The Redox Communication Network as a Master Regulator of Metabolism

International Summer Institute on Network Physiology-2019

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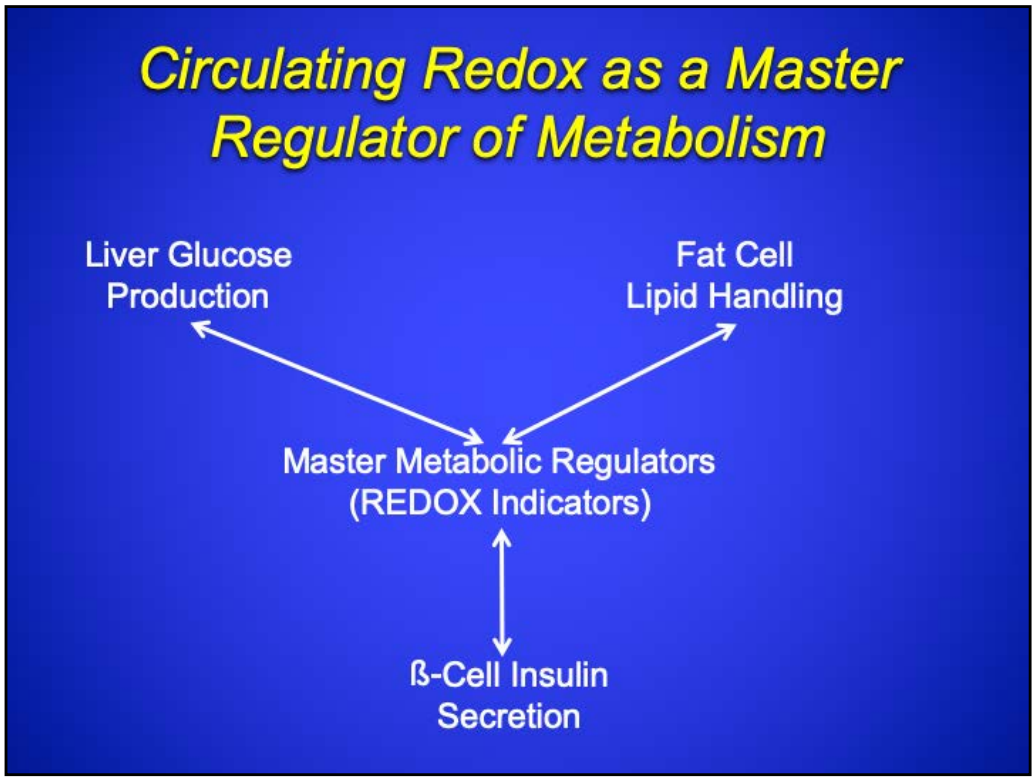
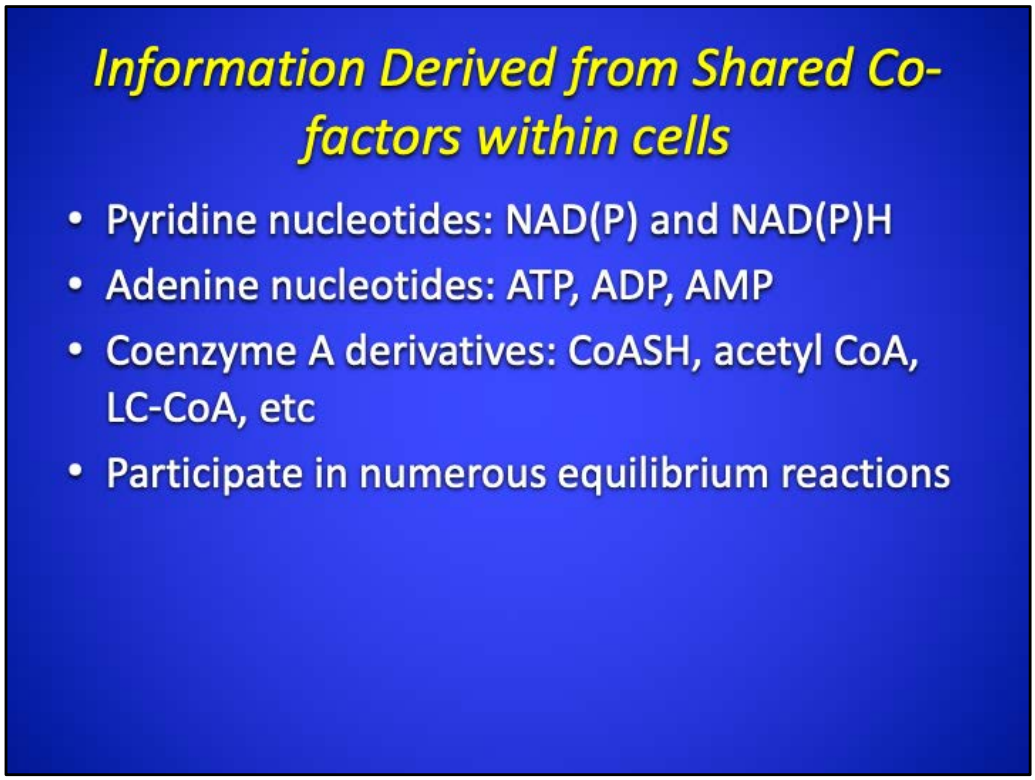


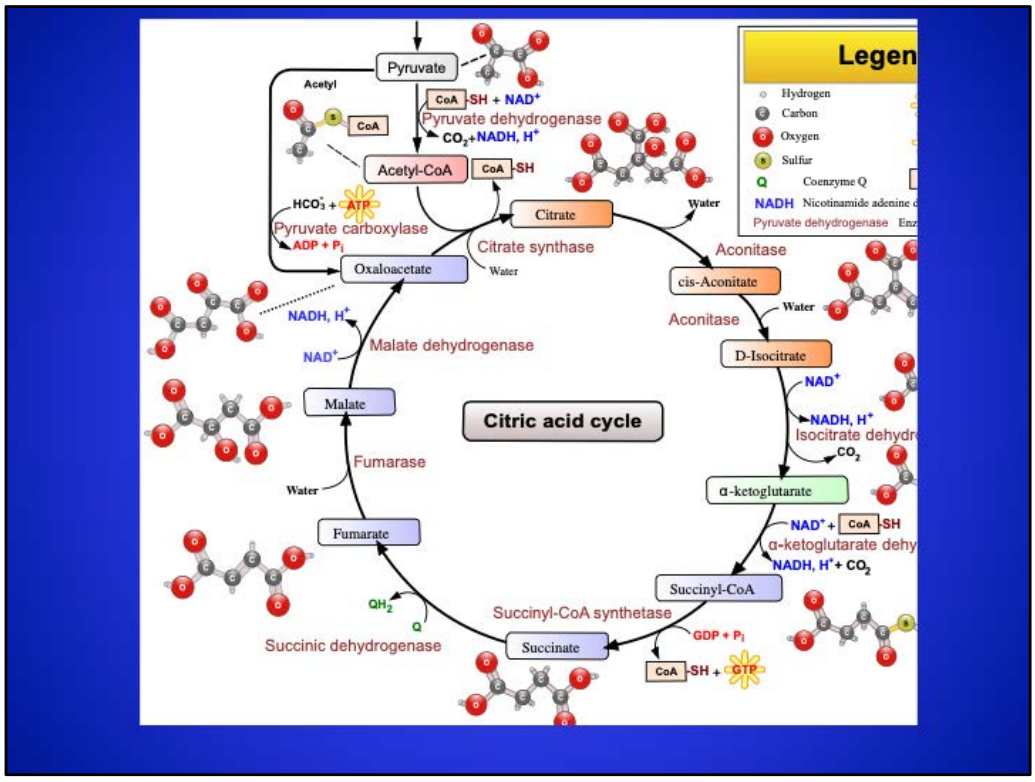
Model of metabolic master regulation. It is important that all tissues in the body know the metabolic status at all times.

How is Energy State Communicated?

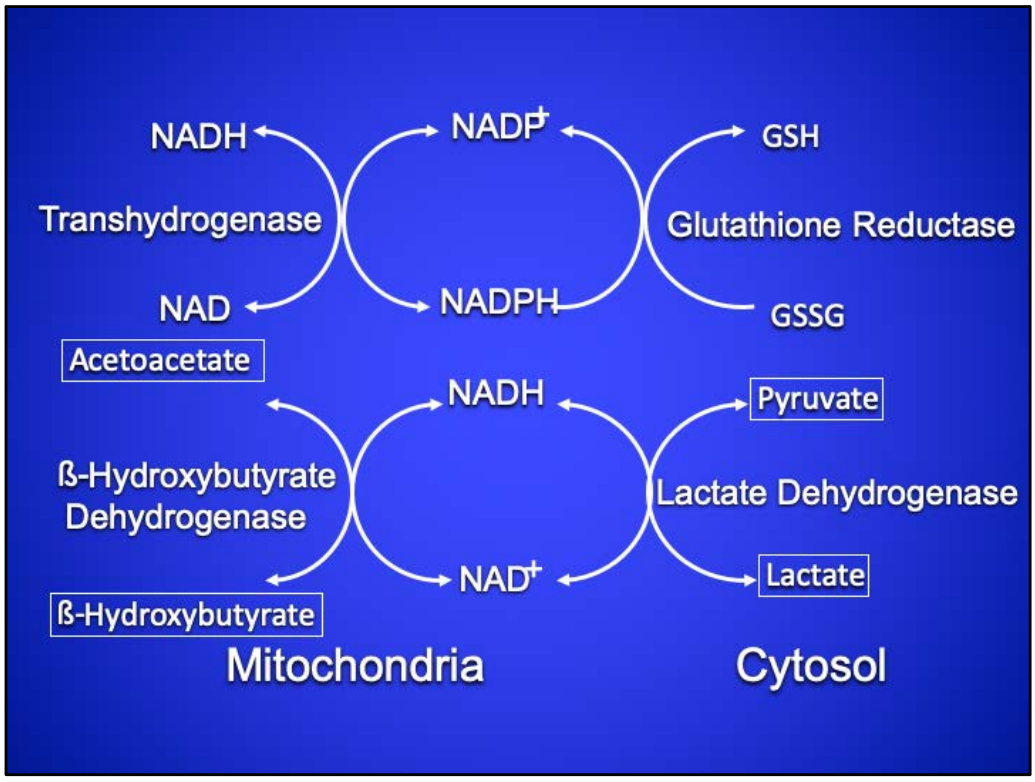
- Information from shared co-factors: pyridine nucleotides, adenine nucleotides, CoA esters and ROS
- And Mitochondrial metabolism
- Via communication to circulating metabolites



