

Why have we Failed to Decrease Obesity and Diabetes?

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We Regard our Hypotheses as Facts!

- Obesity: Eating too much and exercising too little.
- T2D is a failure to compensate for insulin resistance.
- Single site: single tissue defects explain metabolic disease (TARGET-centric pharmacology)

Our Hypotheses have NOT Benefitted Patients, Incidence is Increasing!

- A. Is **overeating** the cause of obesity? Why?
- B. Is **insulin resistance** the cause? How?
- C. Is **inflammation, oxidative stress, ROS** the cause?
- D. Perhaps **Hyperinsulinemia** is the cause of obesity, insulin resistance and diabetes?

A. Eating too much and exercising too little causes obesity.

- Maintenance of reduced or elevated body weight is associated with compensatory changes in energy expenditure, which oppose the change.
- Human energy output decreases during underfeeding and increases during overfeeding
- Individuals with the largest increases in energy output gain least during overfeeding and those with the largest decreases in energy output lose least weight during underfeeding

Variations in Energy Efficiency

- Vermont prisoner study*: lean individuals required 6-8000 cal/d to gain 20% excess wt: increase energy expenditure
- Dieters decrease energy expenditure
- Cells exposed to excess nutrient develop a proton leak that increases energy expenditure
- Proton leak decreases in response to ADP

Can Variations in Energy Metabolism Cause Obesity?

- We ignore this 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

Mouse Models of Weight Management

- L-FABP KO-maintains weight with change in RQ
- FTO point mutation-decreased fat, increased EE
- Y2Y4 DKO-no obesity with HFHS diet
- Sfrp4 KO-no obesity with HFHS diet
- CBR-DKO-no obesity with HFHS diet

Variations in Energy Efficiency

- Can be induced by excess nutrients via a proton leak
- Failure to adapt energy efficiency to nutrient supply rather than overeating may cause obesity
- Sadly, this topic has received little attention
- Environmental effects on neural satiety and hunger sensing is also potentially regulatory

B. Is insulin resistance the cause of Metabolic Disease?

- Obesity, insulin resistance, inflammation, hyperlipidemia and hypersecretion (HI) coexist.
- No evidence that one precedes the others
- Each can cause the others
- Each is the basis for a reasonable hypothesis

MIRKO Mouse

- Muscle-specific insulin receptor knockout (MIRKO) mice do not develop diabetes under physiological conditions despite a marked increase in adiposity and plasma FFA.
- MIRKO mouse displays muscle insulin resistance, visceral obesity, and dyslipidemia but does not develop hyperinsulinemia or diabetes.
- There is an accelerated differentiation of small insulin sensitive adipocytes, an increased secretion of the insulin sensitizer adiponectin

Insulin Resistance may be Beneficial

- Insulin resistance may be an adaptive response to maintain normoglycemia in the presence of high insulin
- Improving insulin sensitivity may cause hypoglycemia!
- ***Curing insulin resistance may be detrimental!***

Bottom Line on Insulin Resistance

- No evidence that IR precedes obesity, inflammation, hyperlipidemia or HI to cause metabolic dysfunction.
- Diminishing obesity, HL or HI decreases IR suggesting it is a consequence
- Evidence is correlative
- Tools to selectively alter IR alone are lacking making it an Untestable Hypothesis

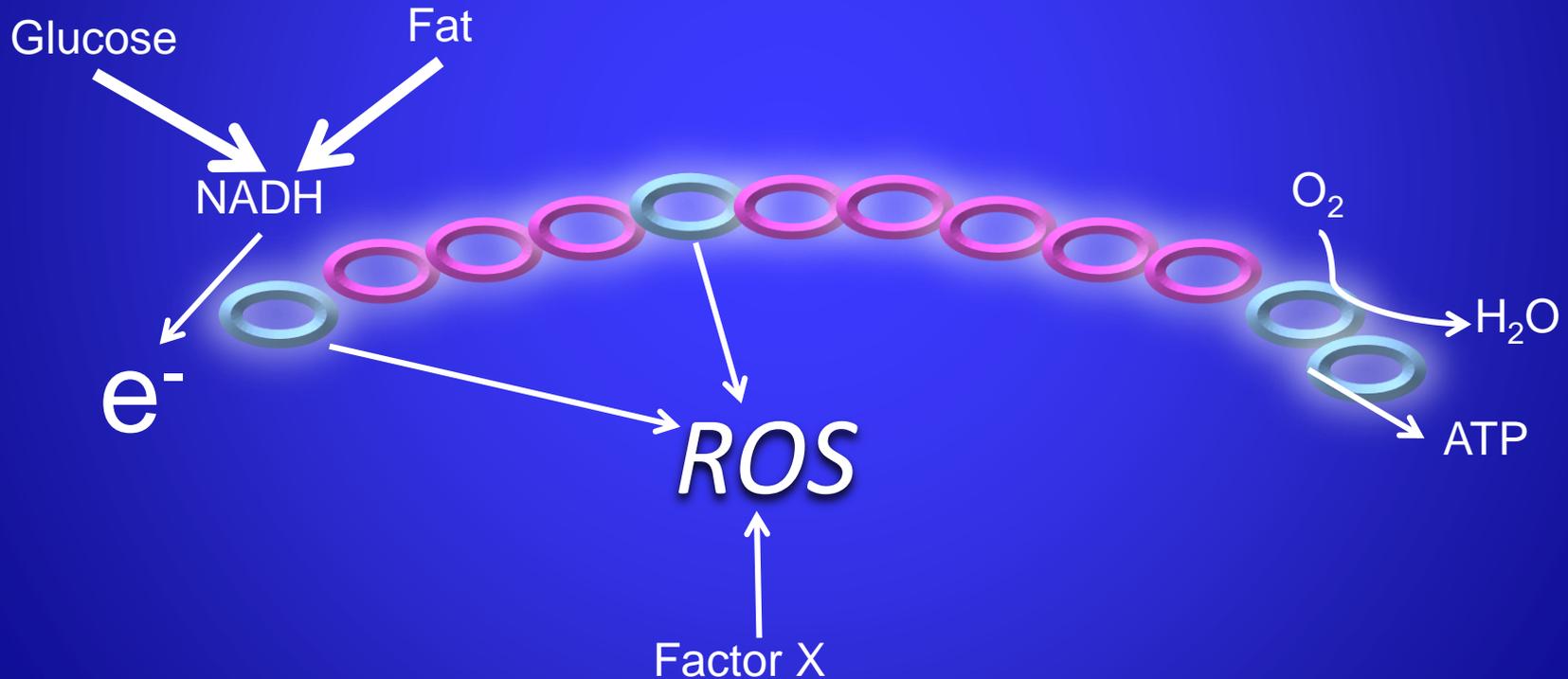
C. Is ROS (inflammation, oxidative stress) the cause of Metabolic Disease?

- Obesity, insulin resistance, inflammation, hyperlipidemia and hypersecretion (HI) coexist.
- No evidence that one precedes the others
- Each can cause the others
- ROS can also be an important signal

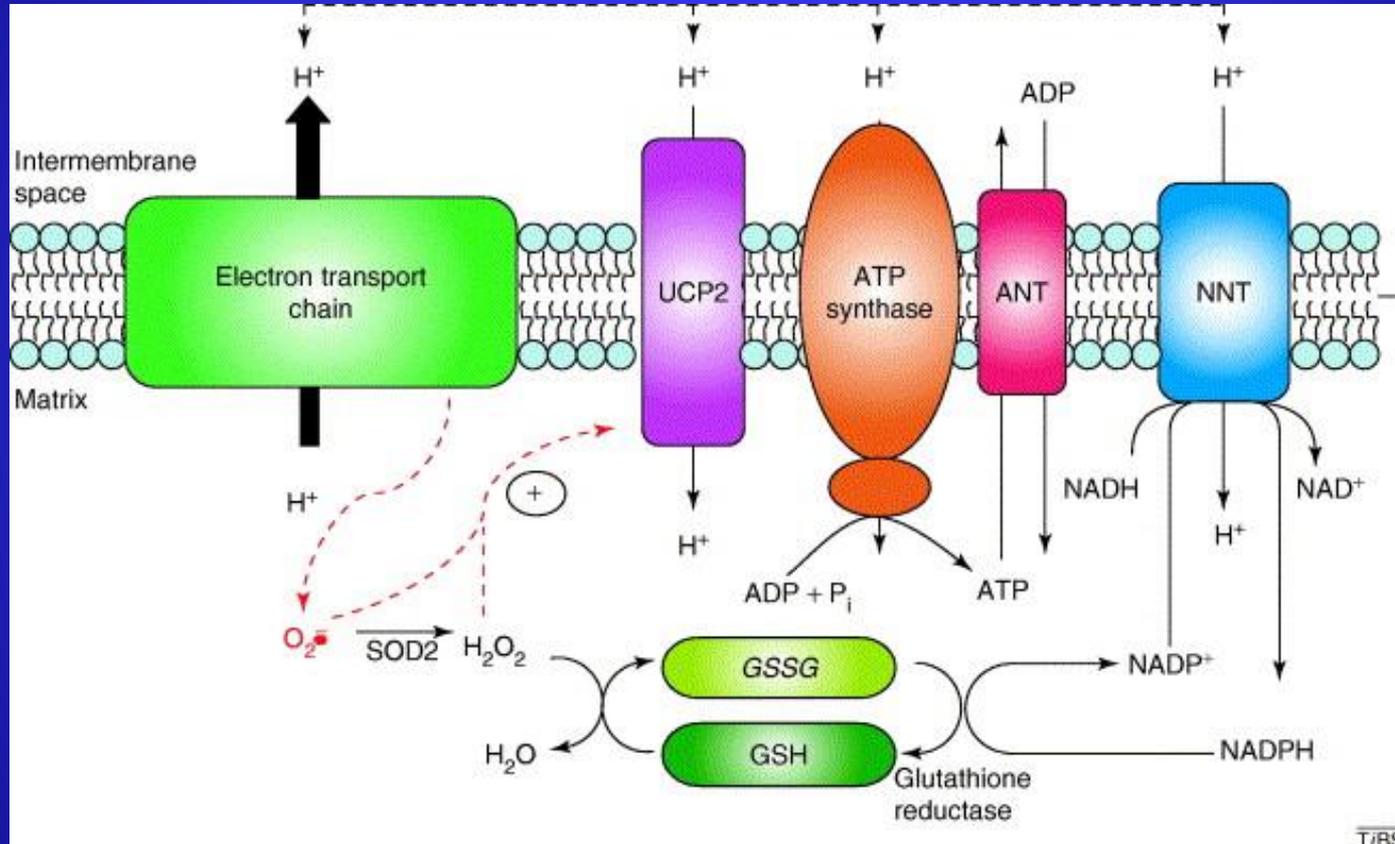
ROS may be Beneficial

- Produced in response to inflammation and cytokines
- Promotes cell growth and wound healing
- Normal product of oxidative phosphorylation
- Produced in response to excess nutrient
- Stimulates insulin secretion and lipid synthesis
- Inhibits gluconeogenesis

ROS are Produced at High NADH (Redox) in the Electron Transport Chain



ROS is Regulated by NNT and GSH



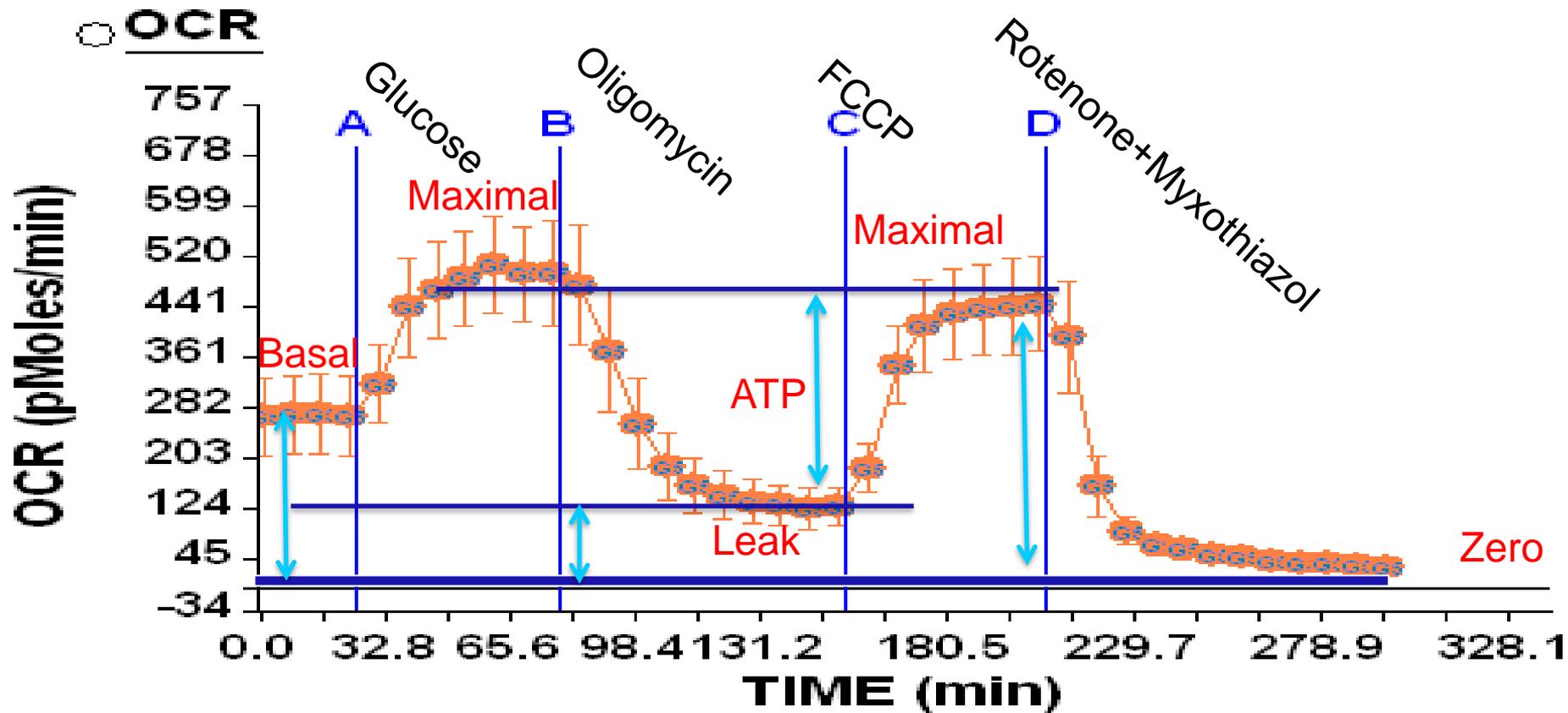
ROS Levels are Regulated

- NNT uses the proton gradient to convert excess NADH to NADPH.
- NADPH is needed for glutathione to convert ROS to water
- NNT flux can be measured as a mitochondrial proton leak
- Exception: C57Bl6J mice used as models for obesity and diabetes lack NNT

ROS Impacts Mitochondrial Energy Efficiency via a Variable Proton Leak?

