Role of Mitochondrial Networks in Regulating Body Weight: Obesity as a Mitochondrial Dysfunction

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Eating too much and exercising too little does NOT cause obesity.

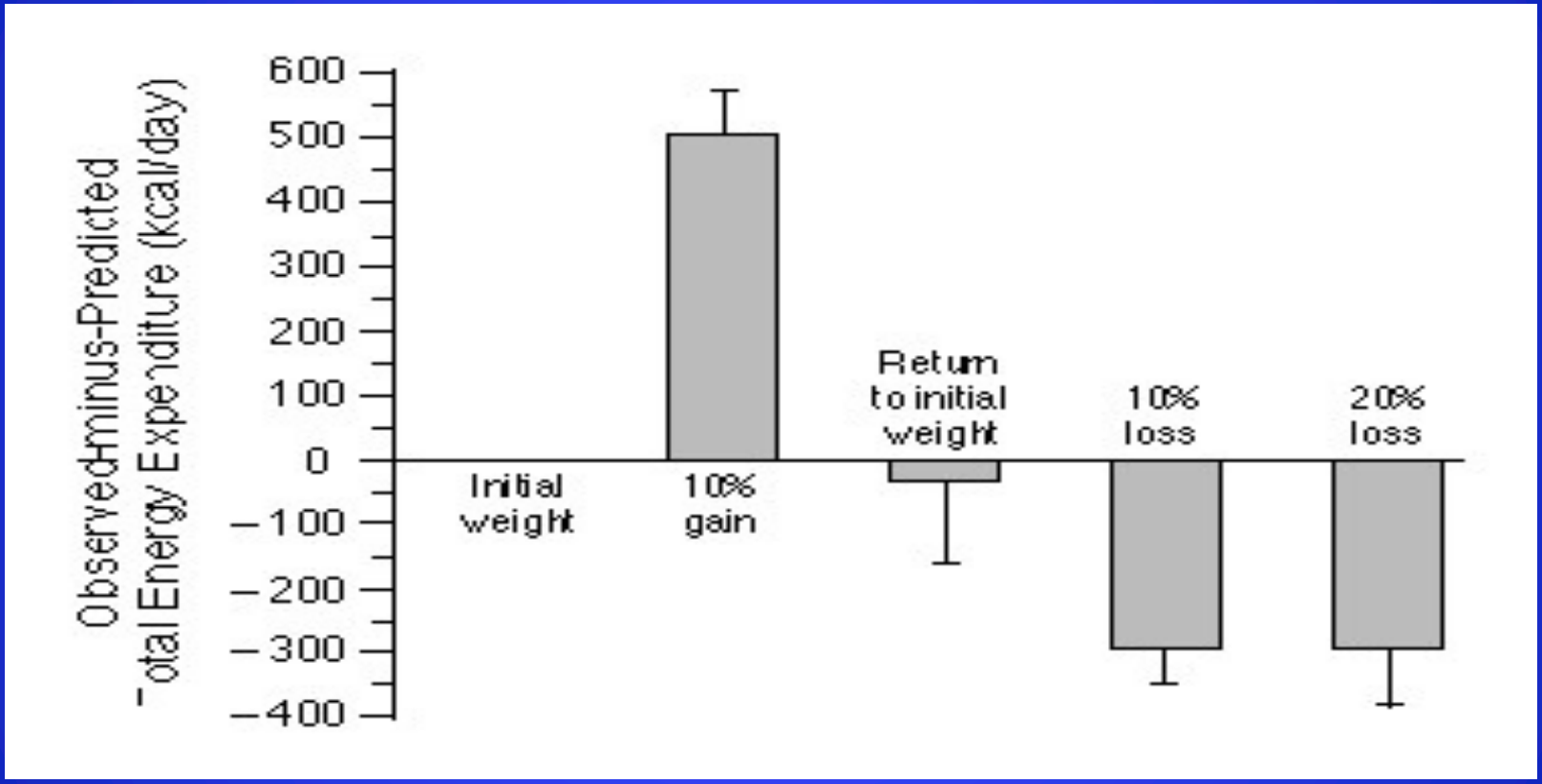
- We forgot the most important variable: involuntary control of energy metabolism
- Hibernating mammals: 4x decrease in EEx
- Migrating birds: 7x increase in EEx
- Children prior to 1980s and lean individuals

Variations Occur in Energy Efficiency

- Vermont prisoner study*: lean individuals required 6-8000 cal/d to gain 20% excess wt: increase energy expenditure
- Energy state is communicated via the Redox Network
- Dieters decrease energy expenditure
- Cells exposed to excess nutrient waste energy

*Salans, Horton, Sims 1976

Mean (±SD) Observed-minus-Predicted Total Energy Expenditure (Shaded Bars) Based on the Regression of Total Energy Expenditure in a Model with a Variable Combining Fat-free Mass and Fat Mass in the Same Subjects at Their Initial Weight.

