Beneficial Effect of Exercise on Diabetes Focused on Molecular Mechanisms

: Overview of current evidences

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In this presentation,

Molecular mechanism underlying the beneficial effects of **long-term exercise training**

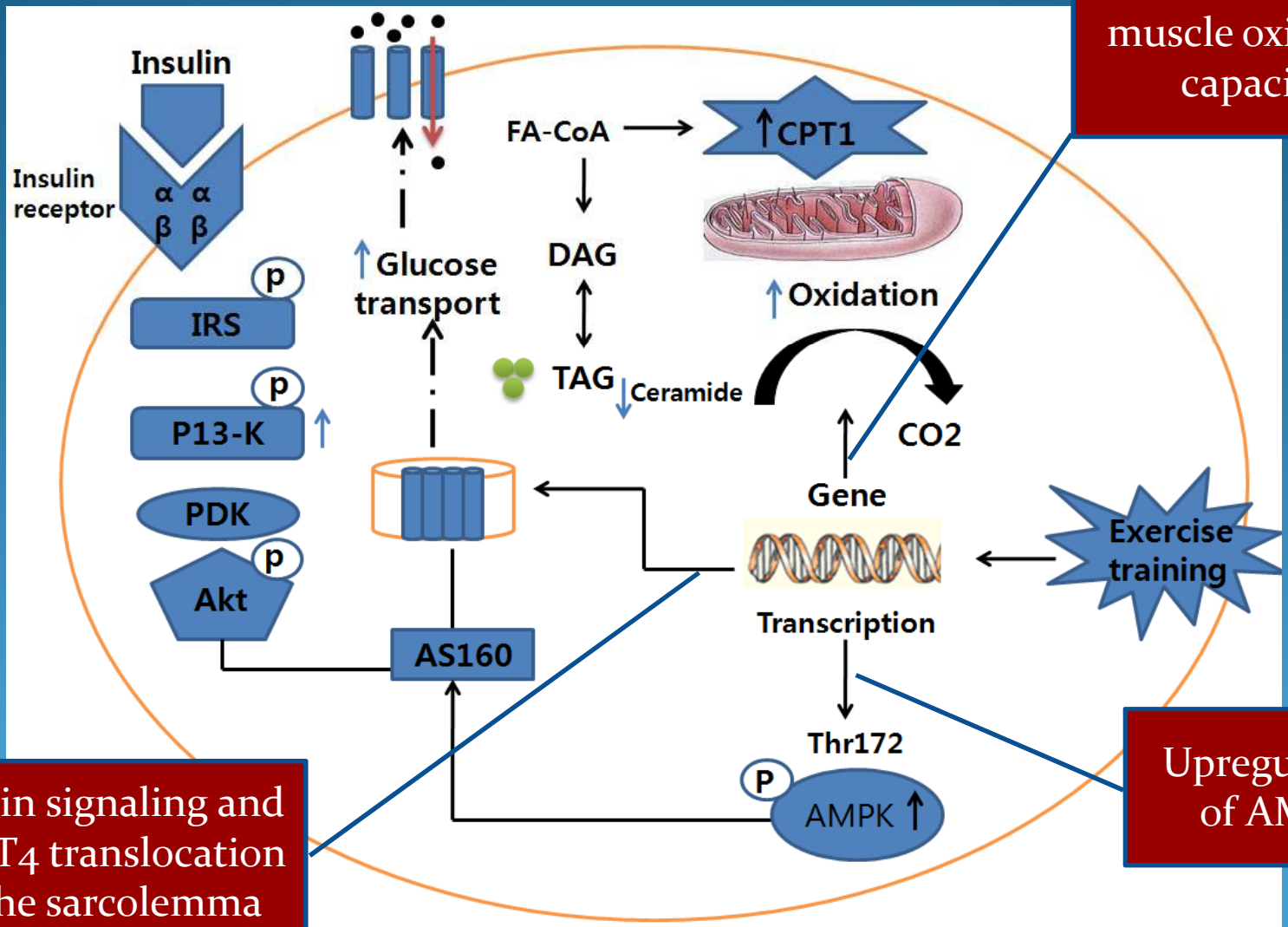
1) Upregulation of **insulin signaling proteins** (i.e., GLUT4, PI3K)

2) Chronic **AMPK** activation

3) Increased expression of proteins involved in **mitochondrial biogenesis** (i.e., PGC-1, PPARα)

4) **Decreased lipid accumulation** that inhibit insulin signal transduction (i.e., ceramide, diacylglycerol)