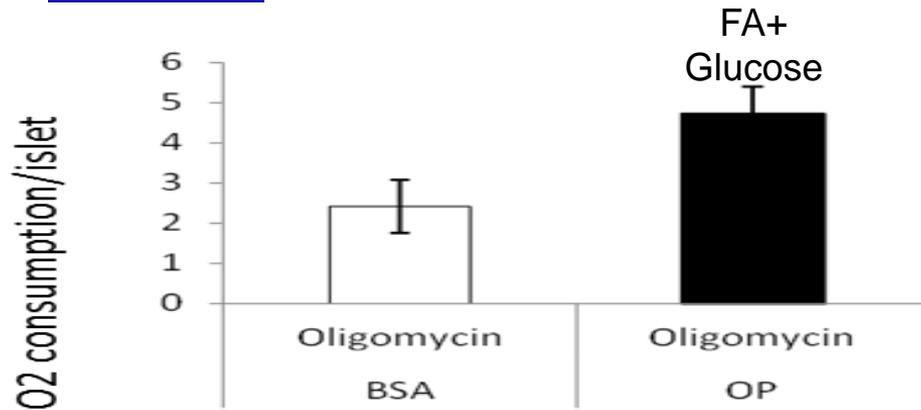
Decreased energy efficiency (less ATP per substrate derived electron)

Mouse Islet respirometry

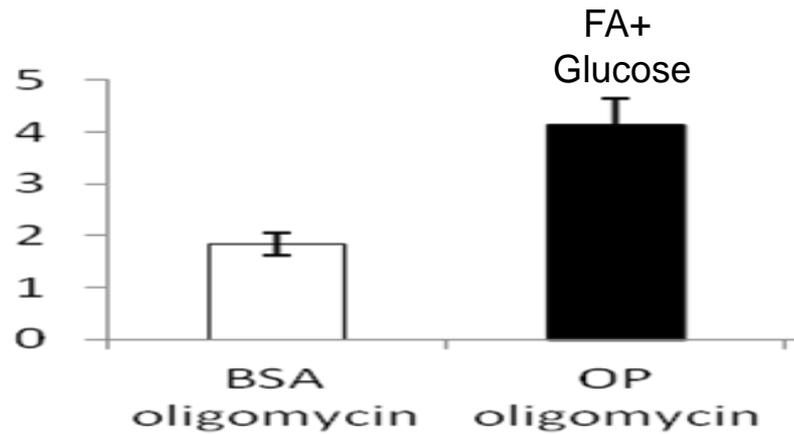


LEAK

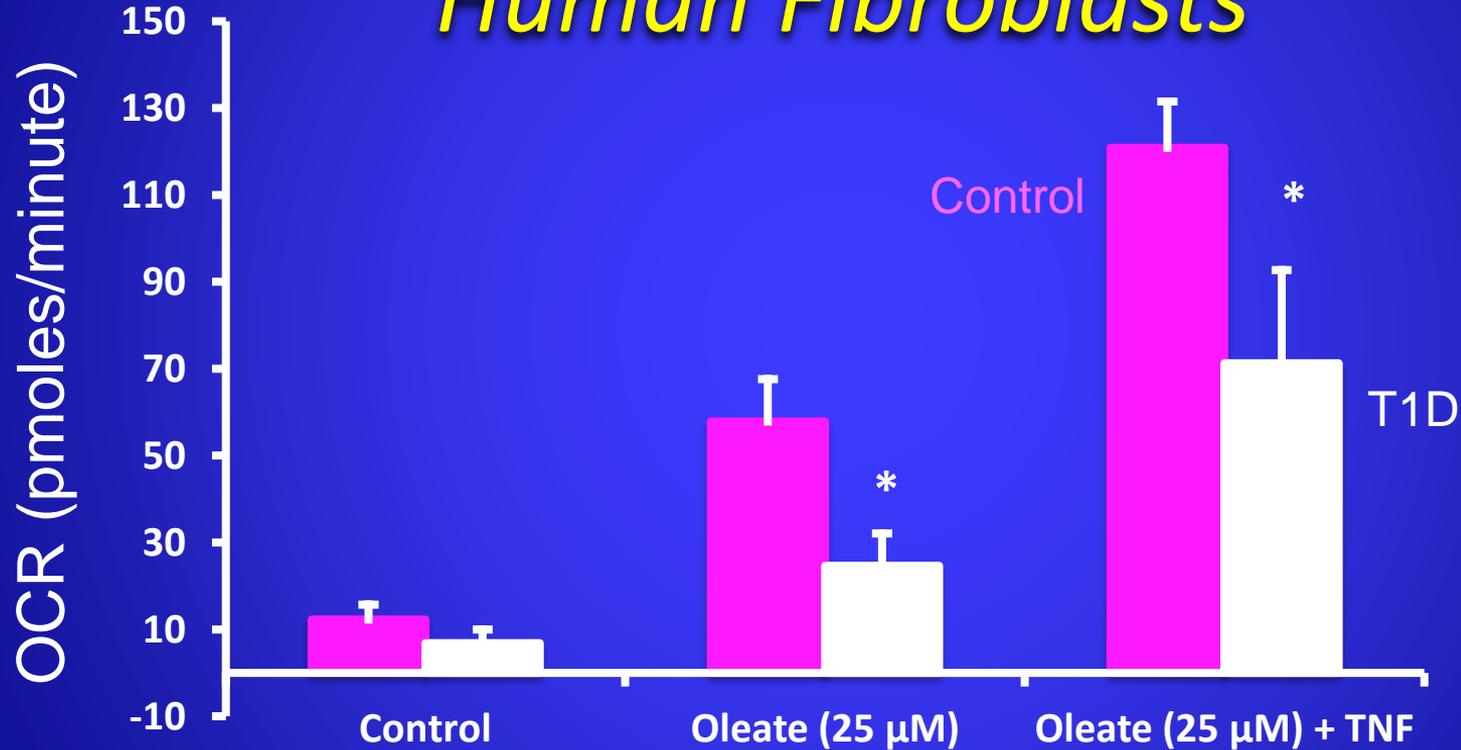
Human (n=4)



Mouse (n=4)



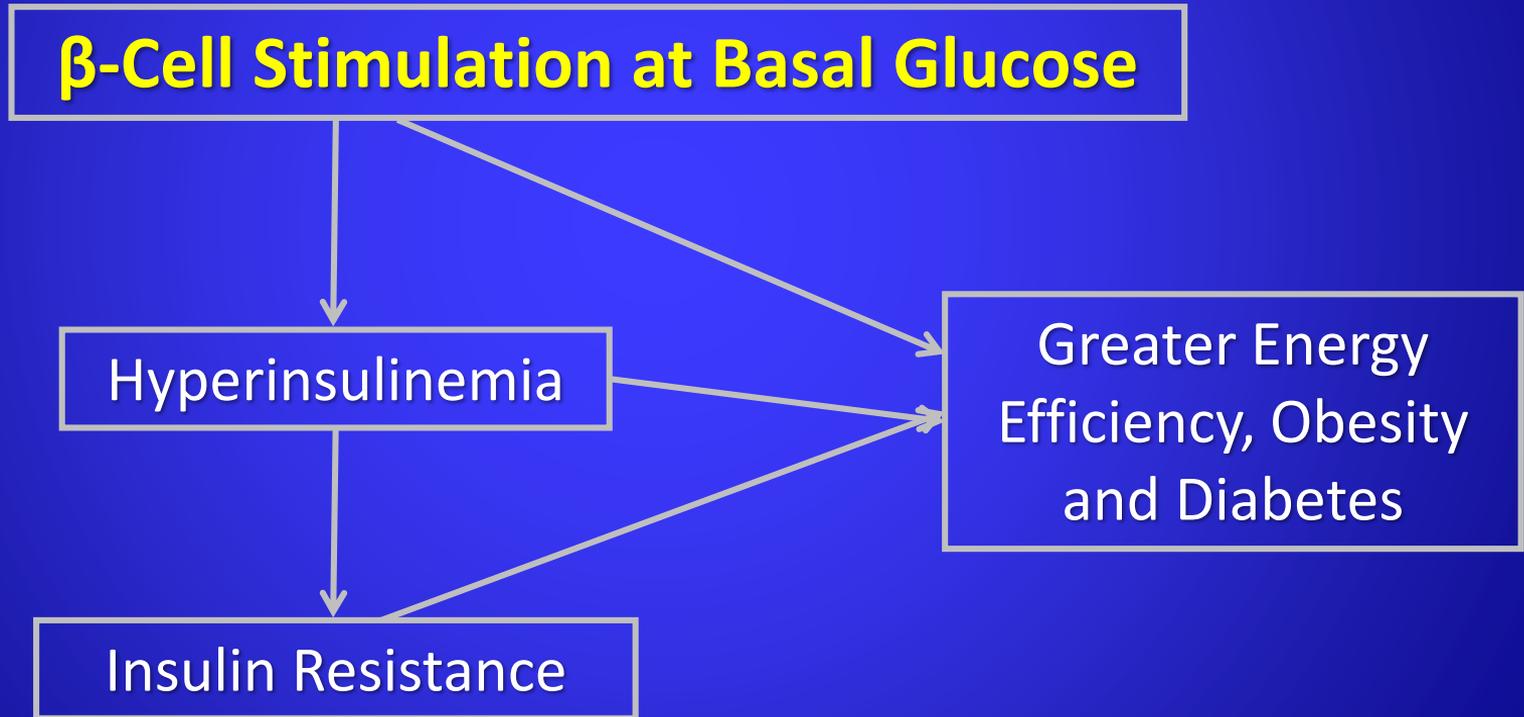
Excess Fuel Increases Proton Leak in Human Fibroblasts



Bottom Line

- ROS levels increase in response to cytokines, excess fuel and possibly environmental toxins
- They are normal cell constituents, normally well-controlled and can serve as signals
- ROS production and removal causes a leak and alters energy efficiency
- A causative role for ROS in obesity has not been established except possibly in C57Bl6J mice

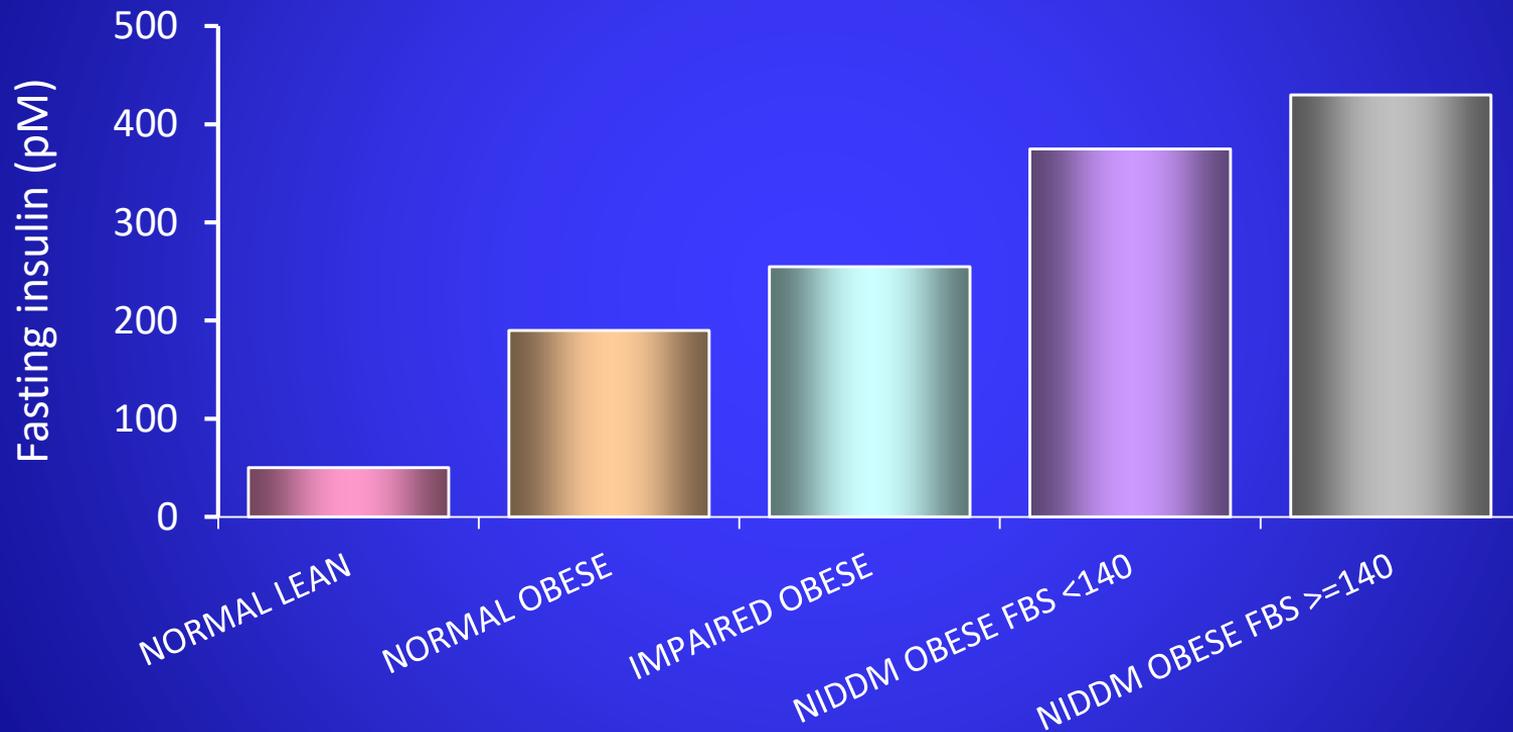
D. Is Hyperinsulinemia (HI) the Cause of Obesity and Metabolic Disease?



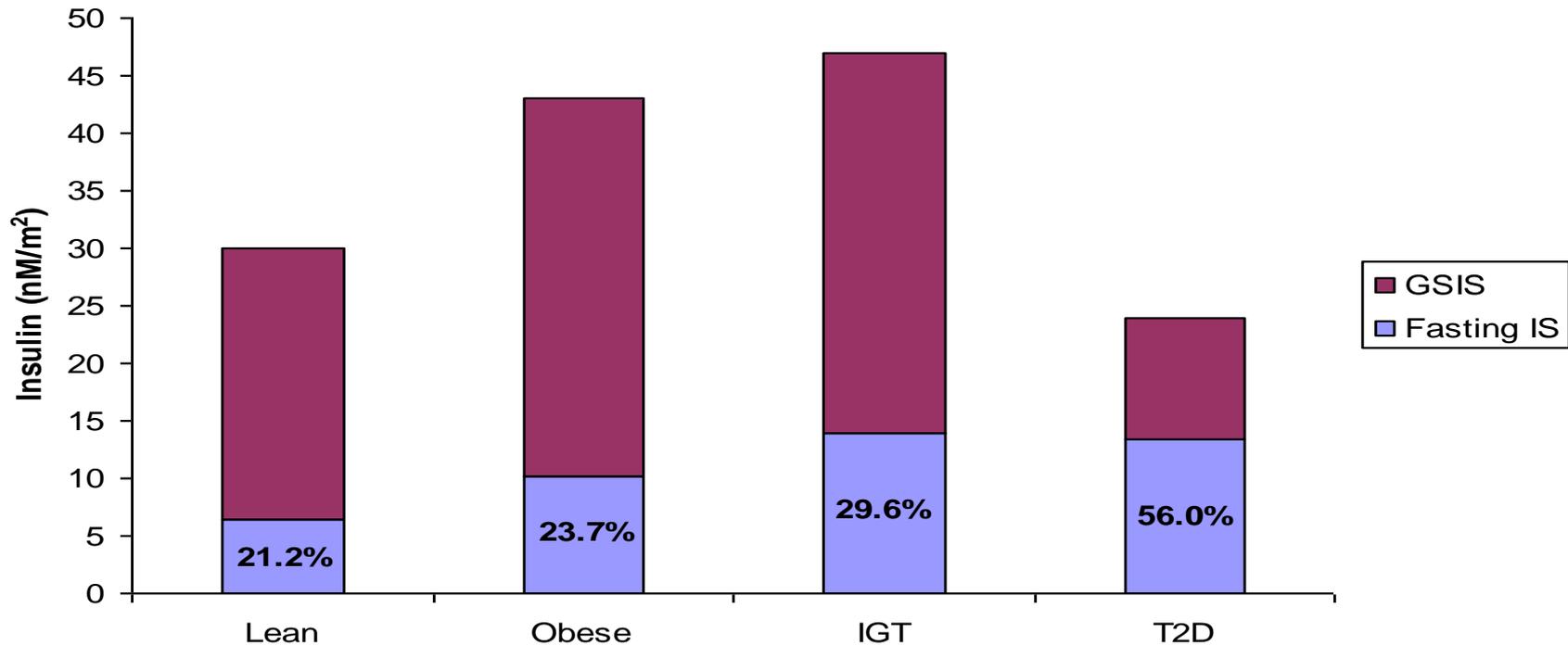
Does HI Cause Obesity?