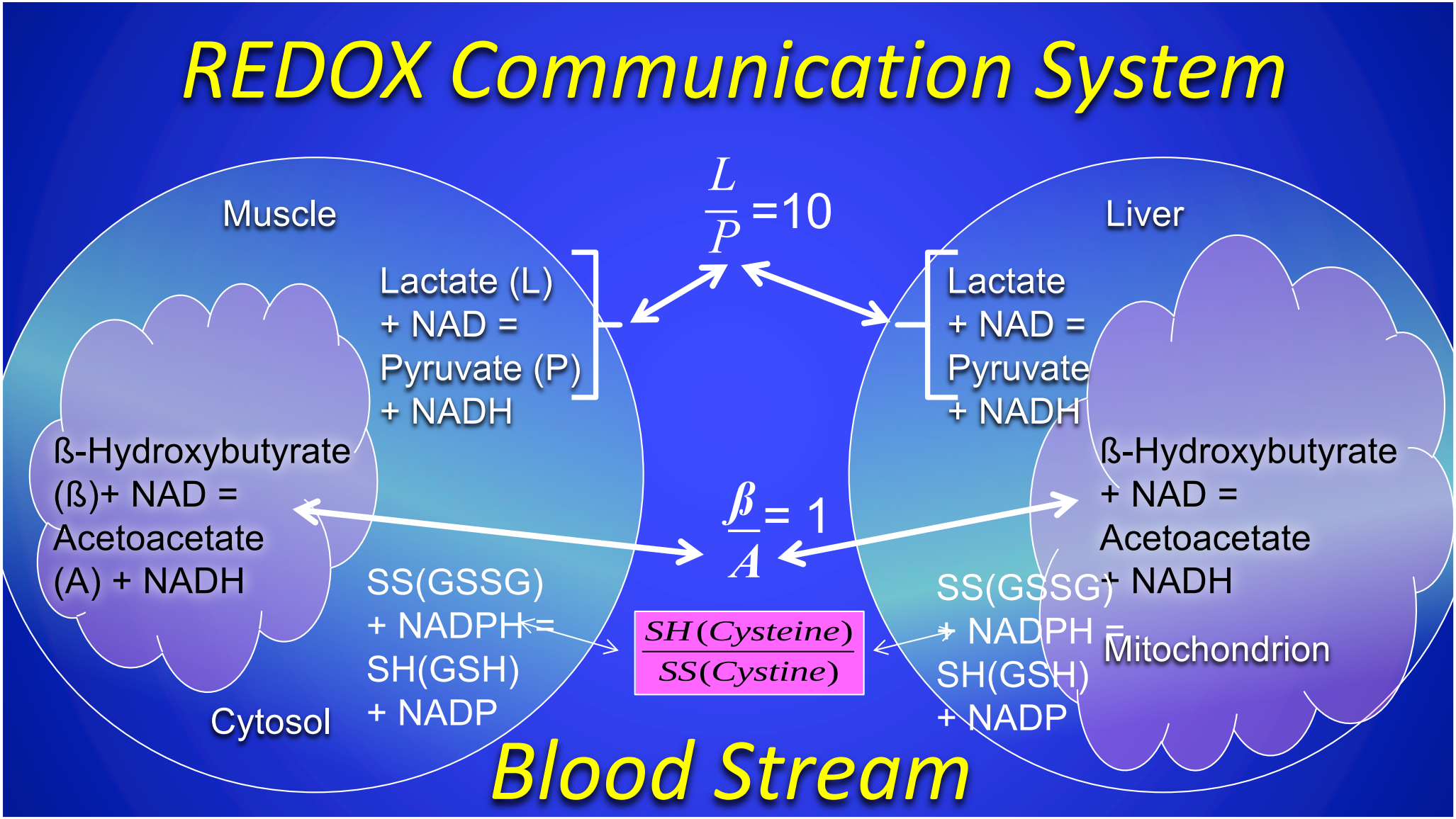


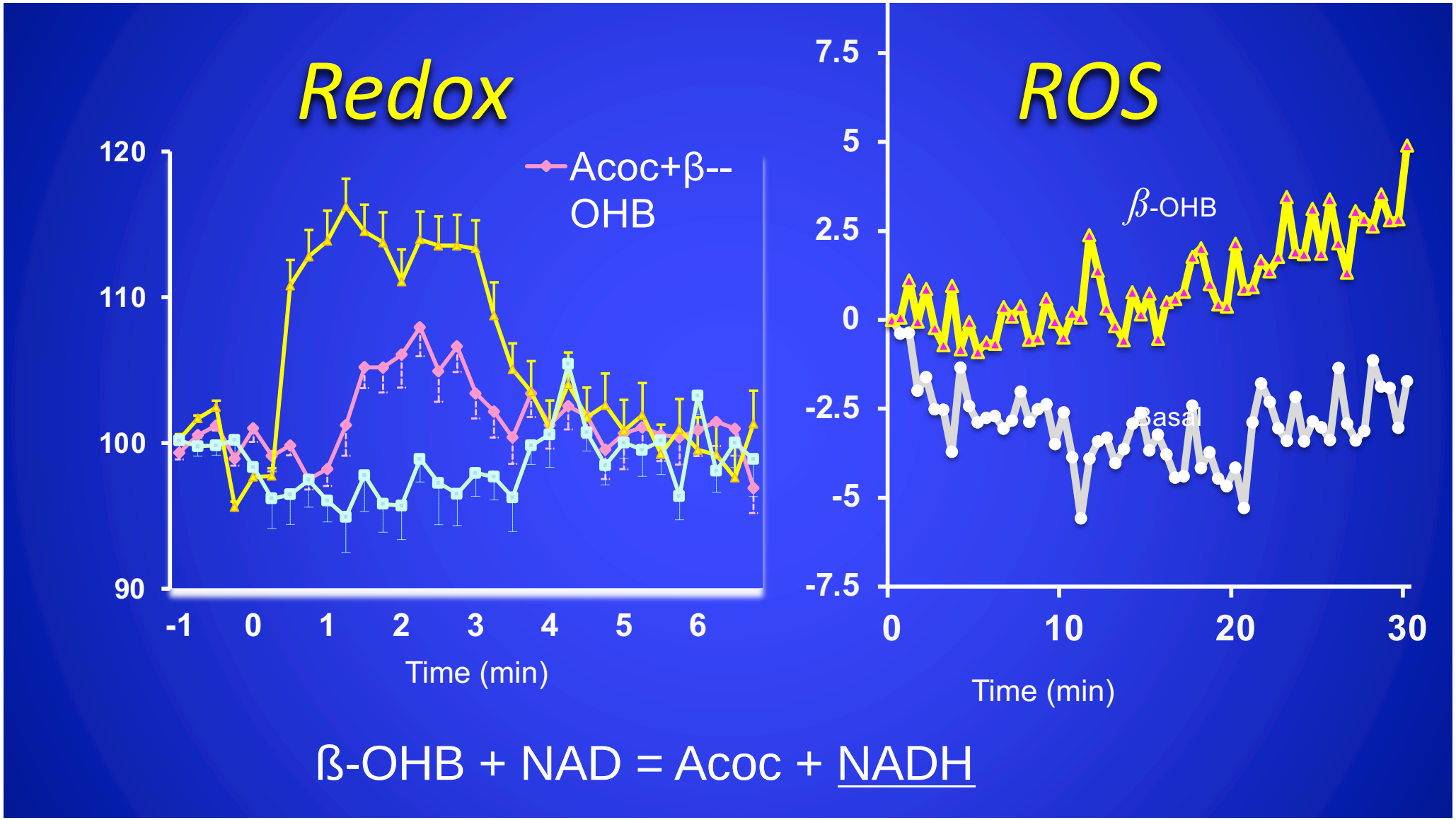
Leibel RL et al. N Engl J Med 1995;332:621-628.

