NASH-TAG Conference

January 5, 2018

Mediators of Insulin Resistance and Organ Cross Talk

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Disclosures

Scientific Advisory Boards: Merck, NovoNordisk, AstraZeneca, Janssen Research and Development

Investigator Initiated Support: HHMI, NIH, Gilead Sciences, Celgene

A grim prediction :

By the year:

2050

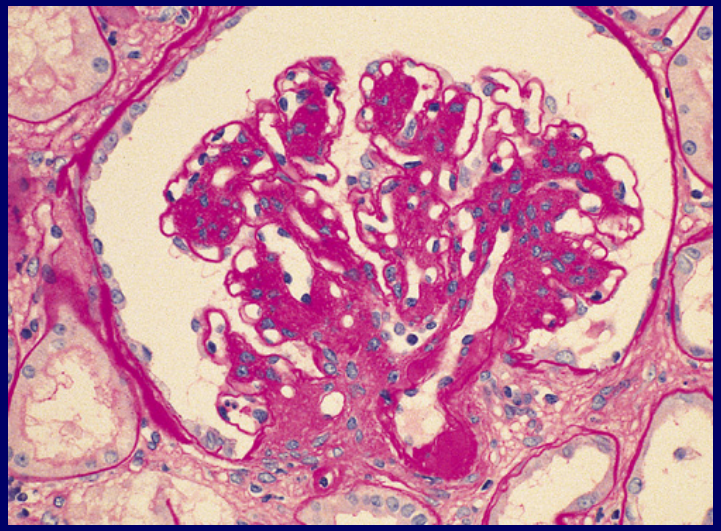
1:3

Americans will have T2D

CDC
SAFER • HEALTHIER • PEOPLE

Complications of Diabetes

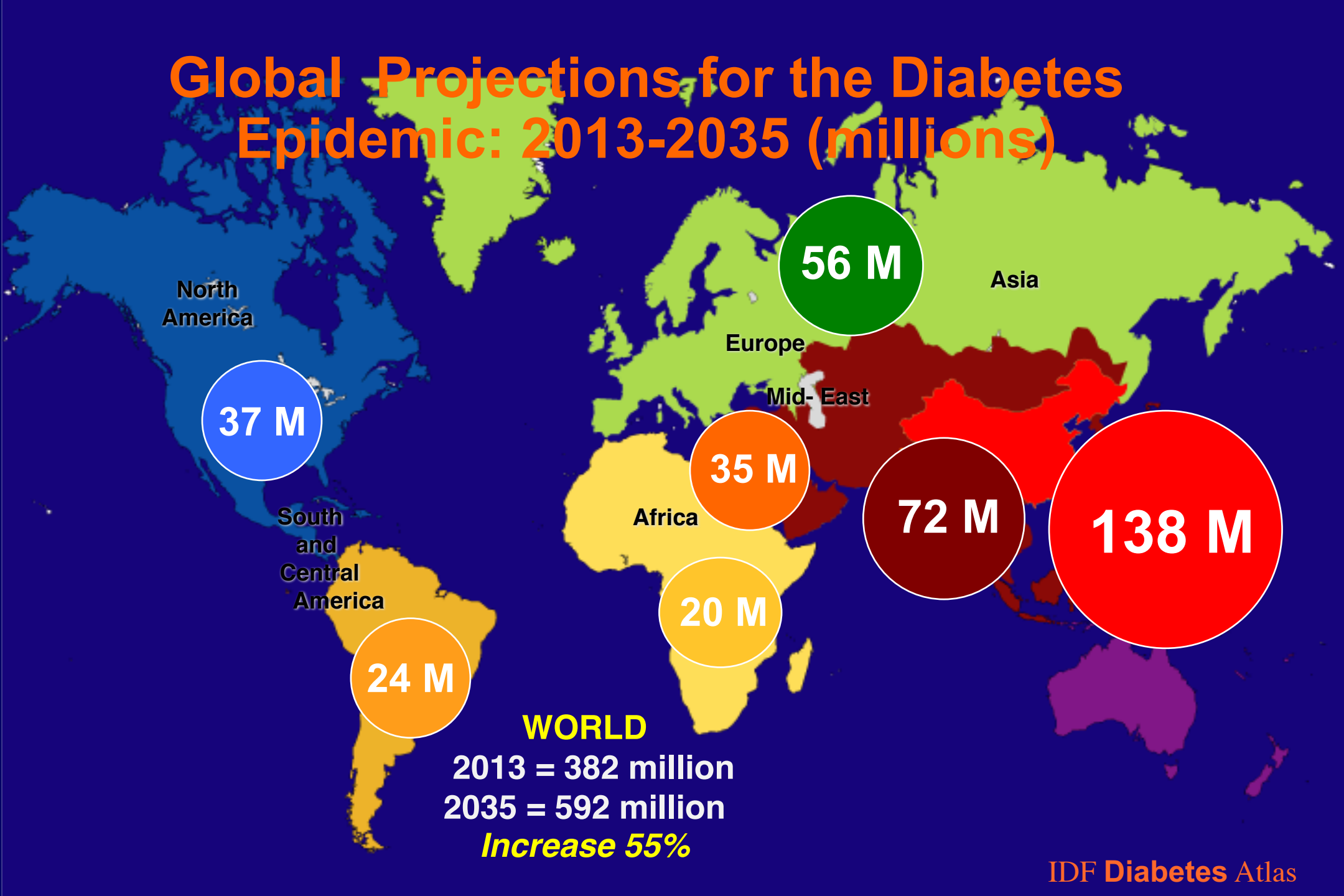
Proliferative Diabetic Retinopathy



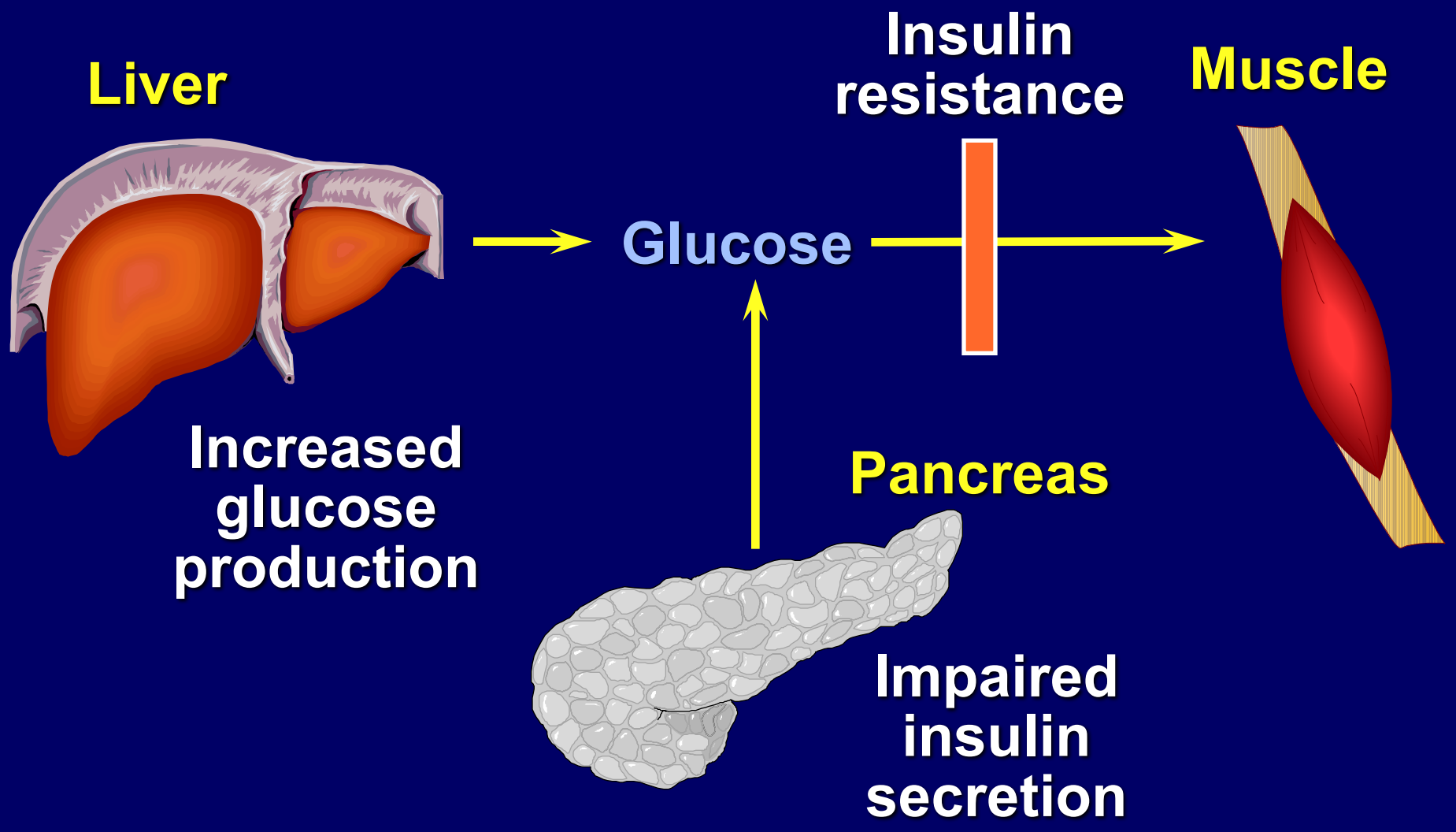
Diabetic Nephropathy

Diabetic Foot Gangrene

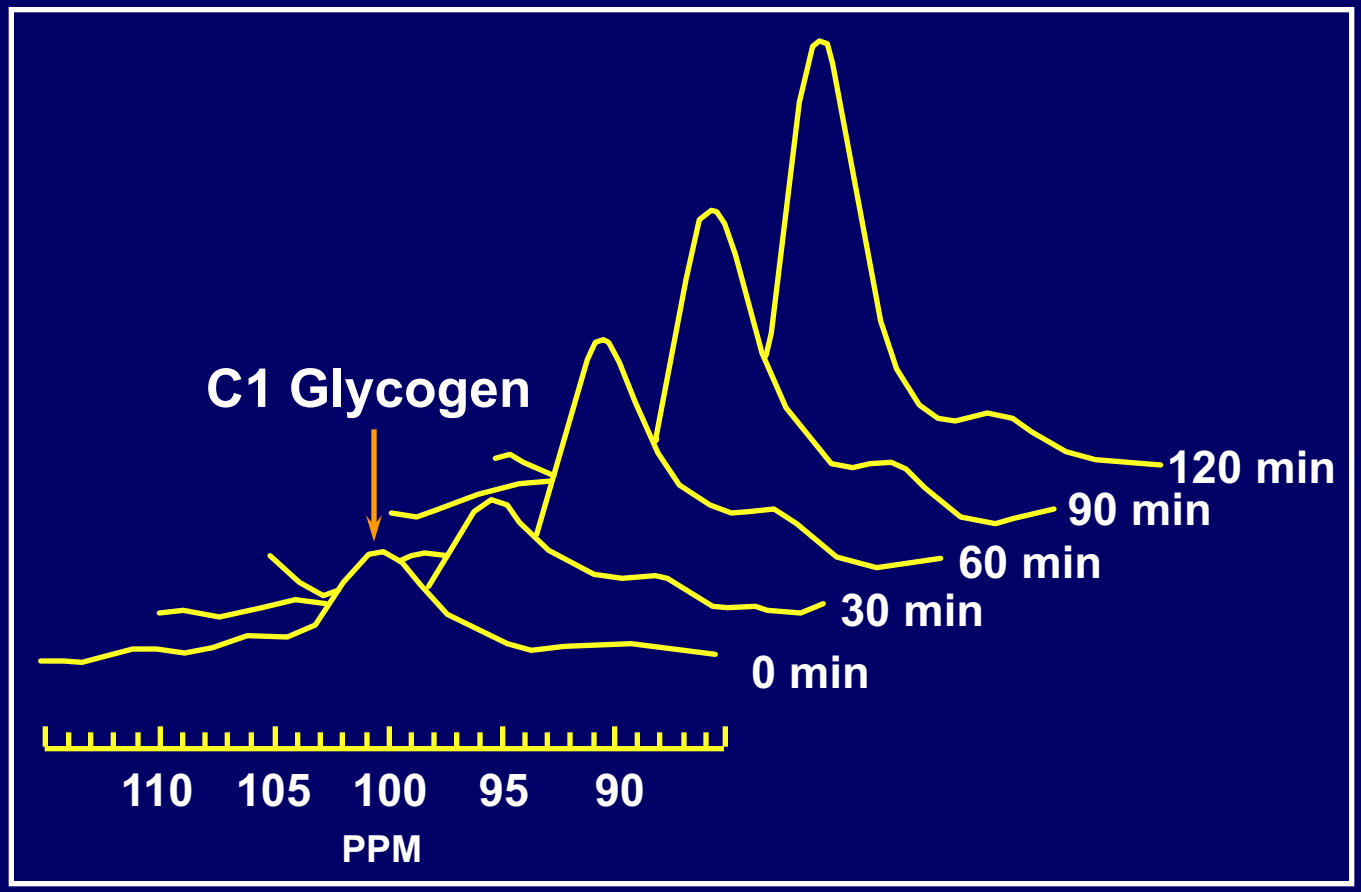
Global Projections for the Diabetes Epidemic: 2013-2035 (millions)



Pathogenesis of Hyperglycemia in Type 2 Diabetes

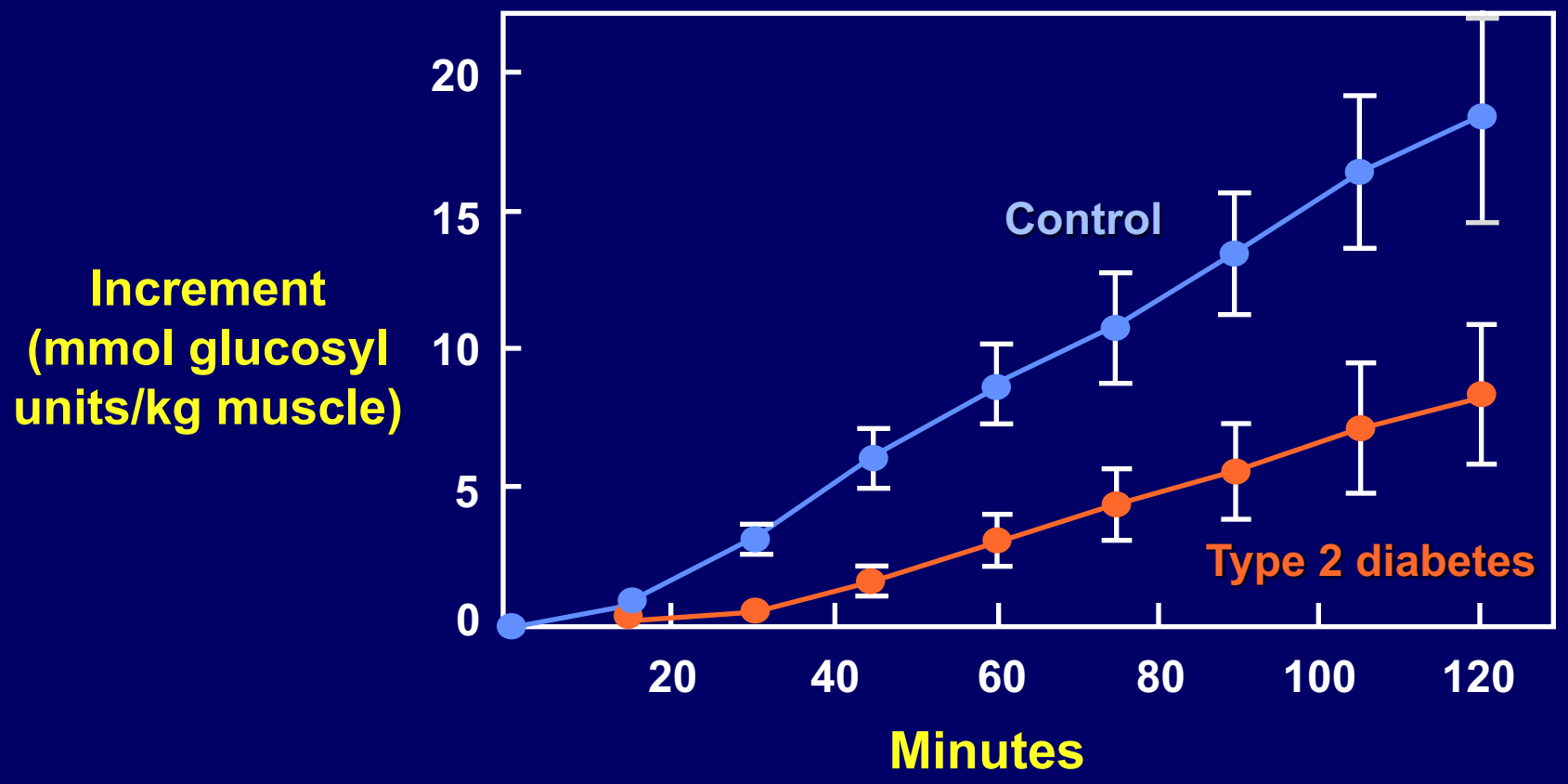


^{13}C NMR Spectra of Muscle Glycogen



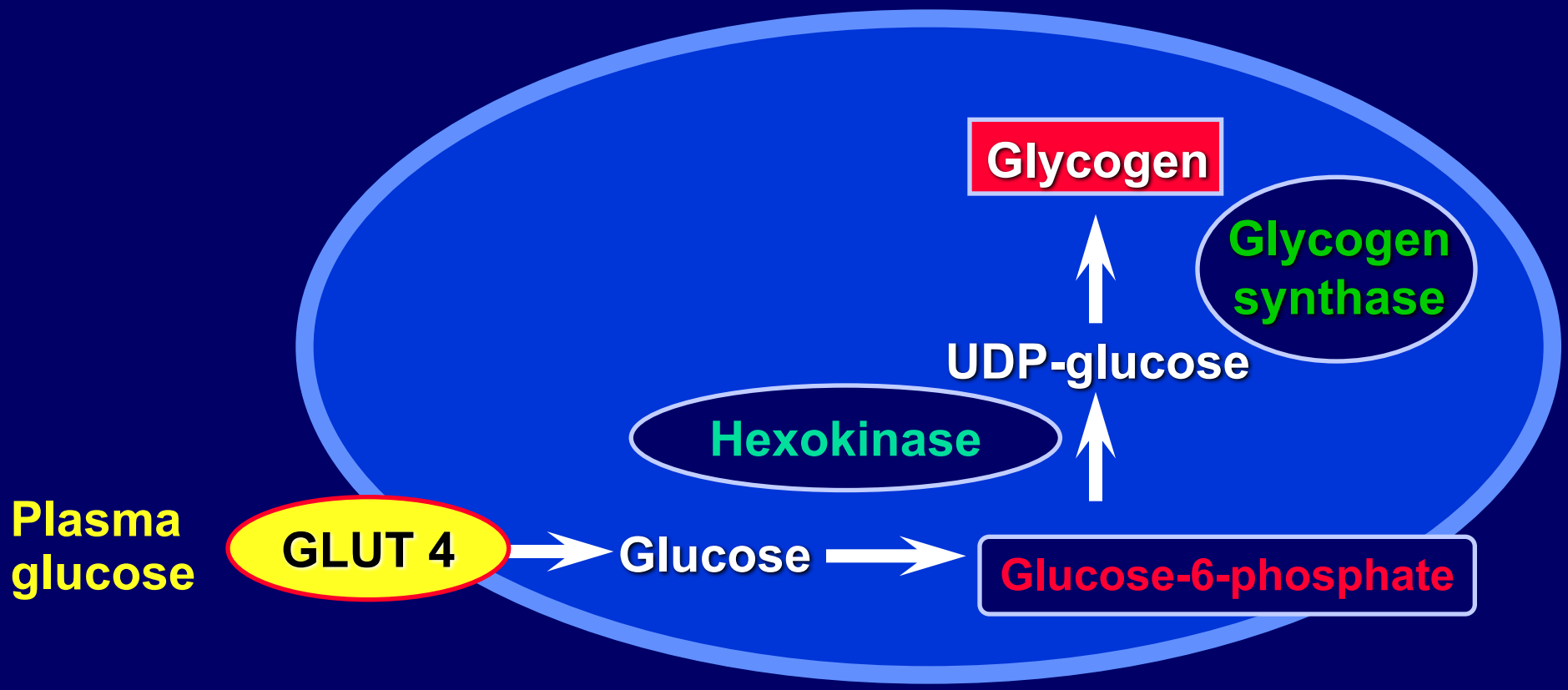
Shulman GI et al. *N Engl J Med.* 1990;322:223–228.

Incremental Change in Muscle Glycogen

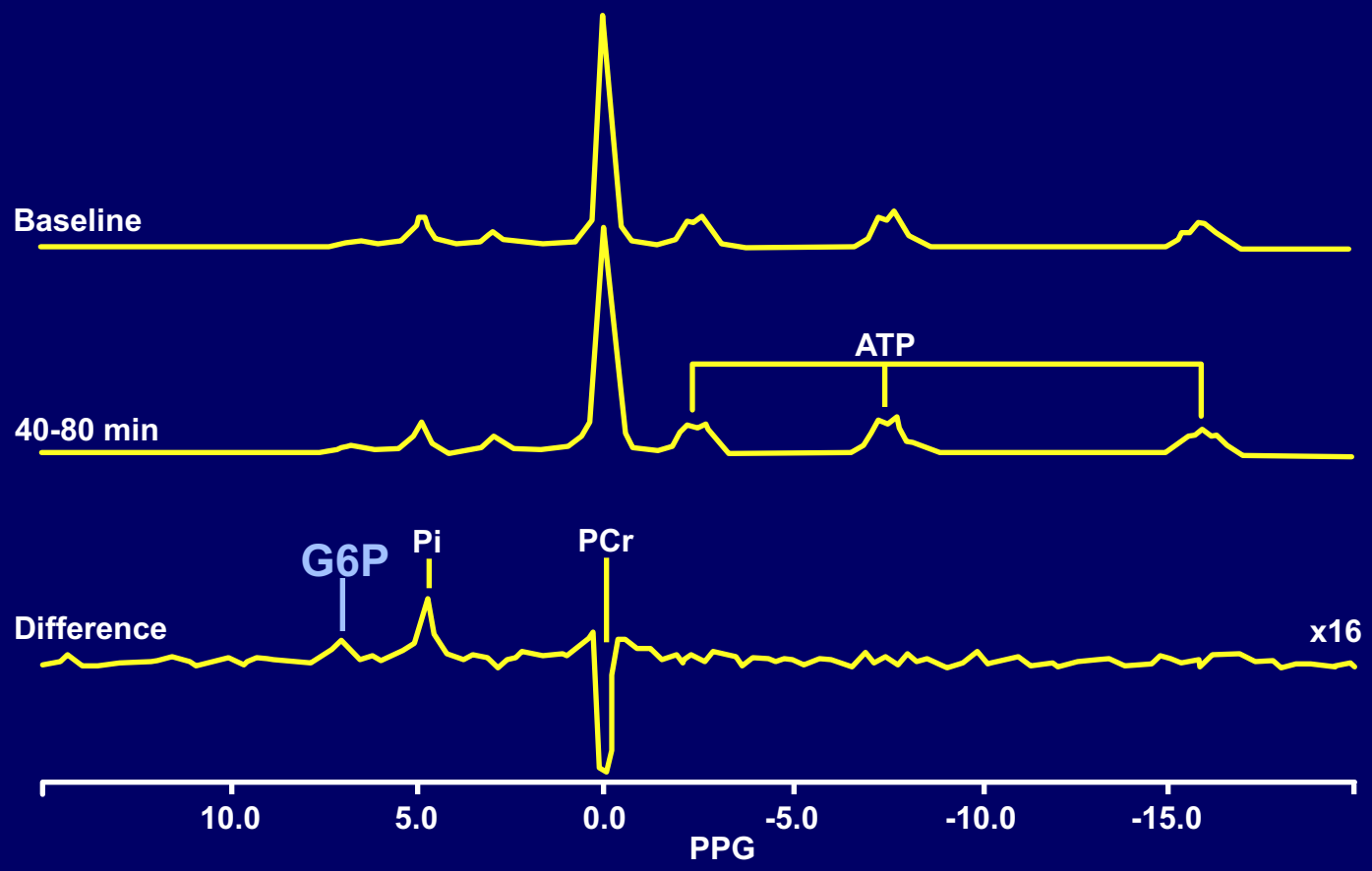


Shulman GI et al. *N Engl J Med.* 1990;322:223–228.

