The Redox Network: Master Regulator of Metabolism

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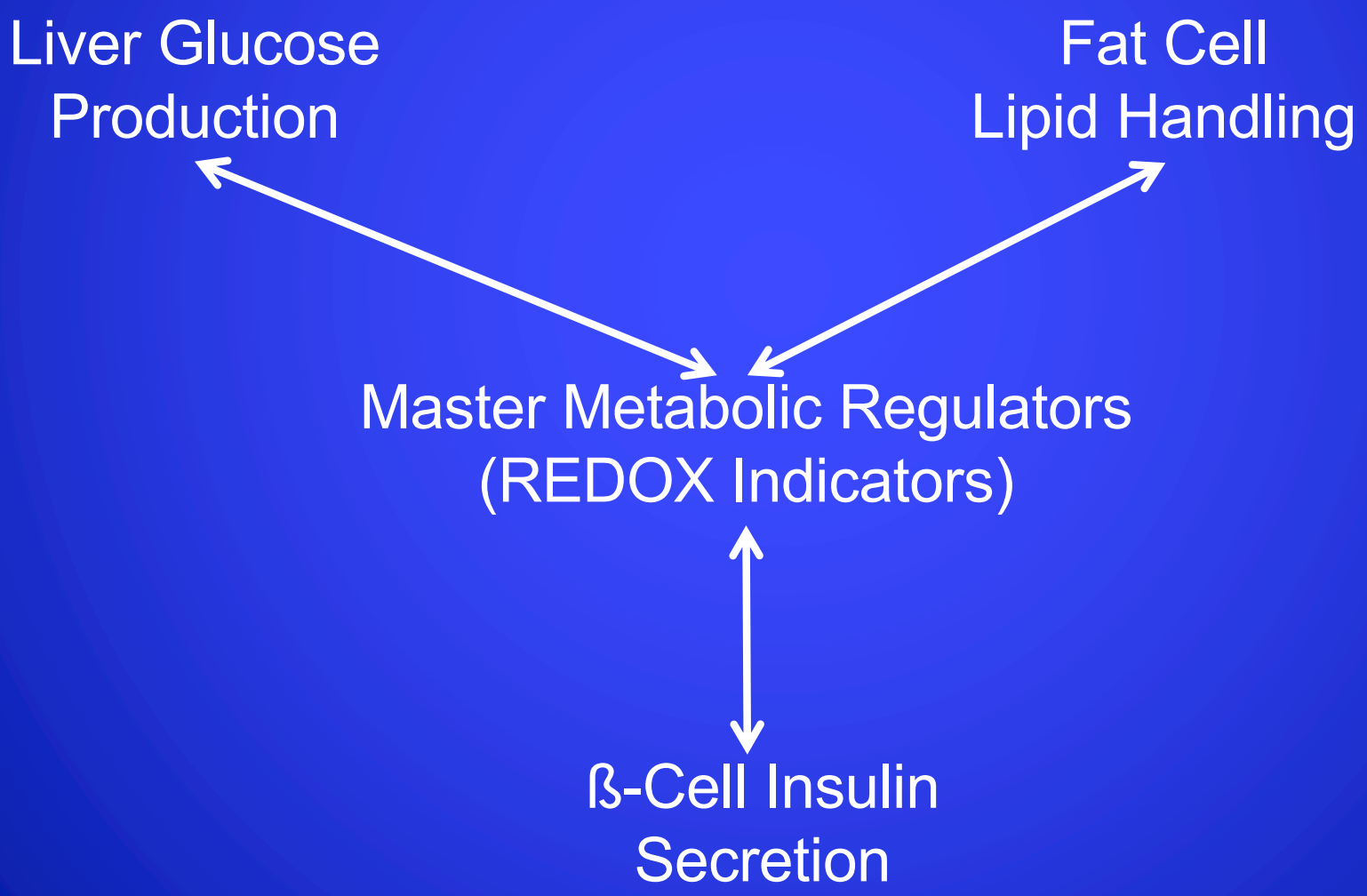
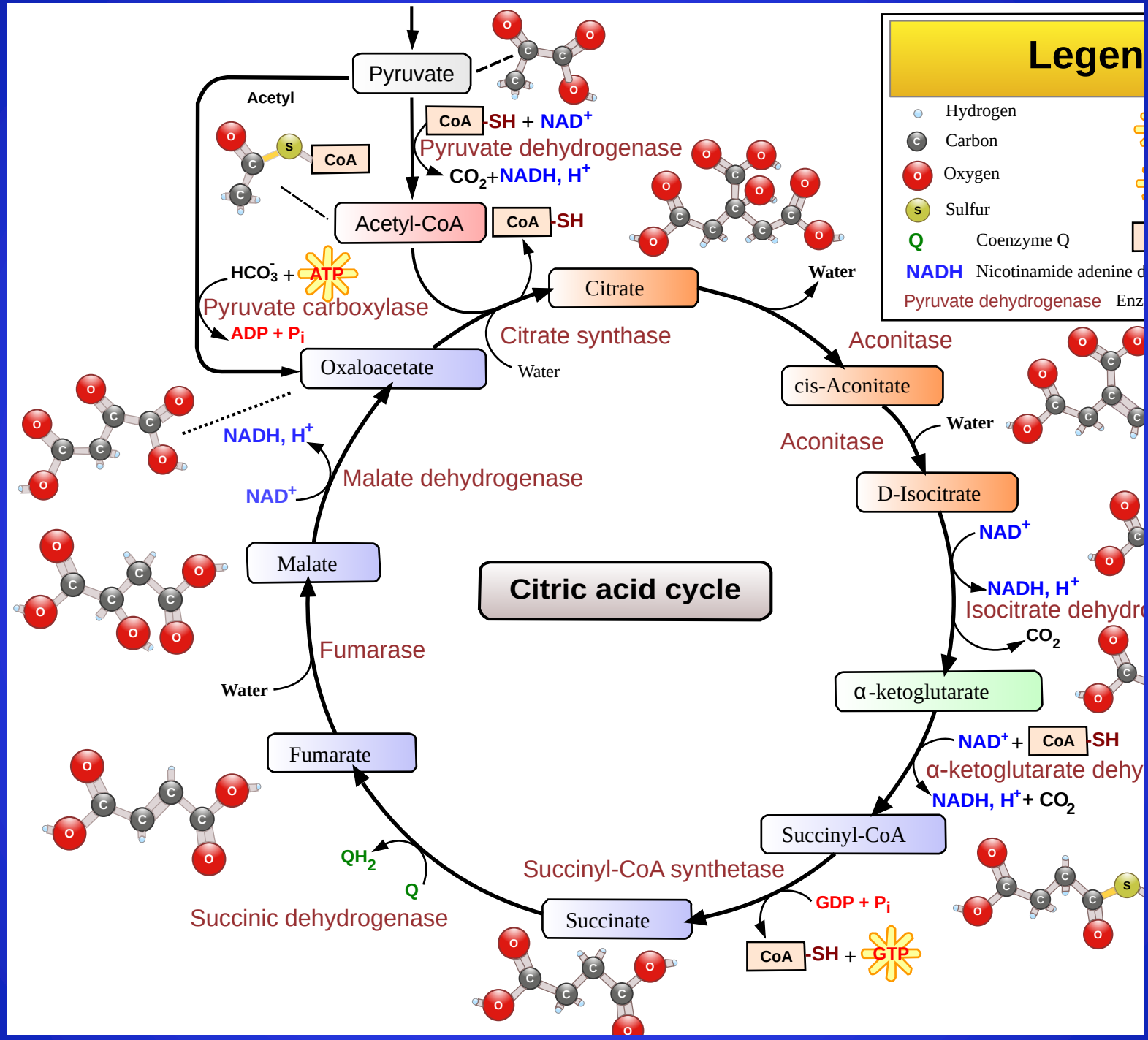
Circulating Redox Changes Frequently and Impacts Function



Energy State is Communicated by Redox Indicators

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



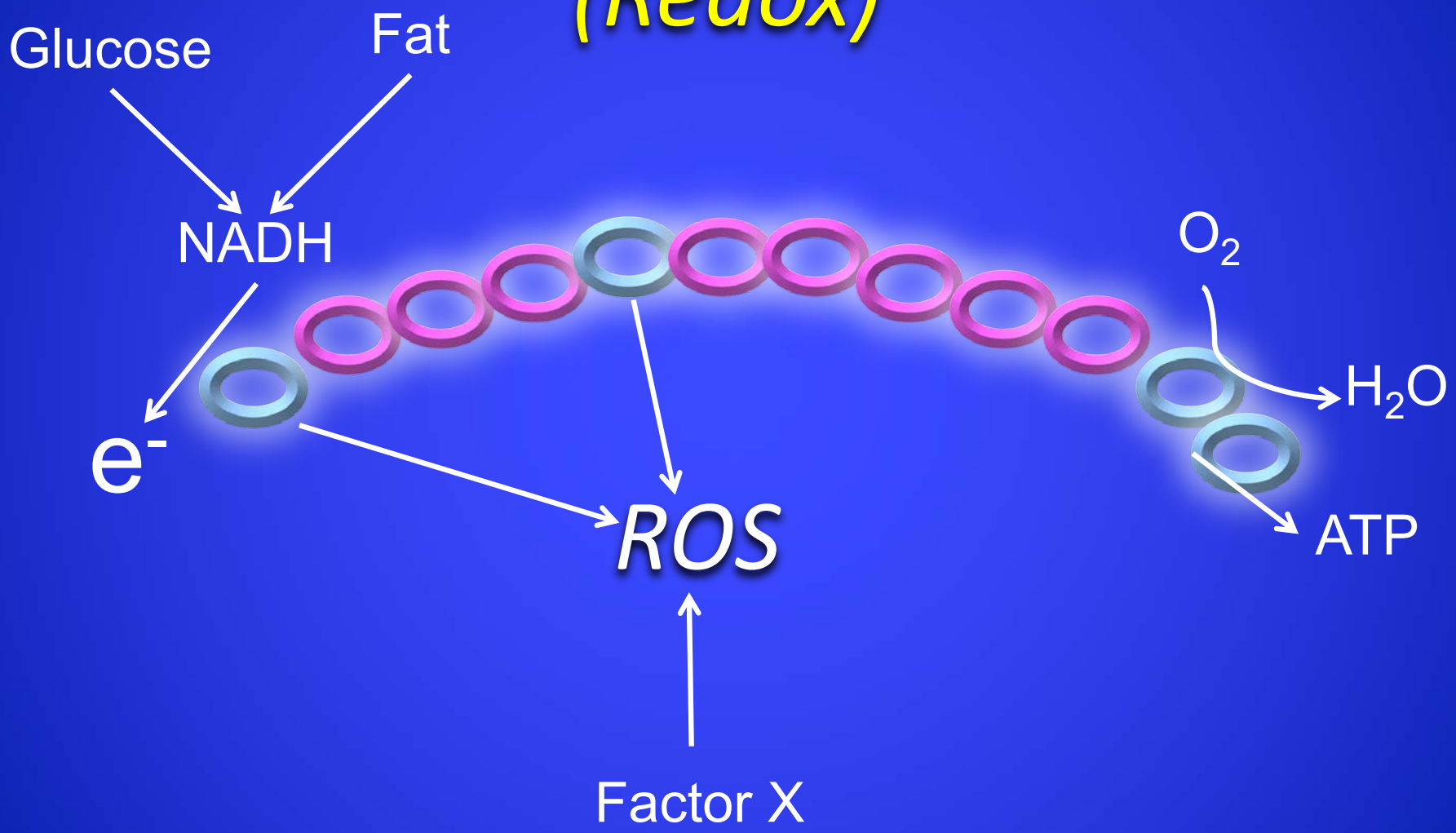
NADH used by ETC is replenished from Acetyl CoA