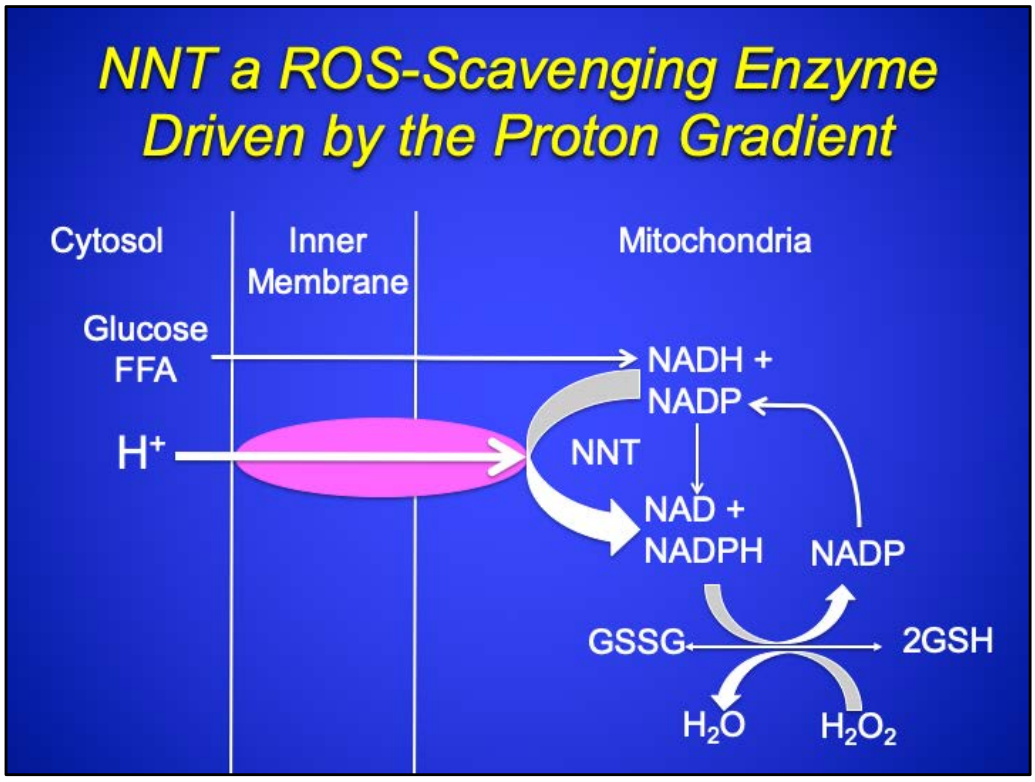
The common currency for enzyme reactions



The citric acid cycle includes multiple reactions that share 18 common co-actors.



Several examples of reactions using shared cofactors.



Nicotinamide Nucleotide Transhydrogenase (NNT) provides an important link between pyridine nucleotide generation by glucose and FFA, reactive oxygen species (ROS) and the thiol redox state (eg, GSH). ROS is a shorthand for all reactive oxygen species including peroxide. Tools are not available to measure the variety of ROS in real time, hence the lack of specificity.

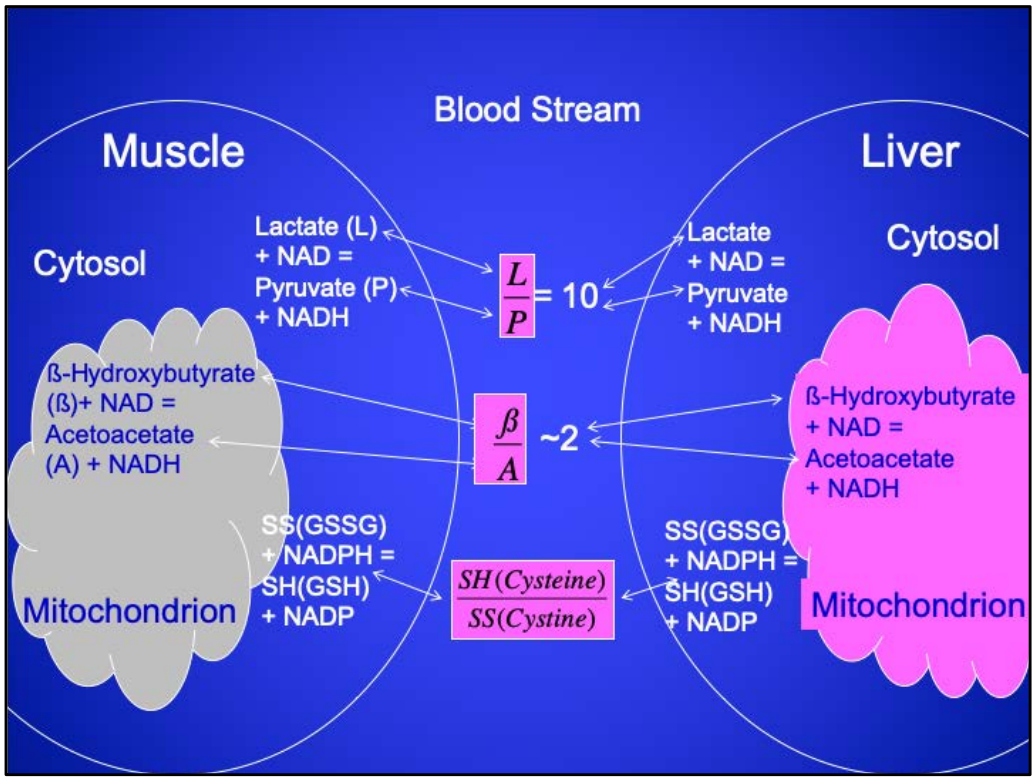
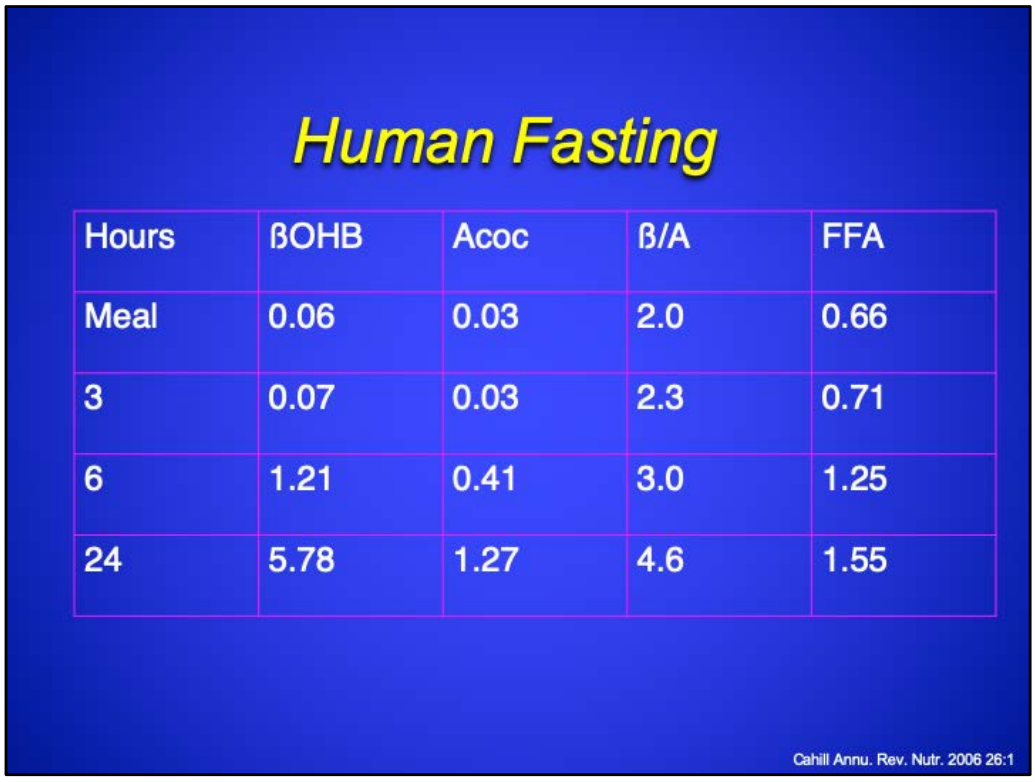
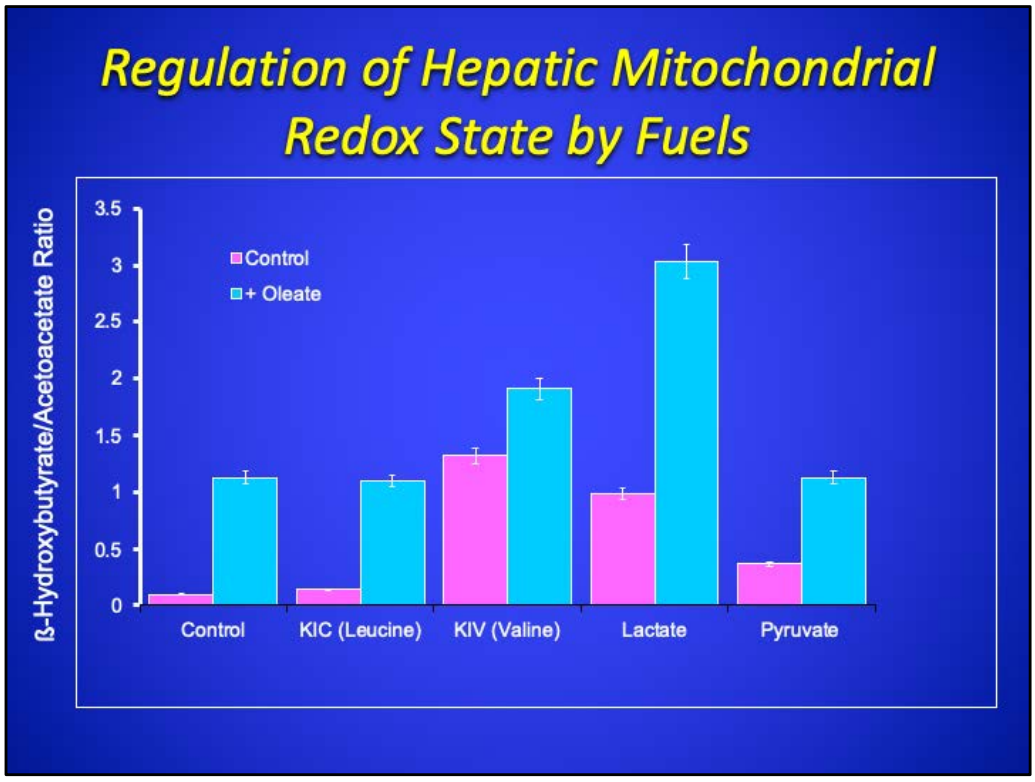