Results of Exercise Training in Insulin Signaling

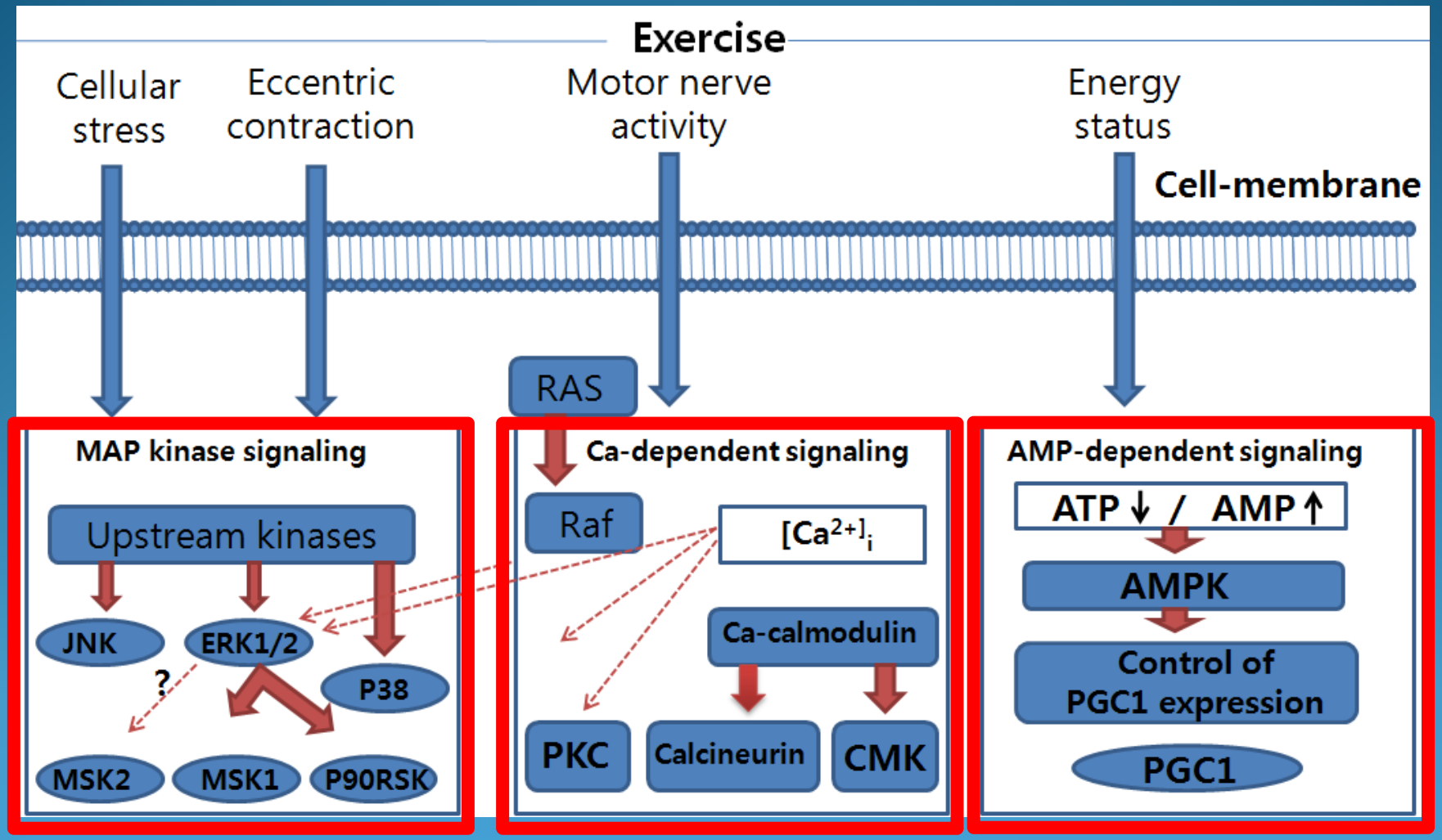


Increased skeletal muscle oxidative capacity

Insulin signaling and GLUT4 translocation to the sarcolemma

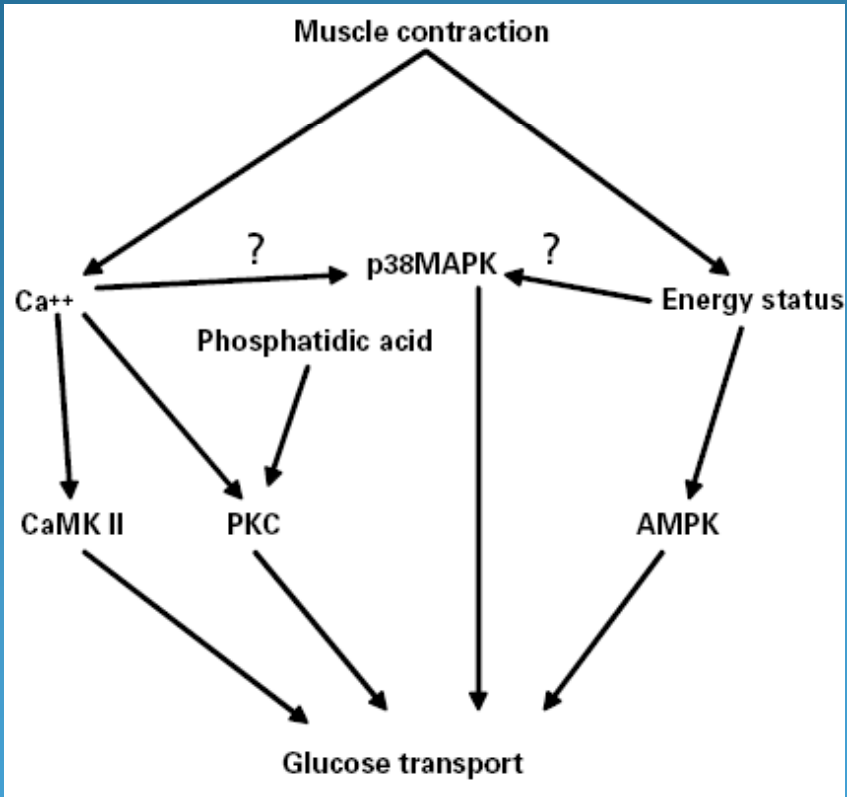
Upregulation of AMPK

Results of Exercise Training in Insulin Signaling



Exercise training for type 2 diabetes

Skeletal muscle is the major source for insulin-stimulated glucose uptake (DeFronzo et al., 1985), any treatment to improve glucose uptake in this tissue will improve whole-body glucose homeostasis.



The observation that exercise training increases both insulin-dependent and **insulin–independent glucose transport** in skeletal muscle is well established.