Co-Factors Interact and are Linked

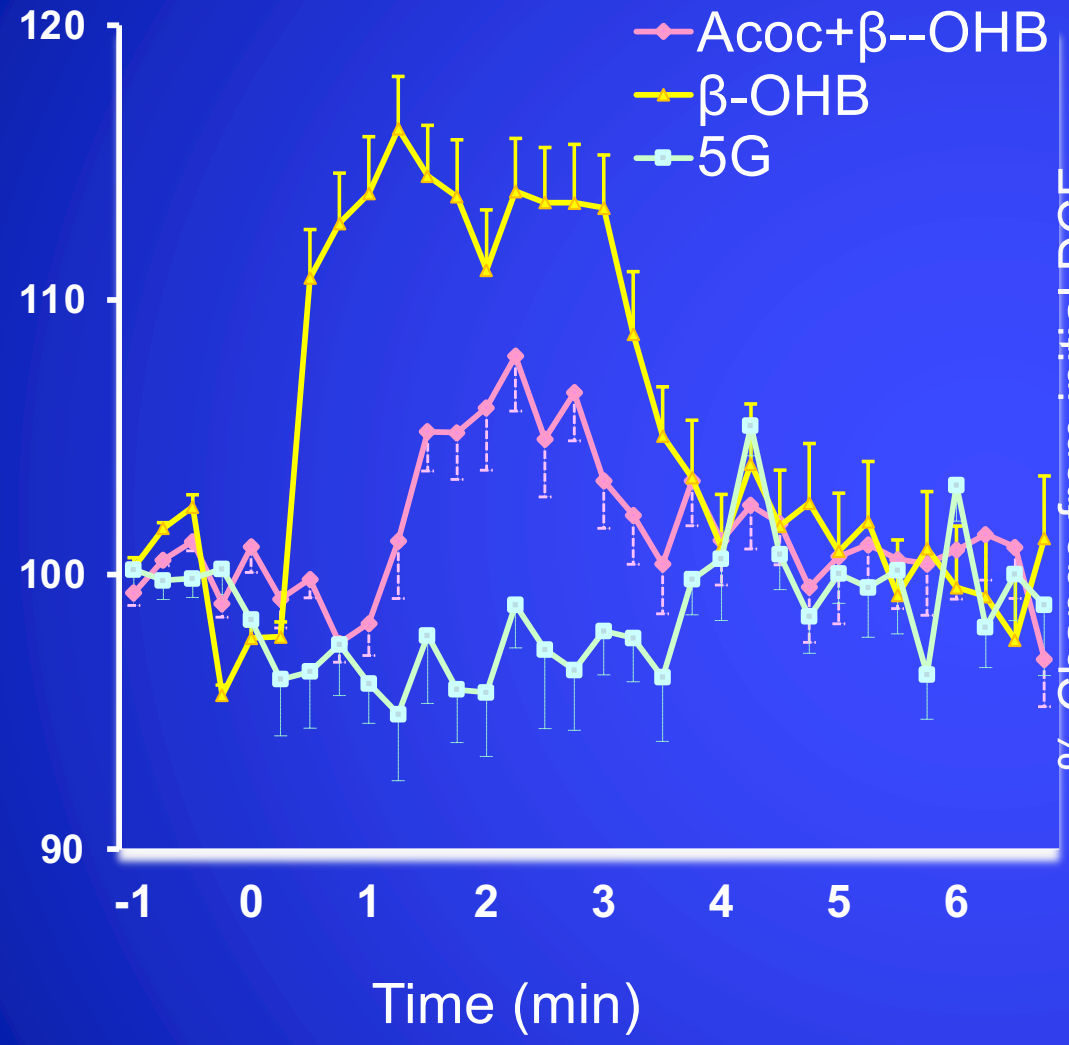
- ADP or the ATP/ADP ratio drives oxidative phosphorylation
- Dehydrogenase equilibrium restores redox as NADH electrons enter electron transport
- Acetyl CoA production sustains electron transport
- Excess fuel produces ROS, drives NNT, impacts thiol redox state

Redox Changes Induce ROS Changes that Impact Thiol Redox

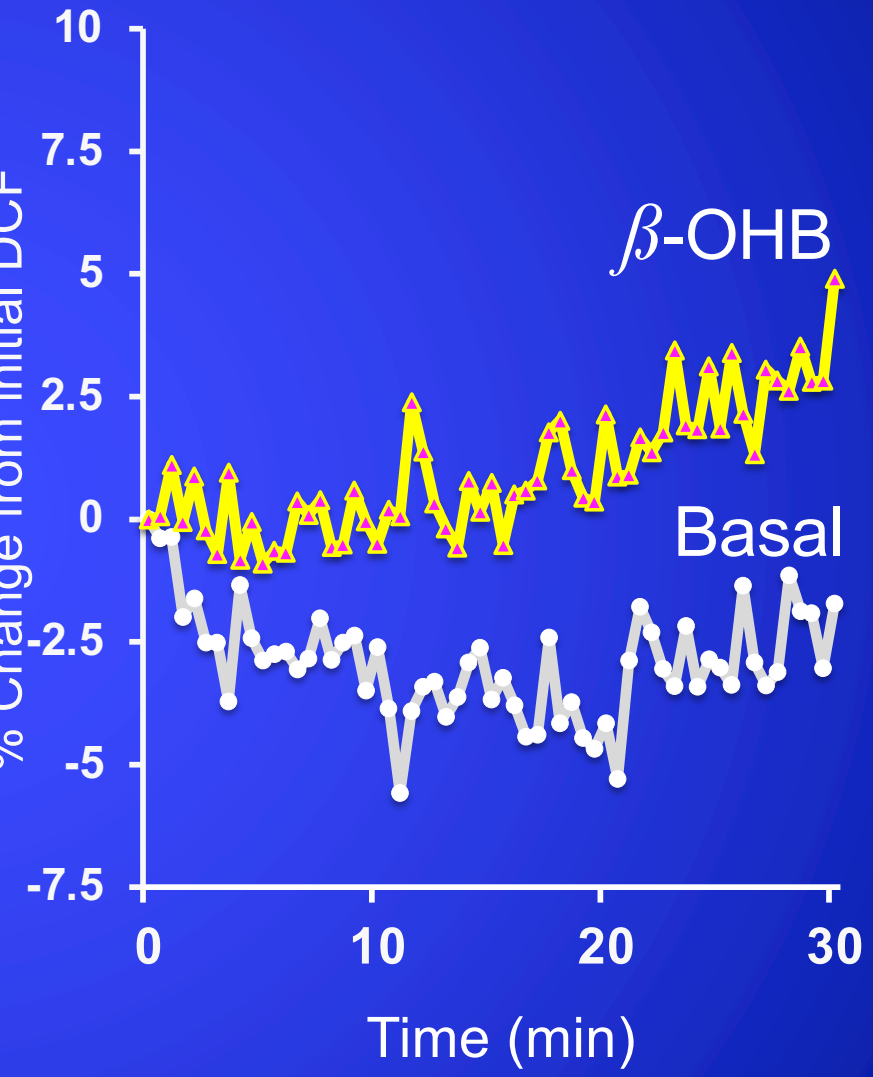
ROS are Produced at High NADH (Redox)