Illustration of how the intracellular redox state is communicated to the blood stream to regulate the redox network. Specific substrate-product pairs (like pyruvate and lactate or acetoacetate and ß-hydroxybutyrate) are in equilibrium with NAD and NADH in their respective compartments. In addition, there are membrane transporters that allow these metabolites to enter and leave the cell rapidly, according to their concentration gradient, moving from higher to lower concentration compartments.

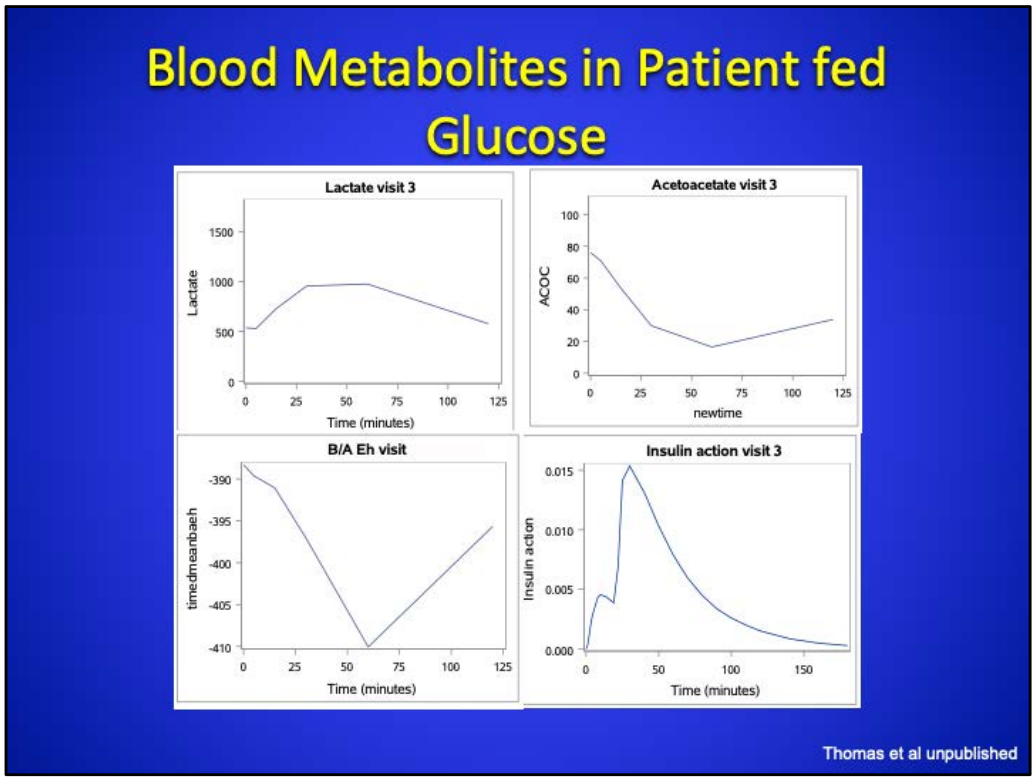
When does Redox Change?



The ketones, acetoacetate and ß-hydroxybutyrate, are formed from fat so their total amount correlates with the circulating FFA. However, the ratio can be high or low depending on the state of fuel supply.



These increases in redox in response to fuels occur within hepatocytes and can be communicated throughout the organism through the metabolites that circulate: ß-hydroxybutyrate and acetoacetate. Note that only the FFA oleate can form ketones but the addition of other fuels that do not form ketones can change their ratio.

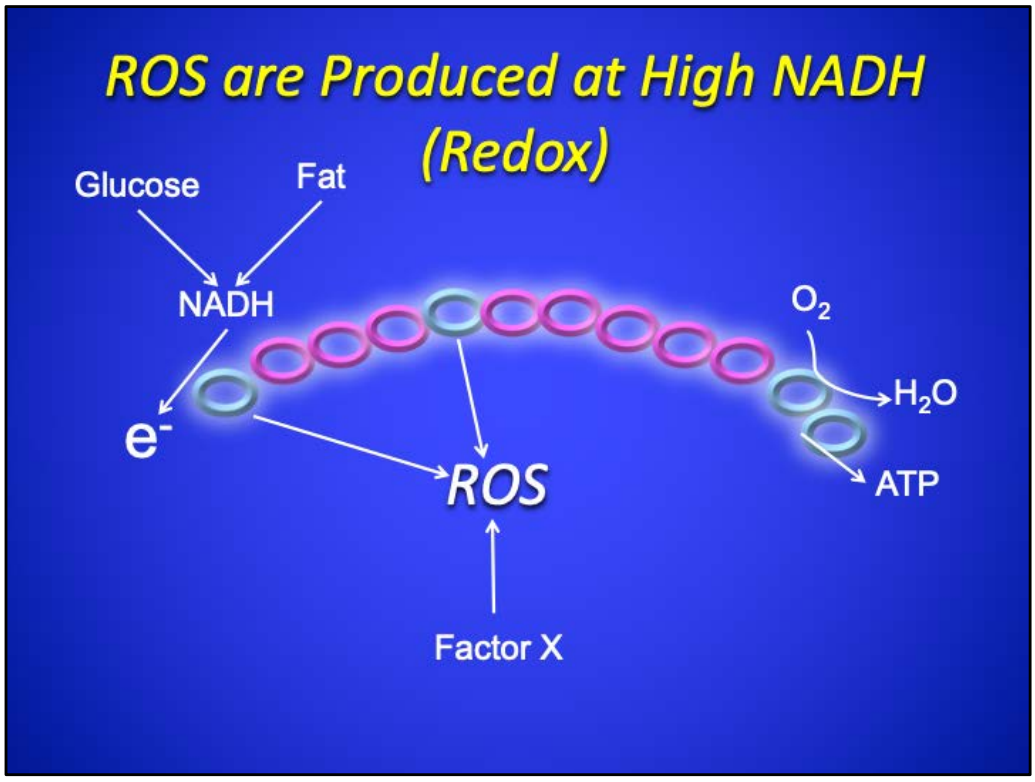


These are changes in blood redox metabolites and insulin action in response to glucose feeding are readily measured.. This is an illustration of data obtained from a single patient from our clinic. Lactate rises because excess glucose is metabolized to lactate. Acetoacete falls because glucose rather than FFA is being used as energy source and the B/A ratio decreases transiently as glucose is being metabolized.

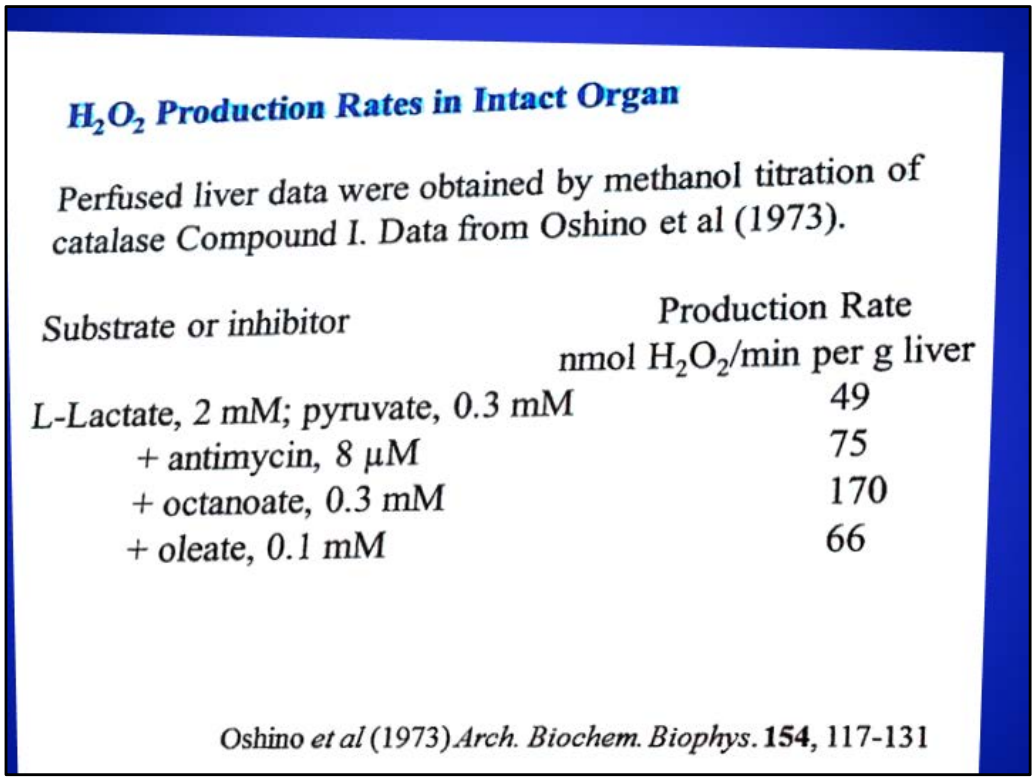
Circulating Redox Changes

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

How do Redox Changes Induce ROS Changes?