Richter EA et al., 2005

Glucose transporter protein

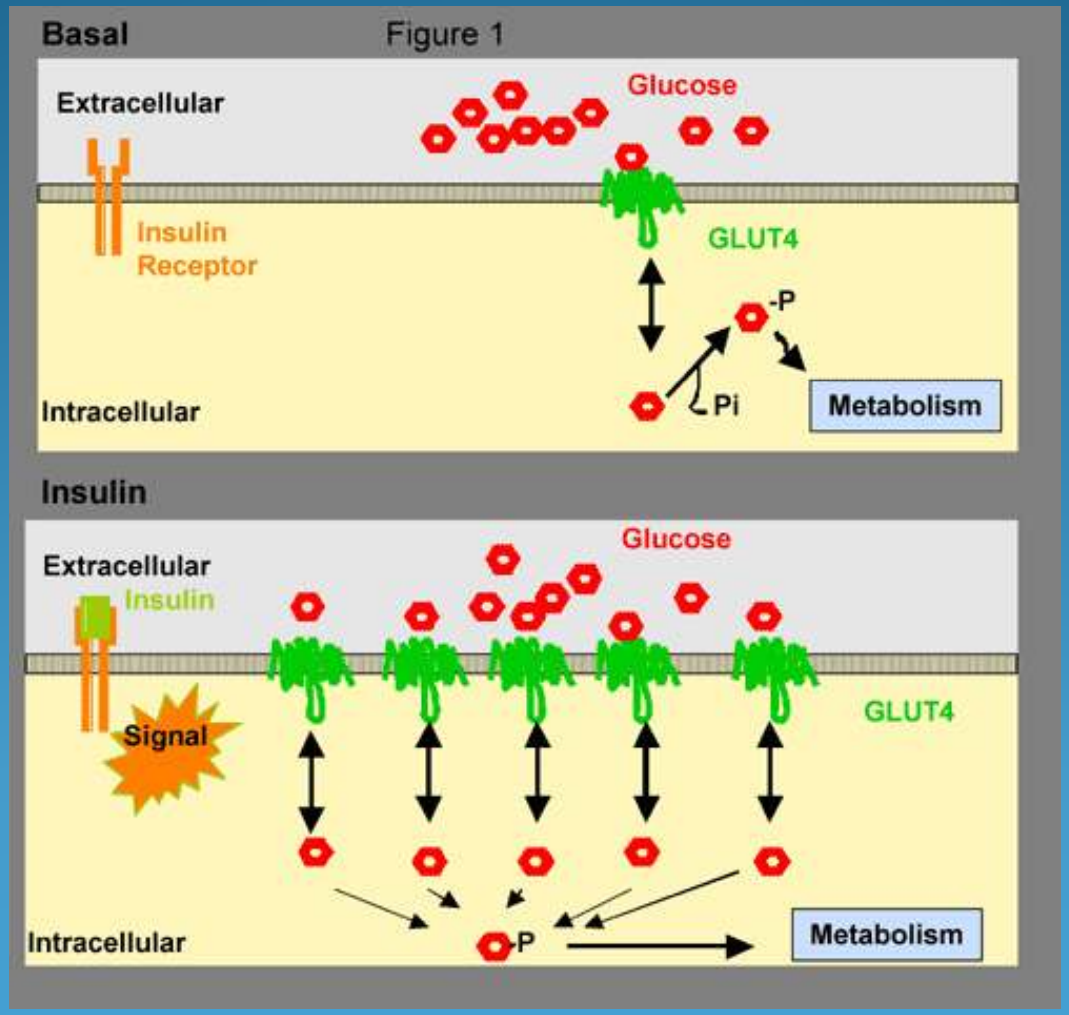
Glucose uptake in skeletal muscle occurs primarily by facilitated diffusion involving the **glucose transporter proteins** (GLUT1-GLUT12)

Human skeletal muscle expresses the glucose transporters **GLUT1** and **GLUT4** . And the GLUT4 isoform accounts for approximately **90%** of the glucose transporter protein s in skeletal muscle. *(Zorzano et al., 1996).*

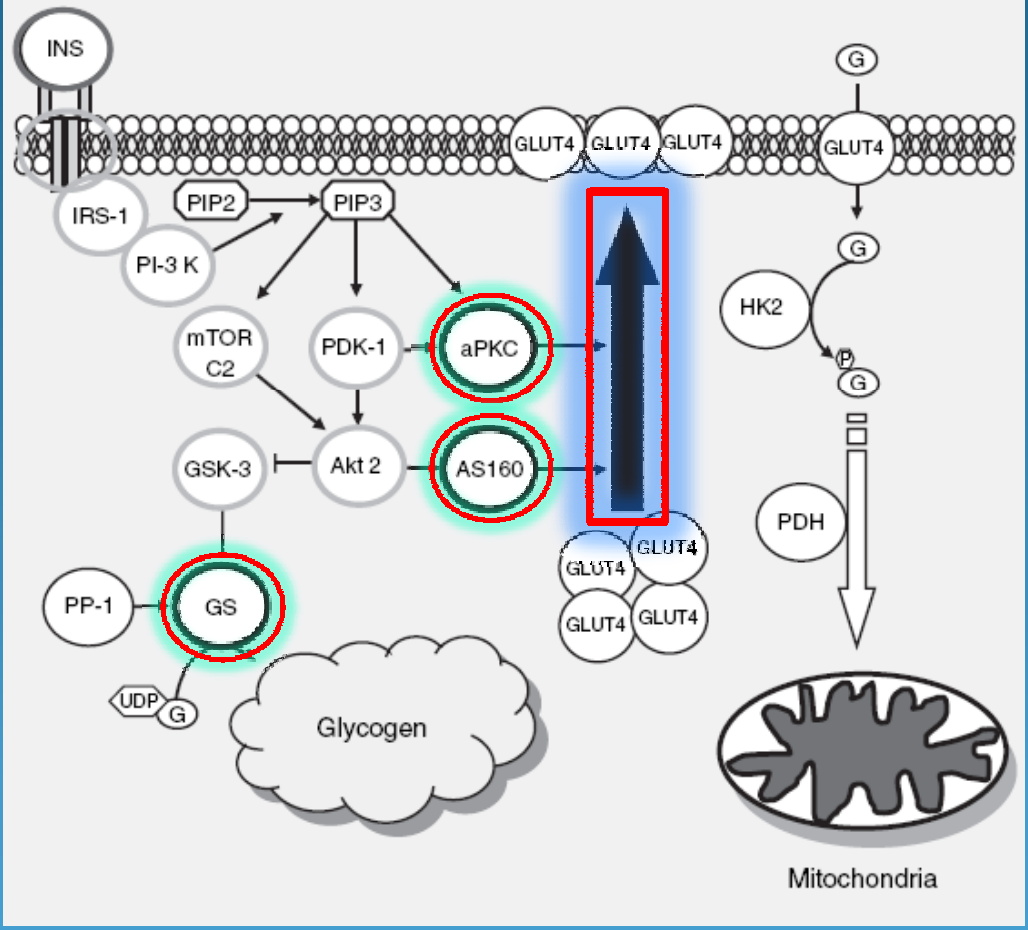
Upon insulin stimulation, vesicles containing **GLUT4 translocate** from an intracellular location to the sarcolemma or to the T-tubules (Wang et al., 1996)

The vesicles fuse with the cell membrane, allowing glucose to enter the cell via **facilitated diffusion .** *(Klip and Marette 1992).*

GLUT4 and insulin signaling



Regulation of GLUT4 expression by exercise



Insulin signaling to GLUT4 translocation and stimulation of glucose uptake after exercise (*Christian Frøsig and Erik A. Richter1, 2009*)