Redox



ROS

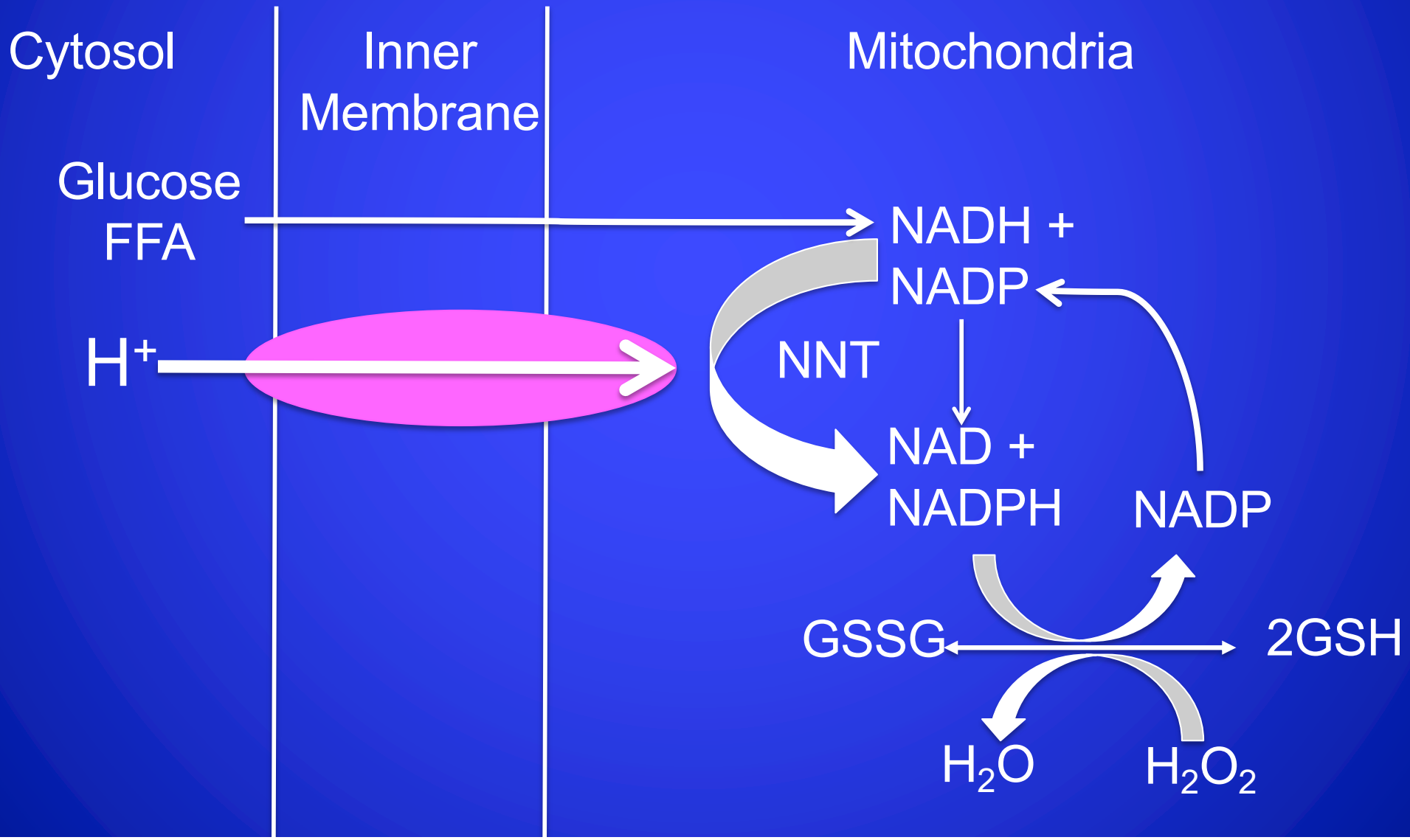


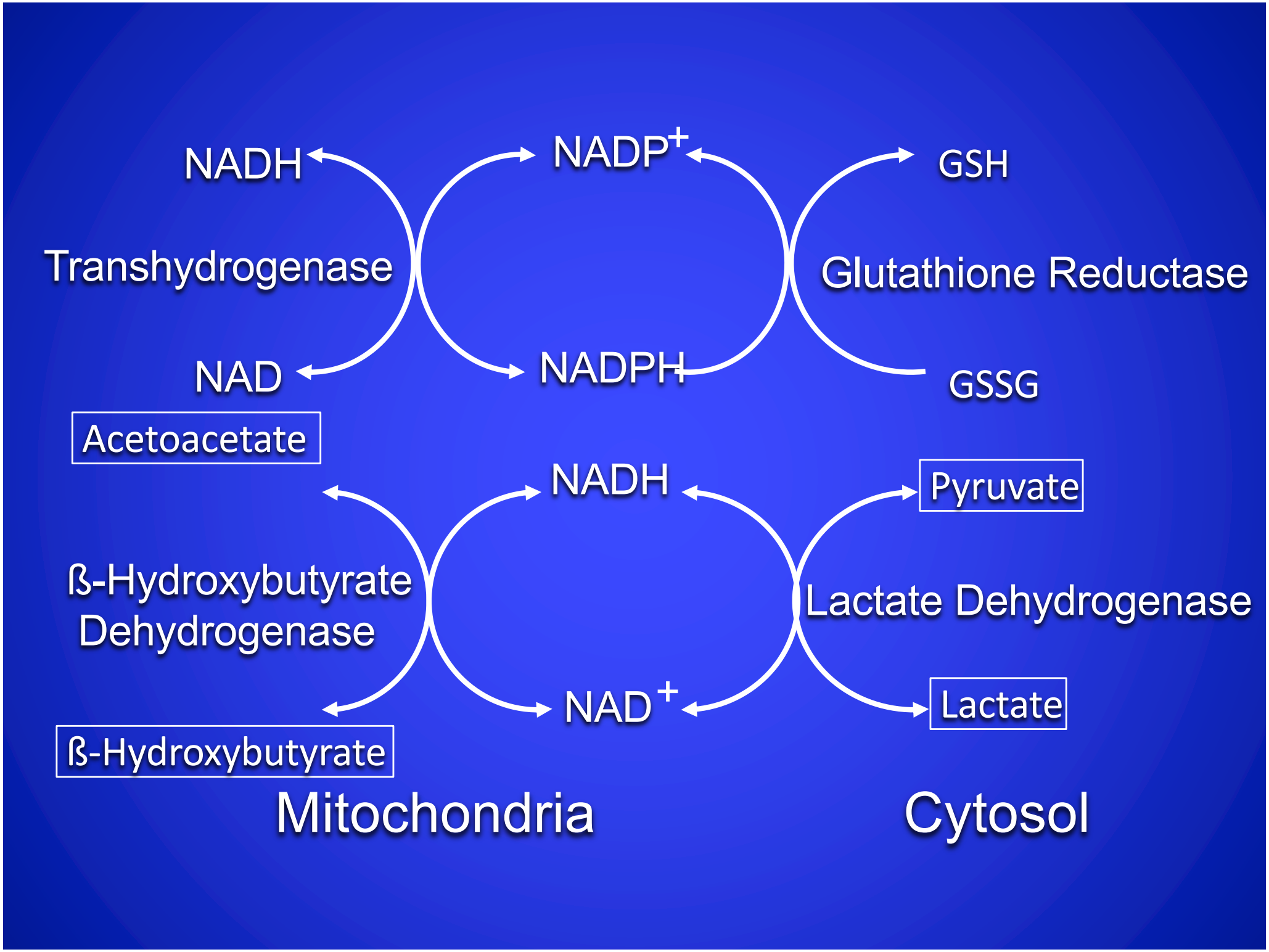
ß-OHBDH

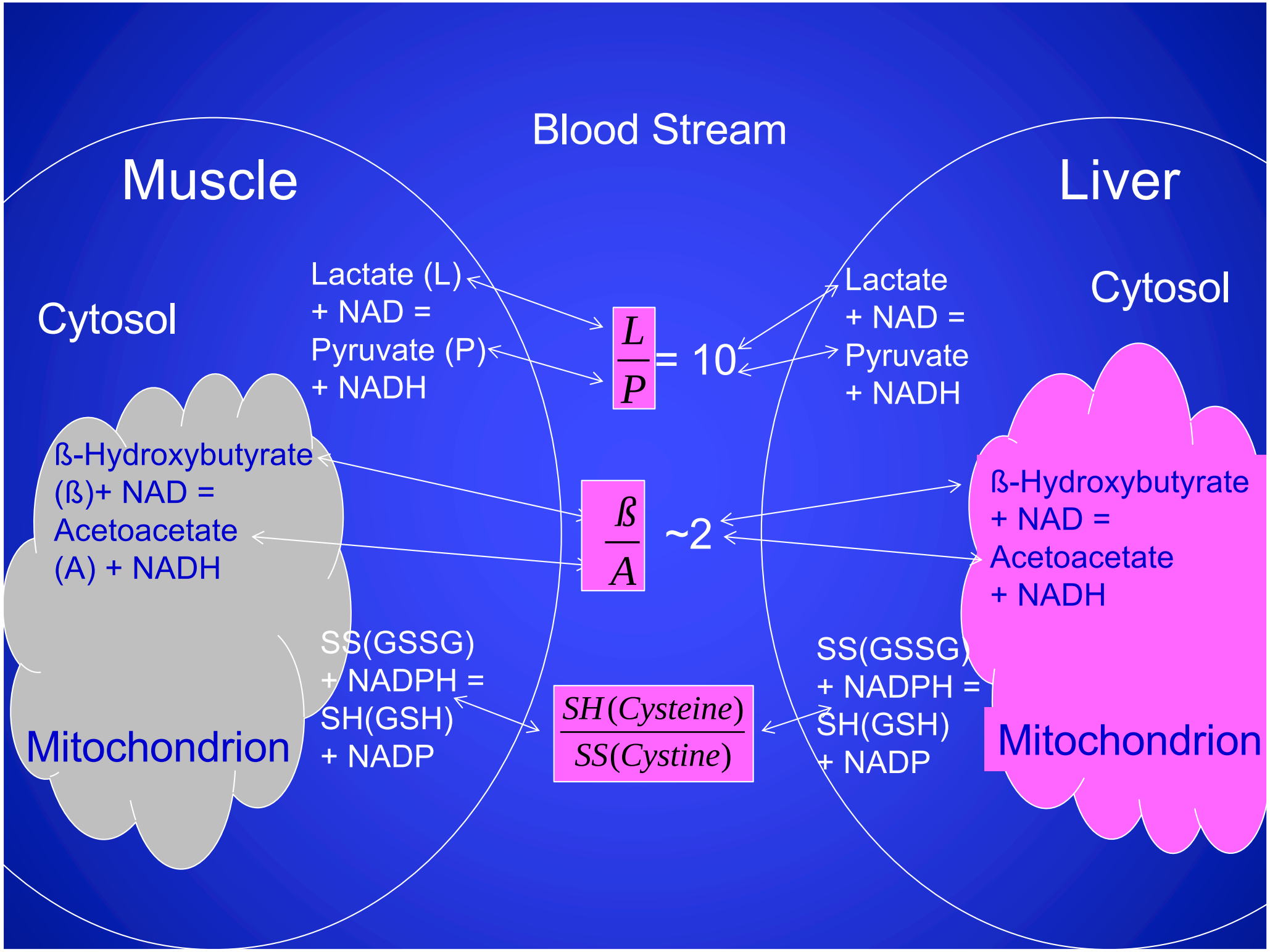
ß-OHB + NAD = Acoc + NADH

Ferrante et al, unpublished

NNT a ROS-Scavenging Enzyme Driven by the Proton Gradient




NADH
Transhydrogenase
NAD
NADP+
NADPH
GSH
Glutathione Reductase
GSSG
Acetoacetate
NADH
ß-Hydroxybutyrate Dehydrogenase
ß-Hydroxybutyrate
NAD+
Pyruvate
Lactate Dehydrogenase
Lactate
Mitochondria
Cytosol


Blood Stream
Muscle
Liver
Cytosol
Cytosol
Lactate (L)
+ NAD =
Pyruvate (P)
+ NADH
$\frac{L}{P}$ = 10
Lactate
+ NAD =
Pyruvate
+ NADH
ß-Hydroxybutyrate
(ß)+ NAD =
Acetoacetate
(A) + NADH
$\frac{ß}{A}$
~2
ß-Hydroxybutyrate
+ NAD =
Acetoacetate
+ NADH
SS(GSSG)
+ NADPH =
SH(GSH)
+ NADP
$\frac{SH(Cysteine)}{SS(Cystine)}$
SS(GSSG)
+ NADPH =
SH(GSH)
+ NADP
Mitochondrion
Mitochondrion

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)

H_2O_2 Production Rates in Intact Organ

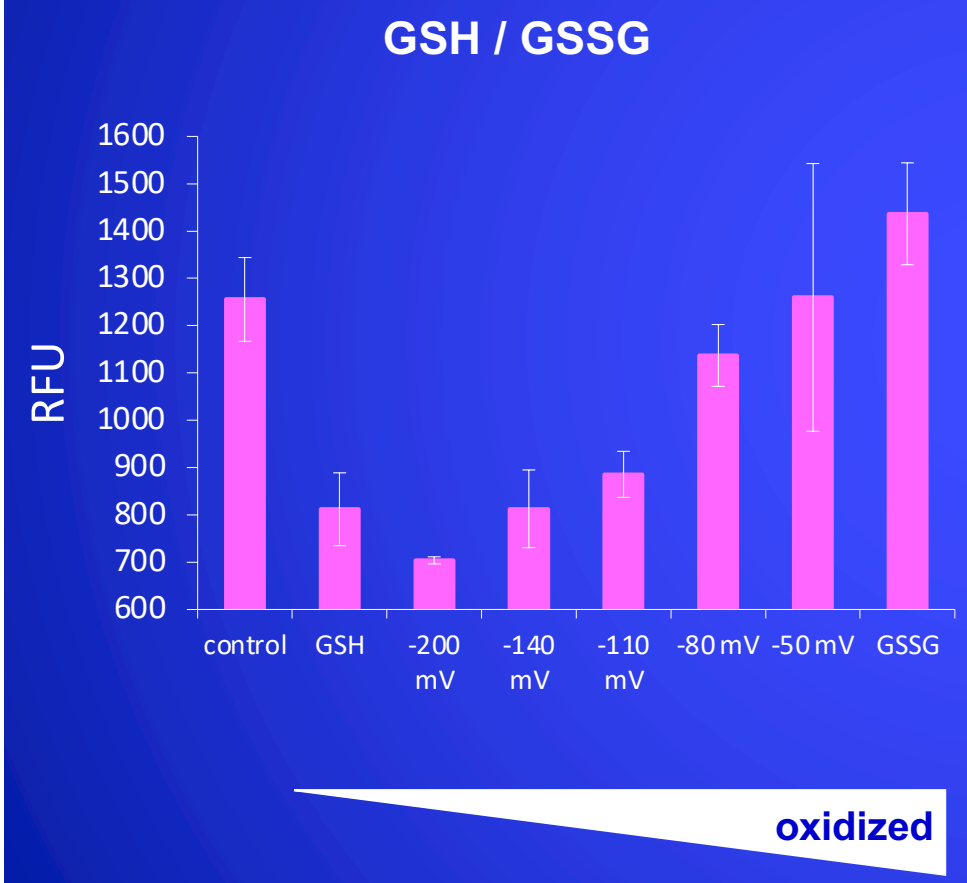
Perfused liver data were obtained by methanol titration of catalase Compound I. Data from Oshino et al (1973).

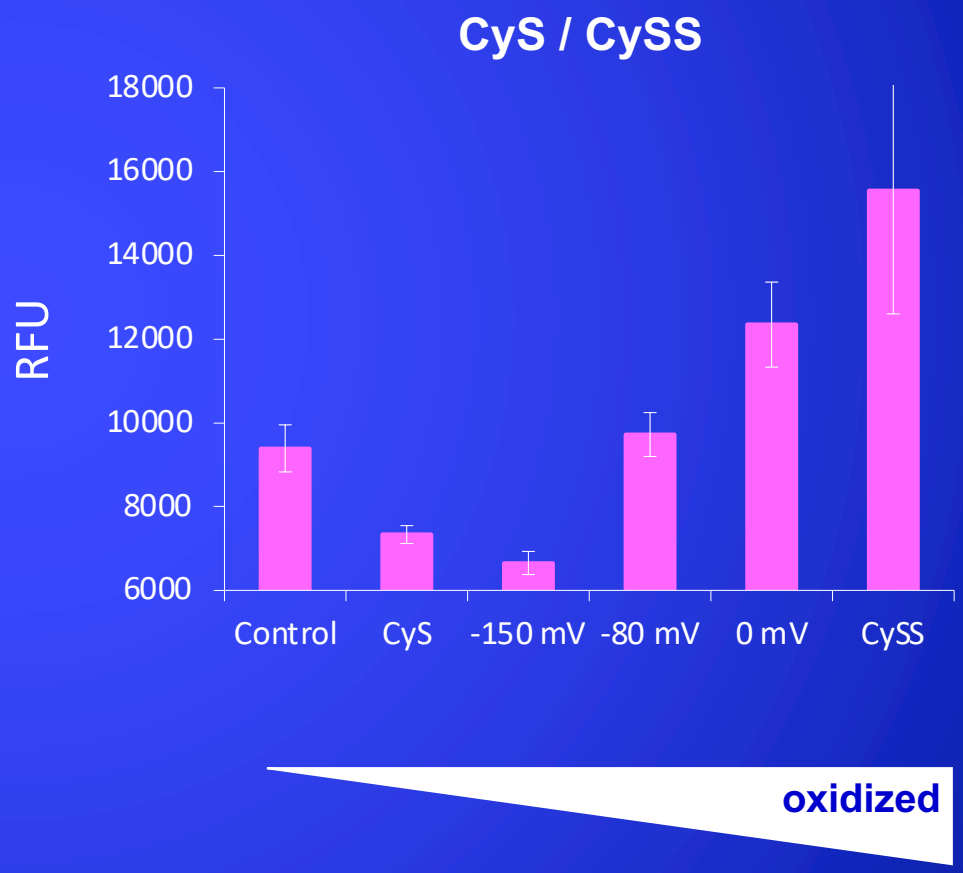
Substrate or inhibitor	Production Rate nmol H_2O_2/min per g liver
L-Lactate, 2 mM; pyruvate, 0.3 mM	49
+ antimycin, 8 μM	75
+ octanoate, 0.3 mM	170
+ oleate, 0.1 mM	66

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

Intracellular Fuels Impact Cellular Redox and ROS.
Do External Circulating Changes affect Intracellular Redox?