ROS is produced in the mitochondrial electron transport chain and is a signal of plenty. This occurs when substrate availability is high (high NADH) but ATP needs have been fulfilled. Factor X implies that external environmental influences can also lead to ROS generation.



H_2O_2 Production Rates in Intact Organ

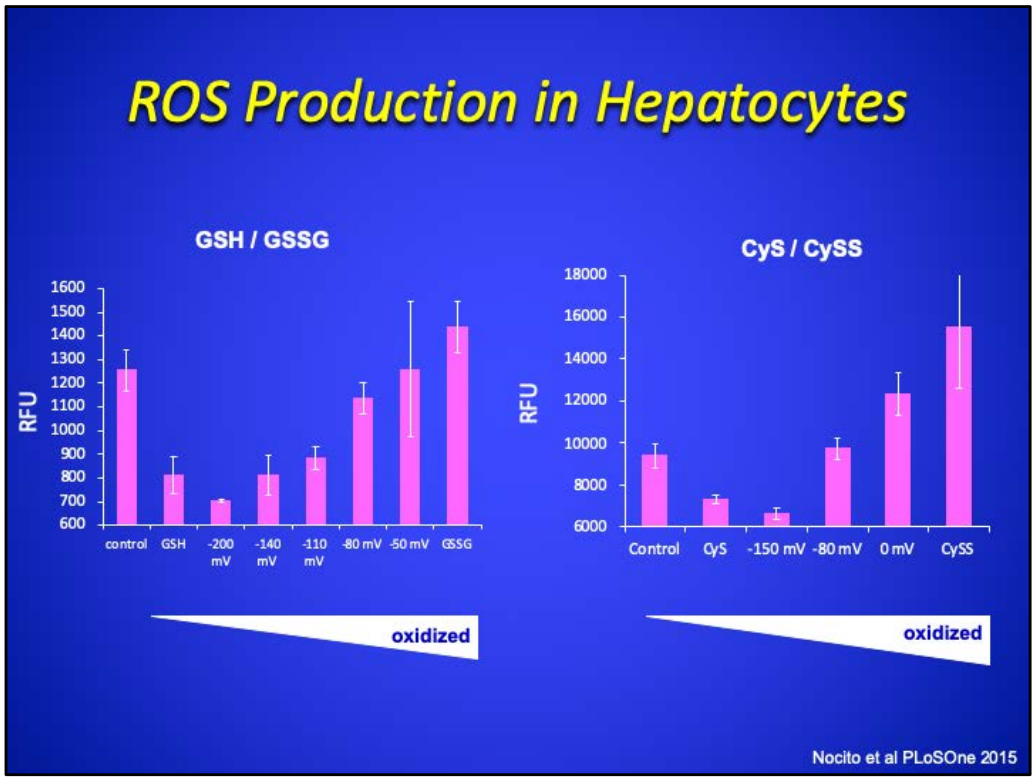
Perfused liver data were obtained by methanol titration of catalase Compound I. Data from Oshino et al (1973).

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

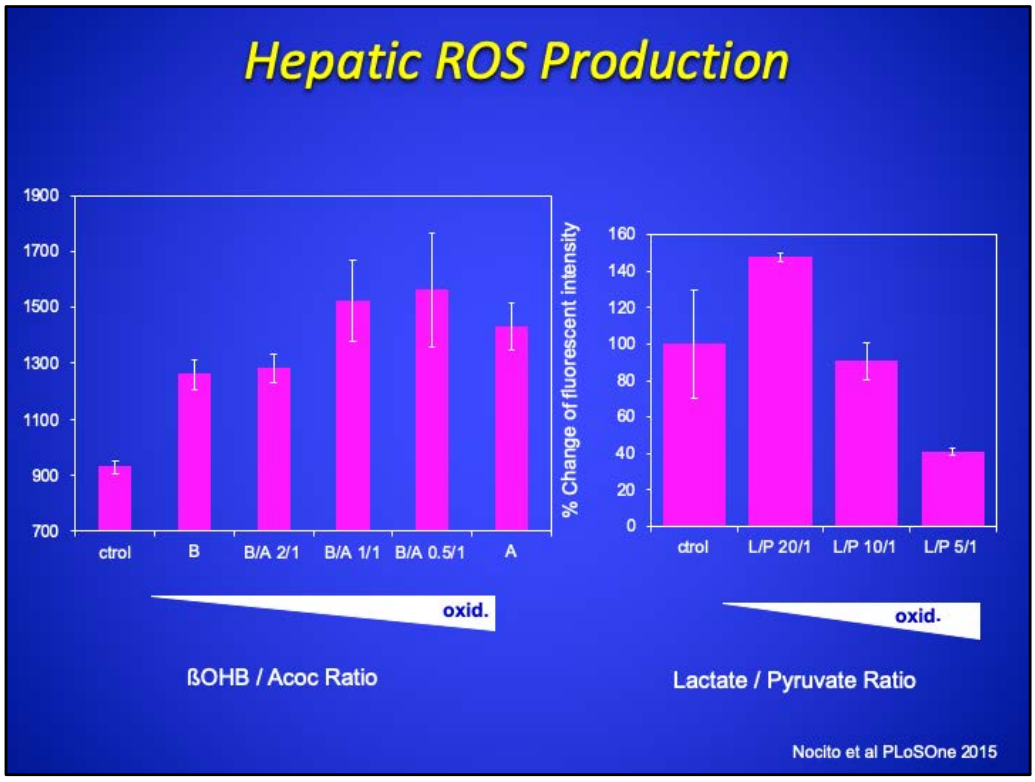
Oshino *et al* (1973) *Arch. Biochem. Biophys.* **154**, 117-131

This old data illustrates that excess fuel, lactate plus pyruvate and FFA stimulate ROS production. Antimycin A inhibits the electron transport chain after the ROS generating step, forcing entering electrons to form ROS.

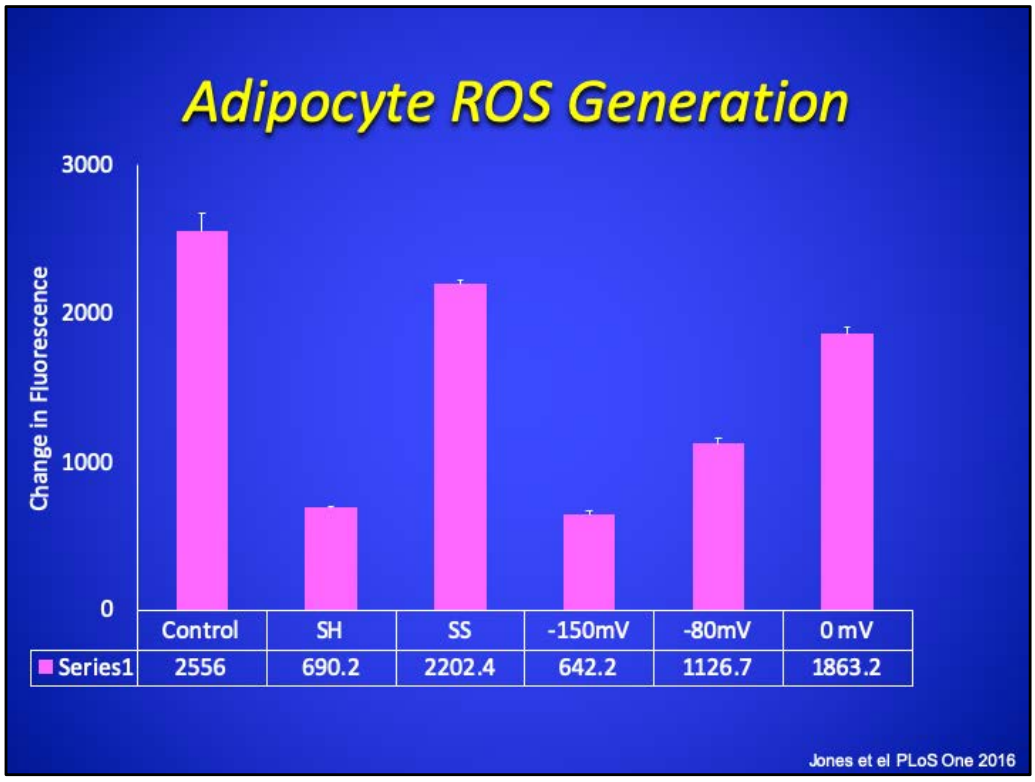
Intracellular Fuels Impact Intracellular Redox.
How do External Changes in Redox Affect Intracellular Redox and Function?



