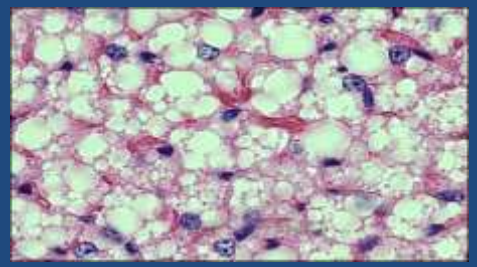
Not All Hypoxias Are Created Equal : Implications For Metabolic Health

Alex Gileles-Hillel, MD

Hadassah-Hebrew University Medical Center

HIPAP 2018 - GALILION

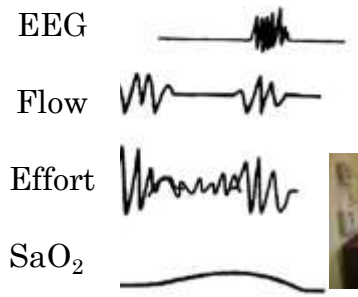


OSA in a Nutshell

OSAS
Adults
4-6%
Children
1-3%

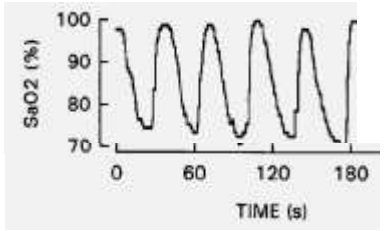
Consequences

Sleepiness
Cardiovascular
Stroke
Metabolic
Neurocognitive
Depression
MVA
Erectile Dysfunction
Cancer…

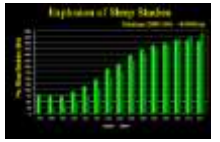


- Arousals
- ↑ Intrathoracic Pressures
- CO_2 ↑
- Hypoxemia

- Autonomic activity
- Hemodynamic changes
- Hypercoagulability
- Inflammation
- Oxidative Stress

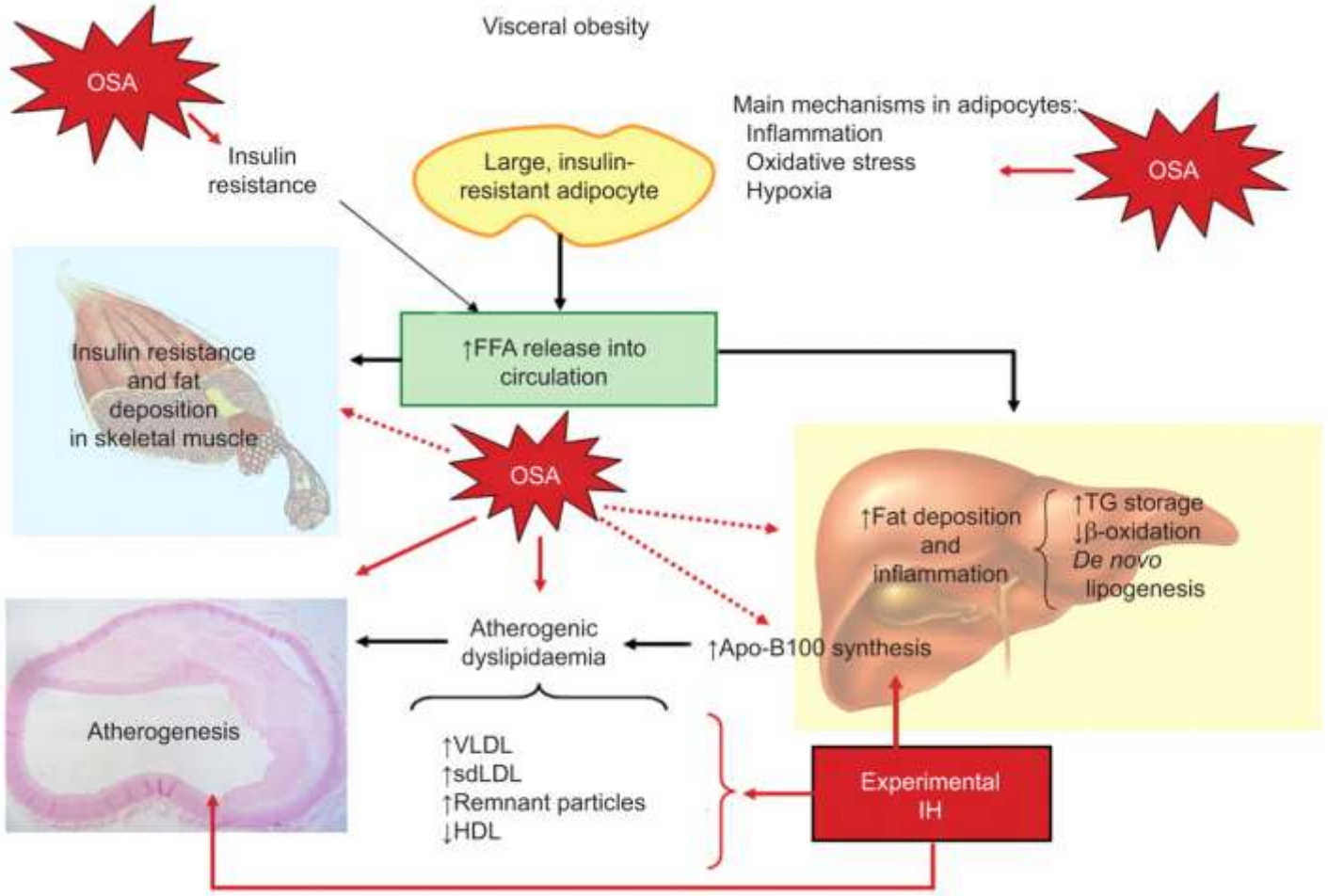


Treatment

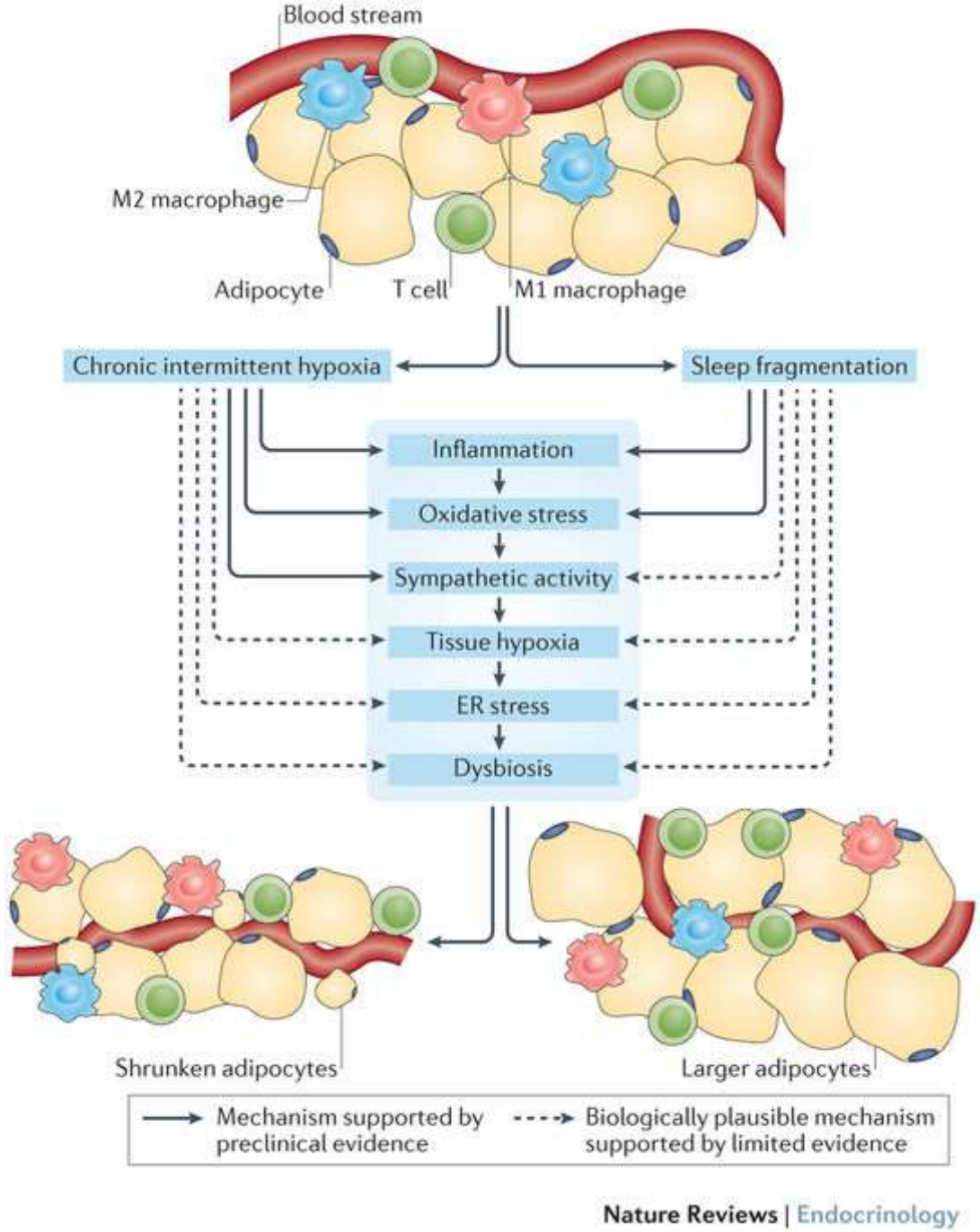


AHI = Apnea-Hypopnea Index (<1, 1-5, >5)