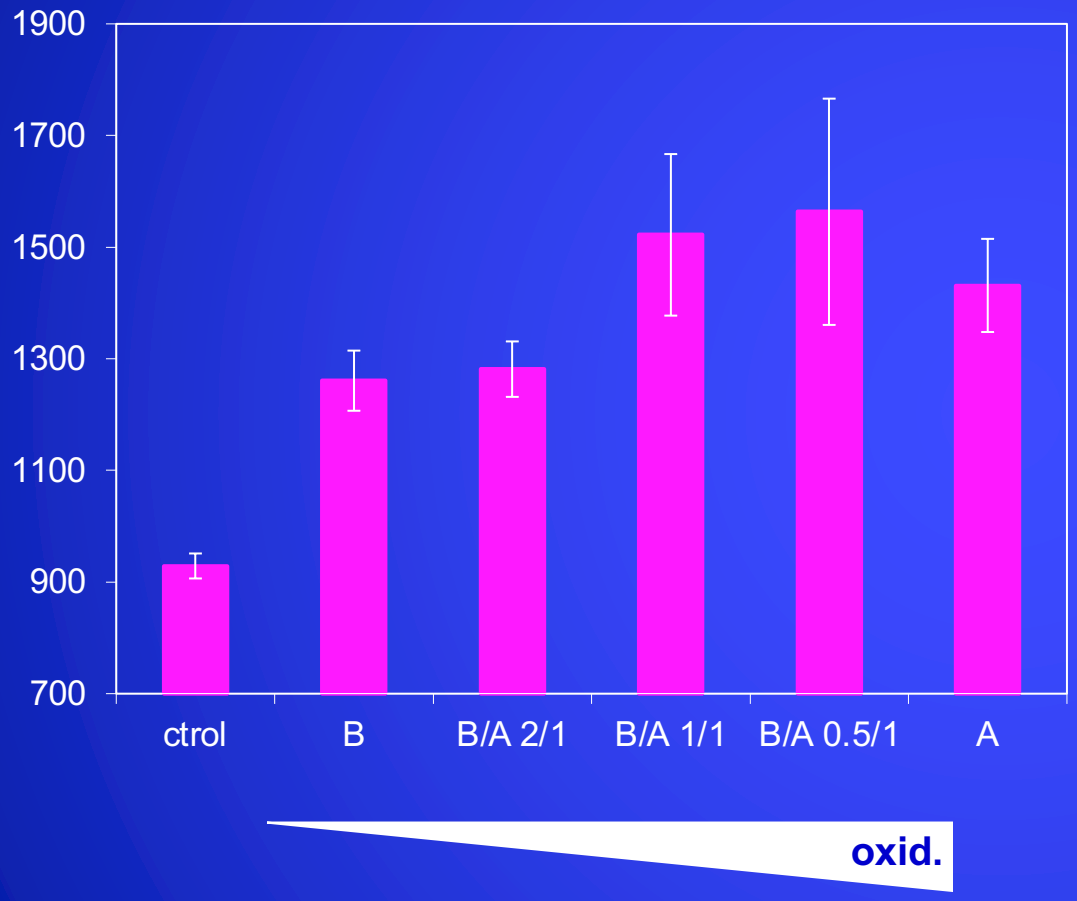
ROS Production in Hepatocytes



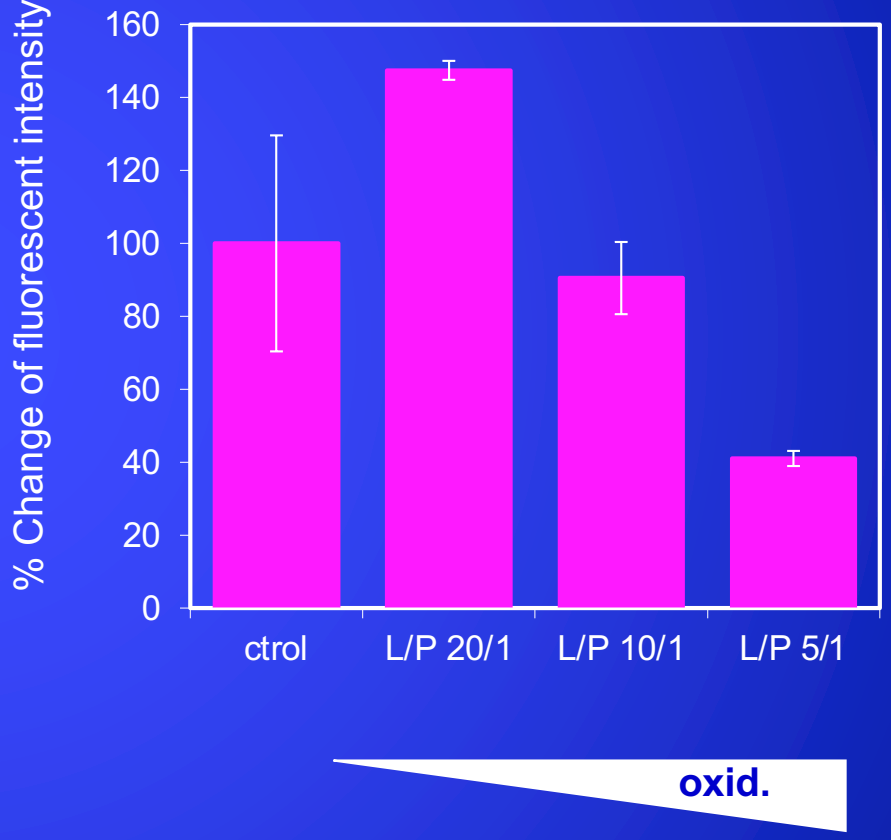


Laura Nocito and Elsia Yoo

Hepatic ROS Production



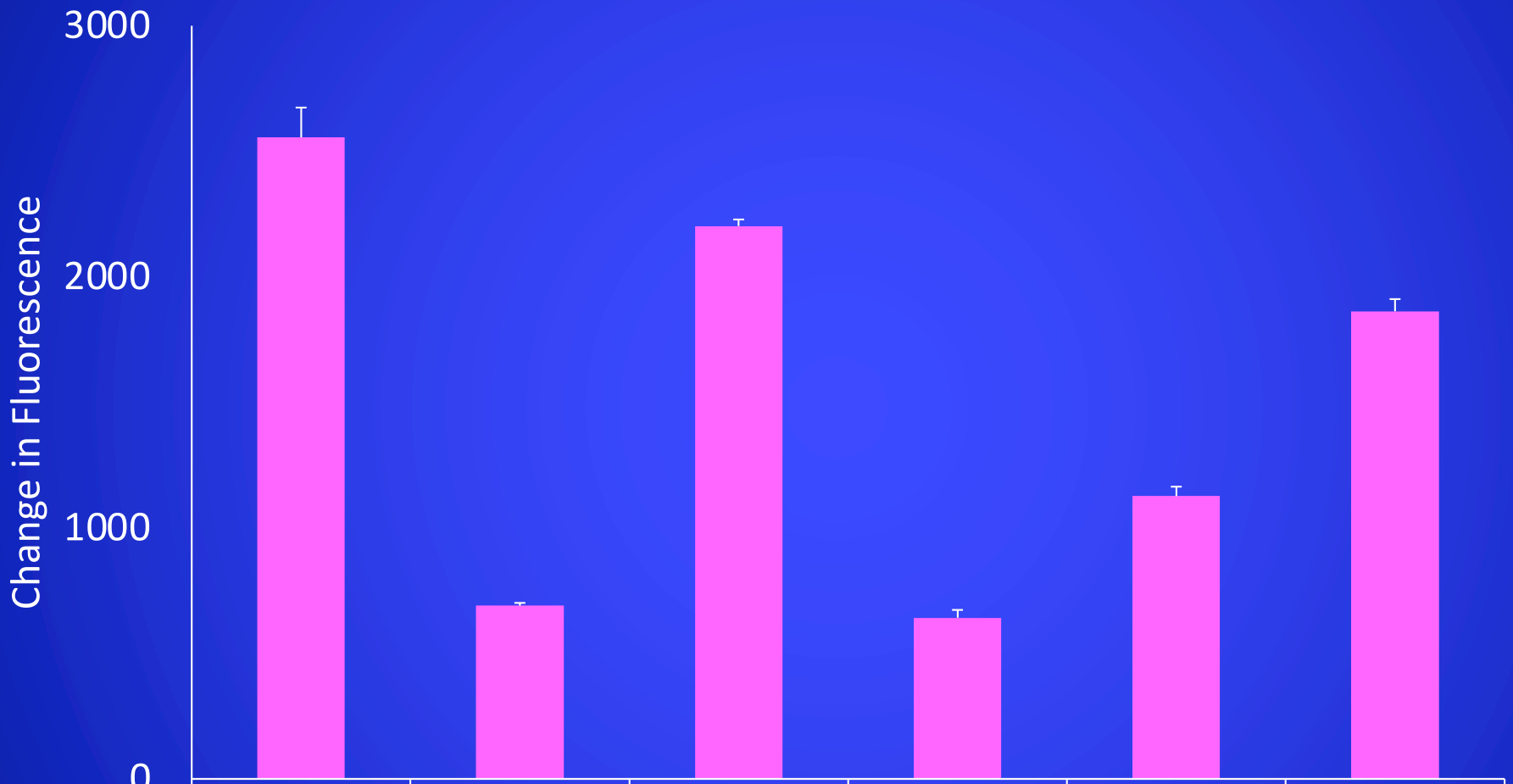
ßOHB / Acoc Ratio



Lactate / Pyruvate Ratio

Laura Nocito

Adipocyte ROS Generation



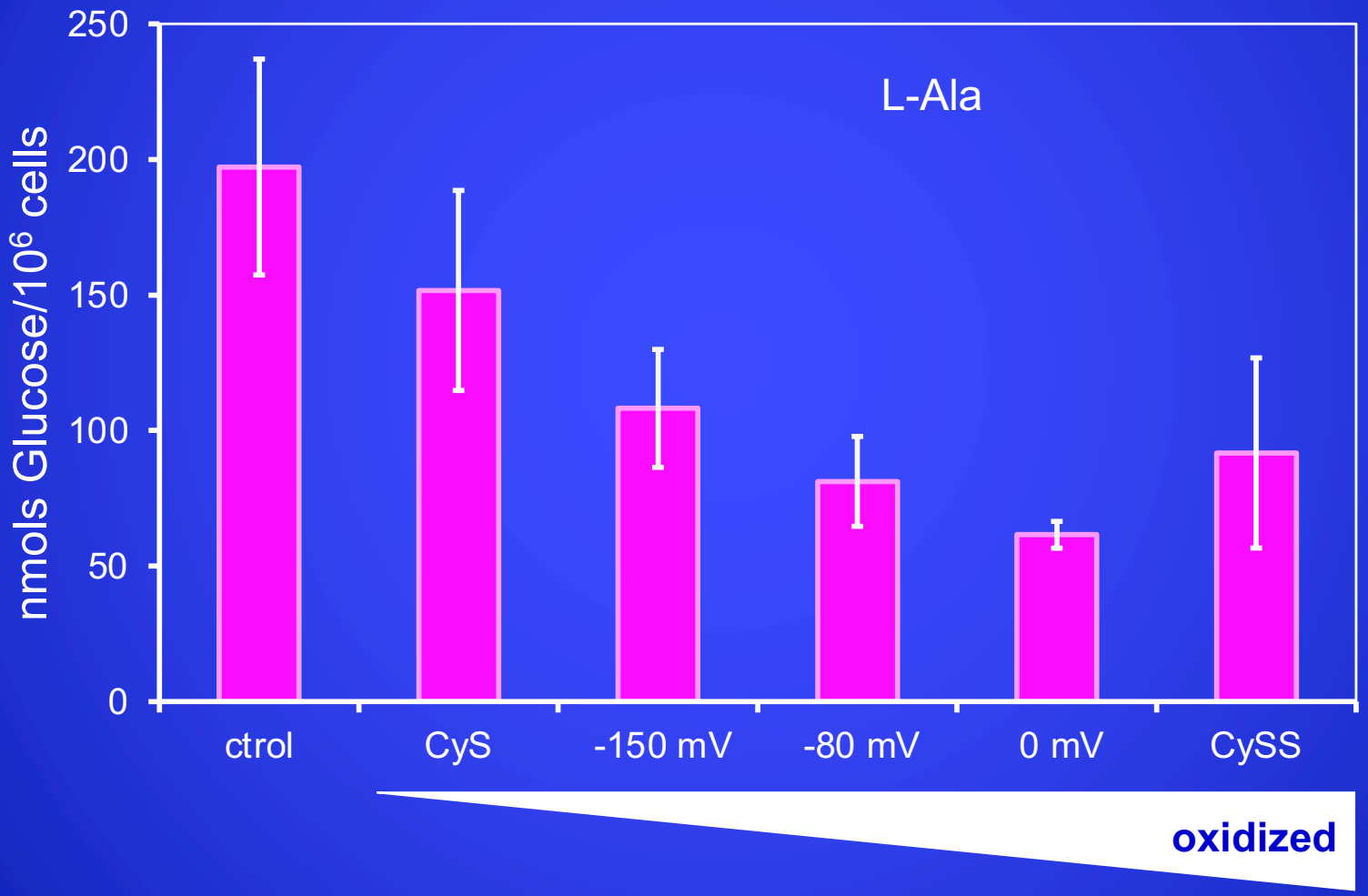
	Control	SH	SS	-150mV	-80mV	0 mV
Series1	2556	690.2	2202.4	642.2	1126.7	1863.2

Tova Meshulam

Yes External Redox Can Control Cellular ROS Production.

