

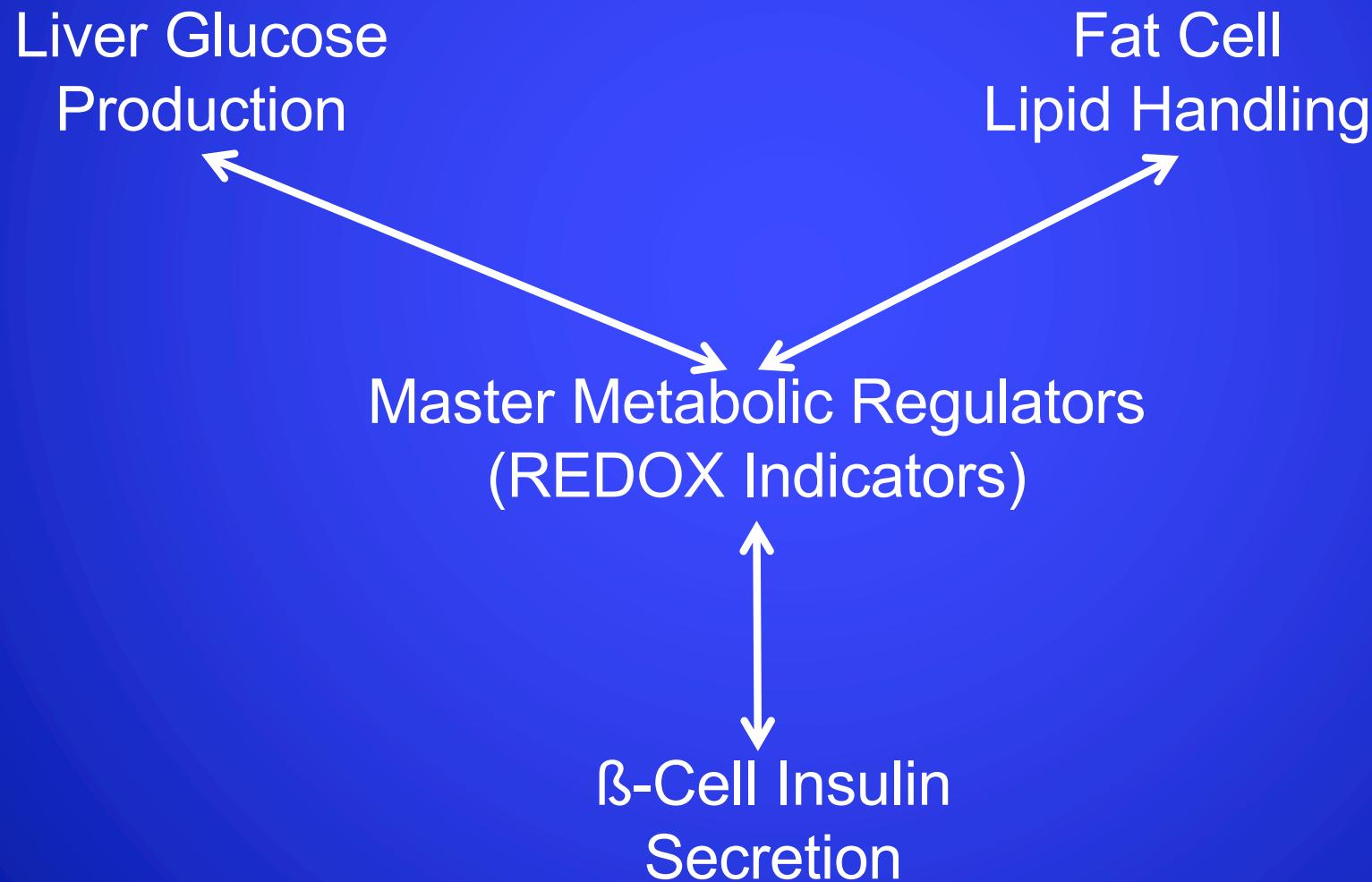
# *The Redox Network: Master Regulator of Metabolism*

Barbara E. Corkey

Obesity Research Center

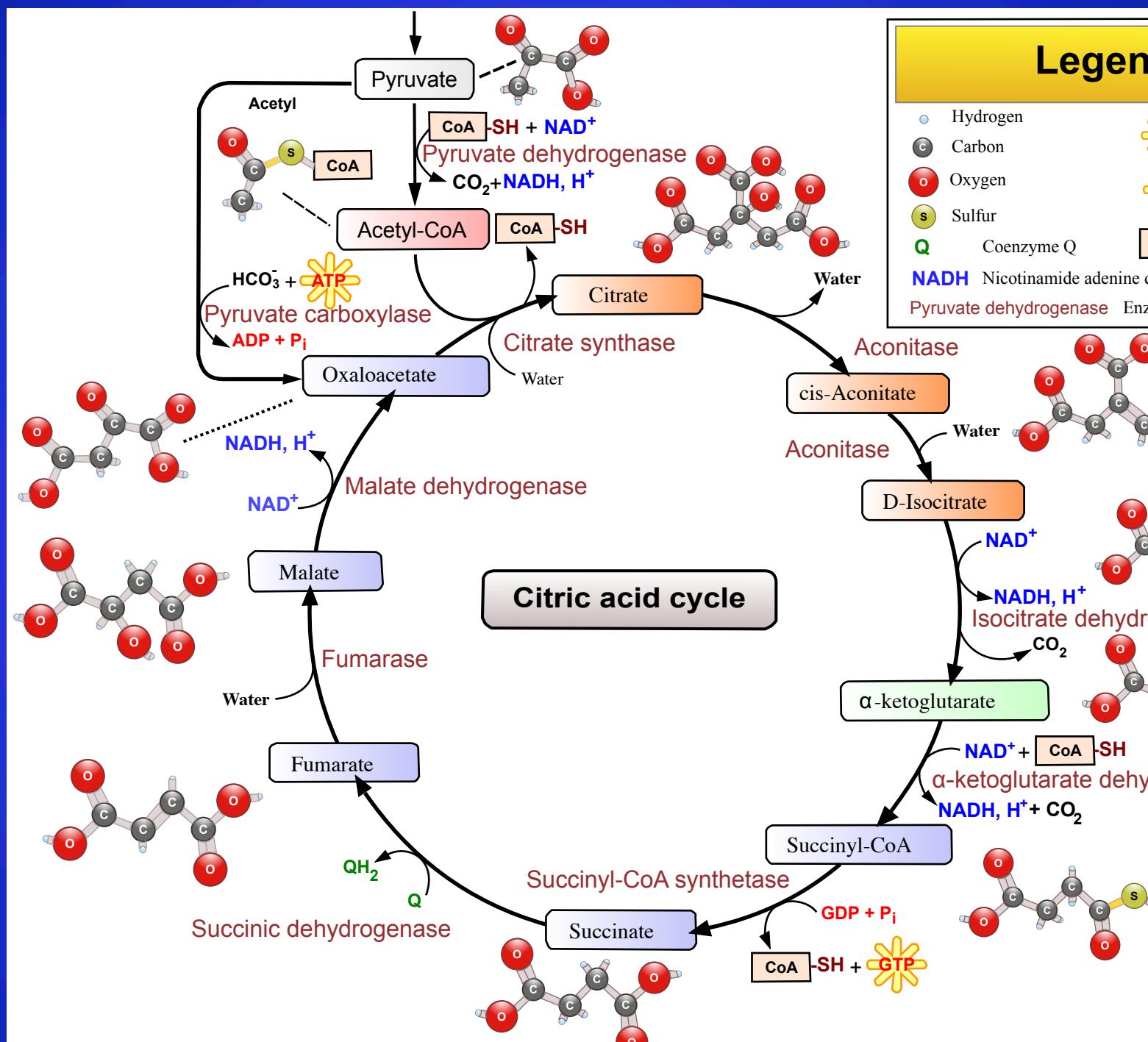
Boston University School of Medicine

# *Circulating Redox Changes Frequently and Impacts Function*



# Energy State is Communicated by Redox Indicators

- Shared co-factors: pyridine nucleotides, adenine nucleotides, CoA esters and ROS
- Mitochondrial metabolism
- Circulating metabolites



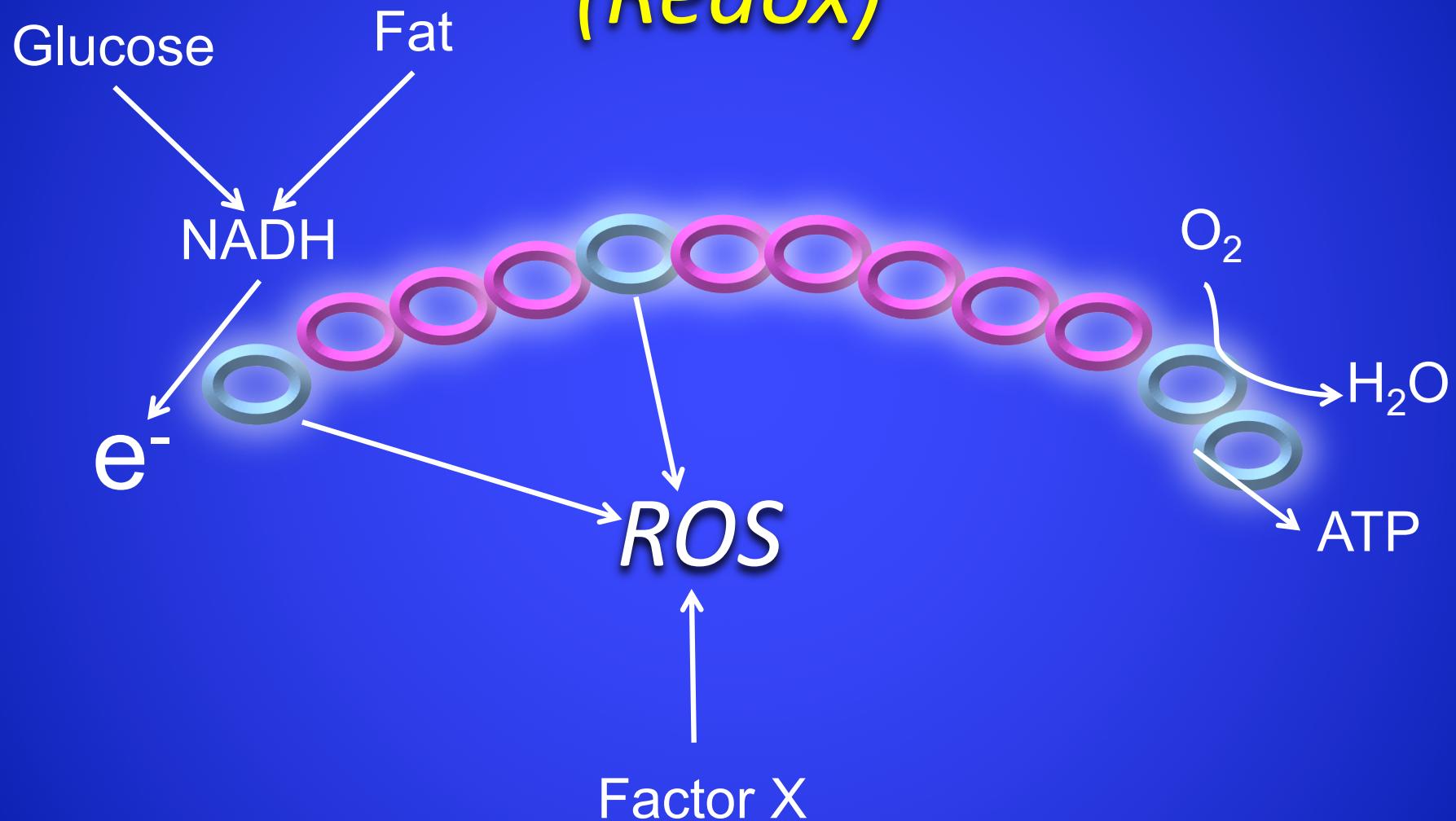
NADH used by ETC is replenished from Acetyl CoA