OSA is a Metabolic Disease

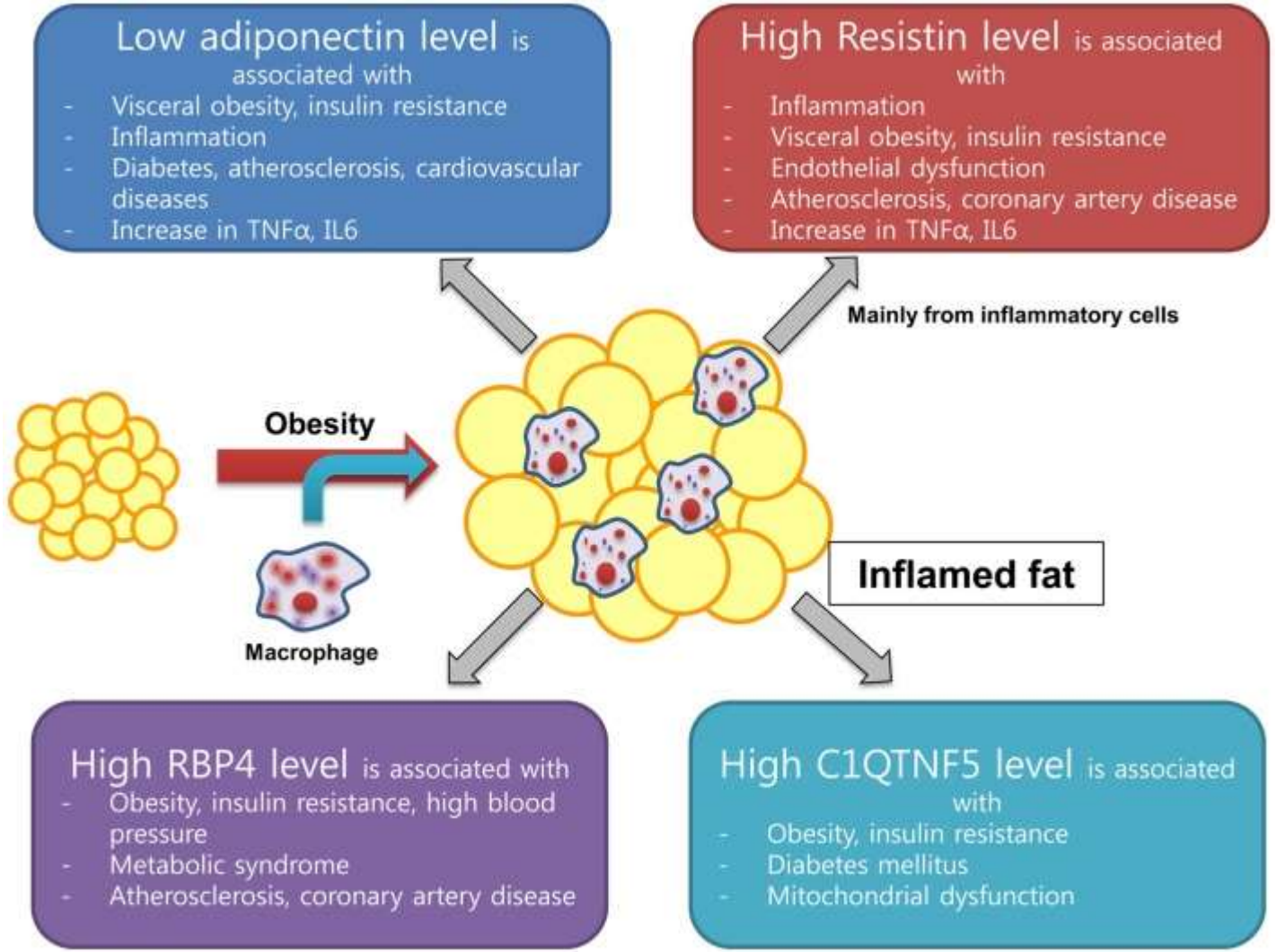


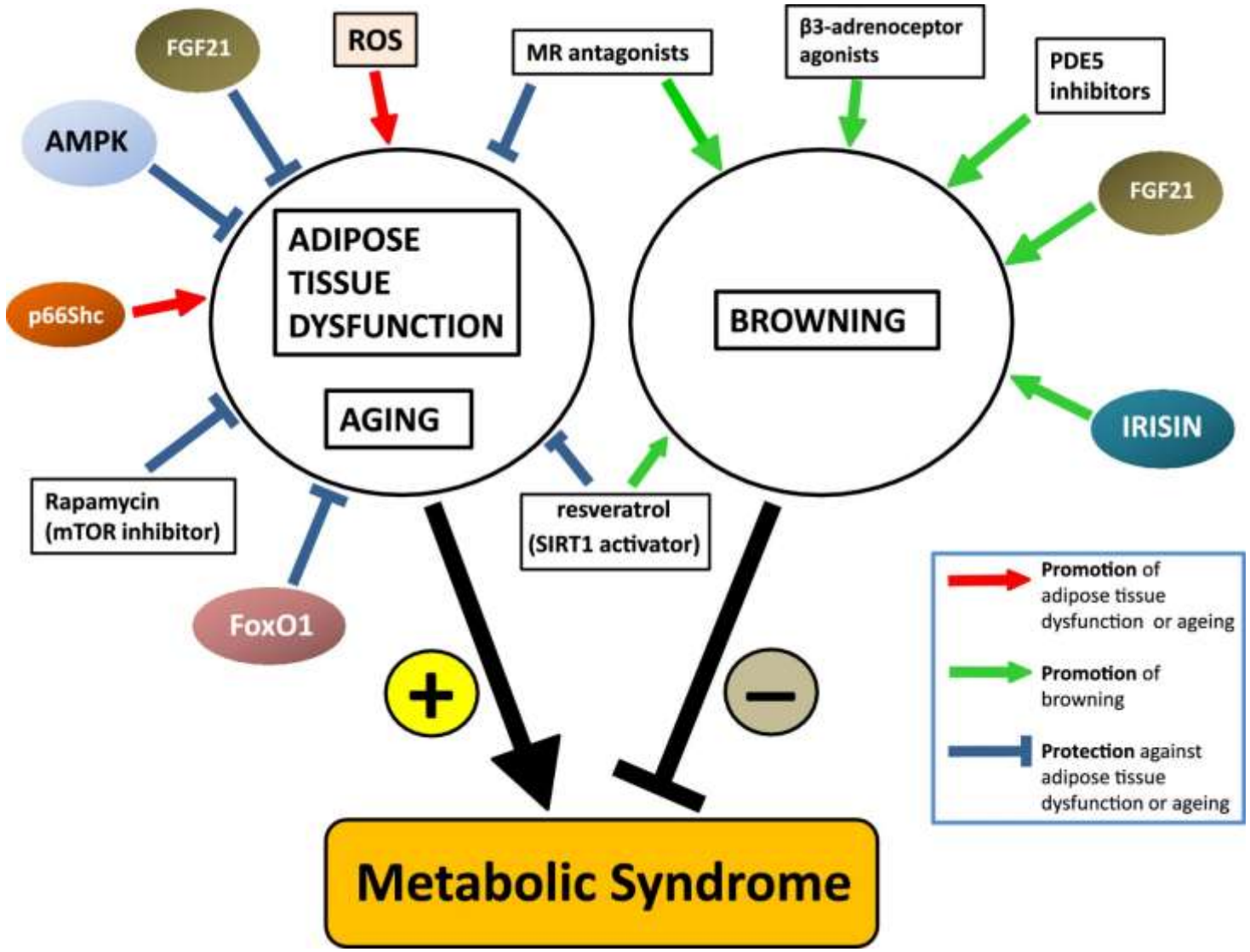
Bonsignore MR. et al, ERJ 2012



Gileles-Hillel A. et al, Nature Reviews: Endocrinology 2016

Fat is Bad

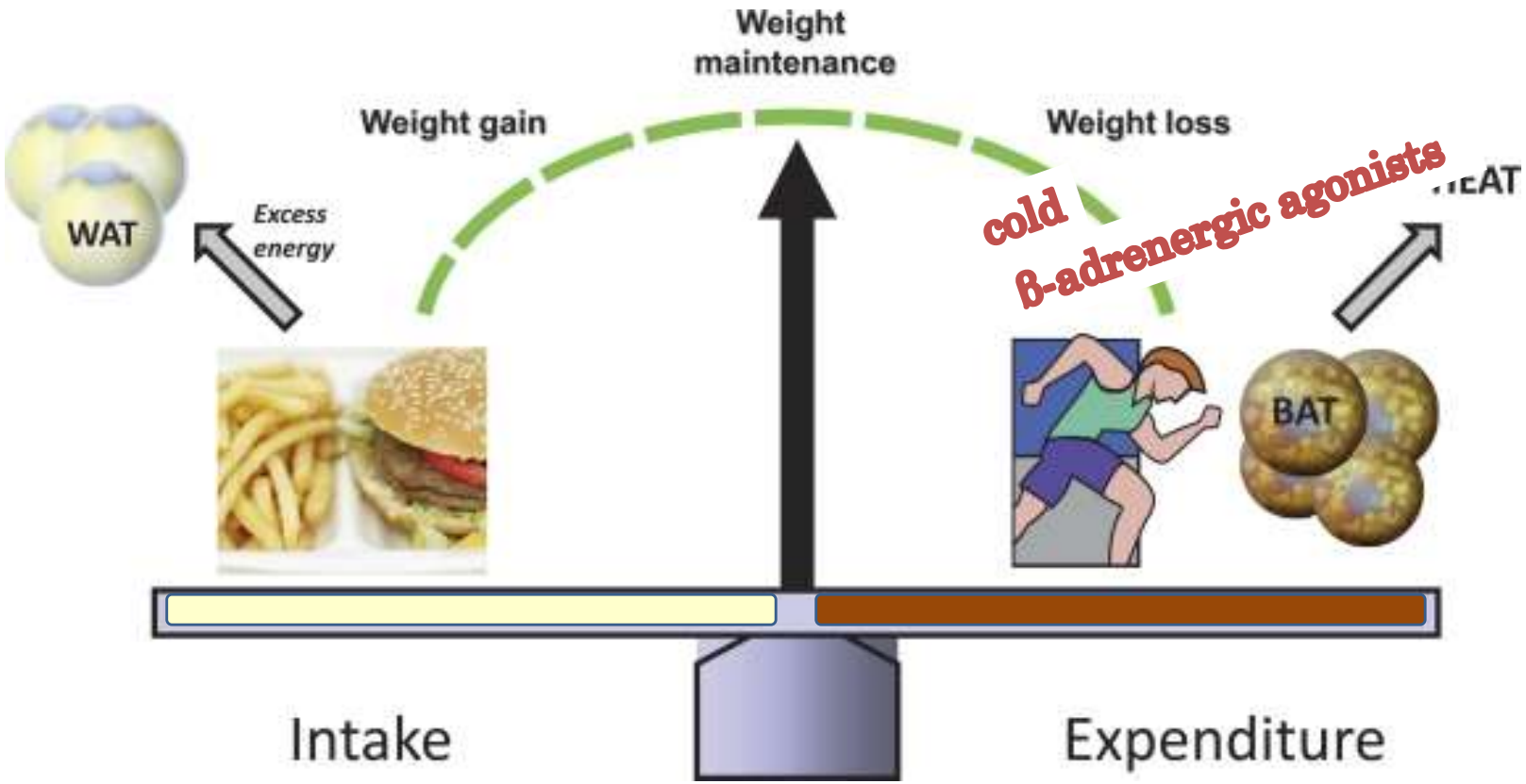

Low adiponectin level is associated with
- Visceral obesity, insulin resistance
- Inflammation
- Diabetes, atherosclerosis, cardiovascular diseases
- Increase in TNFα, IL6
High Resistin level is associated with
- Inflammation
- Visceral obesity, insulin resistance
- Endothelial dysfunction
- Atherosclerosis, coronary artery disease
- Increase in TNFα, IL6
Mainly from inflammatory cells
Obesity
Macrophage
Inflamed fat
High RBP4 level is associated with
- Obesity, insulin resistance, high blood pressure
- Metabolic syndrome
- Atherosclerosis, coronary artery disease
High C1QTNF5 level is associated with
- Obesity, insulin resistance
- Diabetes mellitus
- Mitochondrial dysfunction