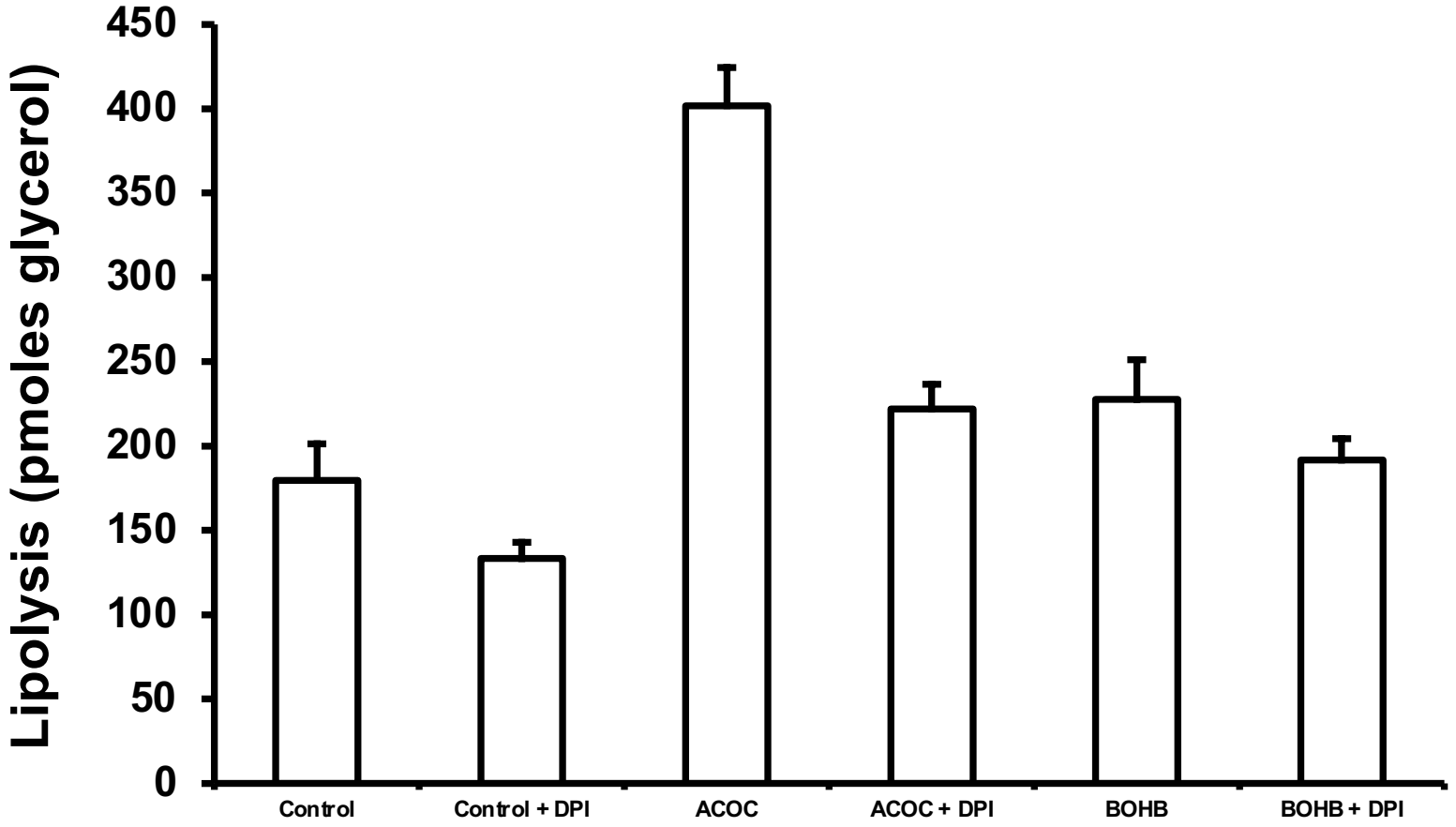
Do Changes in Redox or ROS Alter Function?

