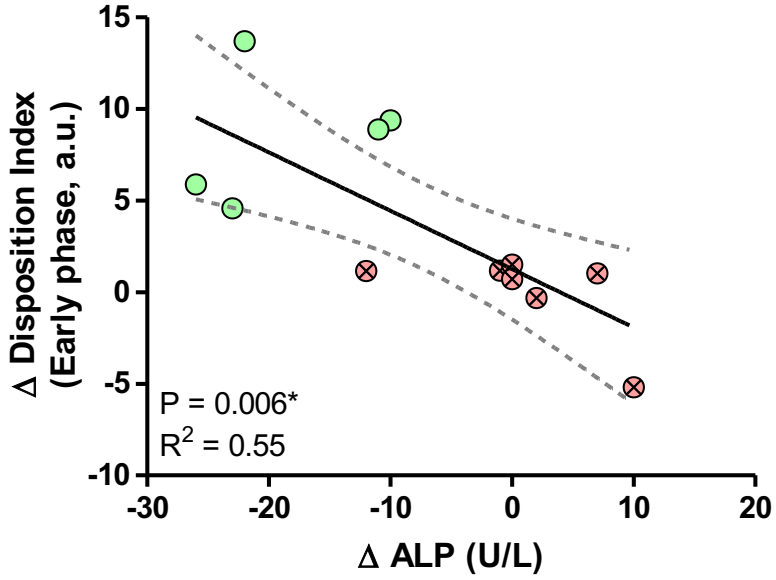
Correlations with β-Cell Function

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

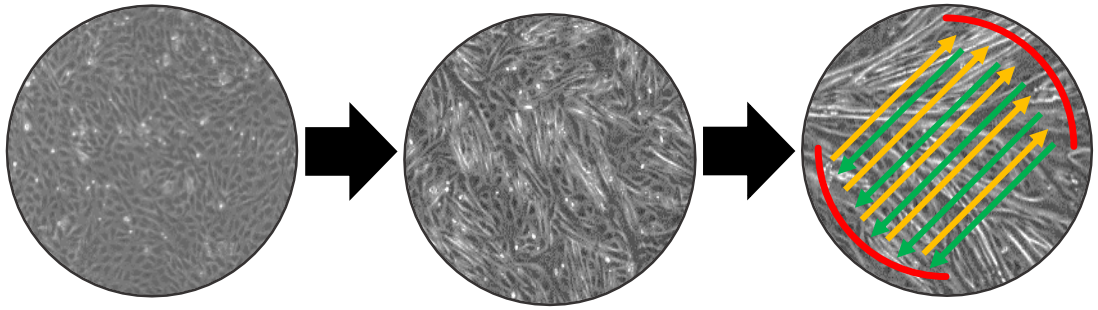
Improvements in function correlate with reduced **Abdominal Fat** and **ALP**

*Responders vs. Non-responders
- Severity of Diabetes

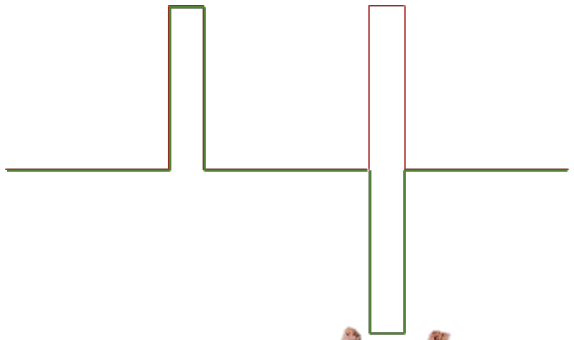
Limitations
- Molecular Mechanisms
- Isolate the function of exercise alone

Exercise in a Petri Dish Model

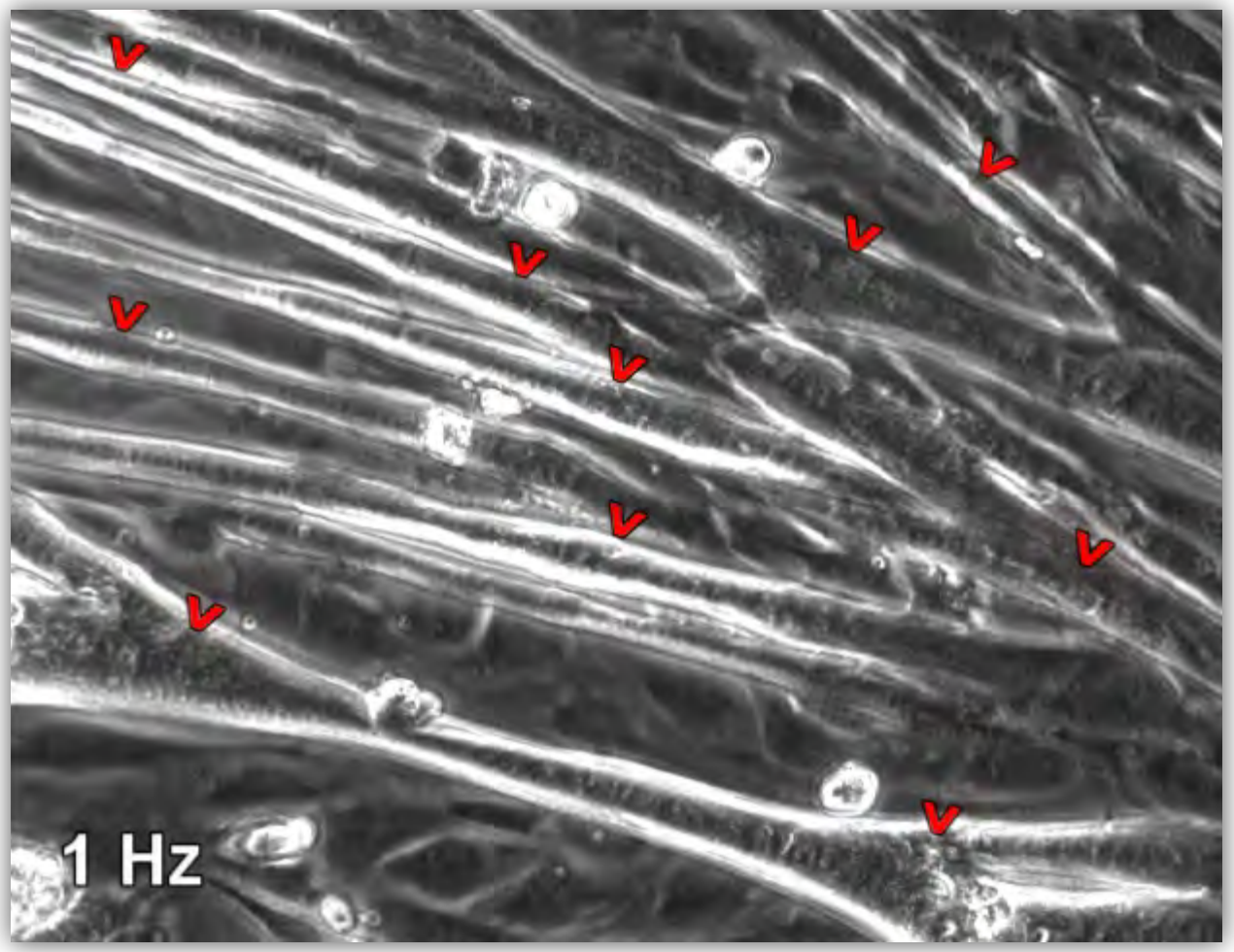
Muscle cells
- C2C12 myocytes
- Differentiation

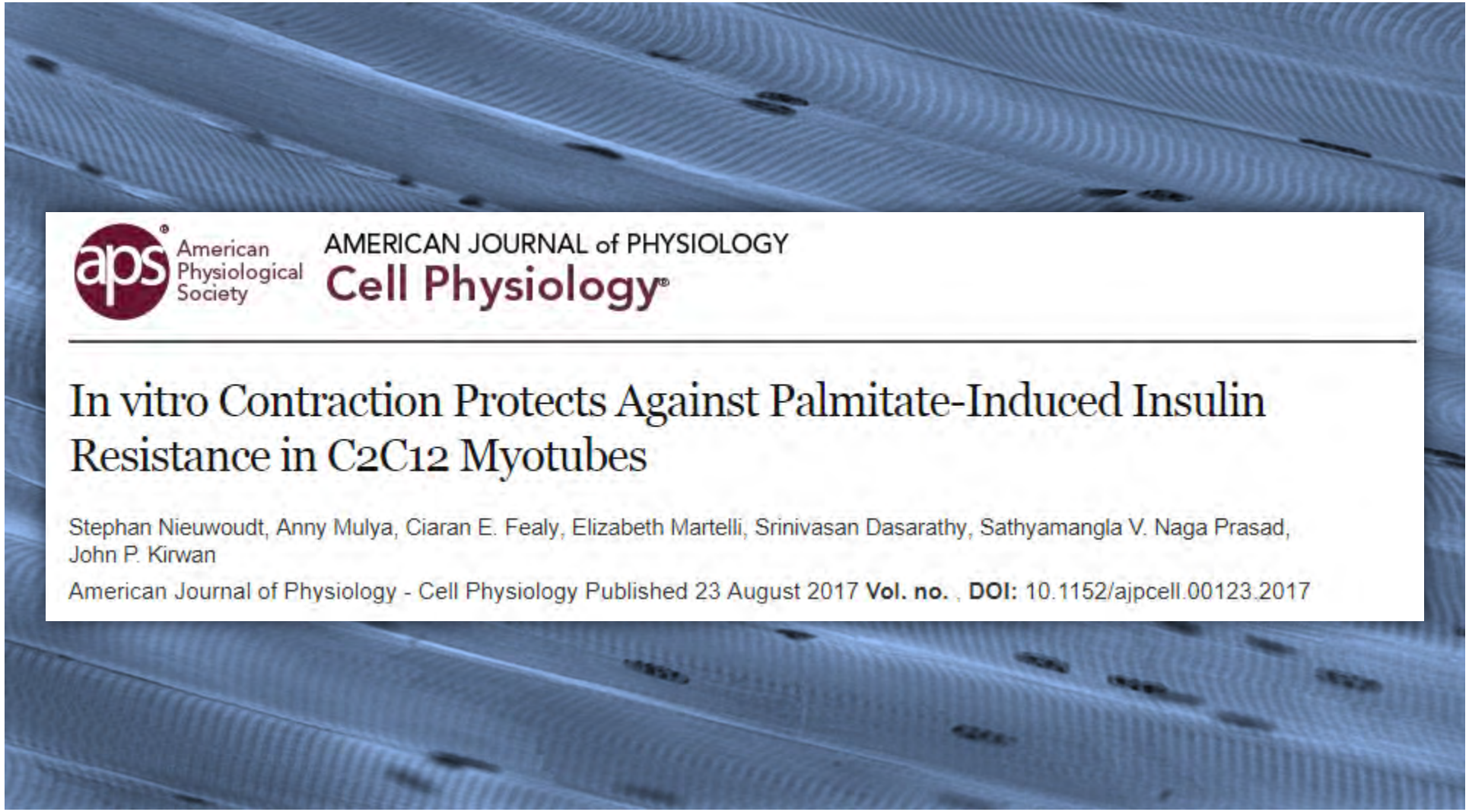


Electrical Pulse Stimulation (EPS)
- Electrodes (Platinum) → Electrical Field
- Electrophoresis
  - Polarity switching