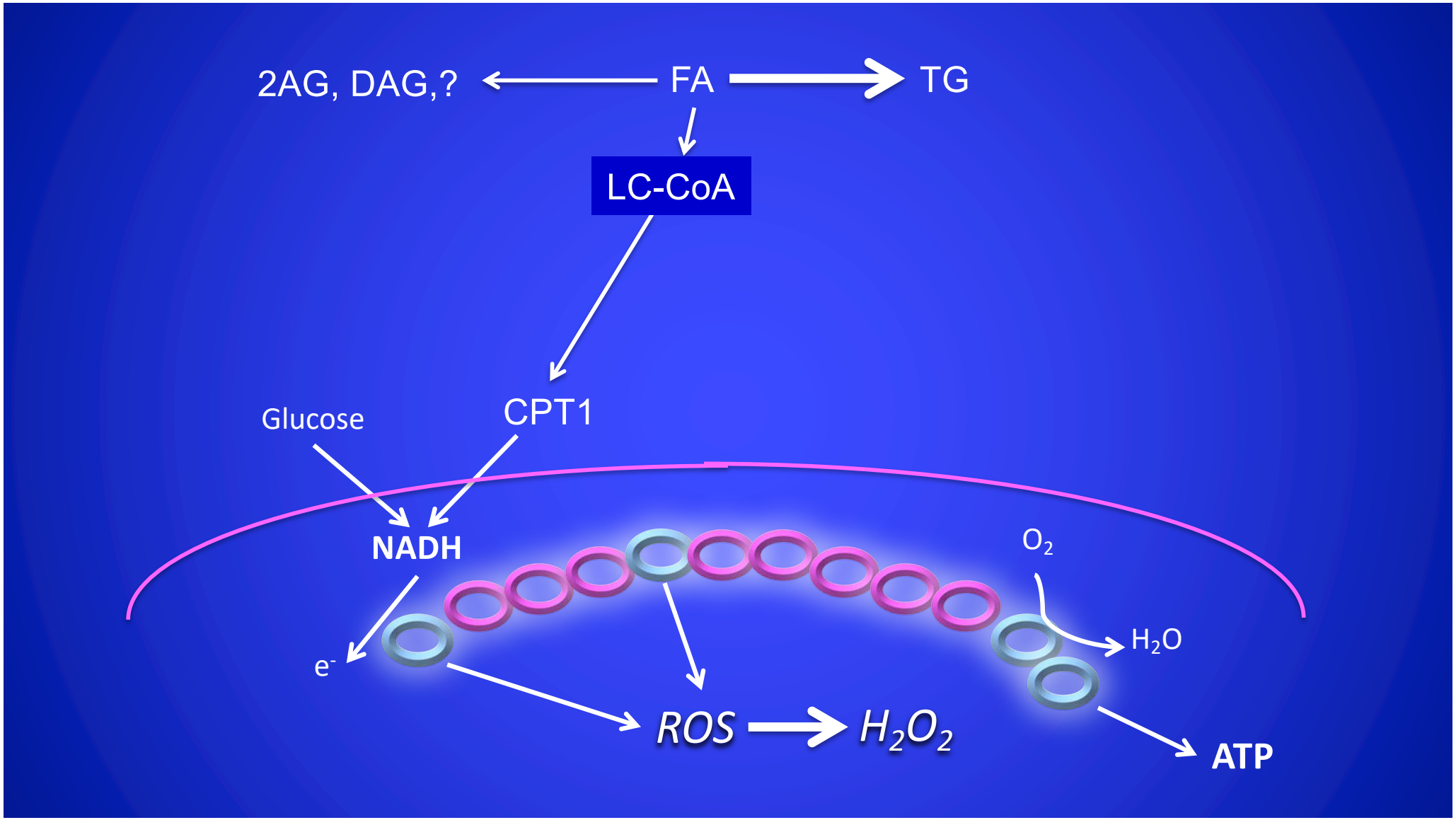
The NEW ENGLAND JOURNAL of MEDICINE

Variations in Energy Efficiency

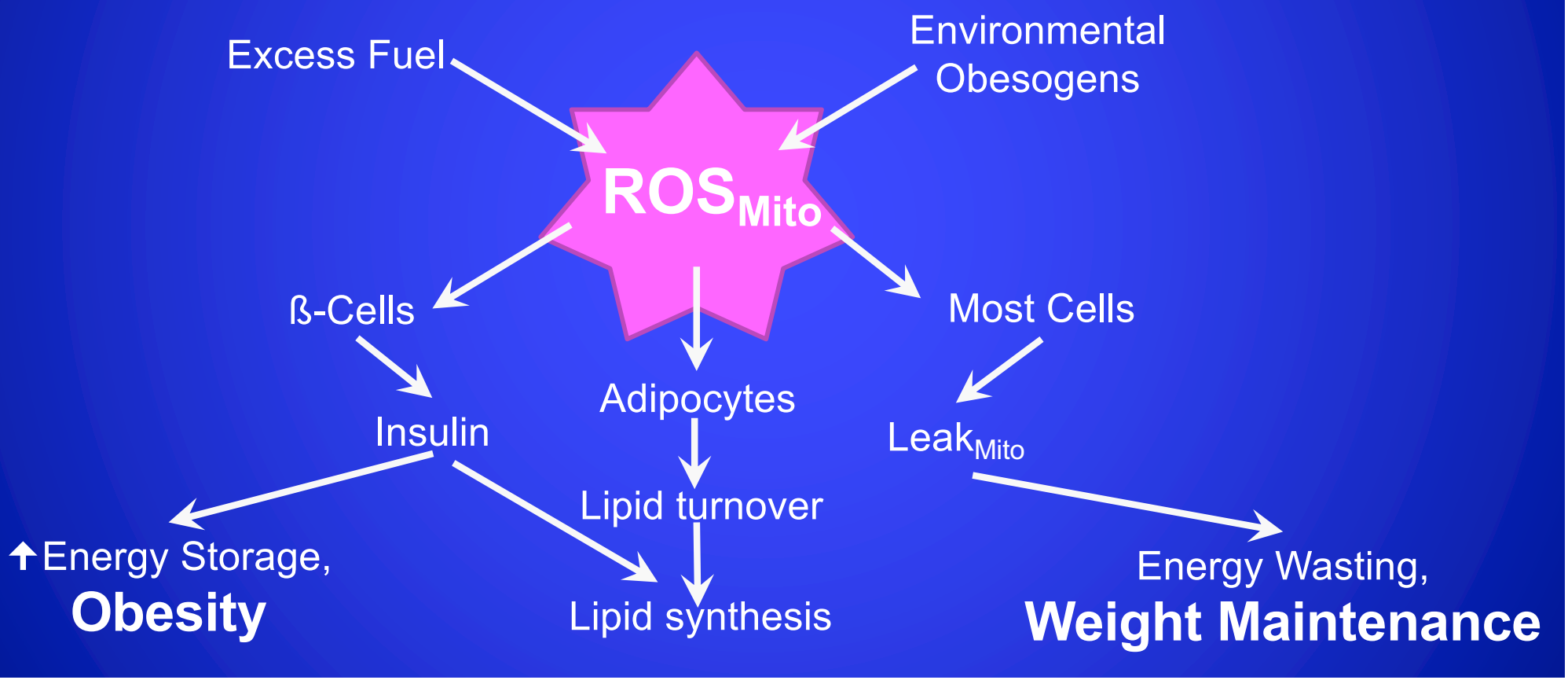
- Linked to the mitochondrial energy state
- Linked to the mitochondrial redox state
- Different effects in different tissues
- Excess energy increases redox and generates ROS
- ROS removal occurs via mitochondrial leak


REDOX Communication System
Muscle
Liver
$\frac{L}{P}$ =10
Lactate (L)
+ NAD =
Pyruvate (P)
+ NADH
Lactate
+ NAD =
Pyruvate
+ NADH
ß-Hydroxybutyrate
(ß)+ NAD =
Acetoacetate
(A) + NADH
$\frac{ß}{A}$ = 1
ß-Hydroxybutyrate
+ NAD =
Acetoacetate
+ NADH
SS(GSSG)
+ NADPH =
SH(GSH)
+ NADP
$\frac{SH(Cysteine)}{SS(Cystine)}$
SS(GSSG)
+ NADPH =
SH(GSH)
+ NADP
Cytosol
Mitochondrion
Blood Stream

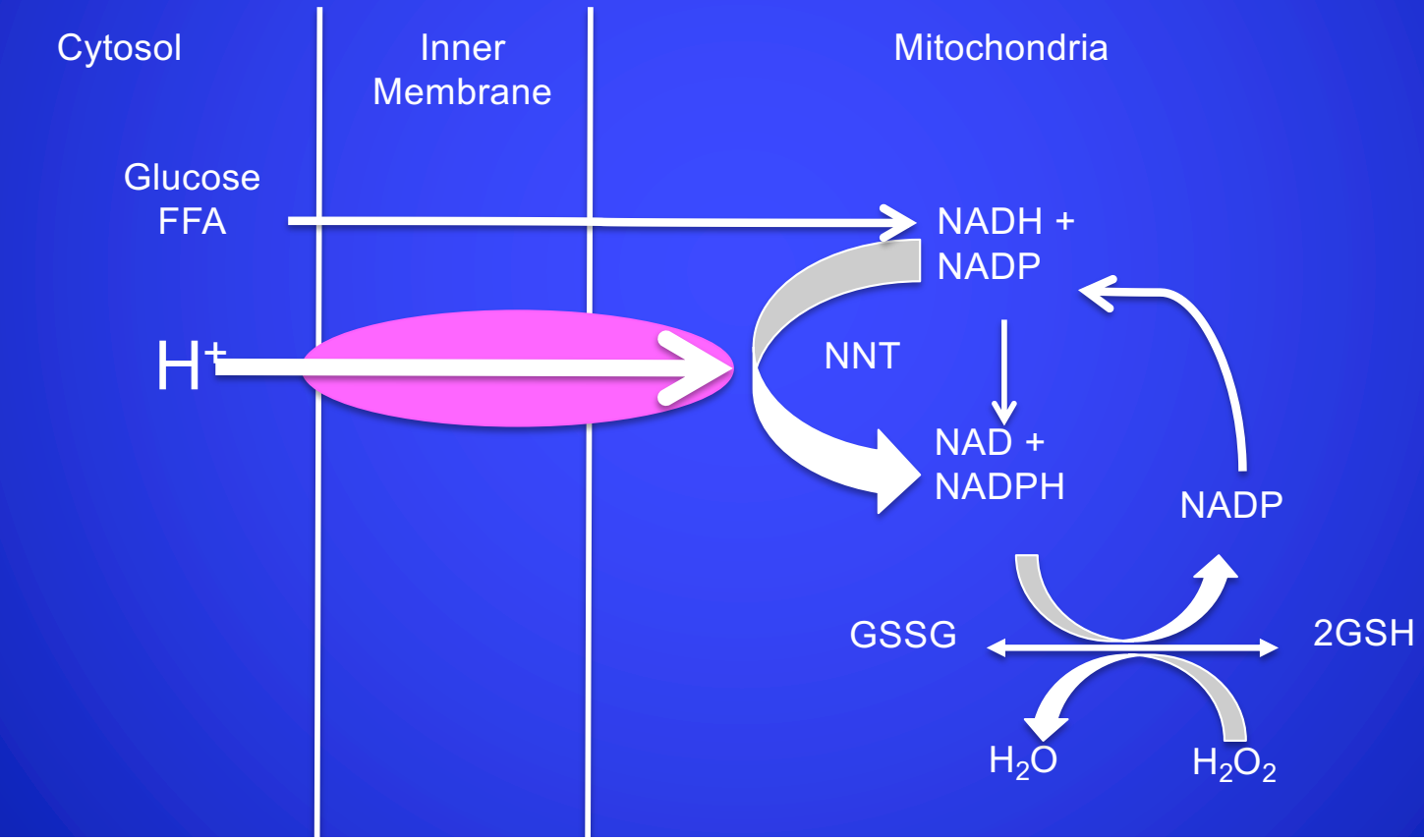

Redox
120
110
100
90
-1
0
1
2
3
4
5
6
Acoc+β--OHB
Time (min)
ROS
7.5
5
2.5
0
-2.5
-5
-7.5
0
10
20
30
β-OHB
Basal
Time (min)
ß-OHB + NAD = Acoc + NADH