# Co-Factors Interact and are Linked

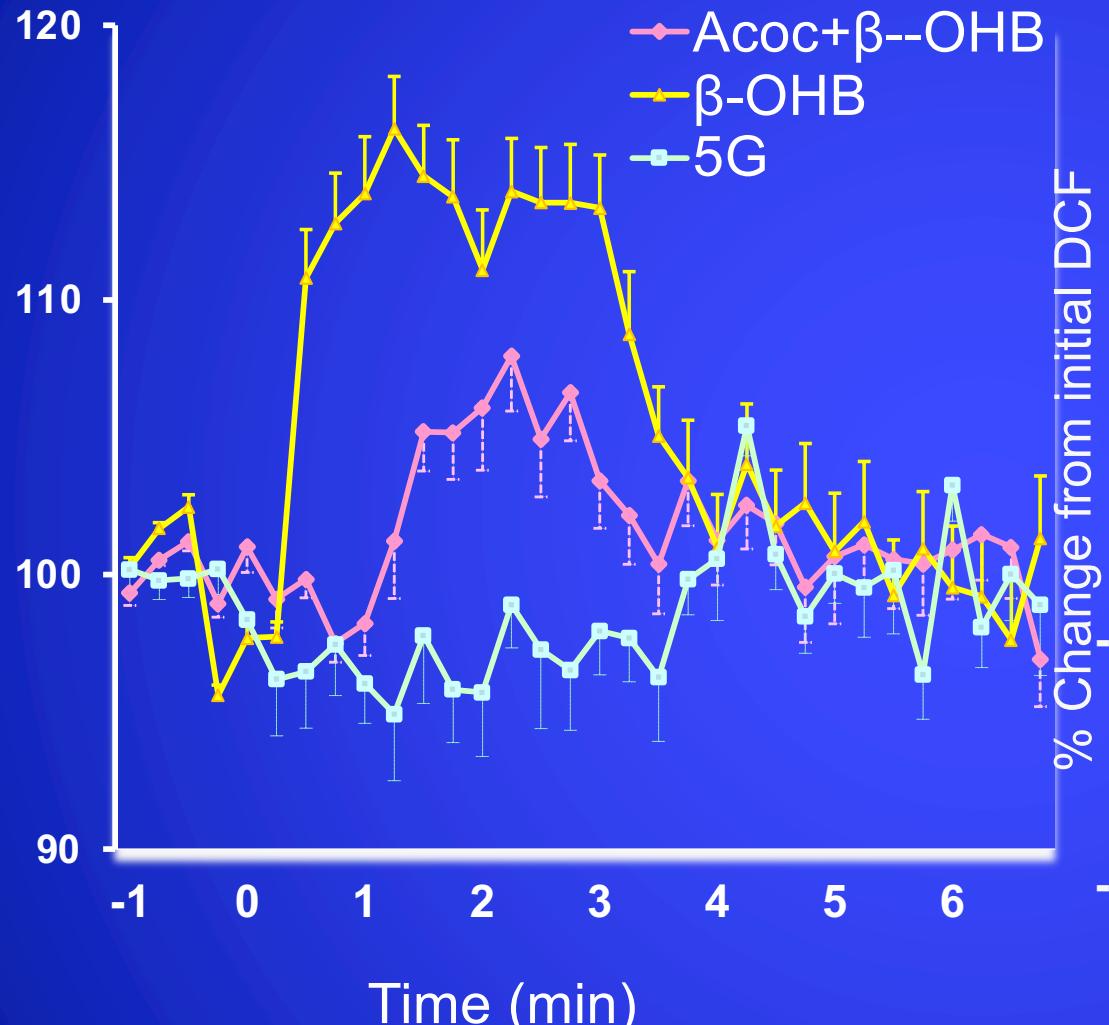
- ADP or the ATP/ADP ratio drives oxidative phosphorylation
- Dehydrogenase equilibrium restores redox as NADH electrons enter electron transport
- Acetyl CoA production sustains electron transport
- Excess fuel produces ROS, drives NNT, impacts thiol redox state

*Redox Changes Induce ROS  
Changes that Impact Thiol Redox*

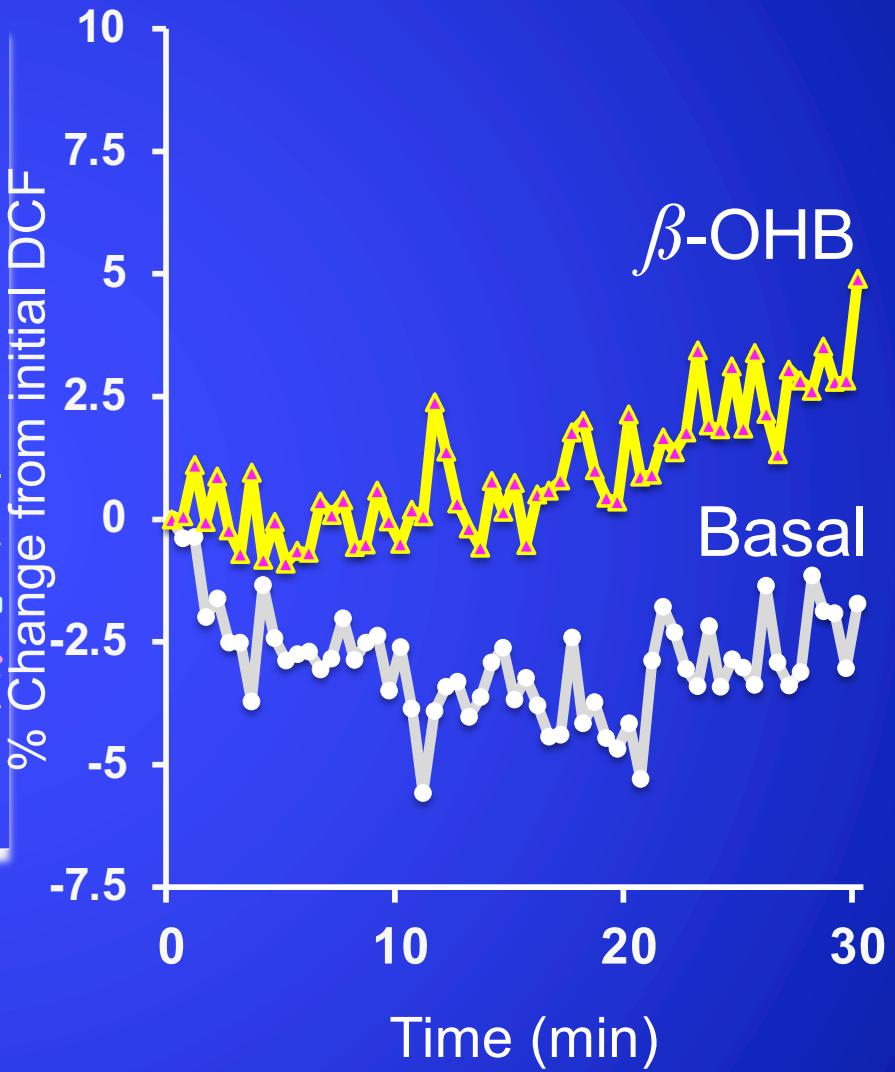
# *ROS are Produced at High NADH (Redox)*