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

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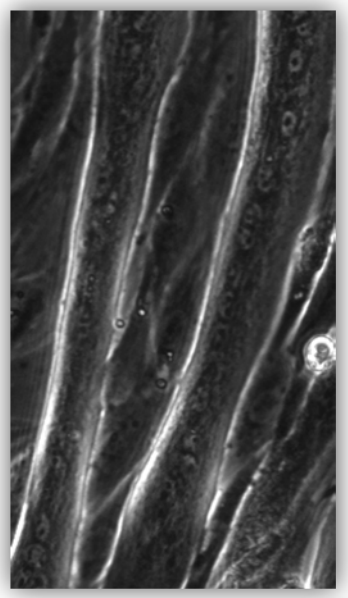

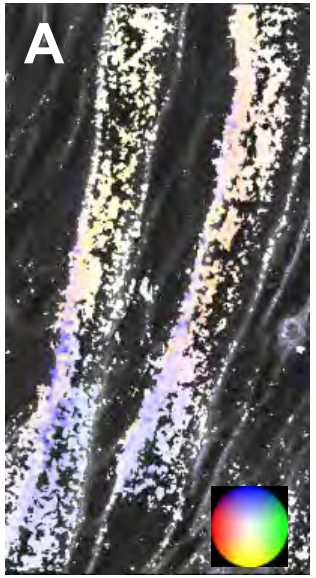
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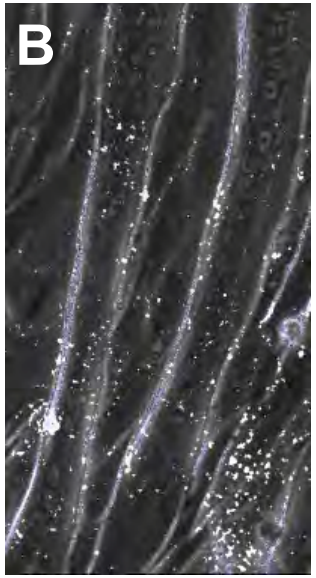
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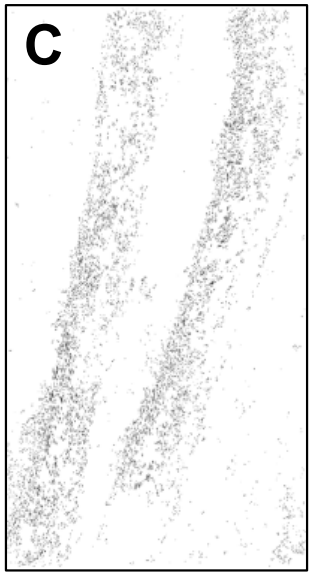
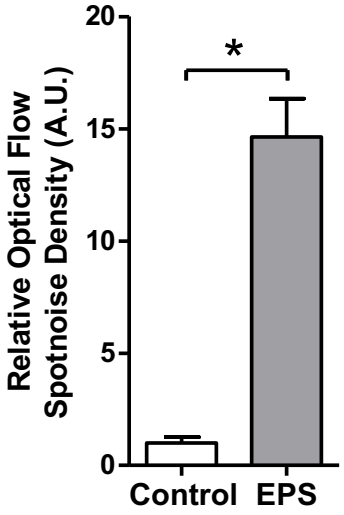
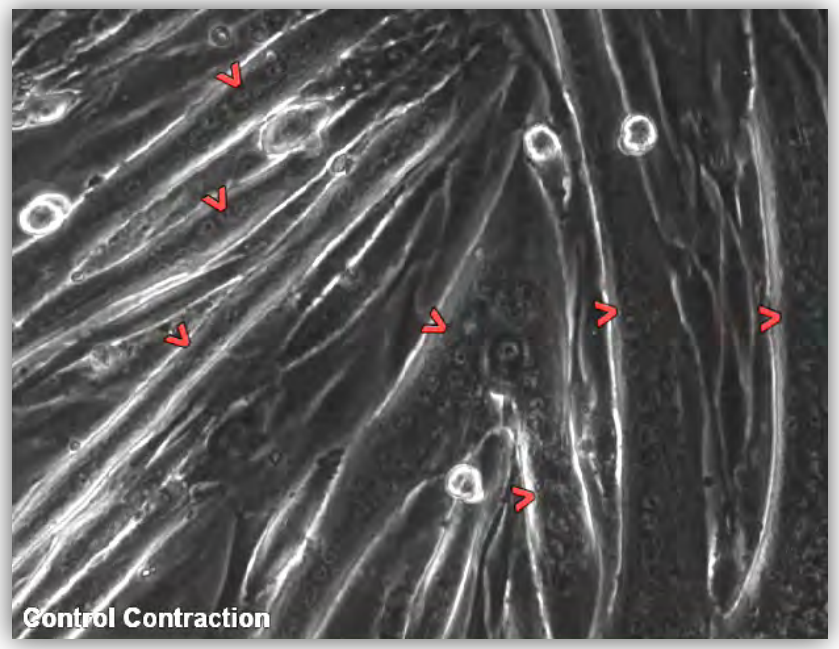
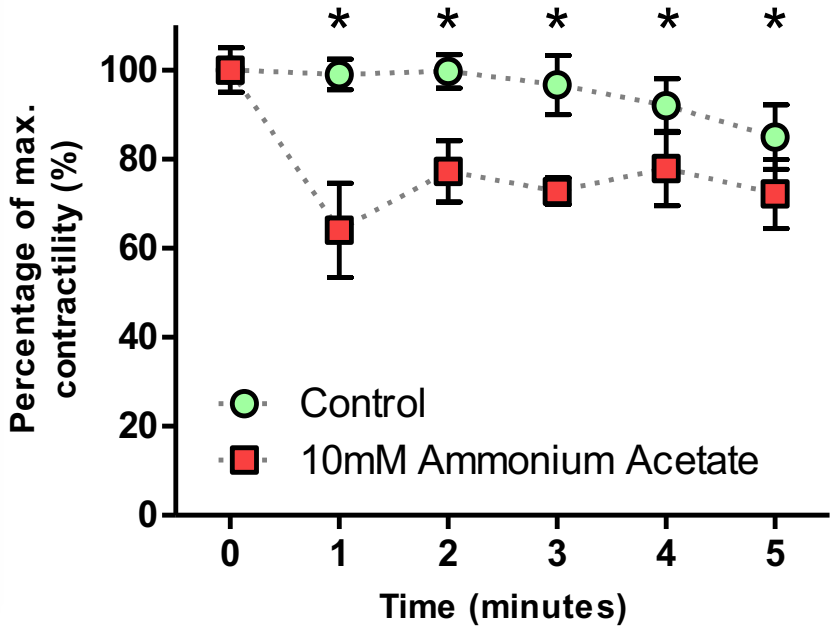