2AG, DAG,?
FA
TG
LC-CoA
Glucose
CPT1
NADH
e-
ROS
H2O2
O2
H2O
ATP

Obesity-Mitochondrial Relationship



NNT Role in ROS-Scavenging Driven by the Proton Gradient



Nicotinamide Nucleotide Transhydrogenase (NNT)

- It spans the inner mitochondrial membrane and is driven by the mitochondrial proton gradient.
- The reaction occurs in the mitochondria.
- $H^+_{out} + NADH_{in} + NADP^+ = H^+_{in} + NAD^+ + NADPH_{in}$

Is NNT Important in Redox Regulation?

- It wastes energy when fuel is excessive
- It serves as a physiological uncoupler
- It protects against obesity
- It protects against mitochondrial ROS damage
- It turns off oxidative phosphorylation in fat cells
- Its absence prevents adaptive energy efficiency
- Deletion in C57Bl6J mice provides the preferred model for metabolic disease

What Regulates NNT?

- Mitochondrial redox state
  - NADPH/NADP = 100
  - NADH/NAD = 1
- Goes in the direction of NADPH formation when NADH and membrane potential are high
- Redoxins such as glutaredoxin and thioredoxin provide the pull
- NNT can be inhibited by high FFA during fasting

Why is NNT Interesting

- Provides NADPH when it is needed
- Important in ROS scavenging
- Sensitive to energy state, redox and ROS
- Links redox communication network to energy efficiency

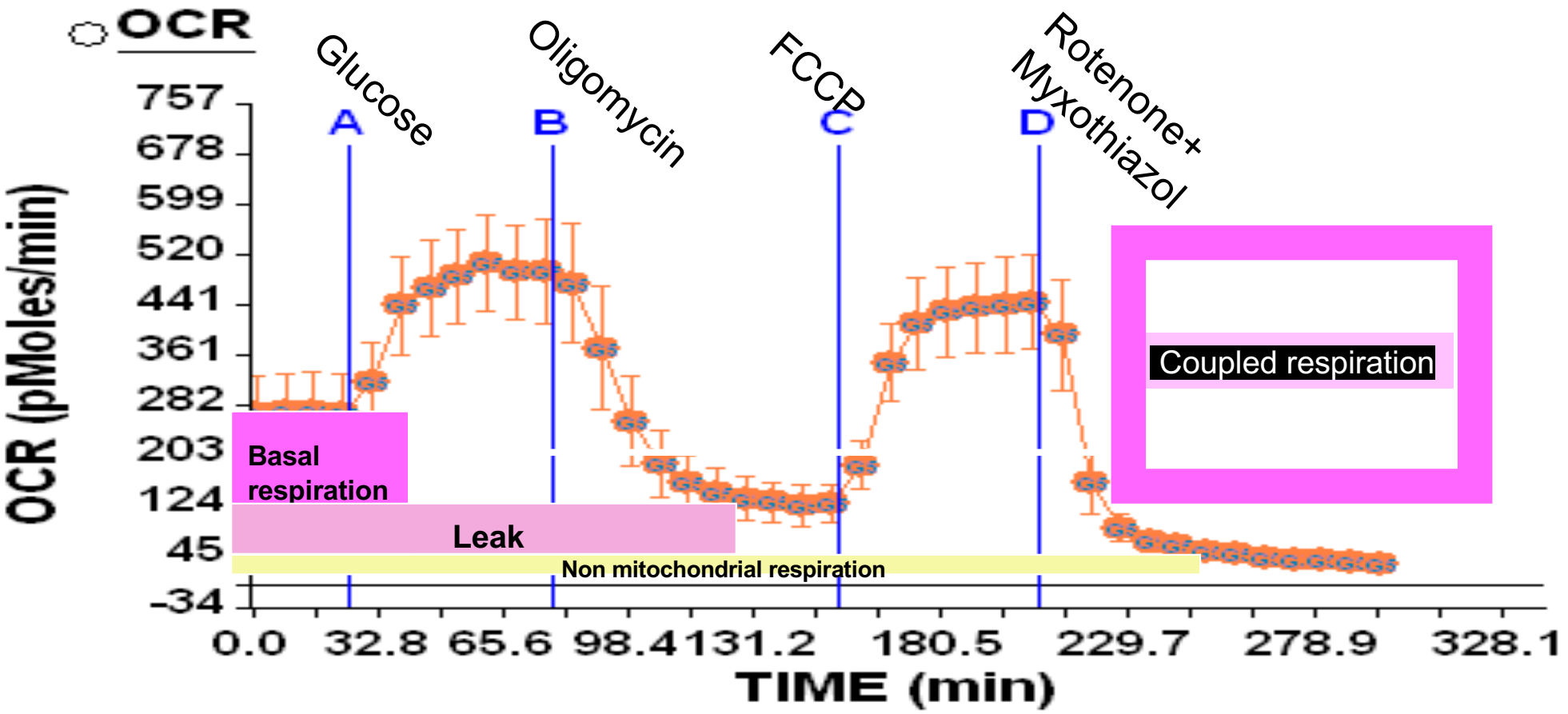
Variations in Energy Efficiency

- Excess nutrients decrease efficiency via a mitochondrial proton leak
- ROS can affect both energy efficiency and respiration
- Dysregulation of energy efficiency rather than overeating may cause obesity

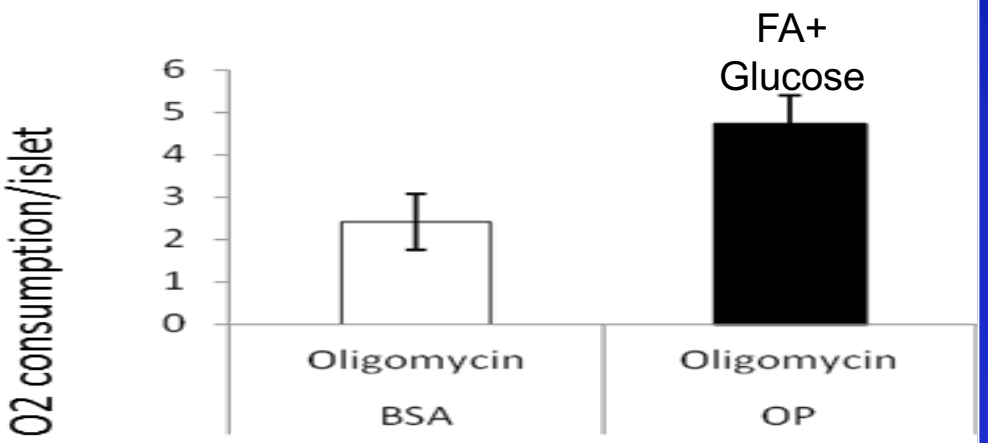
Measuring Mitochondrial Leak

- O_2 consumption not due to ATP production
- Measured by inhibiting ATP synthase (oligomycin)
- Highest when ATP is not needed (Basal state)
- Lowest when ADP is elevated (Working state)
- Maximum when mitochondria are uncoupled (FCCP or DNP)