Potential Rate-Controlling Steps in Muscle Glucose Metabolism

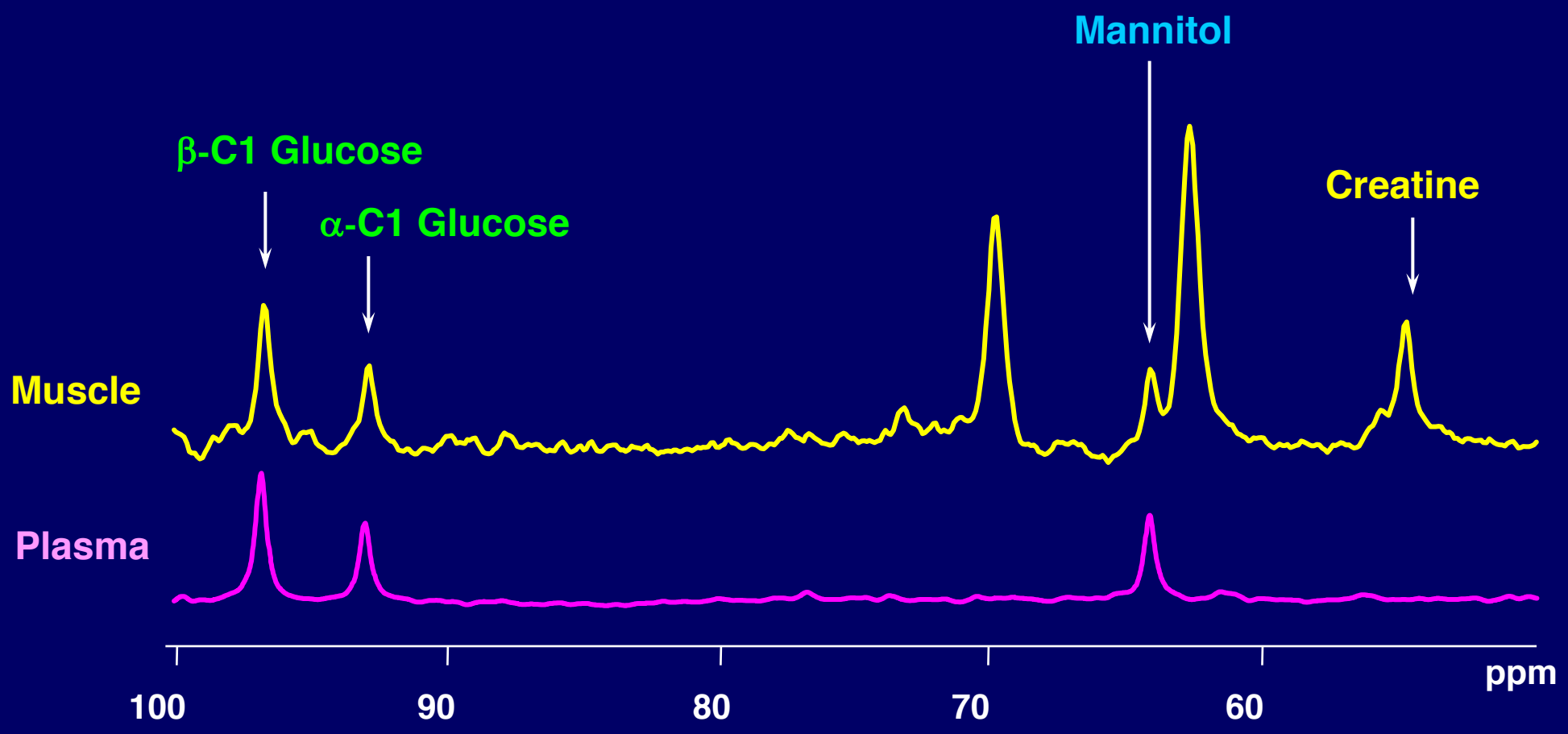


^{31}P NMR Spectra of Human Muscle



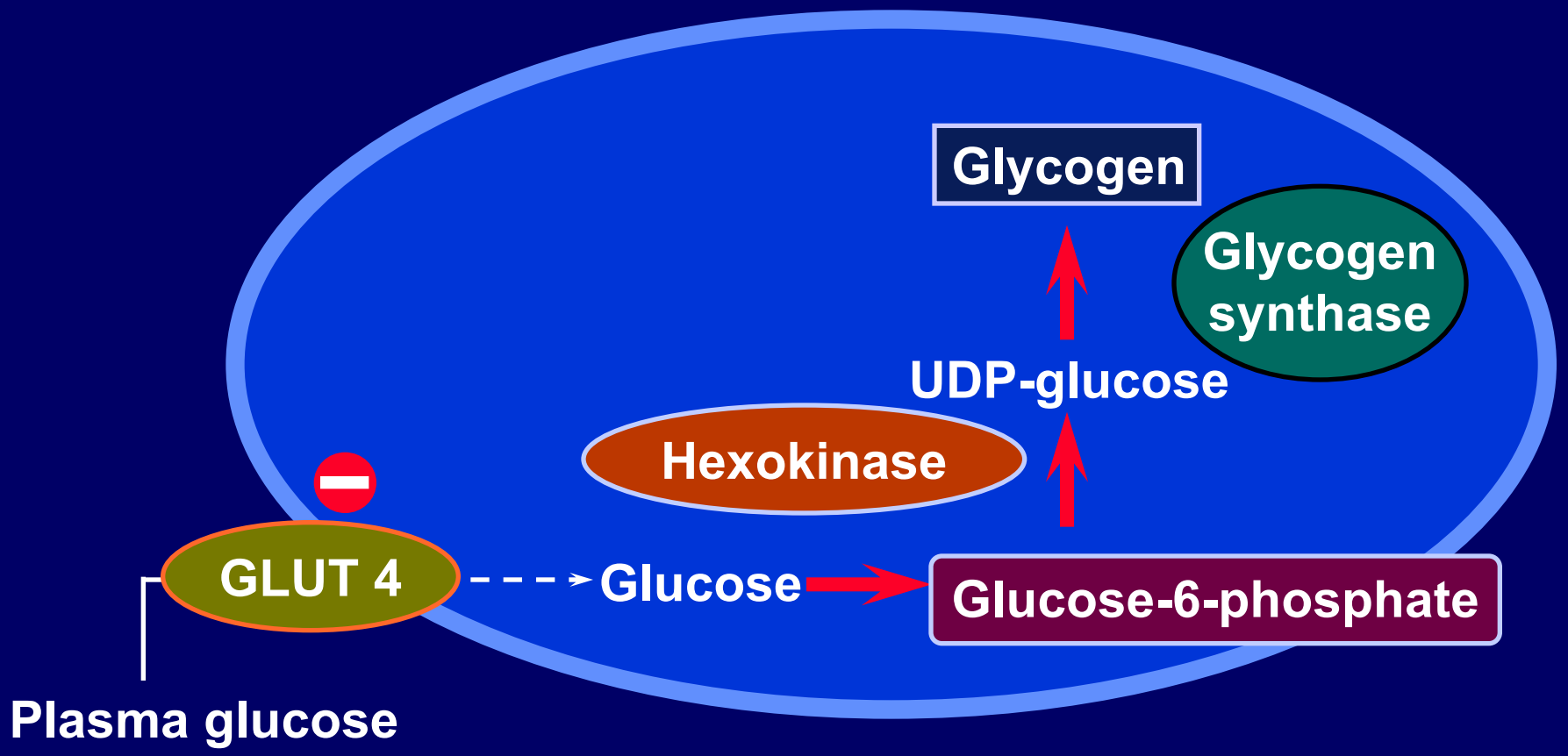
Rothman DL et al. *J Clin Invest.* 1992;89:1069-1075.

^{13}C NMR Spectra of Muscle and Plasma



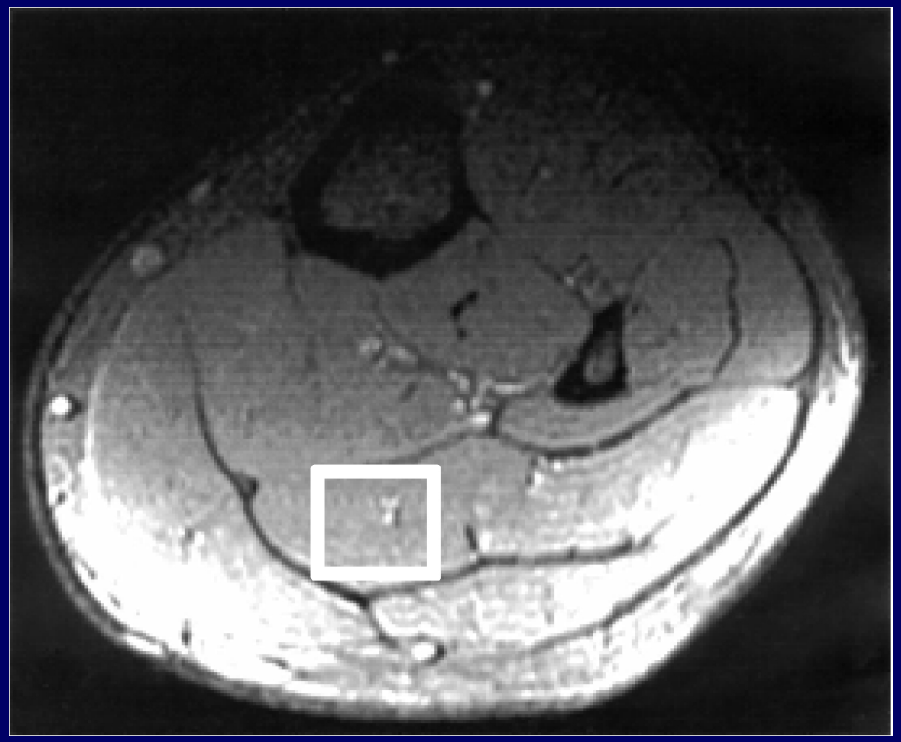
Cline et al, N Engl J Med. 1999:341;240-246

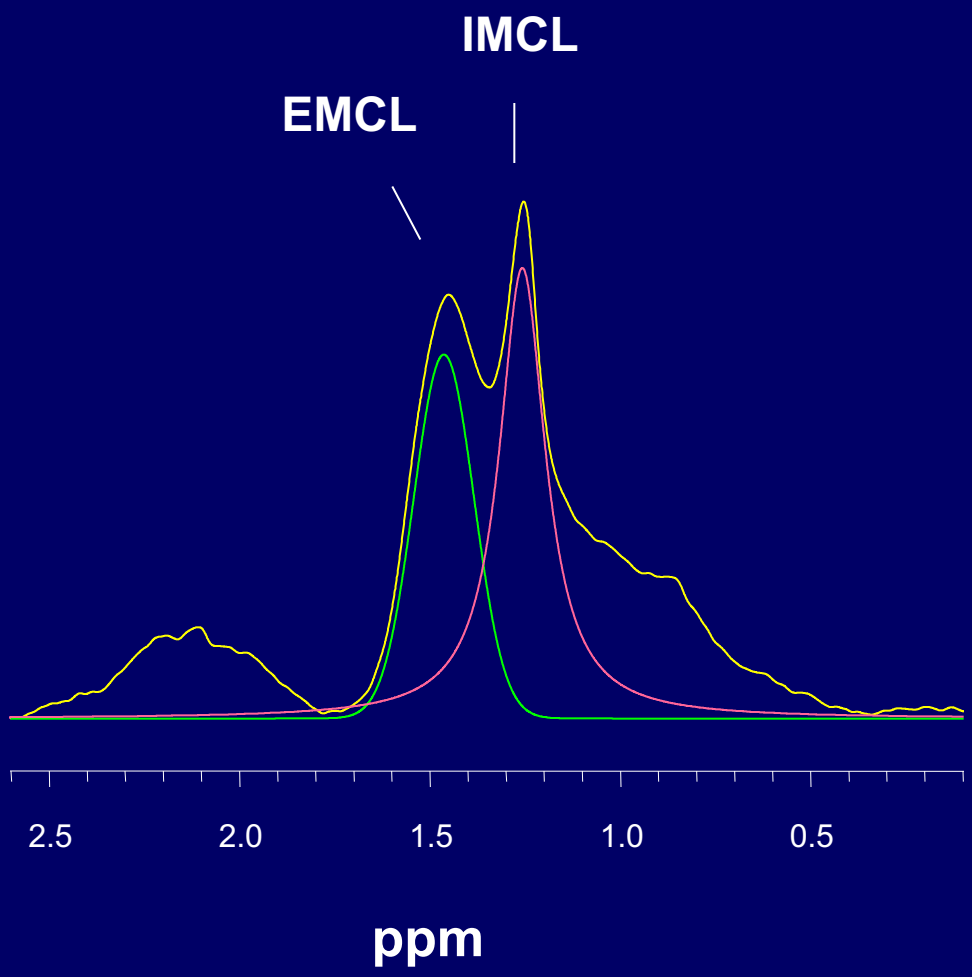
Glucose Transport Activity Is Decreased in Type 2 Diabetes



Cline et al N Engl J Med. 1999:341;240-246

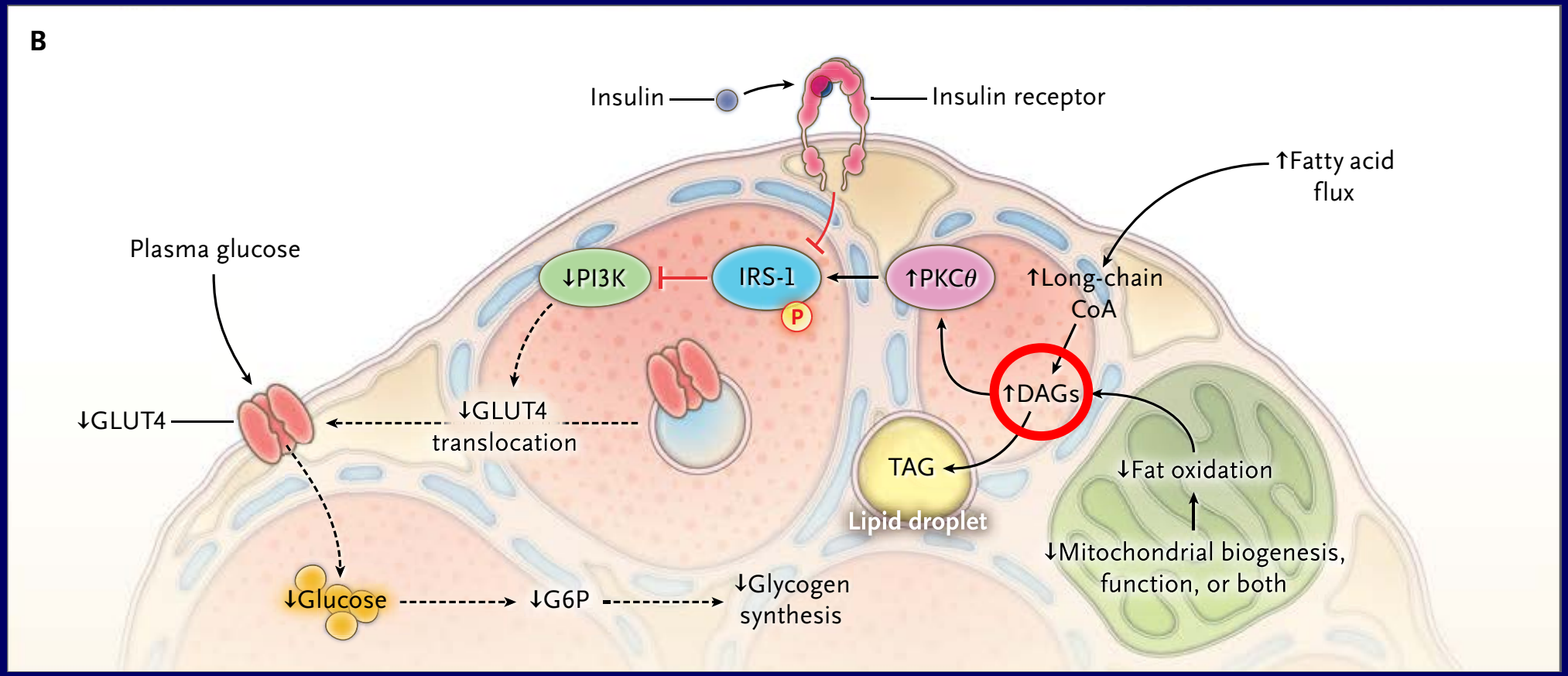
^{1}H spectrum of the soleus muscle of a lean subject





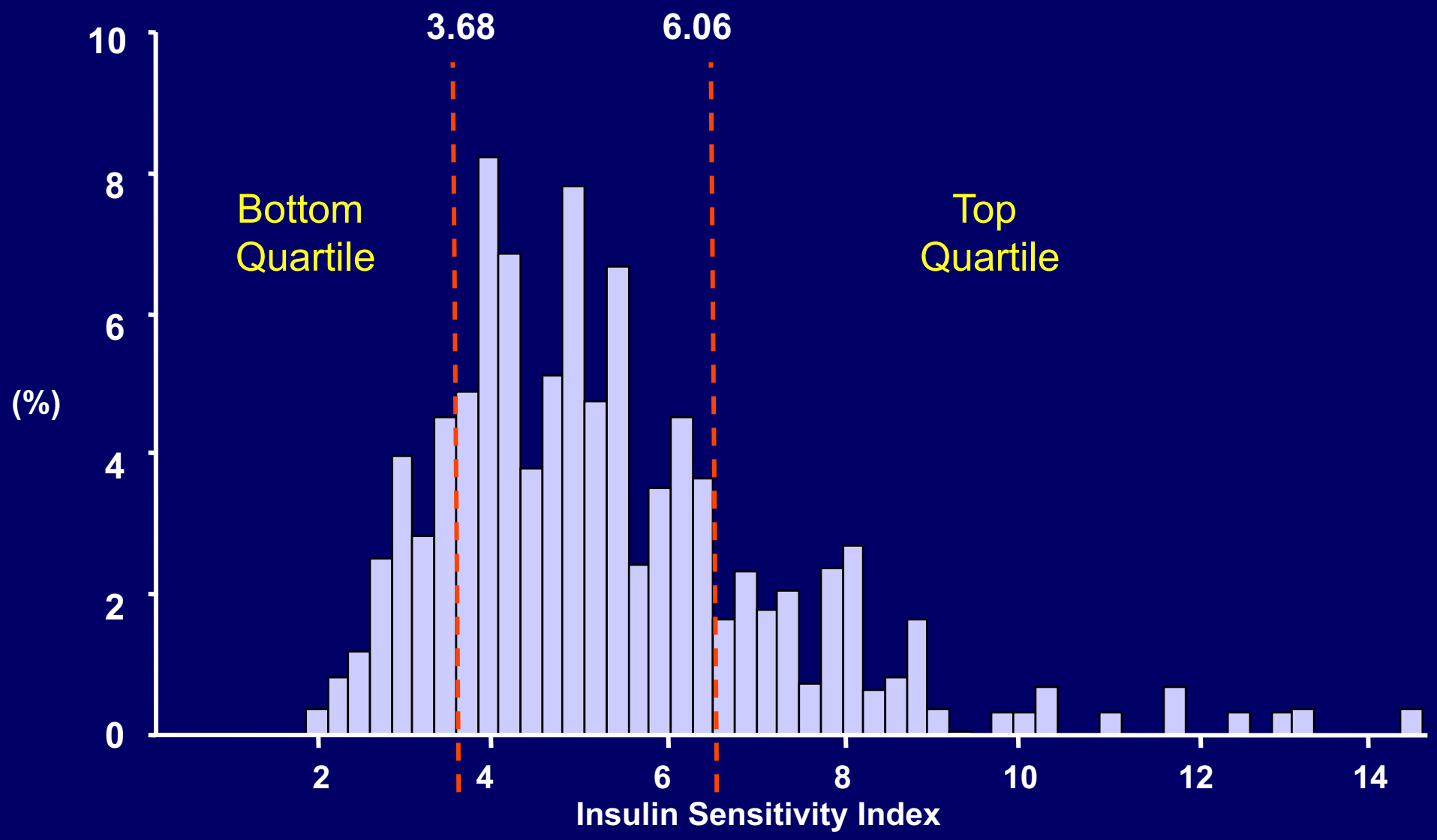
Krssak et al, Diabetologia 42:113-116 (1999)

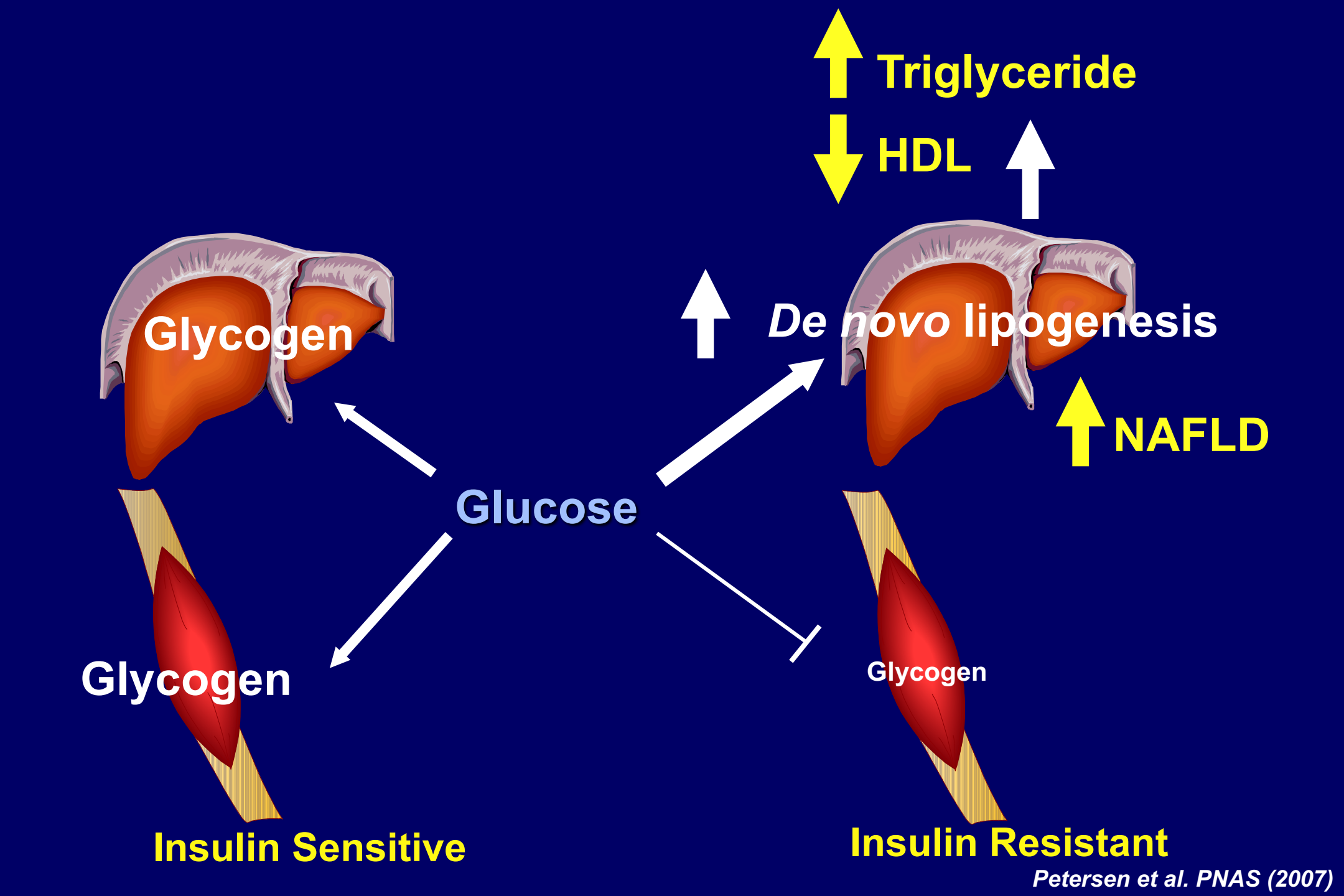
Diacylglycerol (DAG)/PKCθ hypothesis of lipid-induced muscle insulin resistance