C

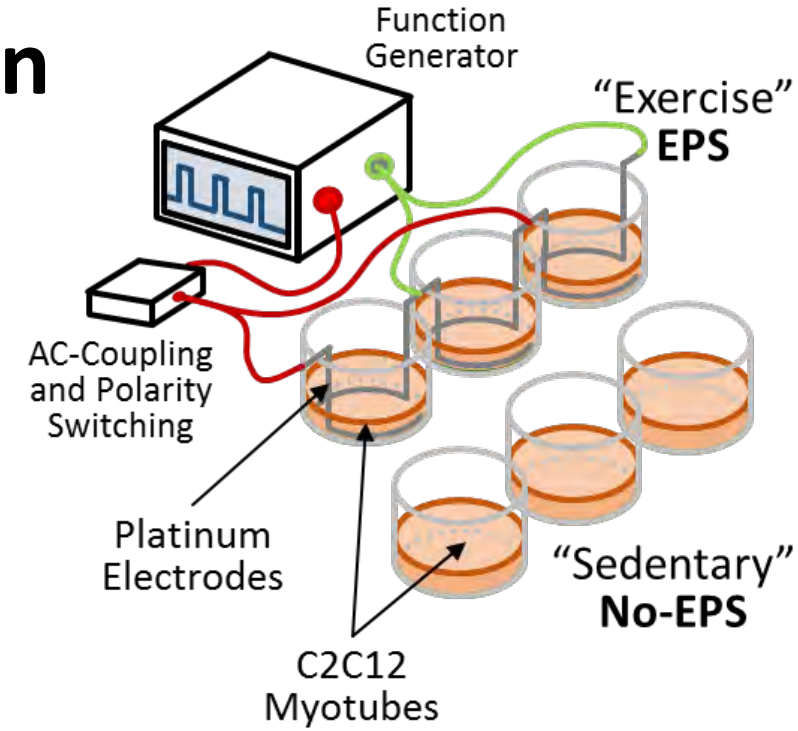

D

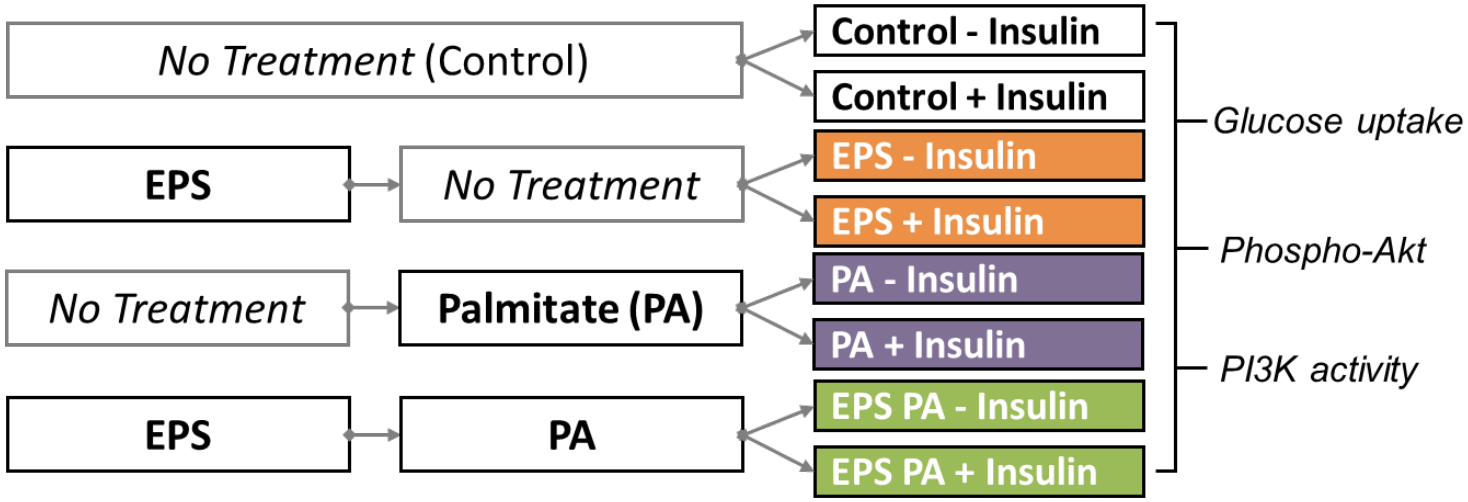

Relative Optical Flow Spotnoise Density (A.U.)
20
15
10
5
0
*
Control
EPS


Control Contraction

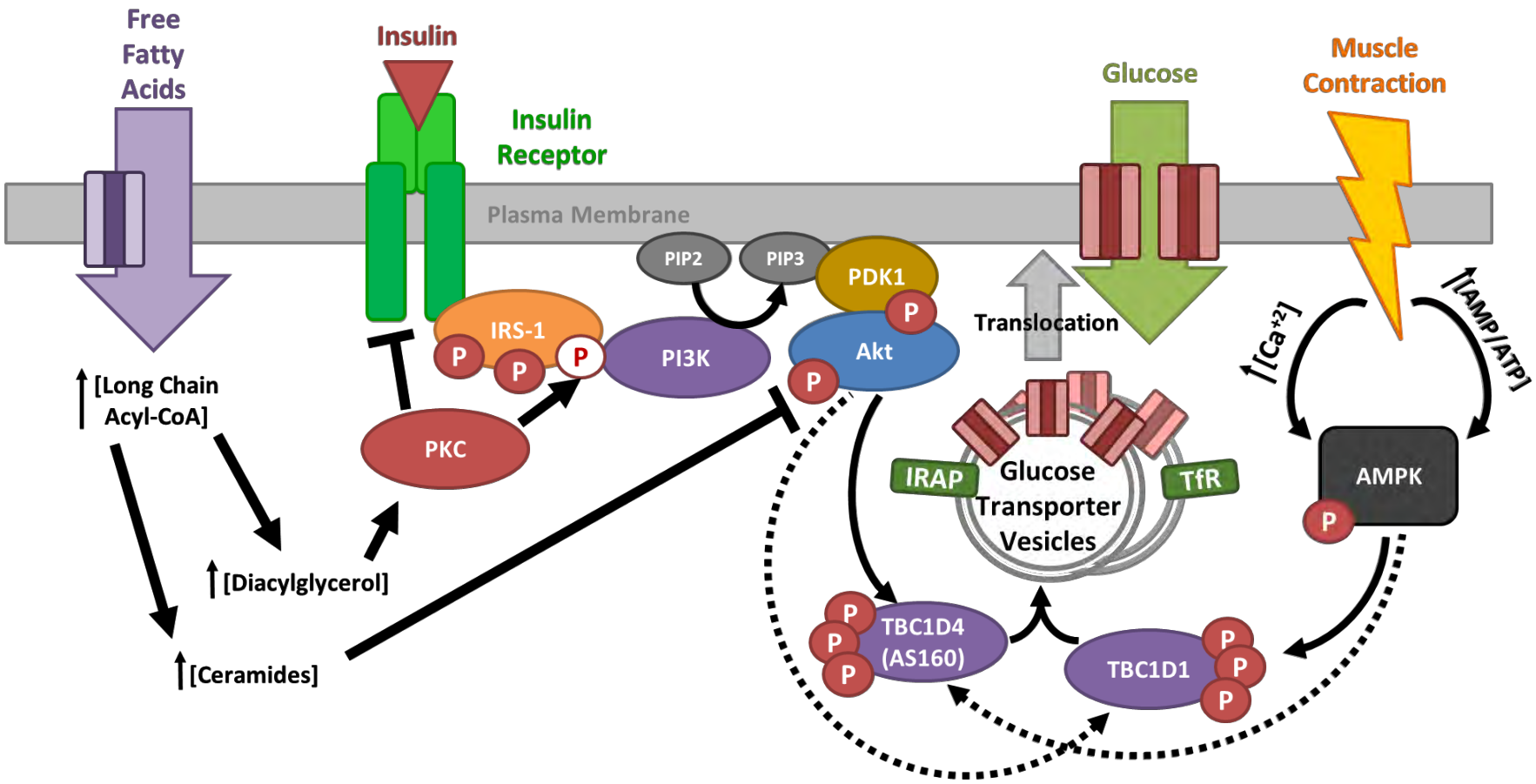

Percentage of max. contractility (%)
100
80
60
40
20
0
*
*
*
*
*
Control
10mM Ammonium Acetate
0
1
2
3
4
5
Time (minutes)