Changes in ROS production occur in response to extracellular thiol couples over a physiological range of electrochemical potentials.

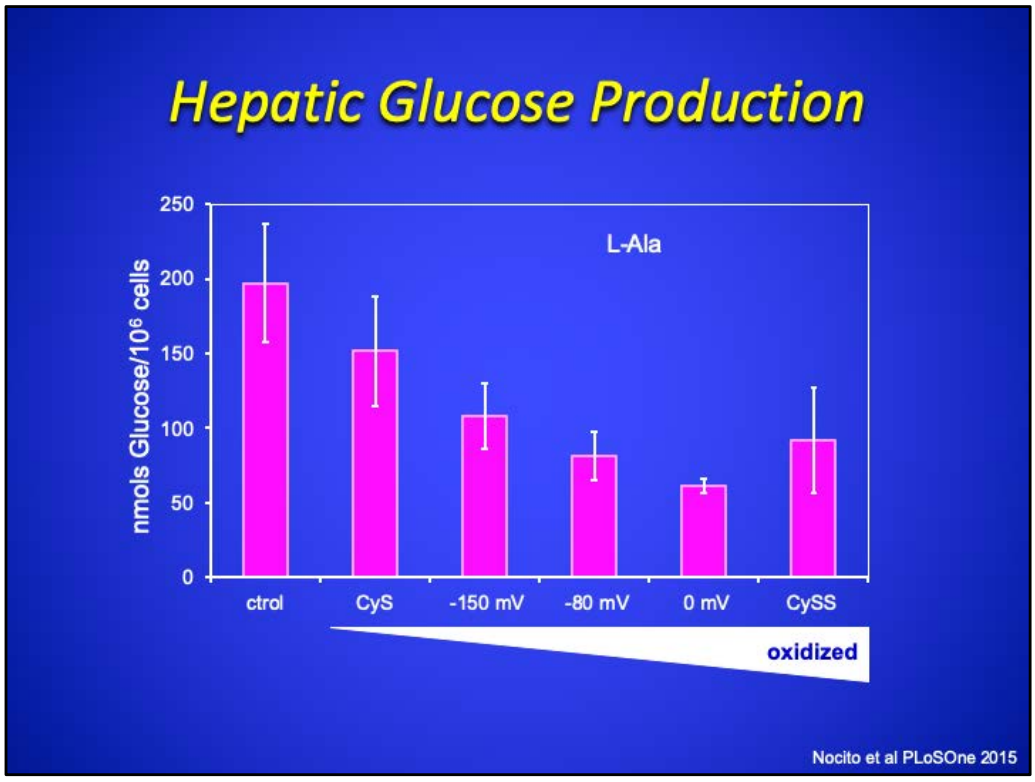


Changes in ROS production occur in response to pyridine nucleotide couples over a physiological range of electrochemical potentials also. Note that changing the cytosolic redox state has the opposite effect to the thiol and mitochondrial redox states, probably due to the abiity of pyruvate to enter the mitochondria and increase NADH.

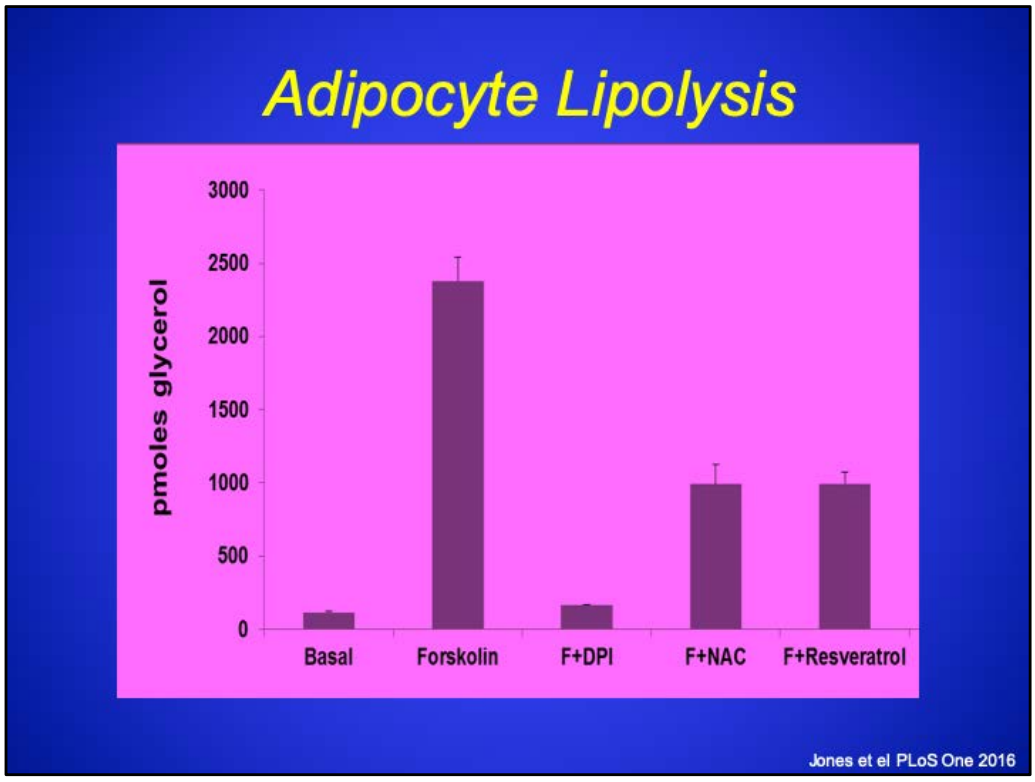


Similar responses to variations in extracellular redox potential occur in many cell types including fat cells.

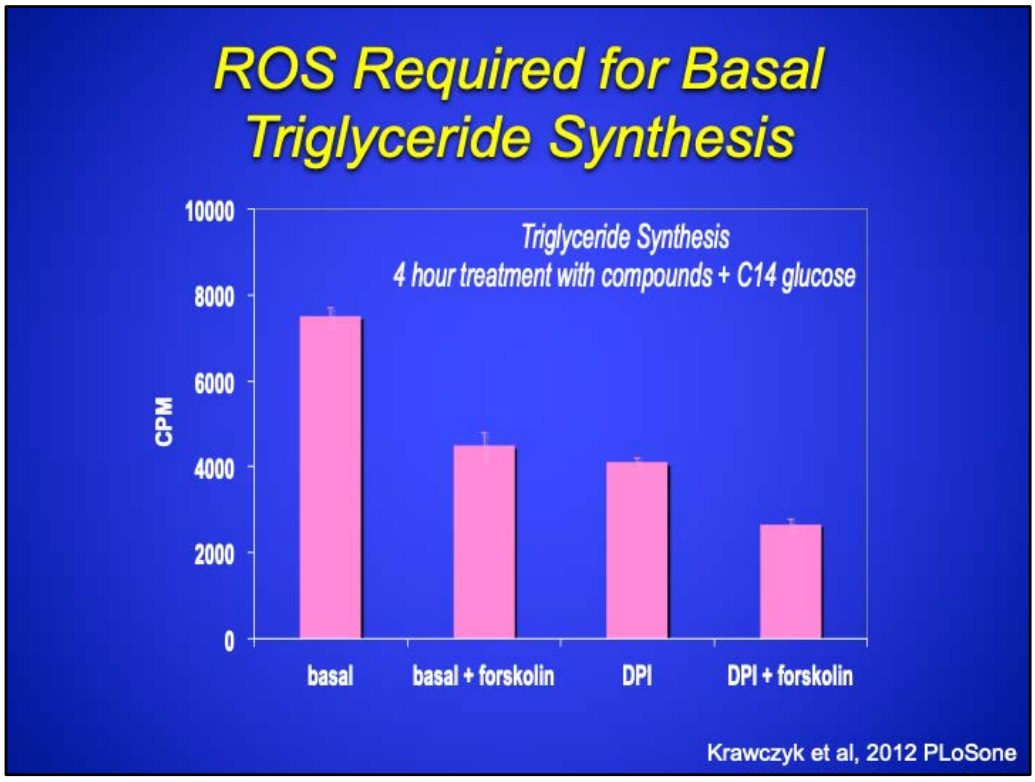
Yes External Redox Can Impact Cellular ROS Production.
Do Changes in Redox or ROS Alter Function?



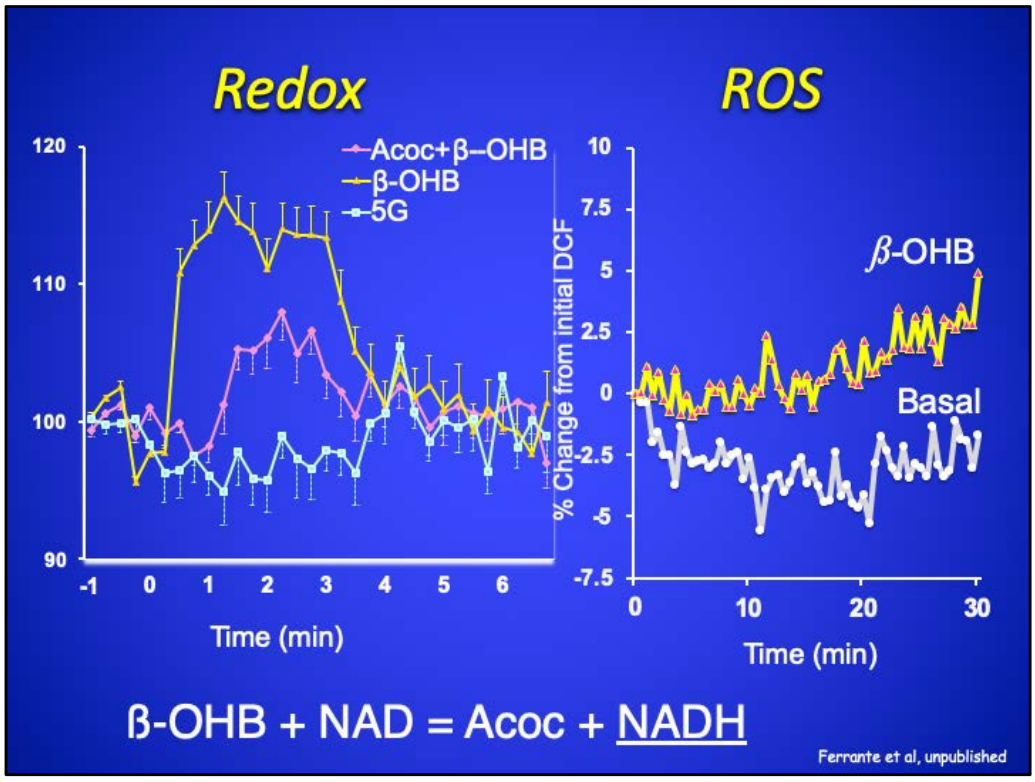
Changes in gluconeogenesis occur in response to thiol couples over a physiological range of electrochemical potentials. Since high ROS that accompanies the more oxidized state is a signal of fuel excess, it is logical that glucose production by the liver should be inhibited.