Hepatic Glucose Production



Laura Nocito, unpublished

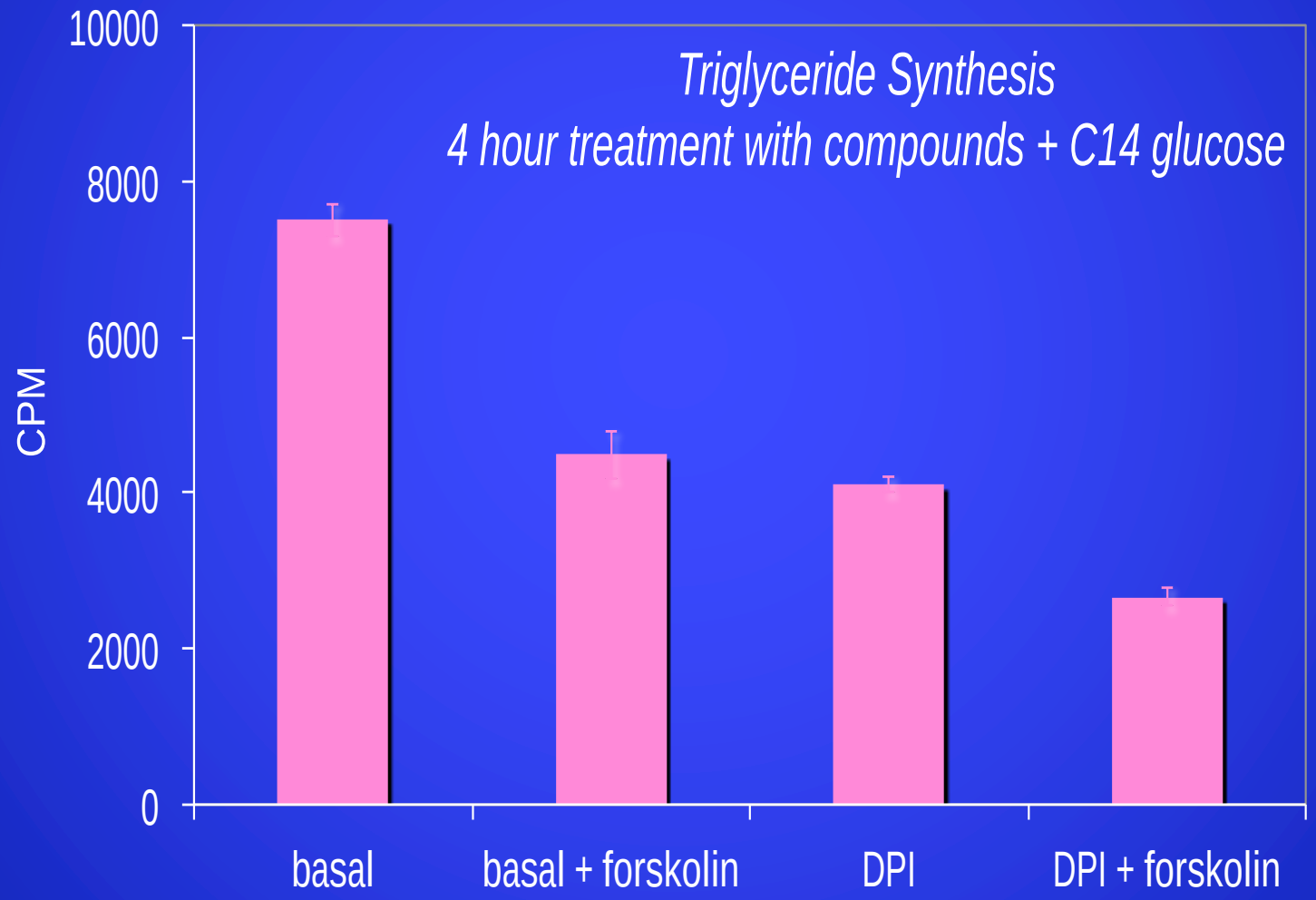
Adipocyte Lipolysis



Oxidized

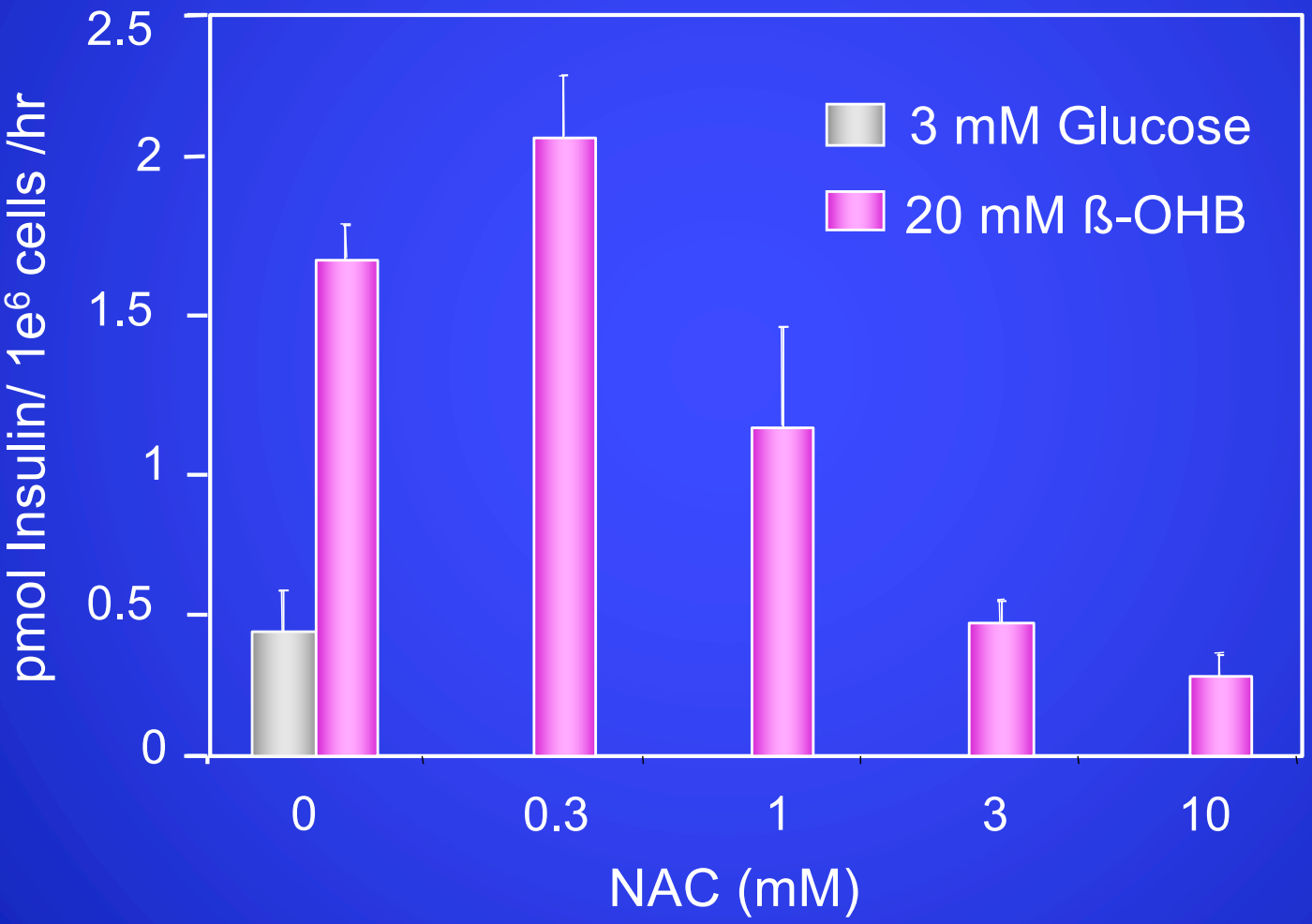
Tova Meshulam. unpublished

ROS Required for Lipid Synthesis



Krawczyk et al, 2012 PLoSone

Effect of ß-OHB and ROS Removal on Insulin Secretion from INS-1 Cells



ß-OHB + NAD = Acoc + NADH

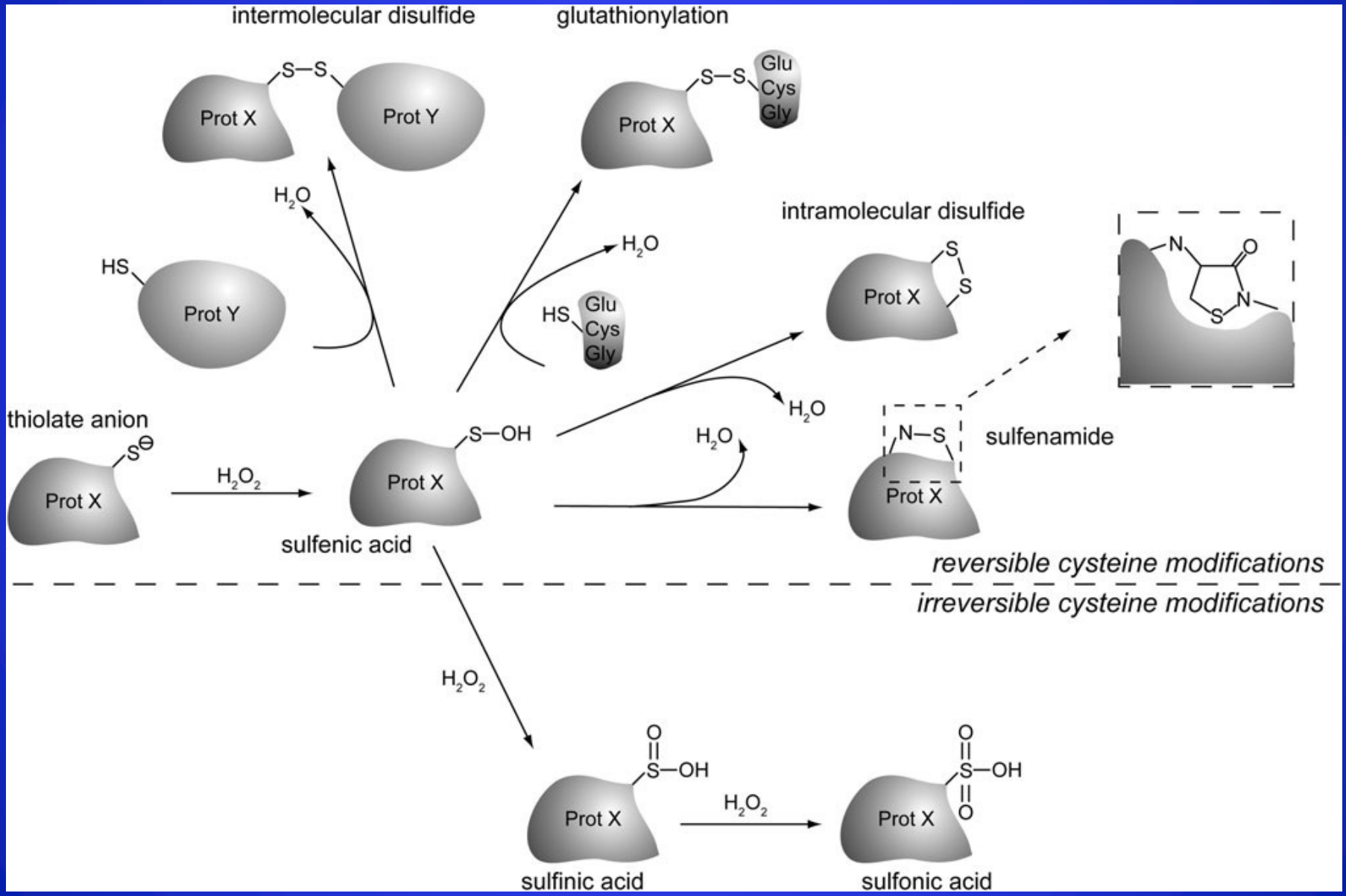
Saadeh et al, PLOSone 2012

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.

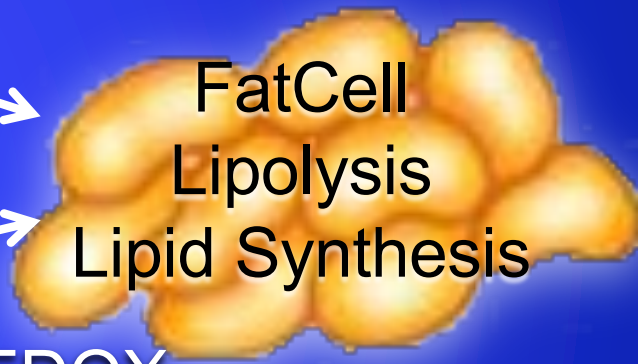
Trends Endocrinol Metab. 2012 Mar;23(3):142-53. Epub 2012 Feb 2. Fisher-Wellman KH, **Neufer PD**.

Cysteines are Modified by ROS

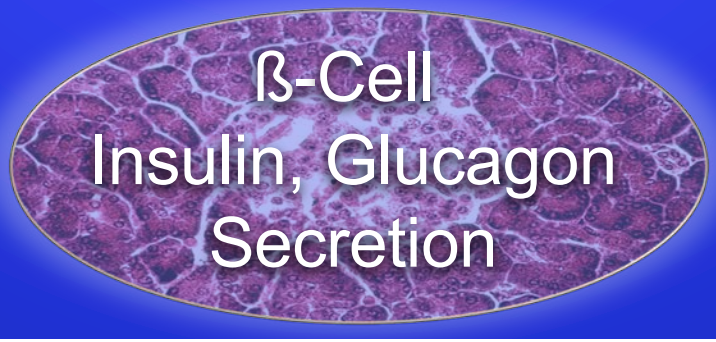


Bachschmid FASEB J. 28: (2014)

Hunger, Satiety



Circulating Master Metabolic REDOX
Regulators (L/P, ß/A, SH/SS)