- In 1937 MacKay showed increased AT mass with local injection
- In 1956 Beaton showed insulin administration in rodents caused weight gain
- VMH lesion requires insulin to cause obesity-York-72
- HI precedes obesity in ob/ob mice

Patients with Type 2 Diabetes Have Insulin Levels 900% of Normal



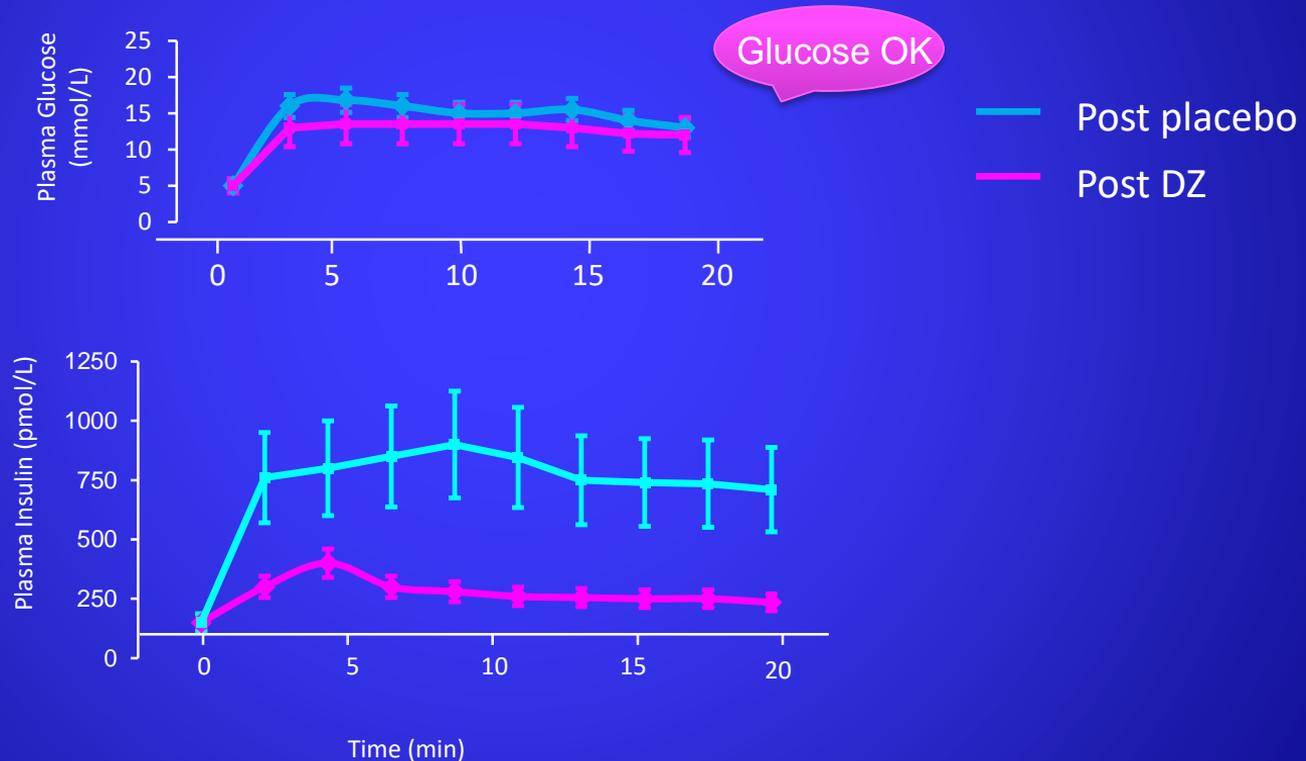
Contribution of Fasting and Glucose-Stimulated Insulin Secretion to Total Insulin Output During an OGTT in 4 Different Cohorts



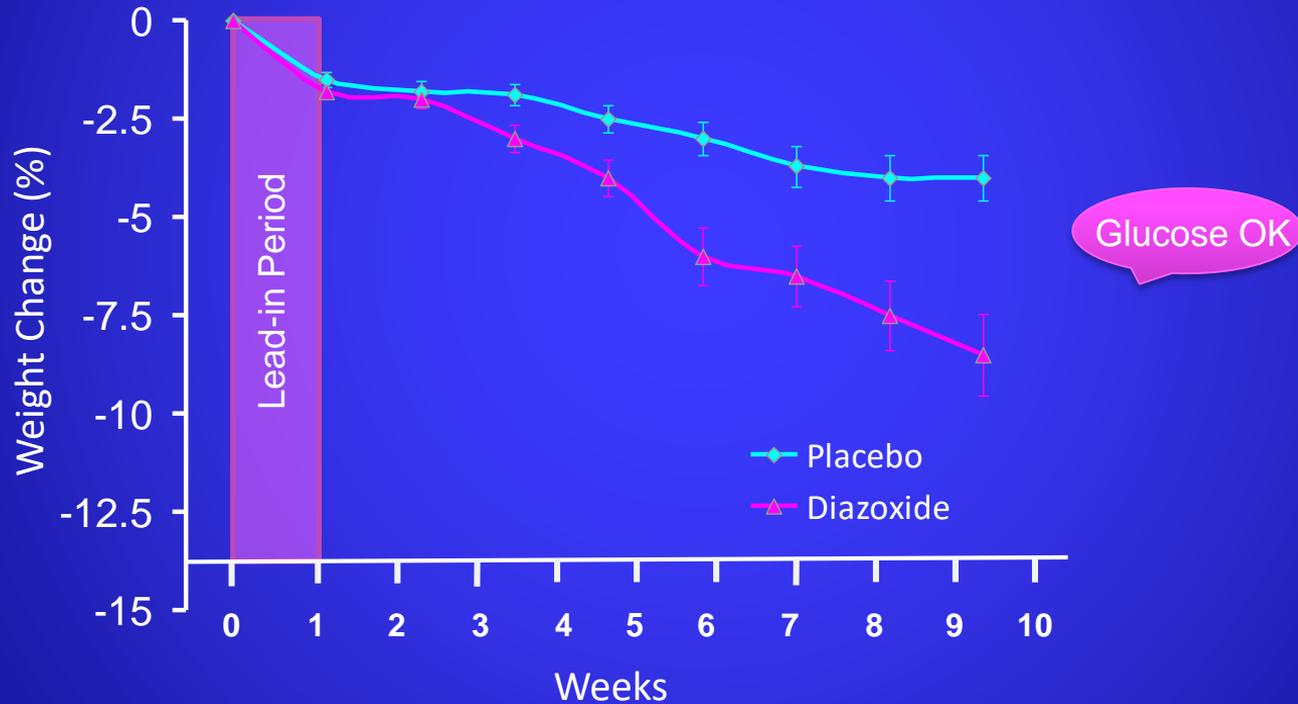
Effect of Reducing HI

- Both pharmacological and nutritional approaches have been used to reduce hypersecretion of insulin as a method for weight loss
- Diazoxide and NNT414 (NovoNordisk)
- Low glycemic index and ketogenic diets

Glucose and Insulin During IVGTT After 10 wks DZ Treatment in Obese Adults



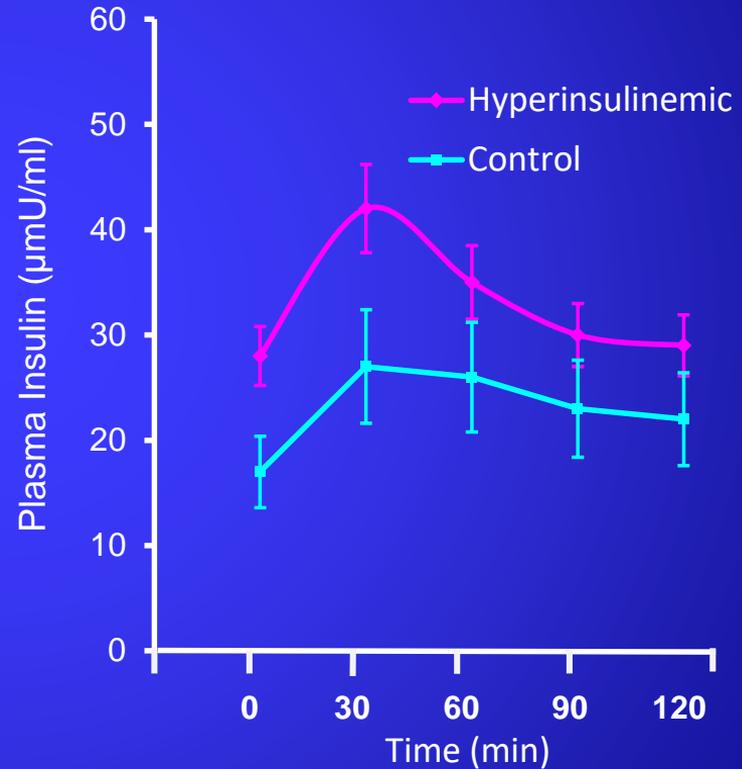
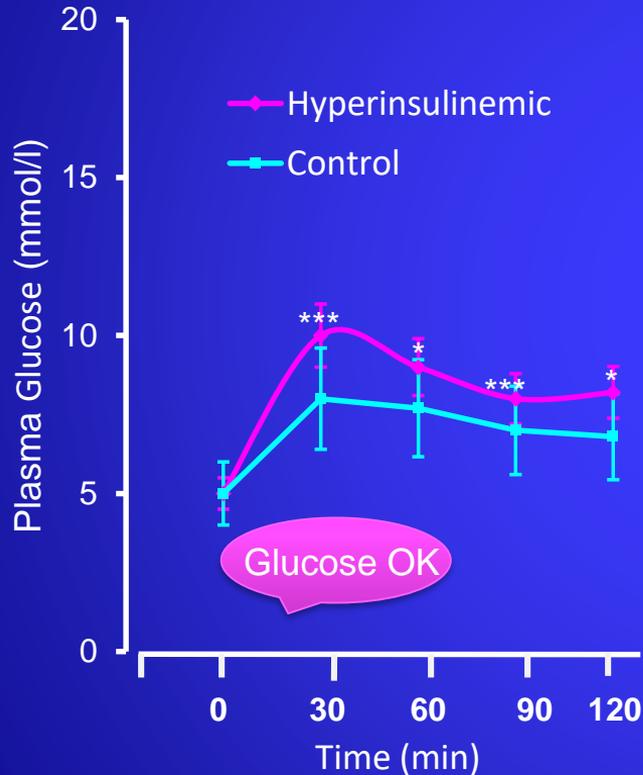
Body Weight Difference Between DZ and Placebo Groups



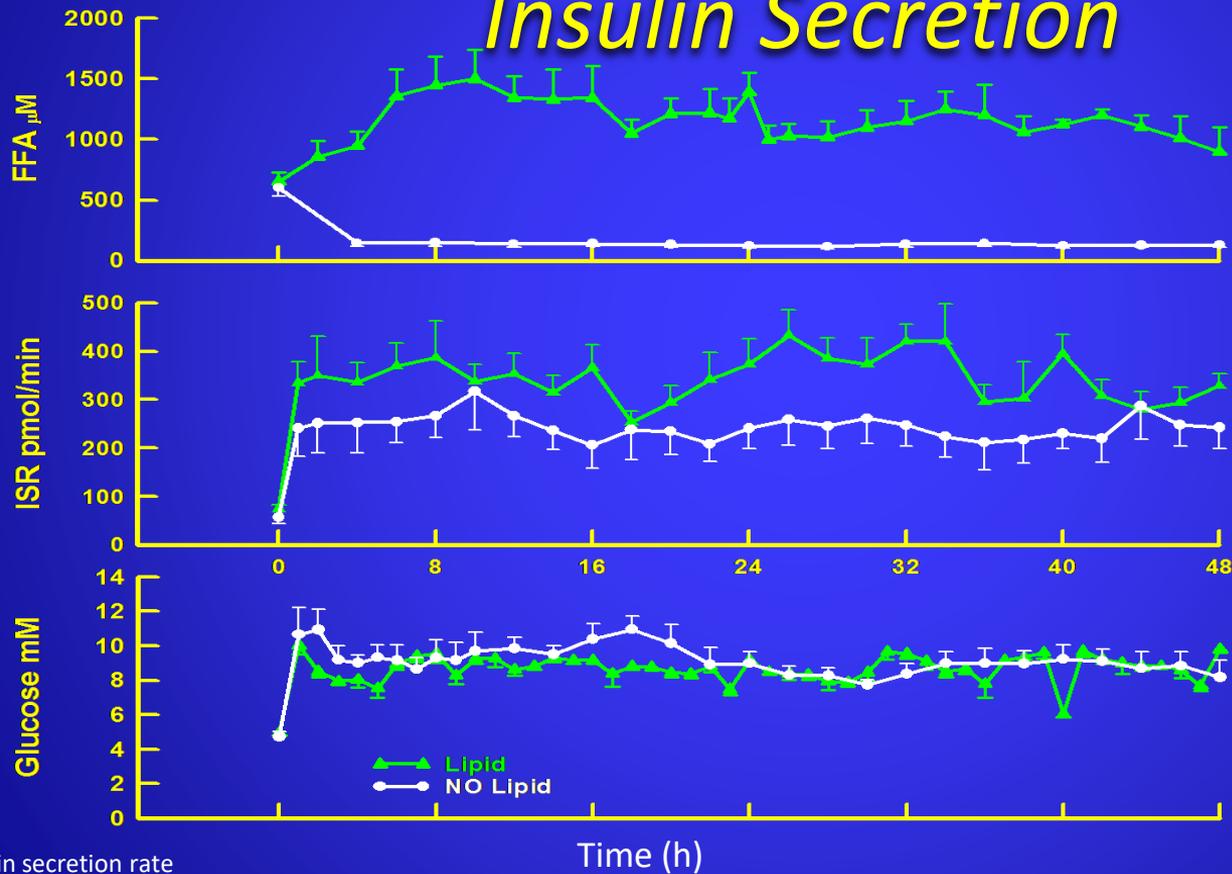
Treatments that Modulate HI in Animals impact Obesity

- Animal Models that are protected from HI do not become obese on high fat/sugar diets
 - Insulin gene KD
 - AT Insulin receptor KO
- Stimulators of FA Oxidation and Lipolysis
- HI impacts Neural Pathways-ICV insulin increases fat mass