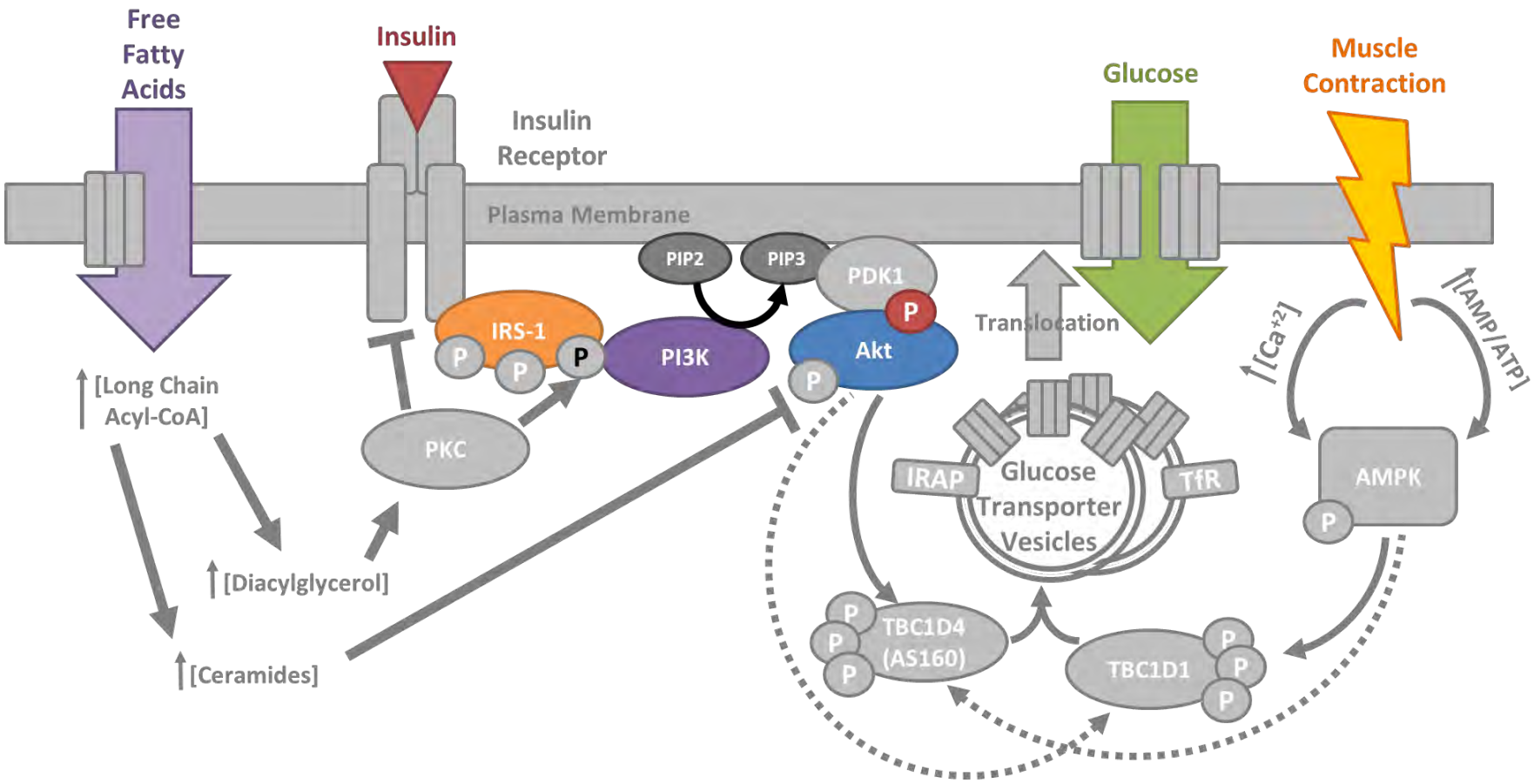
Experimental Design



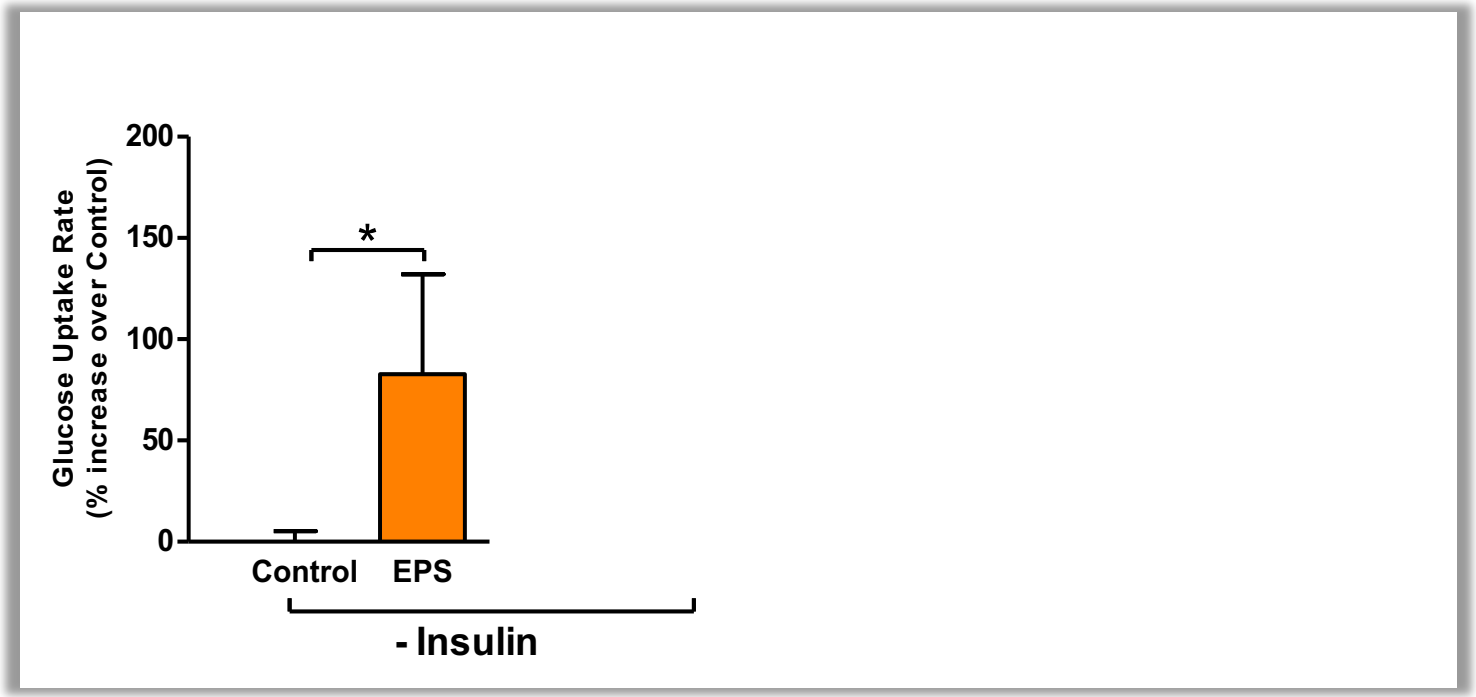


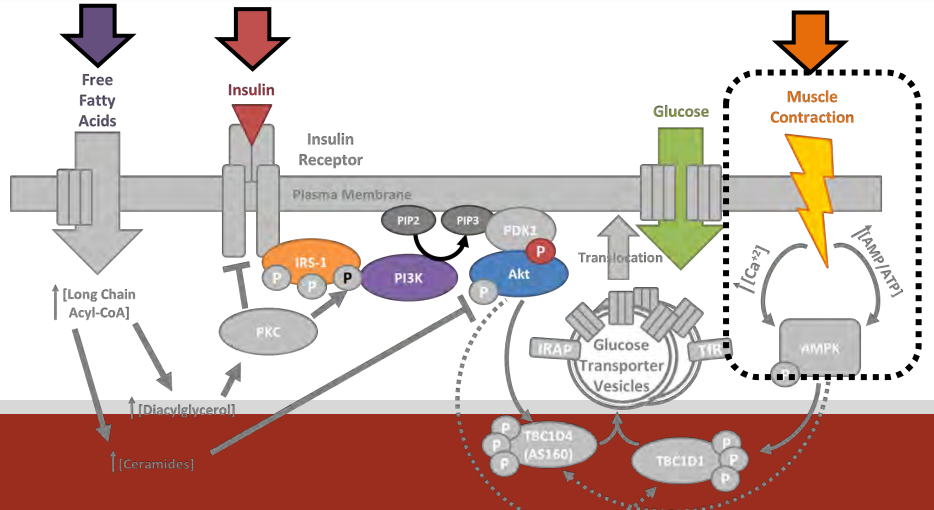
How Does Insulin Regulate Glucose Uptake



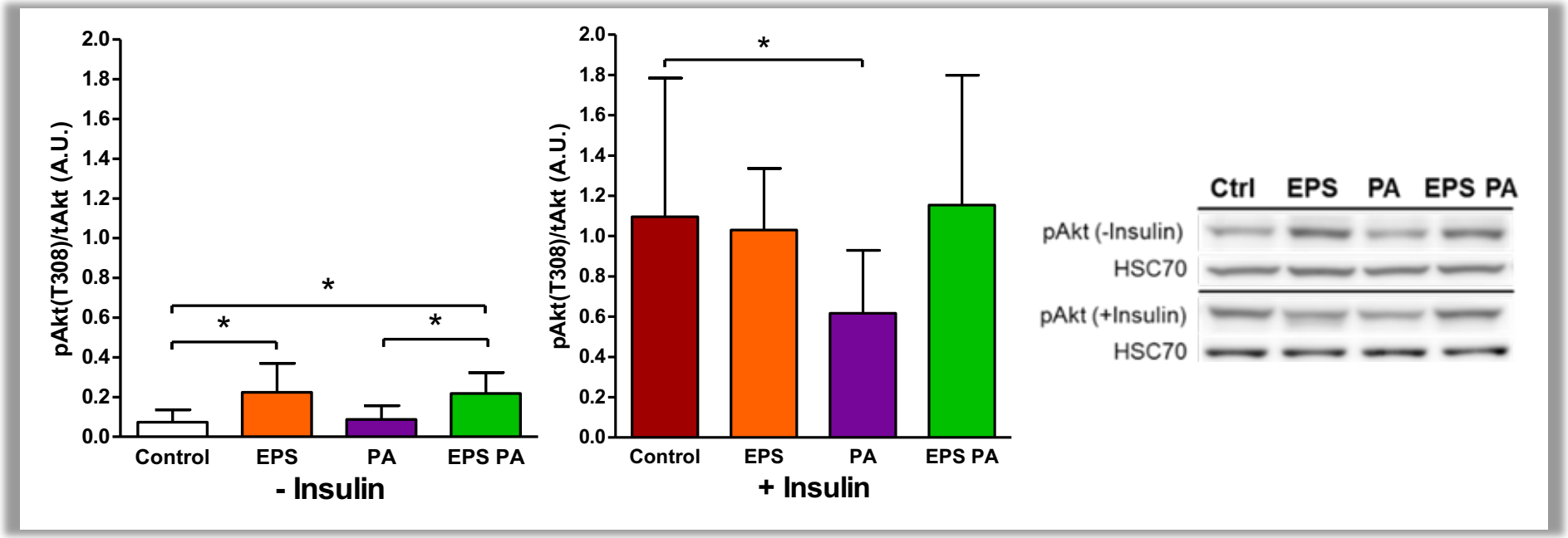

Free Fatty Acids
Insulin
Insulin Receptor
Plasma Membrane
Glucose
Muscle Contraction
PIP2
PIP3
PDK1
P
IRS-1
P
P
PI3K
Akt
P
Translocation
[Ca+2]
[AMP/ATP]
[Long Chain Acyl-CoA]
PKC
IRAP
Glucose Transporter Vesicles
TfR
AMPK
P
[Diacylglycerol]
P
P
P
TBC1D4 (AS160)
TBC1D1
P
P
P
[Ceramides]

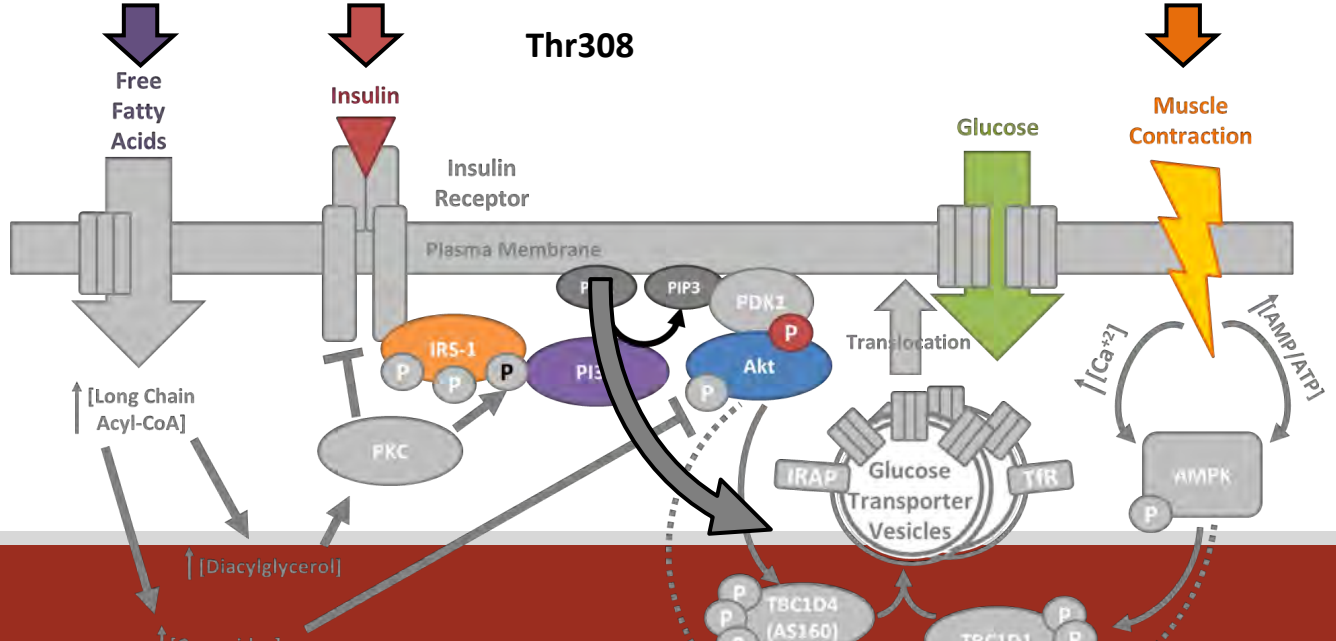
Contraction Model Validation
Glucose Uptake