Regulation of GLUT4 expression by exercise

Citation	Outcome		Results				Statistics
	Variable	Method	Group	Pre-exercise (Mean ± SD)	Post-exercise (Mean ± SD)	Changes (%)	*p* value (pre vs. post)
Hughes *et al.* [30]	GLUT4 protein (O.D. units)	Western blot	EXE	6981 ± 1577.9	11 197 ± 4197.6	+60.4	$p < 0.05$
Dela *et al.* [31]	GLUT4 mRNA	Northern blot	EXE	NR	NR	NR	$p < 0.05$
	GLUT4 protein	Western blot	EXE	NR	NR	+30	$p < 0.05$
Christ-Roberts *et al.* [35]	GLUT4 protein	Western blot	EXE	NR	NR	+22 ± 19.9	$p < 0.05$
	Phosphor-Akt (Ser473)	Western blot	EXE	NR	NR	+30 ± 19.9	$p < 0.001$
	PI-3K		EXE – basal	0.55 ± 0.37	0.46 ± 0.32	−16.4	NS
			–insulin	0.70 ± 0.40	0.56 ± 0.32	−20	NS
Kim *et al.* [37]	GLUT4 protein (%)	Western blot	EXE	107.7 ± 15.3	177.9 ± 20.7	+65.2	$p < 0.01$

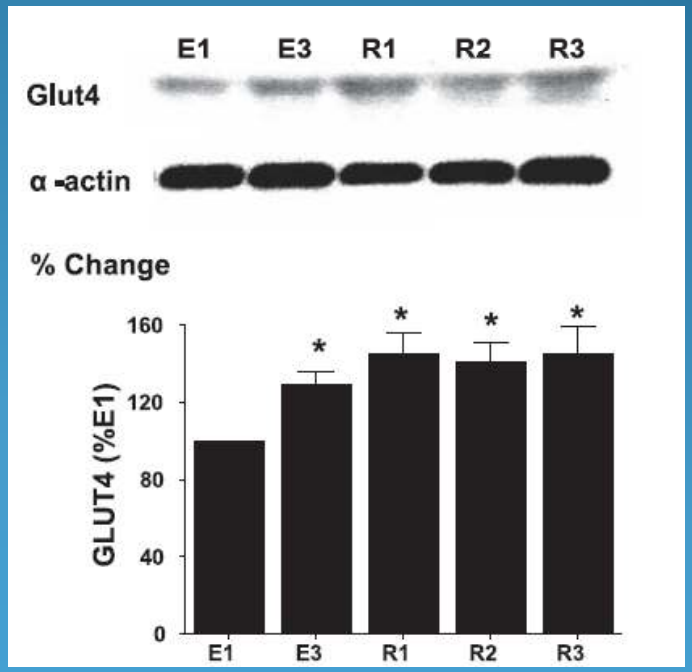
(Wang et al., 2009)

EXE, exercise; NR, not reported; NS, not significant; GLUT4, glucose facilitated transporter 4.

Regulation of GLUT4 expression by exercise

An acute bout of exercise elicits an insulin-independent translocation of GLUT4 to the cell surface and an increase in glucose uptake as well as an increase in expression of GLUT4. *(Lund et al., 1995)*

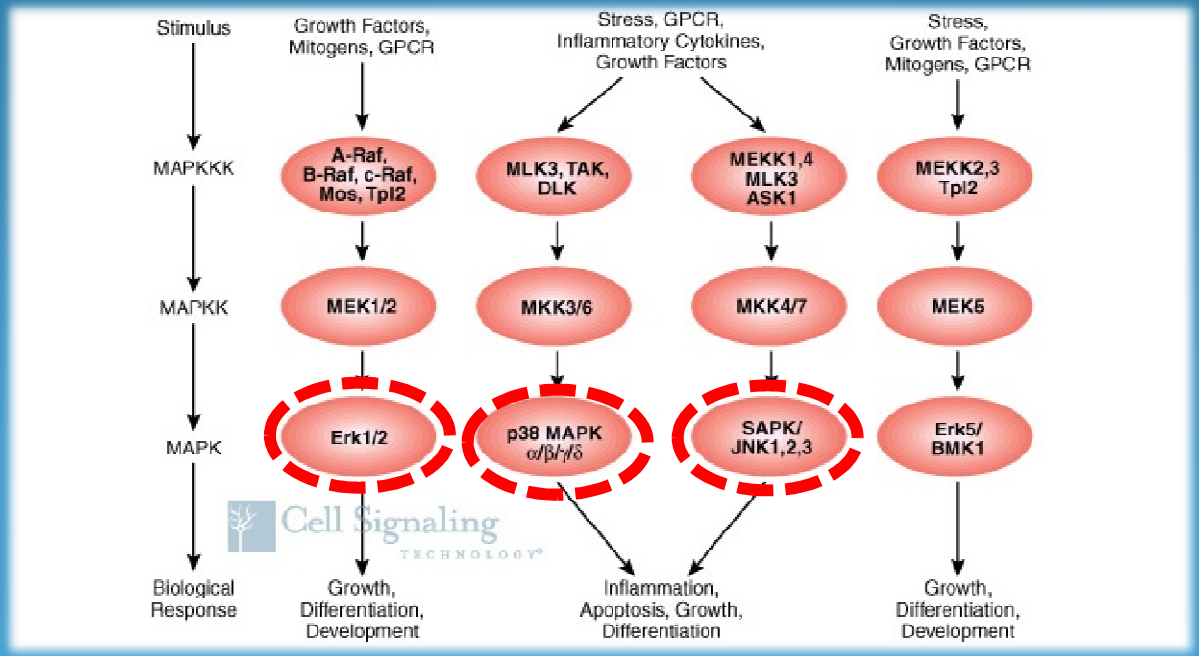
Both post exercise (cycling) on day 1 (E1), day 3 (E3), and during recovery (R1, R2, R3) were analyzed for changes in transporter responses. *(Green HJ et al., 2008)*



Mitogen-activated protein kinases (MAPK)

Several MAPK proteins are activated in direct response to muscle contraction and exercise training *(Long et at ., 2004)*

In skeletal muscle, at least three parallel MAPK signaling cascades are activated in direct response to exercise. These include ERK1/2, p38 MAPK and JNK *(Long et al., 2004)*



MAPK signaling : ERK1/2 pathway

The ERK1/2 pathway is both rapidly and profoundly activated following acute cycling exercise. *(Yu et al., 2003)*

By investigating muscle biopsies obtained from subjects performing one-legged cycling, ERK1/2 is rapidly activated in the exercising muscle and activity returns to basal levels within minutes of exercise cessation *(Krook et al., 2000; Widegren et al., 1998)*

In vitro contraction of isolated rat skeletal muscle is sufficient to elicit ERK1/2 phosphorylation *(Ryder et al.,2000; Wretman et al., 2001)*