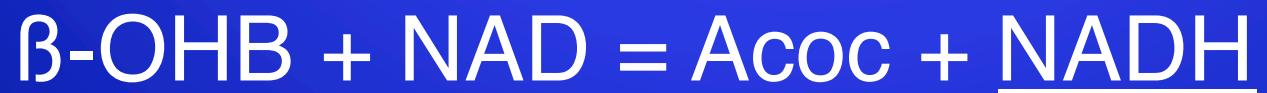
# *Redox*



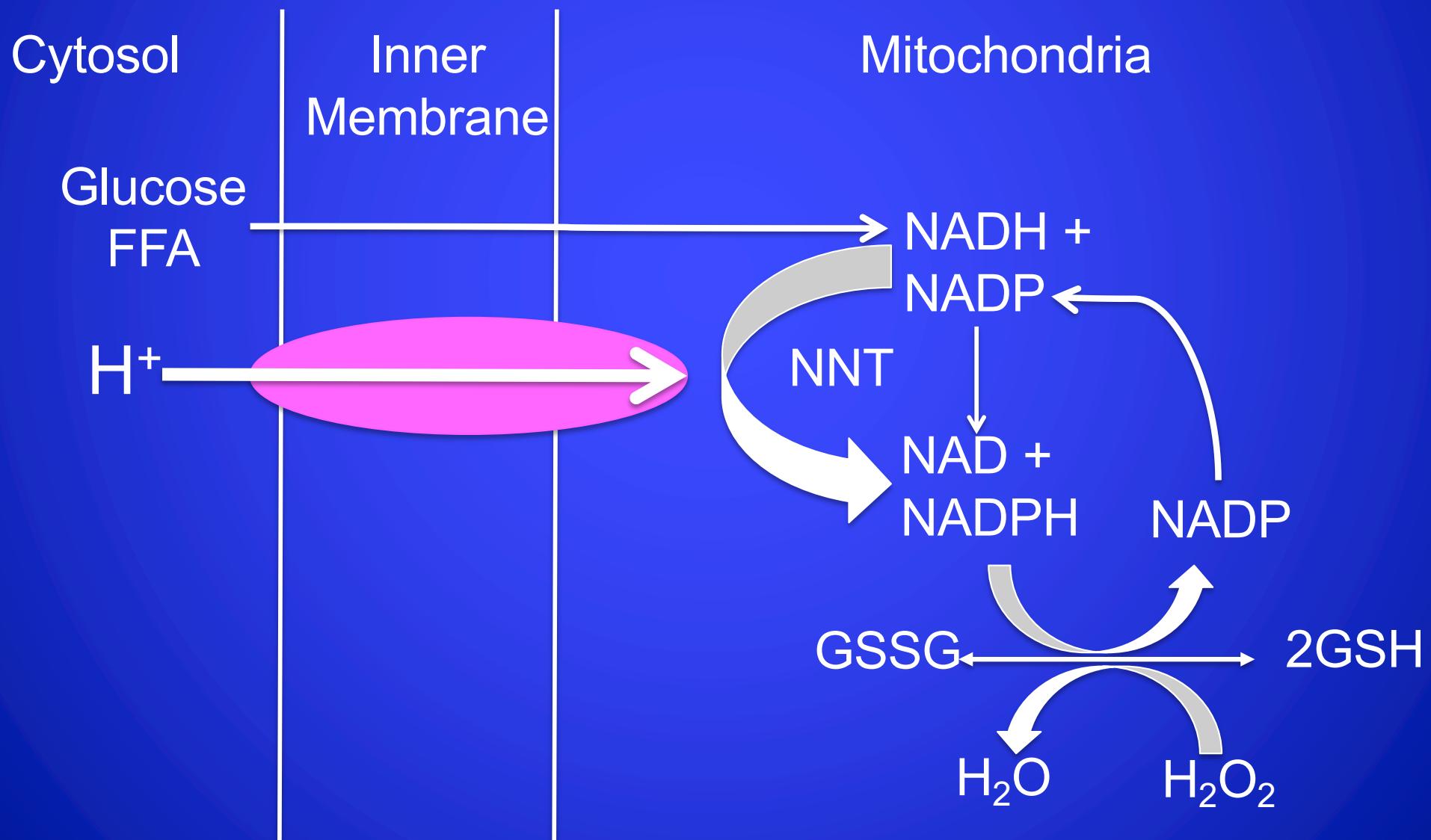
# *ROS*

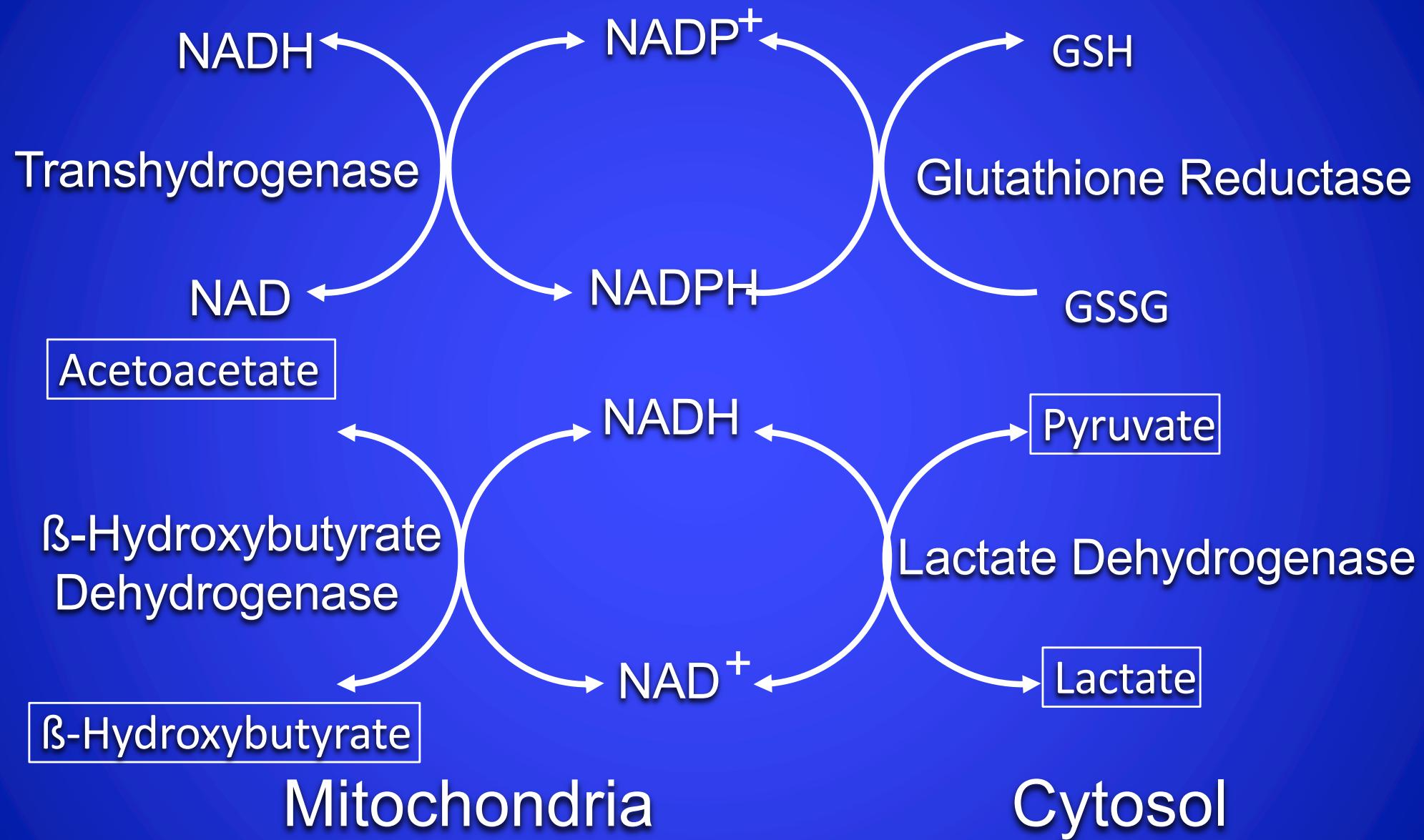


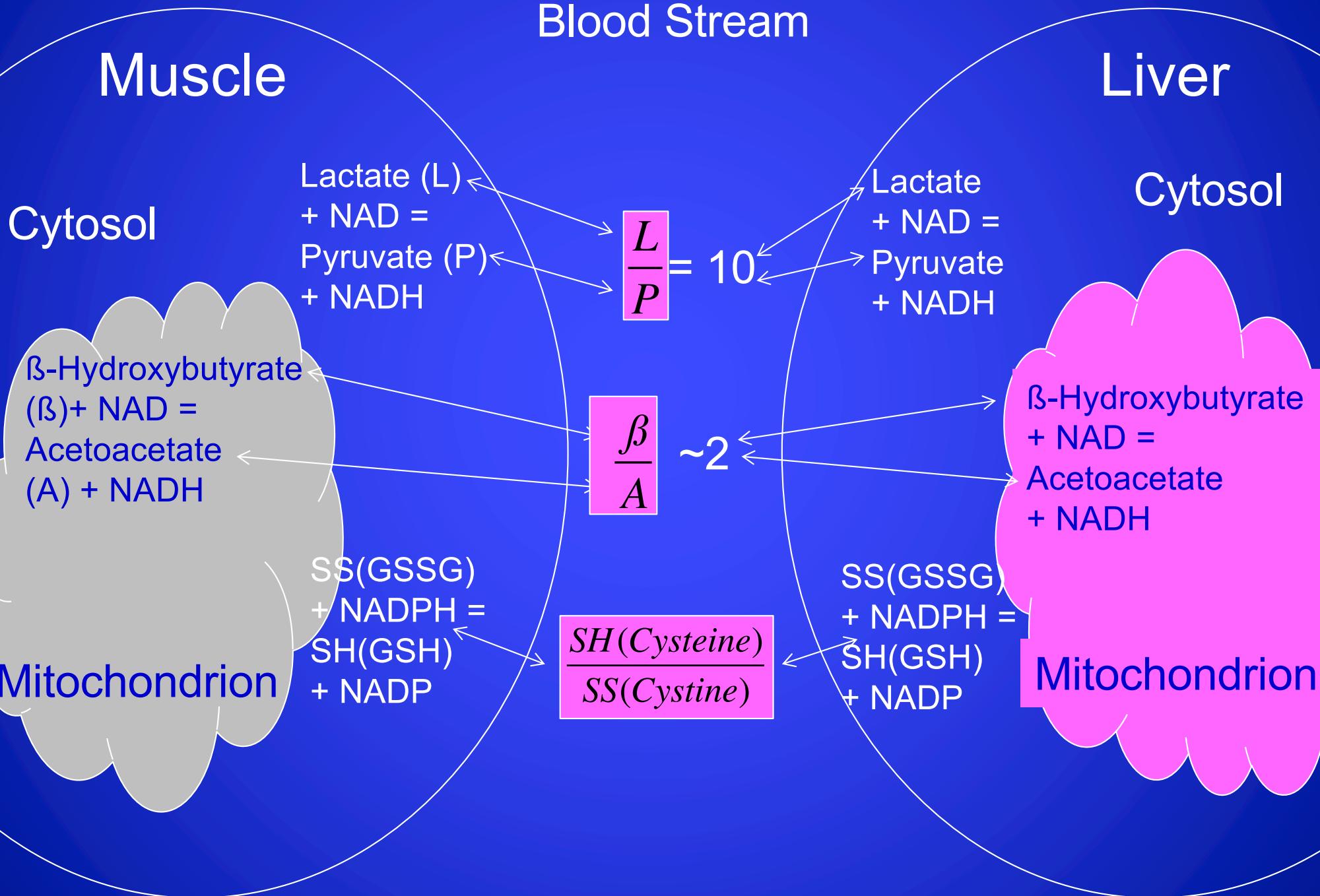
β-OHBDH



# *NNT a ROS-Scavenging Enzyme Driven by the Proton Gradient*







# *Circulating Redox Changes*

- Starvation
- Lean vs obese or high fat diet
- Dean Jones: blood thiol redox in diabetes, aging and cancer becomes oxidized
- Response to fuels
- Lean and obese human subjects undergoing glucose tolerance test (collaboration with Human Metabolism Core directed by Nawfal Isfan)

## $\text{H}_2\text{O}_2$ Production Rates in Intact Organ

Perfused liver data were obtained by methanol titration of catalase Compound I. Data from Oshino et al (1973).

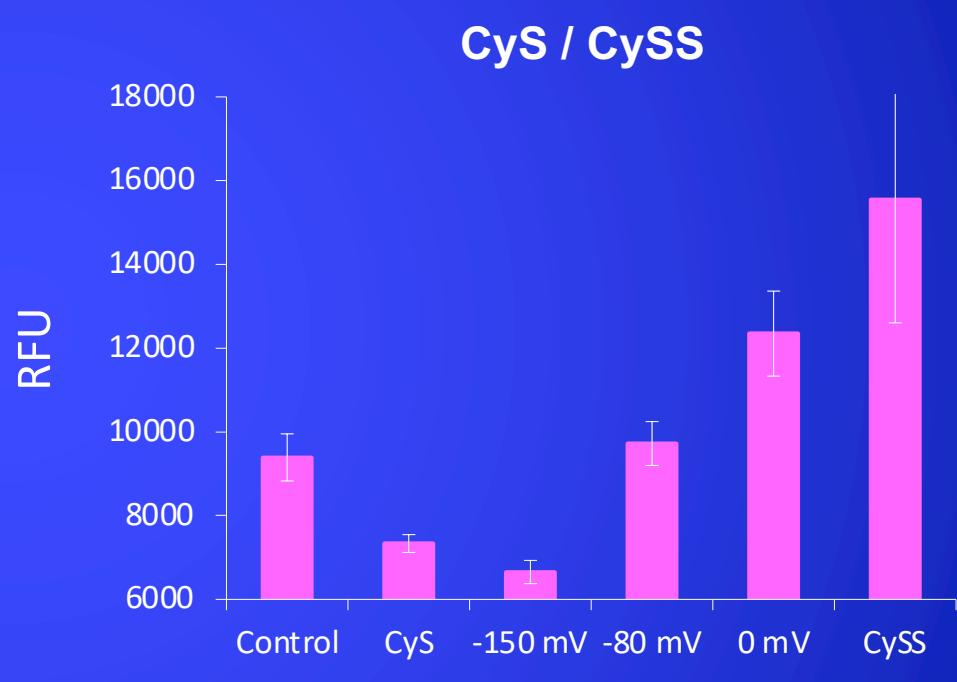
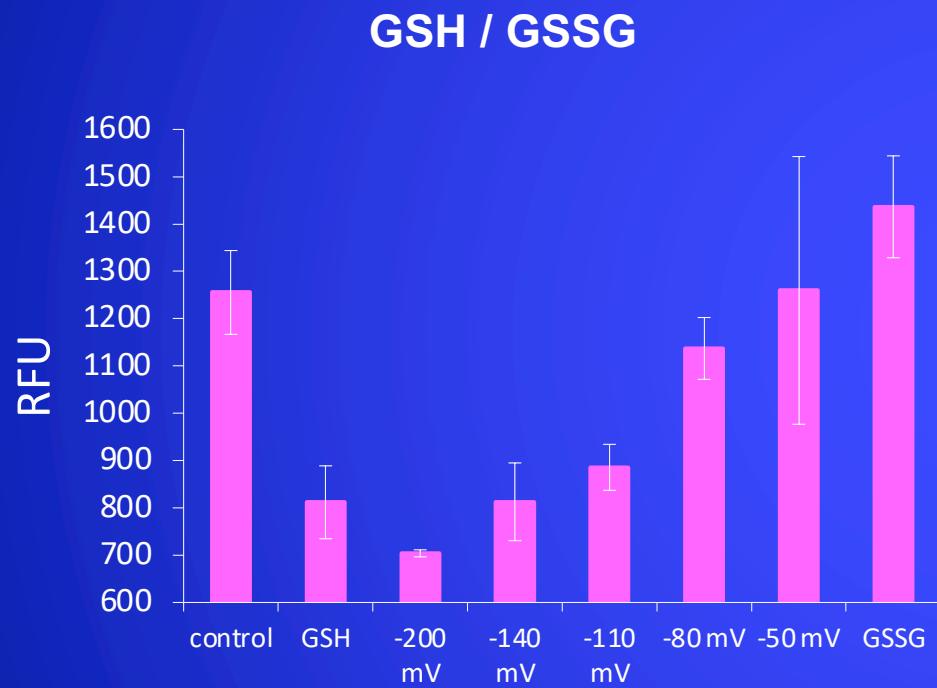
Substrate or inhibitor	Production Rate nmol $\text{H}_2\text{O}_2$ /min per g liver
L-Lactate, 2 mM; pyruvate, 0.3 mM	49
+ antimycin, 8 $\mu\text{M}$	75
+ octanoate, 0.3 mM	170
+ oleate, 0.1 mM	66