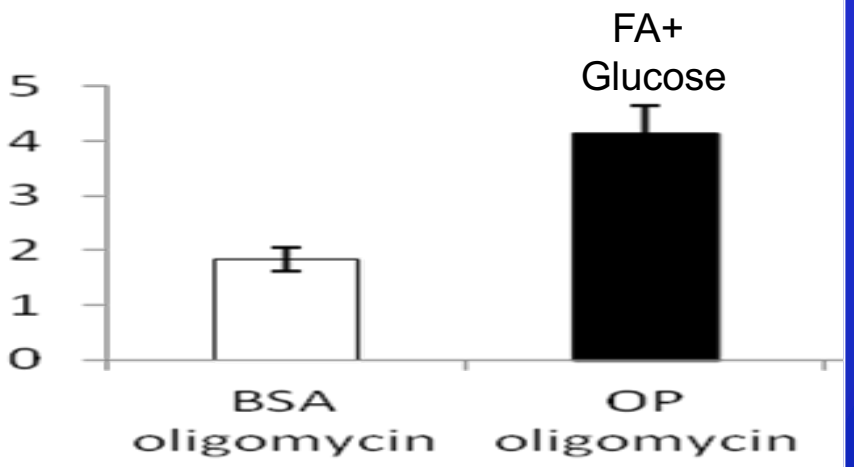
Mouse Islet respirometry



Human (n=4)

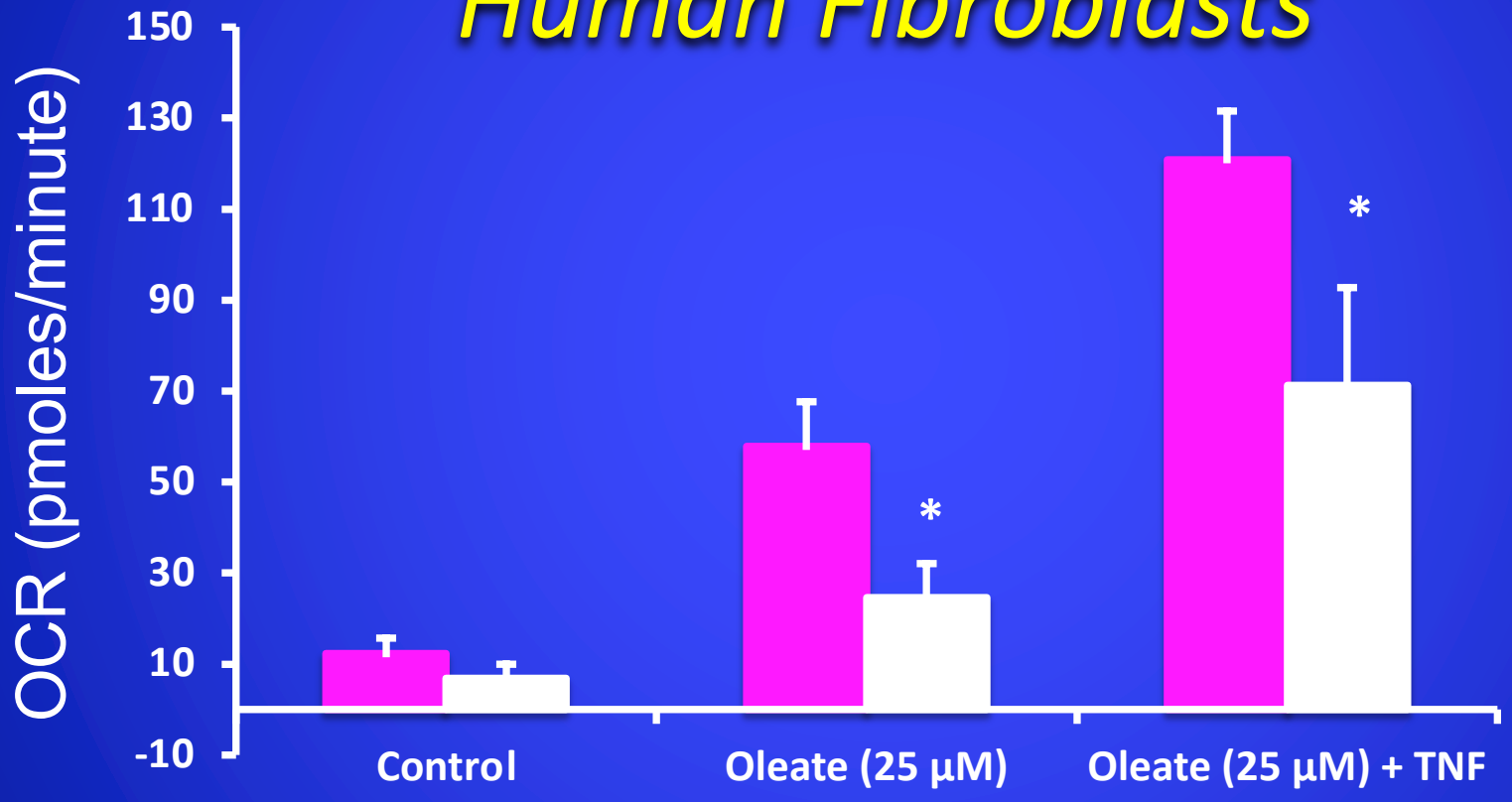


Mouse (n=4)



Unpublished data O. Shirihai

Excess Fuel Increases Proton Leak in Human Fibroblasts

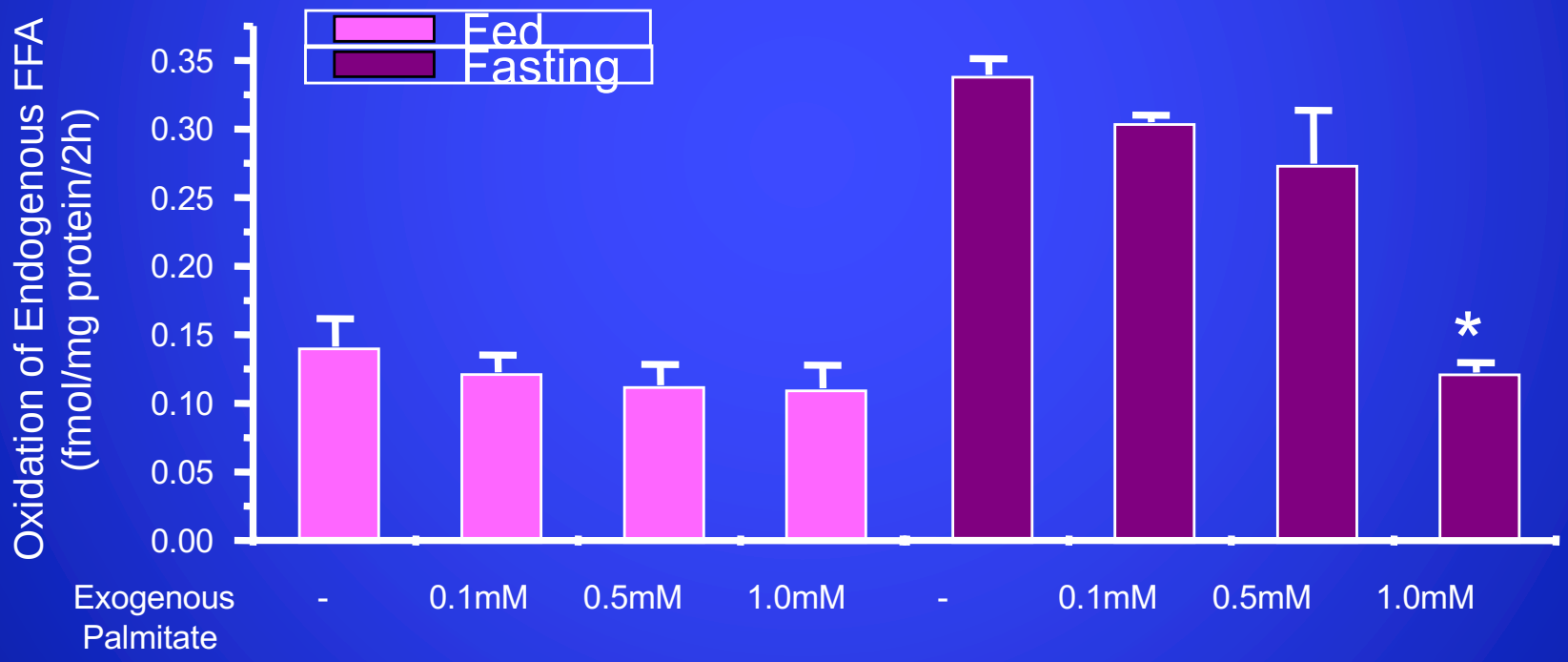


AR Jones et al, unpublished

Respiration of Adipocytes with different Substrates

Substrate	N	Oxygen Consumption (nmol/min/mg)	N	Oxygen Consumption (nmol/min/mg
	Control		FCCP	
Basal (5 mM Glucose)	65	4.25 ±0.32	12	3.80 ±0.43
Methyl-Succinate	4	3.37 ±0.47	4	5.53 ±1.34
Methyl-Succinate/Octanoate	3	4.29 ±1.41	3	5.80 ±1.83
Acetate	3	7.48 ±1.95	3	5.20 ±1.36
Glutamine	3	4.23 ±1.37	3	4.74 ±0.96
Octanoate	3	4.77 ±1.53	3	8.28 ±2.66
Glutamine/Octanoate	3	4.22 ±0.87	3	3.99 ±0.98
Malate	3	4.37 ±1.50	3	6.42 ±2.30
Lactate	3	4.69 ±1.13	3	5.35 ±1.45

The effect of exogenous FFA on endogenous FFA oxidation.