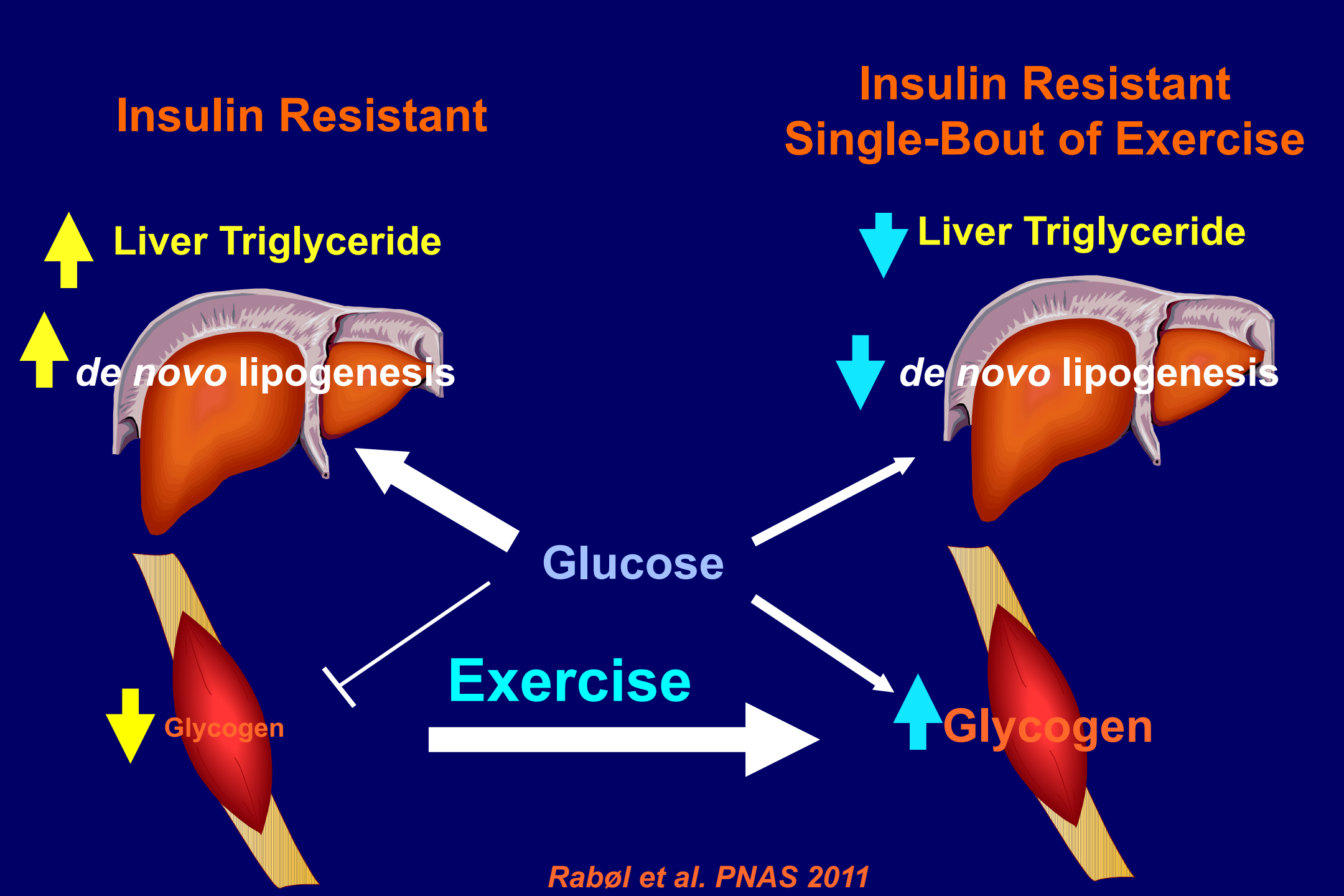
Shulman , N. Eng. J. Med 2014

Insulin Sensitivity Index (n=~400)

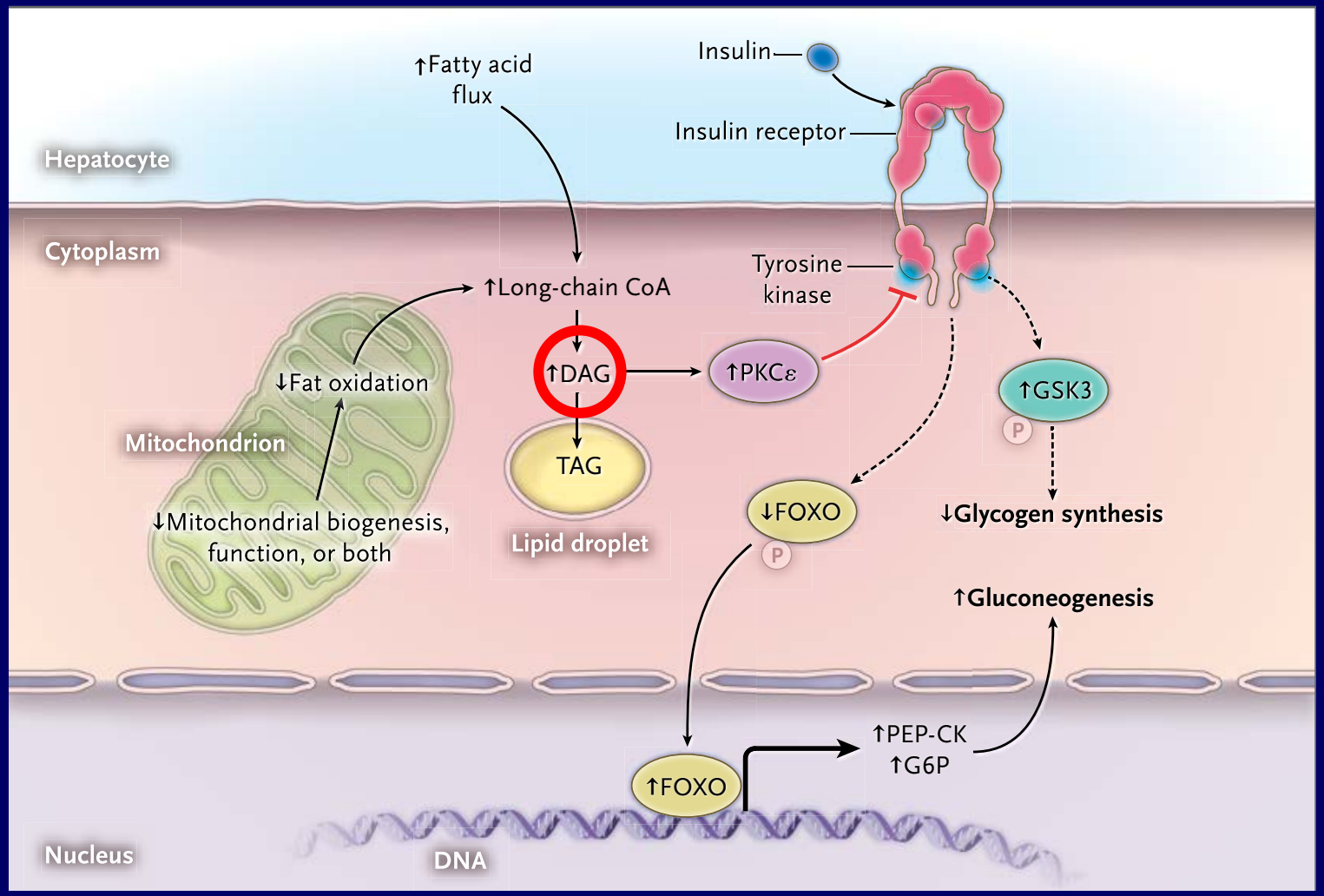




Petersen et al. PNAS (2007)

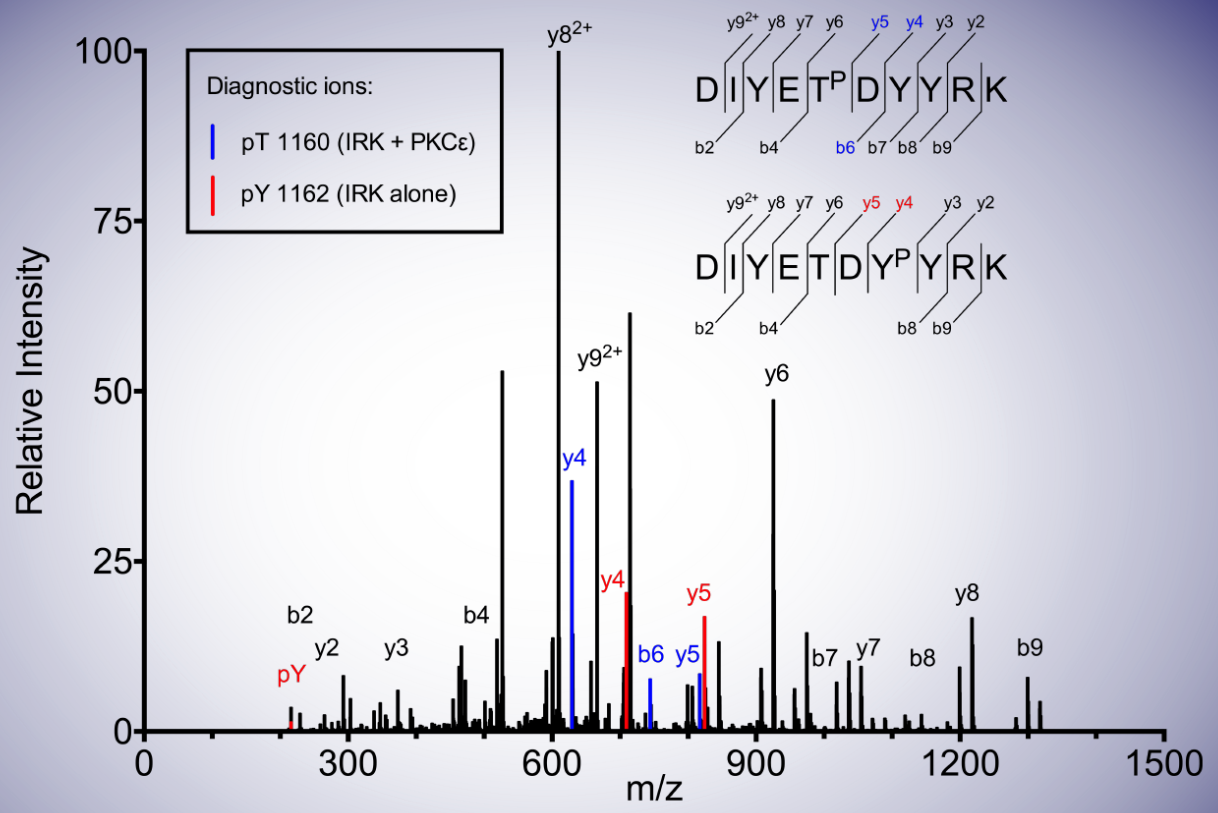

Insulin Resistant
Liver Triglyceride
de novo lipogenesis
Glycogen
Insulin Resistant
Single-Bout of Exercise
Liver Triglyceride
de novo lipogenesis
Glucose
Exercise
Glycogen
Rabøl et al. PNAS 2011

Diacylglycerol (DAG)-PKCε Hypothesis of NAFLD-Induced Hepatic Insulin Resistance



Samuel et al. JBC 2004, Samuel et al. JCI 2007, JCI Shulman, N. Eng. J. Med 2014

Incubation of INSR with PKCε reveals a novel threonine phosphorylation site



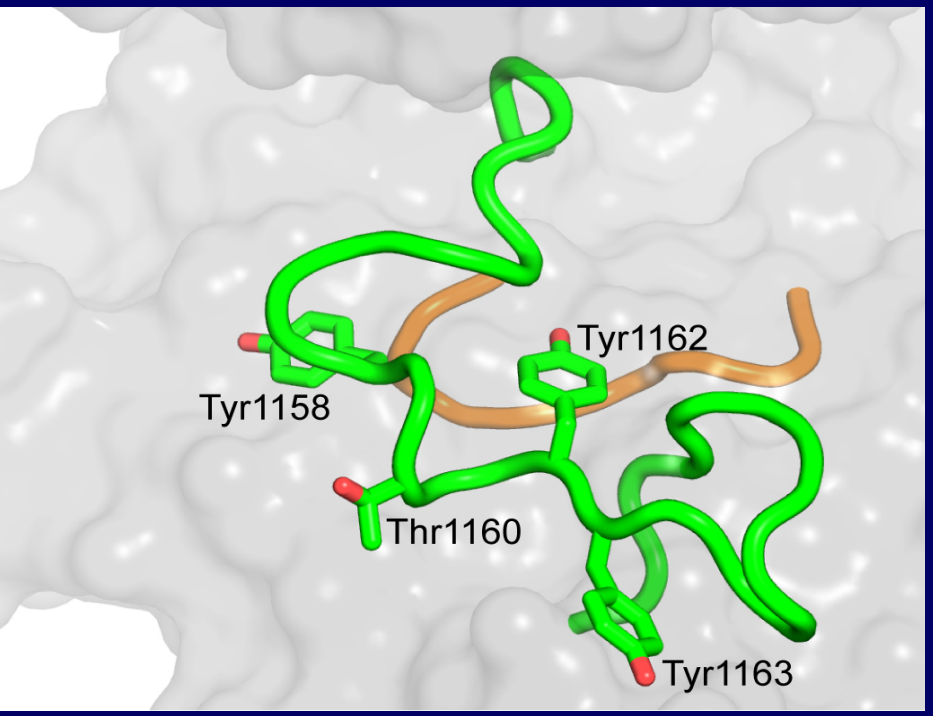
Jesse Rinehart and Brandon Gassaway

Thr^{1160} is conserved to *Drosophila*

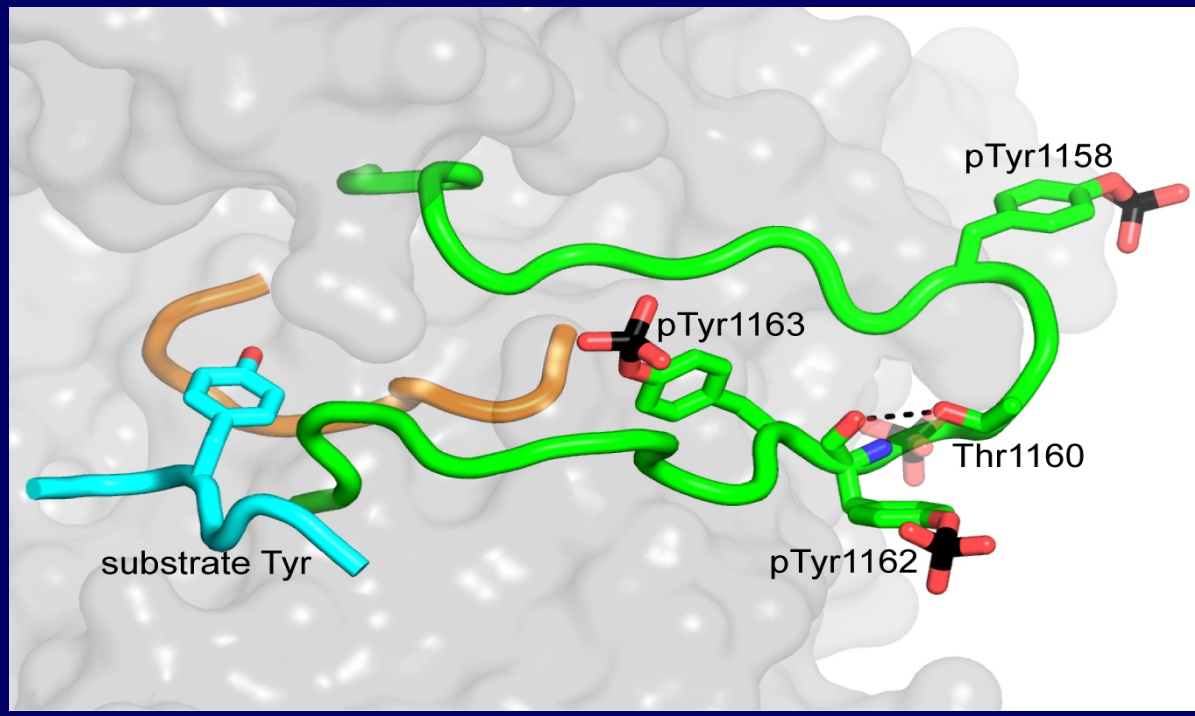
Species	Gene	Sequence
Homo sapiens	*Insr*	DIYETDYYRK
Mus musculus	*Insr*	DIYETDYYRK
Xenopus laevis	*insr*	DIYETDYYRK
Danio rerio	*insra*	DIYETDYYRK
Drosophila melanogaster	*InR*	DIYETDYYRK
Caenorhabditis elegans	*daf-2*	DLFYHDYYKP

Thr^{1160} phosphorylation is predicted to destabilize the active configuration of the Insulin Receptor

Inactive

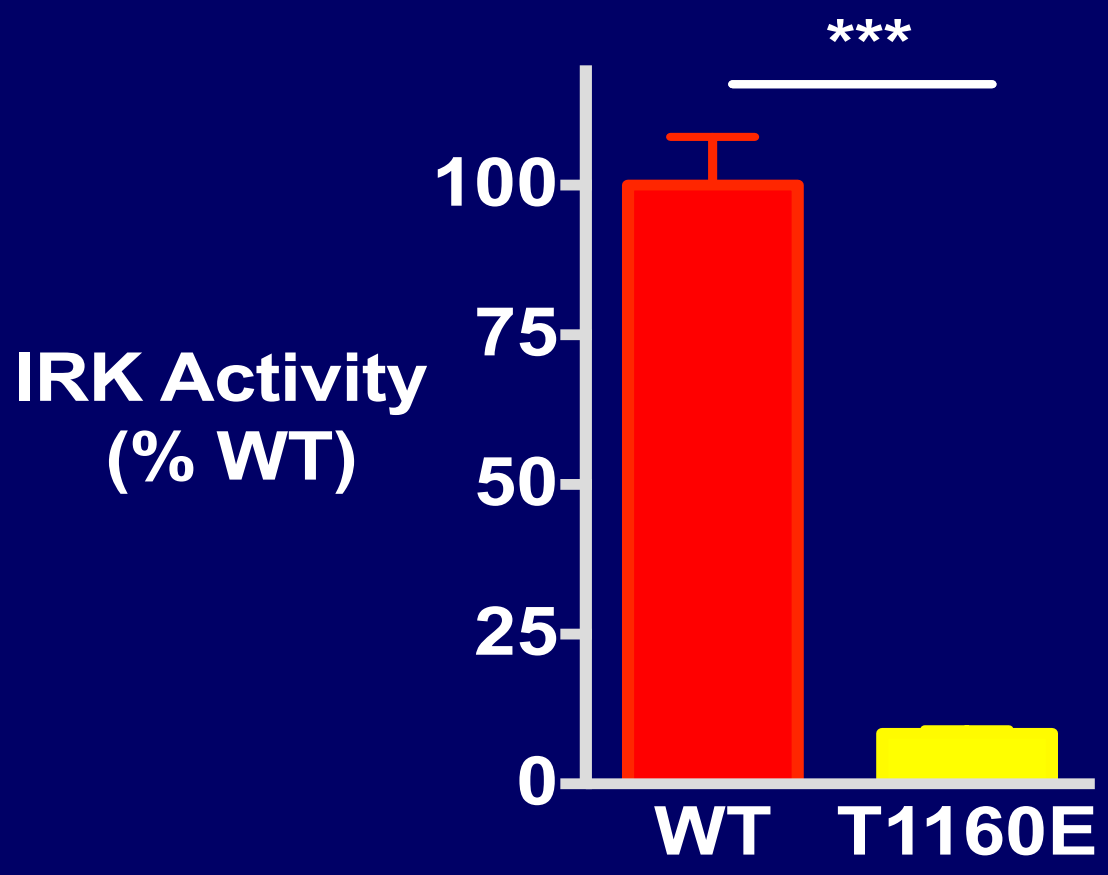


Active



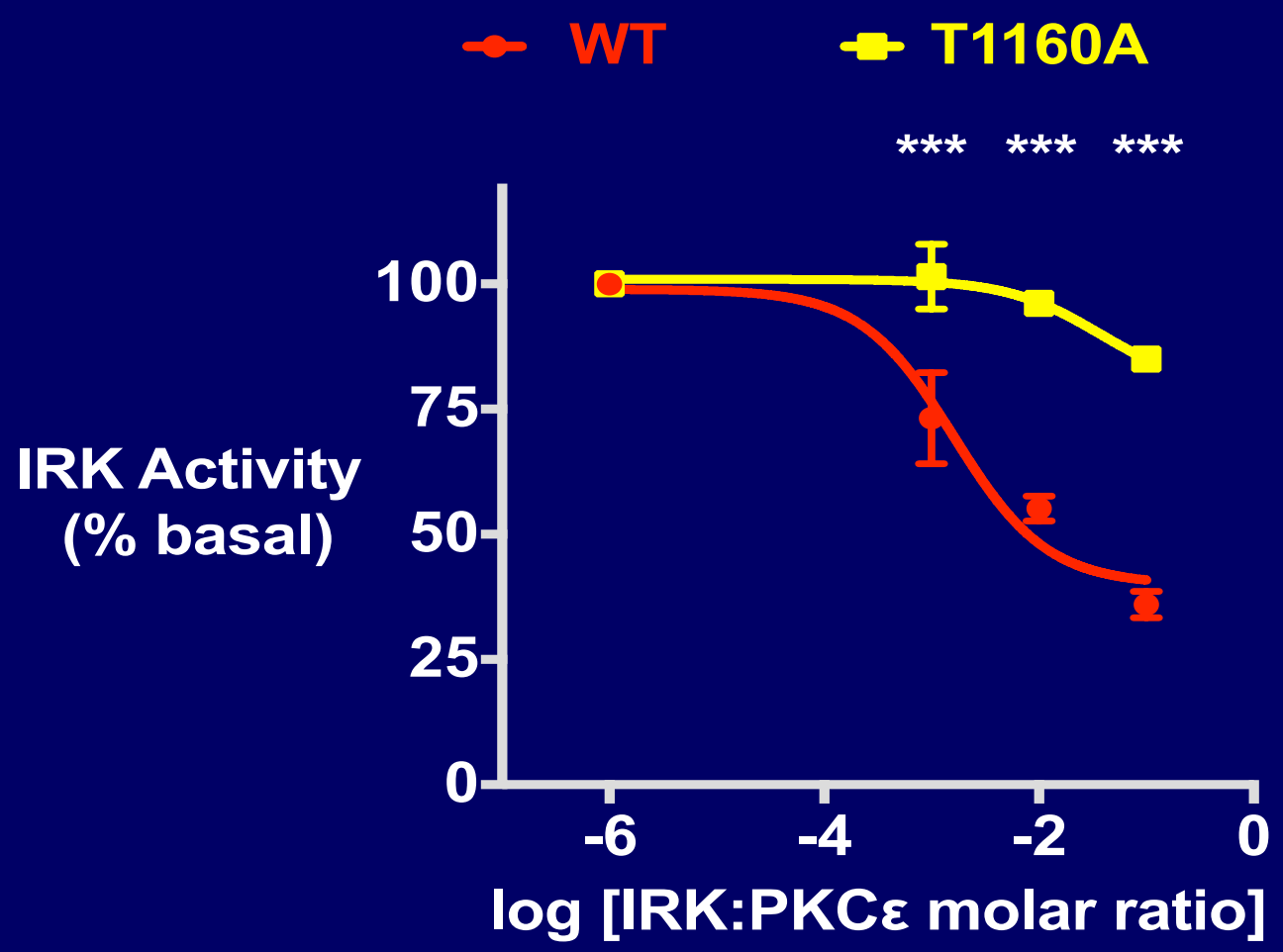
Stevan Hubbard

IRK T1160E is kinase dead



Petersen et al. J Clin Invest 2016

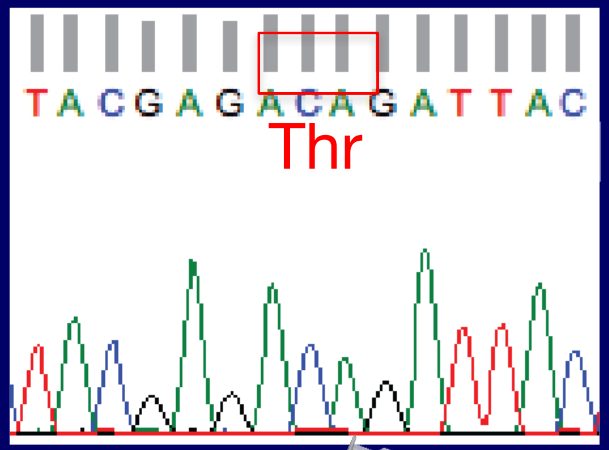
IRK T1160A is protected from PKCε inhibition