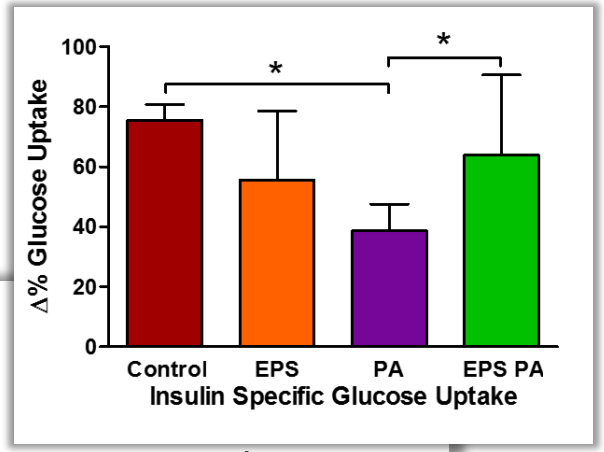
Contraction Model Validation - Akt Phosphorylation

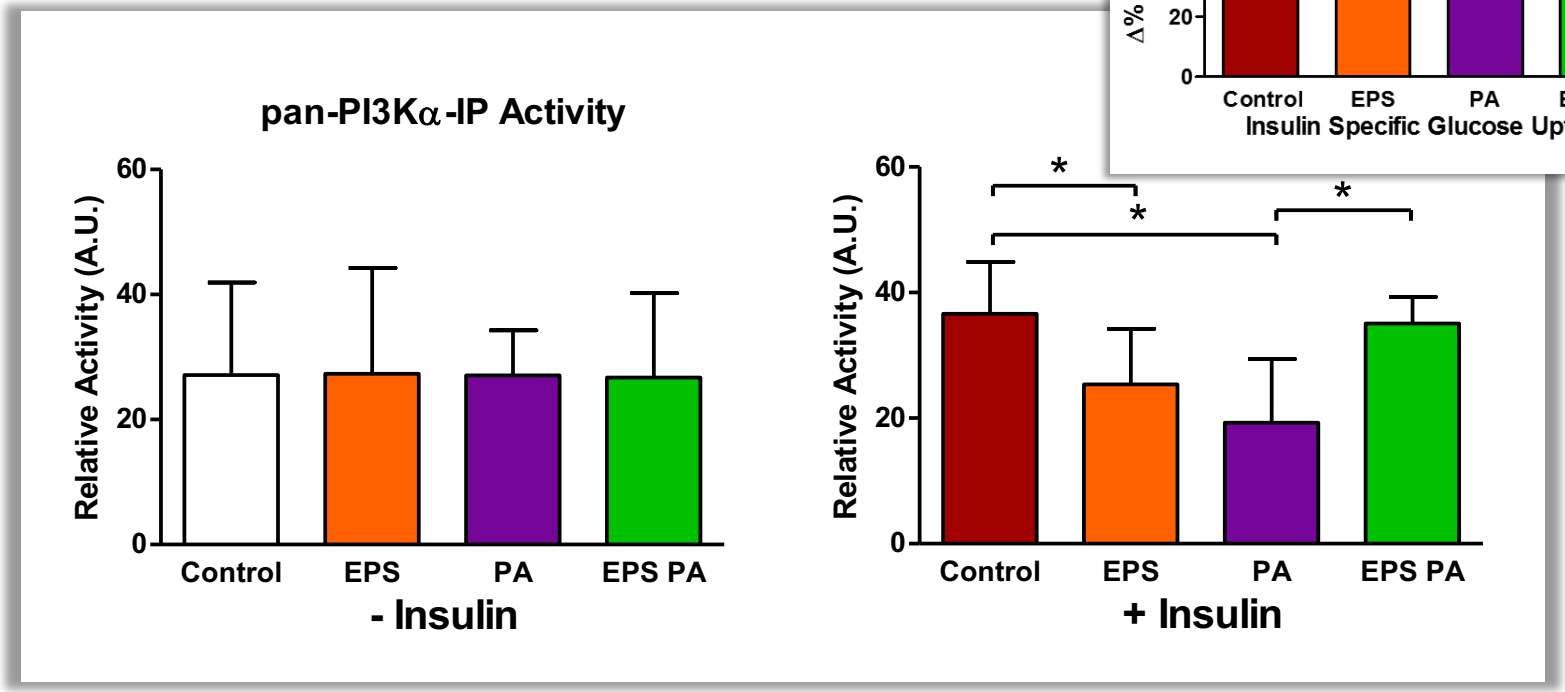


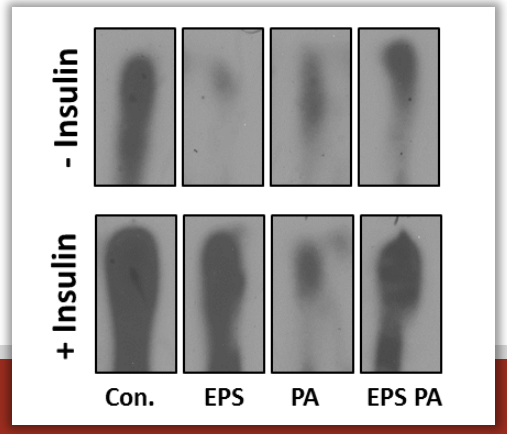


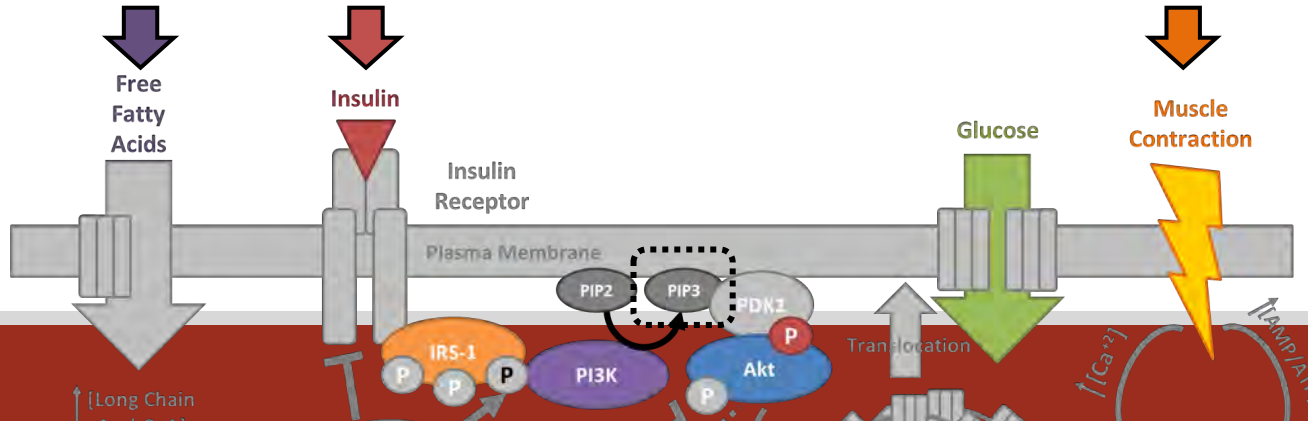
Contraction Model Validation

Whole-cell PI3K activity









Contraction Model Validation

Conclusions

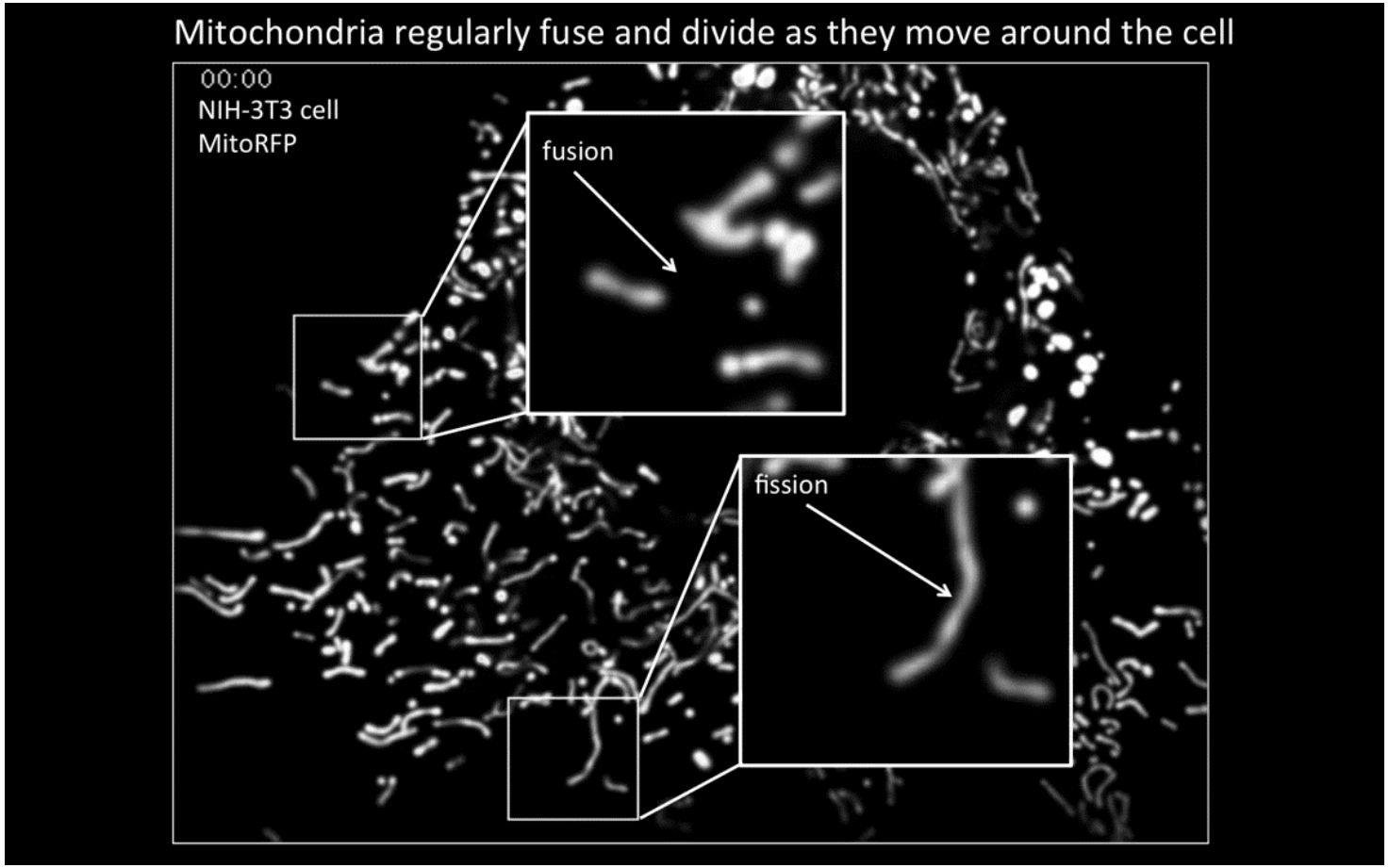
Model is validated by a known phenomenon

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?