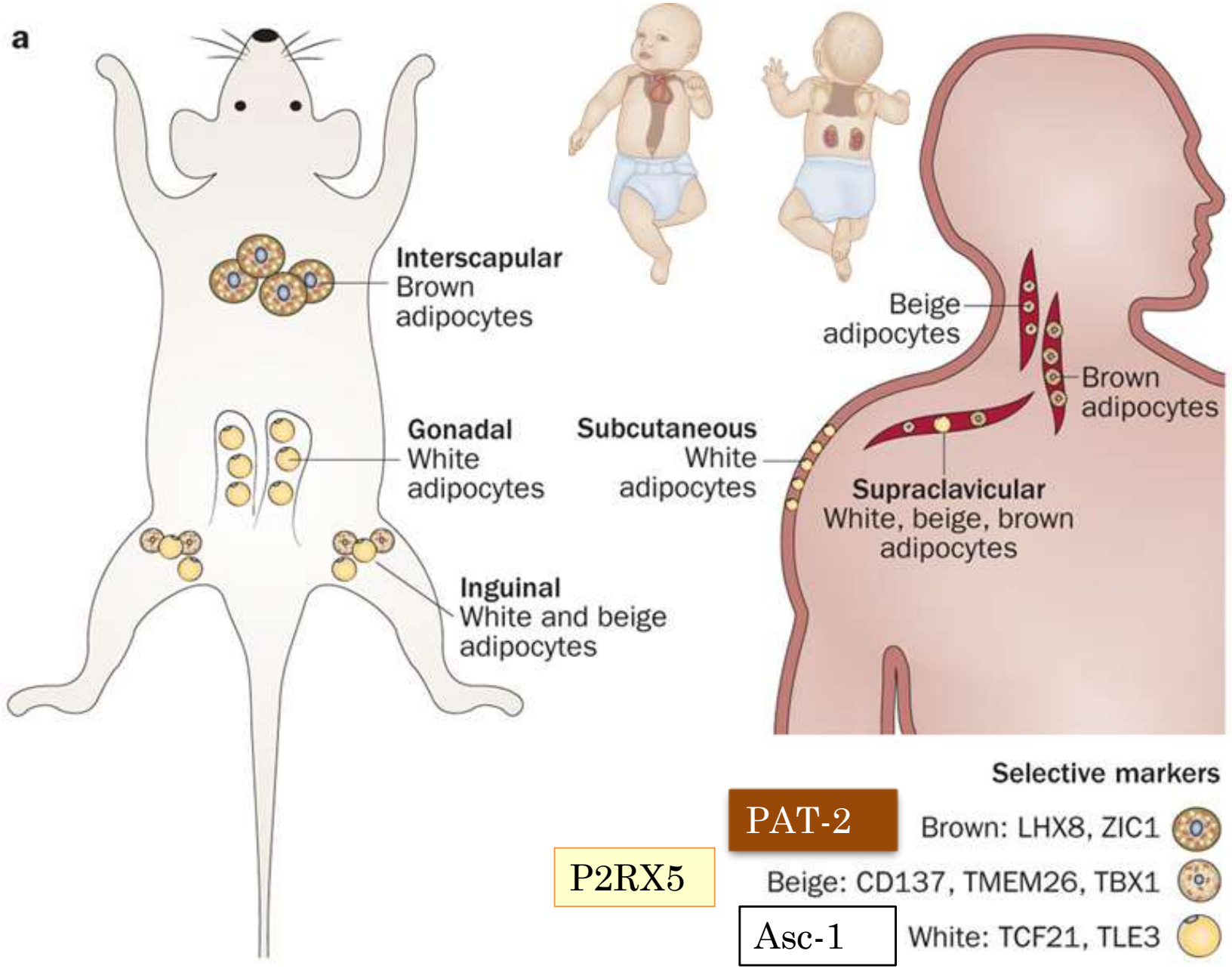
Armani A et al; The FASEB Journal 2017

FASEB

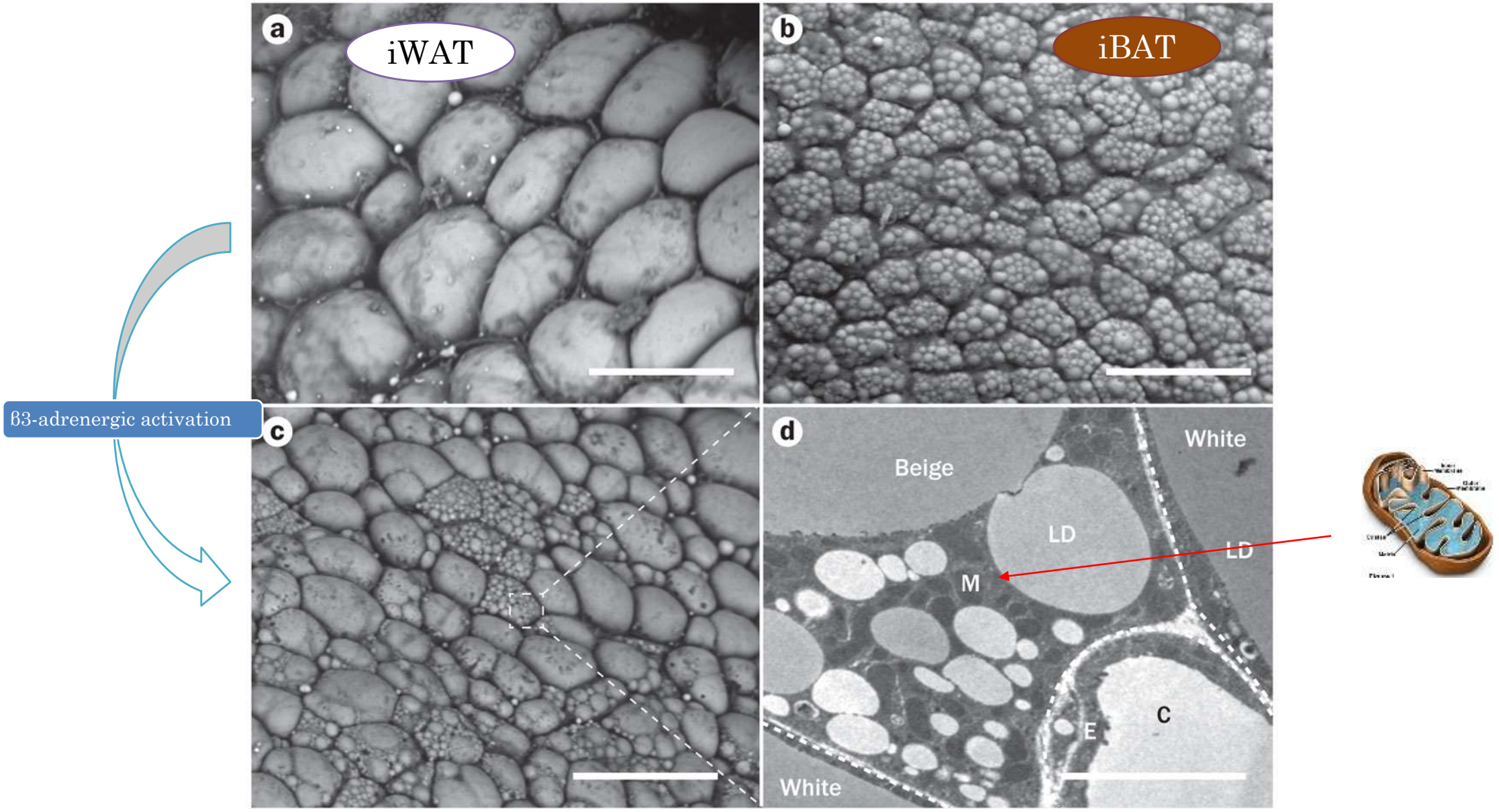
Let talk about Fat



Diabetes. 2009

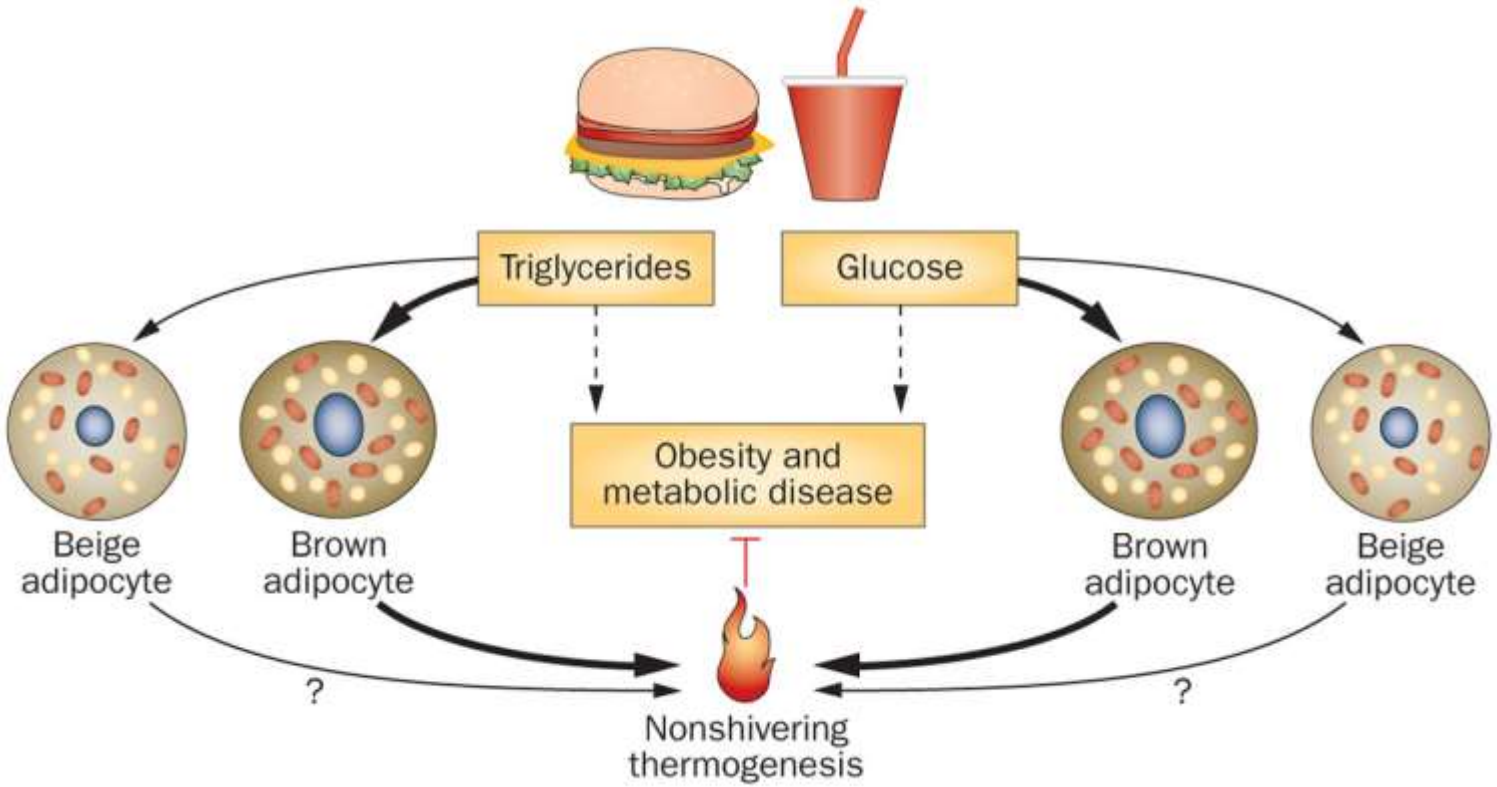


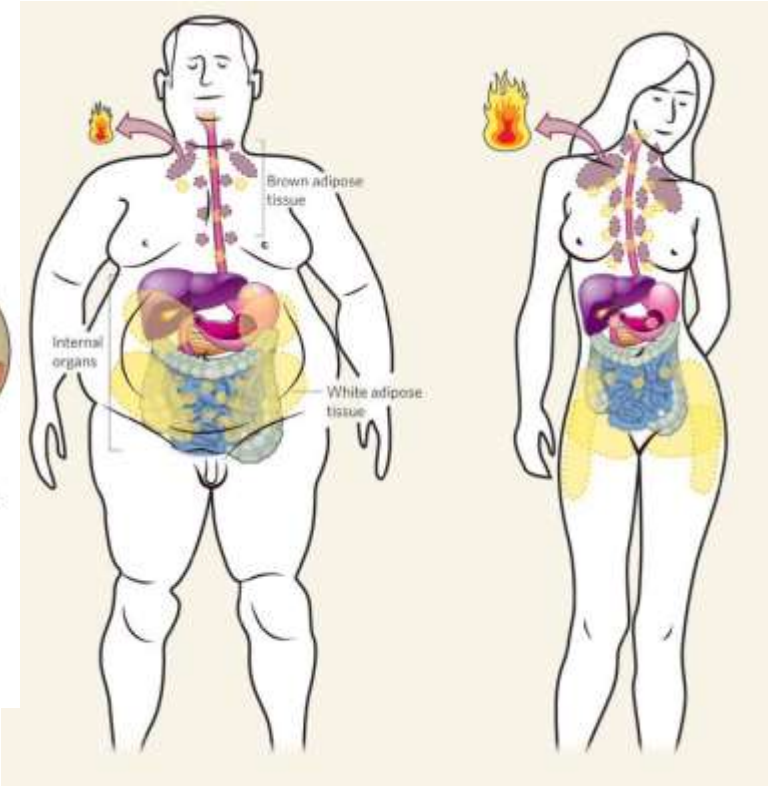
Bartelt, A. & Heeren, J. (2013) Nat. Rev. Endocrinol.
Ussar et al (2014) Sci Tran Med



Bartelt, A. & Heeren, J. (2013) Nat. Rev. Endocrinol.

Contributions of browning to systemic nutrient handling





Bartelt, A. & Heeren, J. (2013) Nat. Rev. Endocrinol.

Is Hypoxia to Blame for Bad Fat?

Physiol Rev. 2013 Jan;93(1):1-21. doi: 10.1152/physrev.00017.2012.

Hypoxia and adipose tissue function and dysfunction in obesity.

Trayhurn P[1].

⊕ Author information

Abstract

The rise in the incidence of obesity has led to a major interest in the biology of white adipose tissue. The tissue is a major endocrine and signaling organ, with adipocytes, the characteristic cell type, secreting a multiplicity of protein factors, the adipokines. Increases in the secretion of a number of adipokines occur in obesity, underpinning inflammation in white adipose tissue and the development of obesity-associated diseases. There is substantial evidence, particularly from animal studies, that hypoxia develops in adipose tissue as the tissue mass expands, and the reduction in Po(2) is considered to underlie the inflammatory response. Exposure of white adipocytes to hypoxic conditions in culture induces changes in the expression of >1,000 genes. The secretion of a number of inflammation-related adipokines is upregulated by hypoxia, and there is a switch from oxidative metabolism to anaerobic glycolysis. Glucose utilization is increased in hypoxic adipocytes with corresponding increases in lactate production. Importantly, hypoxia induces insulin resistance in fat cells and leads to the development of adipose tissue fibrosis. Many of the responses of adipocytes to hypoxia are initiated at Po(2) levels above the normal physiological range for adipose tissue. The other cell types within the tissue also respond to hypoxia, with the differentiation of preadipocytes to adipocytes being inhibited and preadipocytes being transformed into leptin-secreting cells. Overall, hypoxia has pervasive effects on the function of adipocytes and appears to be a key factor in adipose tissue dysfunction in obesity.

contributes to immune cell immigration and activation which further aggravates adipose tissue fibrosis. Fibrosis is initiated in response to adipocyte hypertrophy in obesity.

KEYWORDS: Adipocyte differentiation; Adipose tissue blood flow; Angiogenesis; CAAT/enhancer binding protein (C/EBP); CAAT/enhancer binding protein (C/EBP)-homologous protein (CHOP); Hypoxia-inducible transcription factor-1 (HIF-1) alpha; Inducible nitric oxide synthase (iNOS); Mitochondrial ROS (mtROS); Obesity; Phosphatidylinositol 3-kinase (PI3K); Reactive oxygen species (ROS); Vascular endothelial growth factor (VEGF)

PMID: 28585205 DOI: 10.1007/978-3-319-48382-5_13

[Indexed for MEDLINE]

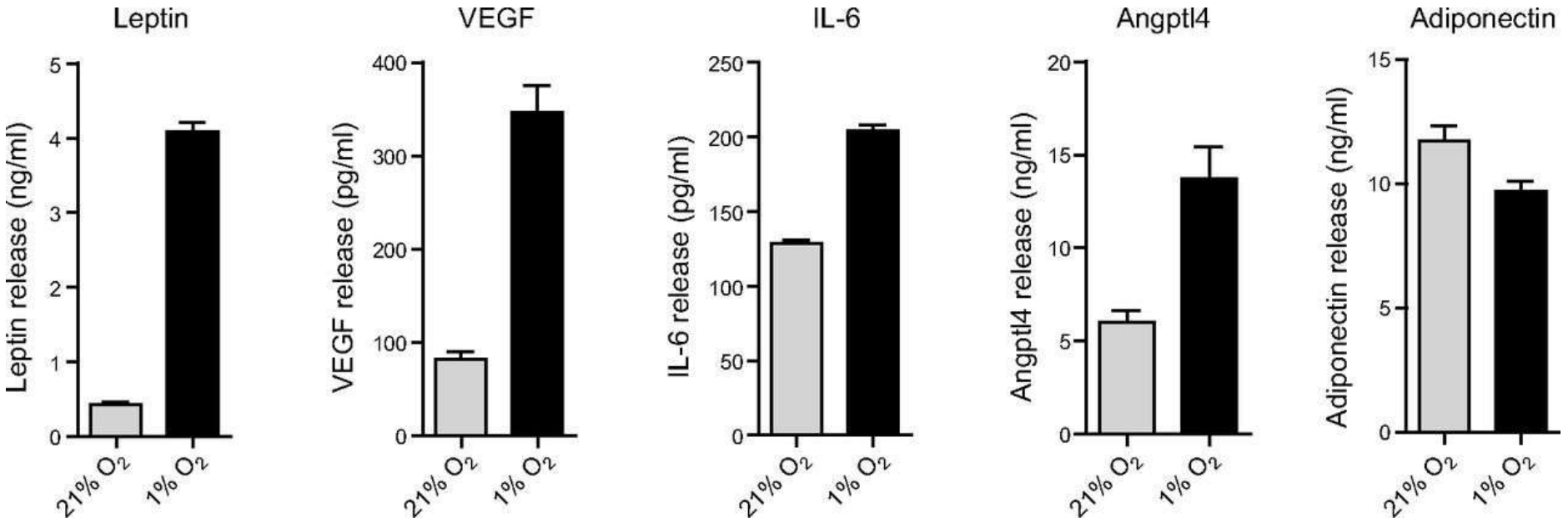


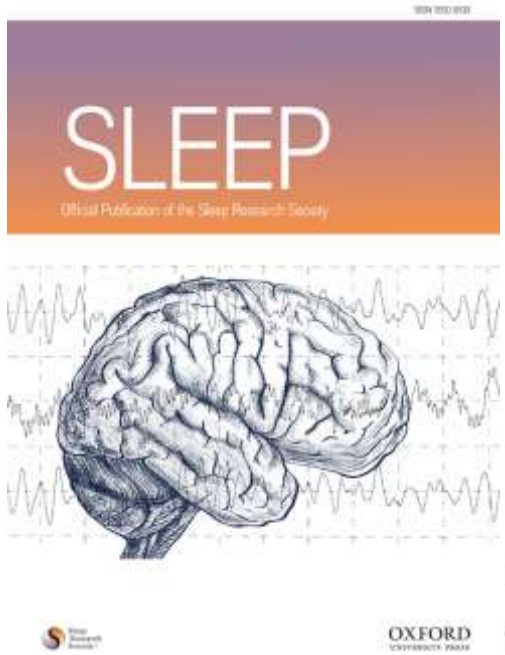
Figure 2. Example of the effects of hypoxia on the secretion of key adipokines by human adipocytes in cell culture. The data are derived from studies in which adipocytes were incubated in either 21% or 1% O2 for 24 h (54, 188). The results are means ± SE (bars; 6 observations per group), and for each adipokine, the difference between the hypoxic and control cells is statistically significant ($P < 0.01$ or better).

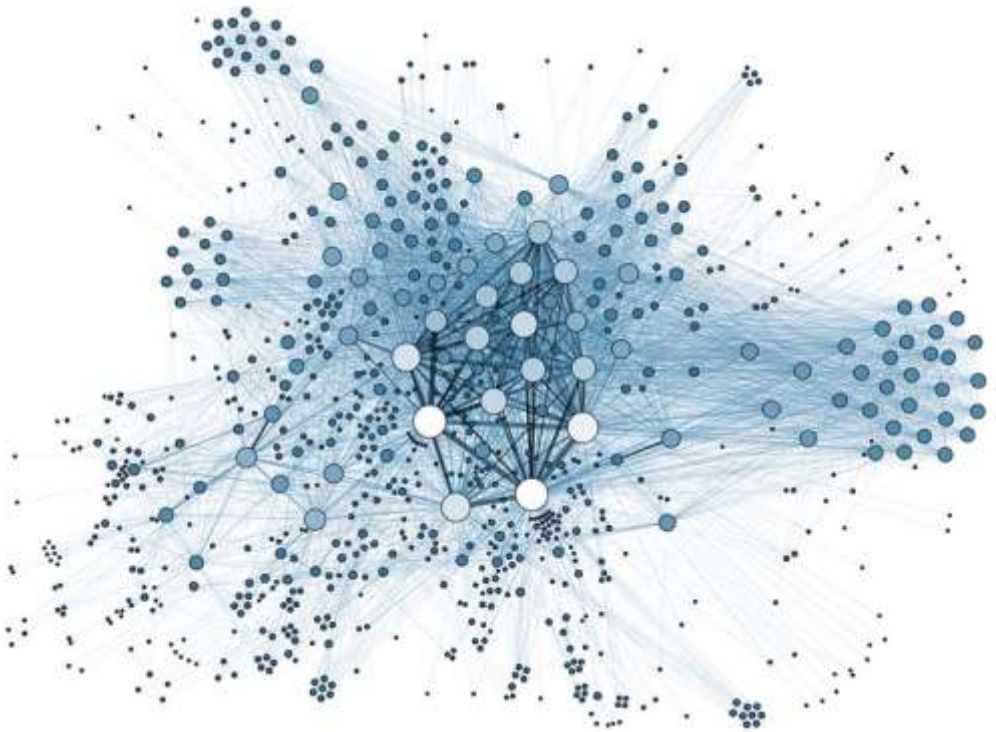
aps American Physiological Society | Physiological Reviews

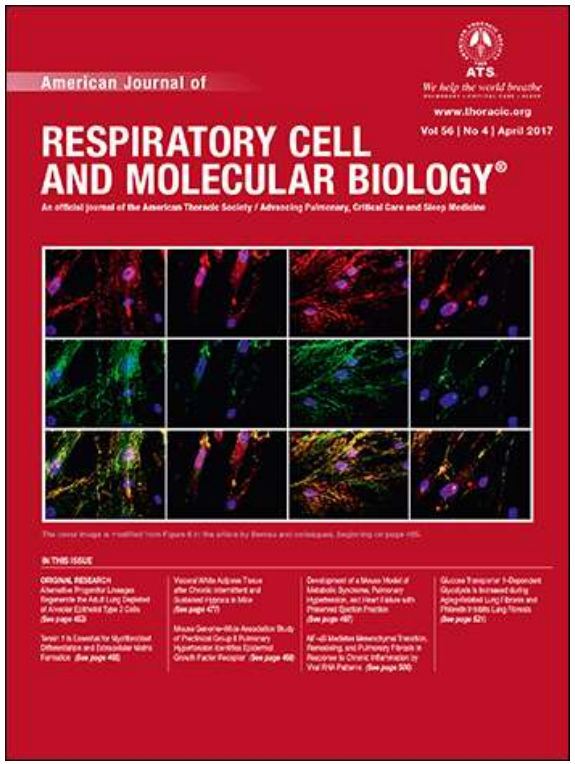
Paul Trayhurn; Physiological Reviews 2013

Is Hypoxia to Blame for Bad Fat?