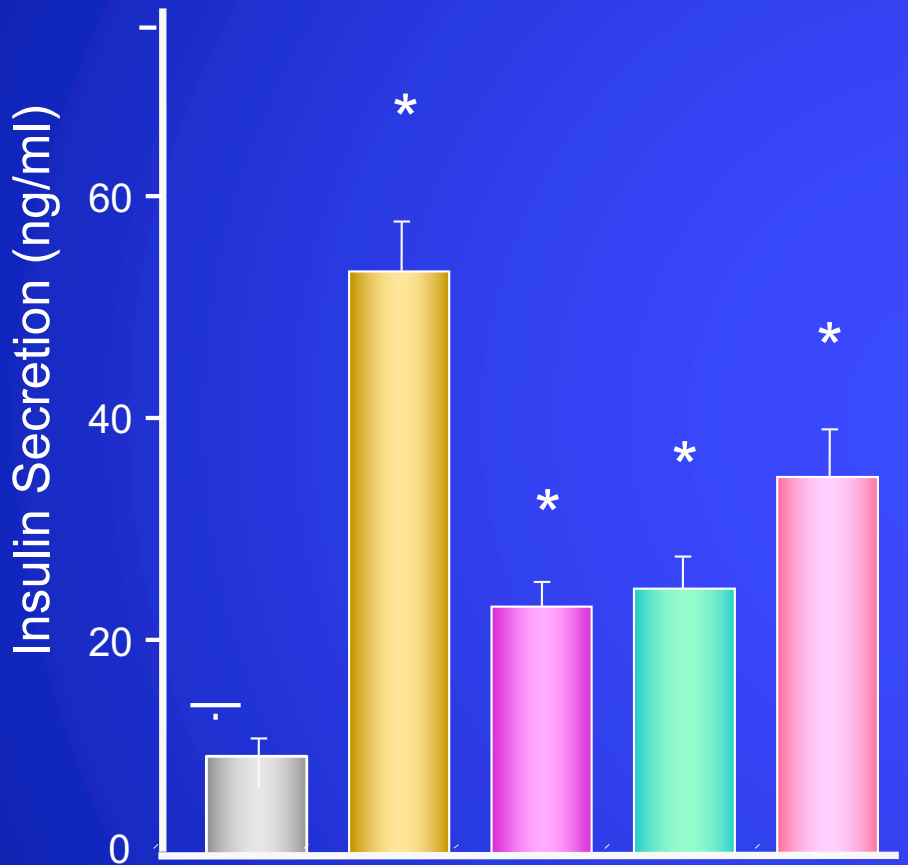


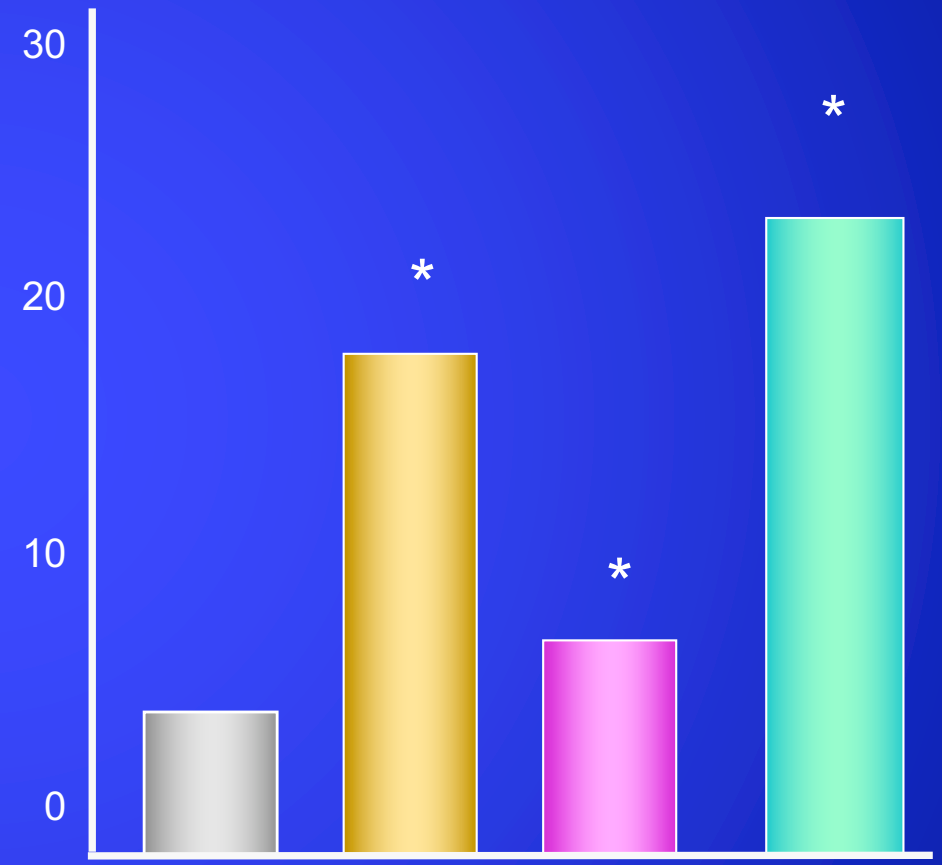
Summary and Implications

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

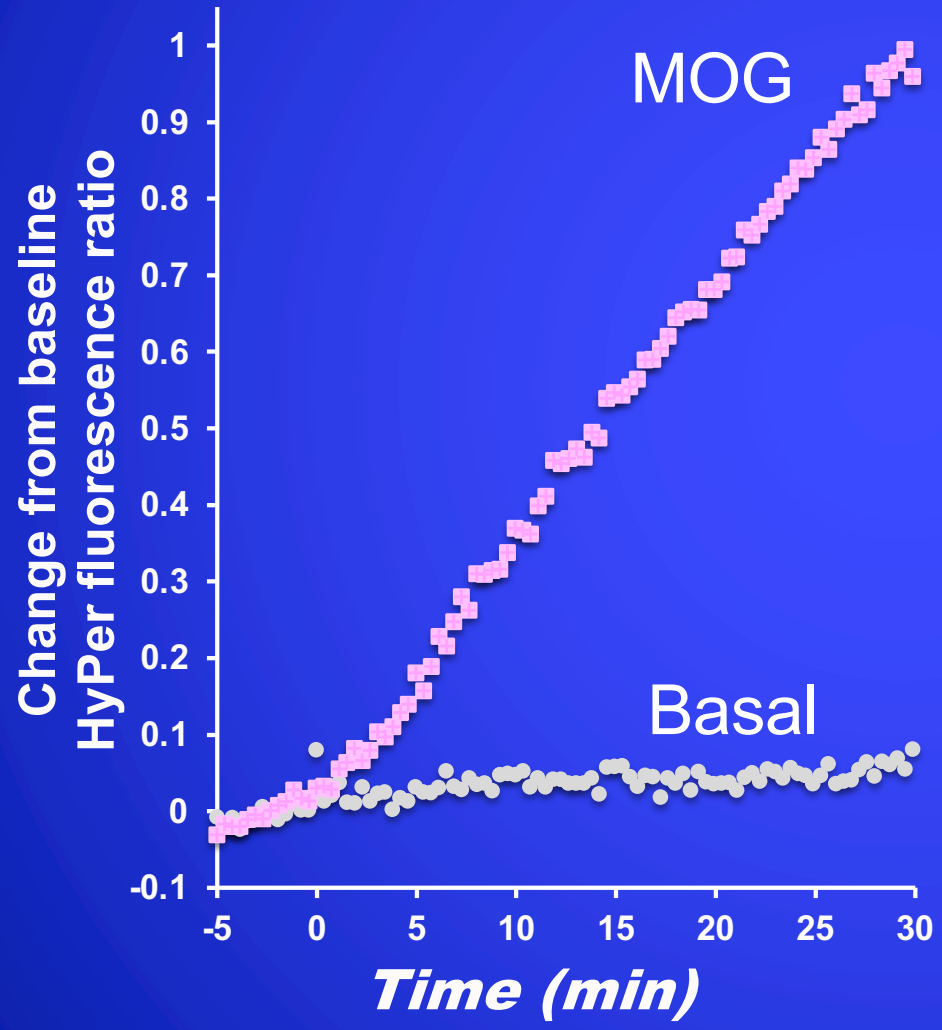
H_2O_2 Increases Insulin Secretion in INS-1 Cells

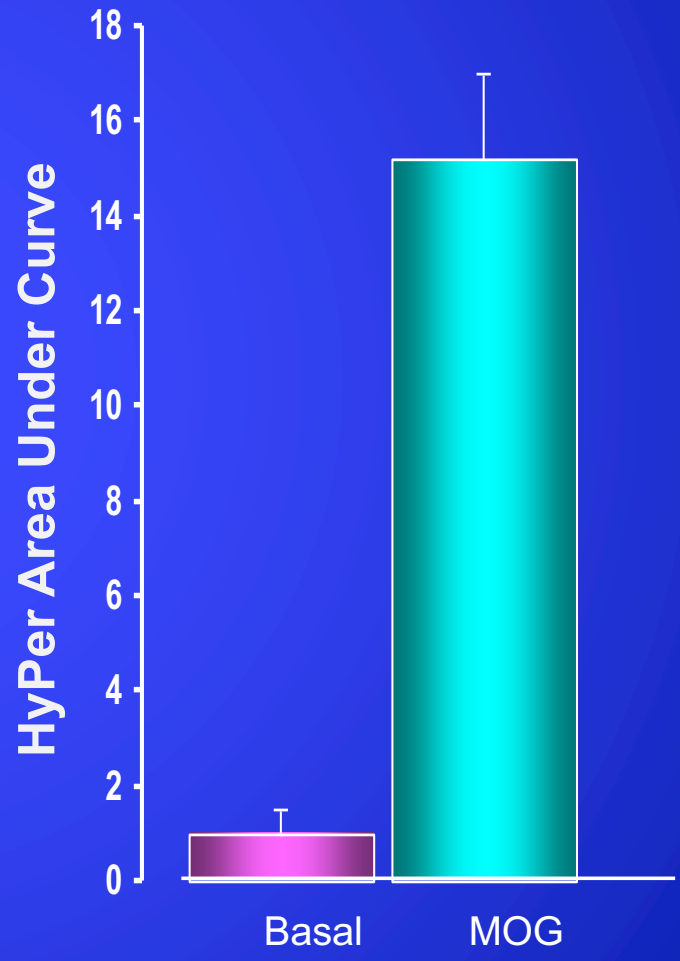




Pi et al, Diabetes 2007

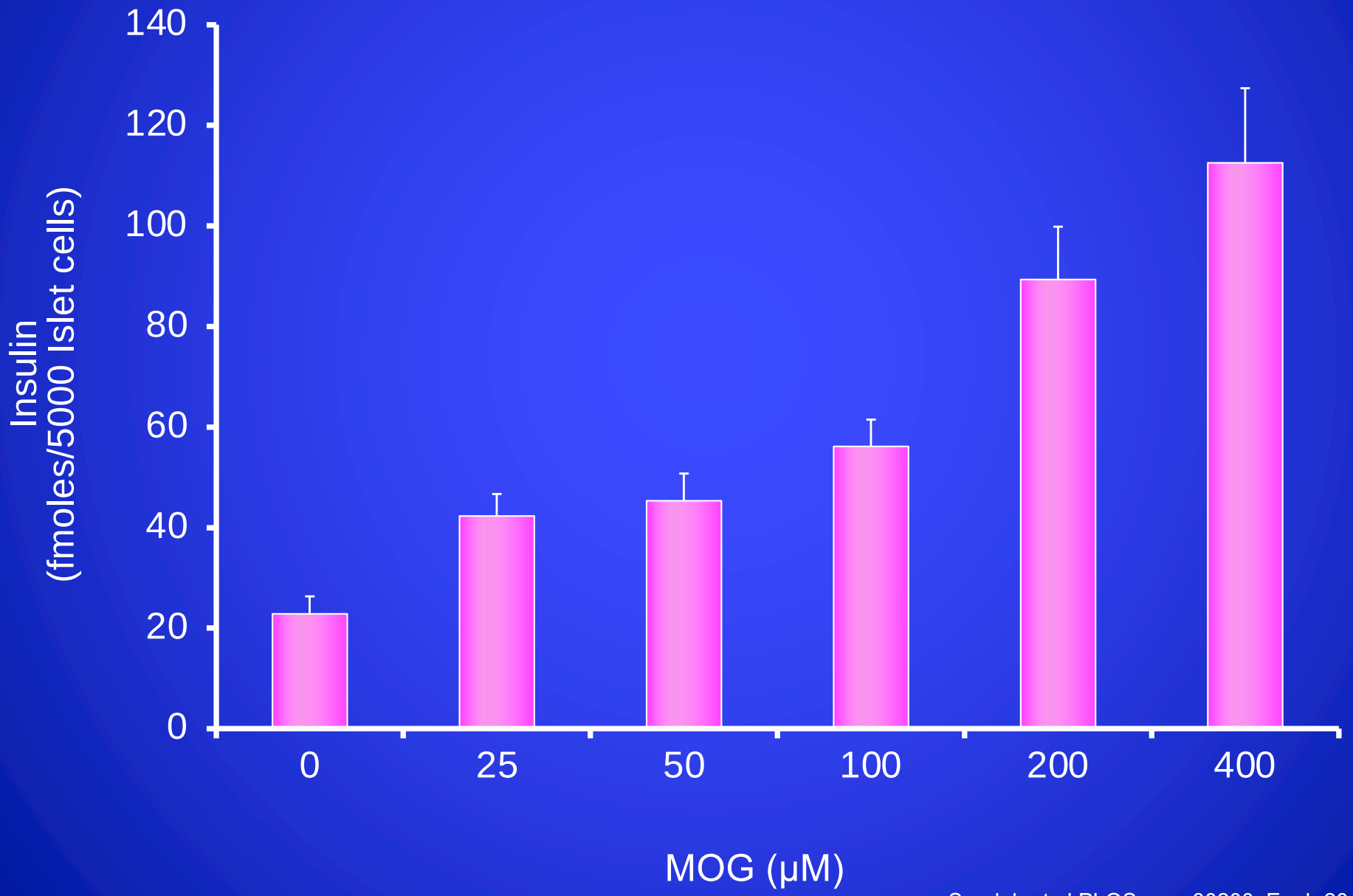
ROS is Generated by MOG





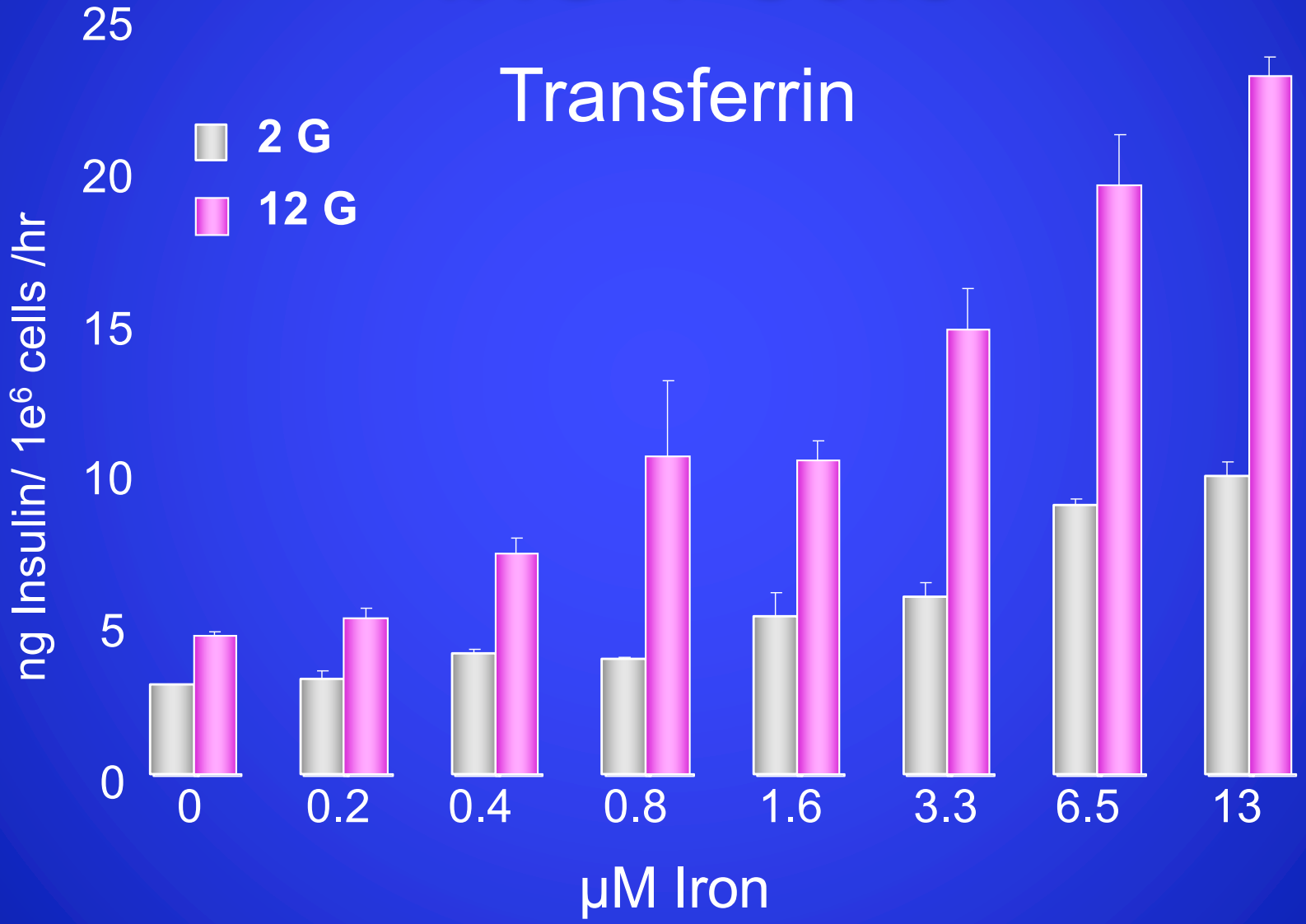
Saadeh et al PLOSone e30200. Epub 2012 Jan 17