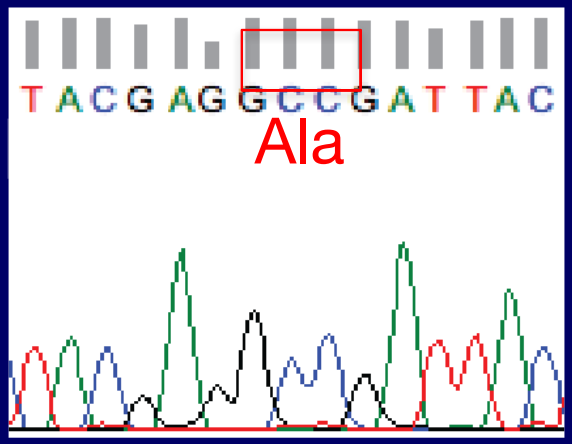
Petersen et al. J Clin Invest 2016

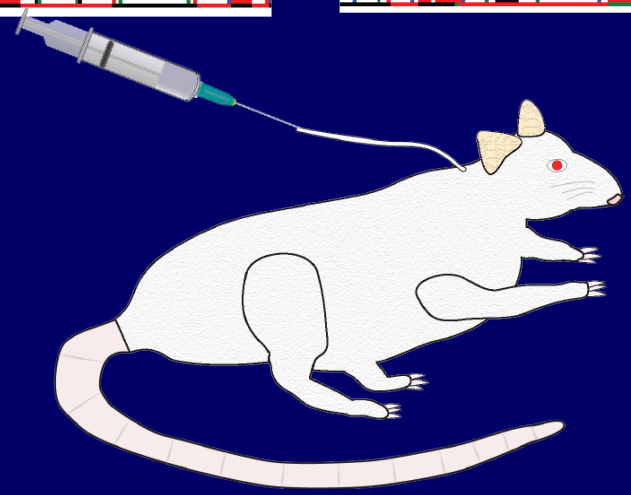
Insr^{T1150A} mice

Insr^{WT}/*Insr*^{WT}

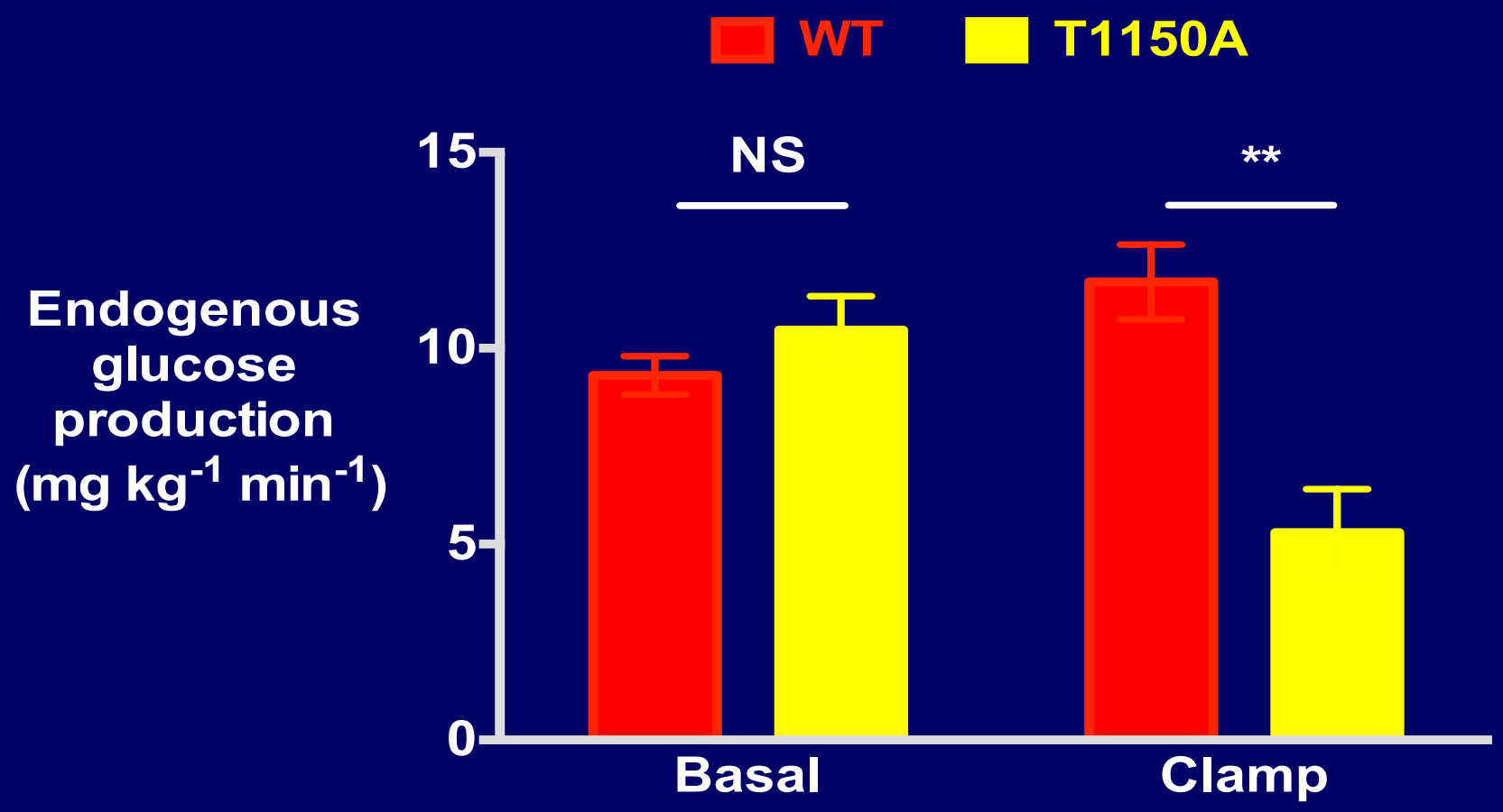


Insr^{T1150A}/*Insr*^{T1150A}



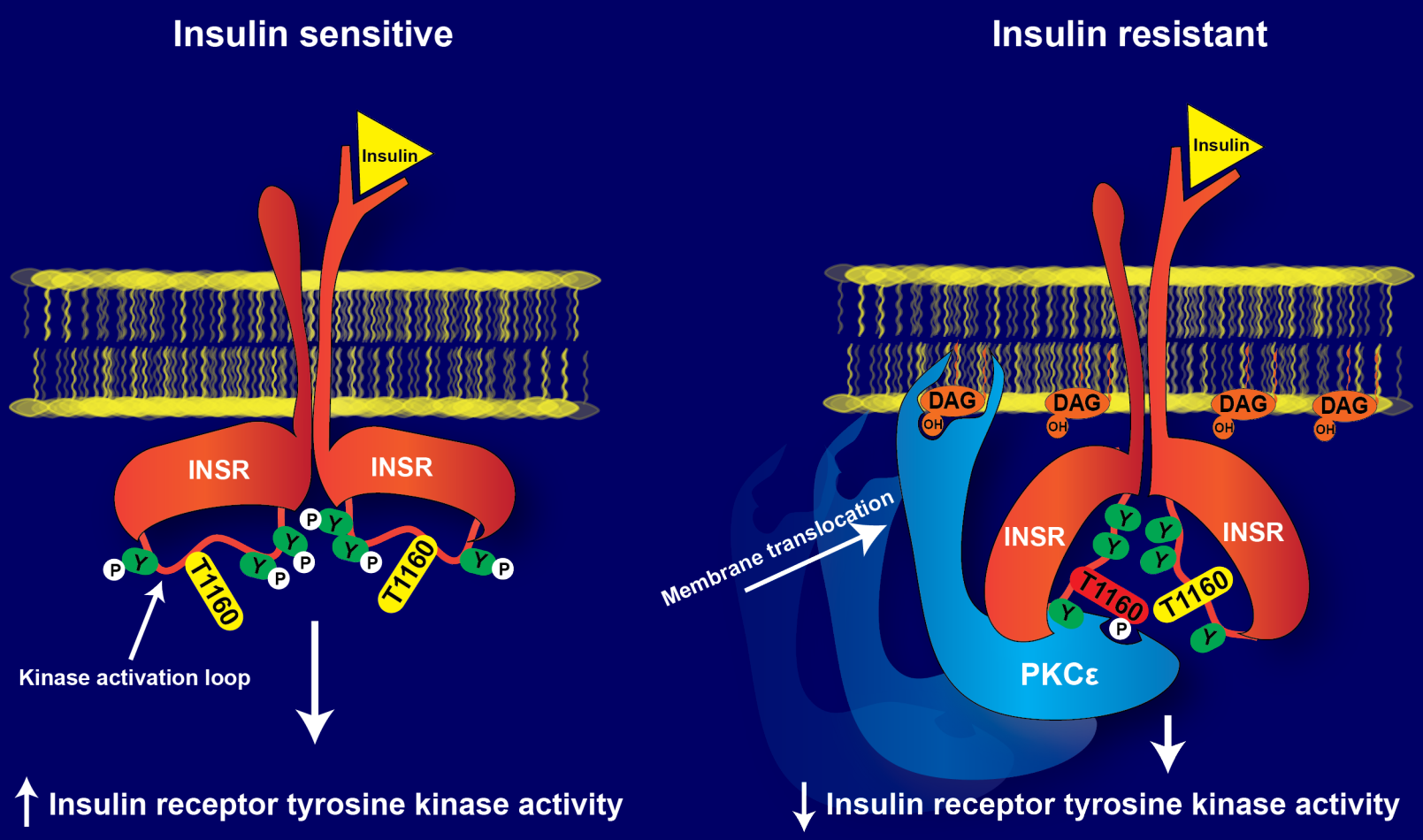


Insr^{T1150A} mice are protected from high-fat diet induced hepatic insulin resistance



Petersen et al. J Clin Invest 2016

Working model: PKCε Inhibition of Insulin Receptor Tyrosine Kinase Activity

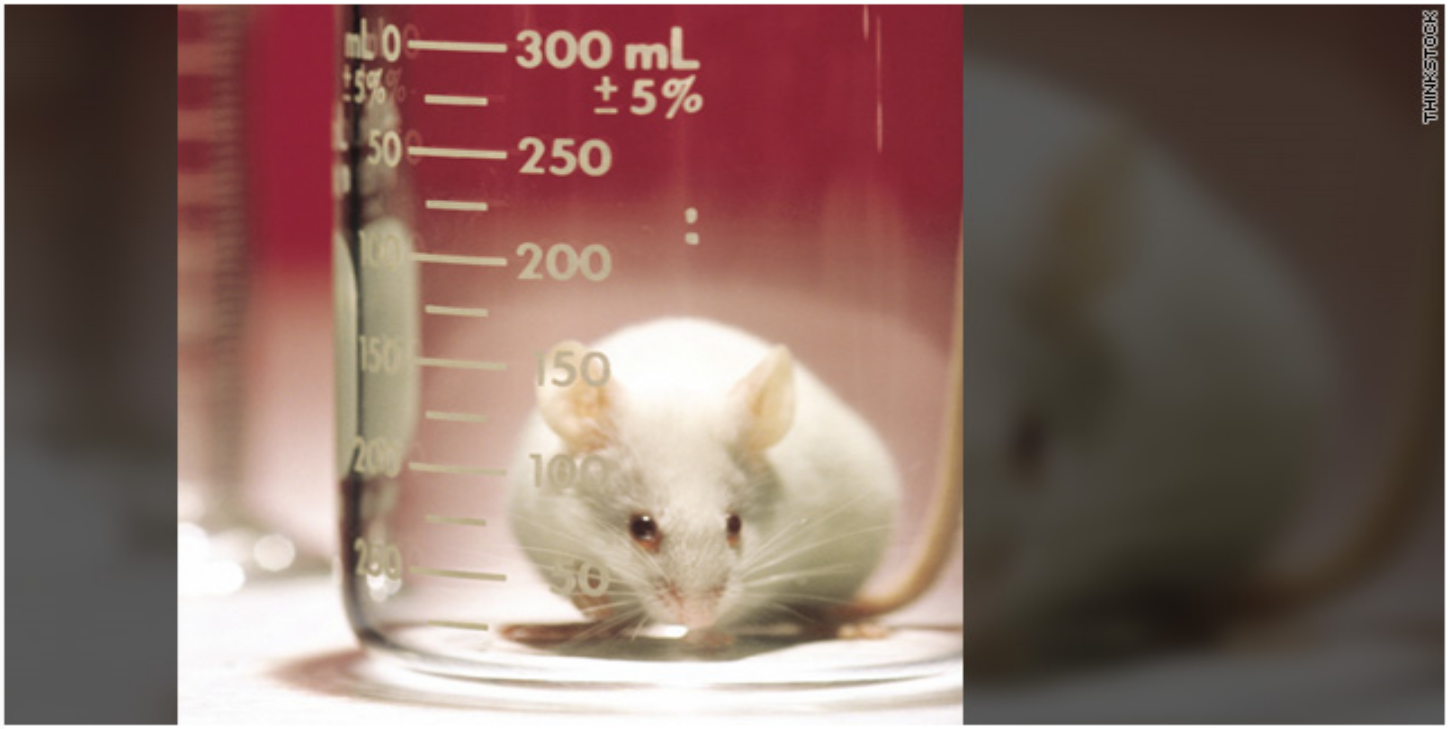


Petersen et al. J Clin Invest 2016, Perry et al. Cell (published on line 1/5/18)

But.. is this relevant to humans?

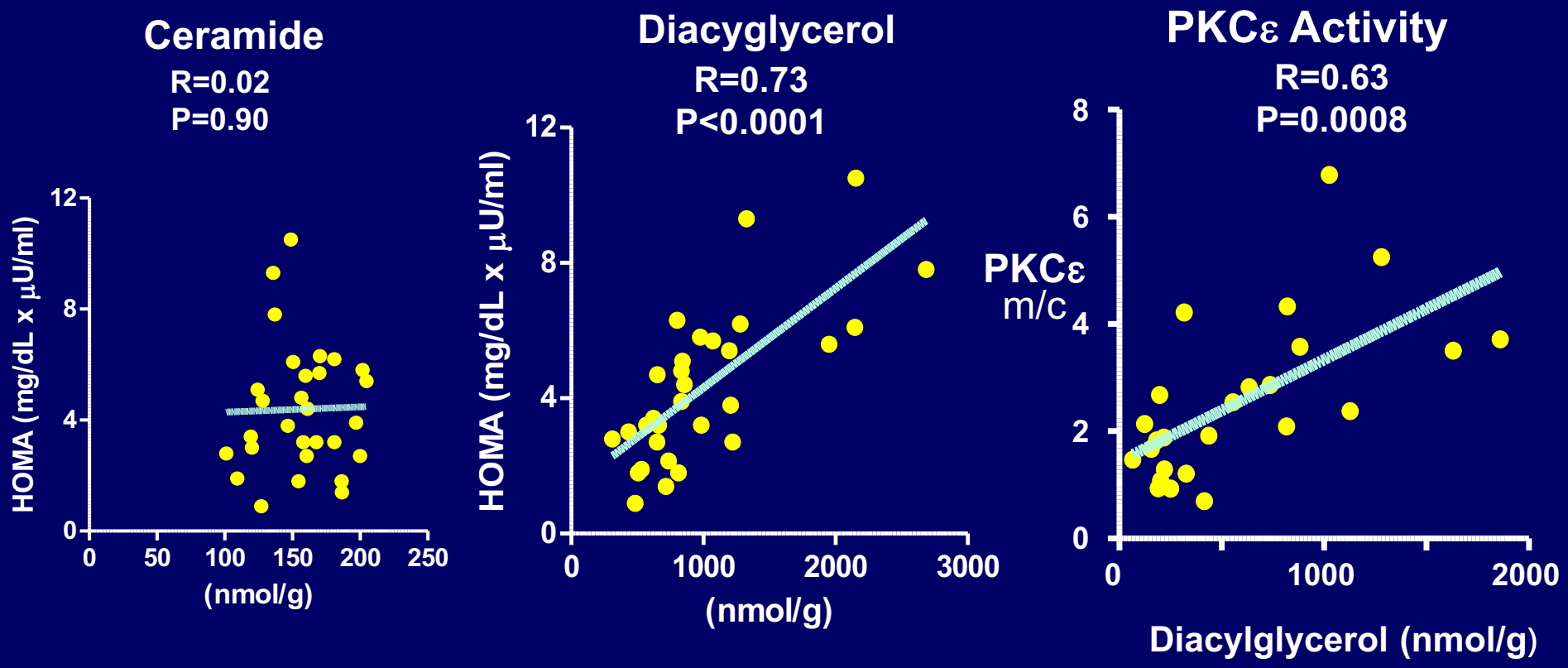
Many studies great news for mice, not so much for humans

By **Elizabeth Landau**, CNN
June 8, 2010 8:18 a.m. EDT

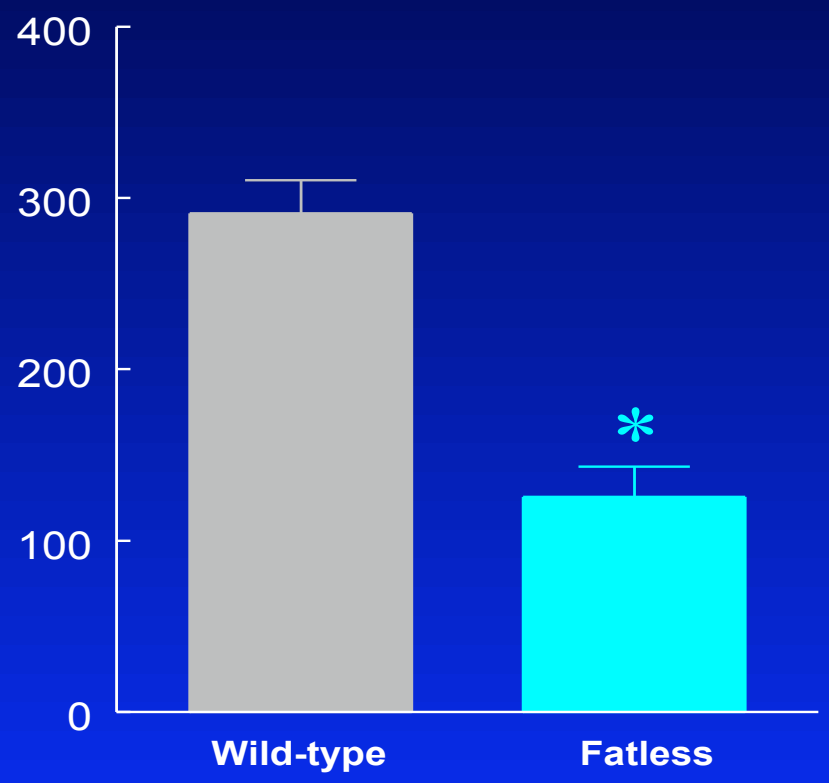


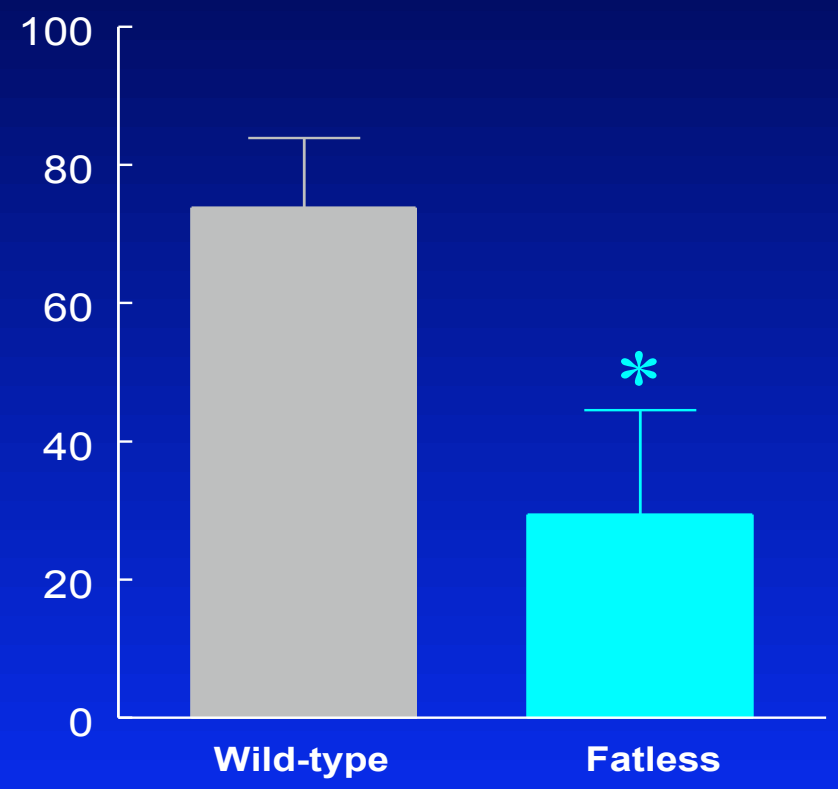
Some study results in rodents are more applicable to humans than others.