Yes and No





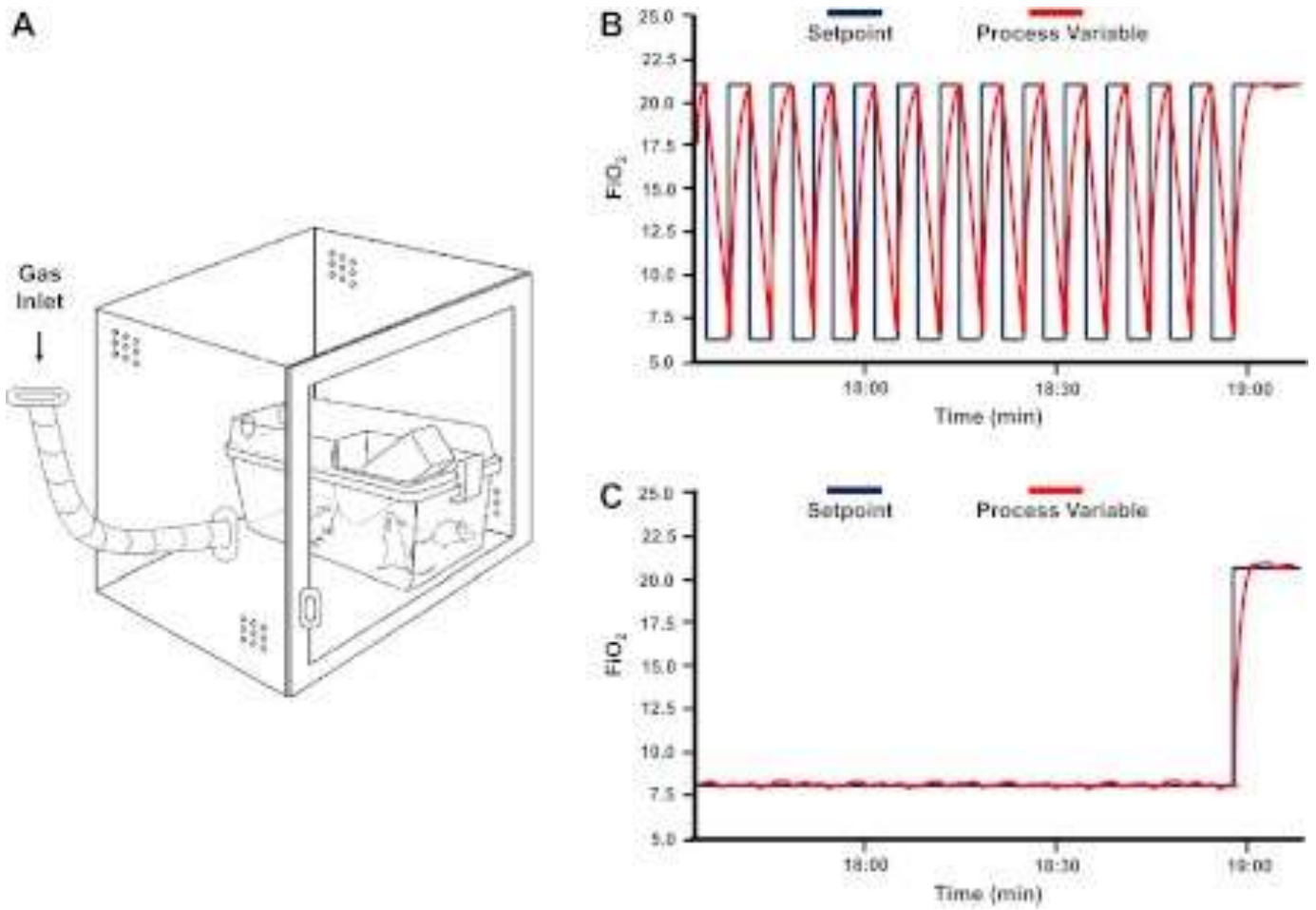


Let's take a look at the data

*** Gileles-Hillel. et al. Prolonged Exposures to Intermittent Hypoxia Promote vWAT Inflammation, Sleep 2017**

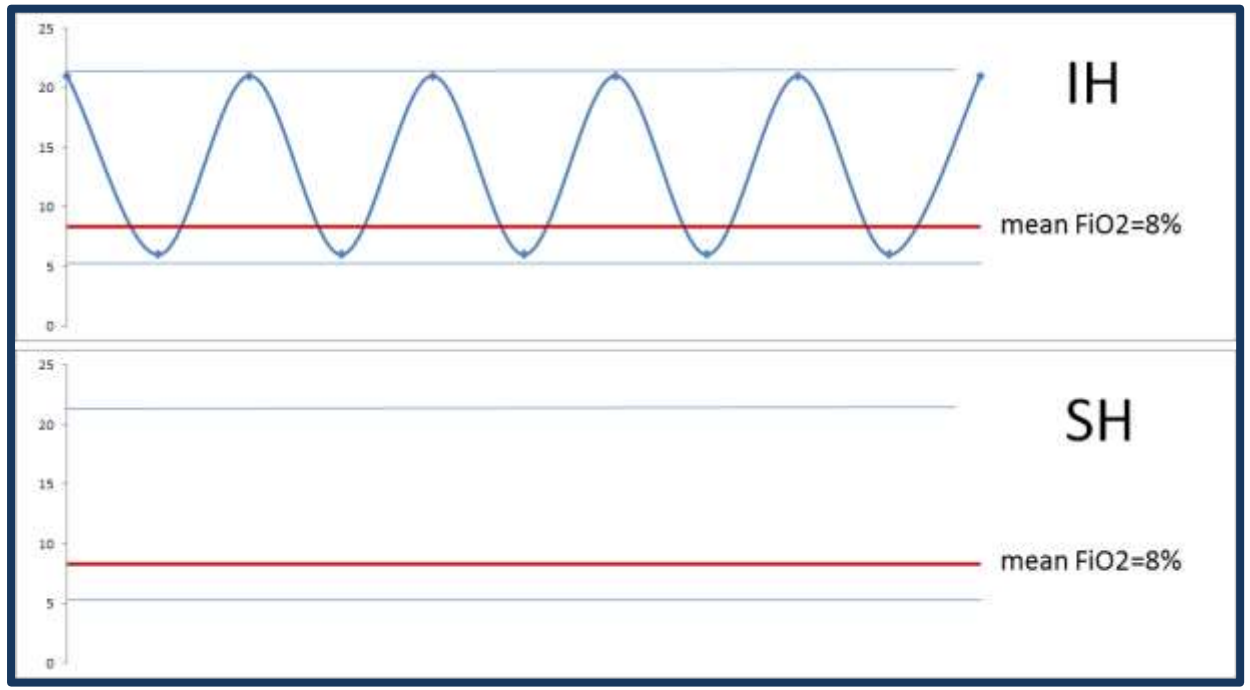
*** Gozal, Gileles-Hillel, Cortese, et al.: Hypoxia and Adipose Tissue AJRCMB 2017**

*** Gileles-Hillel (under preparation)**



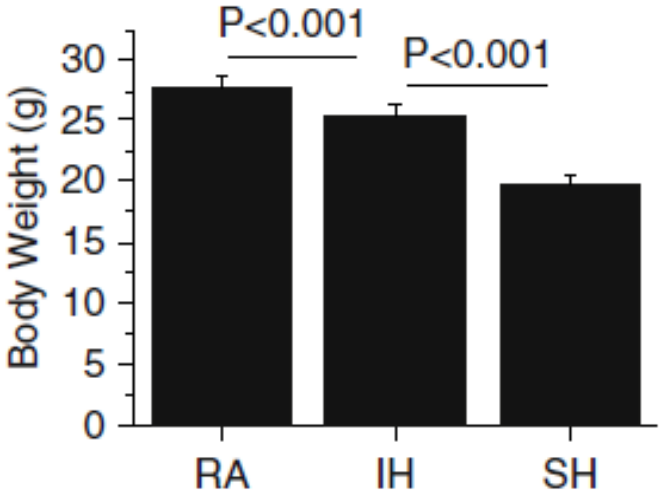
Am J Physiol Regul Integr Comp Physiol. 2012

Sustained Hypoxia **Room Air** **Intermittent Hypoxia**

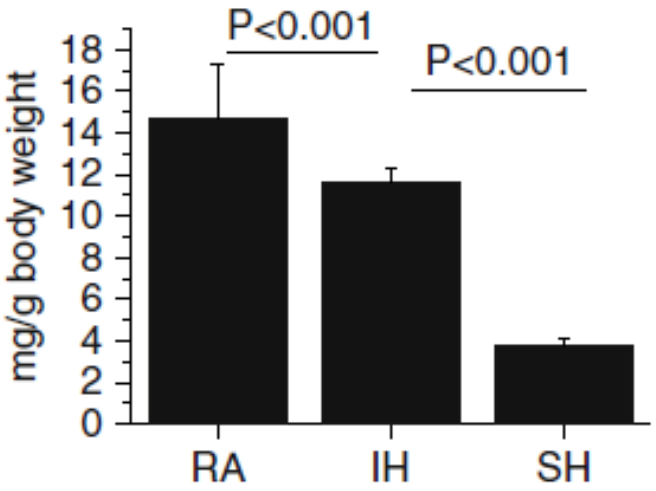


- 8-week old male C57BL/6J mice were exposed to IH (F_IO_2 6.1% alternating 21% every 90s, mean F_IO_2 ~8% for 12-hr/day during the light period), to SH (F_IO_2 8%) or to room air (RA) for 20 weeks.