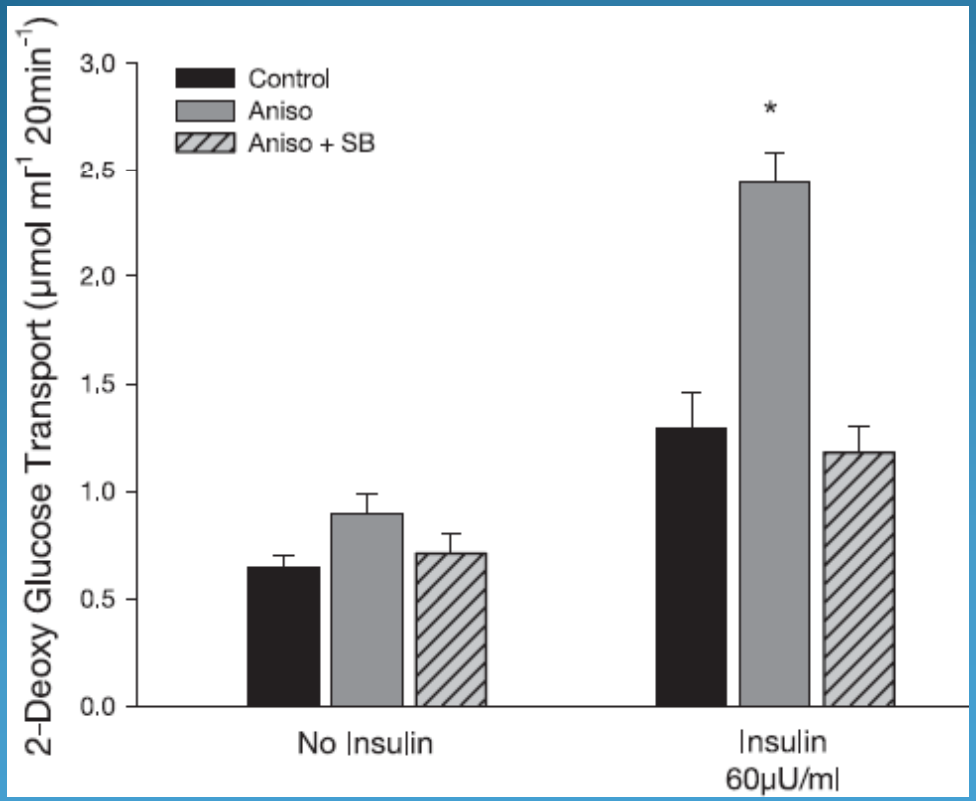
MAPK signaling : p38 pathway

In human skeletal muscle, p38 MAPK was activated after acute exercise and following marathon running. *(Yu et al., 2001; Boppart et al., 2000)*

Exercise-induced signaling responses for p38 MAPK are more profound in untrained men as compared to highly trained individuals even at the same relative cycling exercise intensity. *(Yu et al., 2003)*

Activation of p38 MAPK may play an important role for the subsequent activation of the MEF2 transcription factor as well as the expression of the co-activator PGC-1α.

Activation of p38 MAP kinase enhances sensitivity of muscle glucose transport to insulin



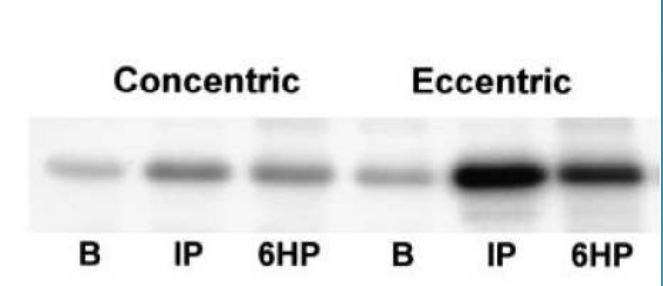
Anisomycin
increases p38 phosphorylation 2.5-fold

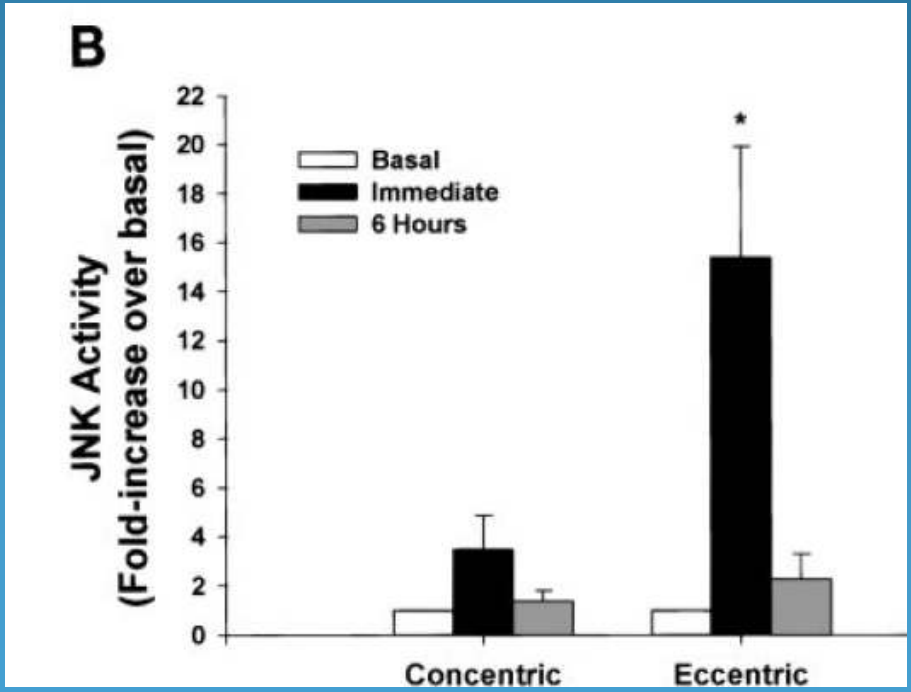
SB-202190 is p38 inhibitor

Paige C et al., 2004

MAPK signaling : JNK pathway

Activation of the JNK pathway appears to relate somewhat to the degree of injury the muscle sustains with exercise, and JNK is affected more by eccentric as opposed to concentric exercise. *(Boppart et al., 2000)*