Oshino et al (1973) *Arch. Biochem. Biophys.* **154**, 117-131

**Intracellular Fuels Impact Cellular  
Redox and ROS.**

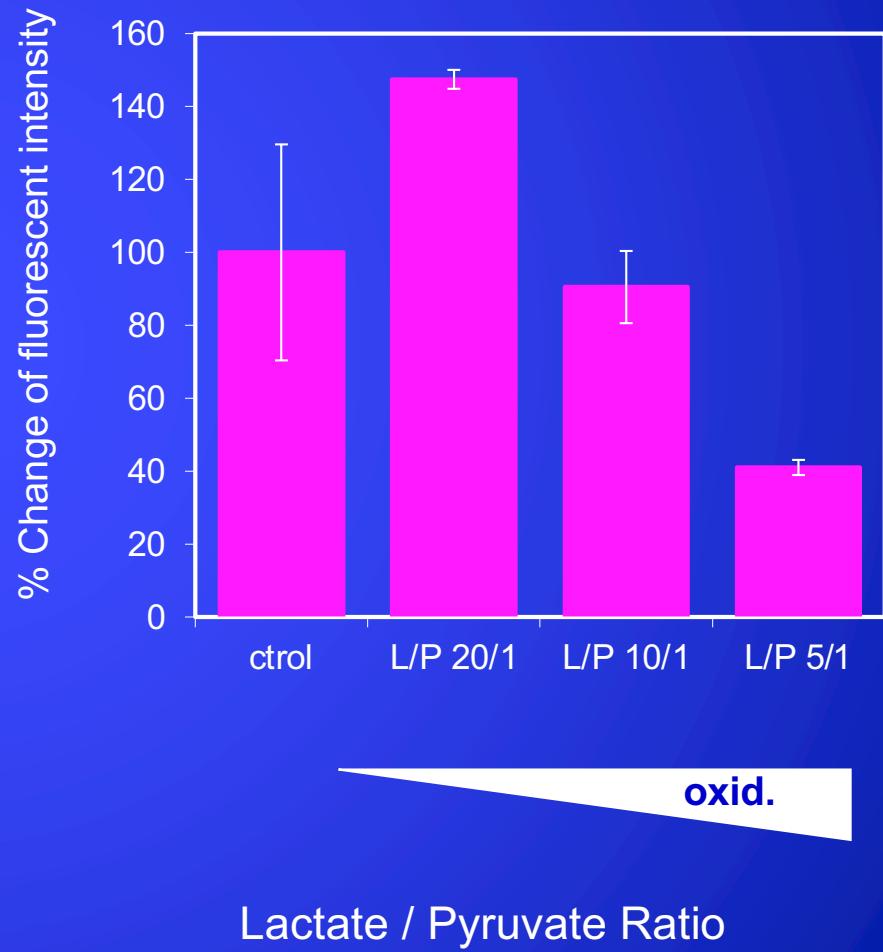
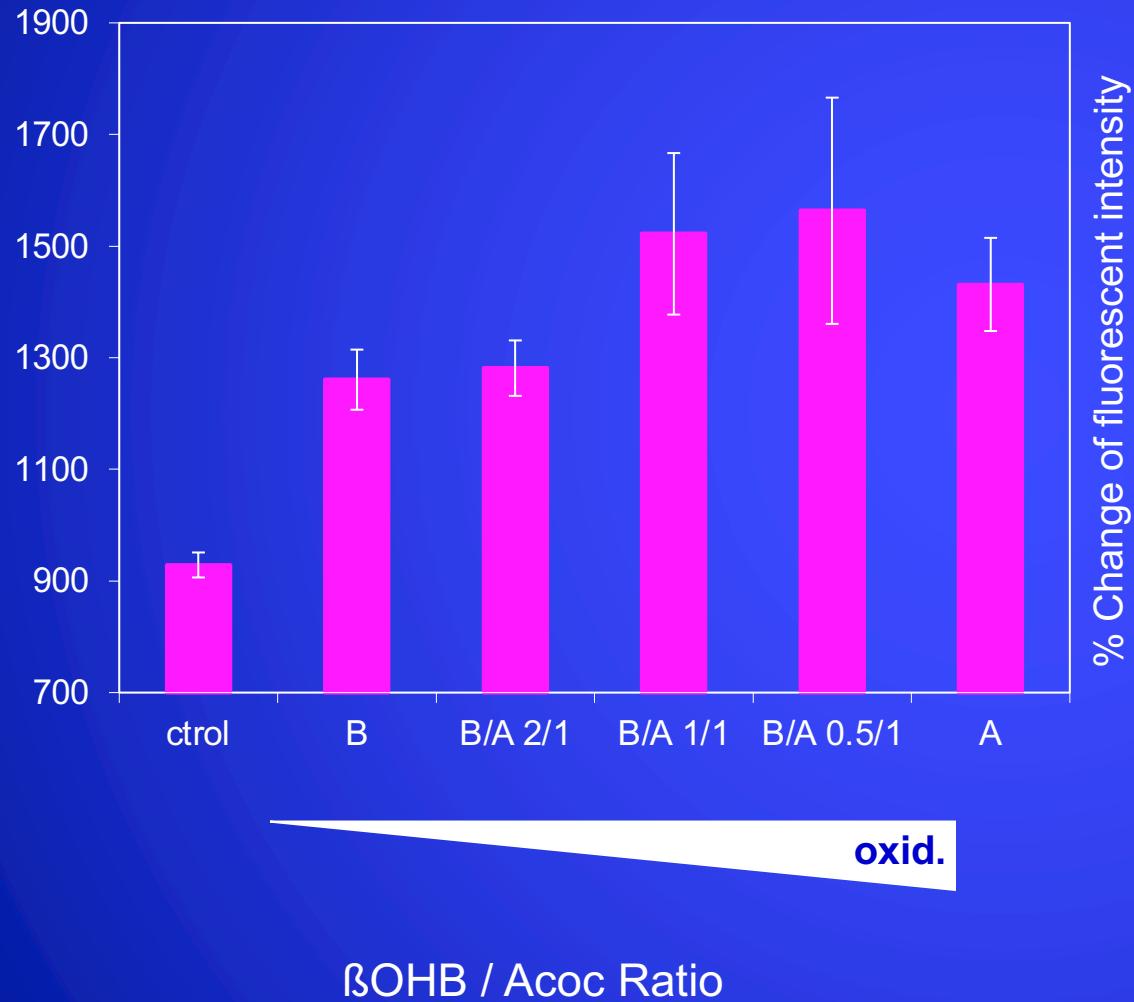
**Do External Circulating Changes affect  
Intracellular Redox?**