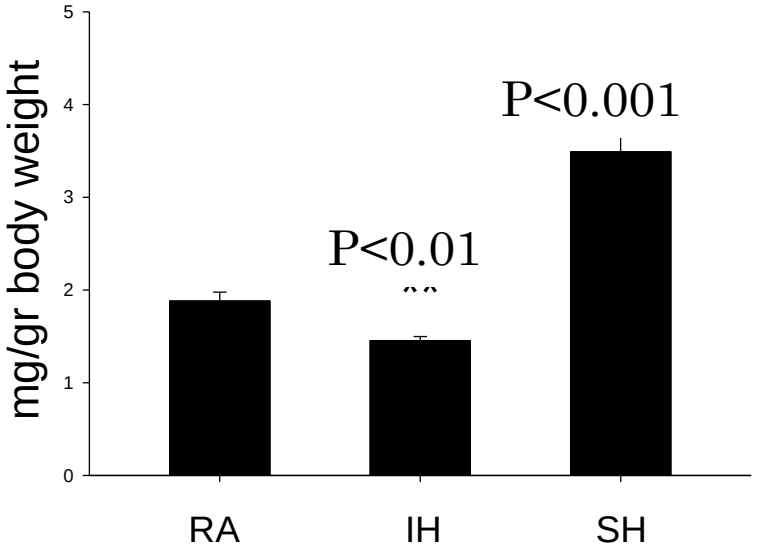
Results



Total Body Weight

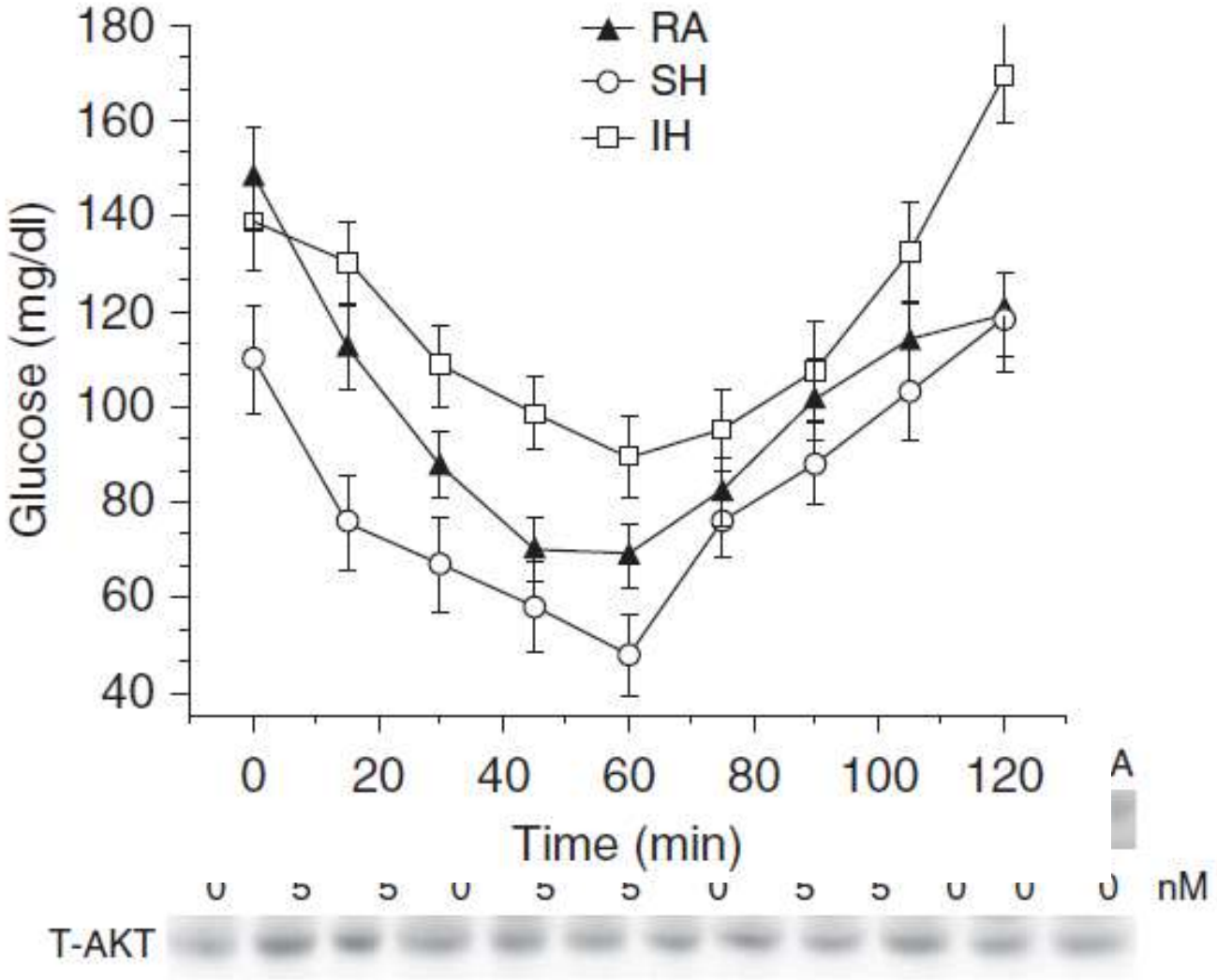


vWAT Amount

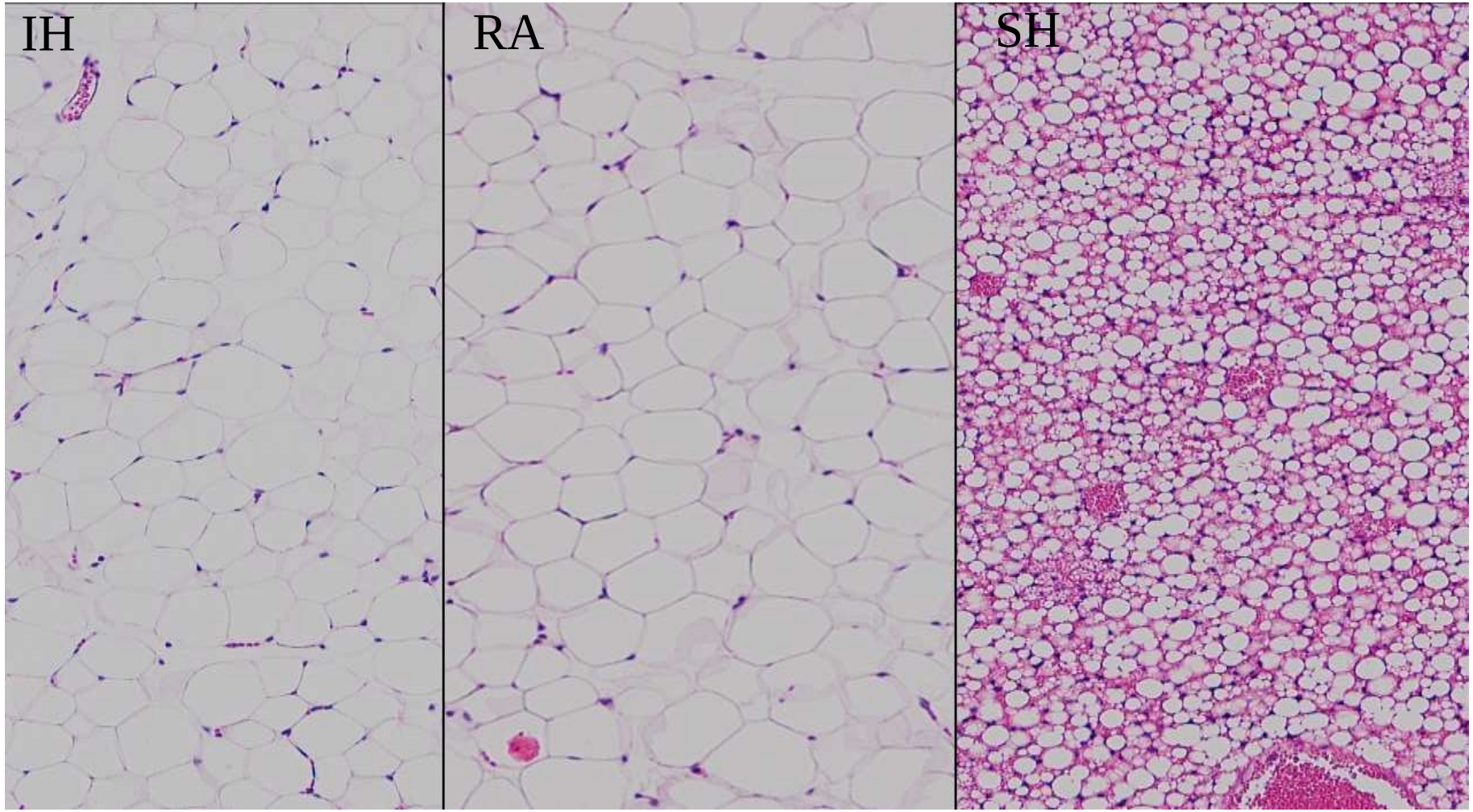


iBAT Amount

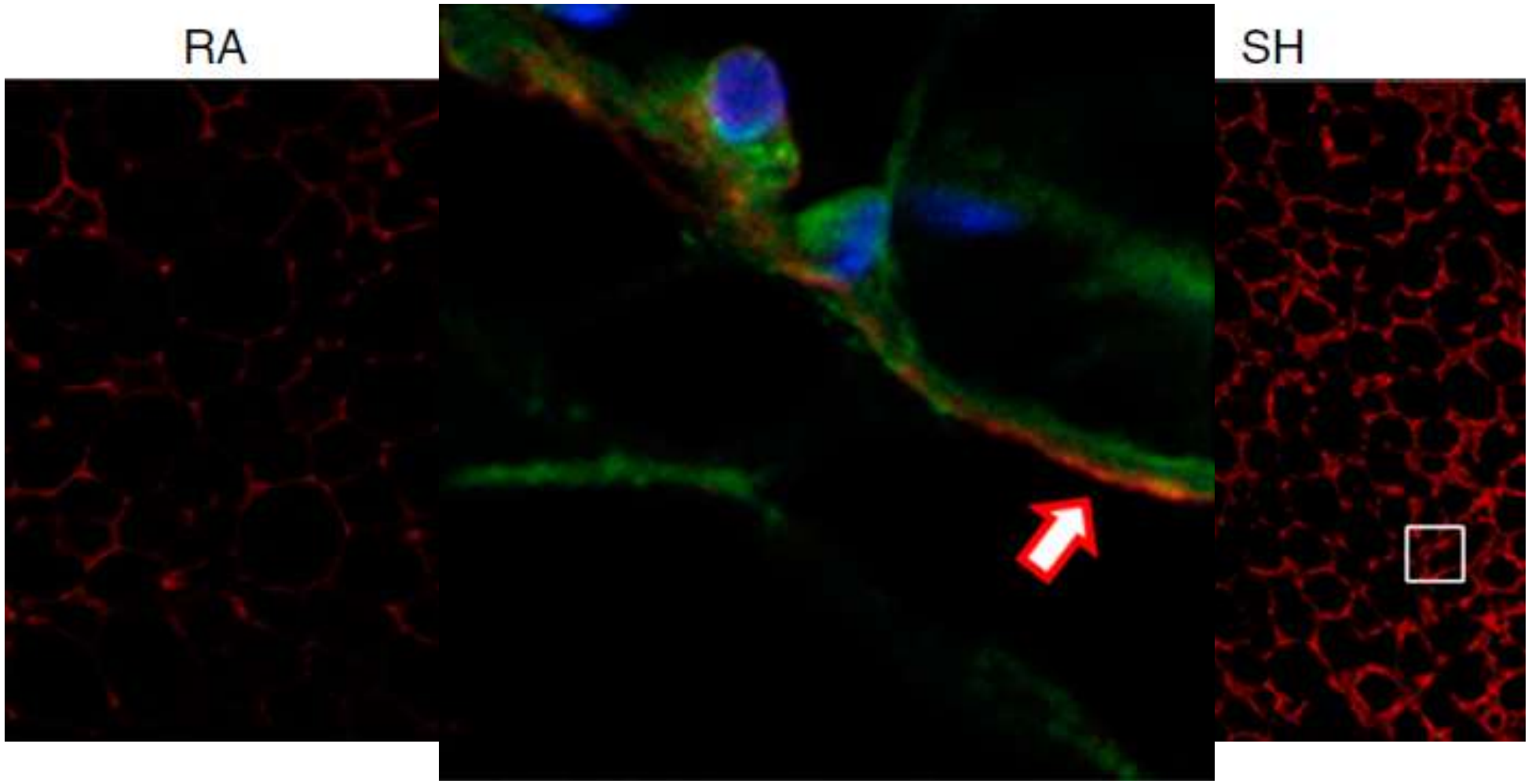
Insulin Sensitivity



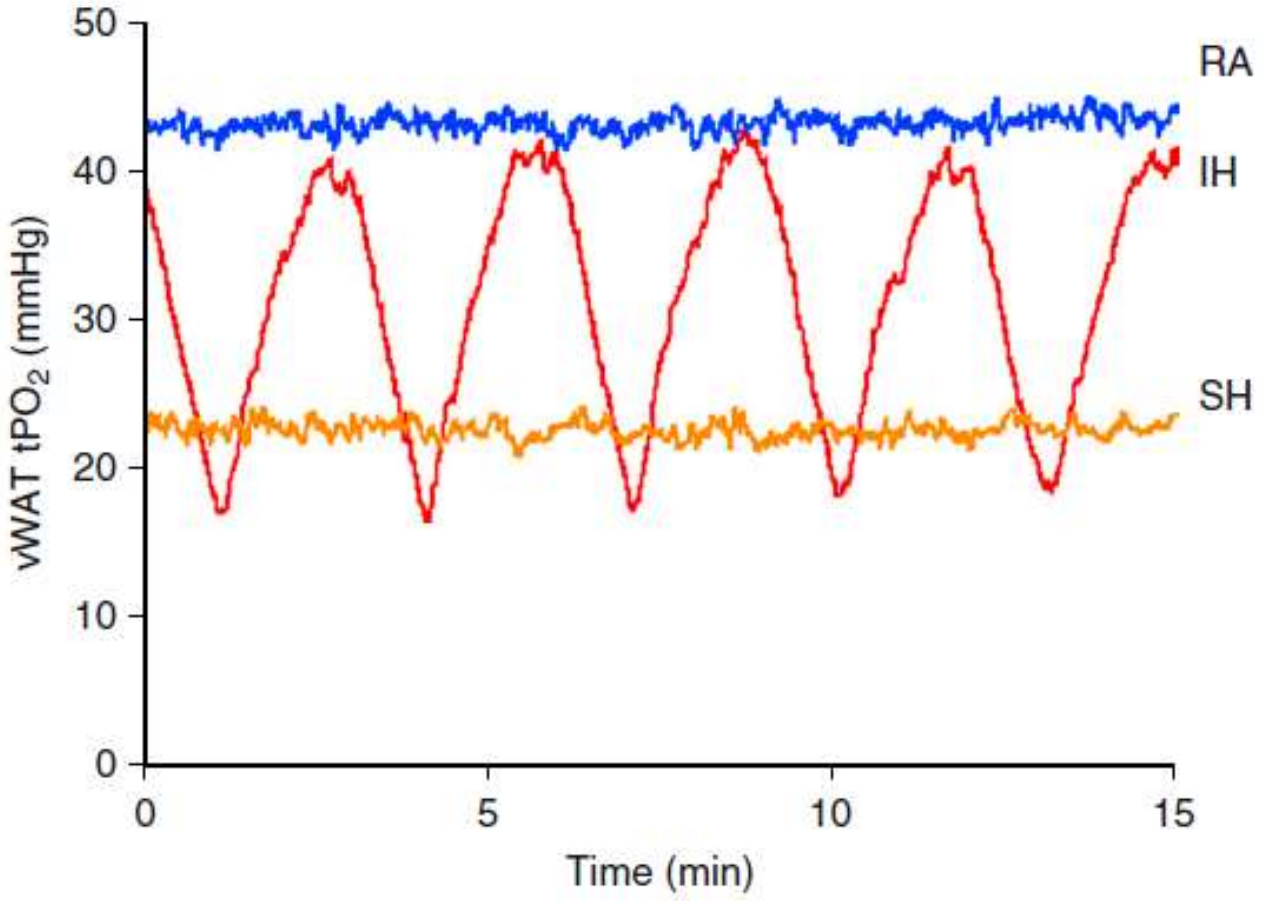
Structure



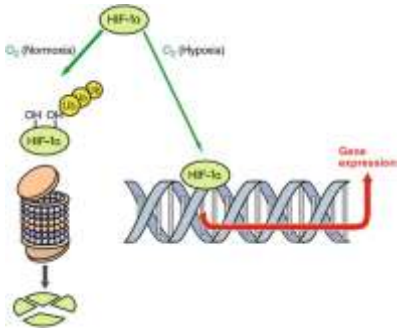
Vascularity in vWAT



What does actually happen in the fat?



HIF1-α



Cell. 2014 Jun 5;157(6):1339-52. doi: 10.1016/j.cell.2014.05.012.

Increased adipocyte O2 consumption triggers HIF-1α, causing inflammation and insulin resistance in obesity.