Hepatic Diacylglycerol and PKCε Activation Correlate with Insulin Resistance in Humans

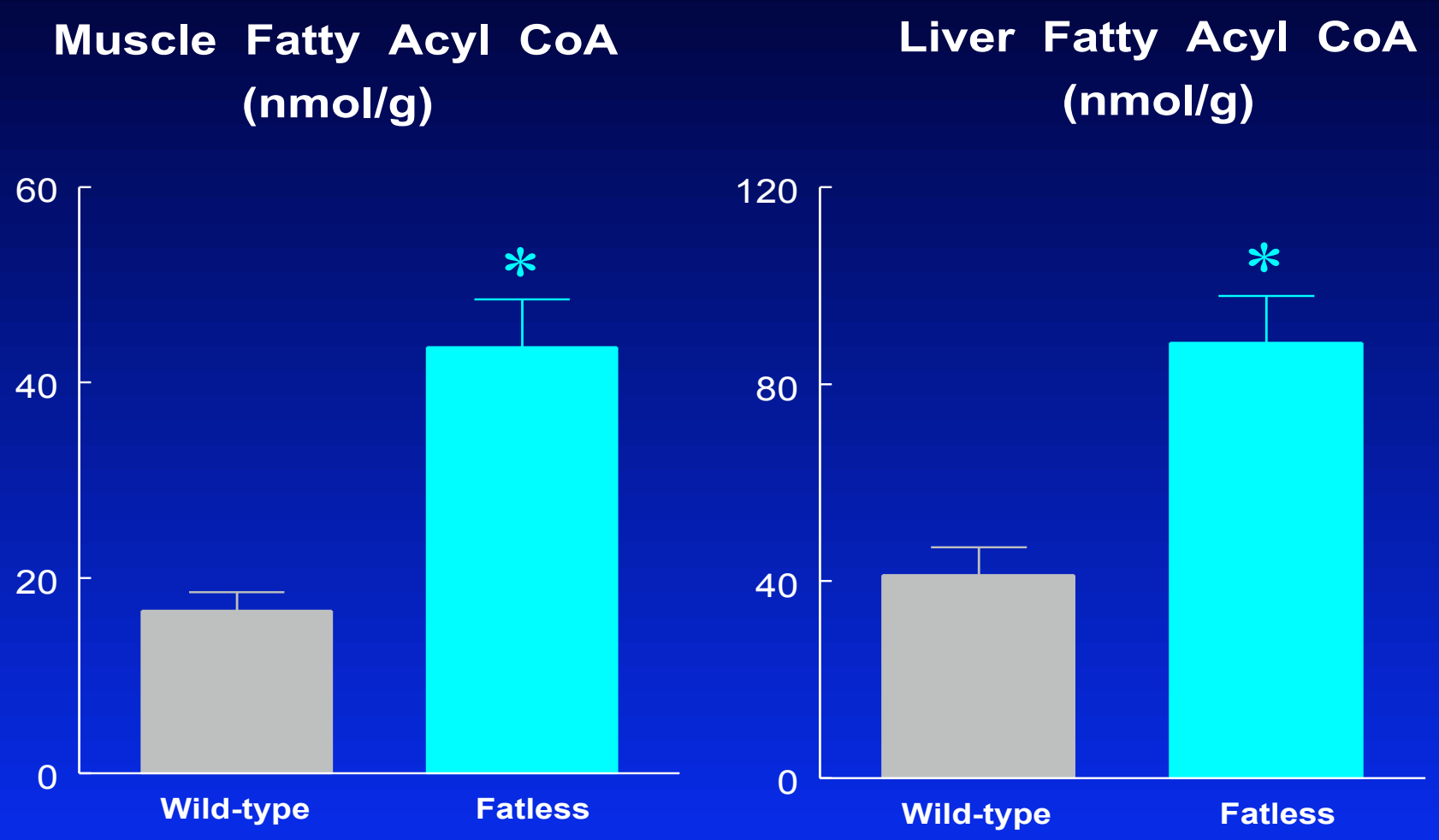


Kumashiro et al. PNAS 2011

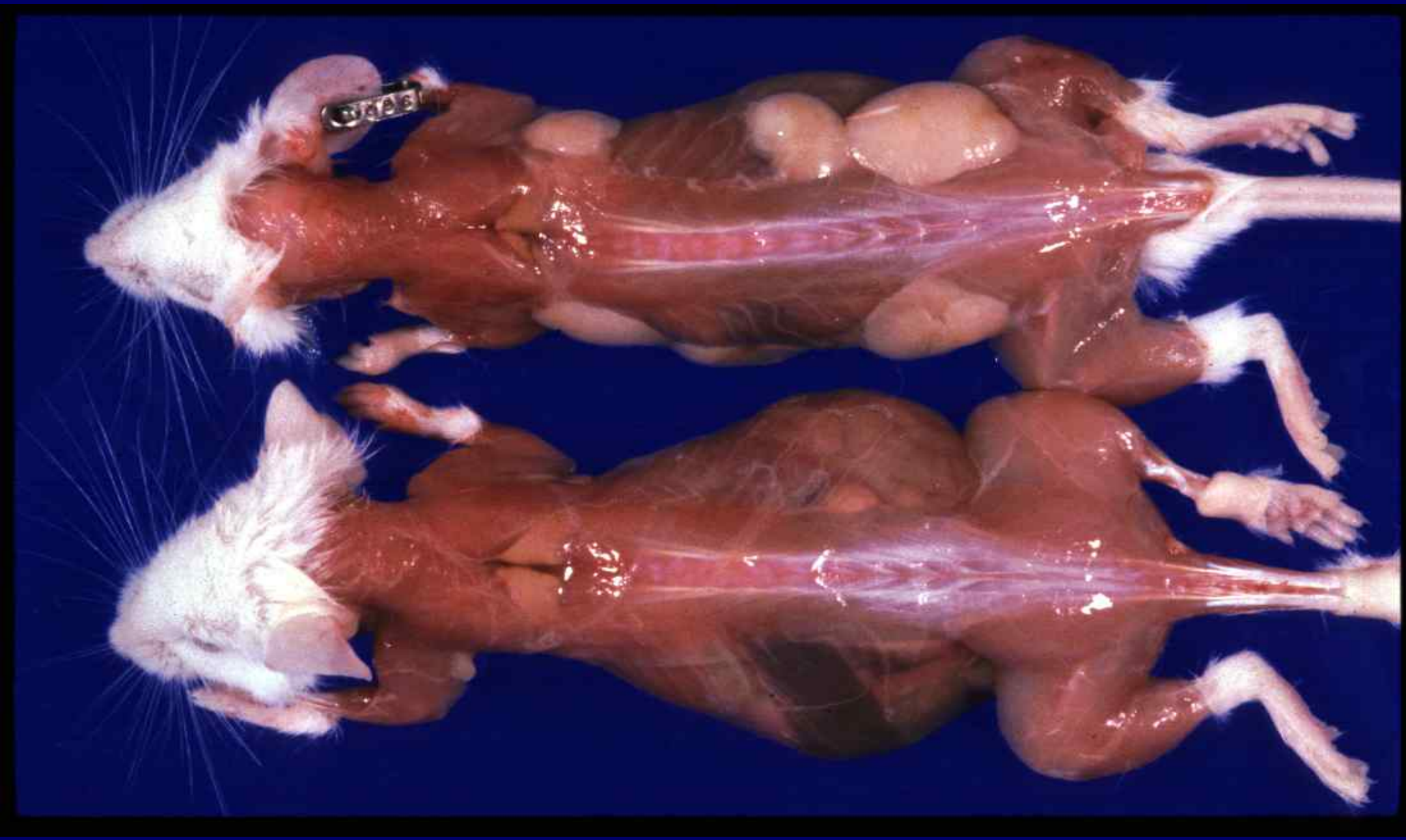




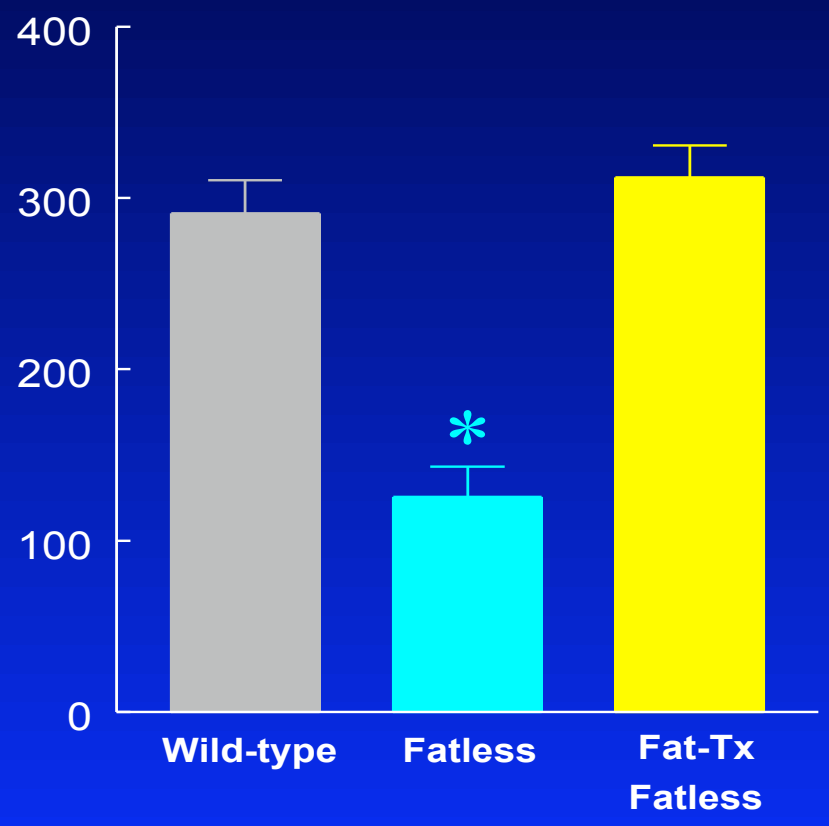
Kim et al. J. Biol. Chem. 275:8456-8460, 2000

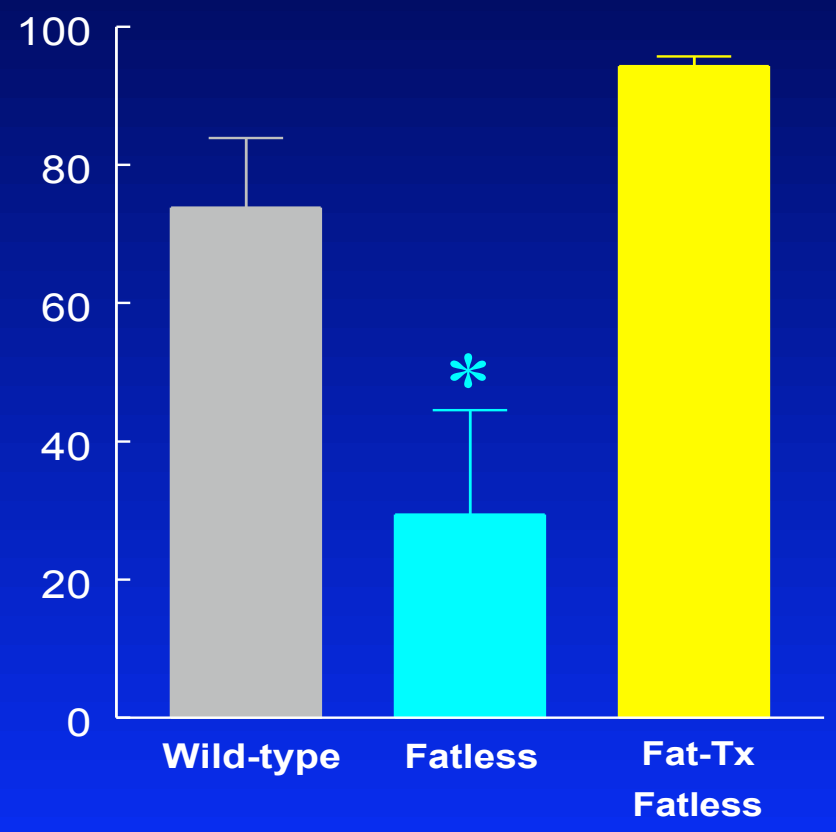


Kim et al. J. Biol. Chem. 275:8456-8460, 2000

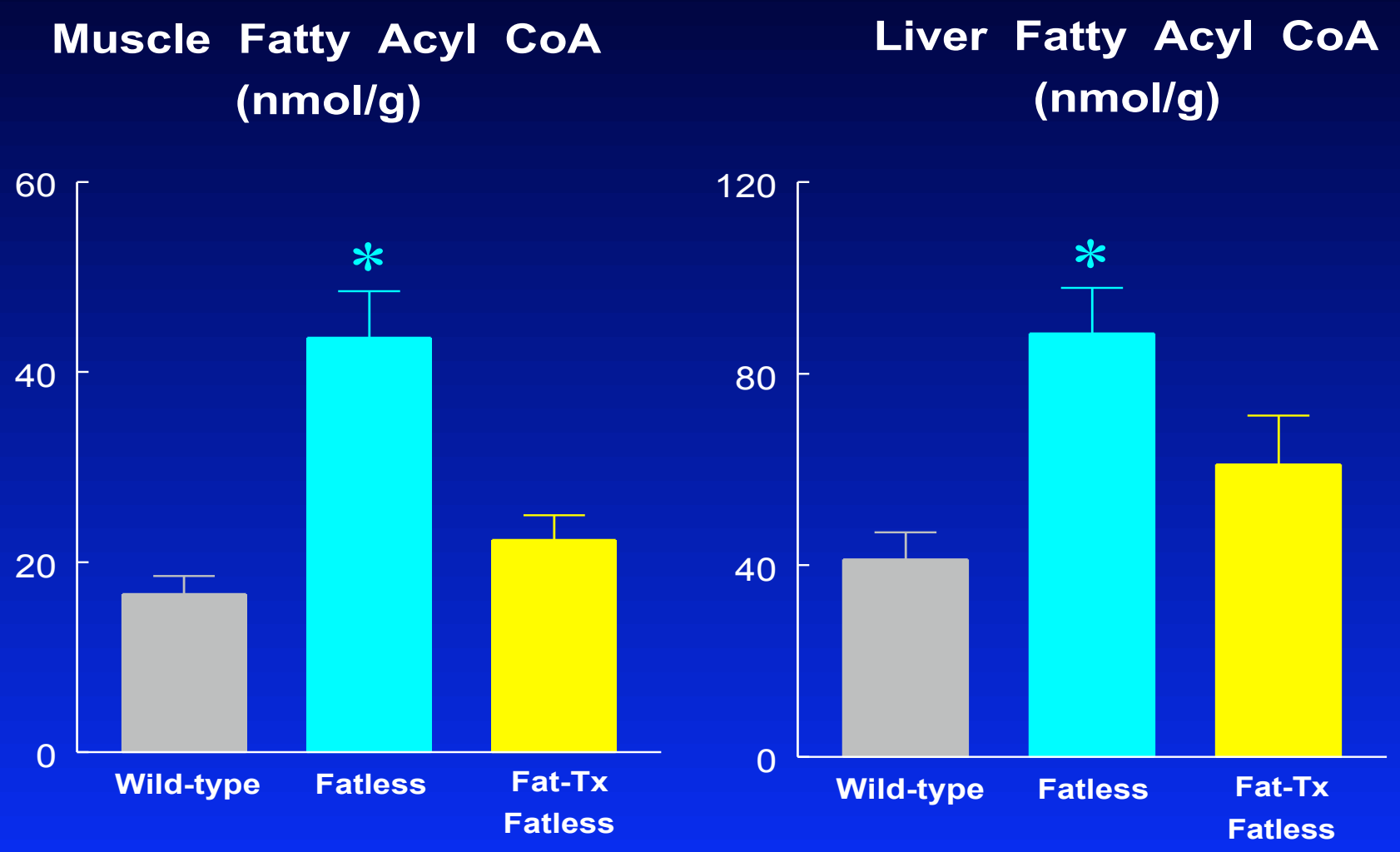


J. Biol. Chem. 275:8456-8460, 2000





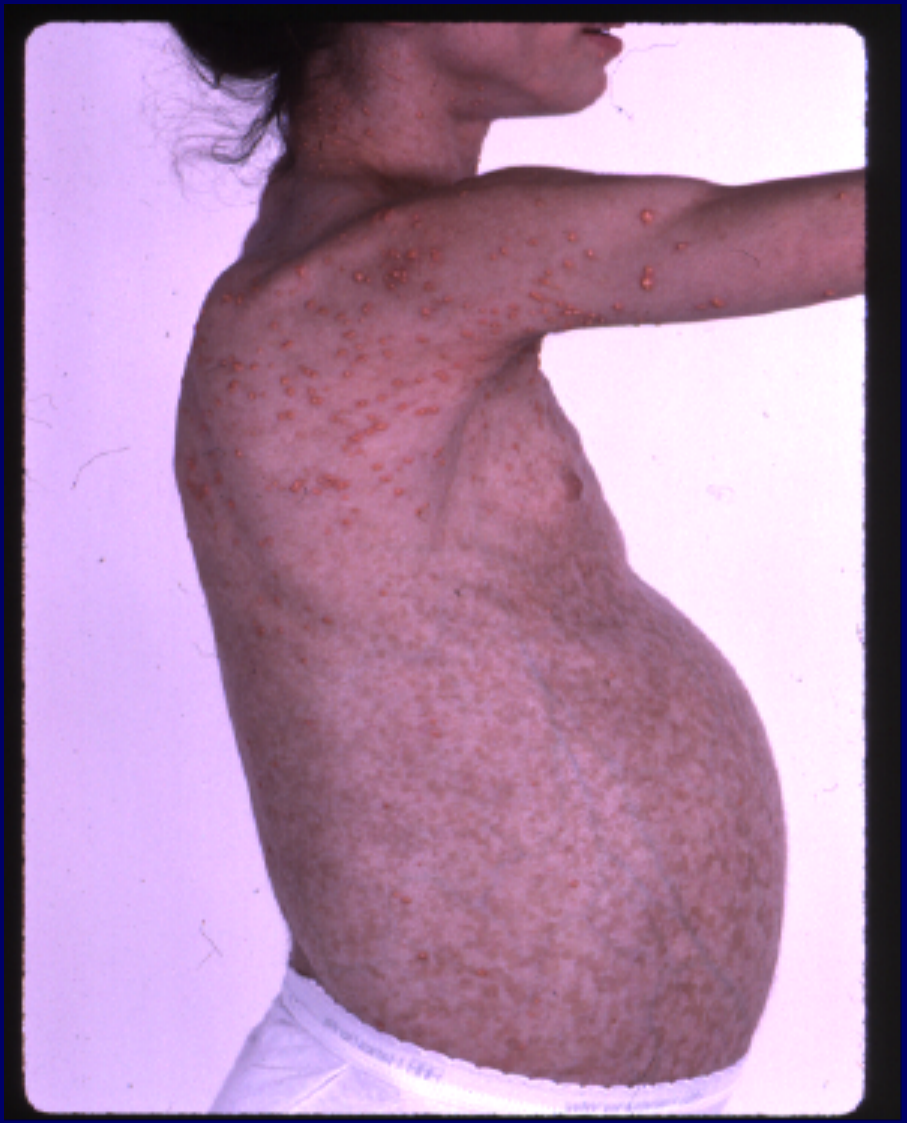
J. Biol. Chem. 275:8456-8460, 2000



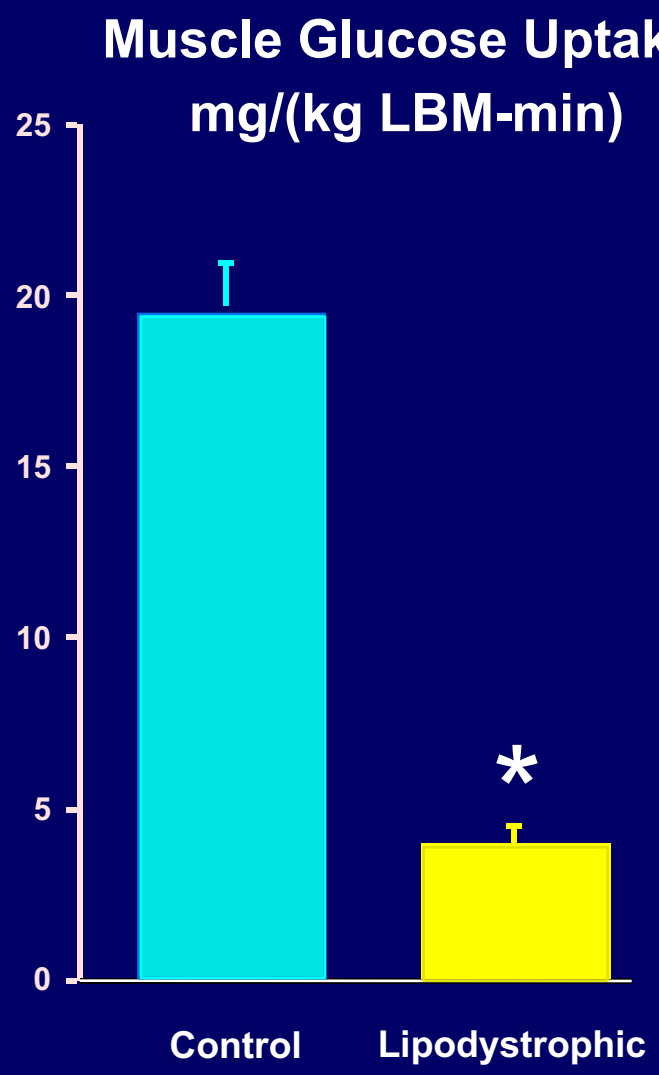
Kim et al. J. Biol. Chem. 275:8456-8460, 2000