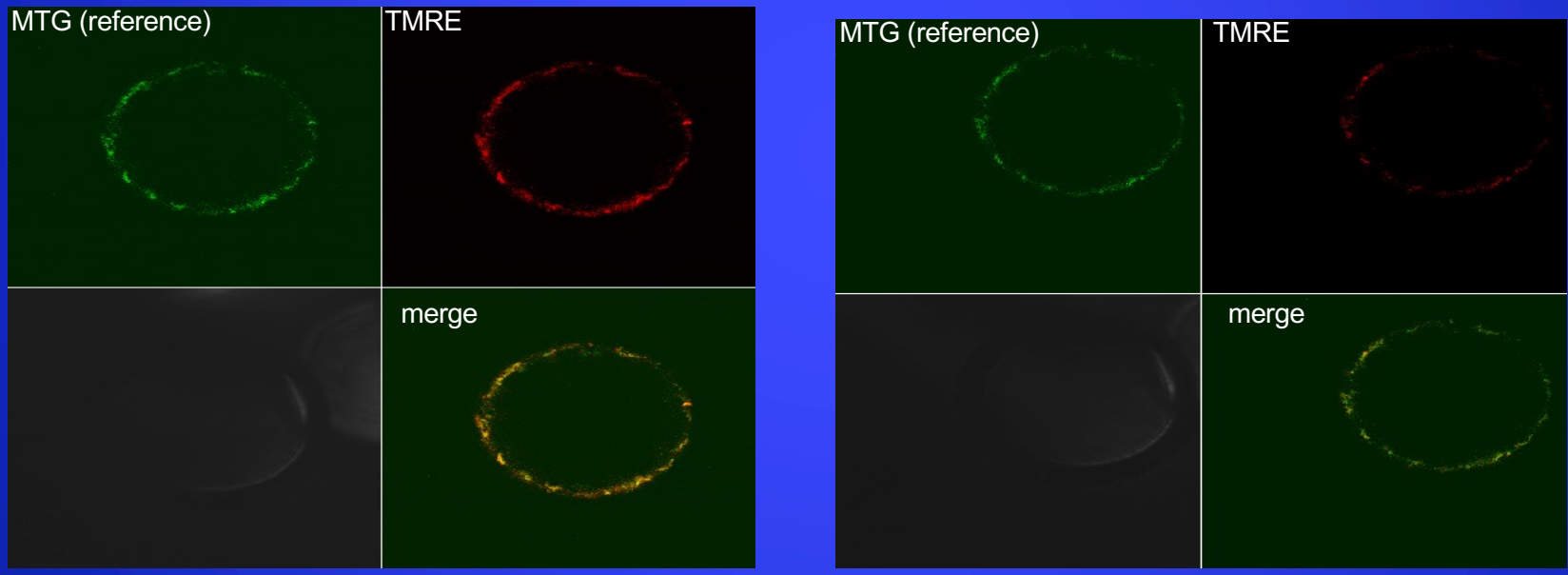


Fat Cells Do NOT Oxidize Fat!