# *ROS Production in Hepatocytes*



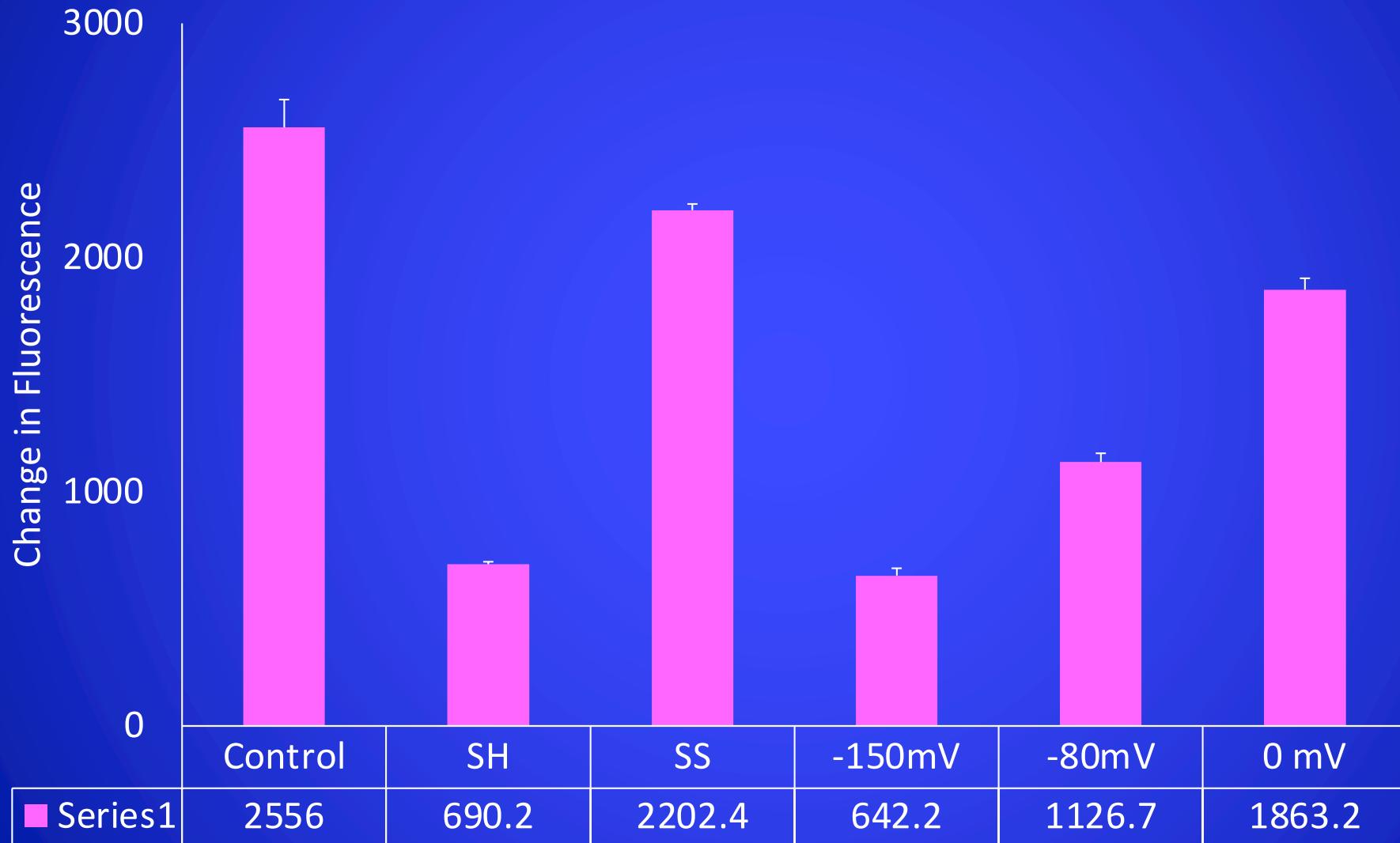
oxidized

# *Hepatic ROS Production*



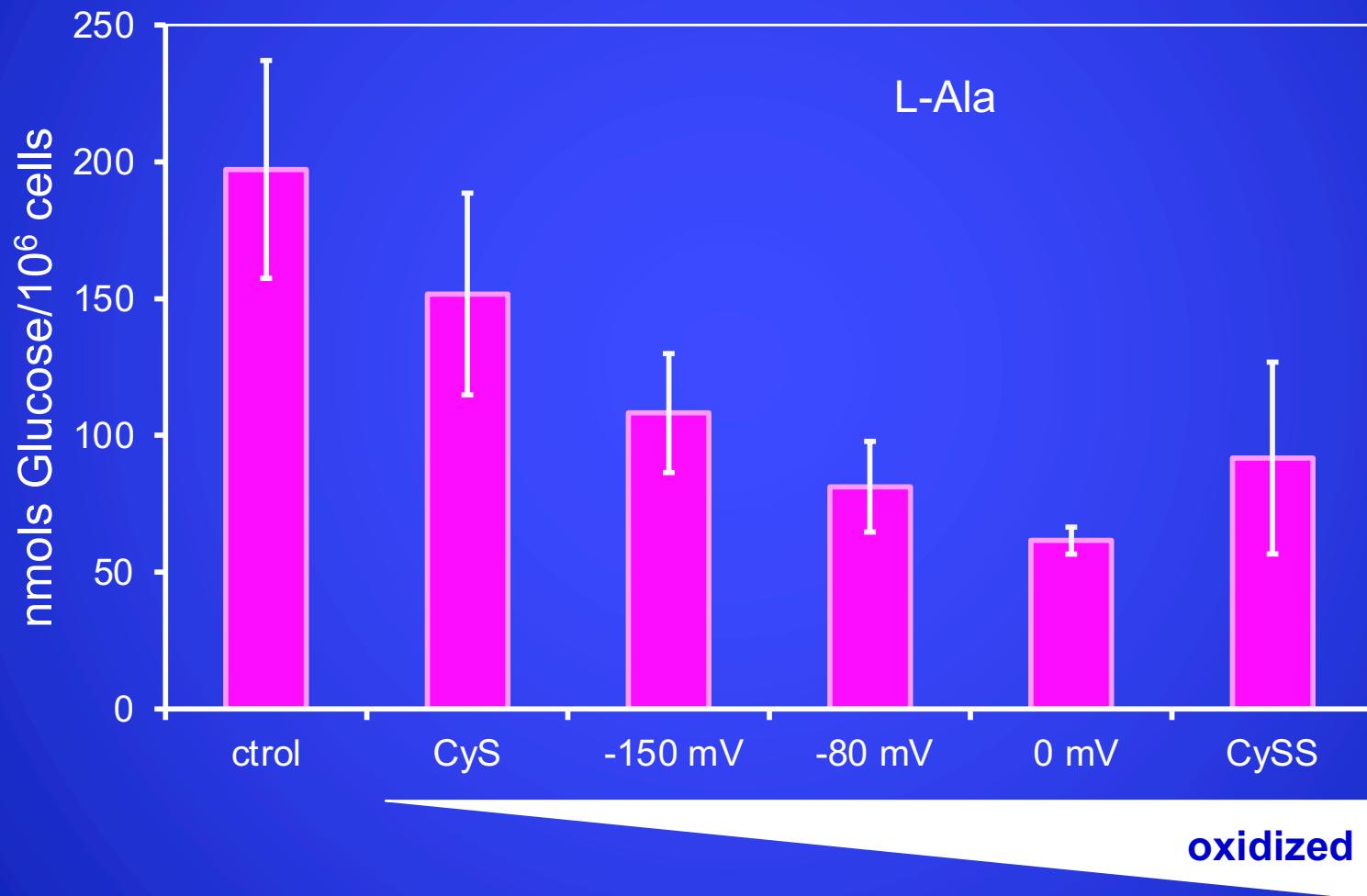
Laura Nocito

# *Adipocyte ROS Generation*

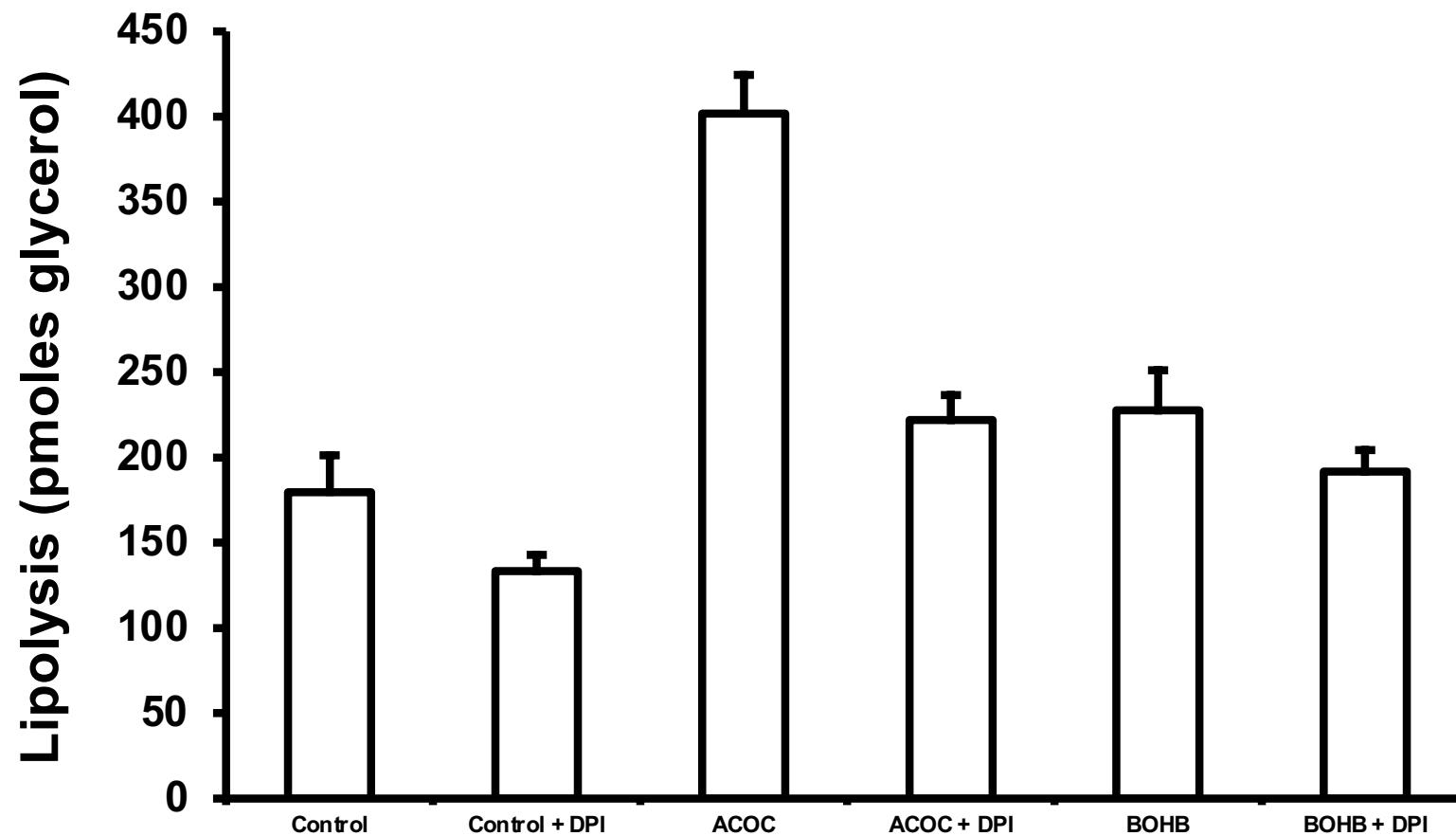


*Yes External Redox Can Control  
Cellular ROS Production.  
Do Changes in Redox or ROS Alter  
Function?*

# *Hepatic Glucose Production*

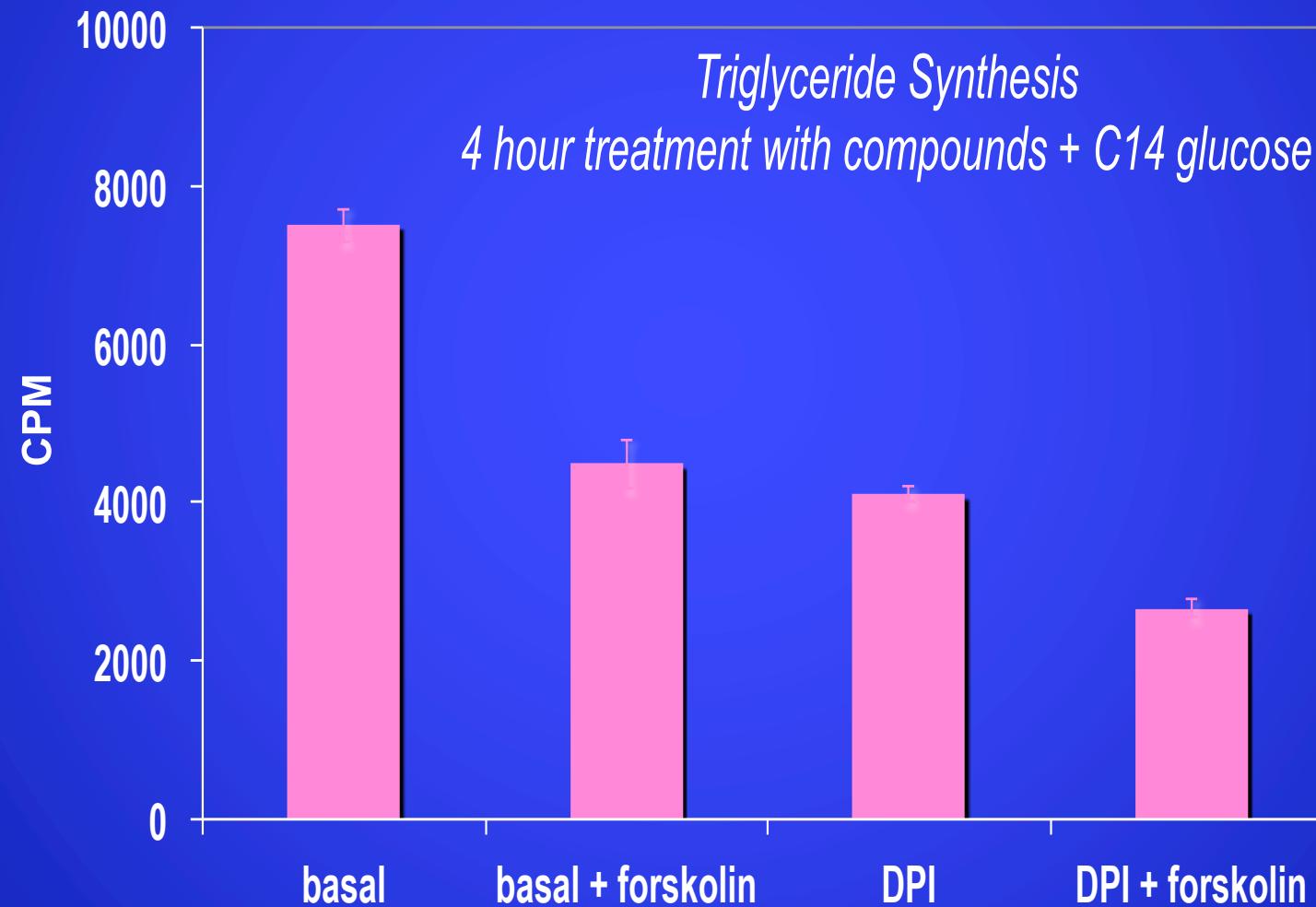


# Adipocyte Lipolysis

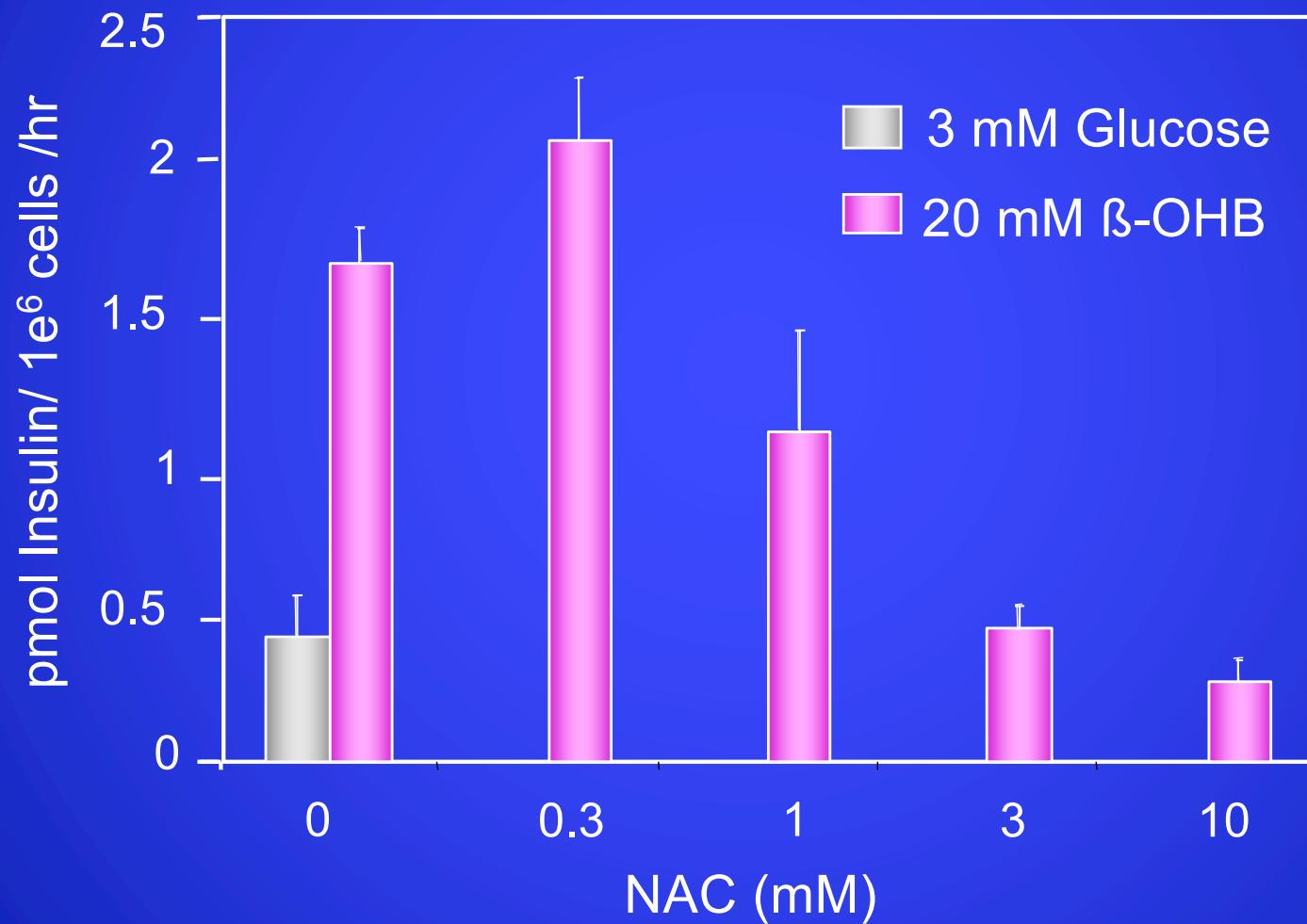


Oxidized

# *ROS Required for Lipid Synthesis*



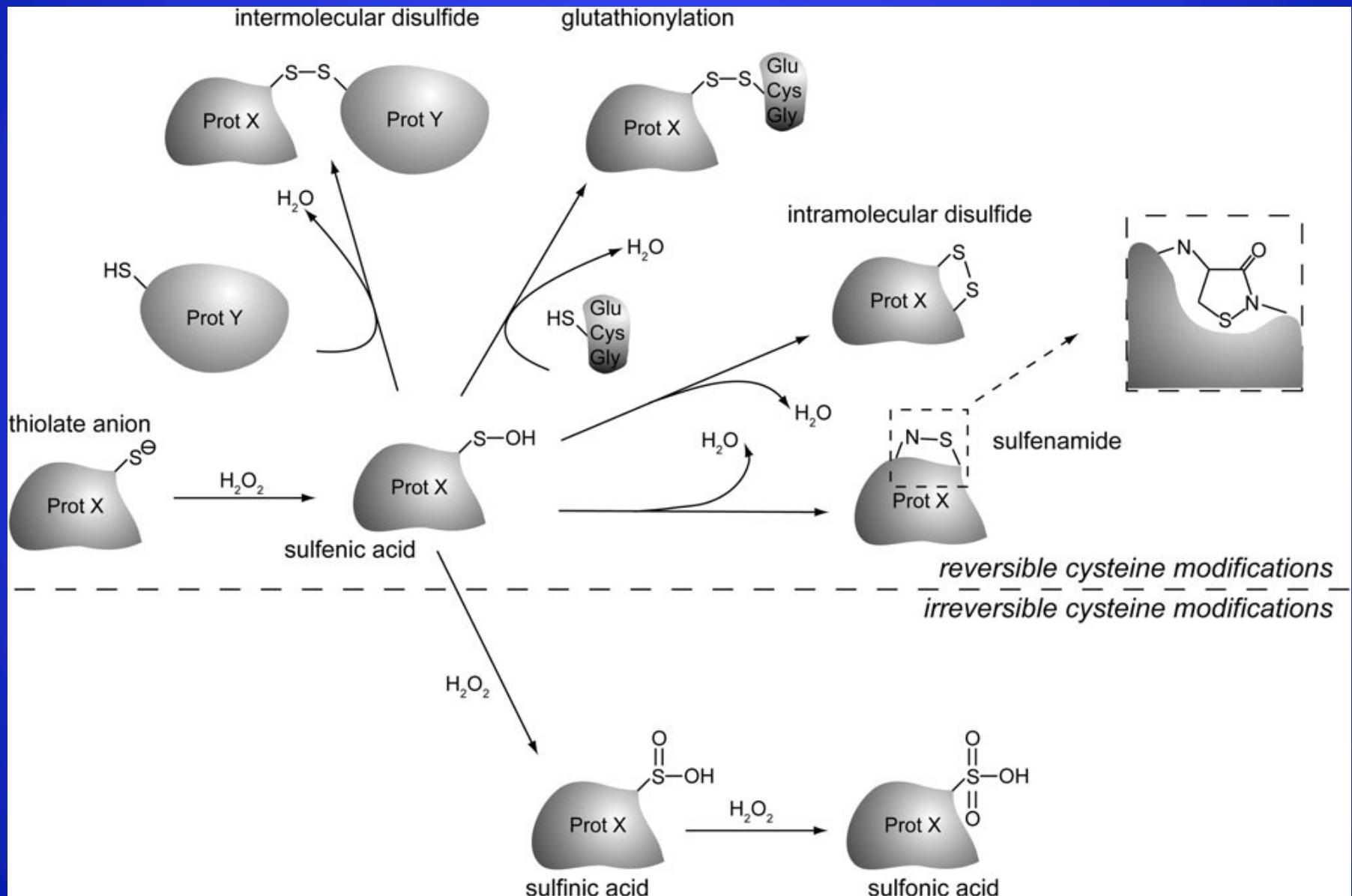
# *Effect of $\beta$ -OHB and ROS Removal on Insulin Secretion from INS-1 Cells*