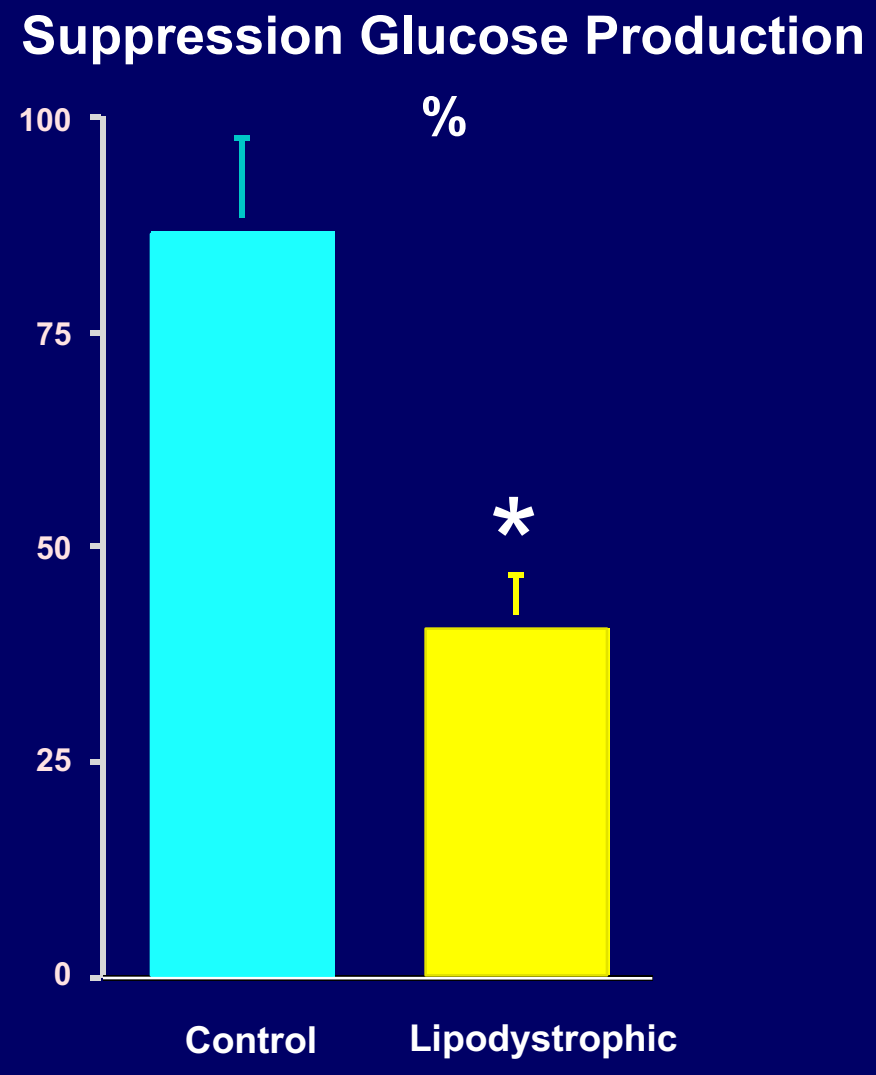
Lipodystrophy Syndromes

- Paucity of fat
- Insulin resistance
- Hypertriglyceridemia
- Fatty infiltration of liver and other tissues
- Deficiency of adipocyte hormones (e.g. leptin)



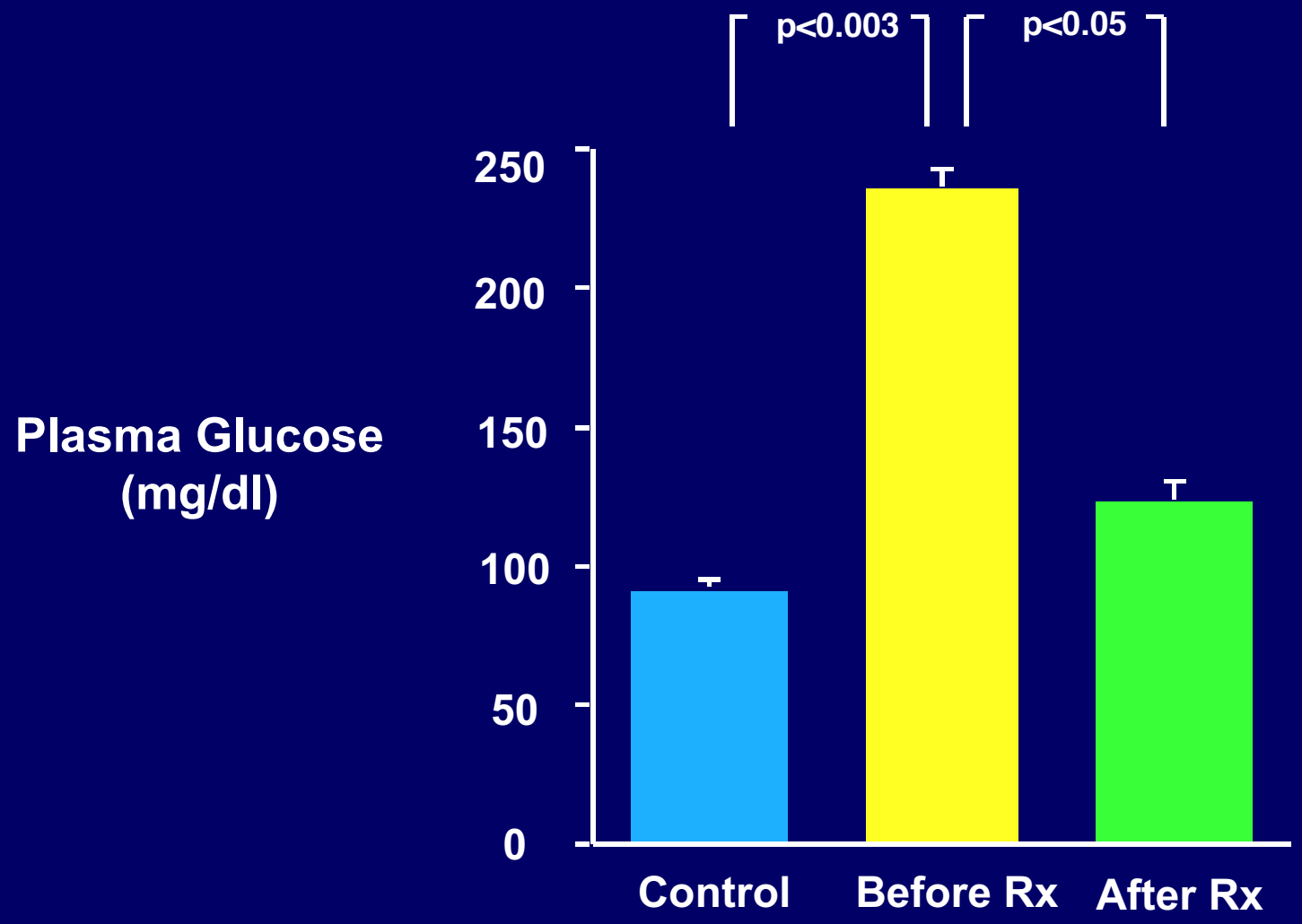
Insulin Action: Control vs Lipodystrophy





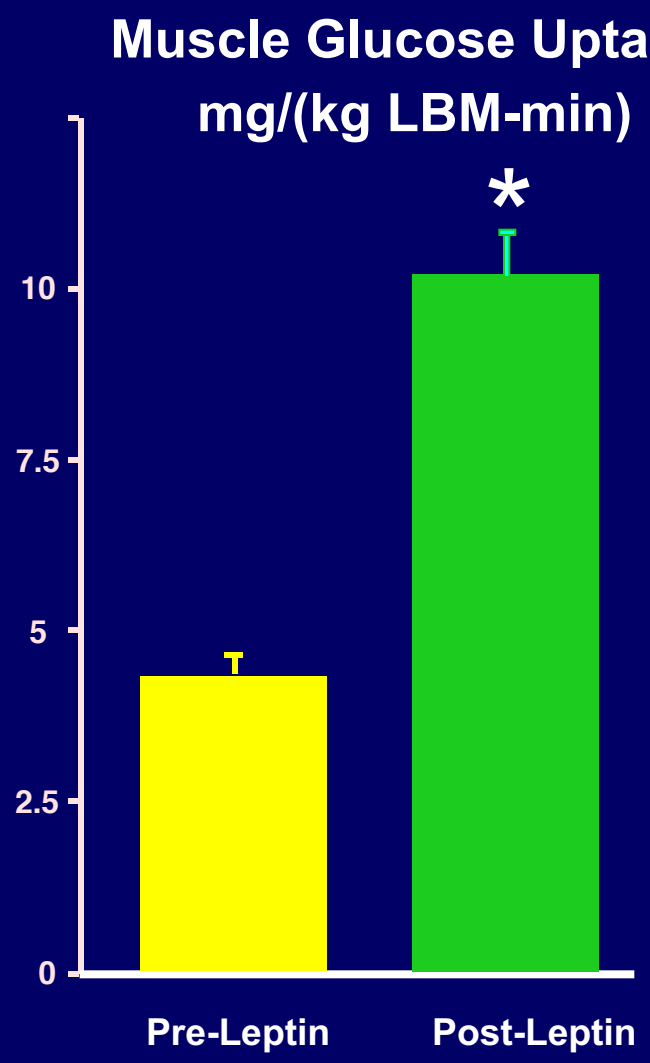
Petersen et al. J. Clin. Invest. 109:1345, 2002

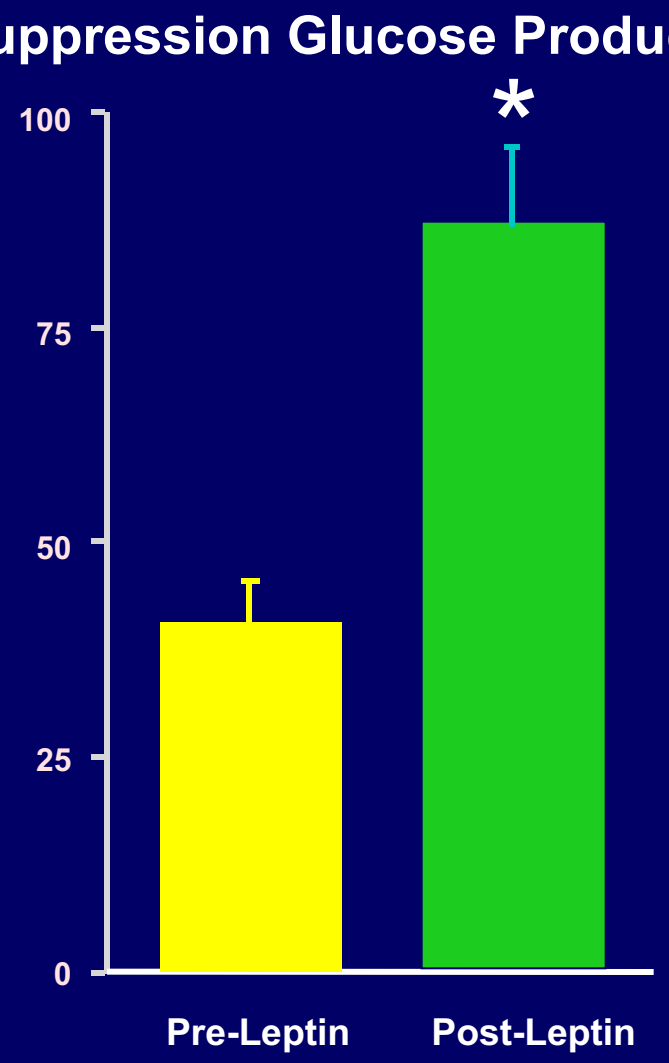
Fasting Plasma Glucose Concentrations



Petersen et al. J. Clin. Invest. 109:1345, 2002

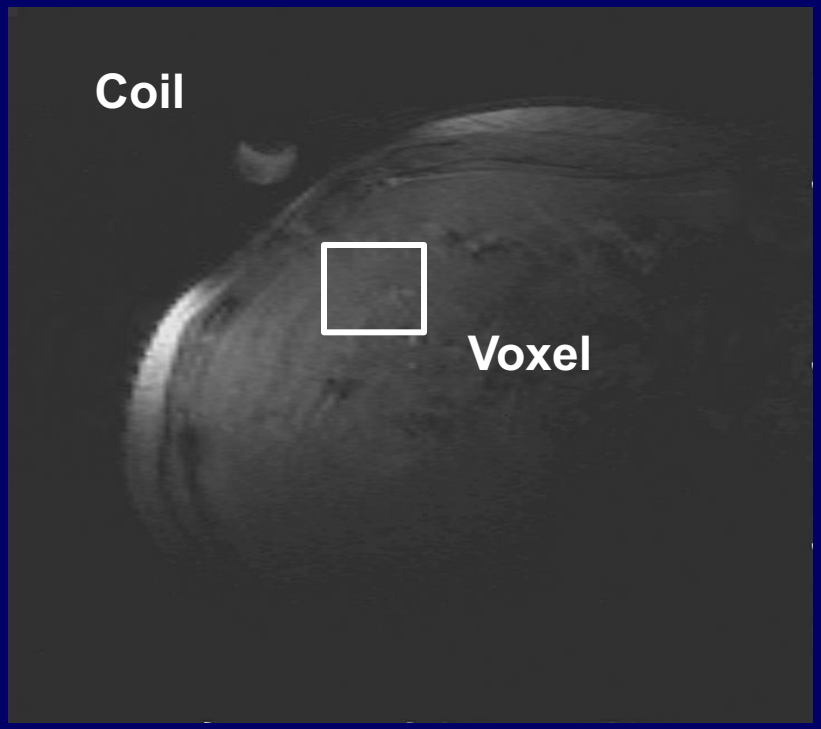
Effect of Leptin on Insulin Action

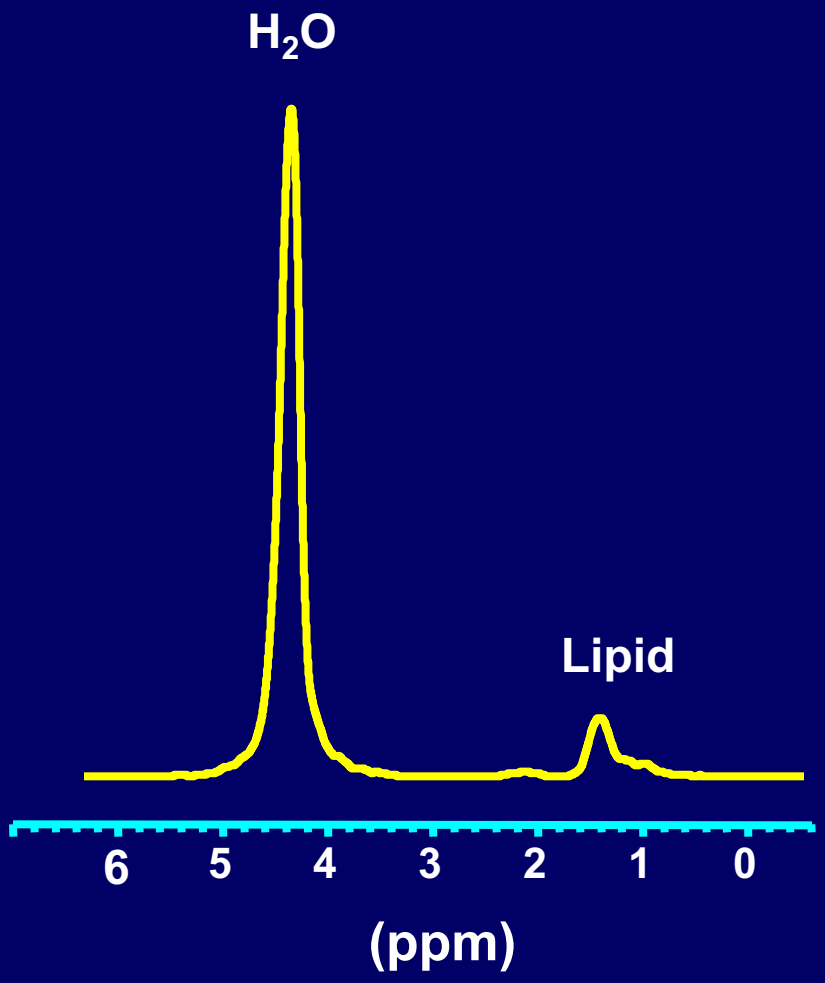




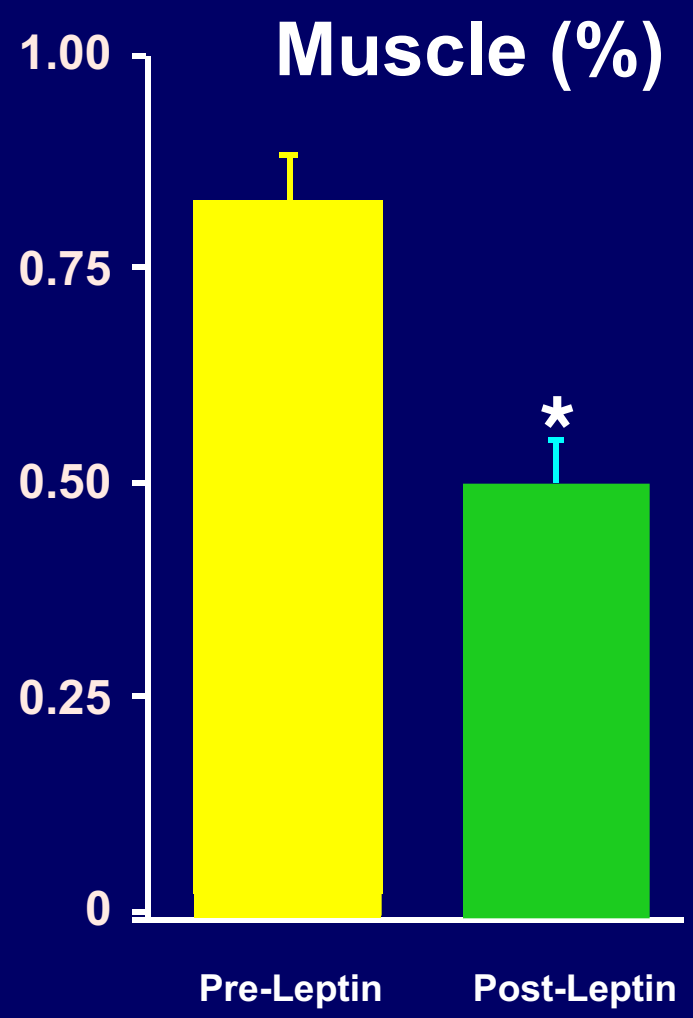
Petersen et al. J. Clin. Invest. 109:1345, 2002