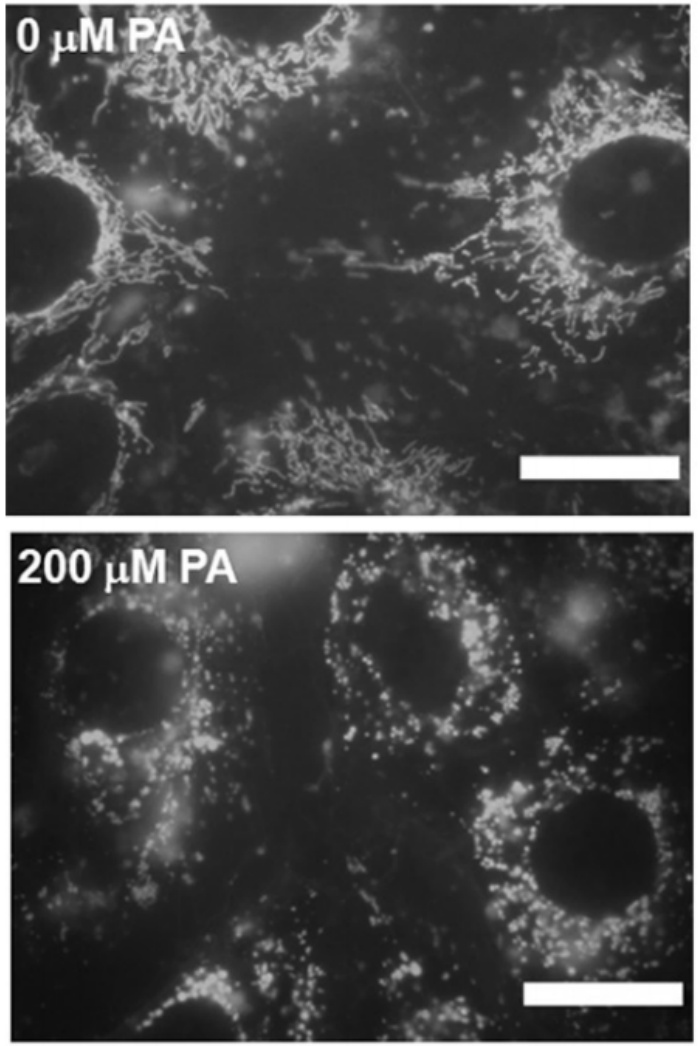
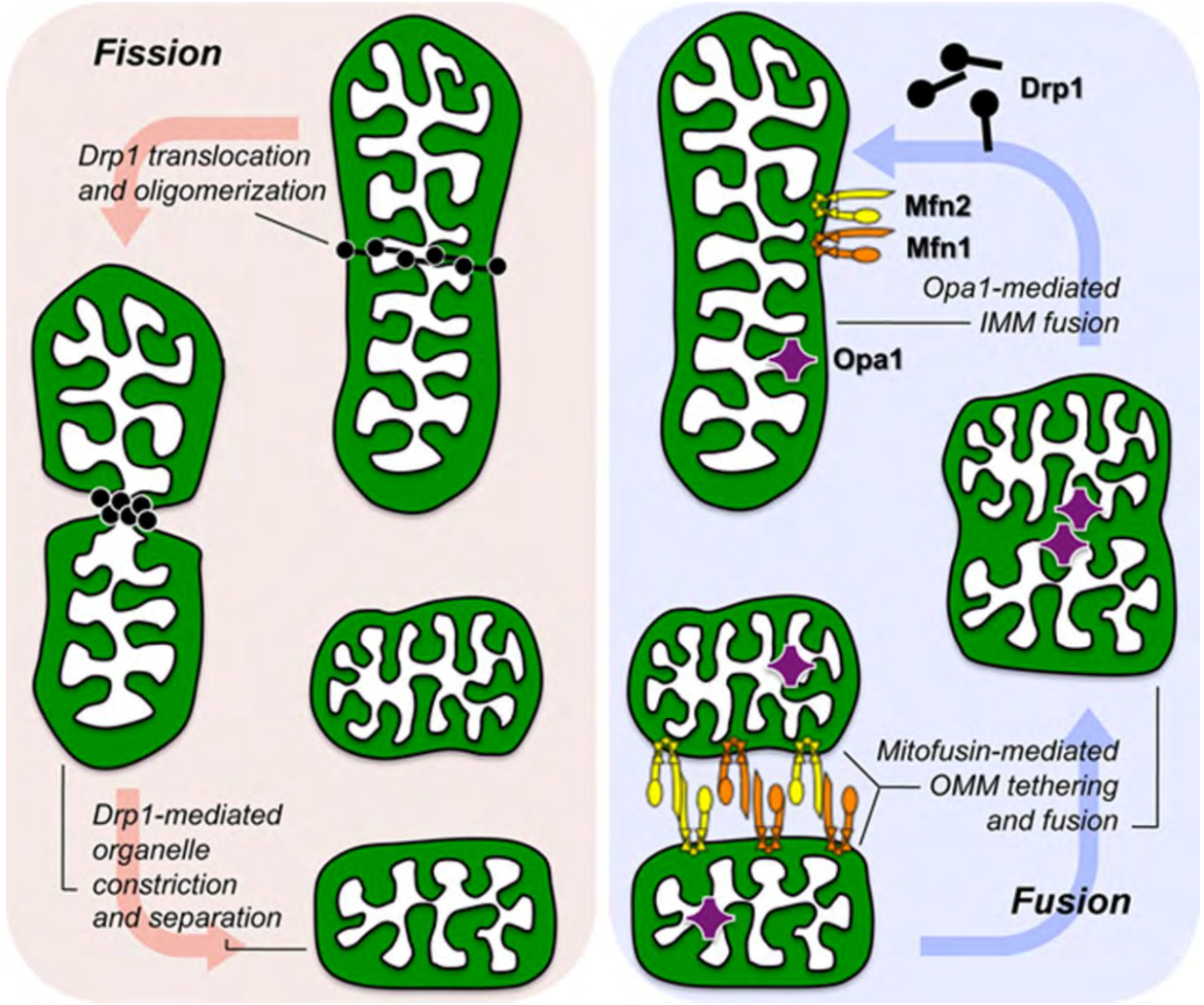


Figure 1. Treatment with PA induces mitochondrial fragmentation in C2C12 cells. Jheng et al. (2011)

Mitochondrial Dynamics: A Primer



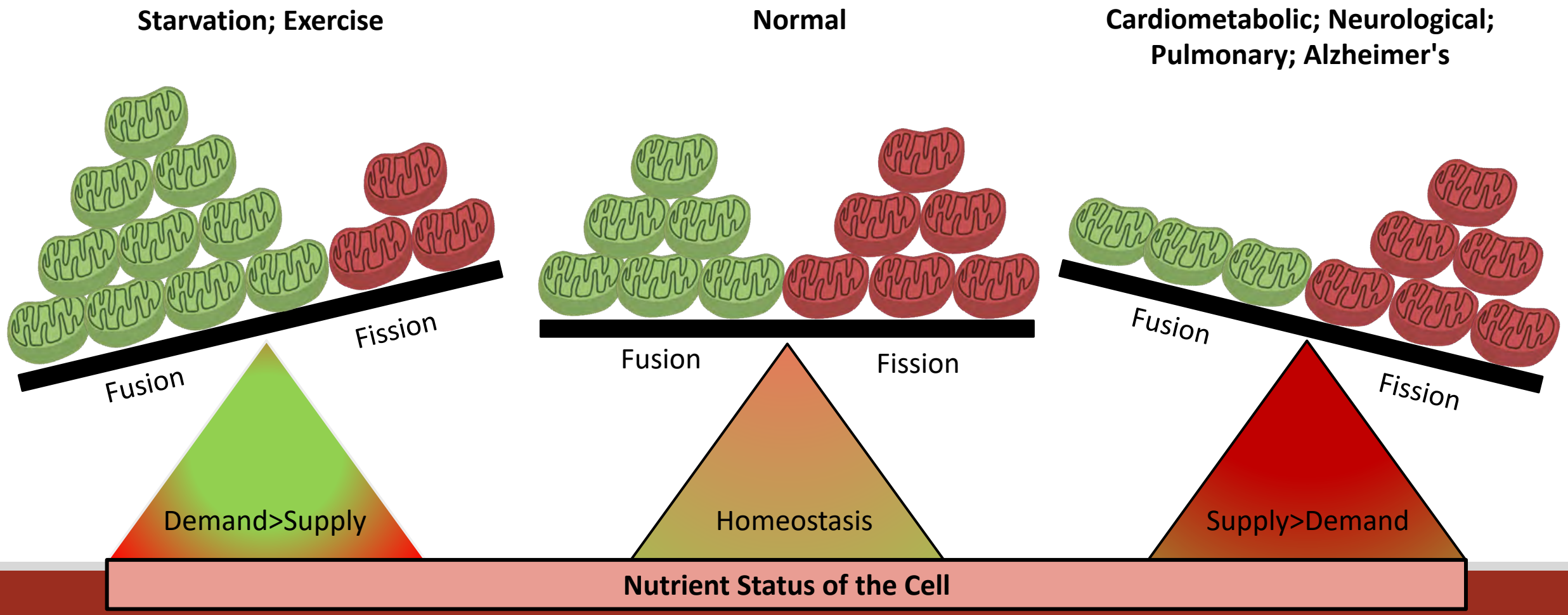
Mitochondrial Fission:
DRP1 (Cystosol)
MFF (OMM)
Mid49 (OMM)
Mid51 (OMM)

Mitochondrial Fusion:
MFN1 (OMM)
MFN2 (OMM)
OPA1 (IMM)

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

Obtained from Dom et al. (2015). The Mitochondrial Dynamism-Mitophagy-Cell Death Interactome. *Circulation Research*, 116: 167-182.