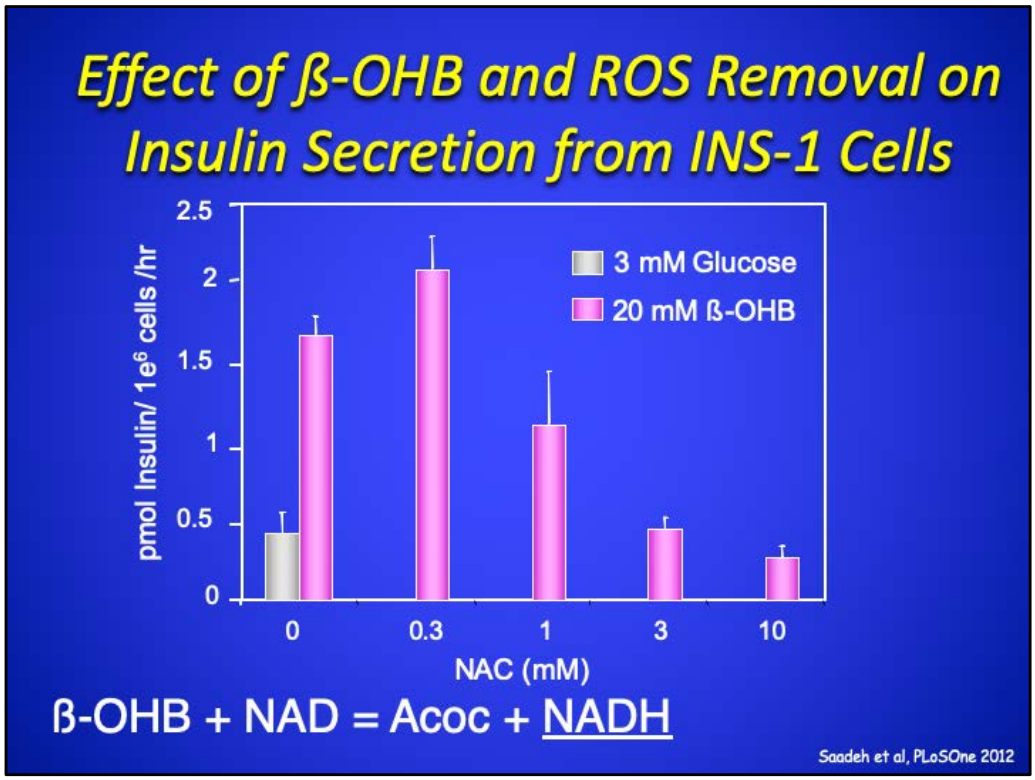
Lipolysis is stimulated by the drug forskolin. Addition of DPI, NAC or resveratrol, ROS scavengers, inhibits lipolysis.



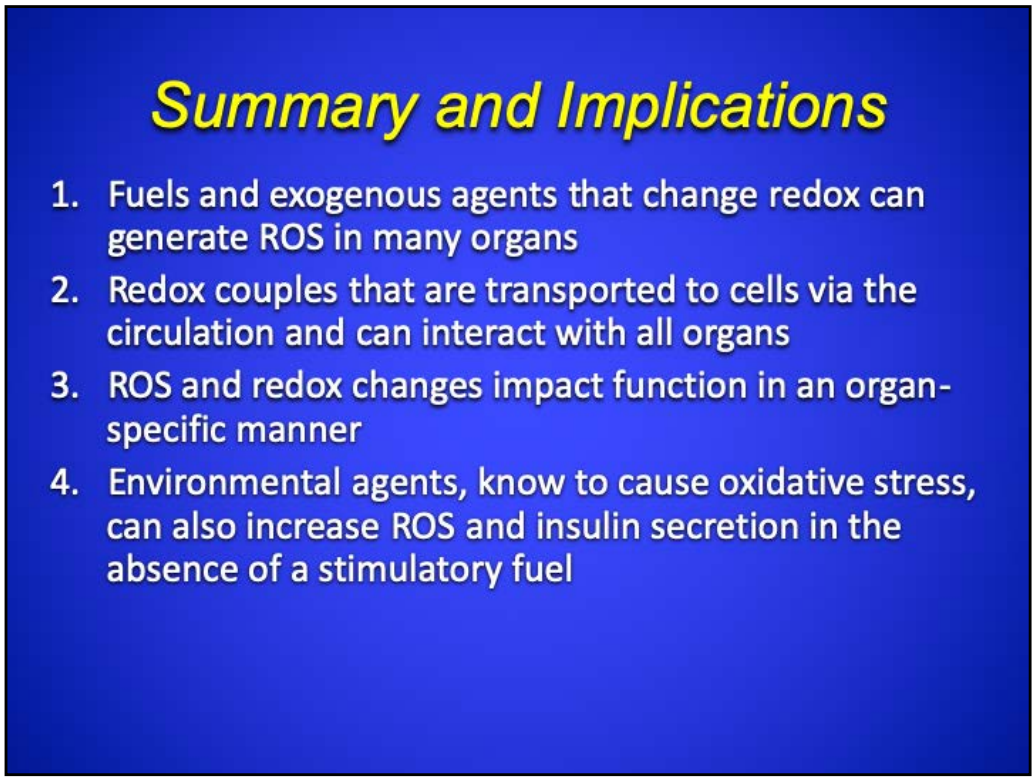
Triglyceride synthesis occurs rapidly in adipocytes. Forskolin that stimulates lipolysis diminishes triglyceride synthesis. ROS removal with the ROS scavenger, DPI inhibits lipid synthesis in fat cells whose main function is to store fat by this pathway.



Circulating metabolites like ß-OHB and Acetoacetate can enter cells and cause changes in redox and ROS in ß-cells.



A consequence of the entry of circulating metabolites like ß-OHB is stimulation of insulin secretion in ß-cells. Scavenging ROS with N-acetylcysteine inhibits insulin secretion.



Exogenous agents can mimic the effect of fuels.