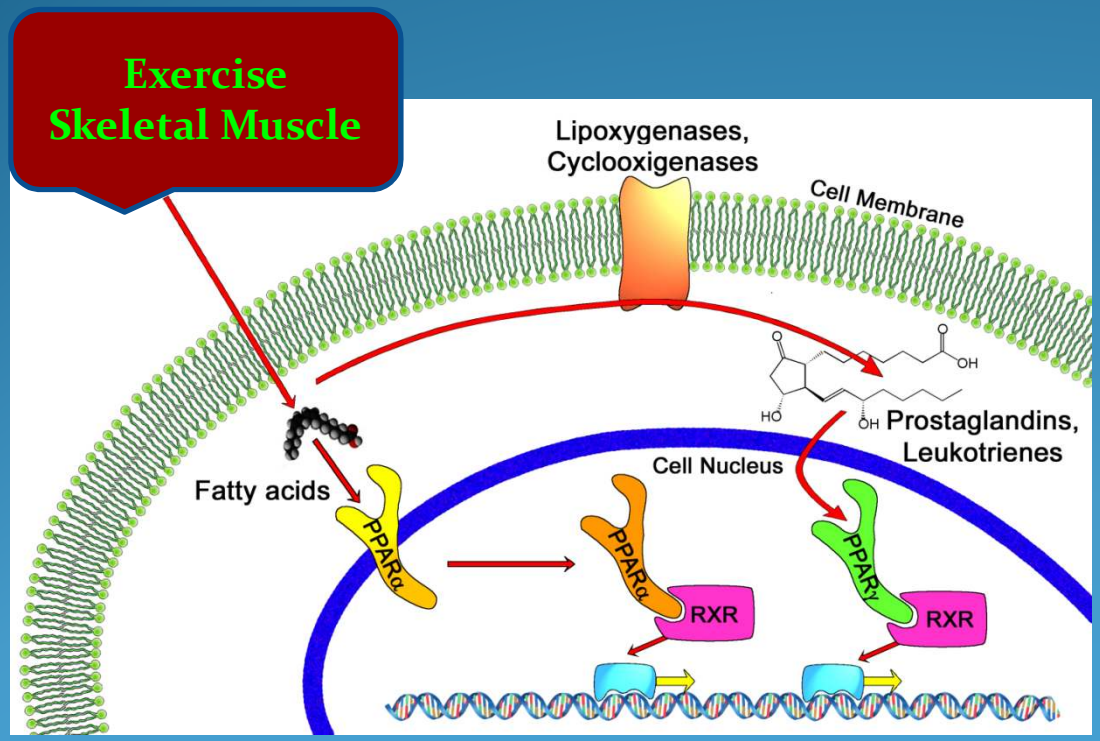




Boppart et al., 2000

Peroxisome Proliferator-Activated Receptors (PPARs)

PPARs are nuclear receptors and transcription factors that play central roles in substrate utilization and have received attention as pharmacological targets for treating metabolic diseases.



The PPARs are activated by dietary lipids and are therefore considered to be nutritional lipid sensors and to control lipid homeostasis . *(Smith et al., 2005)*

Exercise-mediated regulation of PPARs

PPARγ mRNA was elevated in vastus lateralis muscle from healthy young man 3 h following cycling exercise *(Mahoney et al., 2005)* and in rodents after 16 wk of treadmill exercise training *(Kawamura et al., 2004)*.

Gene Name	Accession Number	3 H	48 H	Potential Relevant Function
*PPARγ coactivator 1 α	N89673	2.9±0.8	0.6±0.1	• regulates mitochondrial biogenesis
*PPARγ	AA088517	2.7±0.7	1.4±0.6	• positively regulates fat metabolism
Nuclear receptor binding protein 2	N30573	2.6±0.4	3.8±0.9	• binds to and co-modulates PPARα
Aminolevulinate δ syntetase 2	AA699919	2.3±0.4	1.5±0.1	• catalyzes first step in the heme biosynthesis
Interferon regulatory factor 1	AA478043	2.1±0.3	1.0±0.1	• transcription factor for iNOS expression
IL-6 signal transducer (gp130)	T61343	2.0±0.1	1.5±0.1	• component for IL-6 receptor complex
↑PPAR δ	n/a	2.6±0.6	1.1±0.1	• positively regulates fat metabolism
↑PPAR α	n/a	1.7±0.1	1.6±0.4	• positively regulates fat metabolism

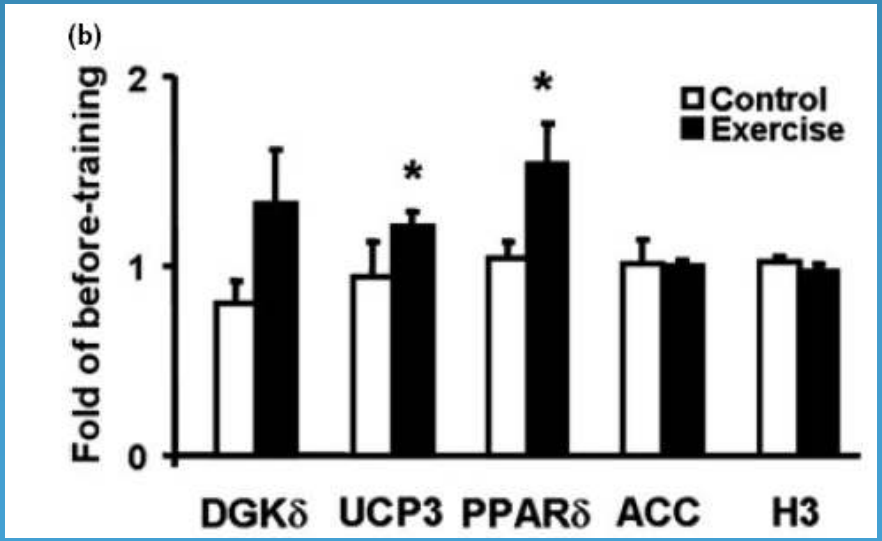
(Mahoney et al., 2005)