Mitochondrial Dynamics and Metabolic Disease



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 O_2 consumption rates
  - Uncoupled respiration
  - Slowed ATP synthesis

Hyperinsulinemia results in order to accommodate inadequate energy production

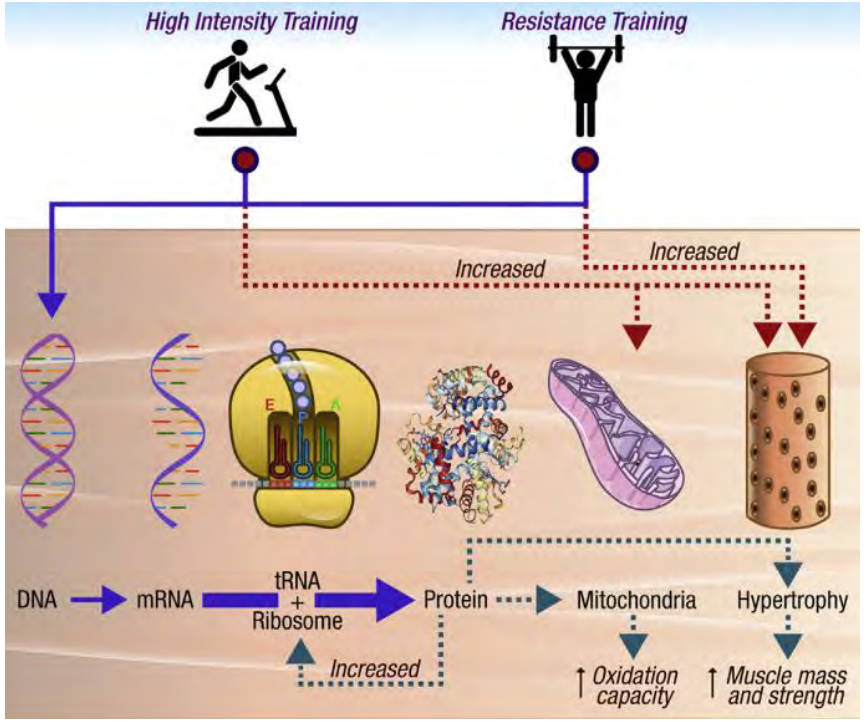
With continual overload on the mitochondria, insulin action worsens

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?

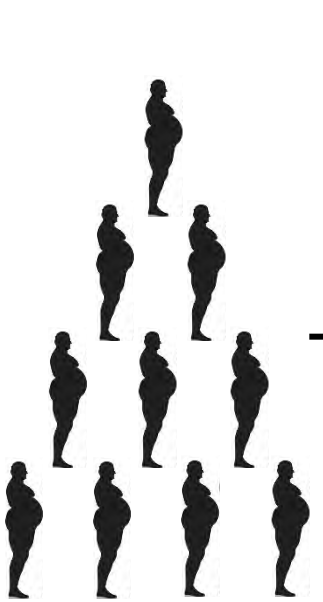
Hypothesis 1:

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



Week 0

Week 12

12 Weeks Treadmill Walking/Jogging @ 85% HR_{MAX}
5X/weekly

*

Clamp Study
Muscle Biopsies
Indirect Calorimetry
VO_{2MAX} Testing
DEXA Scan

*

Clamp Study
Muscle Biopsy
Indirect Calorimetry
VO_{2MAX} Testing
DEXA Scan

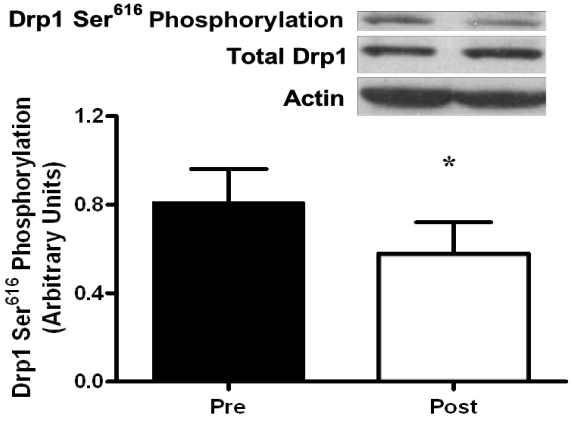
Hyperinsulinemic-Euglycemic Clamp Study

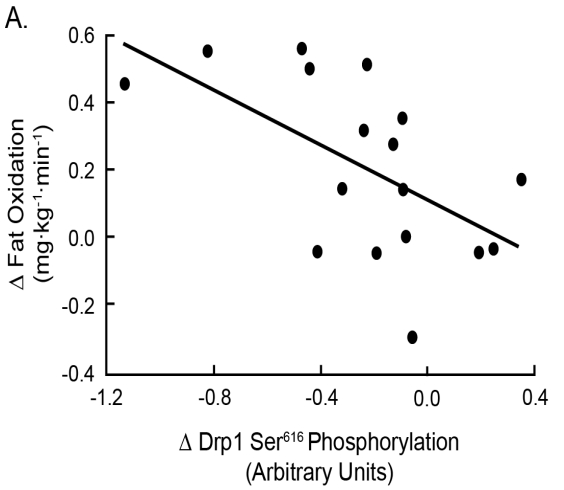
Exercise Training Improves Metabolic Phenotype

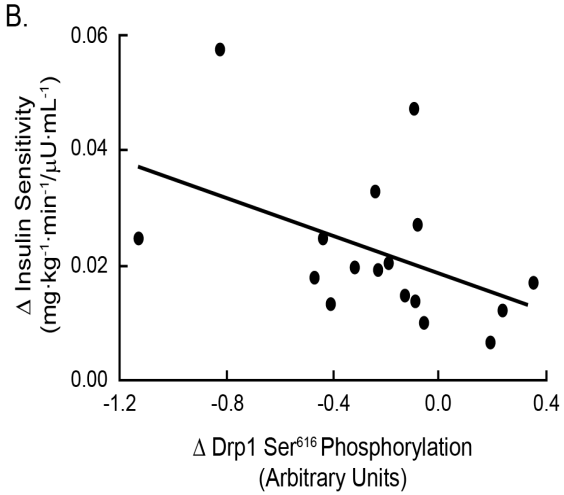
Table 1. **Changes in subject characteristics after 12 weeks of exercise training**

Characteristic	*M*	*SD*	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_{2MAX} (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