They Only Store Fat

Mitochondrial Membrane Potential

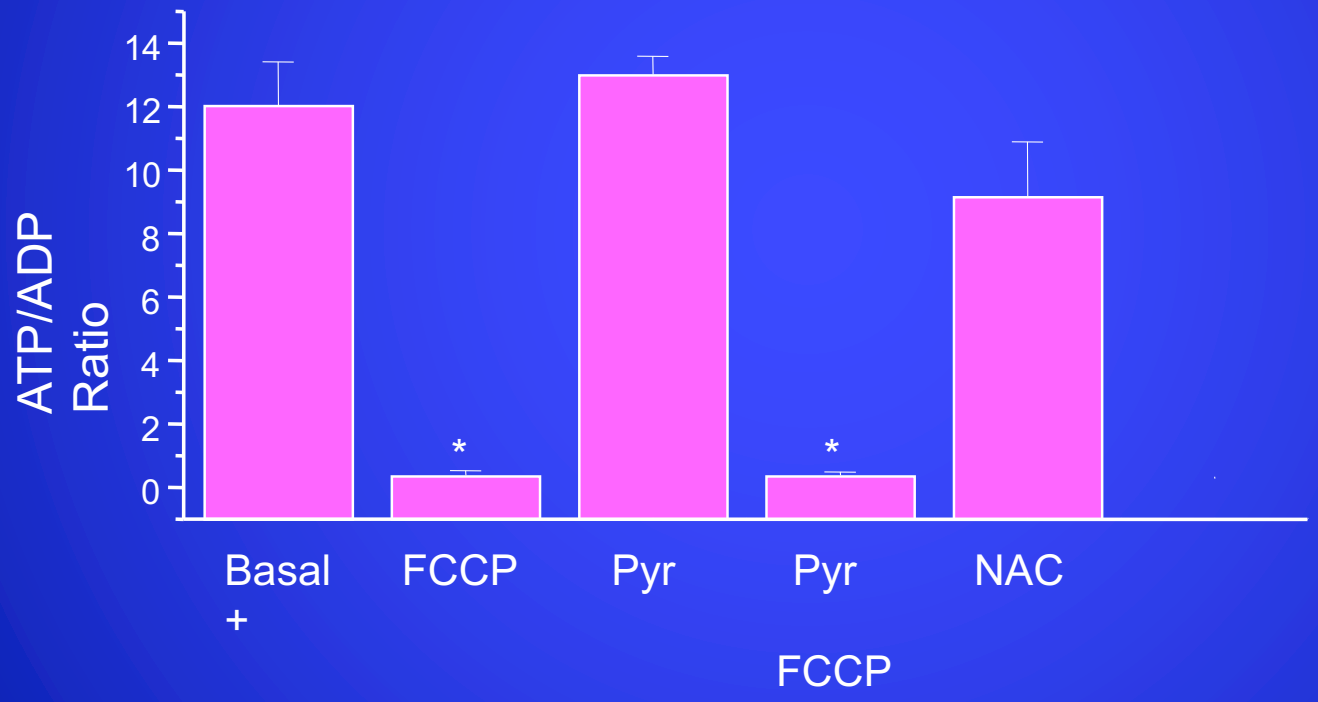
FCCP



Before

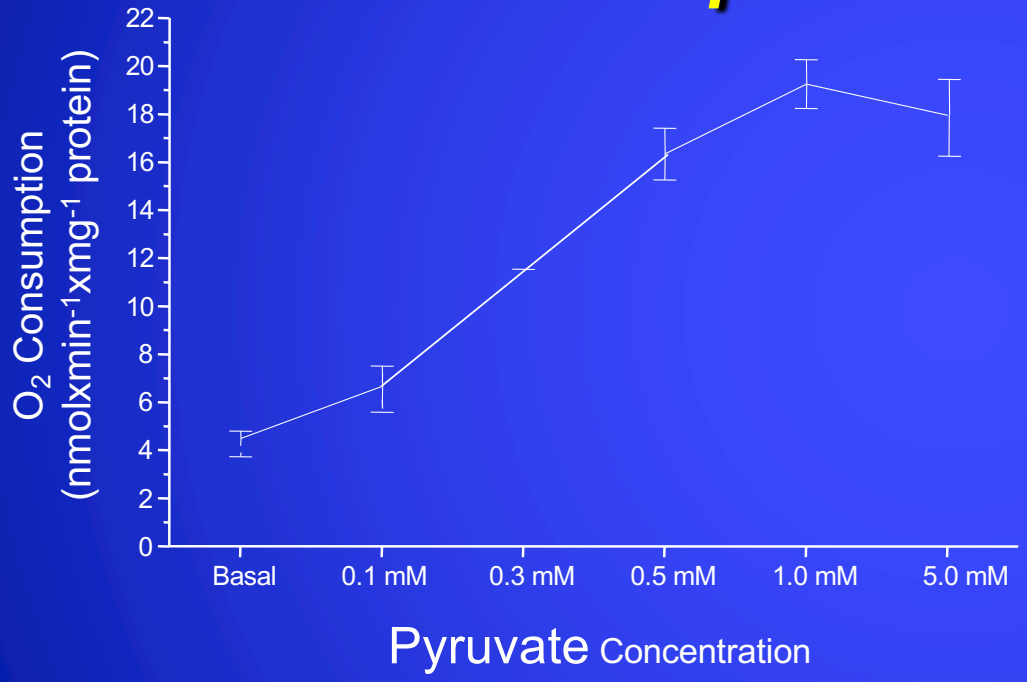
After

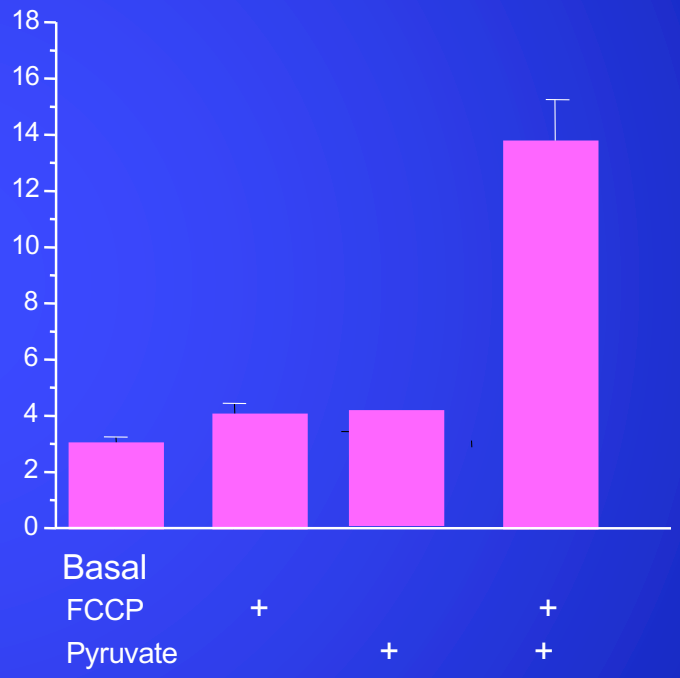
ATP/ADP Ratio Confirms



V. Schultz Unpublished data

Maximum Adipocyte Respiration Required Pyruvate





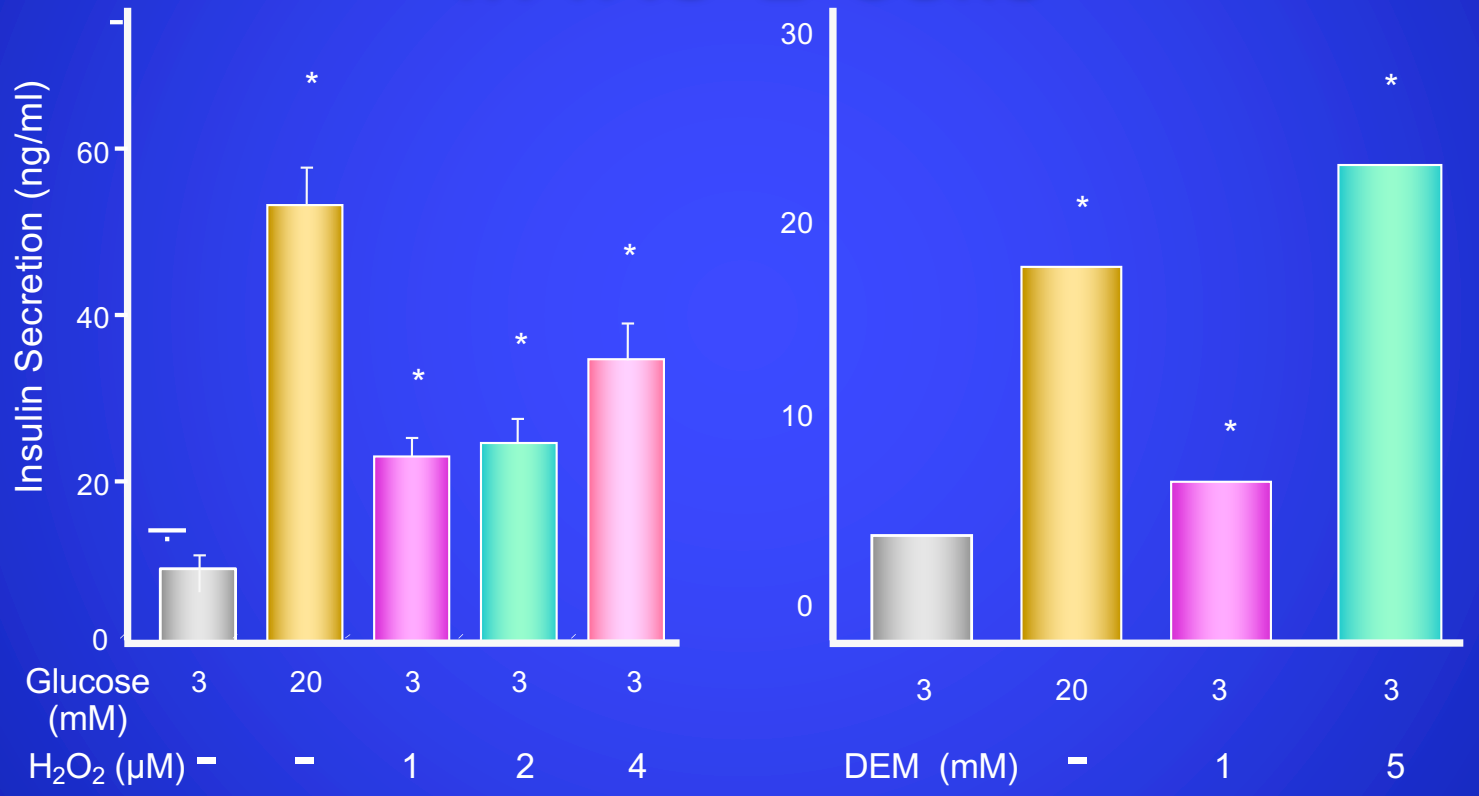
ROS Inhibits Fat Cell Respiration

- Inhibition is Reversed by Pyruvate that Scavenges ROS
- Excess nutrients cause a ROS-mediated leak that increases respiration in all but fat cells
- ROS stimulates lipid turnover in fat cells
- ROS increases fat storage at high insulin

ROS is Different in Fat Cells

- It does not stimulate leak
- It inhibits respiration and FFA use for energy
- It stimulates TG synthesis
- It stimulates lipolysis
- When insulin is elevated synthesis prevails

H_2O_2 Increases Insulin Secretion in INS-1 Cells



Pi et al, Diabetes 2007

Agents Cause Insulin Secretion in the Absence of a Stimulatory Fuel by Generating ROS

- MOG, a lipid food emulsifier and preservative
- Saccharin, an artificial sweetener
- Iron, an essential mineral
- Bisphenol A, contained in plastics