High-intensity of cycling lasted ~75 min

Exercise-mediated regulation of PPARs

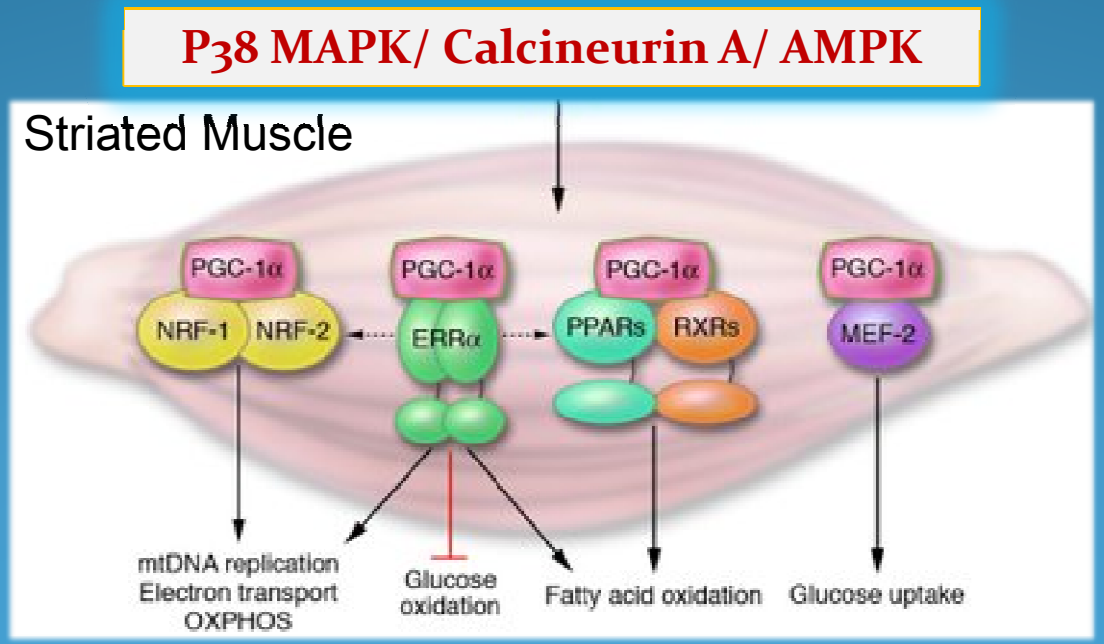
Both PPARα and PPARδ mRNA are increased following an acute 3 h exercise bout (Watt et al., 2004). Endurance training has also been reported to elevate PPARα mRNA (Russell et al., 2003)

Recently protein expression of PPARδ in skeletal muscle increased significantly after physical exercise in patients with type 2 diabetes following a 4 mo, low-intensity combined exercise program (Friz et al., 2006)



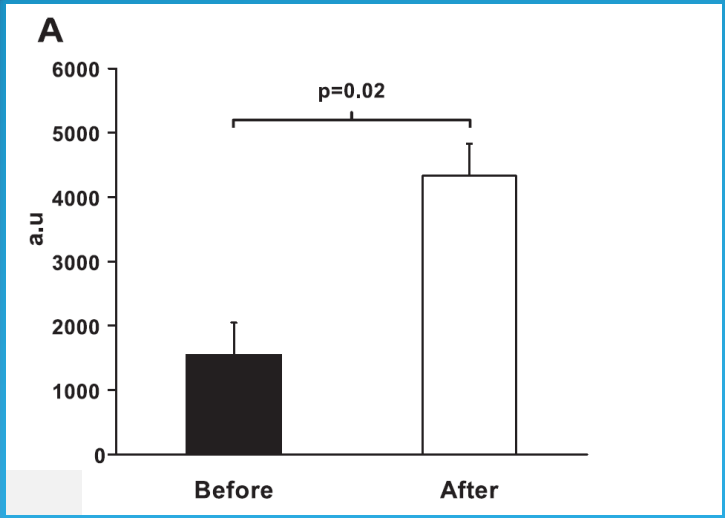
PPAR Gamma Co-activator 1 (PGC-1)

A key feature of most of the transcription factors involved in mitochondrial biogenesis is their binding to the nuclear coactivator PGC-1 or PGC-1-related coactivator (PRC).



PPAR Gamma Co-activator 1 (PGC-1)

An acute bout of exercise markedly increases PGC-1α mRNA immediately following the activity. PGC-1α mRNA returns to pre-exercise levels within 24 h. *(Pilegaard et al., 2003)*



(Kuhl et al., 2006)

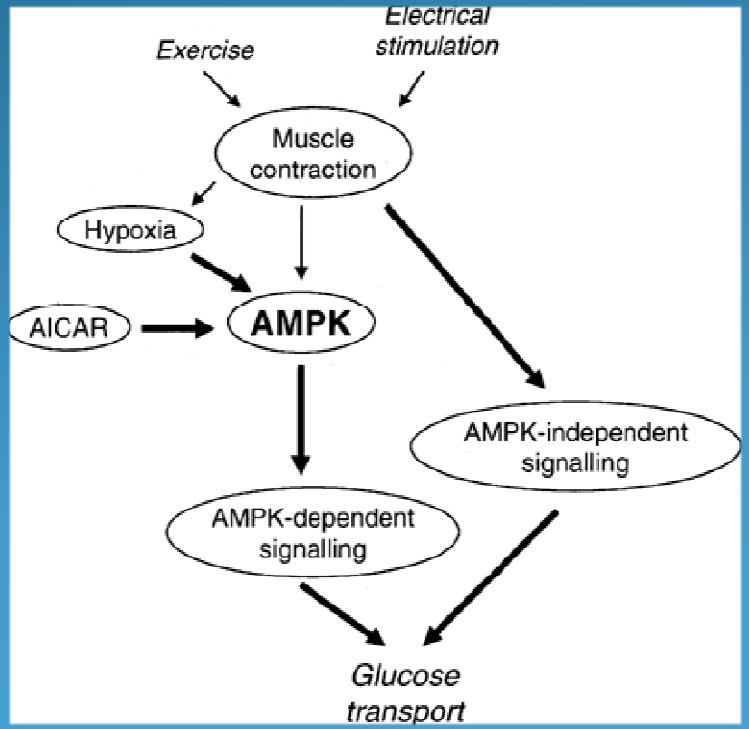
Several bouts of exercise training lead to a sustained increase in PGC-1α.
(Kuhl et al., 2006; Short et al., 2003)

DNA polymorphisms in PGC-1α have been linked to reduced cardiovascular fitness and to greater odds of developing type 2 diabetes. *(Barroso et al., 2006)*

AMP-activated protein kinase (AMPK)

Several key discoveries suggest that AMPK signaling is important for the prevention and treatment of type 2 diabetes.