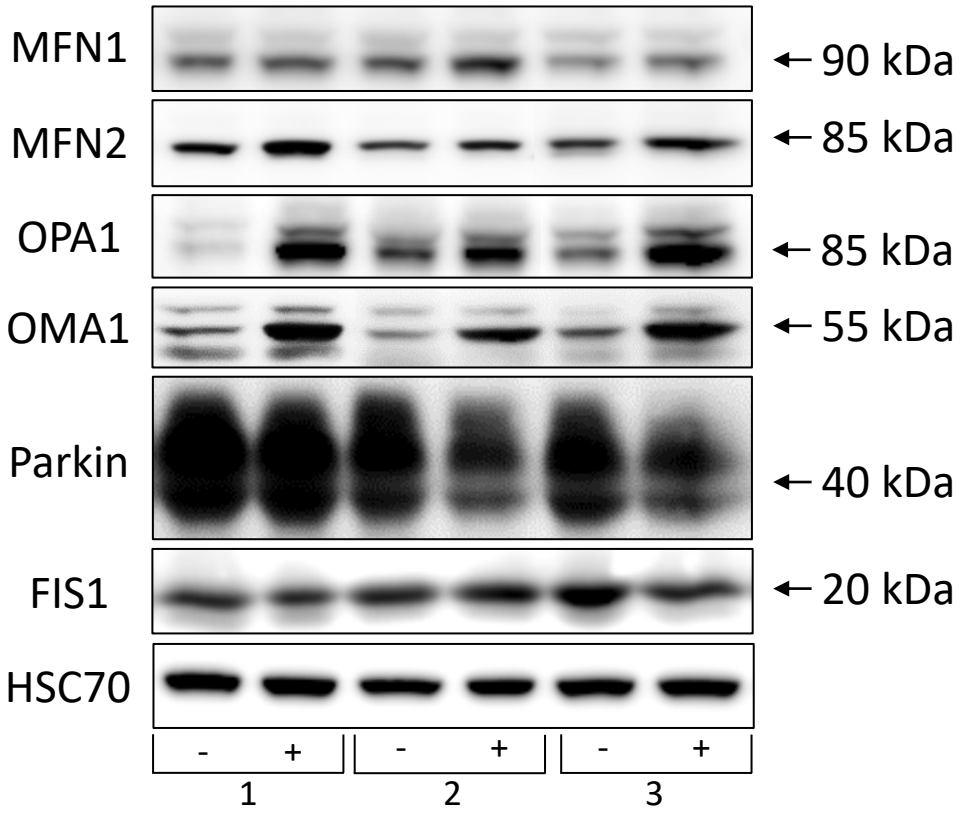


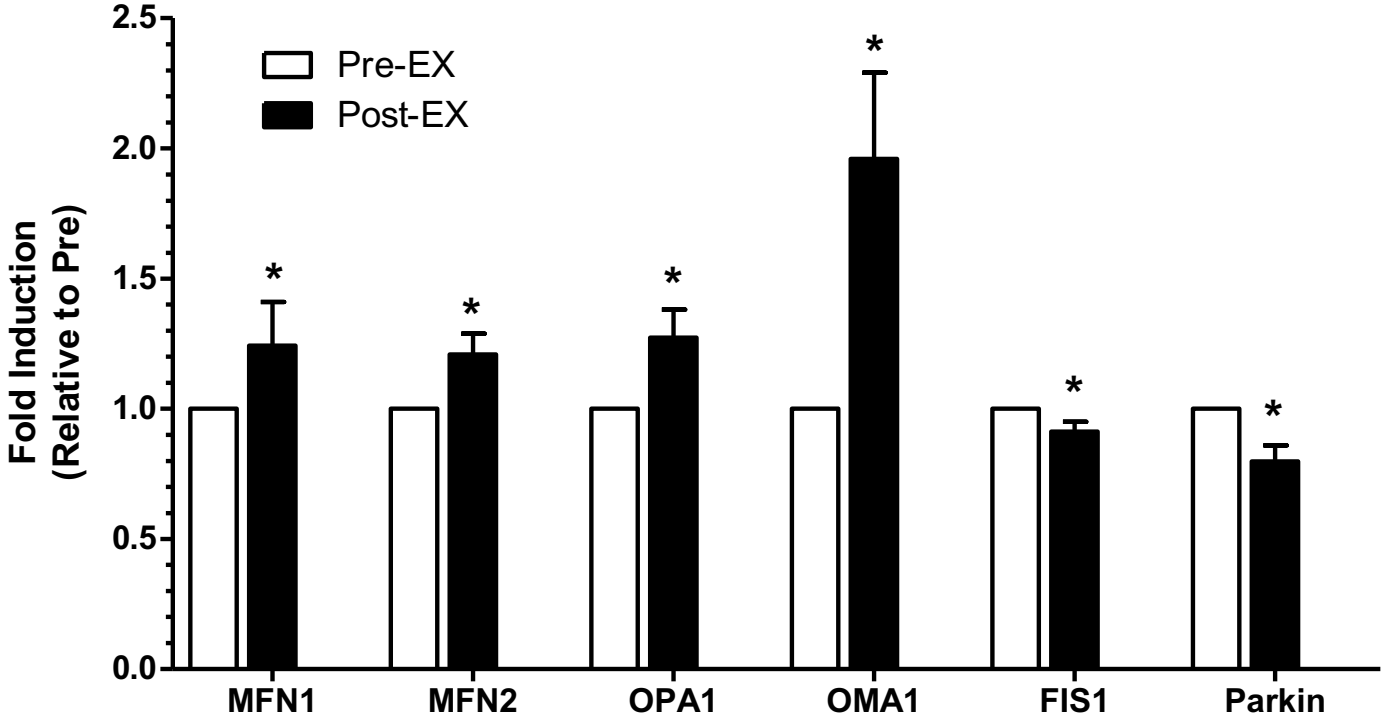


- Reductions in Drp1 phosphorylation in association with improved insulin resistance and fat oxidation supports the hypothesis that Drp1 mediated mitochondrial fission may link mitochondrial function with insulin sensitivity

Fealy et al. (2014)

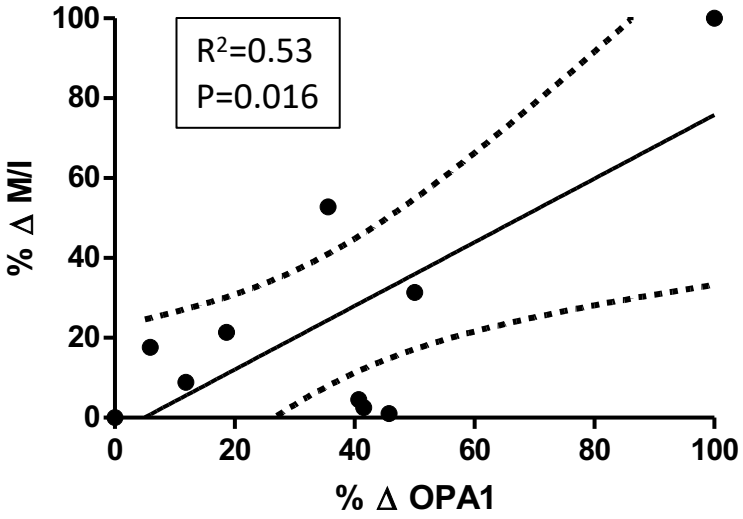
Exercise Training Improves Mitochondrial Dynamics

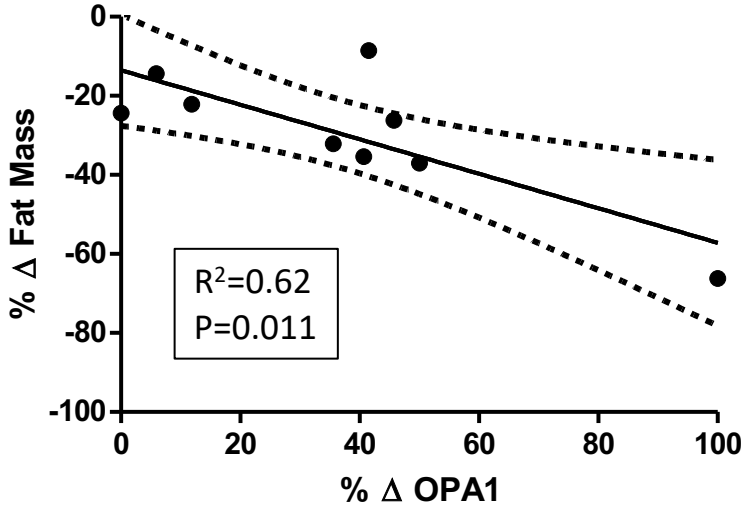


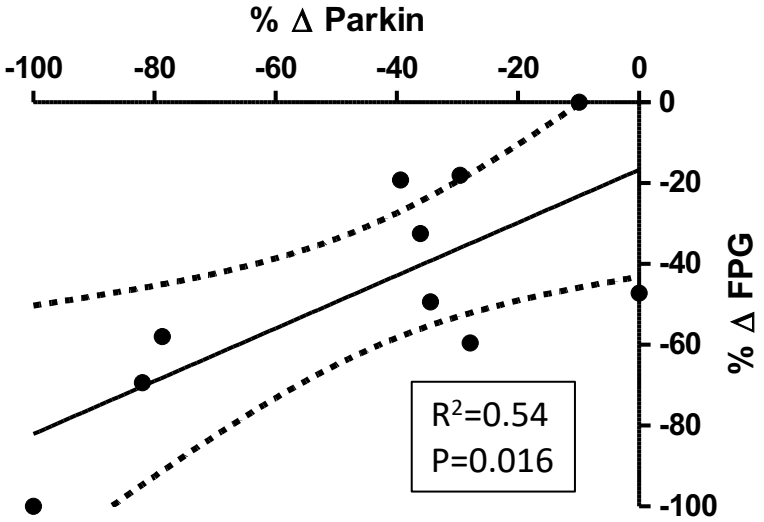


Representative immunoblots of regulators of mitochondrial dynamics from human skeletal muscle tissue. ± indicates either pre (-) or post (+) exercise training. Quantification of protein expression expressed as fold induction relative to pre-intervention corrected to loading control (HSC70).

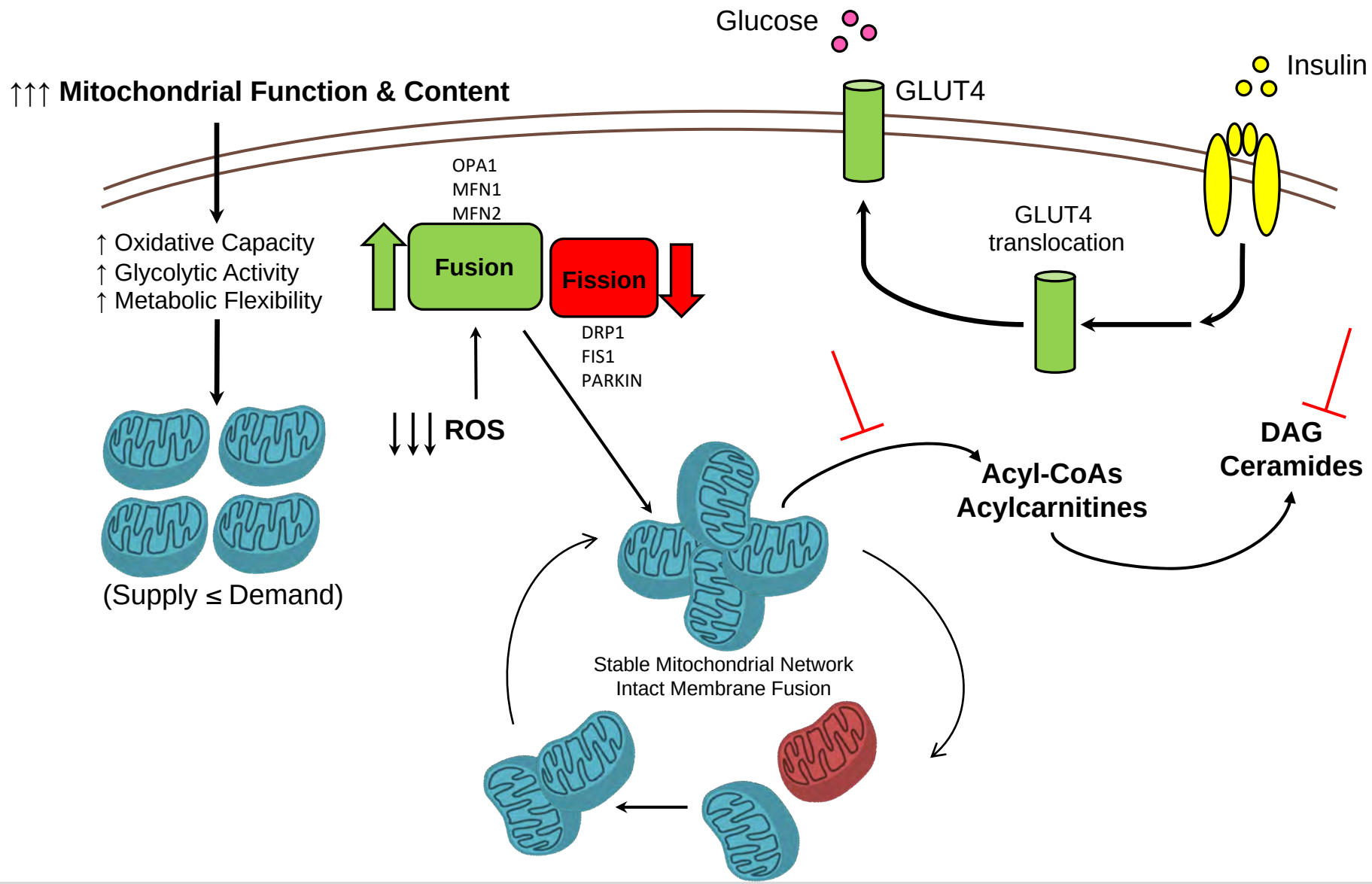
Mitochondrial Dynamics & Insulin Sensitivity







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

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Questions?