Lee YS[1], Kim JW[2], Osborne O[1], Oh DY[1], Sasik R[1], Schenk S[3], Chen A[1], Chung H[1], Murphy A[4], Watkins SM[5], Quehenberger O[1], Johnson RS[6], Olefsky JM

⊕ Author information

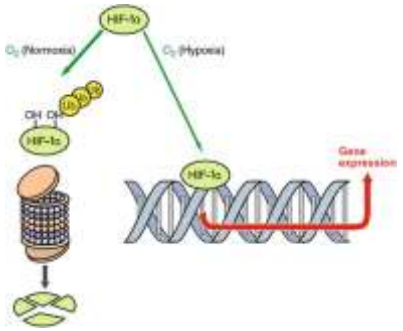
Abstract

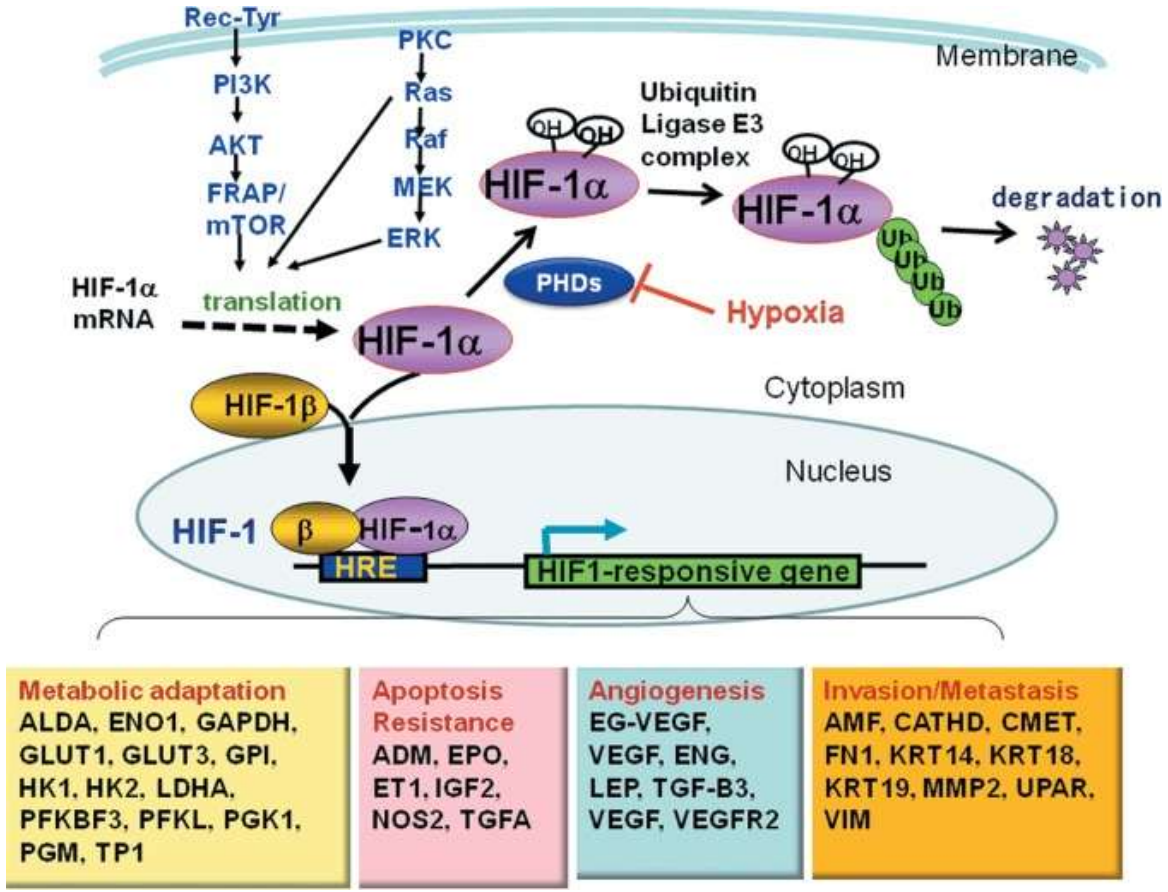
Adipose tissue hypoxia and inflammation have been causally implicated in obesity-induced insulin resistance. Here, we report that, early in the course of high-fat diet (HFD) feeding and obesity, adipocyte respiration becomes uncoupled, leading to increased oxygen consumption and a state of relative adipocyte hypoxia. These events are sufficient to trigger HIF-1α induction, setting off the chronic adipose tissue inflammatory response characteristic of obesity. At the molecular level, these events involve saturated fatty acid stimulation of the adenine nucleotide translocase 2 (ANT2), an inner mitochondrial membrane protein, which leads to the uncoupled respiratory state. Genetic or pharmacologic inhibition of either ANT2 or HIF-1α can prevent or reverse these pathophysiologic events, restoring a state of insulin sensitiv and glucose tolerance. These results reveal the sequential series of events in obesity-induced inflammation and insulin resistance.

PMID: 24906151 PMCID: PMC4114226 DOI: 10.1016/j.cell.2014.05.012

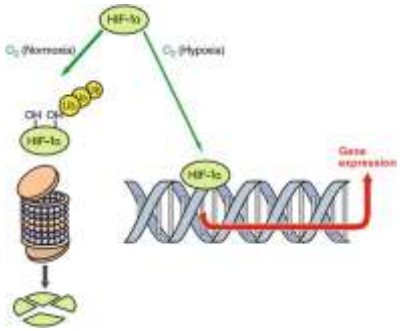
[Indexed for MEDLINE] Free PMC Article

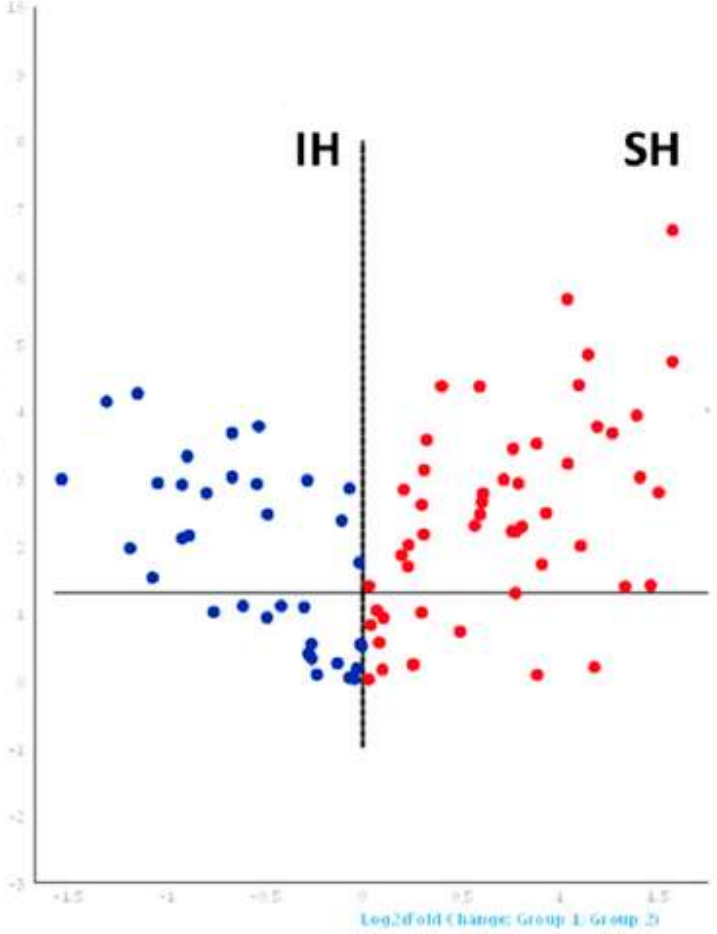
HIF1-α



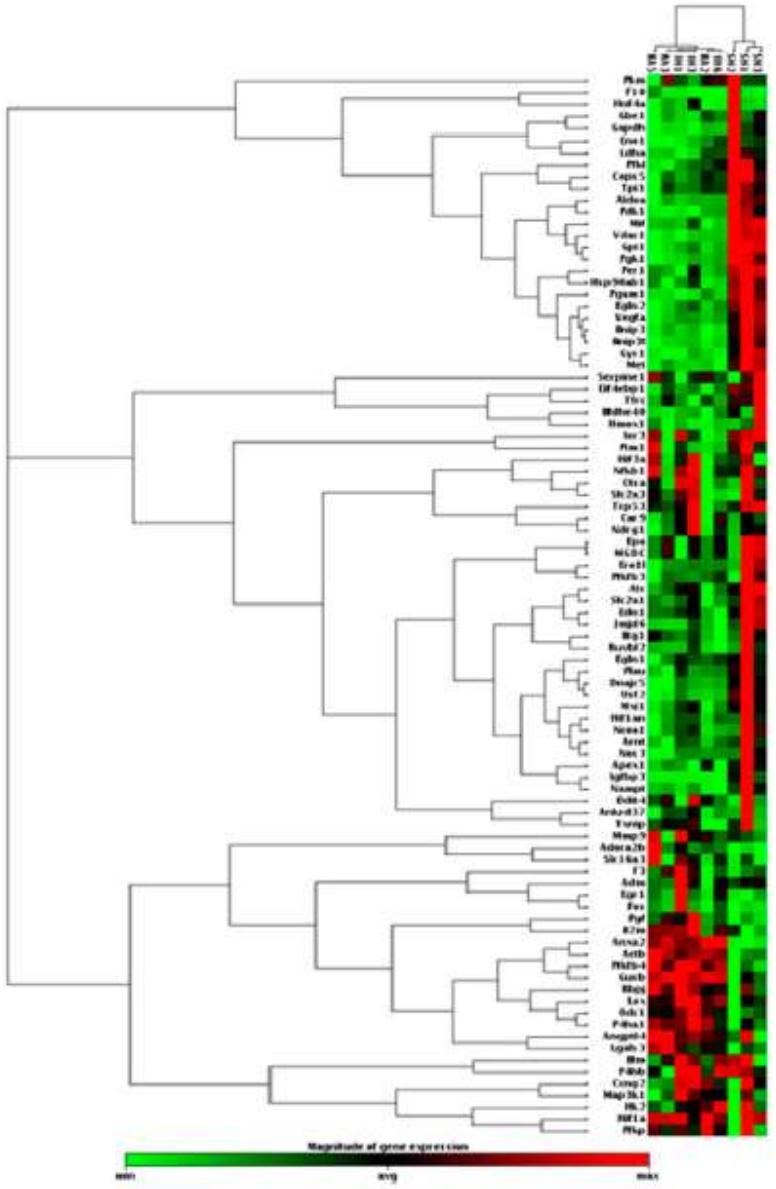

Rec-Tyr
PKC
Membrane
PI3K
Ras
AKT
Raf
FRAP/
mTOR
MEK
ERK
Ubiquitin
Ligase E3
complex
HIF-1α
HIF-1α
degradation
HIF-1α
mRNA
translation
PHDs
Hypoxia
HIF-1α
HIF-1β
Cytoplasm
Nucleus
HIF-1
β
HIF-1α
HRE
HIF1-responsive gene
Metabolic adaptation
ALDA, ENO1, GAPDH, GLUT1, GLUT3, GPI, HK1, HK2, LDHA, PFKBF3, PFKL, PGK1, PGM, TP1
Apoptosis Resistance
ADM, EPO, ET1, IGF2, NOS2, TGFA
Angiogenesis
EG-VEGF, VEGF, ENG, LEP, TGF-B3, VEGF, VEGFR2
Invasion/Metastasis
AMF, CATHD, CMET, FN1, KRT14, KRT18, KRT19, MMP2, UPAR, VIM