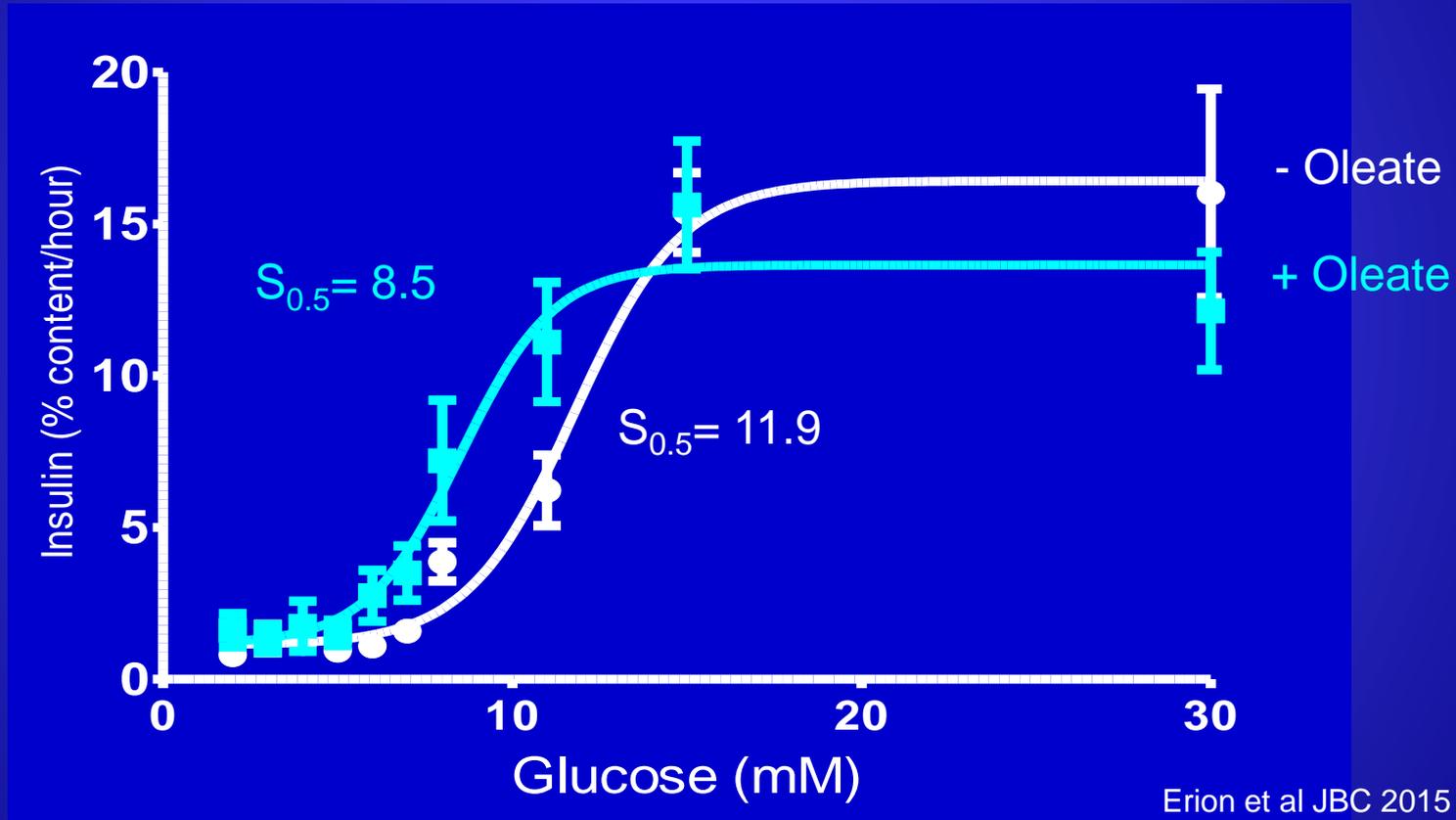
10 Days Insulin Minipump in Rats



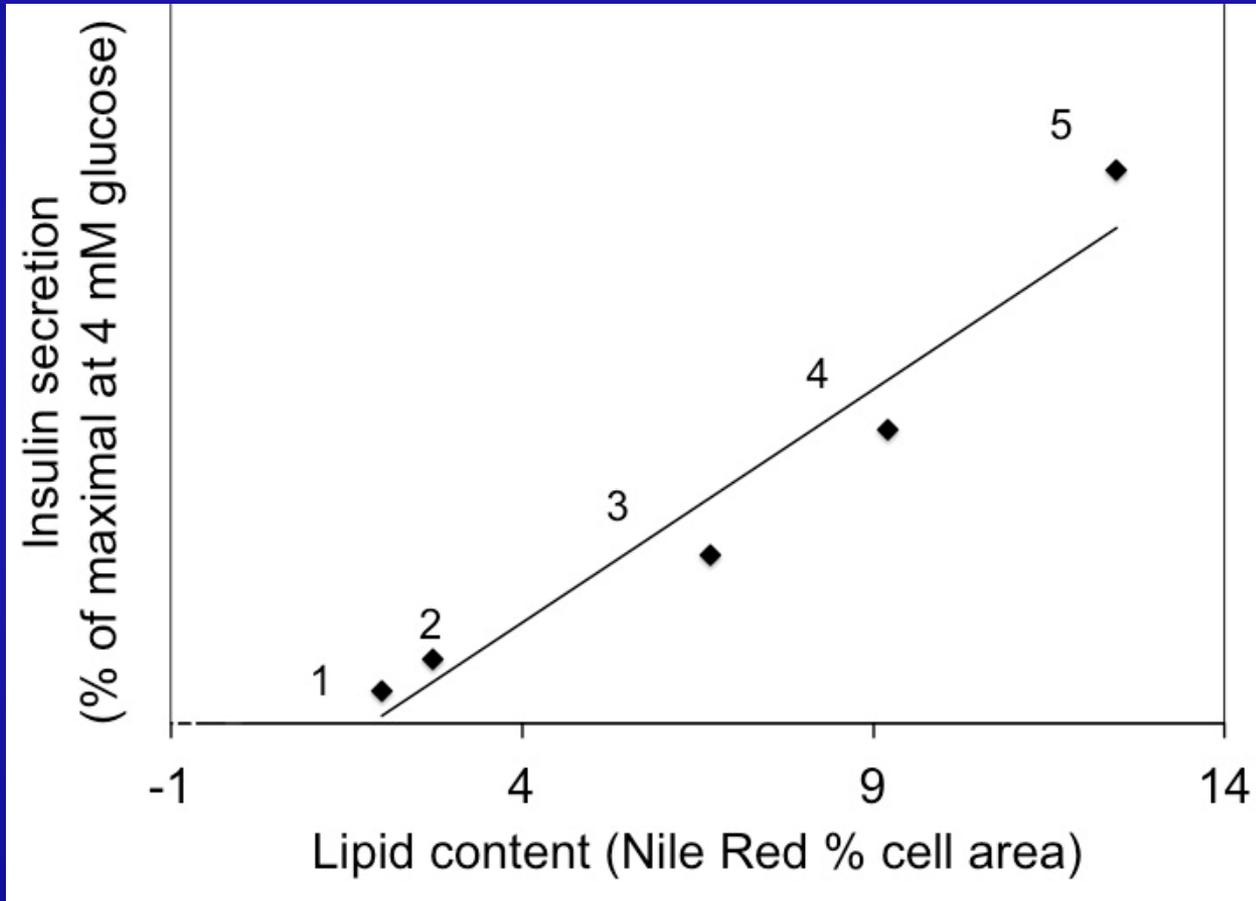
FFA Potentiate Glucose-Stimulated Insulin Secretion



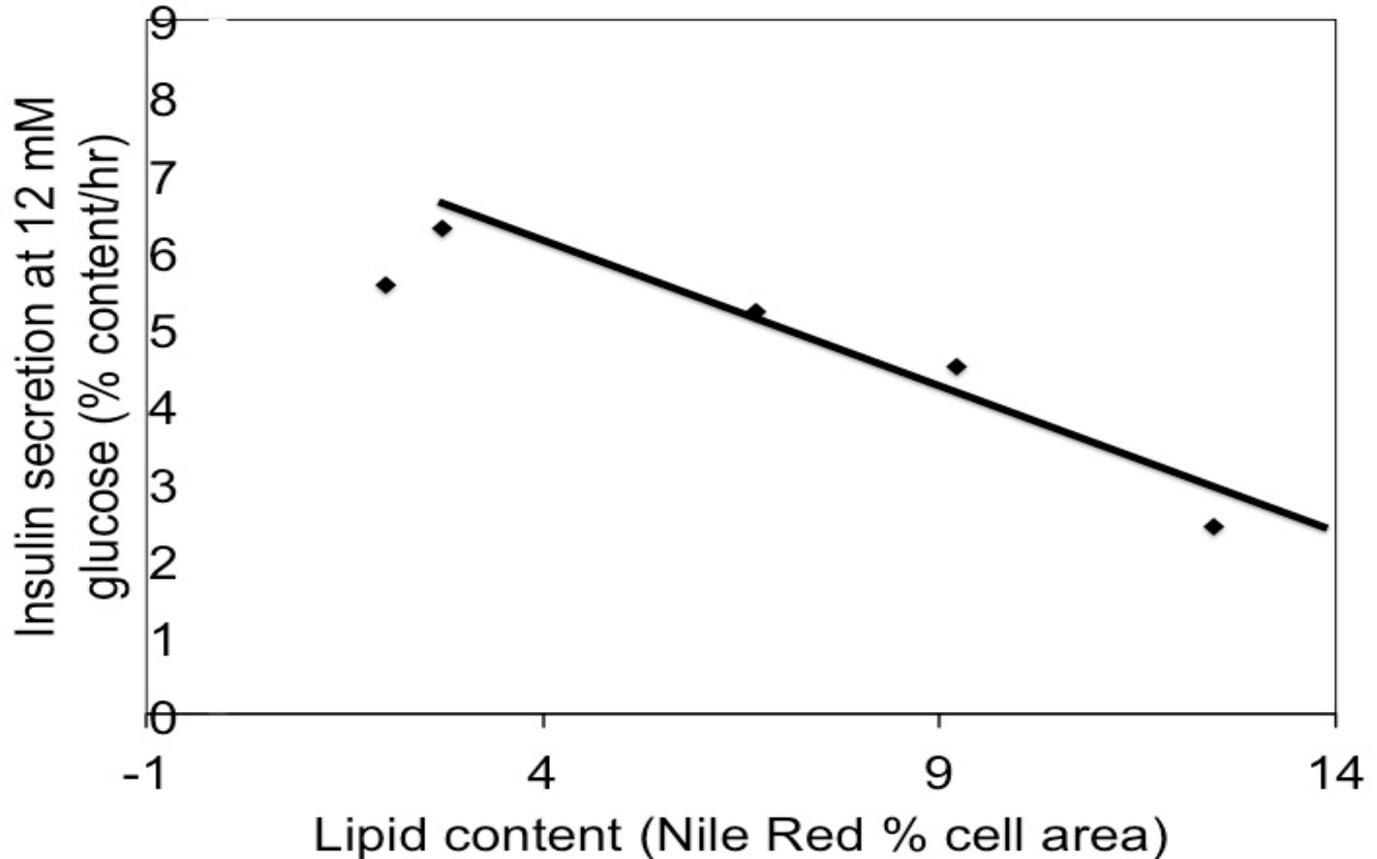
GSIS in Islets Cultured \pm Oleate

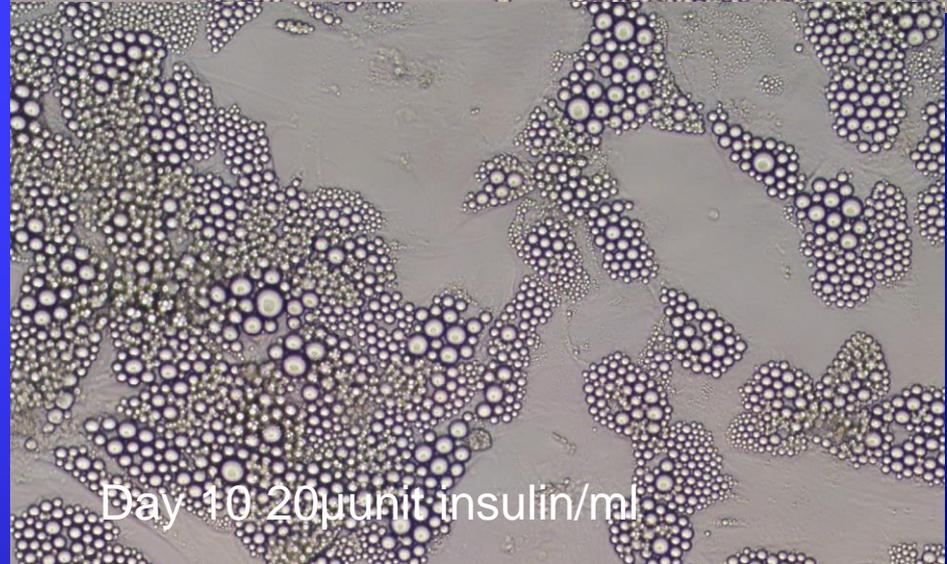
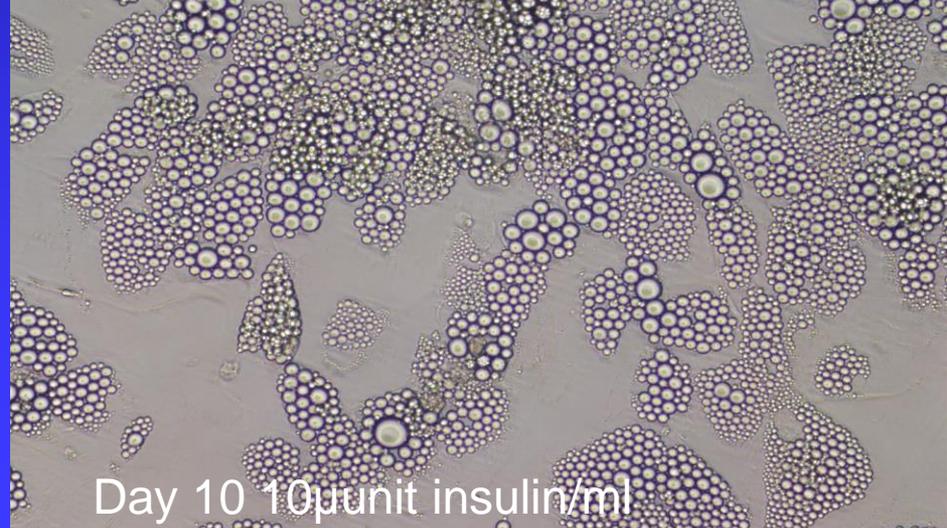
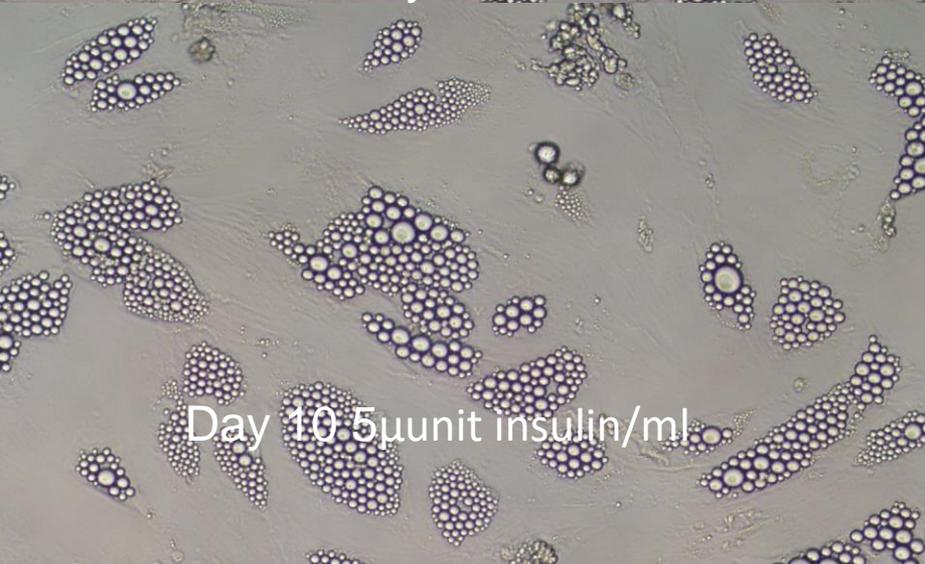
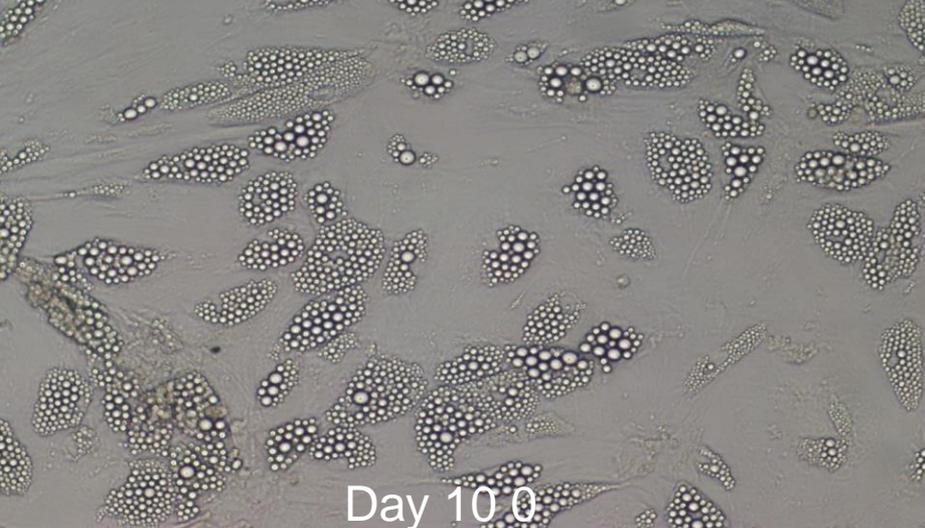


Basal HI Correlates + with Lipid



GSIS Correlates - with Lipid





Food Today is Different!