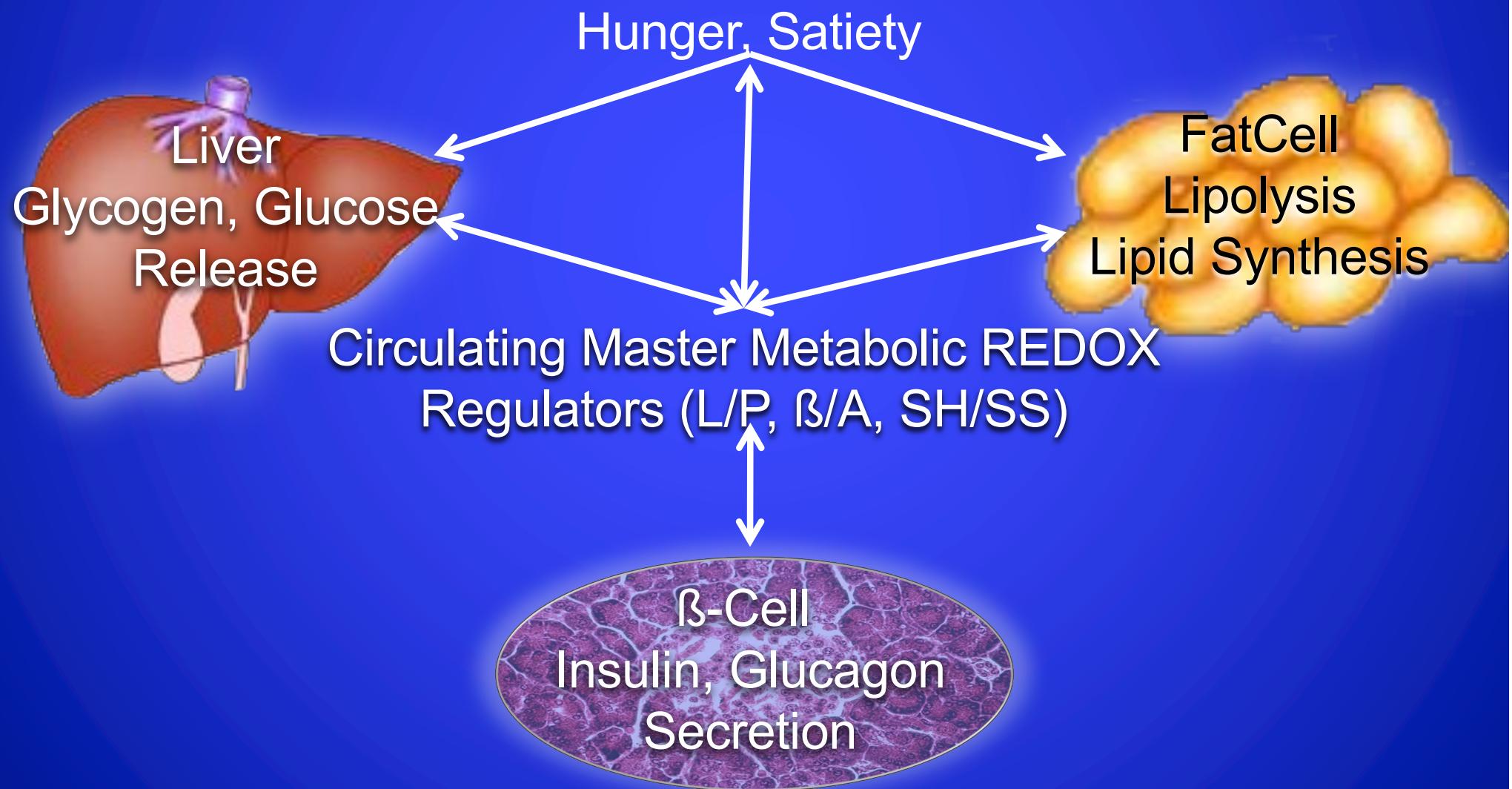
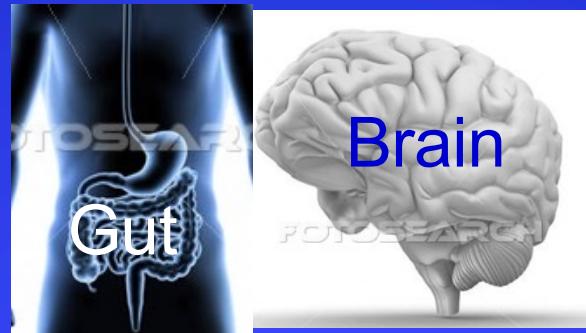


# *Mitochondrial bioenergetics link to insulin responses via redox biology*

- Under the normal reducing conditions of the intracellular redox environment, phosphatase tone is elevated, ensuring that net kinase activity is suppressed and specific protein targets are dephosphorylated.
- An oxidative shift in the redox environment lowers phosphatase tone to a level which allows for kinase activity to dominate and thus leads to phosphorylation of target proteins.

# Cysteines are Modified by ROS



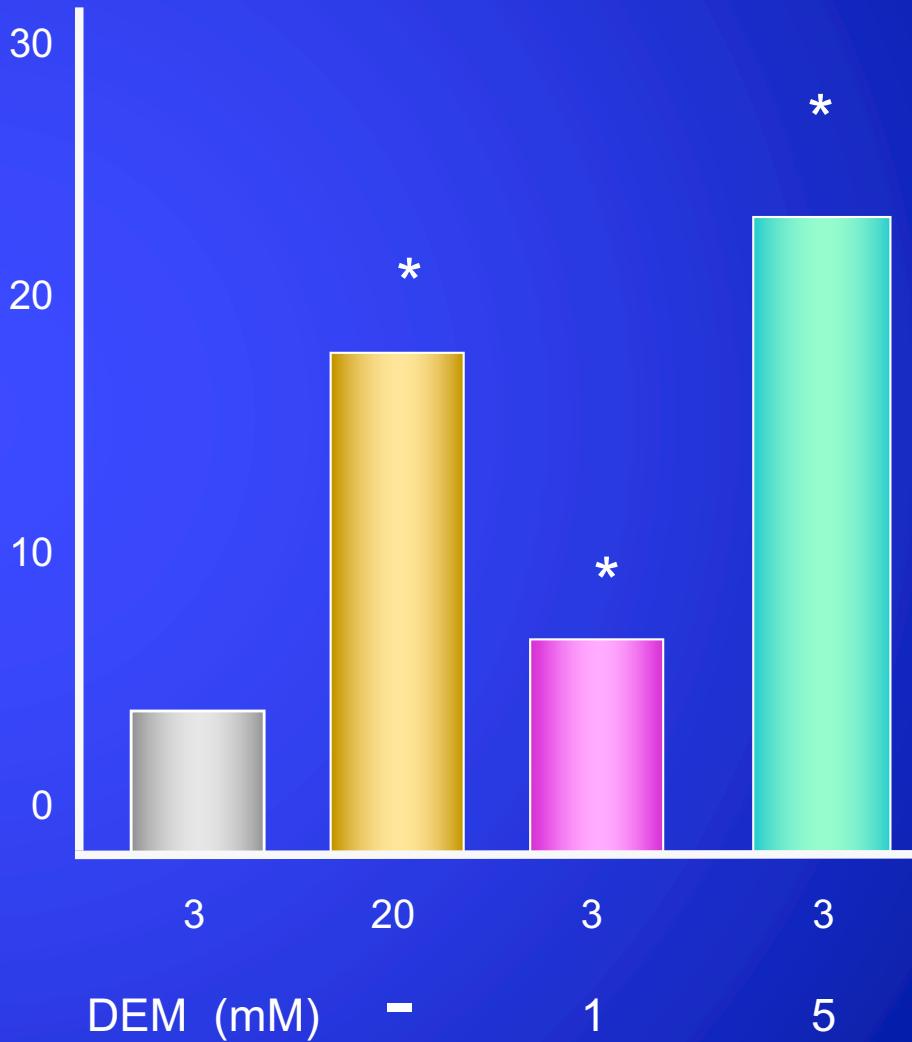
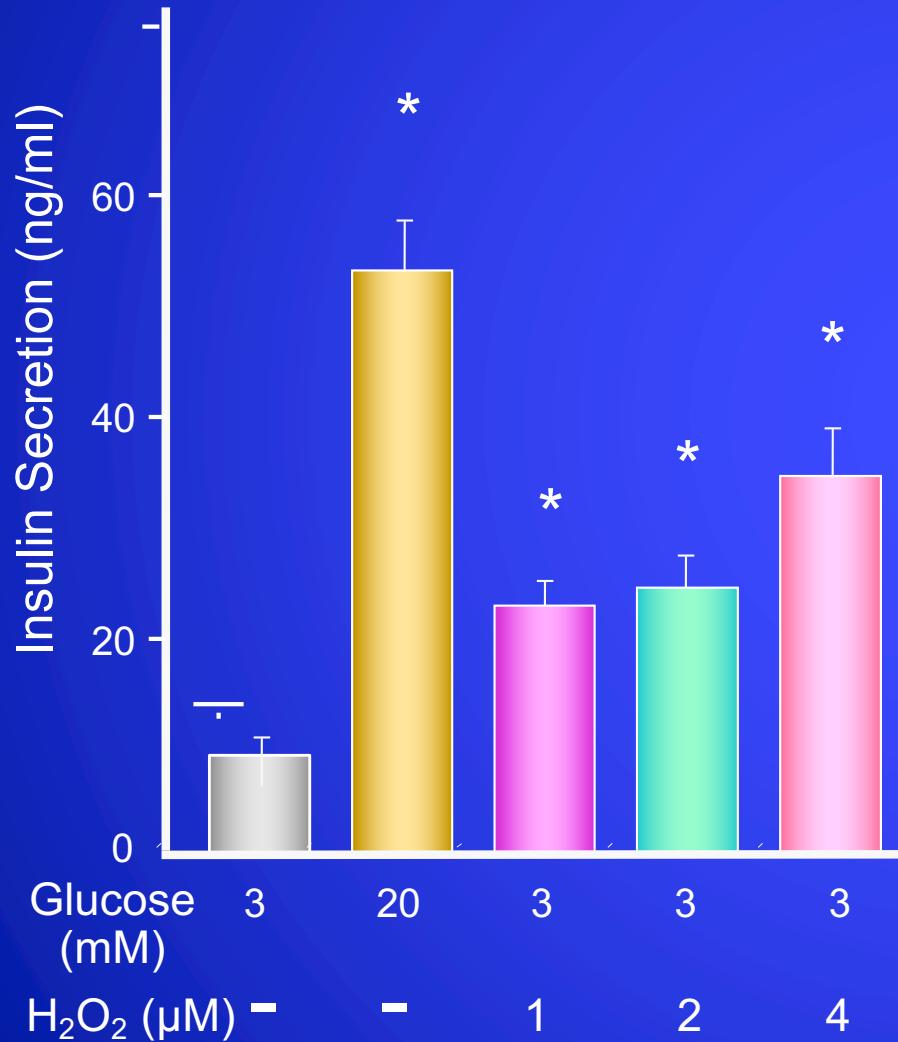