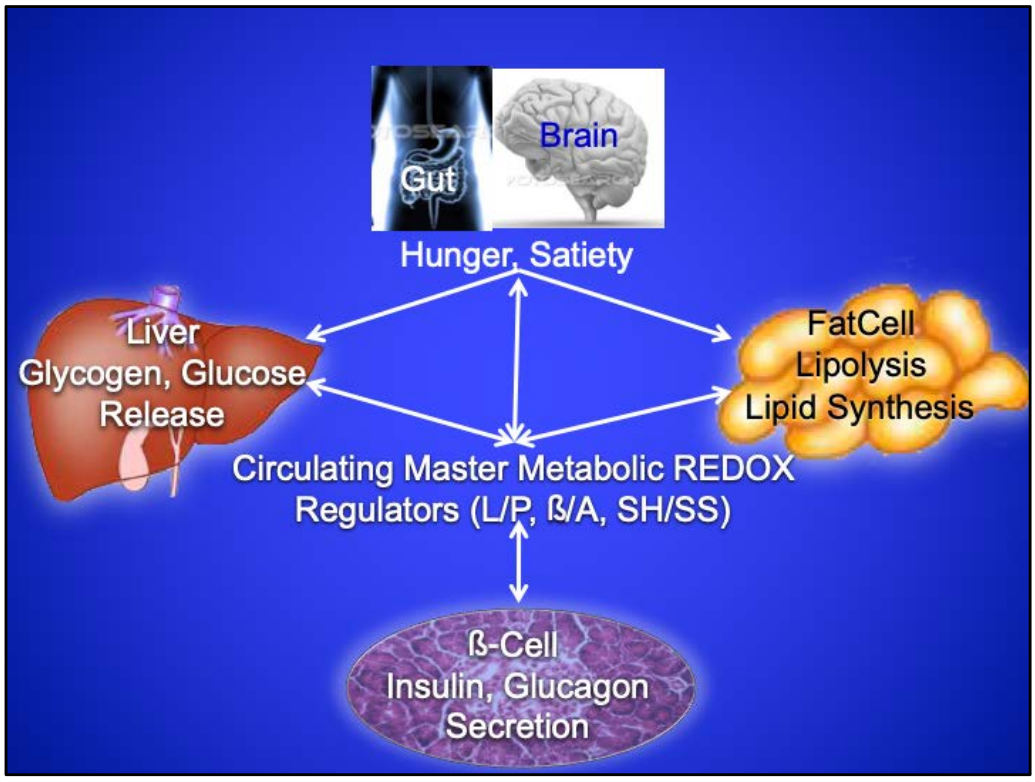
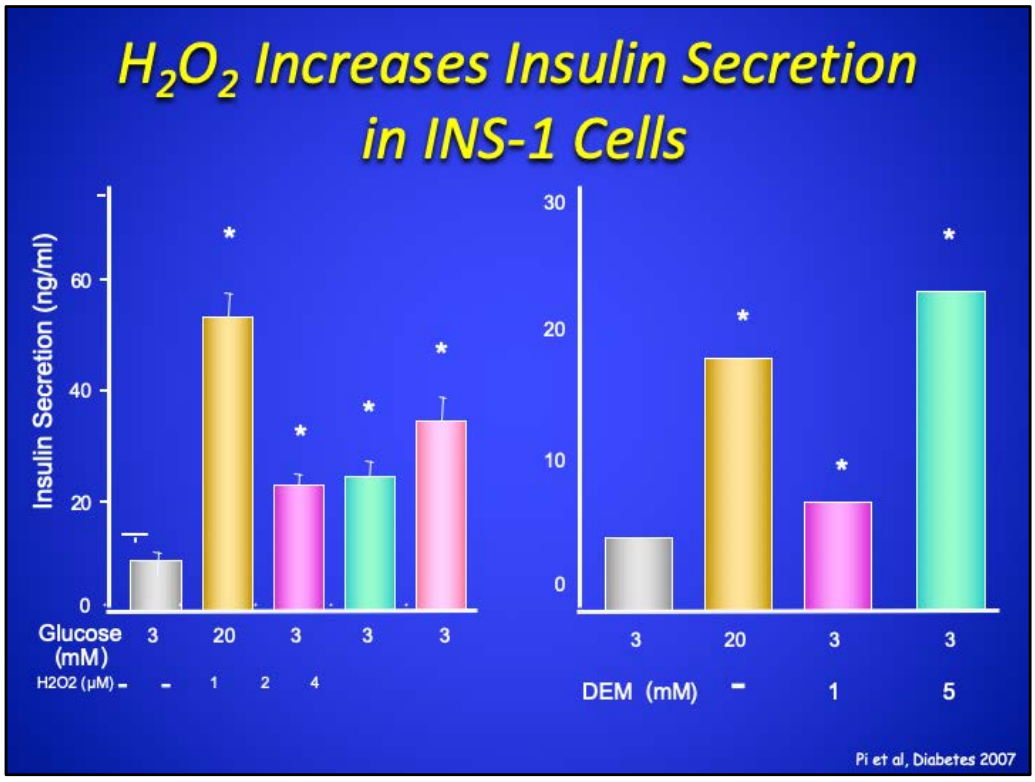
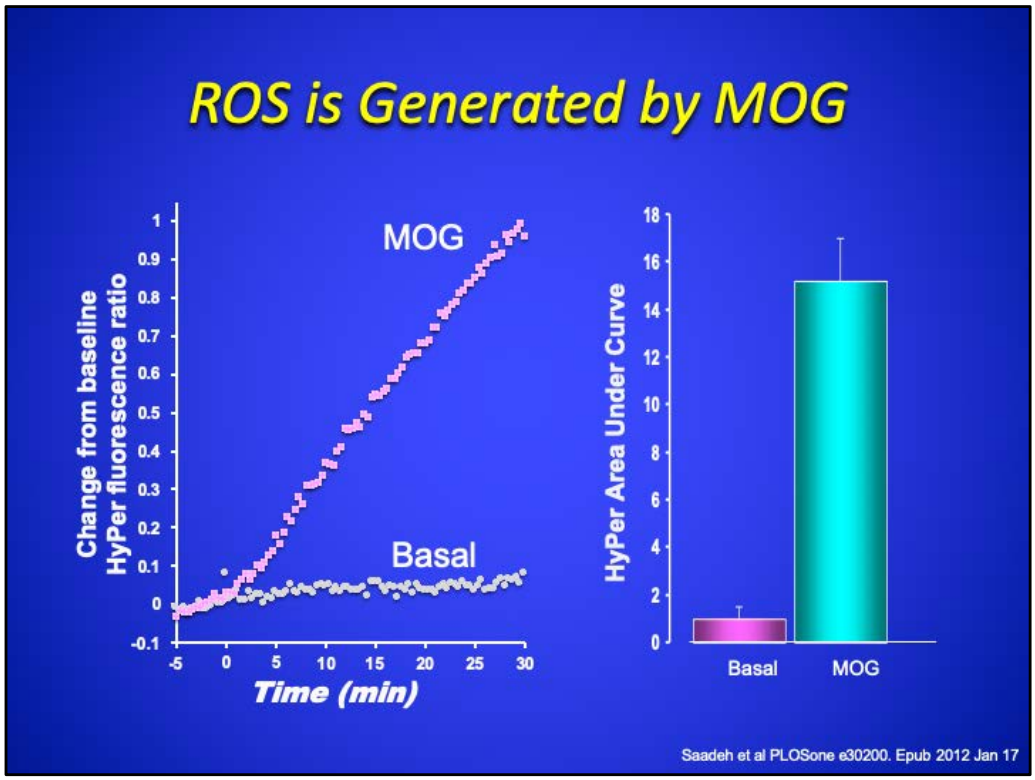

Gut
Brain
Hunger, Satiety
Liver
Glycogen, Glucose
Release
FatCell
Lipolysis
Lipid Synthesis
Circulating Master Metabolic REDOX
Regulators (L/P, ß/A, SH/SS)
ß-Cell
Insulin, Glucagon
Secretion

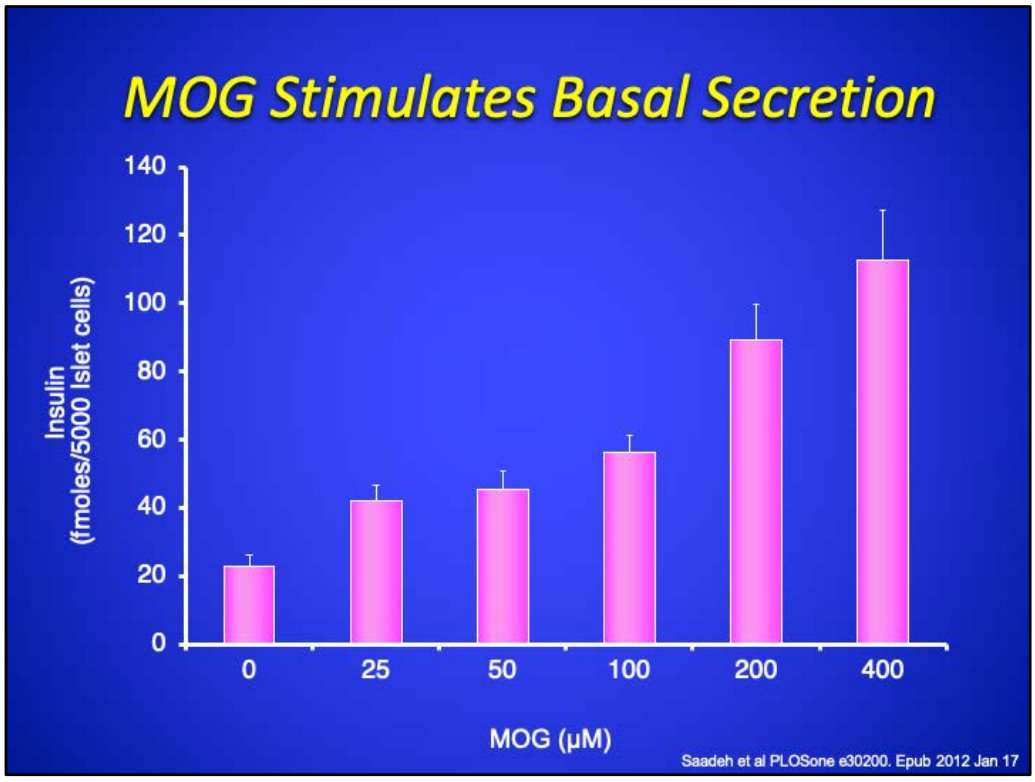
Illustration of some Exogenous Compounds that Induce ROS?



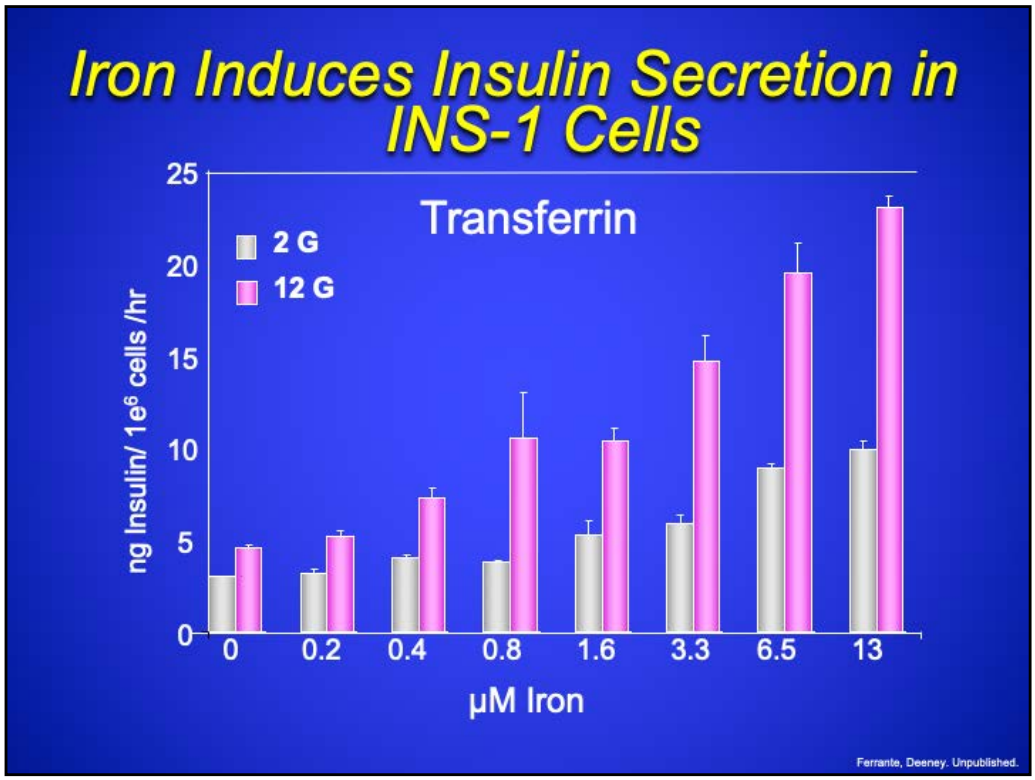
Increases in hydrogen peroxide stimulate insulin secretion like excess fuel but in the absence of a stimulatory fuel. H_2O_2 can be added outside the cell or generated within the cell by DEM.