- Processed food
- 4,000 new agents
- Almost none evaluated as causes of diabetes or obesity
- Food animals are different (chickens and beef)

Fruits and Vegetables have Changed

- Fruits 27% less zinc
- Meats 41% less calcium more iron
- Apples and oranges 67% less iron
- Broccoli 75% less calcium
- Spinach 96% less copper
- Rutabaga 110% more phosphorus

Plastics in Food

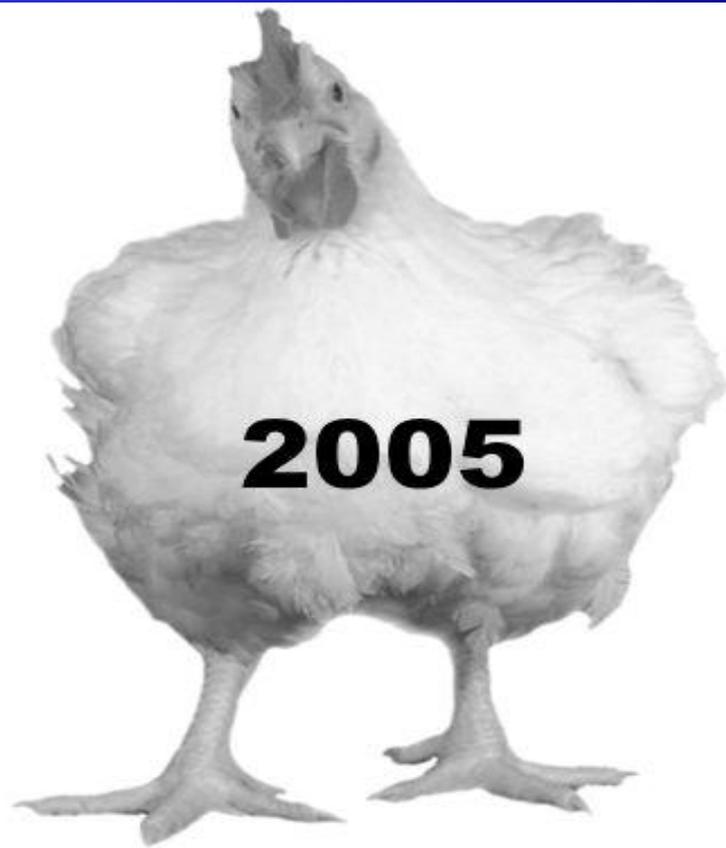
- Salad dressing and cooking oil bottles made from PVC (polyvinyl chloride)
- Soda bottles, water bottles, peanut butter jars and cooking oil bottles made from PET (polyethylene terephthalate)
- Meat trays, foam take-out food containers and cups, foam packing materials made from polystyrene (PS)



905 g



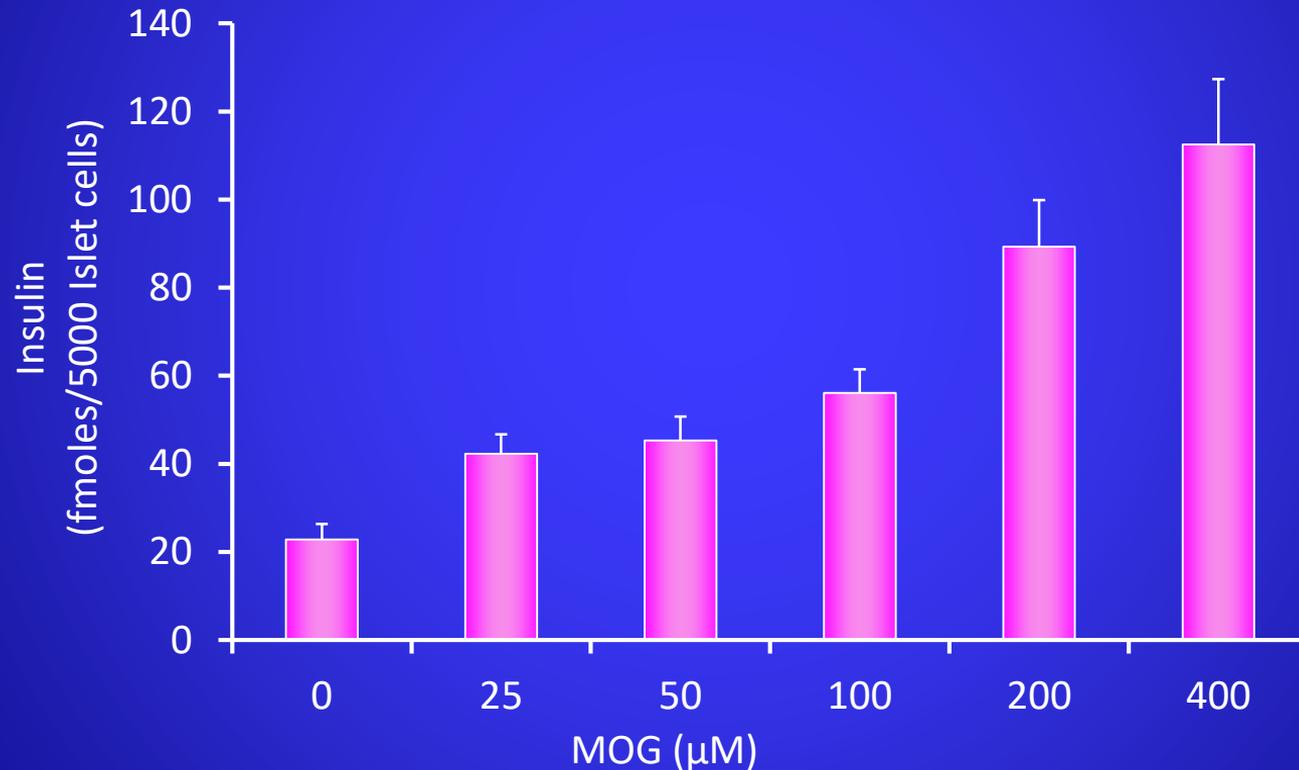
1,808 g



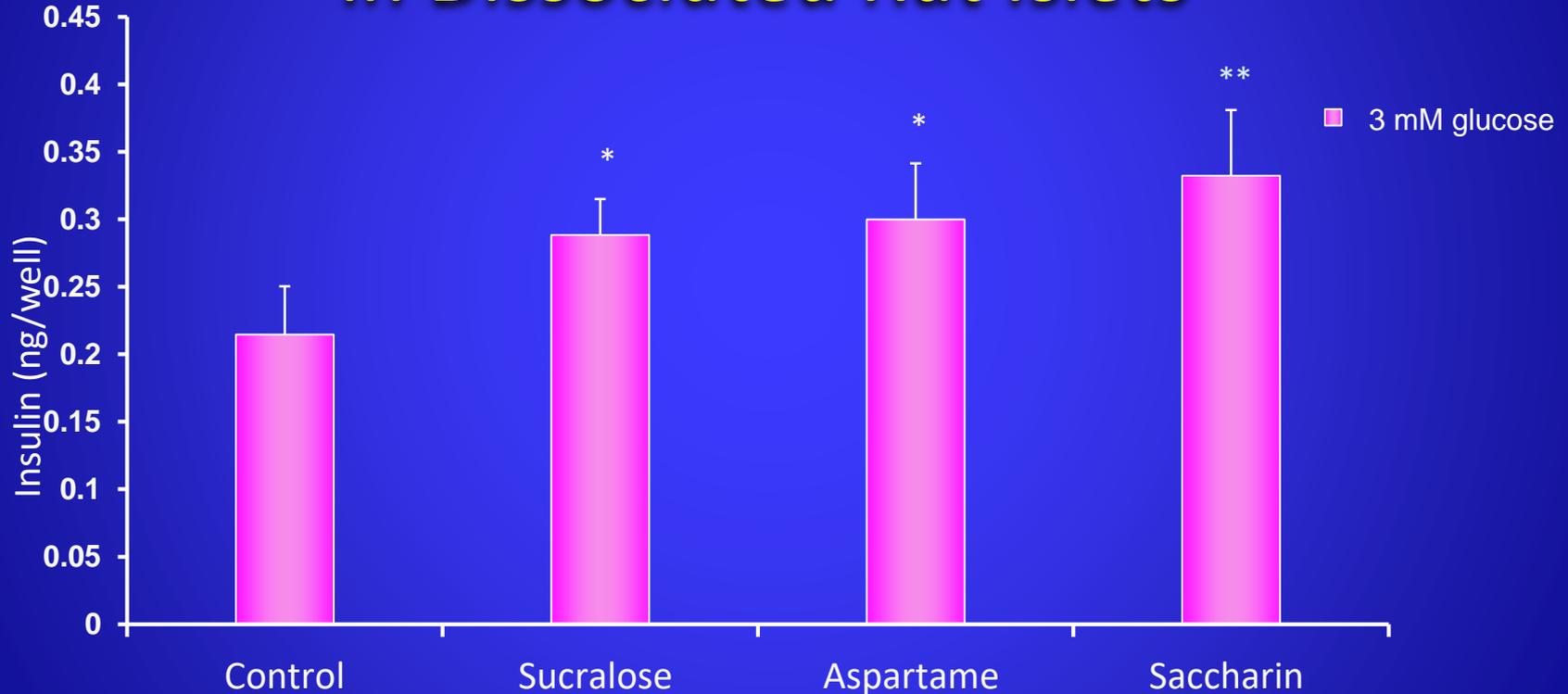
4,202 g

- 1) Chickens today are bigger than those in the 1950s: The 2005 chicken on the right ended up being about four times as heavy, as the 1957 breed on the left — despite being fed the same foods.
- 2) Chickens today are more efficient at turning feed into breast meat. The researchers' metric for this was something they called the "breast conversion rate" of grams of feed into grams of breast meat. The 2005 breed was roughly three times as efficient as the 1950s one.
- 3) But the growth of chickens helped make chicken a popular food and a much cheaper food.
- 4) Is it possible that such changes in efficiency have been imposed on people?

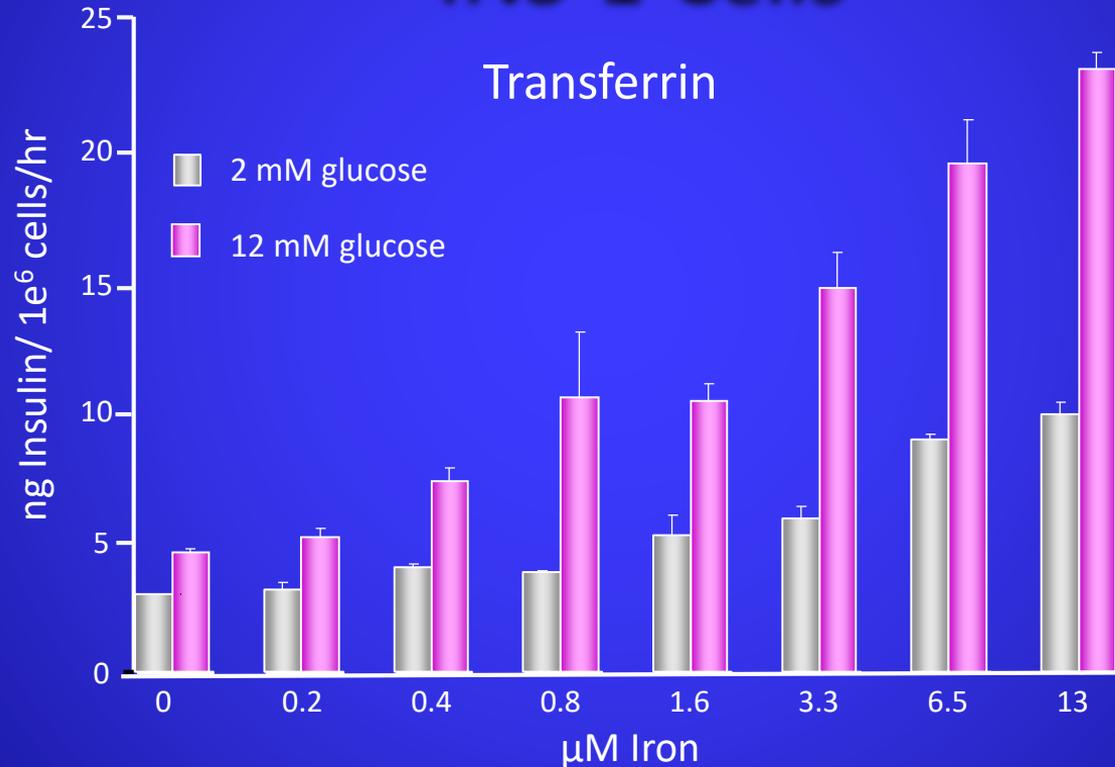
MOG Stimulates Basal Secretion



Artificial Sweeteners Affect Insulin Secretion in Dissociated Rat Islets



Iron Induces Insulin Secretion in INS-1 Cells

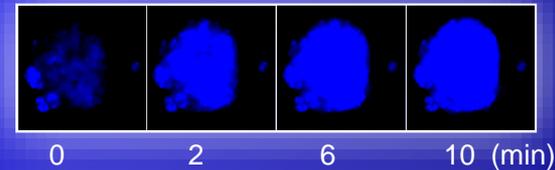
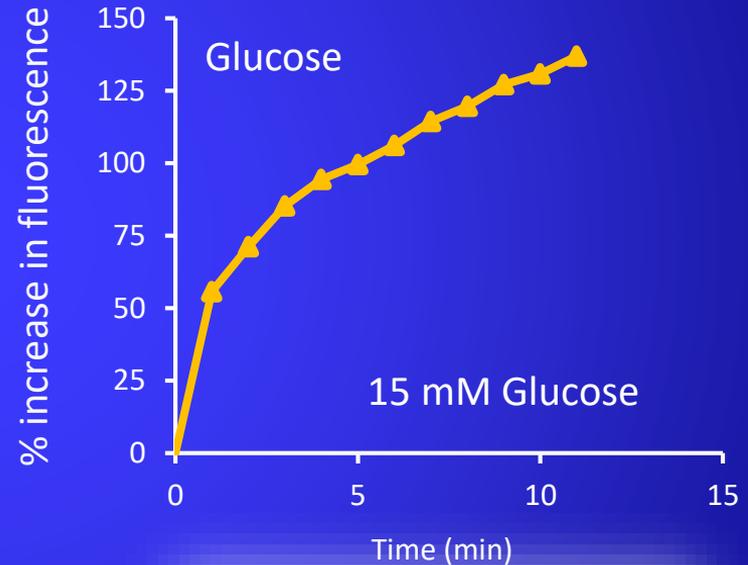
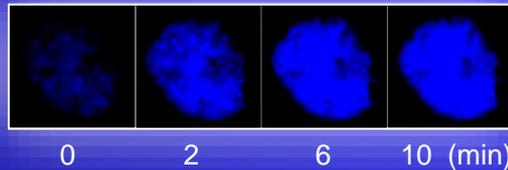
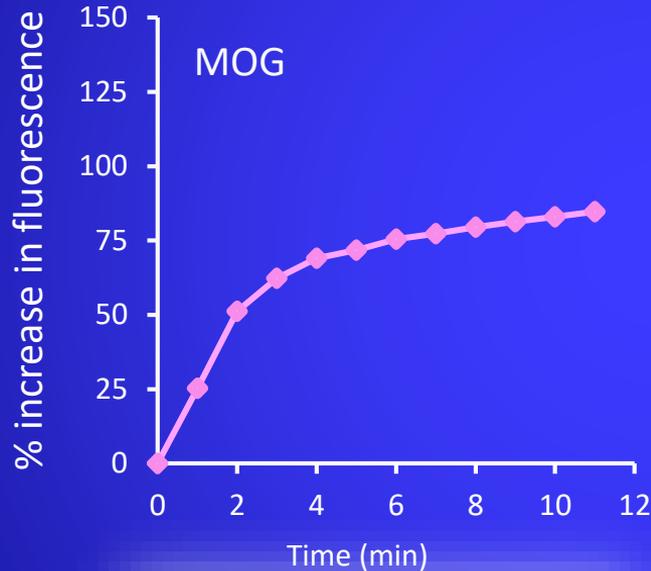


What Agents Cause Insulin Secretion in the Absence of a Stimulatory Fuel?