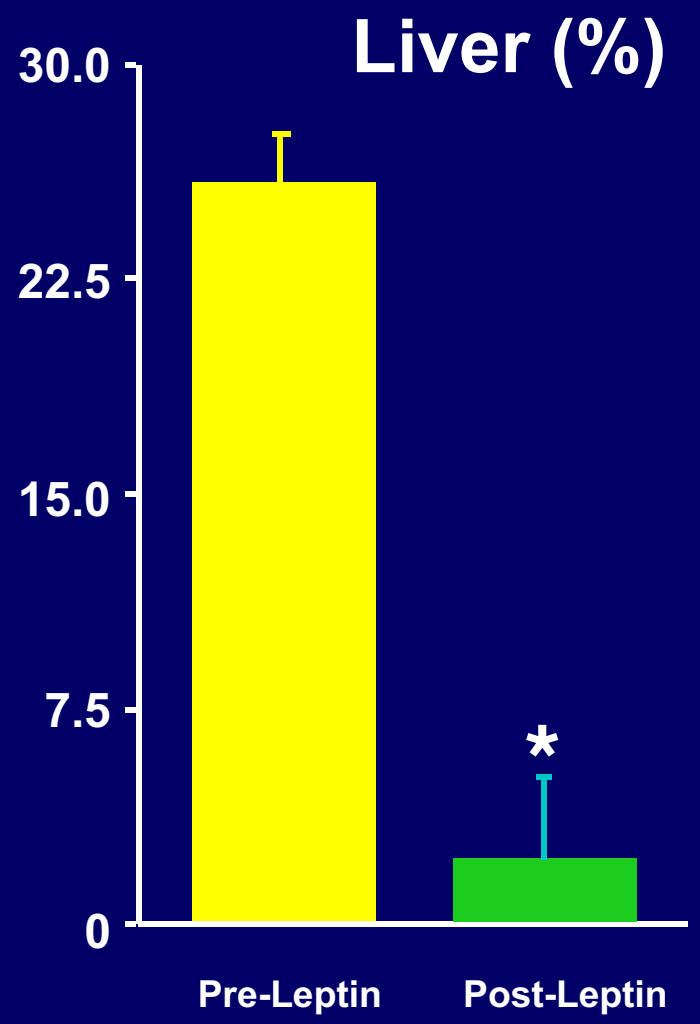
^{1}H MRS Spectrum of Liver





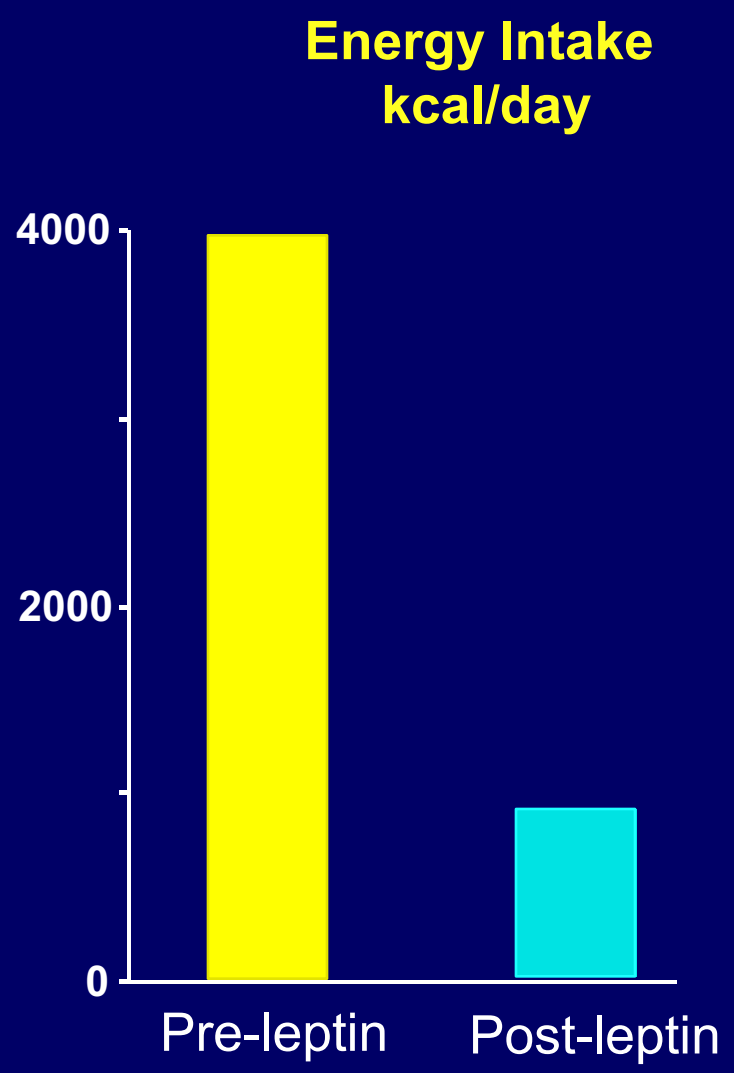
Effect of Leptin on Tissue Triglyceride

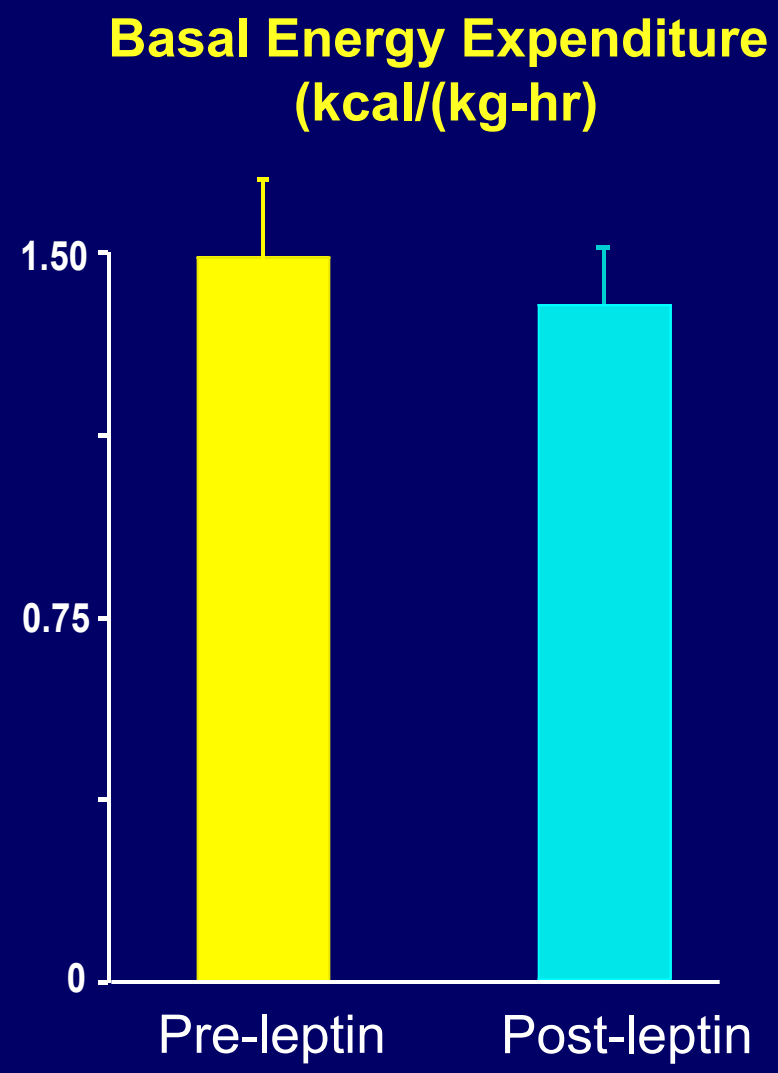




Petersen et al. J. Clin. Invest. 109:1345, 2002

Effect of Leptin on Energy Balance





Petersen et al. J. Clin. Invest. 109:1345, 2002

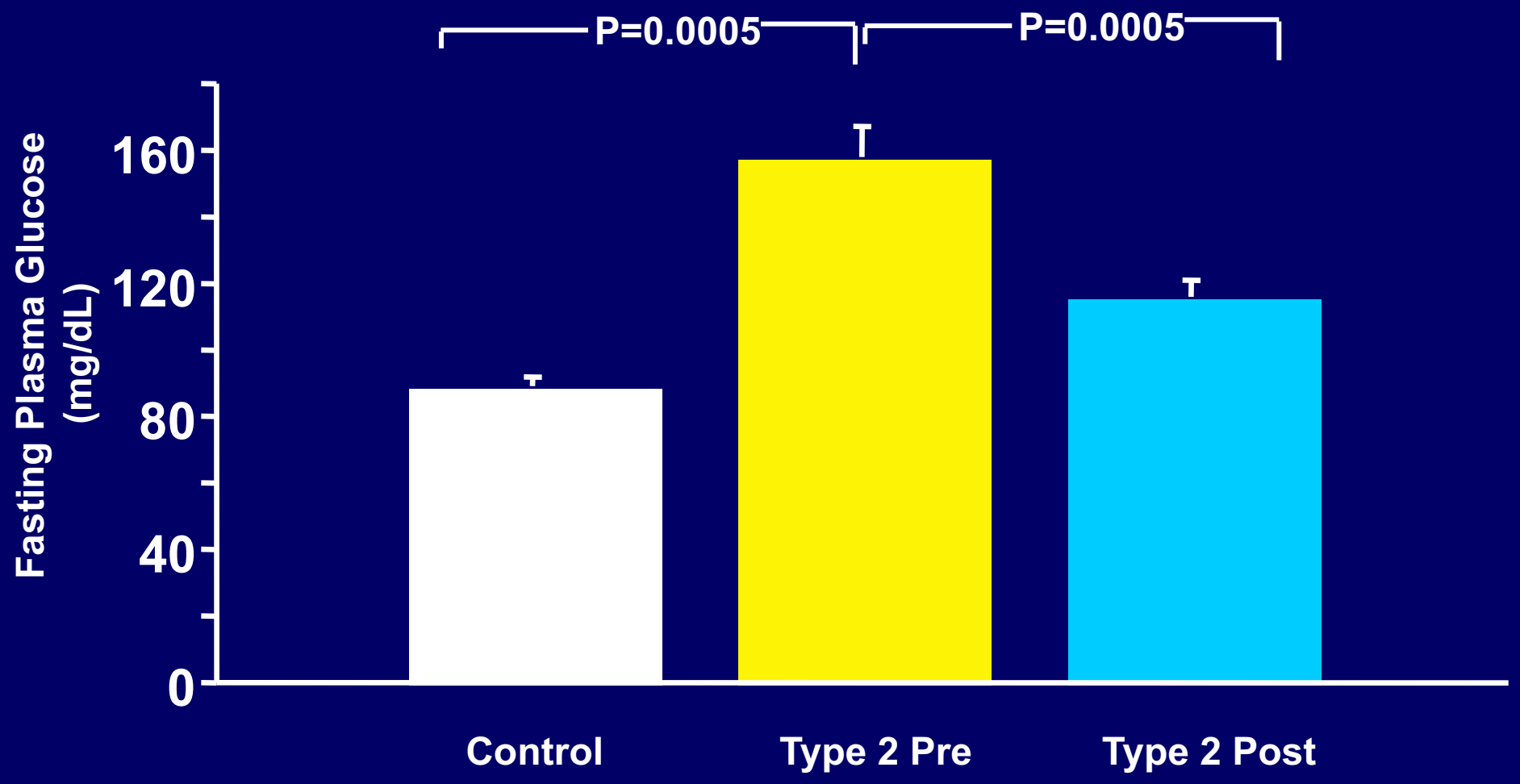
Effect of Leptin Treatment in Lipodystrophy

Before Leptin

1 year on Leptin

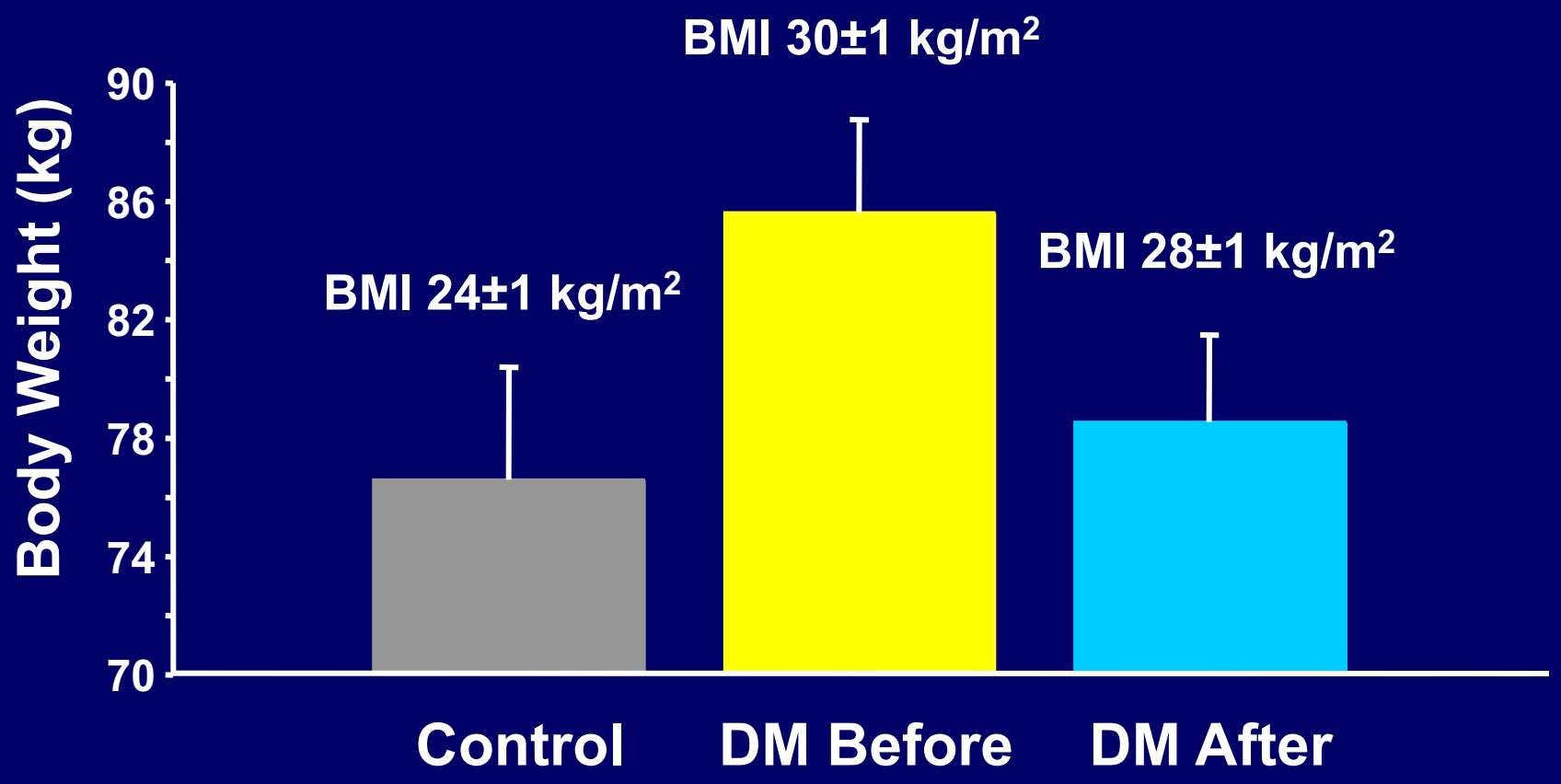
Effects of Weight Loss in Obese Type 2 Diabetics