MOG Stimulates Basal Secretion



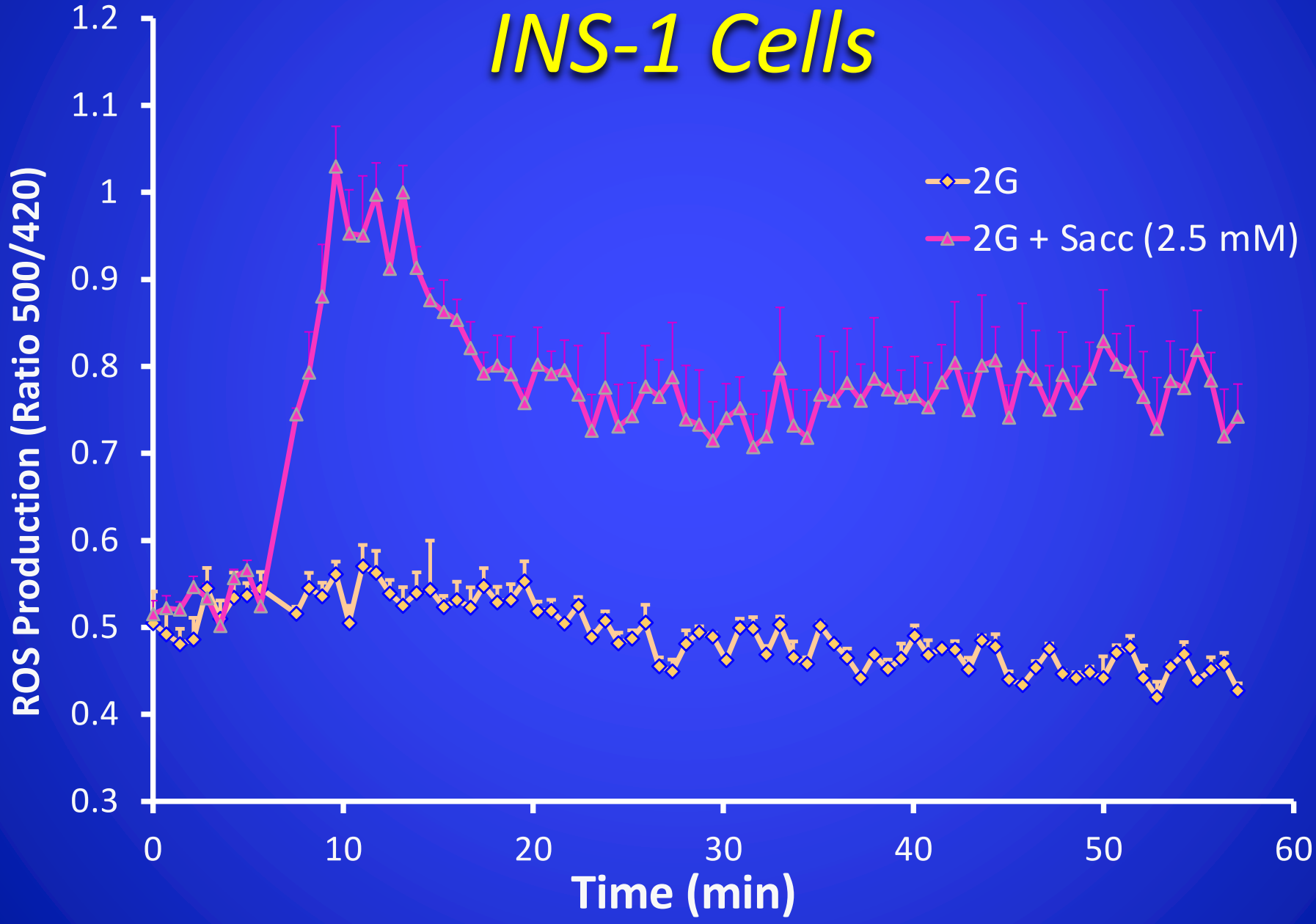
Saadeh et al PLOSone e30200. Epub 2012 Jan 17

Iron Induces Insulin Secretion in INS-1 Cells



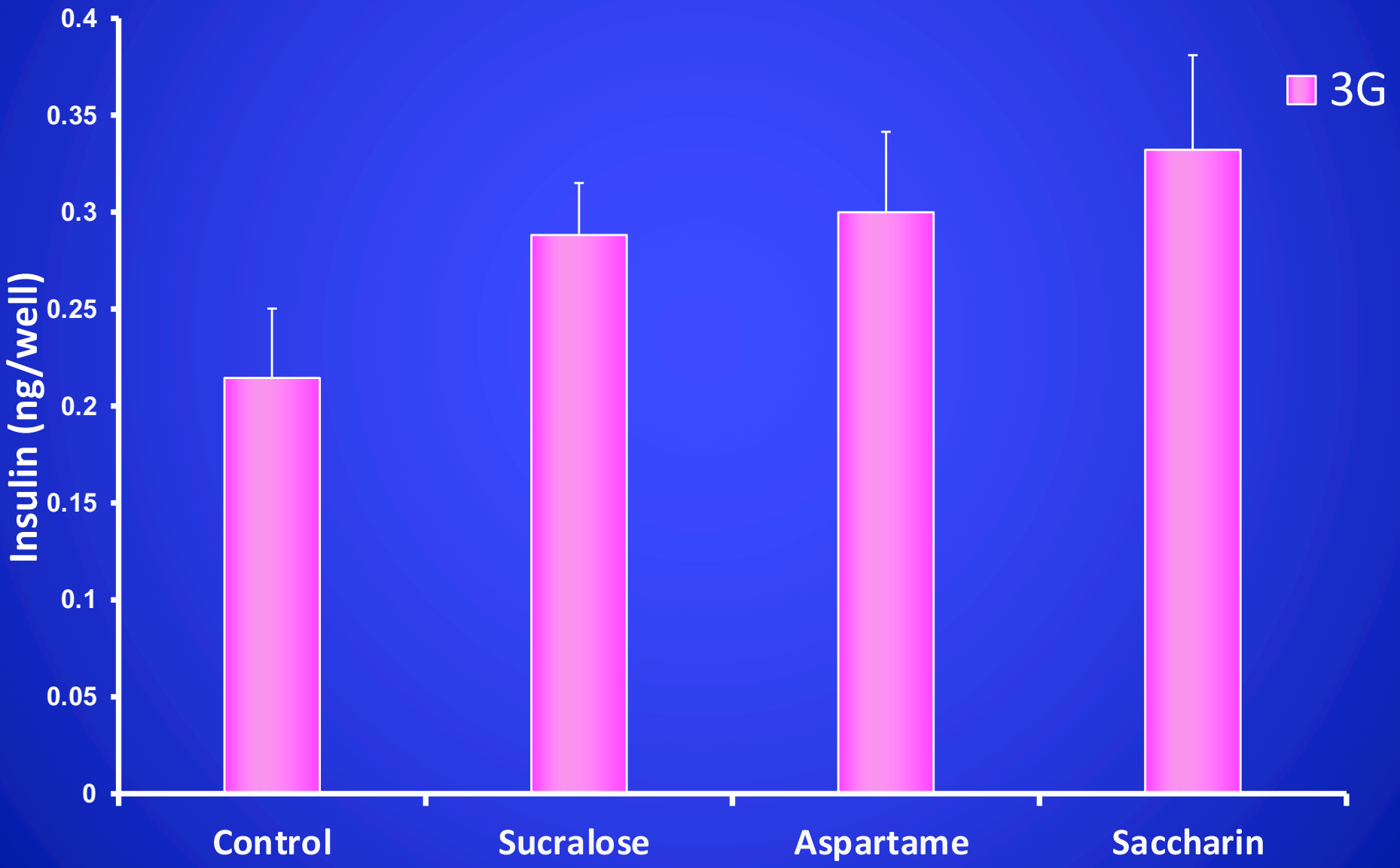
Ferrante, Deeney. Unpublished.

Effect of Saccharin on ROS in INS-1 Cells



Ali Al-Saleh Thesis, unpublished

Artificial Sweeteners Affect Insulin Secretion in Dissociated Rat Islets

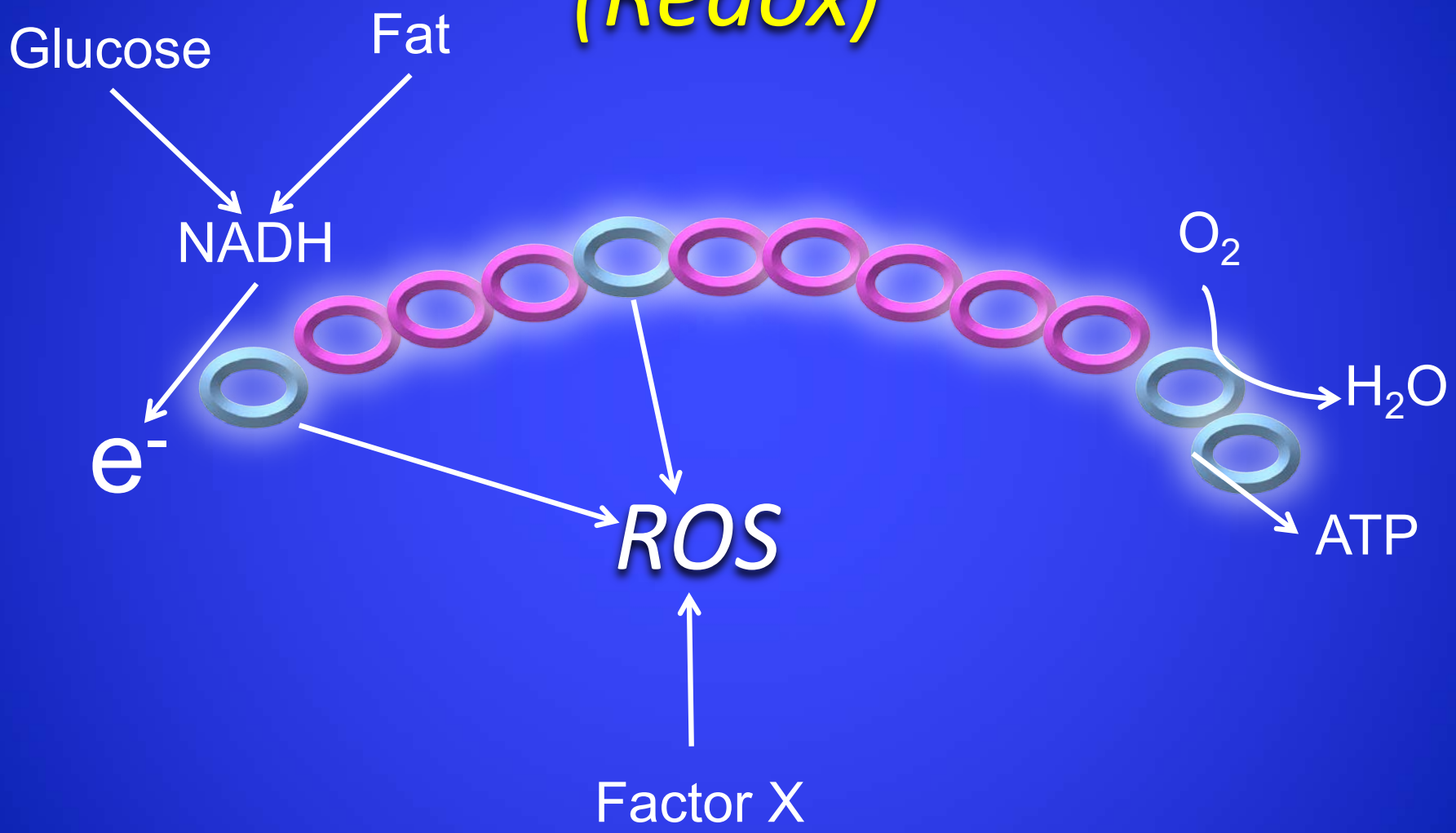


Ali Al-Saleh Thesis, unpublished

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

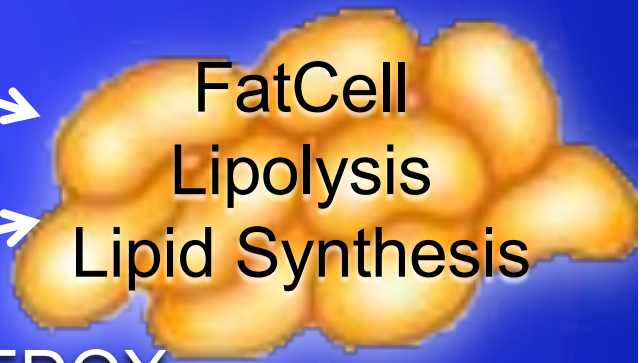
- MOG, a lipid food emulsifier and preservative
- Saccharin, an artificial sweetener
- Iron, an essential mineral
- Bisphenol A, contained in plastics

ROS are Produced at High NADH (Redox)



False Signals

Hunger, Satiety



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Regulators (L/P, ß/A, SH/SS)

Thank You