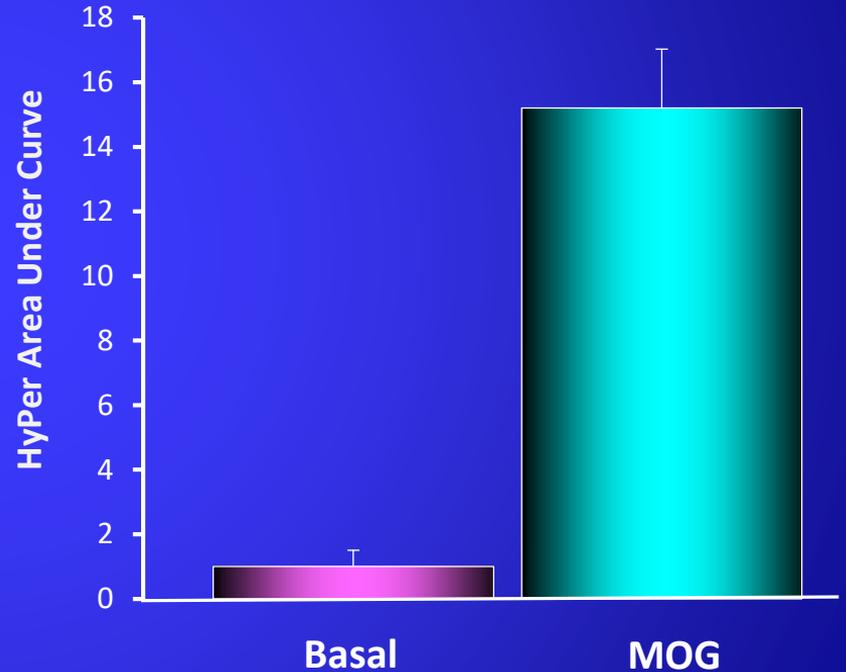
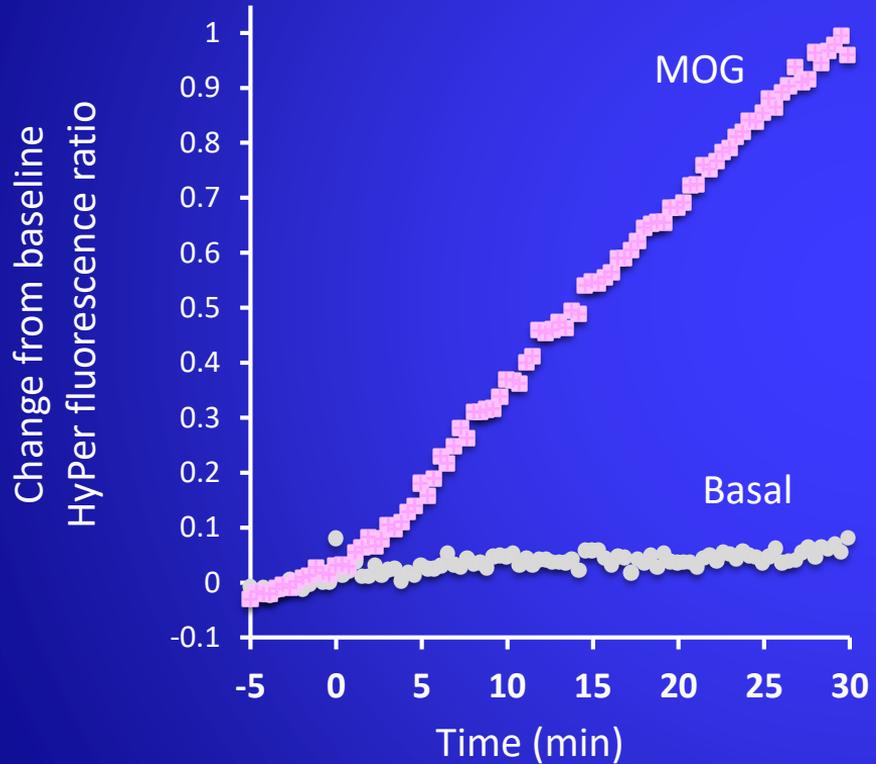
- MOG, a lipid food emulsifier and preservative
- Saccharin, an artificial sweetener
- Iron, an essential mineral

*How Does Hyperinsulinemia Cause
Problems?*

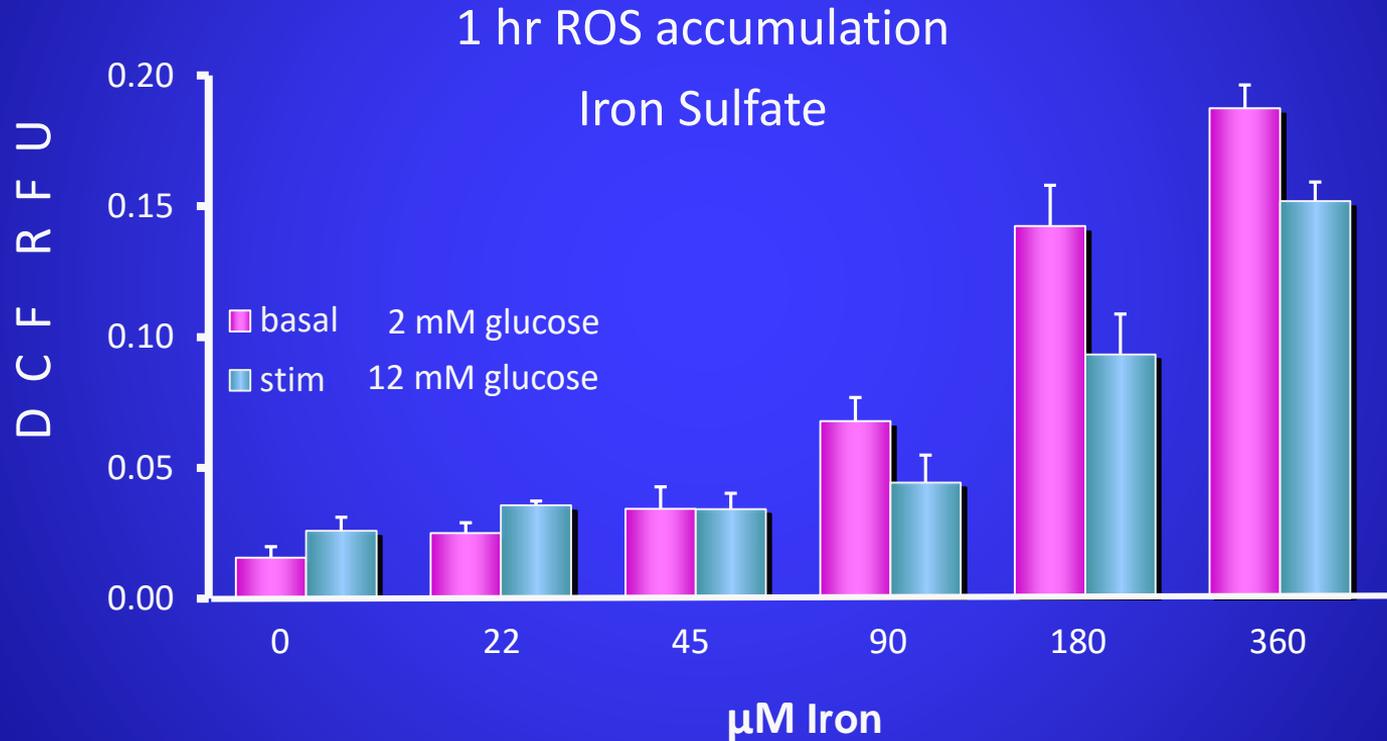
Effect of MOG and Glucose on Rat Islet REDOX State



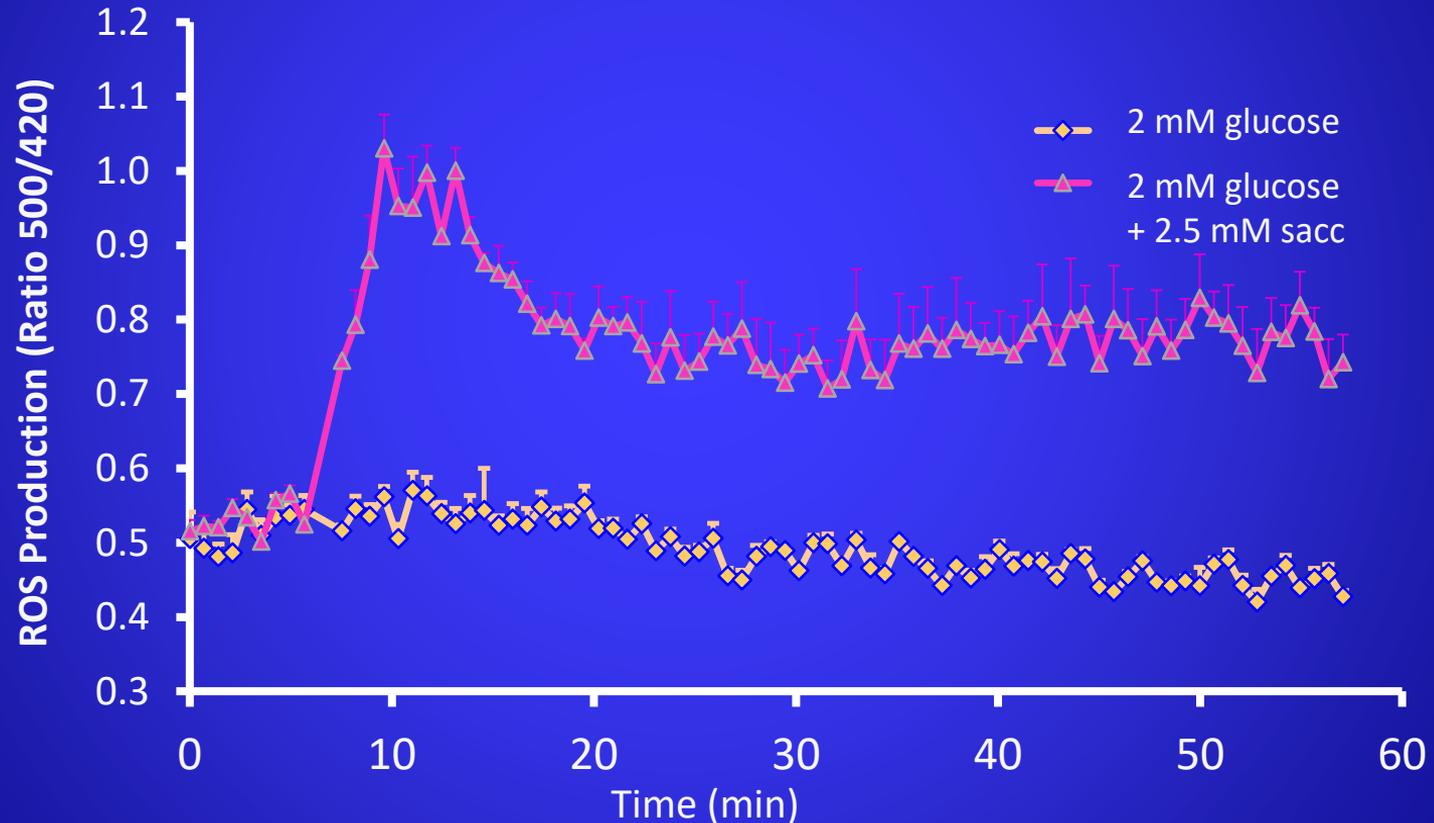
ROS is Generated by MOG



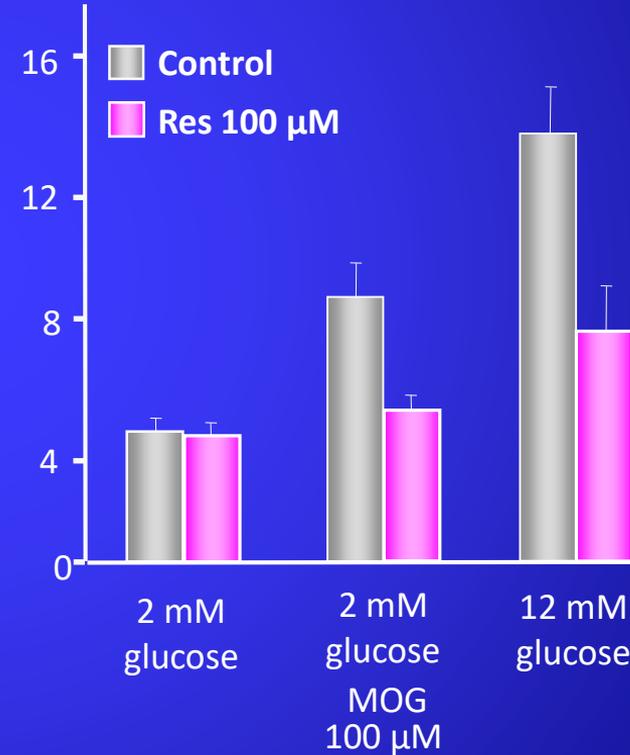
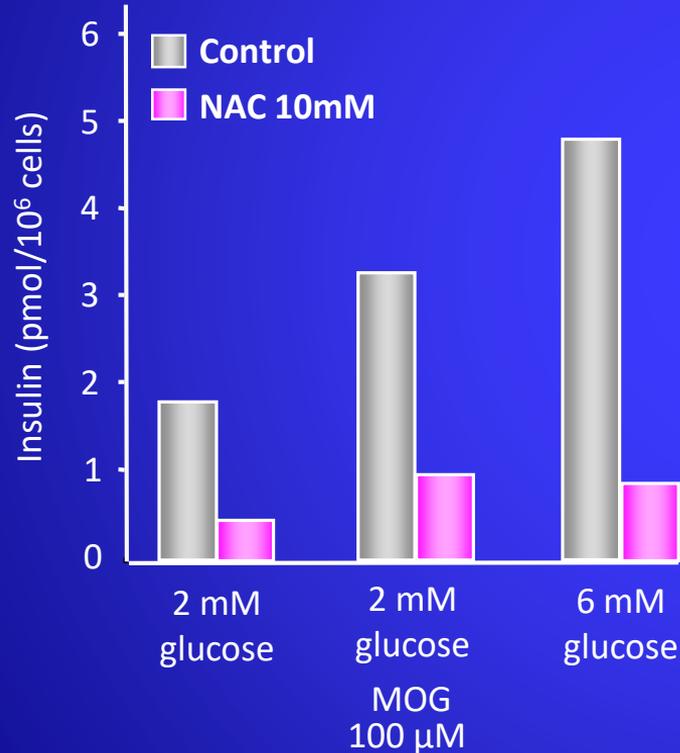
Iron Increases ROS