HIF1-α

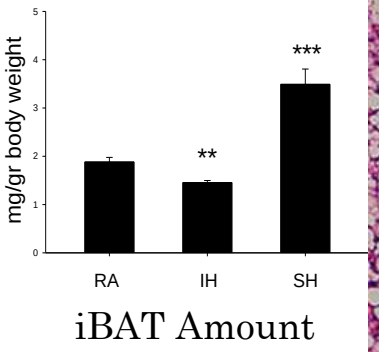




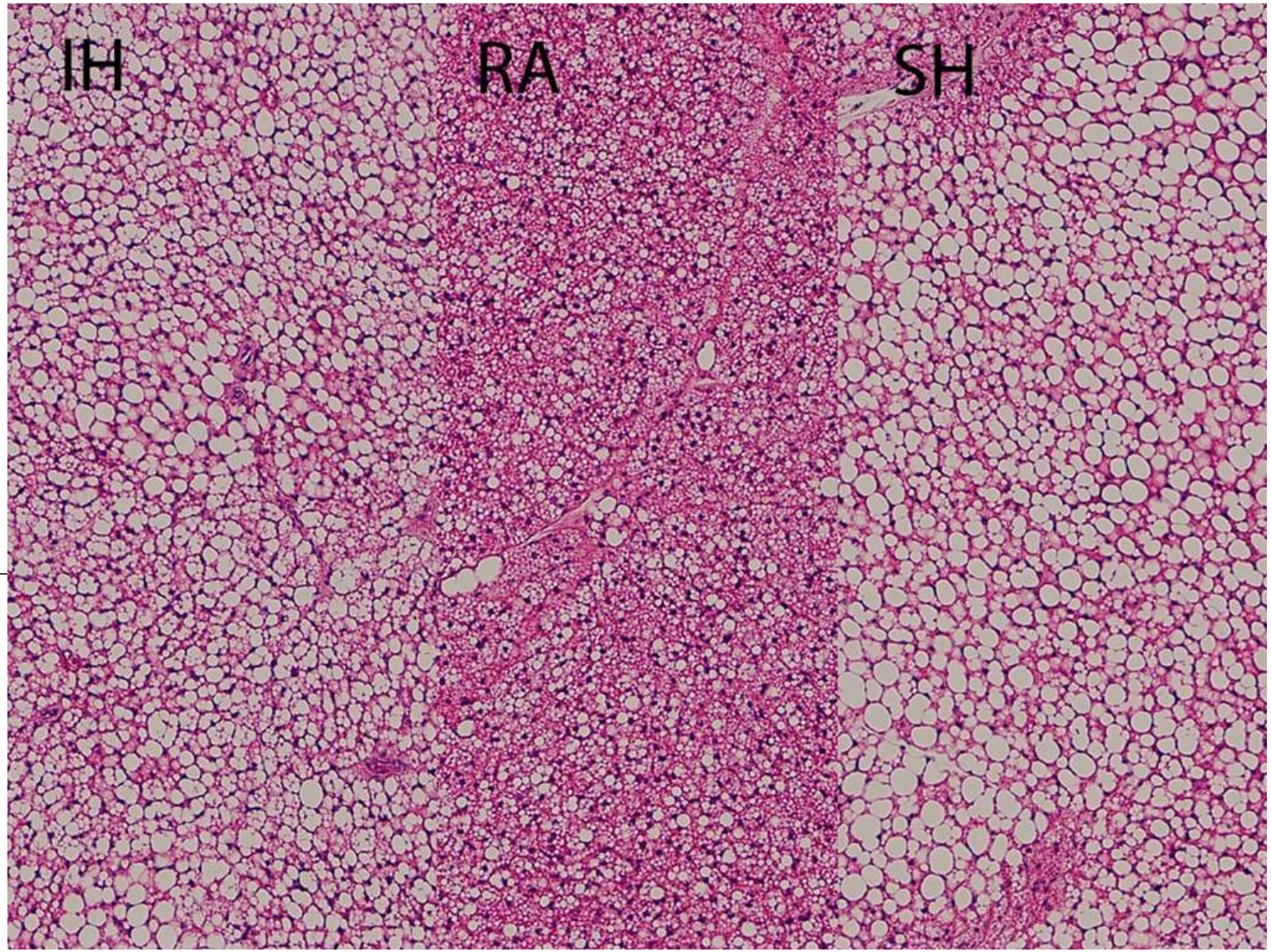
RAIH SH



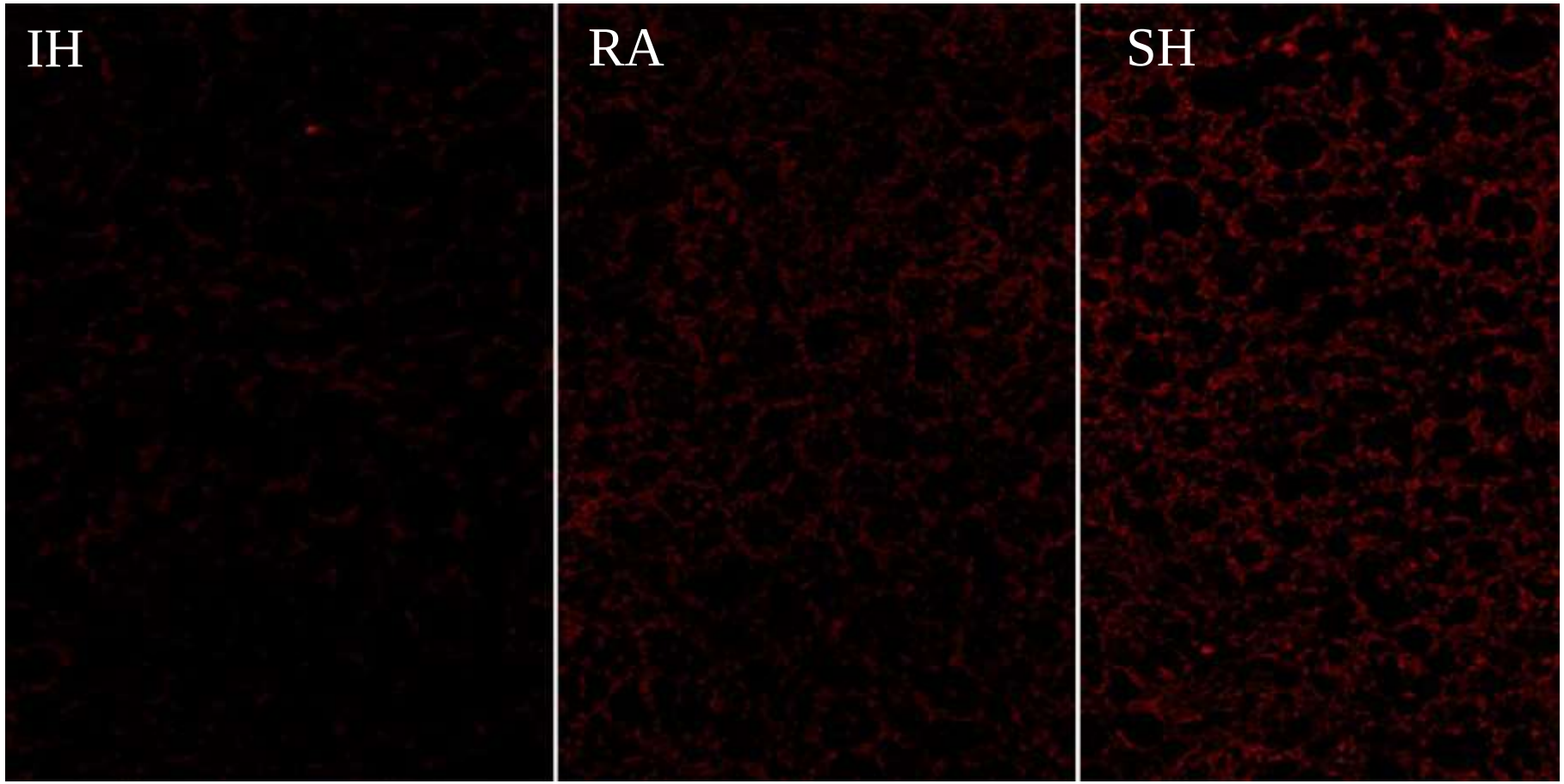
Further on BAT



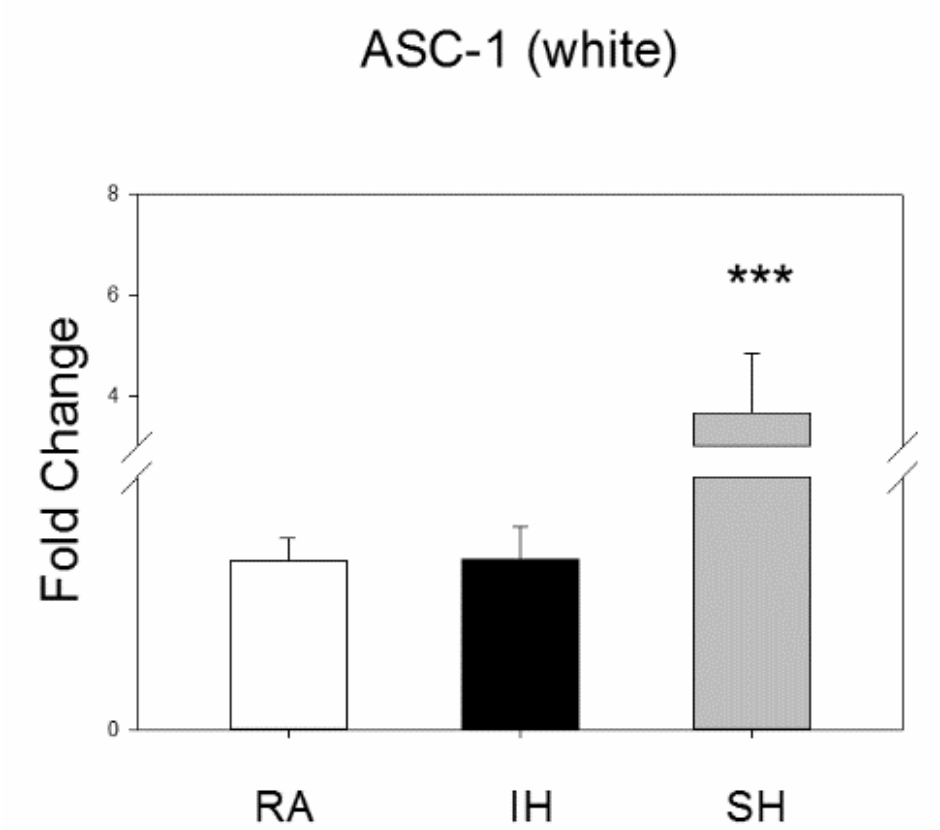
iBAT Amount

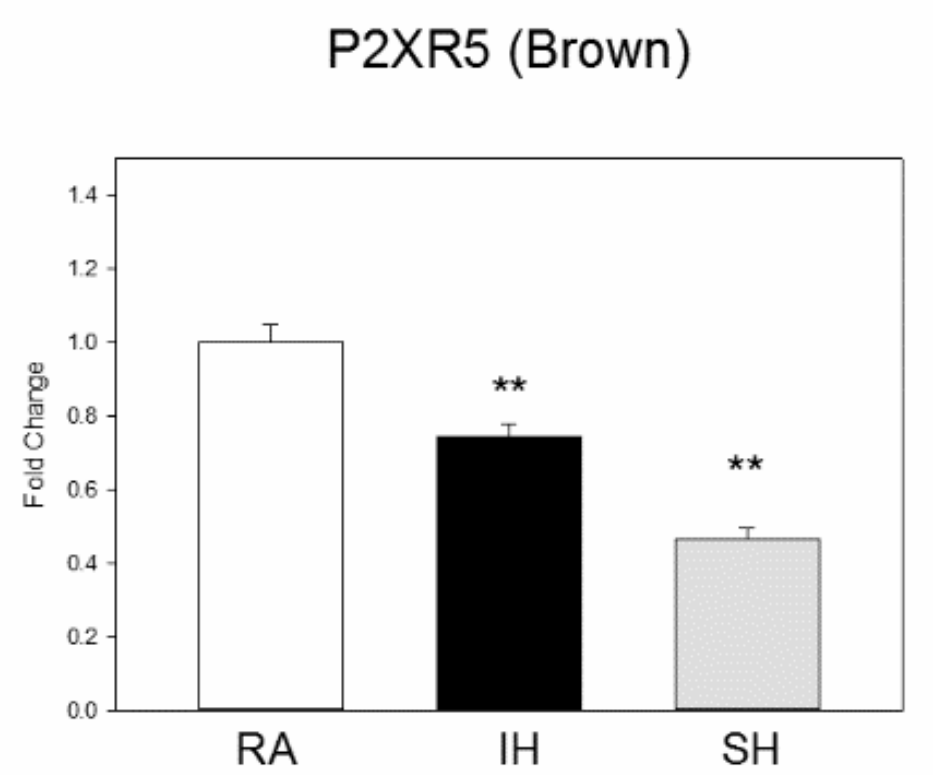


Vascularity in iBAT



White or Brown?





Mitochondria in iBAT

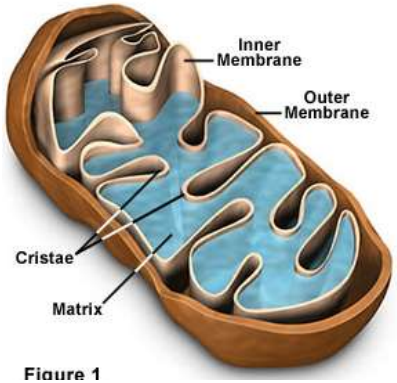
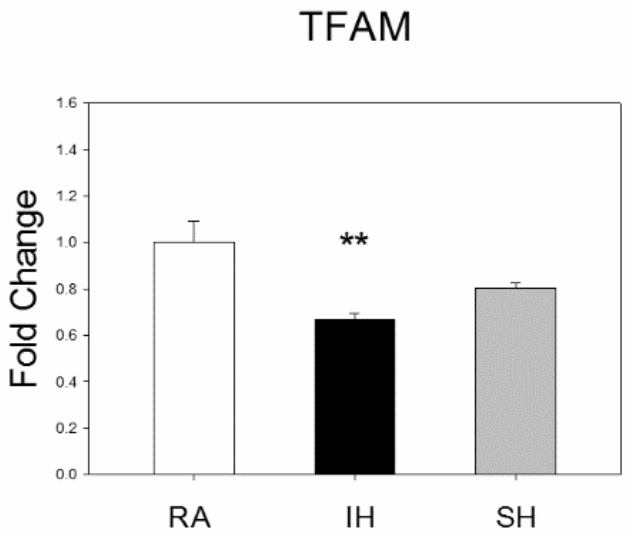
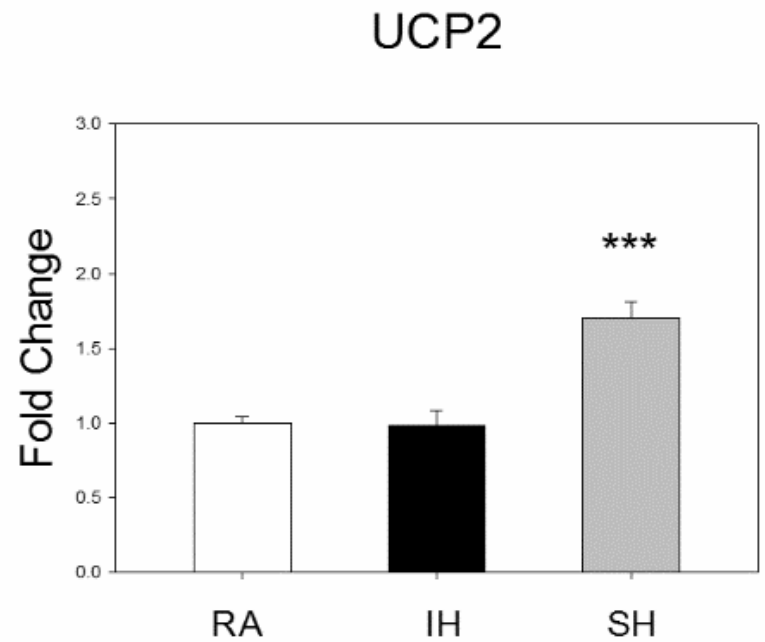
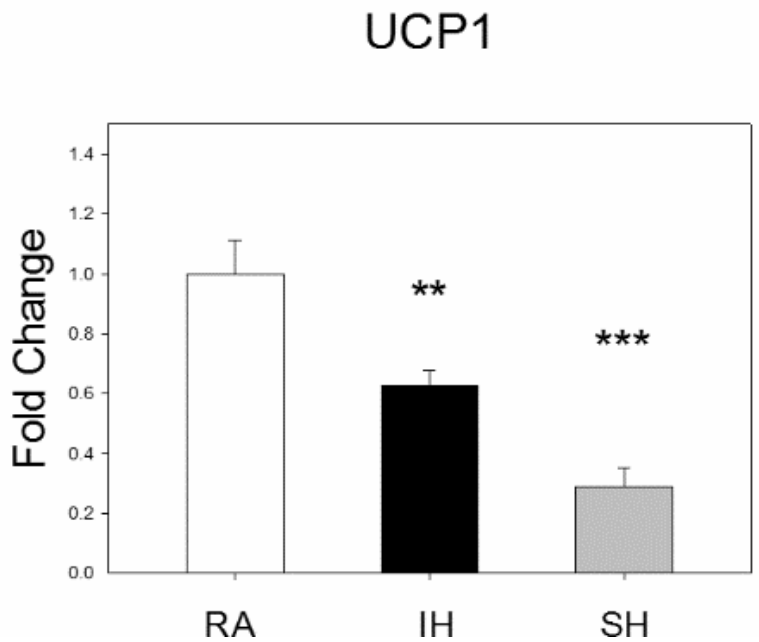