First, AMPK is activated in response to muscle contraction.
Second, in resting muscle AMPK can be activated chemically by the drug

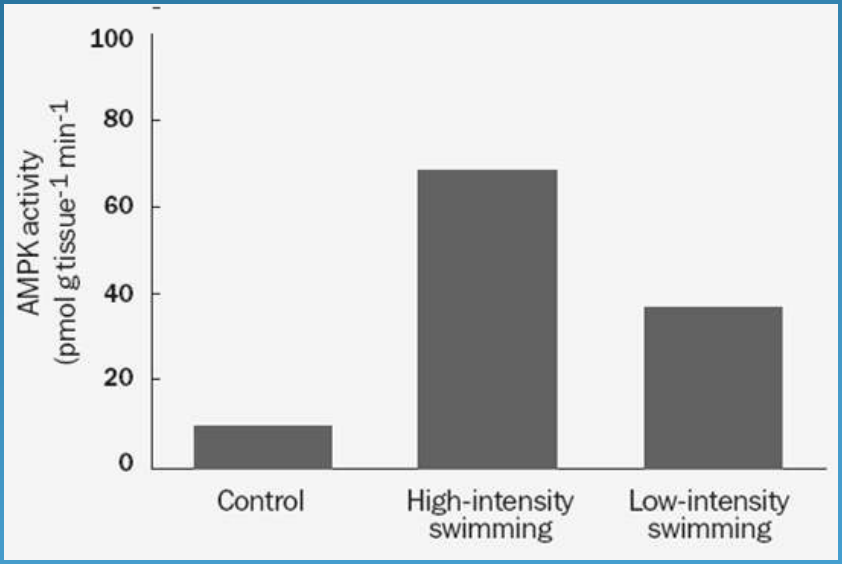


AICAR can be used to probe for down stream actions of AMPK in muscle and other tissues. In perfused rat hind limb, AICAR triggers not only an increase in fatty acid oxidation but also an increase in glucose uptake across the hind limb *(Merrill et al., 1997)*

AMP-activated protein kinase (AMPK)

AMPK is activated during exercise and may play an important role in regulating metabolic events both acutely and chronically. AMPK activation may also to some extent improve muscle insulin sensitivity.

(Fisher et al., 2002; Oakes et al., 1997)



Since chemical activation of AMPK increases muscle insulin sensitivity and expression of the GLUT4 gene, it seems intuitive that AMPK activation during the exercise bouts is responsible for the increased mitochondrial capacity and GLUT4 expression associated with training.

Exercise mimetics (pills) arguments

FOR

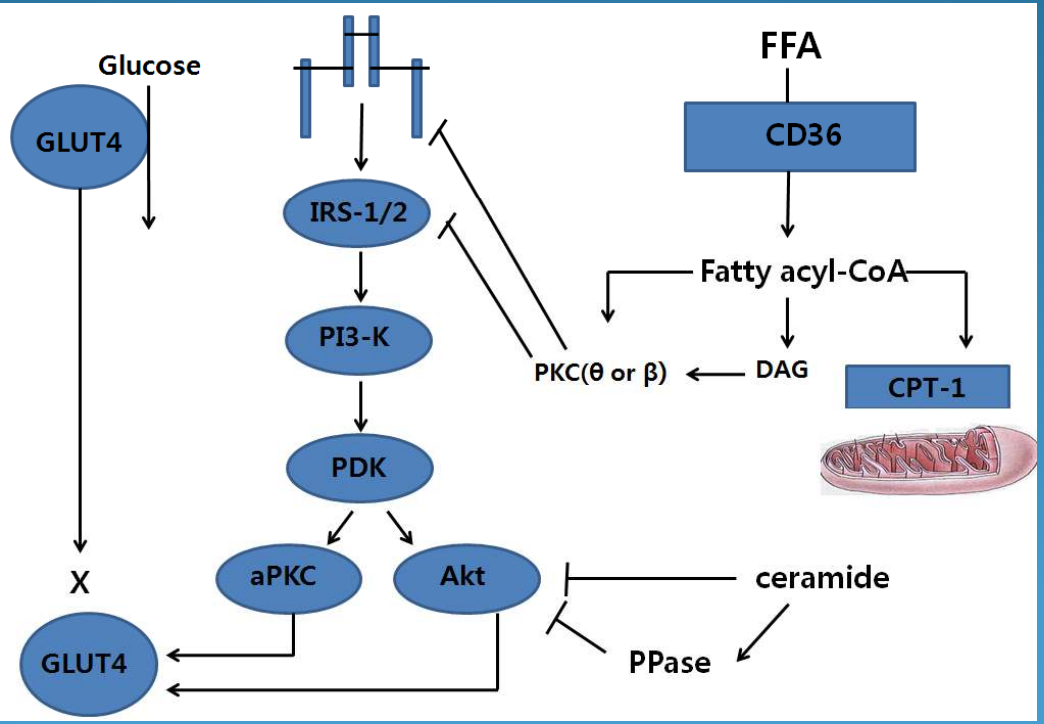
-Narker et al (Cell, 2008)
"identification of orally active agents that mimic the effects of endurance exercise is a long standing medical goal..."
- AICAR, GW1516 (PPARd agonist)
- Increased muscle mitochondria
- Increased running distance

AGAINST

- By numerous exercise scientist (Nature, 2008)
-Chronic treatment of AICAR?? "catabolic→ wasting"
- Poor bioavailability after oral ingestion

Lipid Metabolism in Skeletal Muscle

Increased fatty acid uptake and decreased fatty acid catabolism contribute to the increased lipid accumulation that is observed with obesity and type 2 diabetes.



Proposed mechanism of lipid accumulation that occurs in cases of obesity or diabetes

Decreased lipid accumulation in muscle

Regulation of lipid turnover and utilization is another potential mechanism by which exercise training may improve insulin sensitivity *(Bruce and Hawley 2004; Hawley and Lessard 2007)*

Increased oxidative capacity following exercise training was recently associated with increased CPT1 activity and decreased ceramide and DAG content in the muscle of obese subjects *(Bruce et al. 2006)*

Exercise training may improve muscle insulin sensitivity by increasing the proportion of lipids targeted for oxidation, thereby reducing the accumulation of lipid species that inhibit insulin signal transduction

Paradox: endurance athlete case

Previous speculation suggested that elevated intramyocellular lipid (IMCL) content was a predictor of insulin resistance in skeletal muscle and a risk factor for type 2 diabetes.

An **apparent paradox** exists in which in which endurance-trained individuals have enhanced insulin sensitivity despite IMCL (Intra-MyoCellular Lipid) levels similar to *(Goodpaster et al., 2001)* or greater than *(van Loon et al., 2004)* those observed in individuals with type 2 diabetes.

Summary

Underlying mechanisms of effect of exercise

1. Upregulation of insulin signaling proteins such as GLUT4 and PI3K
2. Chronic AMPK activation
3. Increased oxidative capacity of skeletal muscle by upregulating the expression of proteins involved in mitochondrial biogenesis such as PGC-1 and PPARs
4. Decreased lipid accumulation that inhibit insulin signal transduction

Exercise-induced improvements in skeletal muscle insulin sensitivity