# *Summary and Implications*

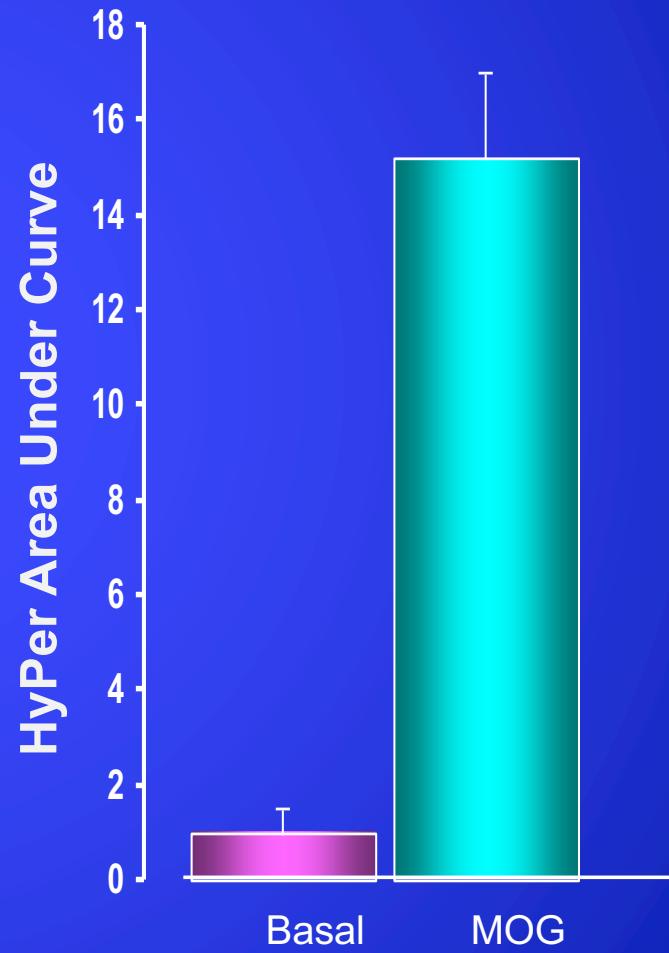
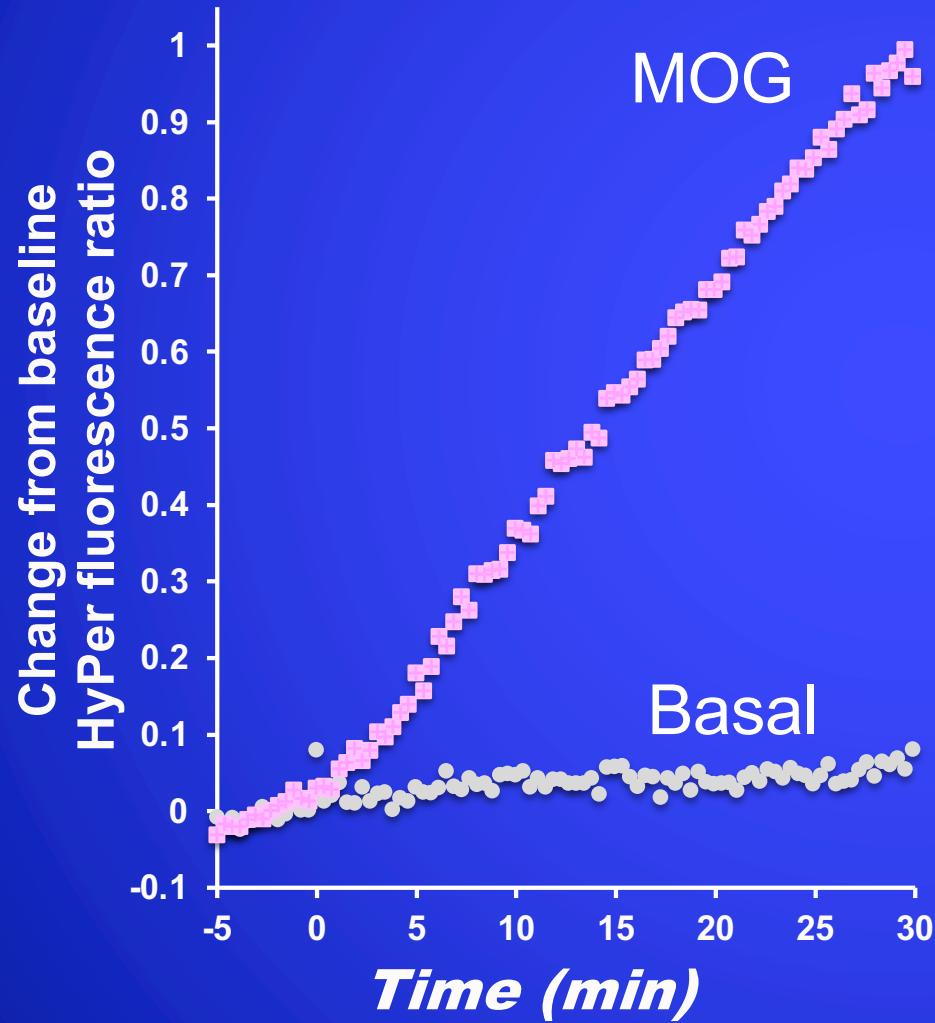
1. Fuels and exogenous agents change redox and can generate ROS in many organs
2. Redox couples are transported among cells via the circulation and thus interconnect all organs
3. ROS and redox changes impact function in an organ-specific manner
4. Environmental agents can increase ROS and insulin secretion in the absence of a stimulatory fuel
5. Such ROS constitutes a misleading signal

*Certain Exogenous Compounds  
can also Induce ROS*

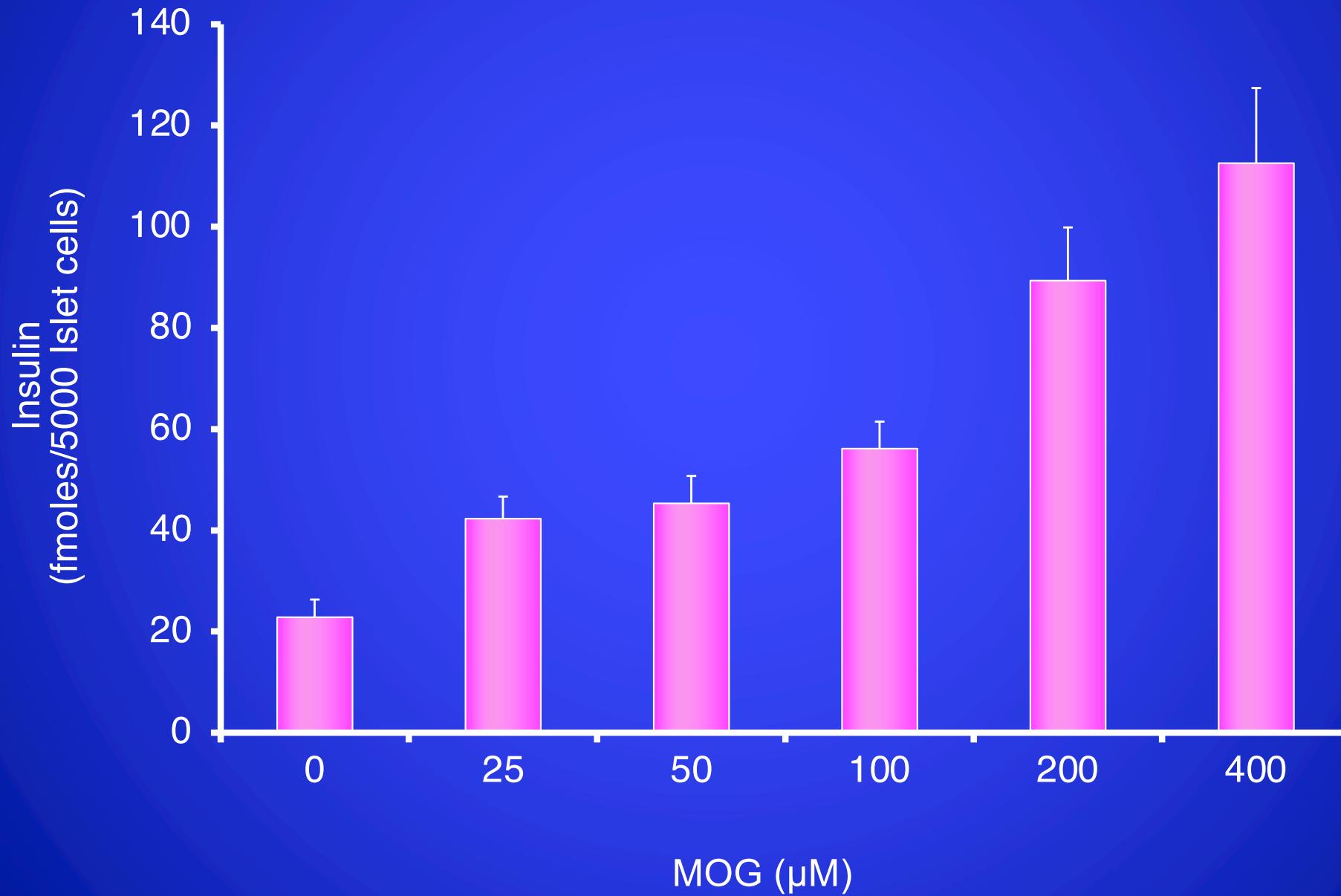
# $H_2O_2$ Increases Insulin Secretion in INS-1 Cells