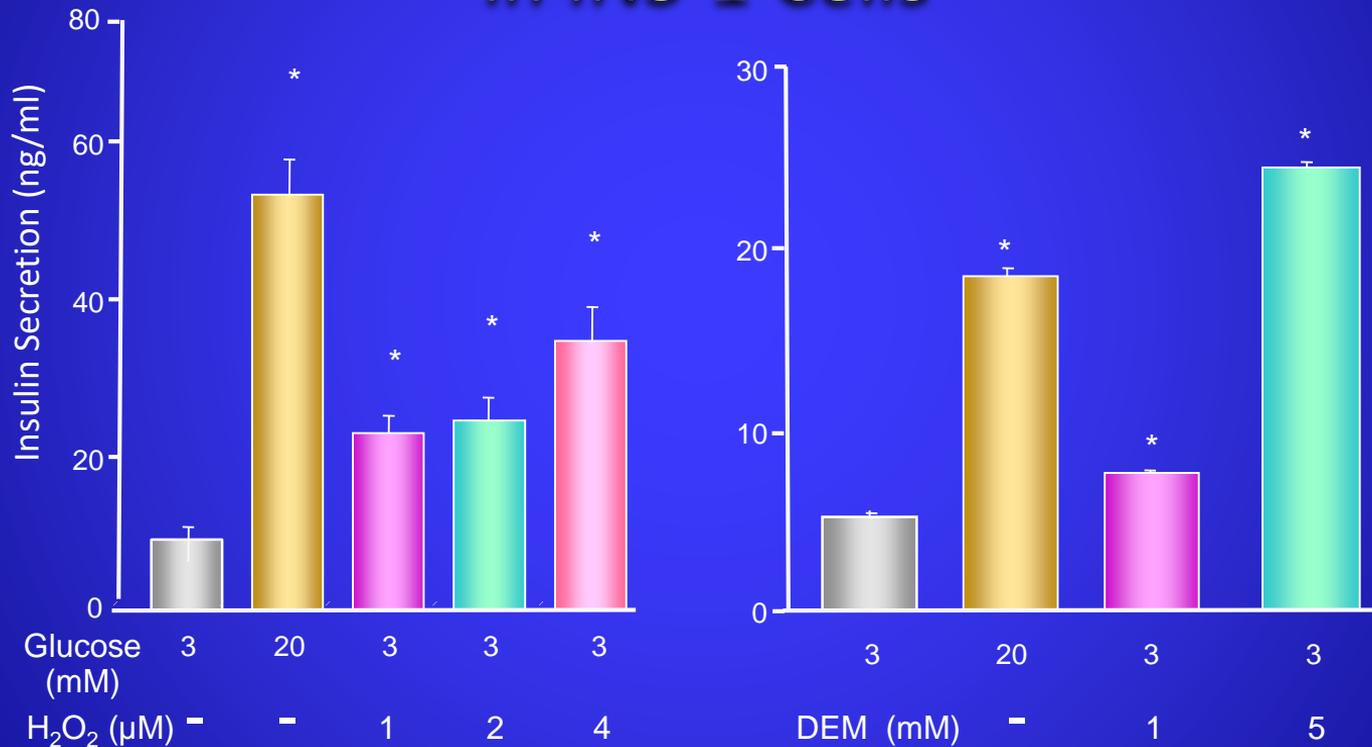
Effect of Saccharin on ROS in INS-1 Cells



Effect of ROS Scavengers on Insulin Secretion from INS-1 cells

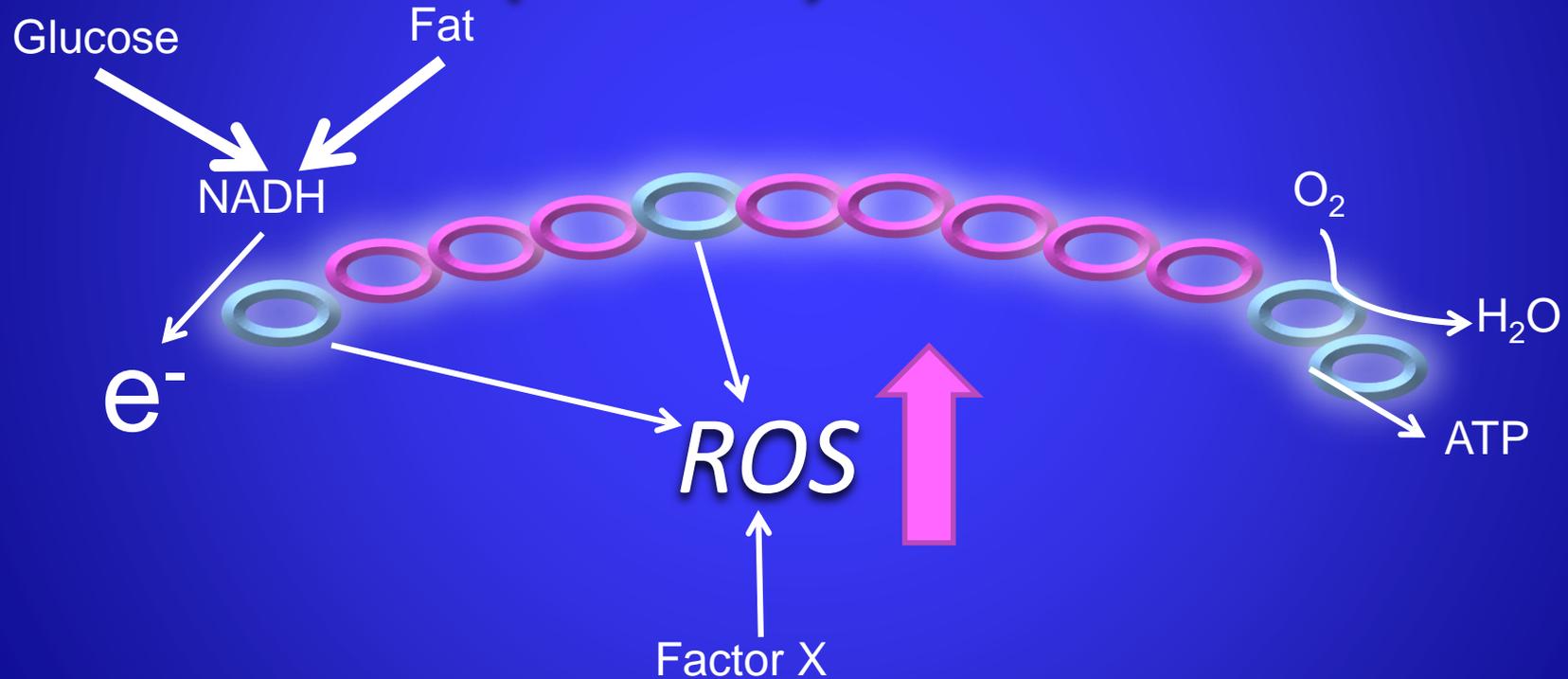


H_2O_2 Increases Insulin Secretion in INS-1 Cells



* $p < 0.05$
DEM, diethylmaleate

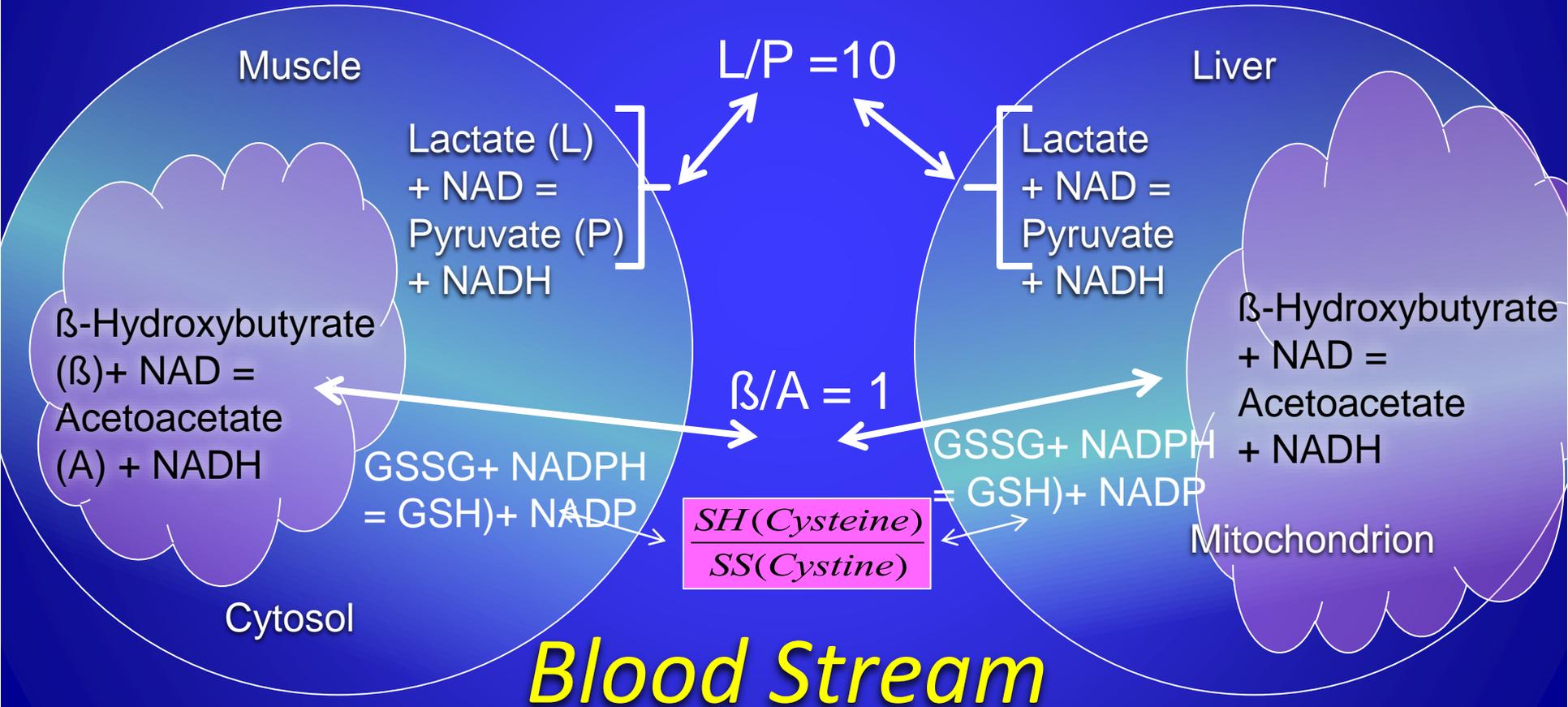
ROS are Produced at High NADH (Redox) in the ETC

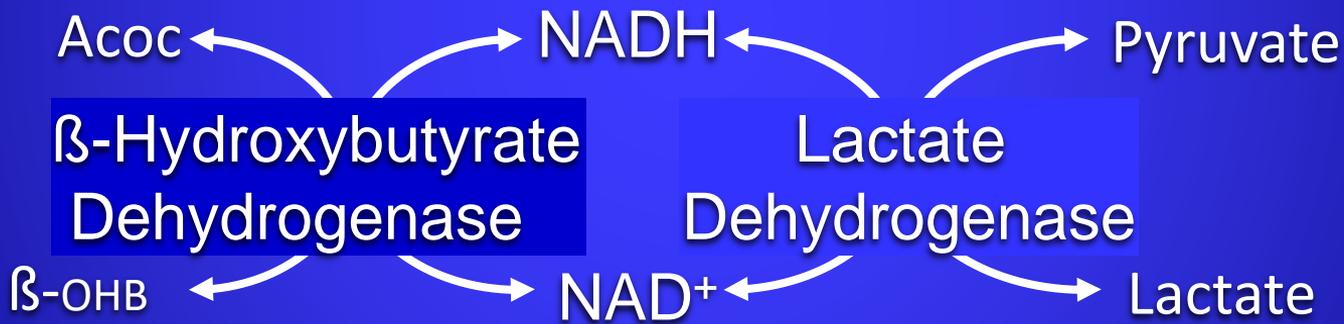
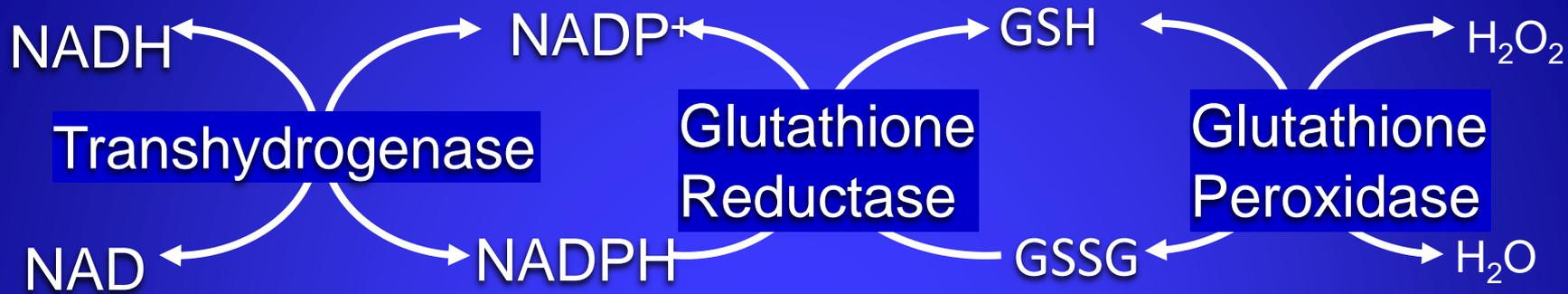


How Do These Agents and Excess Fuels Stimulate Basal Insulin Secretion?

- Through increases in redox: NADH production or less use
- Through changes in ROS: more production or less scavenging
- BOTH ROS AND REDOX CONTRIBUTE TO THE CIRCULATING REDOX STATE