Figure 1



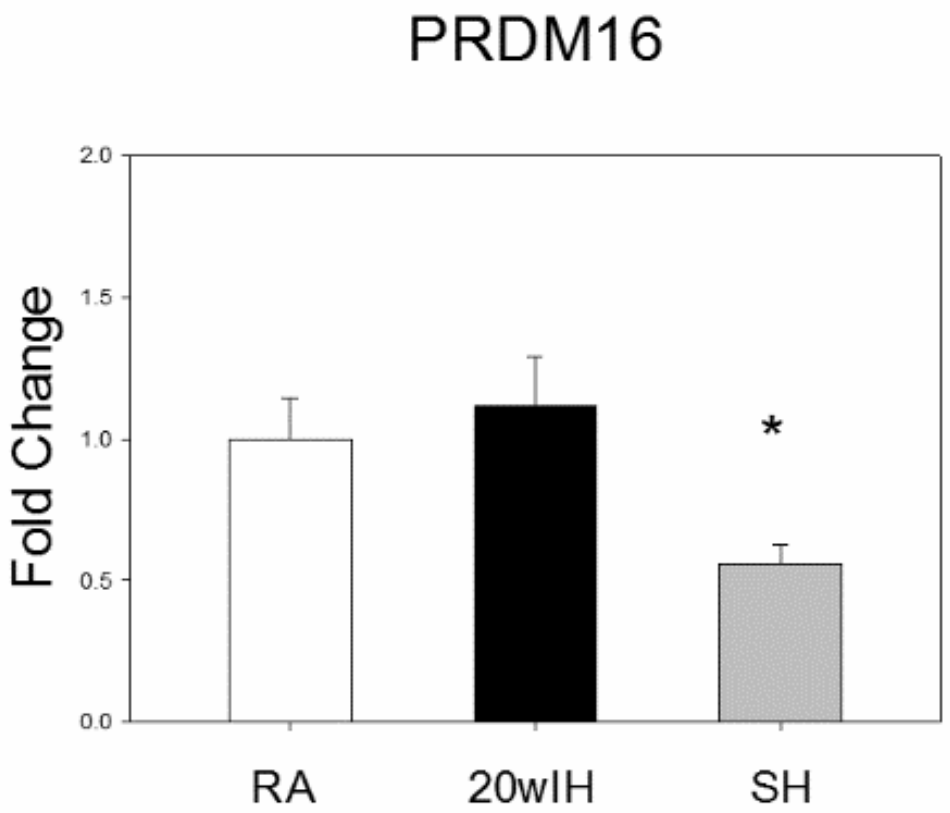




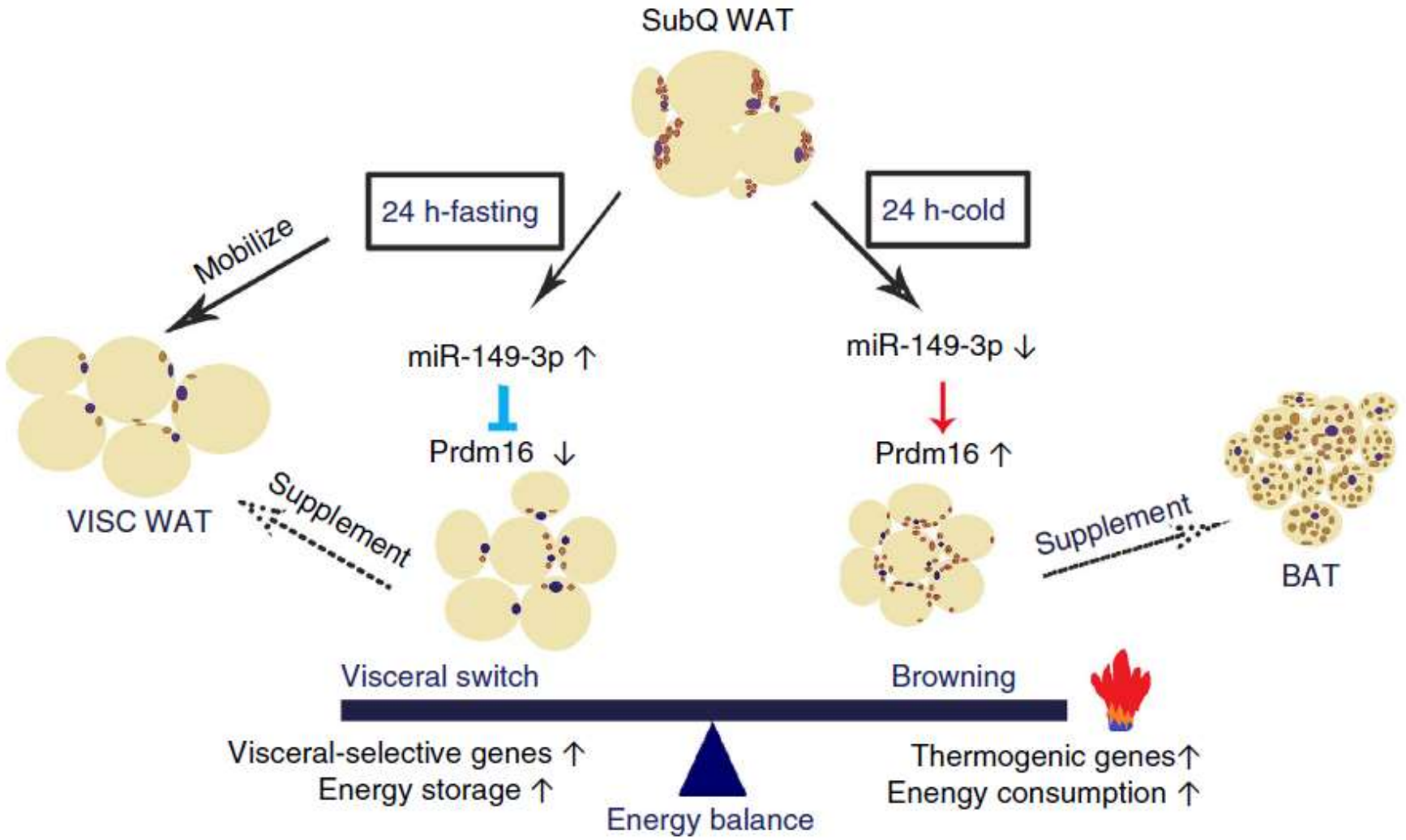
Sustained? Intermittent? White? Brown?

		SH	IH
Body Weight		---	--
Insulin sensitivity		IS	IR
WAT	Amount	---	-
	White vs Brown	Br	W
	Vascularity	+++	--
BAT	Amount	+++	-
	White vs Brown	W	~
	Vascularity	+	--

What is happening here?



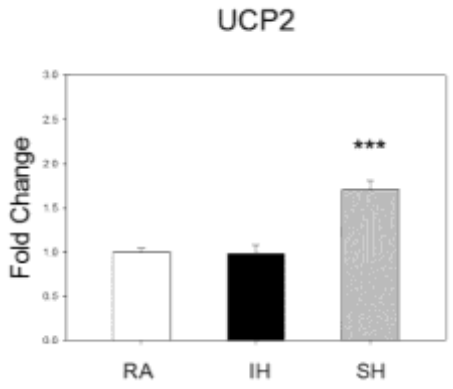
nature COMMUNICATIONS

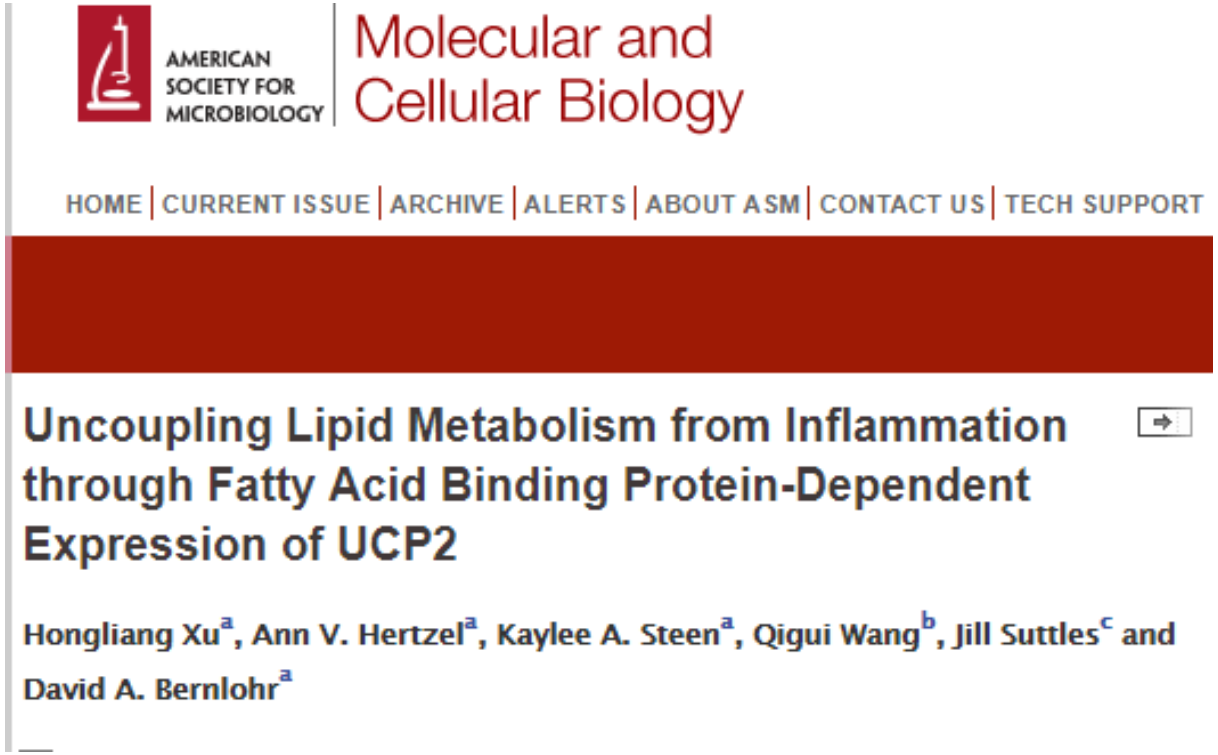


Ding H et al, Nature Communications 2016

What about the UCPs?

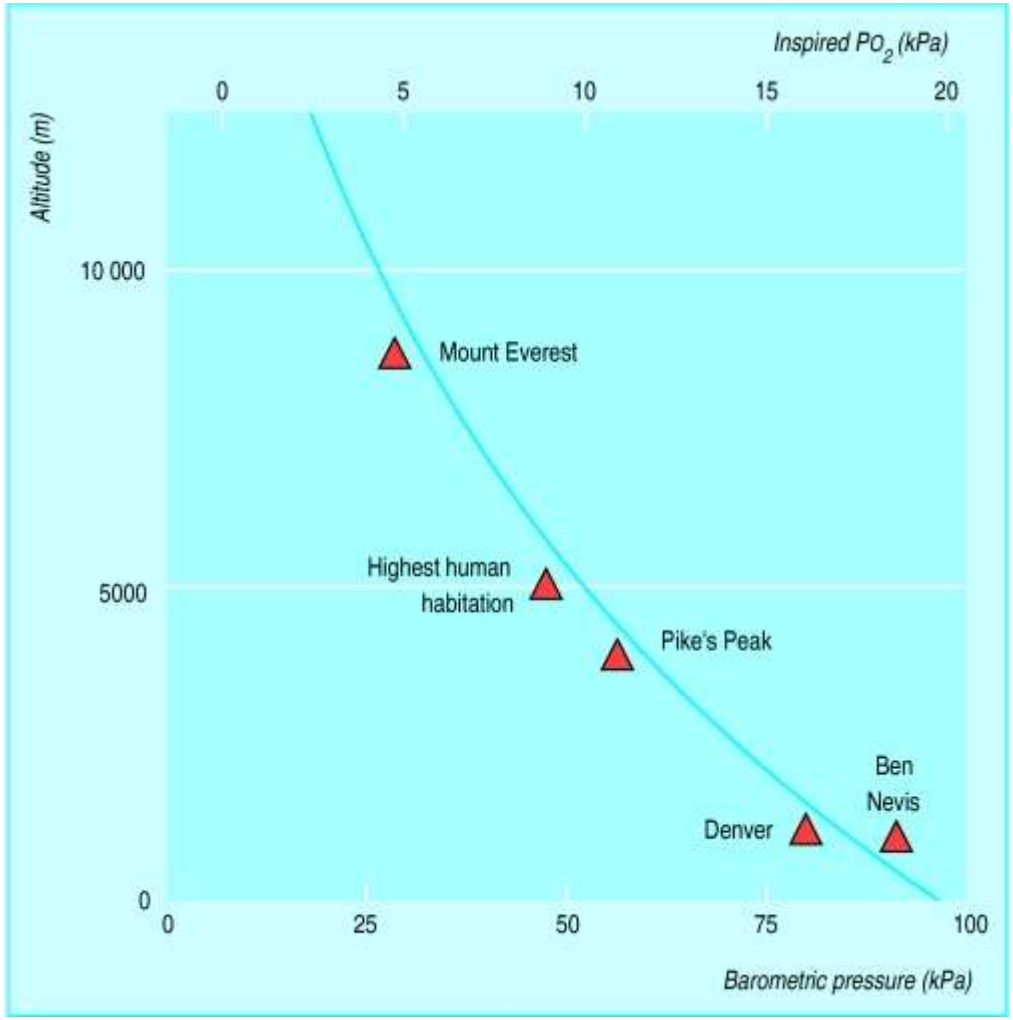
Decreased UCP2 expression has been associated with increased risk of obesity, decreased insulin level, and type 2 diabetes in humans





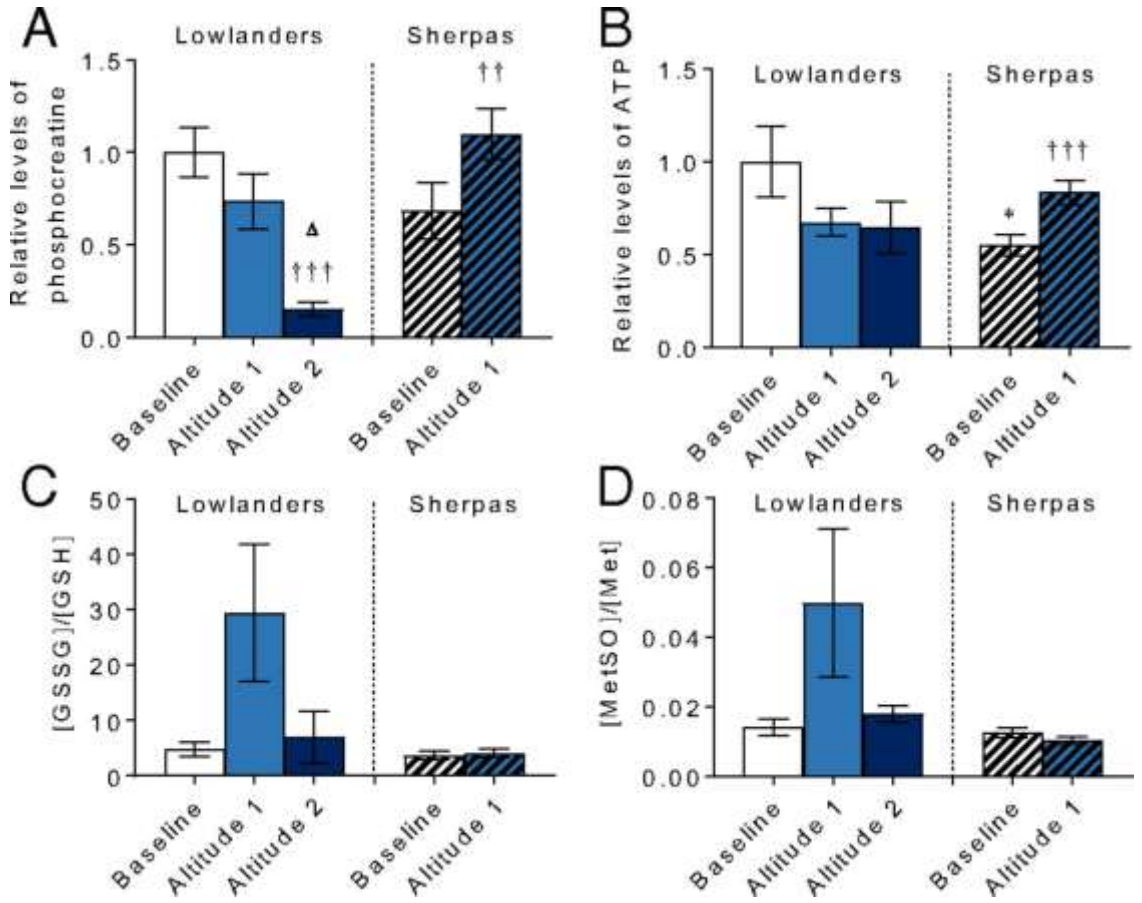
Donadelli, M., Dando, I., Fiorini, C. et al. Cell. Mol. Life Sci. (2014)

Back to Tibet



Peacock A, BMJ. 1998

Muscle energetics and oxidative stress in Highland Dwellers



lower fatty acid β-oxidation and improved mitochondrial coupling compared with Lowlanders, with a possible compensatory increase in fatty acid ω-oxidation

James A. Horscroft et al. PNAS 2017

PNAS

Questions?

DAVID GOZAL

Isaac Almendros

Mahzad Akbarpour

Qiao Zhuahong

Rene Cortese

Abdelnaby Khalyfa