Fasting Plasma Glucose Before and After Wt Loss



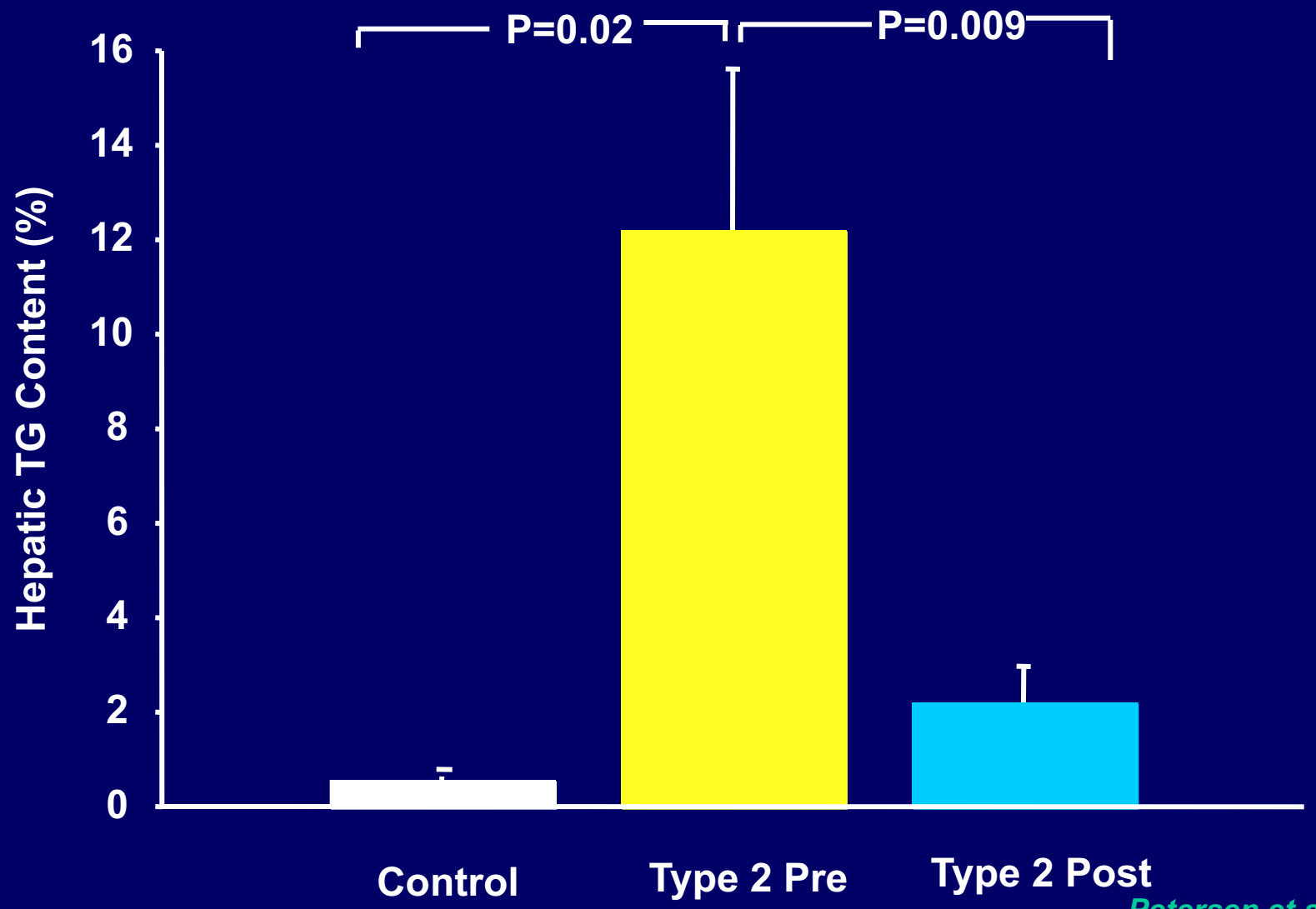
Petersen et al, Diabetes 54:603, 2005

Body Weight Before and After Diet



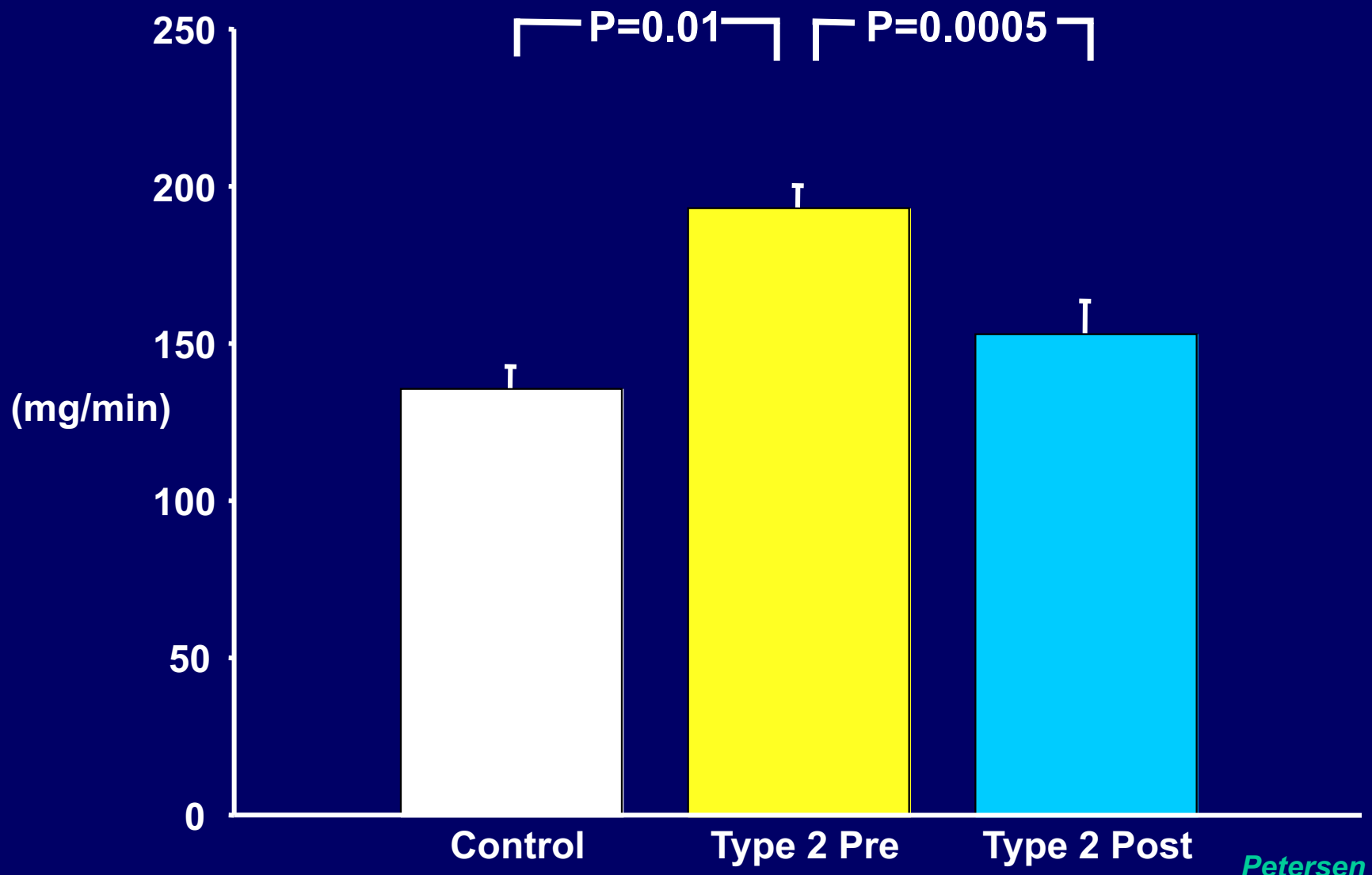
Petersen et al., Diabetes 54:603, 2005

Hepatic Lipid Content



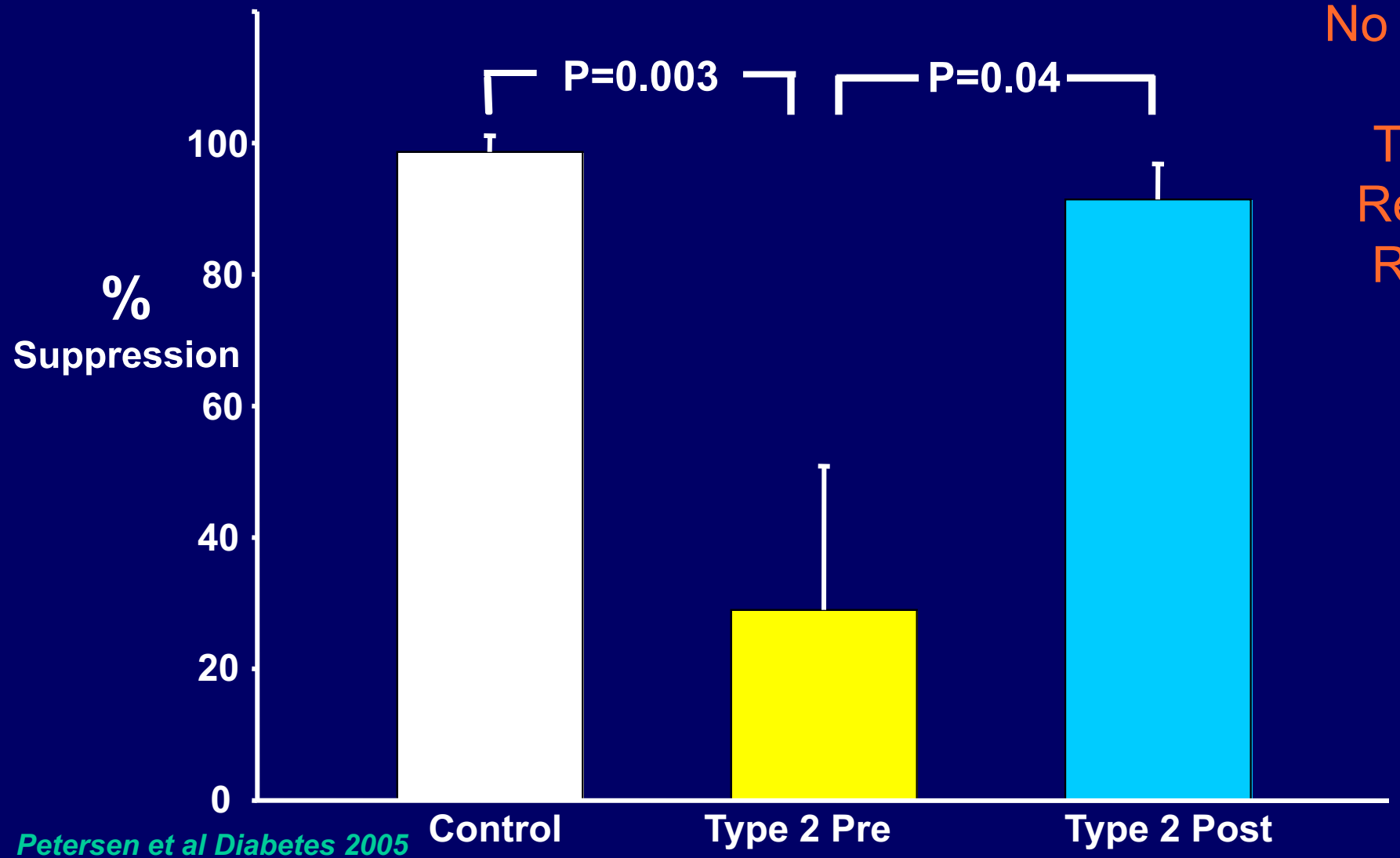
Petersen et al Diabetes 2005

Rates of Glucose Production



Petersen et al Diabetes 2005

Insulin Suppression of Glucose Production

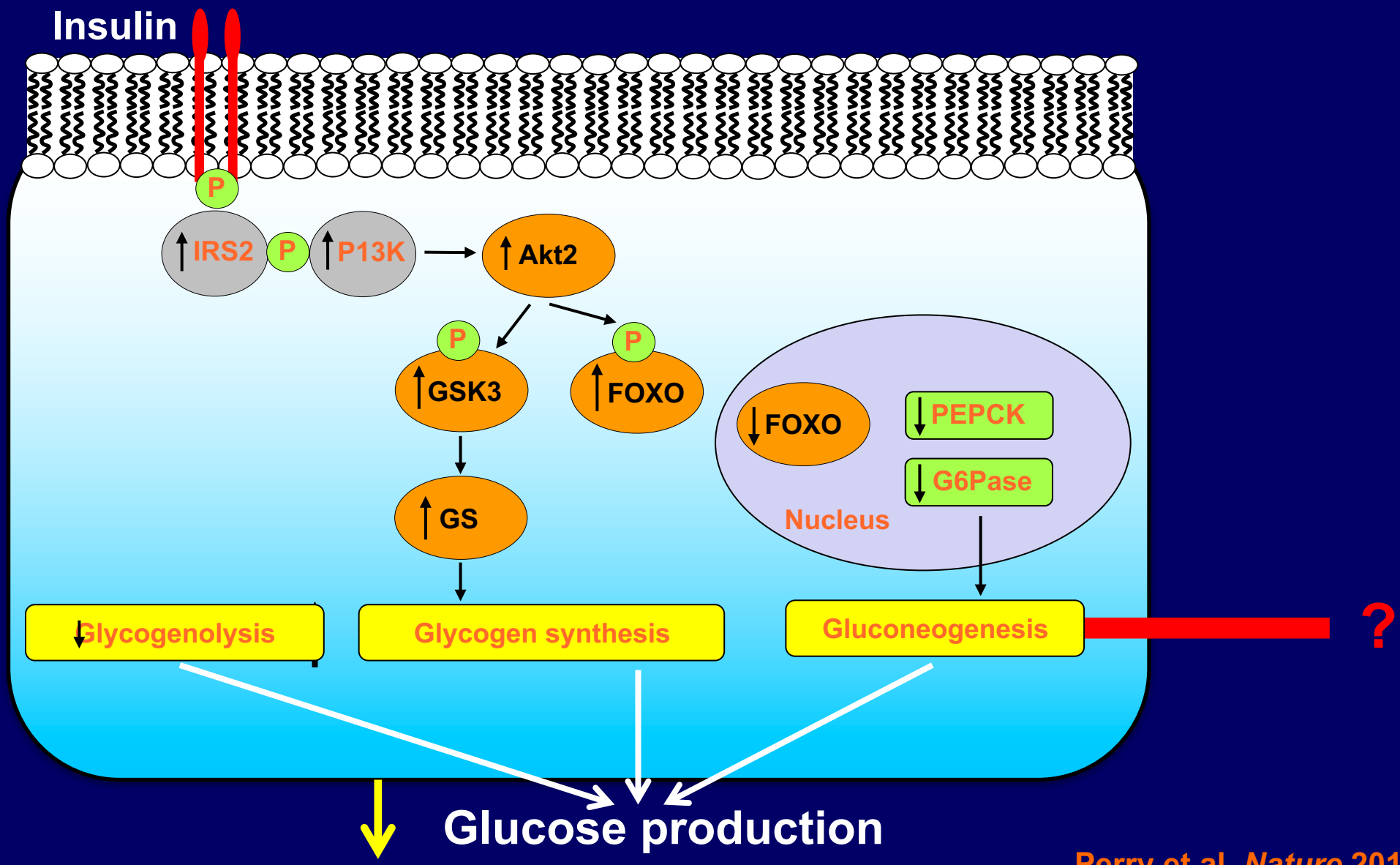


No change
IL-6
TNF-α
Resistin
RBP-4

Petersen et al Diabetes 2005

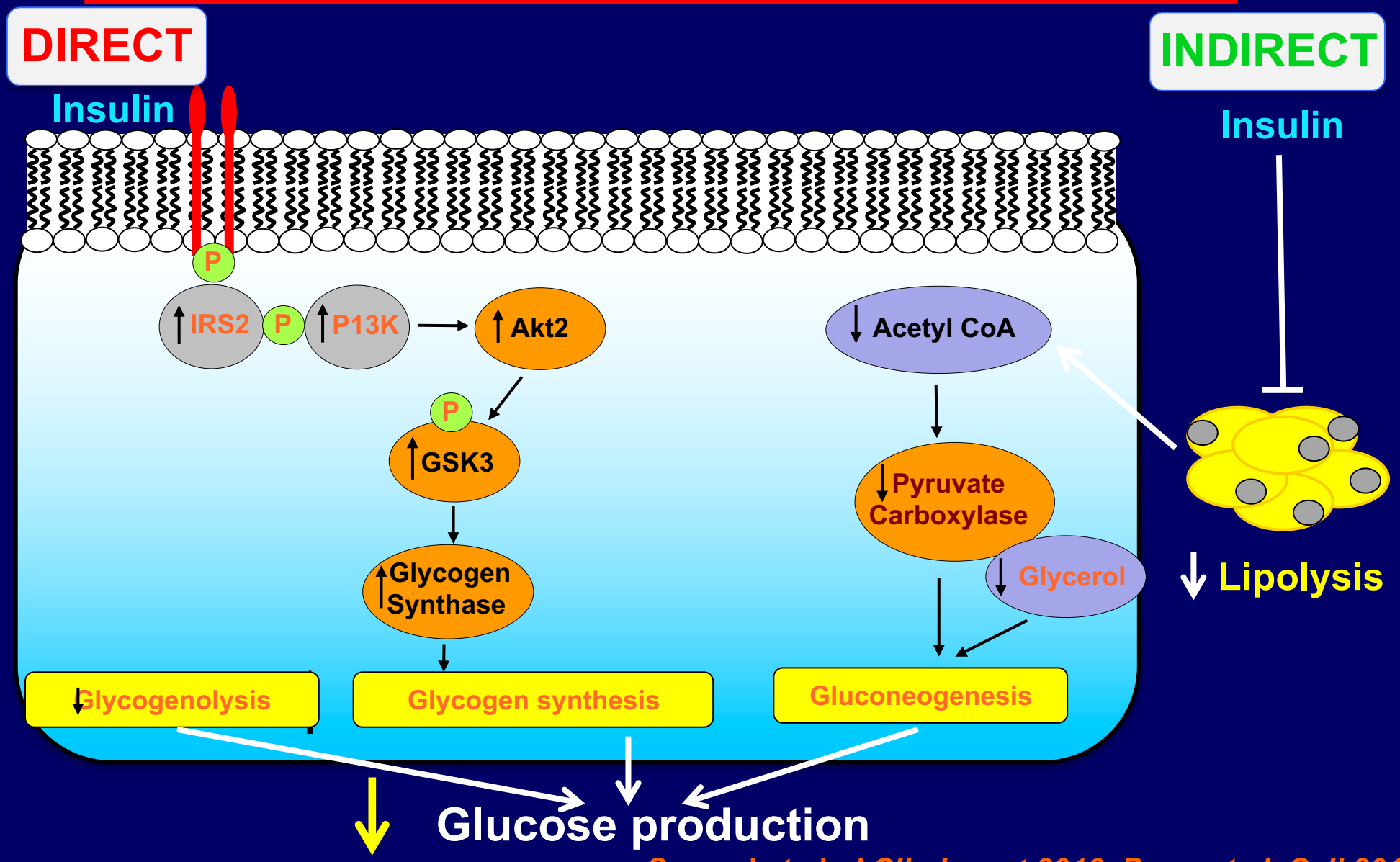
How Insulin Works

Canonical insulin signaling of hepatic glucose metabolism



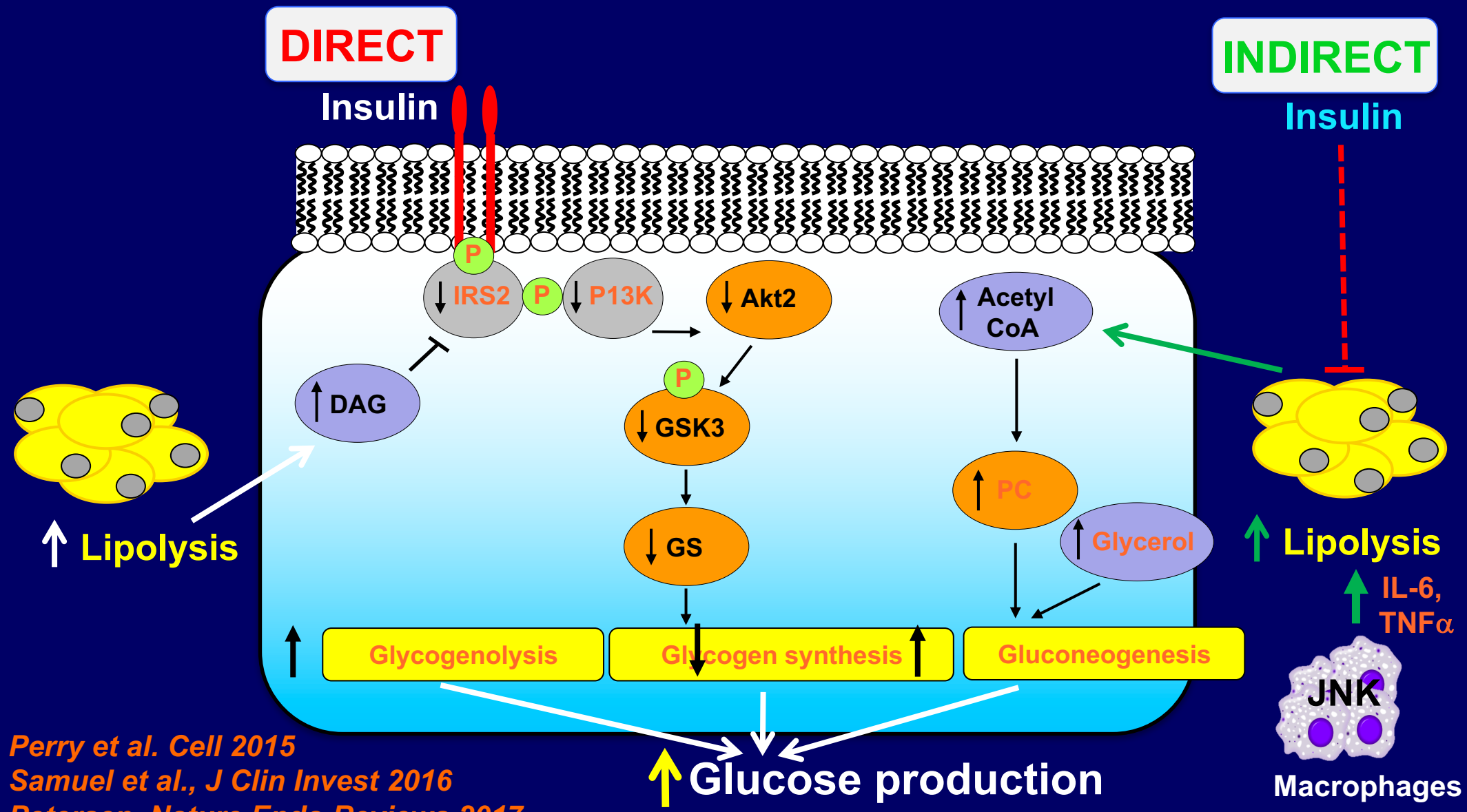
Perry et al. *Nature* 2014

DIRECT Effects of Insulin to Stimulate Glycogen Synthesis
INDIRECT Effects of Insulin on Lipolysis to Inhibit Gluconeogenesis



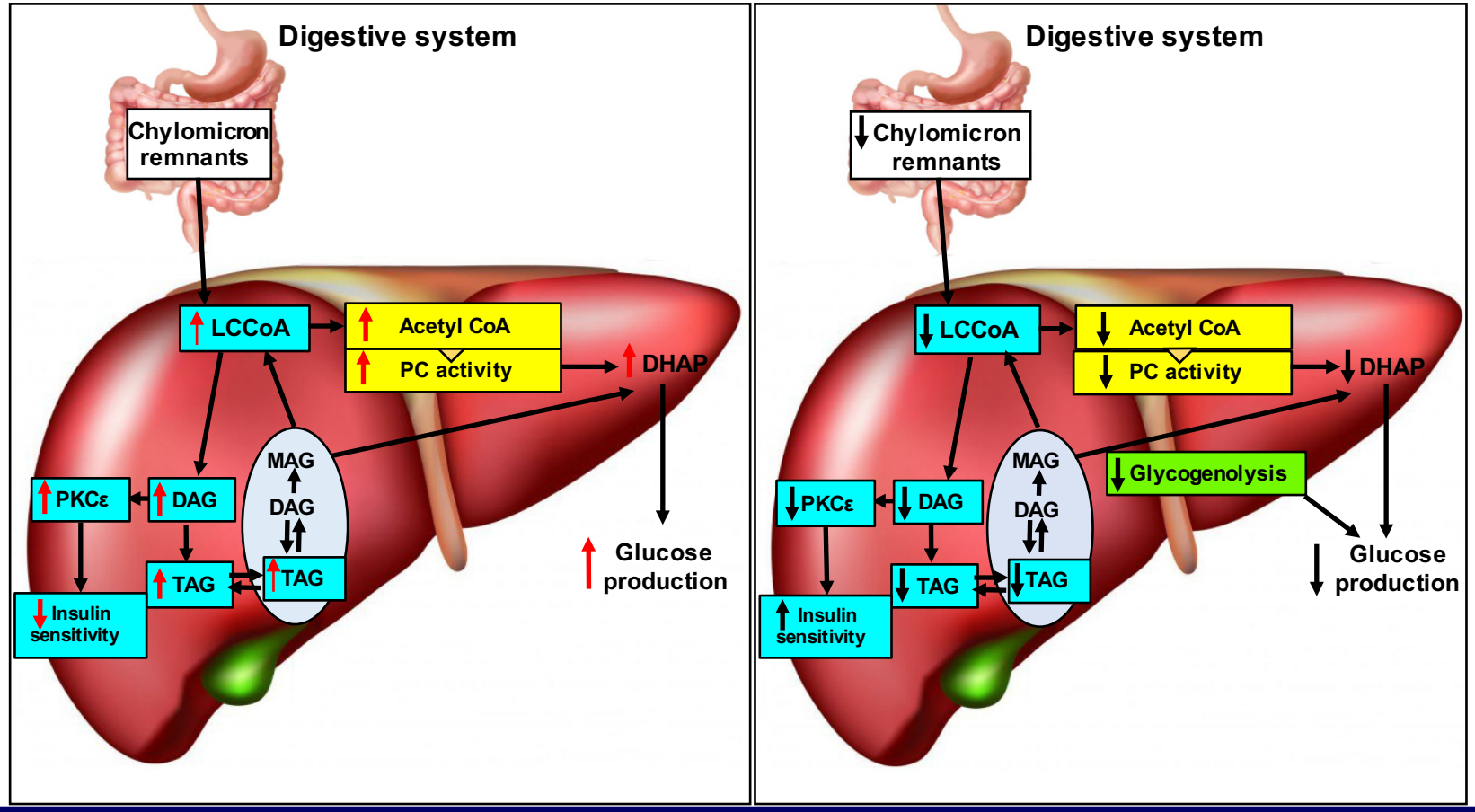
Samuel et al. *J Clin Invest 2016*, Perry et al. *Cell 2015*

Mechanisms by which Increased Lipolysis Inhibits Hepatic Glycogen Synthesis and Increases Hepatic Gluconeogenesis in T2D



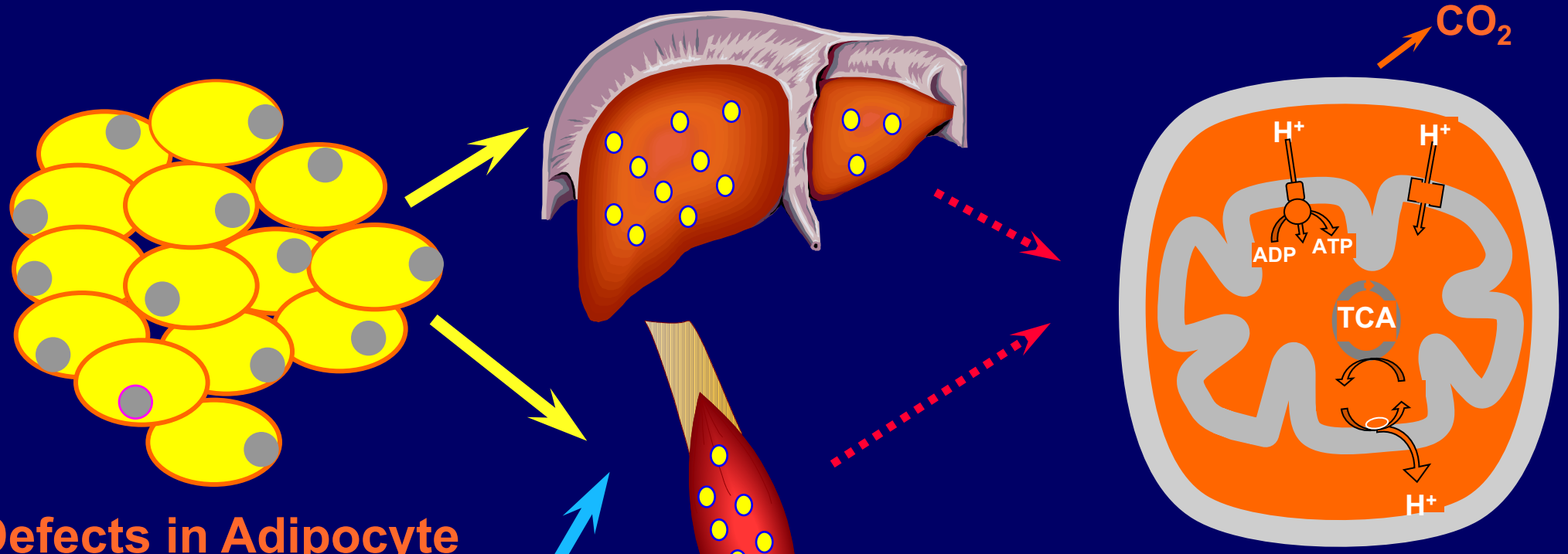
Perry et al. Cell 2015
Samuel et al., J Clin Invest 2016
Petersen, Nature Endo Reviews 2017

Mechanism by Which a Very Low Calorie Diet Reverses Diabetes



Perry et al. Cell Metabolism (published on line: November 9, 2017)

Cellular Mechanisms of Insulin Resistance



Defects in Adipocyte Fatty Acid Metabolism

Caloric Intake

Acquired (aging) or Inherited (IR Offspring) Defects in Mitochondrial Metabolism

Samuel et al., J Clin Invest 2016, Petersen et al., Nature Endo Reviews 2017

Cell Metabolism
Perspective

Nonalcoholic Fatty Liver Disease as a Nexus of Metabolic and Hepatic Diseases

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http://dx.doi.org/10.1016/j.cmet.2017.08.002

Cell Metabolism – published on line August 31, 2017

Cell PRESS

Cell Metabolism
Short Article

Reversal of Hypertriglyceridemia, Fatty Liver Disease, and Insulin Resistance by a Liver-Targeted Mitochondrial Uncoupler

Rachel J. Perry,[1,2,3] Taehan Kim,[4] Xian-Man Zhang,[1] Hui-Young Lee,[1,3] Dominik Pesta,[1] Violeta B. Popov,[2] Dongyan Zhang,[1] Yasmeen Rahimi,[1] Michael J. Jurczak,[2] Gary W. Cline,[1] David A. Spiegel,[4,5] and Gerald I. Shulman[1,2,3,6,*]
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http://dx.doi.org/10.1016/j.cmet.2013.10.004

Cell Metabolism 2013

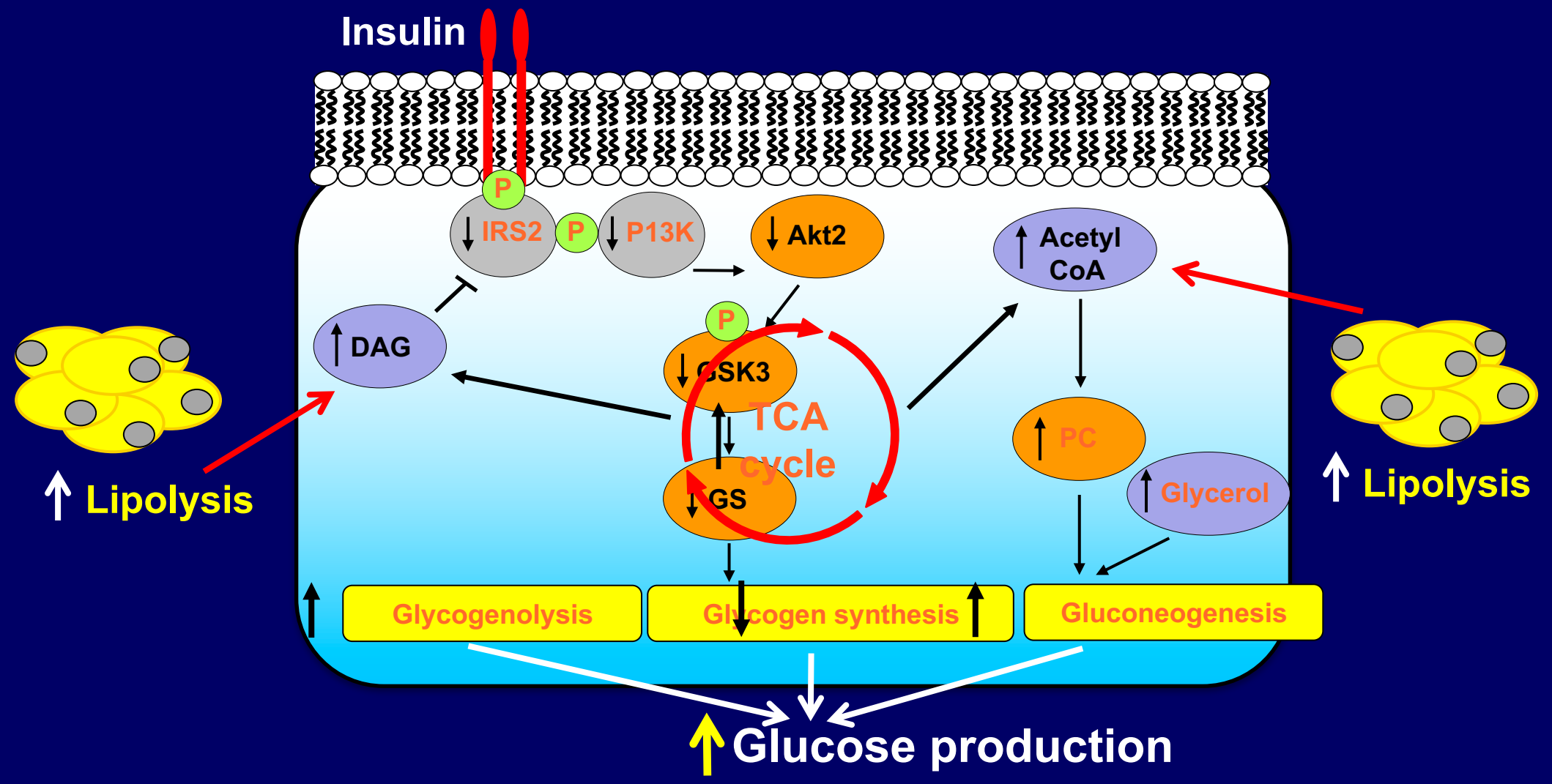
METABOLIC DISEASE

Controlled-release mitochondrial protonophore reverses diabetes and steatohepatitis in rats

Rachel J. Perry,[1,2,3] Dongyan Zhang,[1] Xian-Man Zhang,[2] James L. Boyer,[2,4] Gerald I. Shulman[1,2,3]*

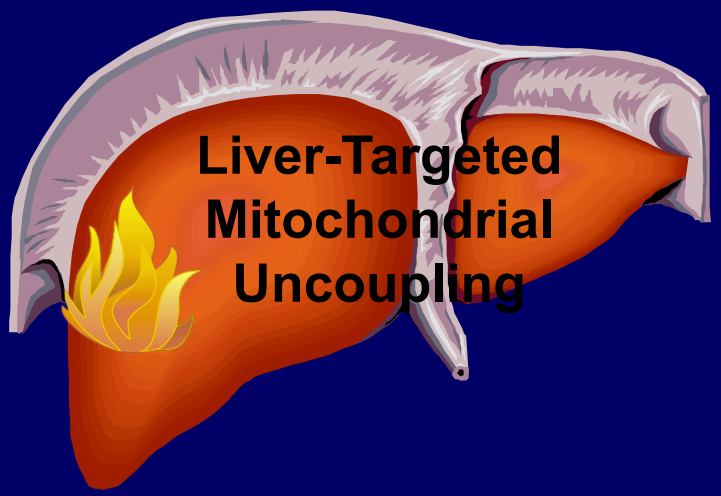
Science 2015

Mechanisms by which Increased Lipolysis Inhibits Hepatic Glycogen Synthesis and Increases Hepatic Gluconeogenesis

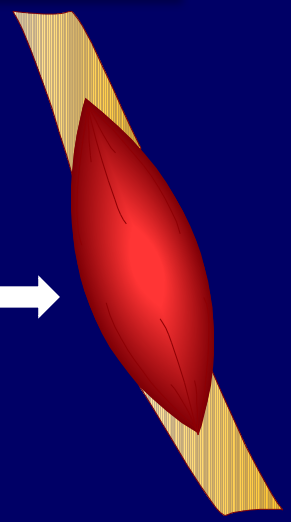


Perry et al. Cell 2015, Samuel and Shulman *J Clin Invest* 2016

Liver-Targeted Mitochondrial Uncoupling



↓ Hypertriglyceridemia →



↑ V_{TCA}, fat oxidation → ↓ VLDL export

↓ Hepatic TAG, DAG, ↓ acetyl CoA

↓ PKCε translocation

↑ Hepatic insulin sensitivity ↓ Fasting gluconeogenesis

↓ Intramyocellular TAG, DAG

↓ PKCθ translocation

↑ Peripheral insulin sensitivity

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