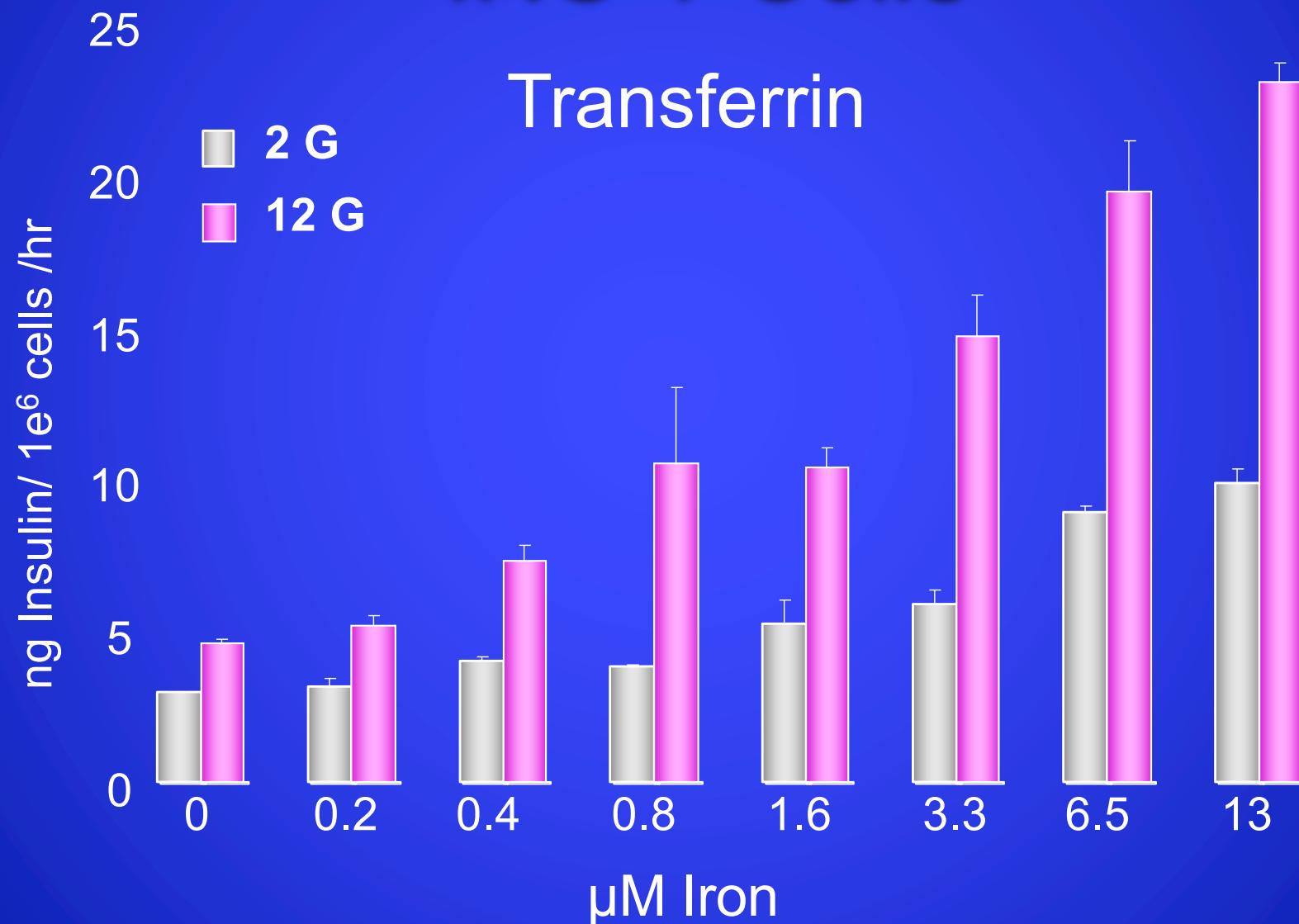
# *ROS is Generated by MOG*



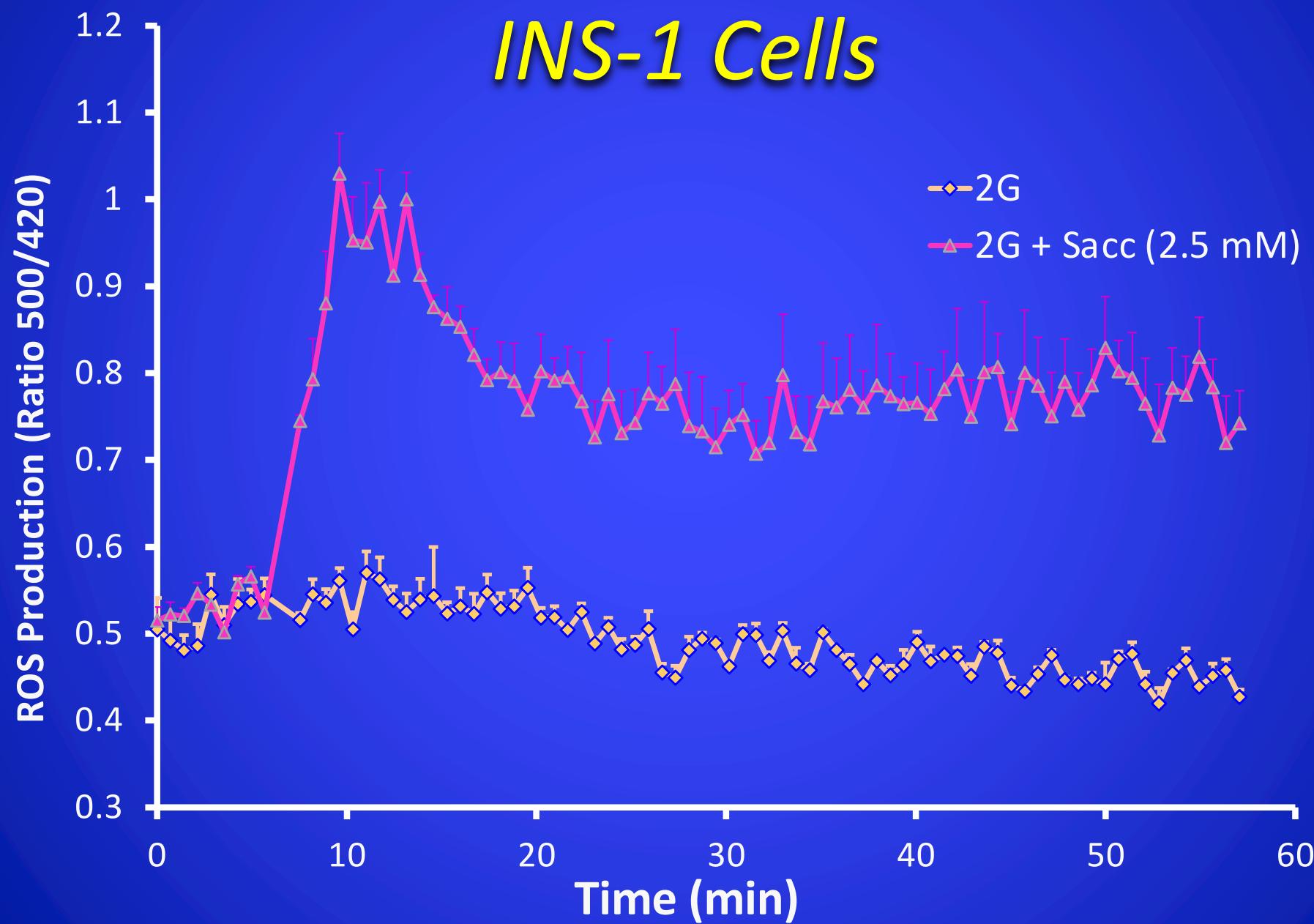
# *MOG Stimulates Basal Secretion*



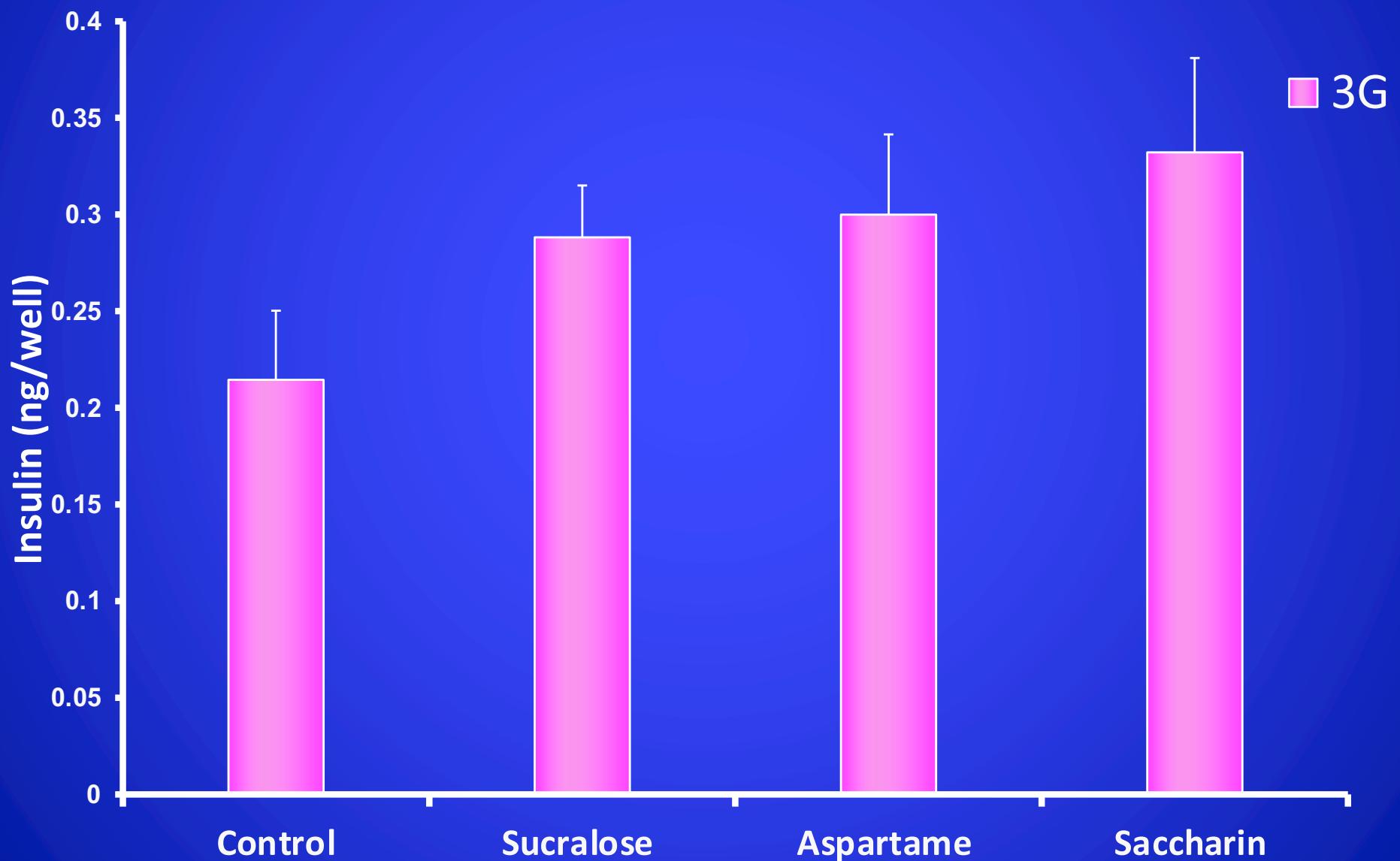
# *Iron Induces Insulin Secretion in INS-1 Cells*



# *Effect of Saccharin on ROS in INS-1 Cells*



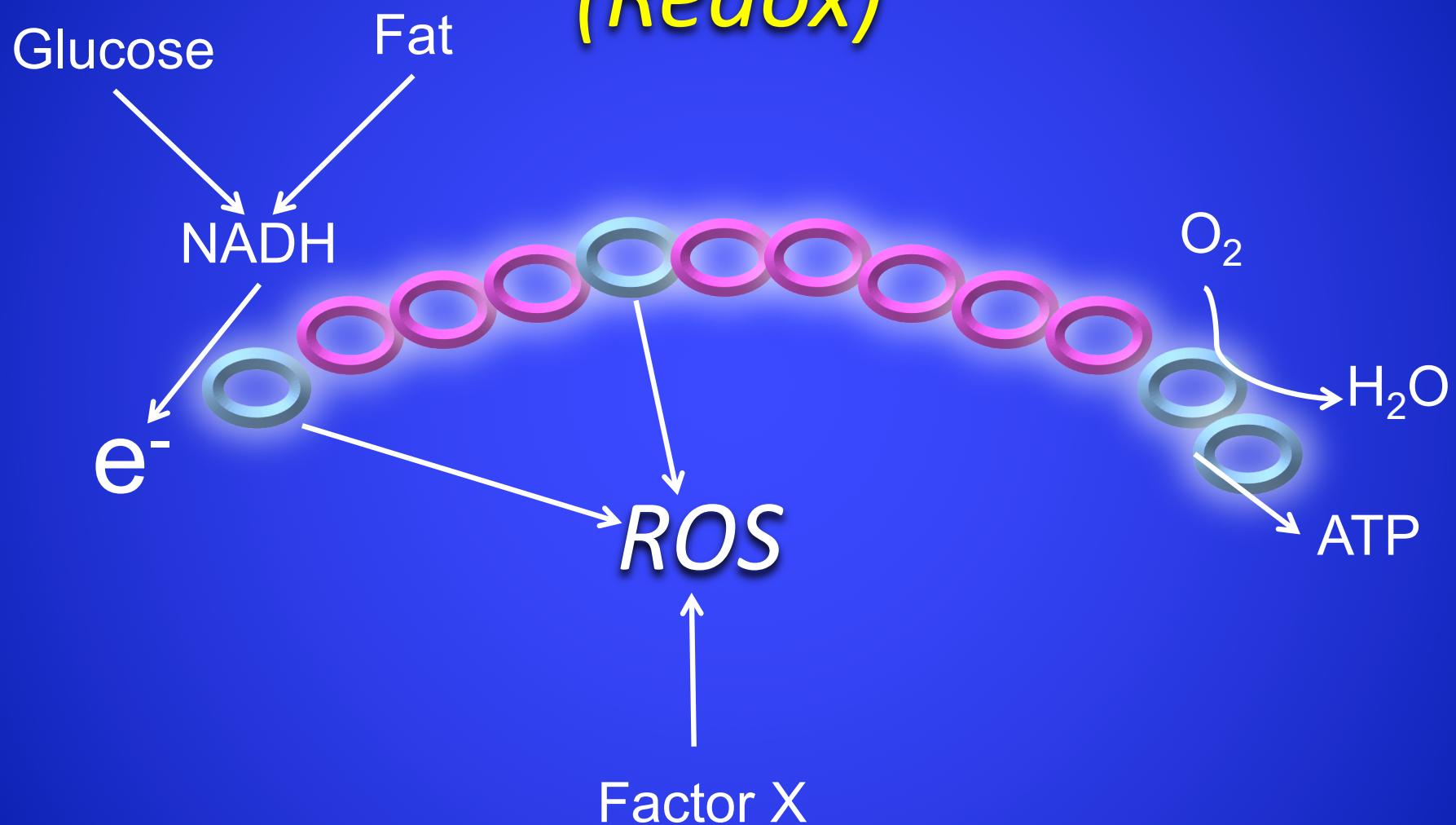
# *Artificial Sweeteners Affect Insulin Secretion in Dissociated Rat Islets*



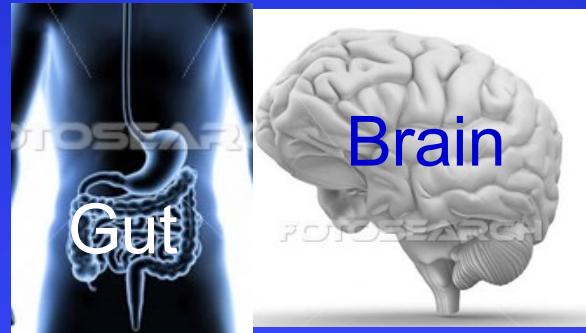
# *Agents that Cause Insulin Secretion in the Absence of a Stimulatory Fuel by Generating ROS*

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

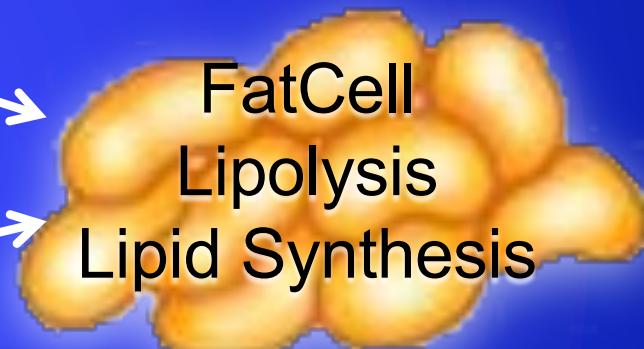
# *ROS are Produced at High NADH (Redox)*



# False Signals



Hunger, Satiety



Circulating Master Metabolic REDOX  
Regulators (L/P,  $\beta$ /A, SH/SS)



# Thank You