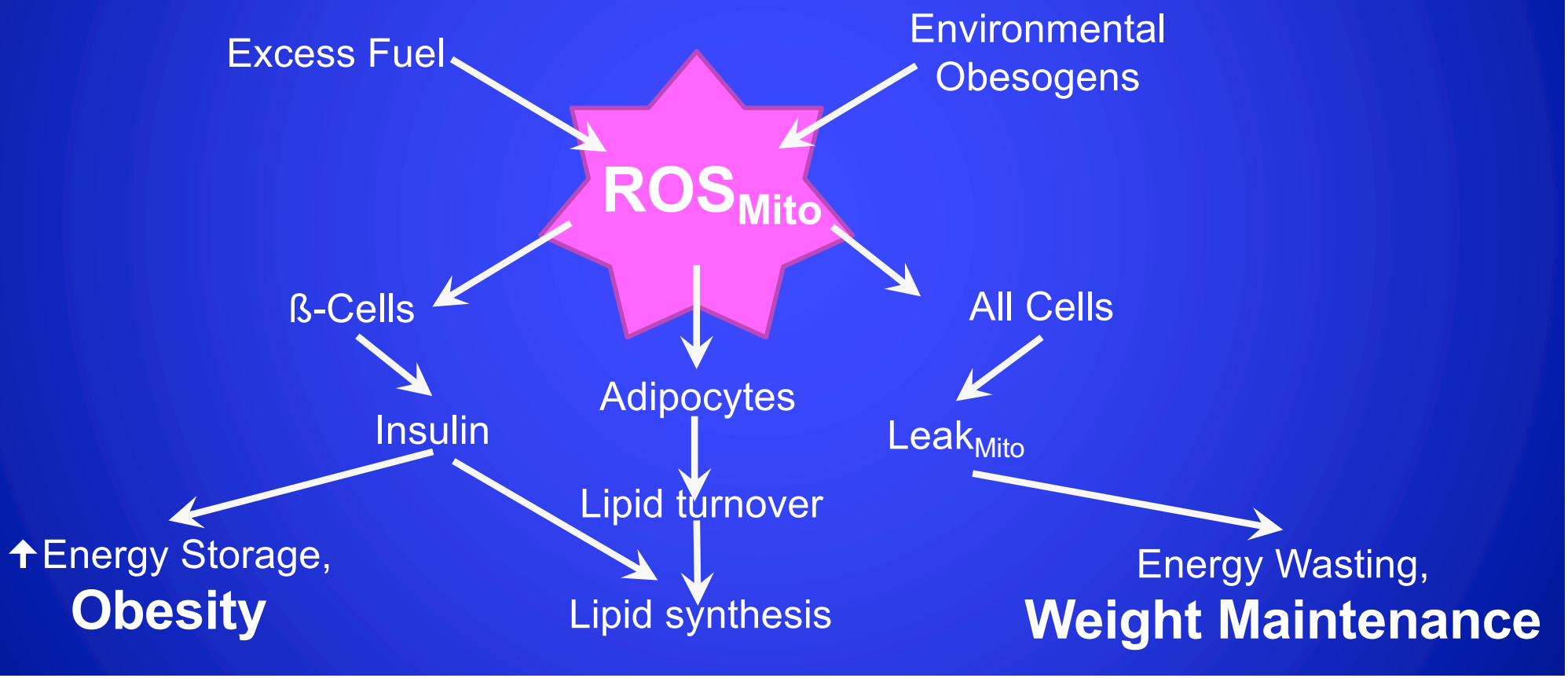
Variations in Energy Efficiency

- Linked to the mitochondrial redox state
- Linked to the mitochondrial energy state
- Variations occur in most tissues but not fat
- Depend on NNT and ROS scavenging capacity
- Explain post-meal increased heat production

Variations in Energy Efficiency Accompany Changes in Redox in Most Cells

- Can be induced by excess nutrients via a proton leak induced by ROS
- ROS influences energy efficiency via a leak
- Failure to adapt energy efficiency to nutrient supply rather than overeating may cause obesity
- Sadly, this topic has received little attention

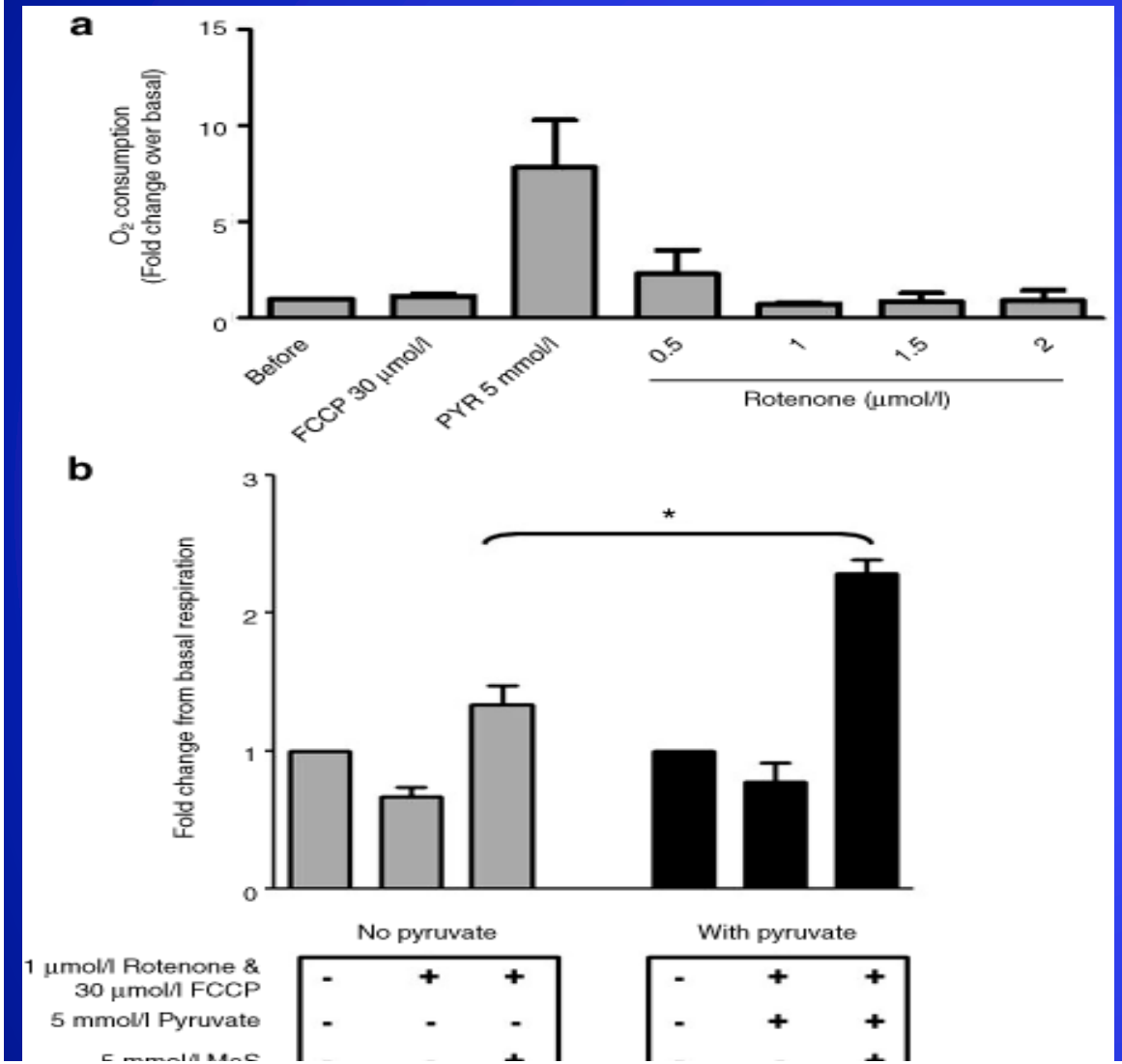
Obesity-Mitochondrial Relationship



The Good and the BAD

1. Fuels and exogenous agents change redox and can generate ROS to communicate energy state via the circulation
2. Rise in NADH (redox) indicates fuel in excess of ATP need, increases ROS
3. High NADH favors NADPH formation needed to remove ROS
4. This induces a proton leak and alters energy efficiency via NNT
5. Altered efficiency can prevent weight loss with calorie reduction (dieting) and weight gain with calorie increase (forced feeding)
6. Failure to adjust the leak to energy stores may cause obesity
7. Lack of NNT (C57Bl6) or NADPH (excess fuel) for ROS scavenging induces/ promotes obesity!

Thank You



Respiration in Adipocytes is Inhibited by Reactive Oxygen Species