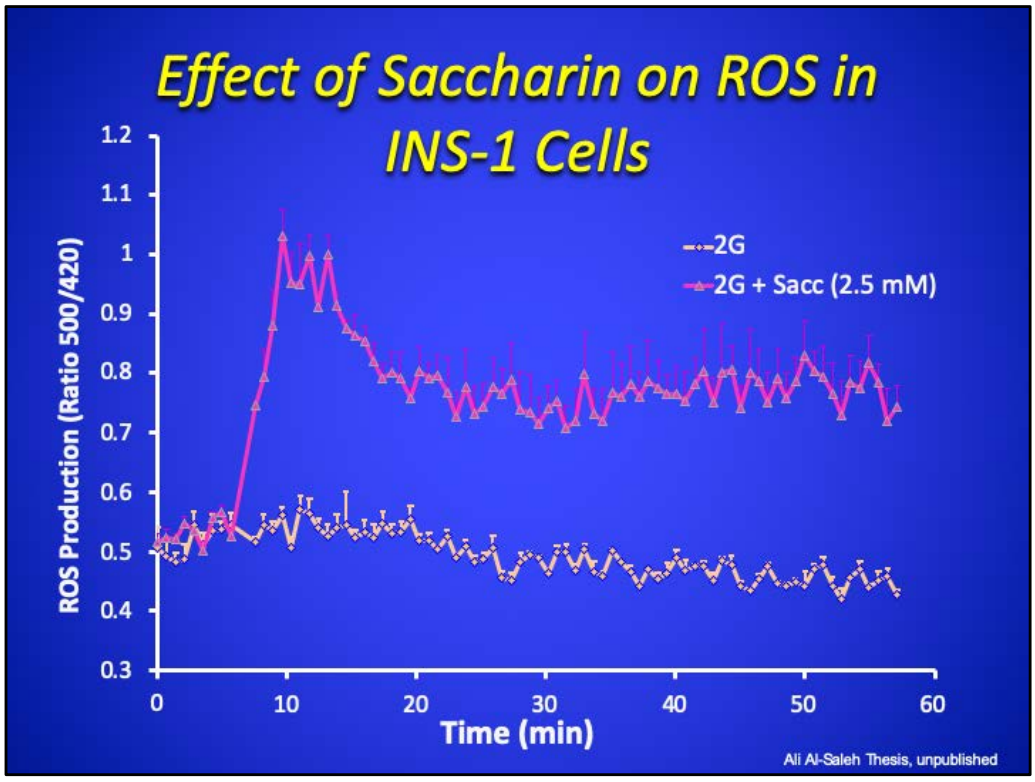
MOG, mono-oleoyl glyceride is a natural product and a common additive to most dairy products that serves as an emulsifier (to prevent cream from separating) and preservative. ROS is generated when it is added to an unstimulated ß-cell.



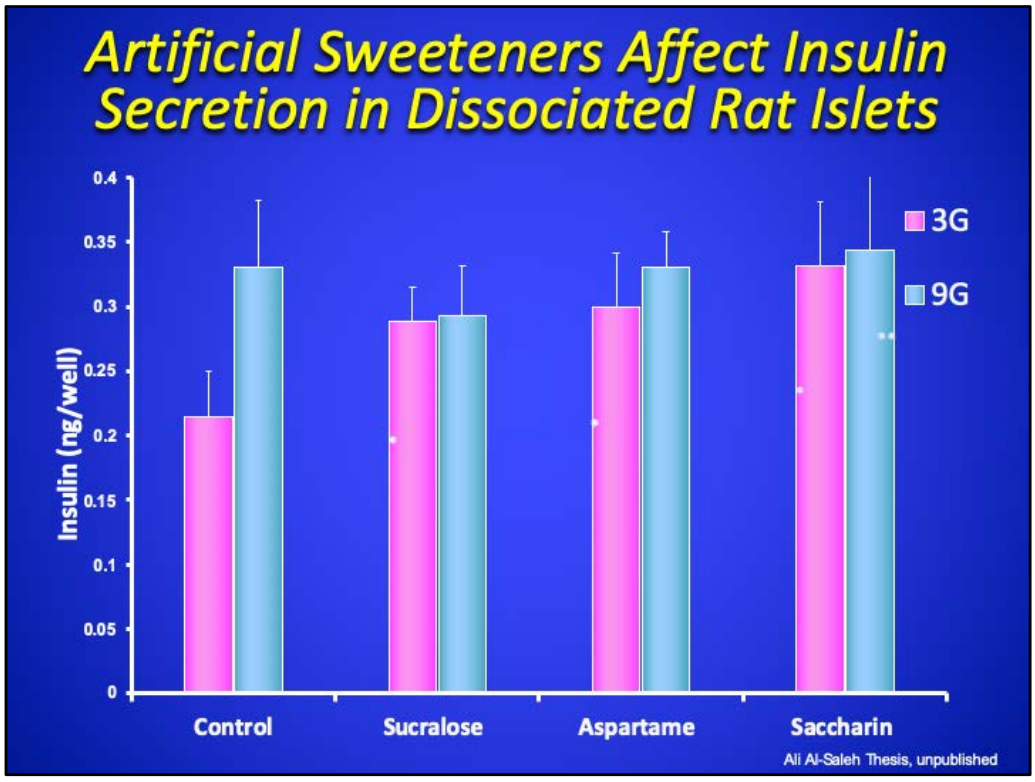
At concentrations that increase ROS, MOG stimulates insulin secretion inappropriately at low glucose.



Iron exposure induces Insulin Secretion in clonal ß-cells & dissociated mouse islets due to ROS generation. Lean red meats contain more iron than other meats.



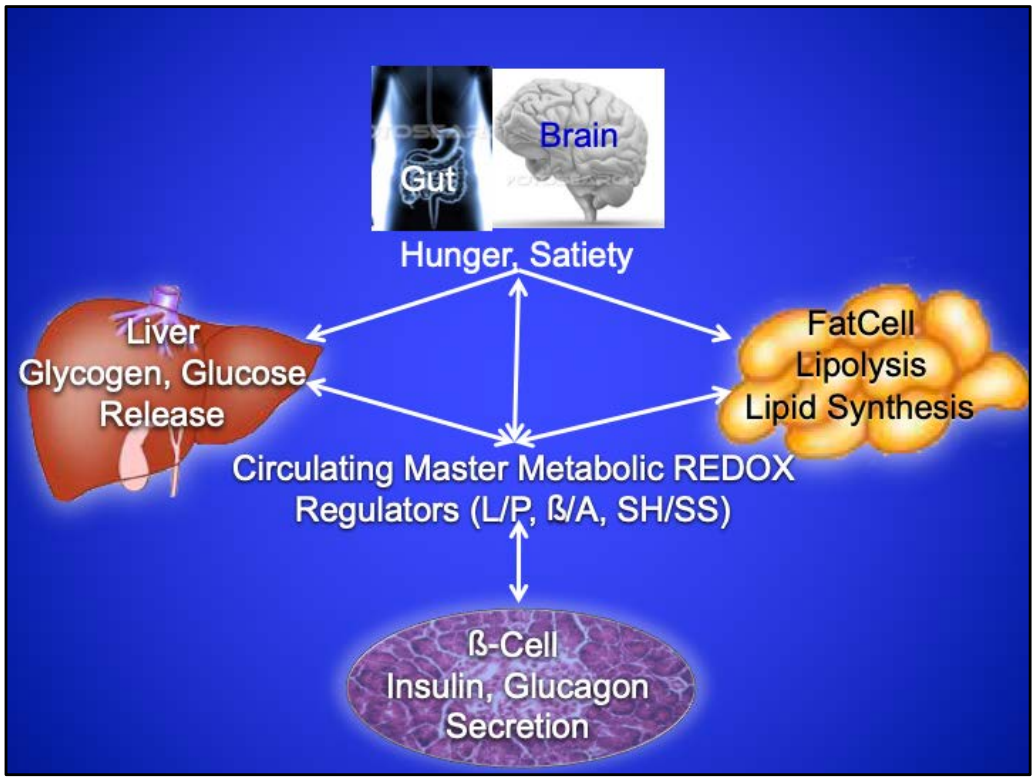
Artificial sweeteners increase ROS



All sweeteners tested generate ROS and increase insulin secretion at low non-stimulatory glucose.

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



Much has been learned about the individual processes that comprise metabolic regulation, however, there has been little focus on how the complex network interacts and the manner in which moment to moment energy is continuously maintained. This new discipline will develop tools and approaches to better understand complex interactions.

Thank You