REDOX is a Linked Communication System

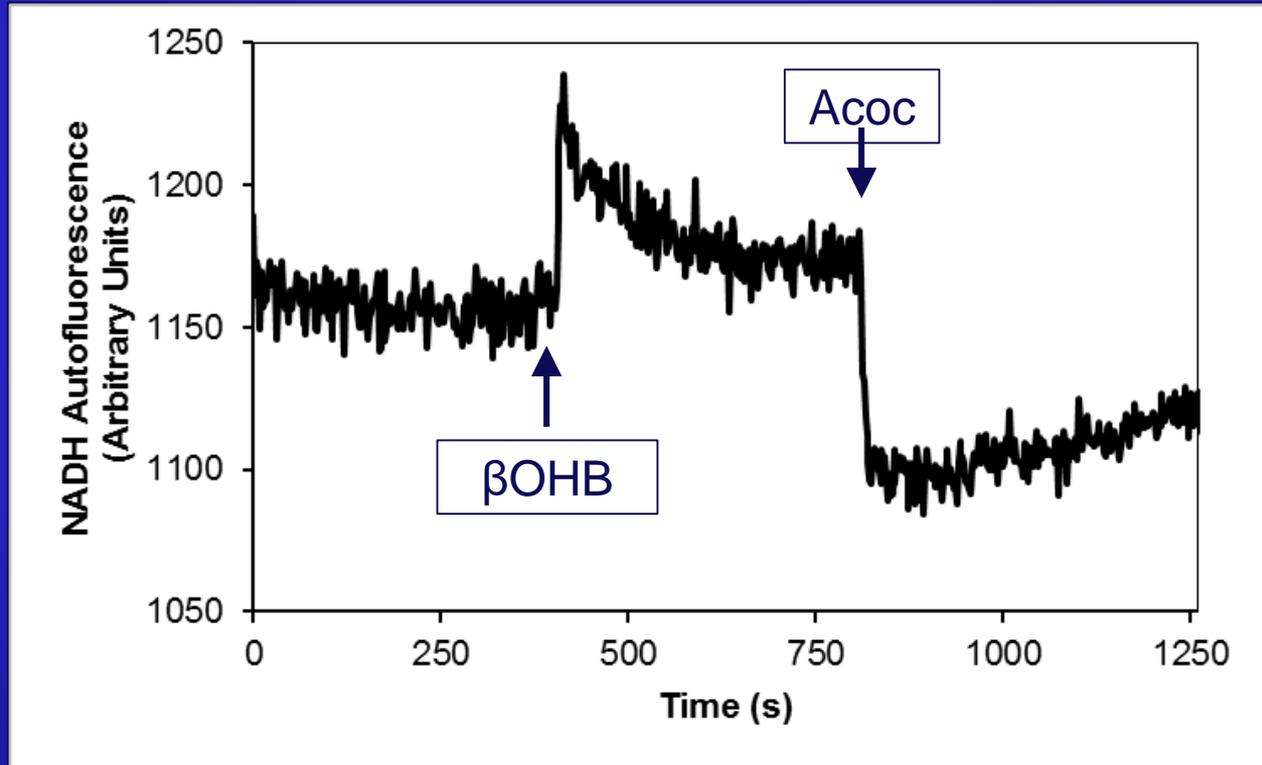




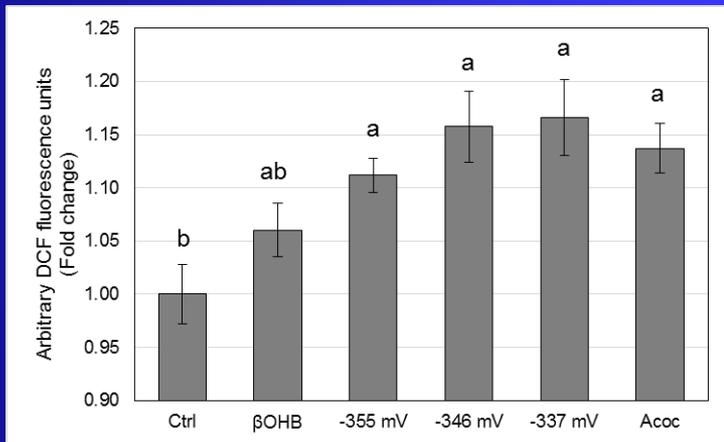
Mitochondria

Cytosol

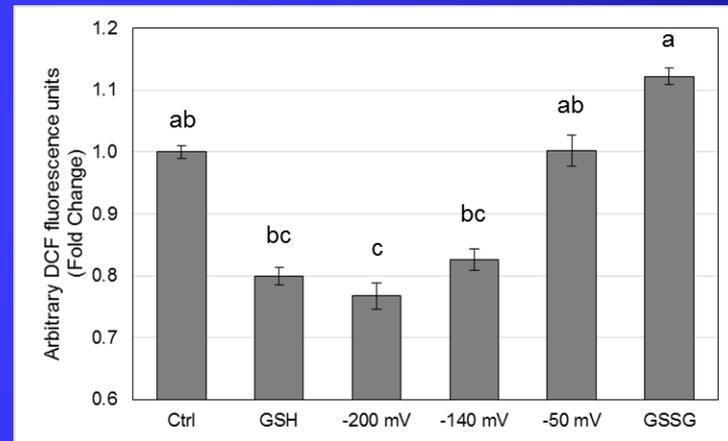
Extracellular Addition Changes Intracellular Redox



Extracellular Redox Changes Affect Hepatic ROS Production

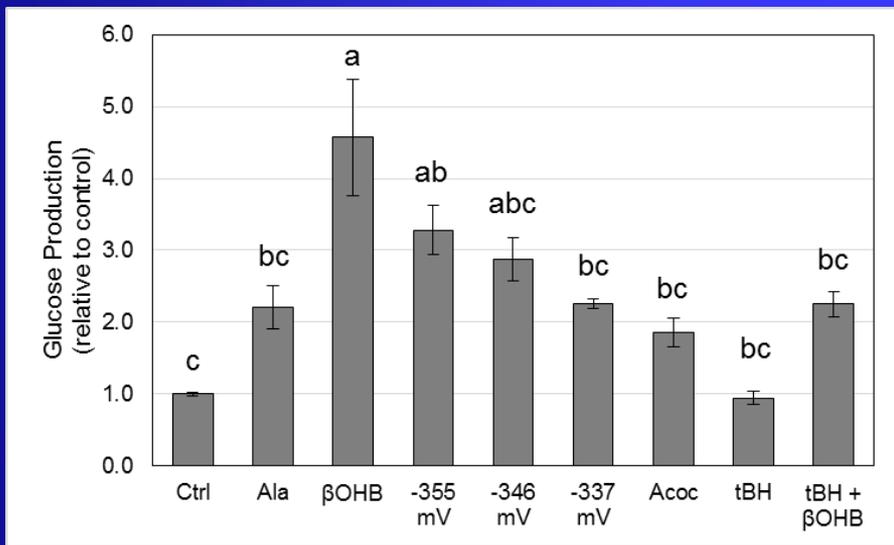


oxidized

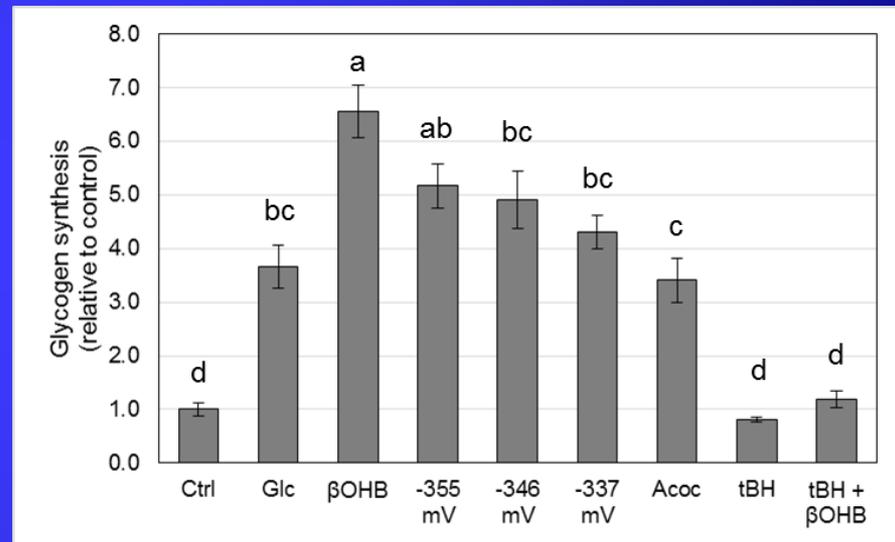


oxidized

Glucose Production and Glycogen Synthesis

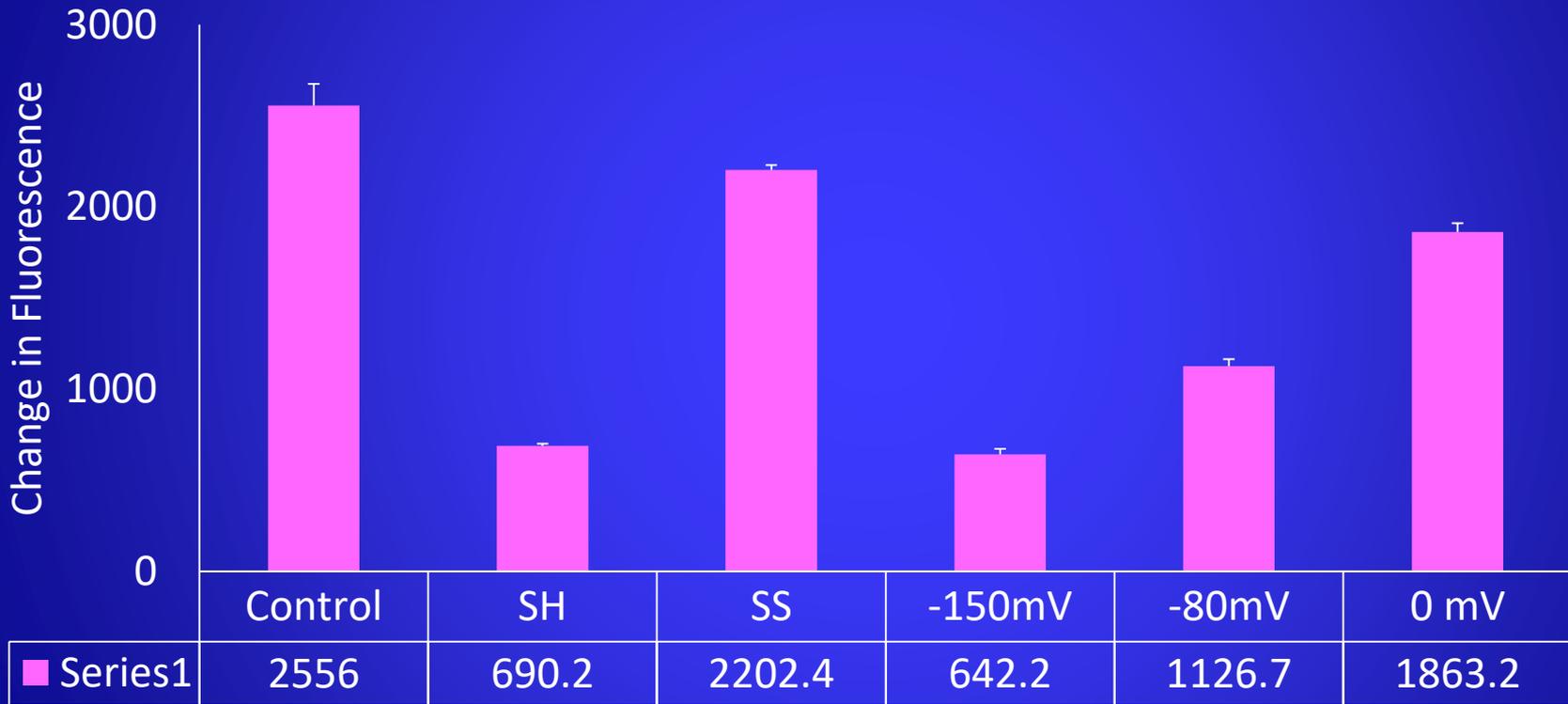


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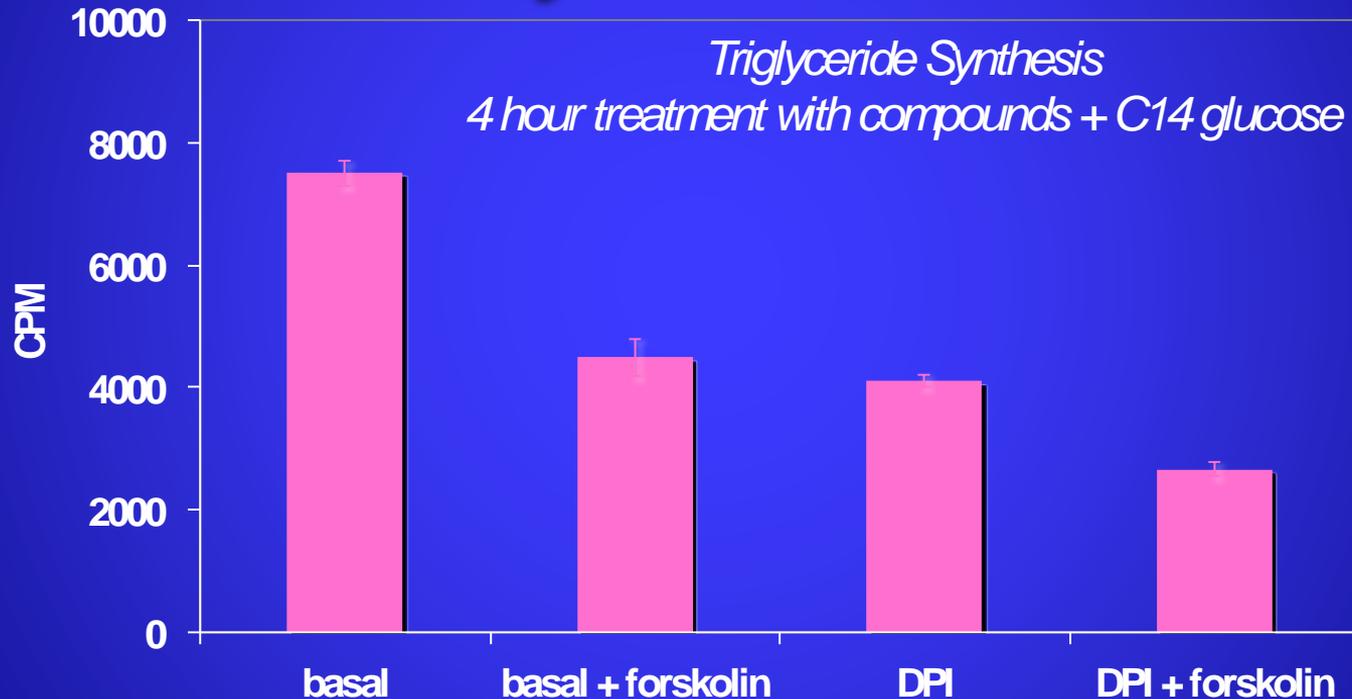


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Adipocyte ROS Generation

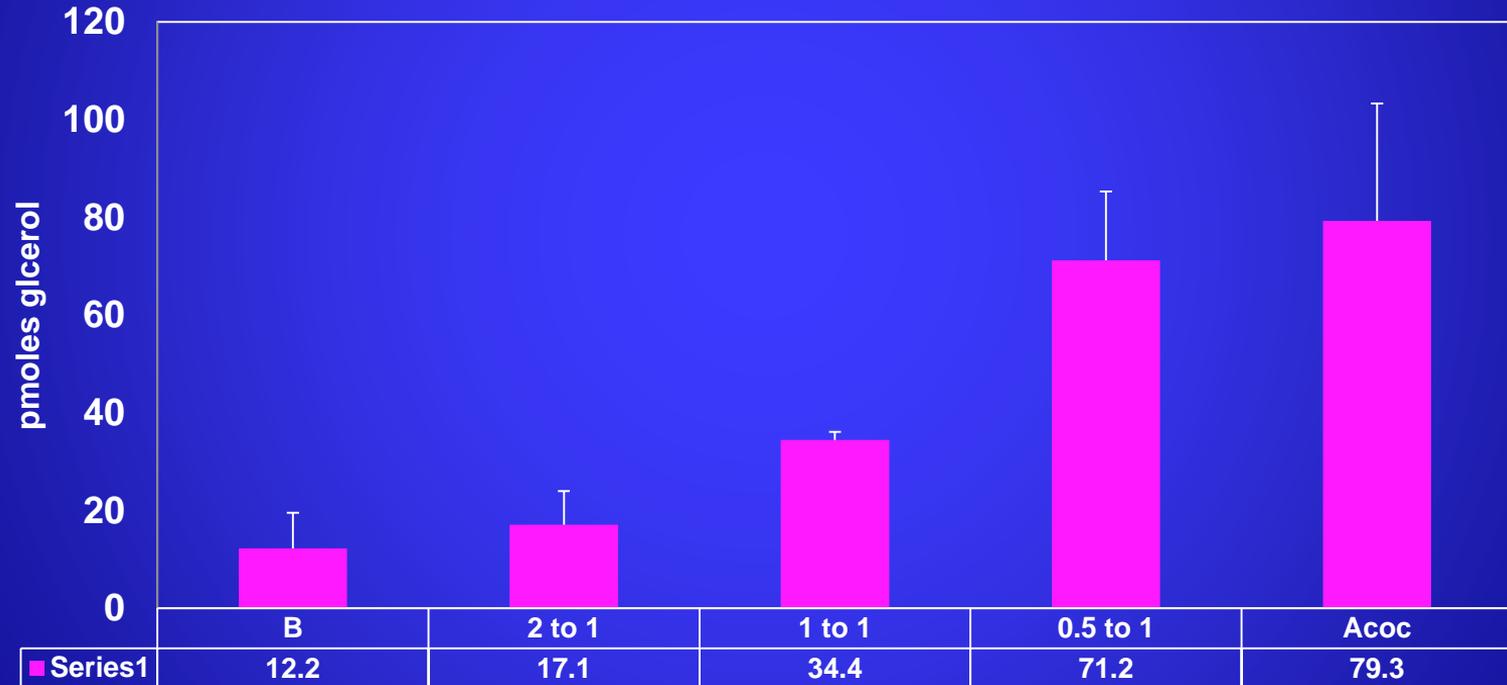


ROS Required for Basal Lipid Synthesis



Redox Alters Adipocyte Lipolysis

4 hours



Roles of ROS

- Response to excess fuel
- Indicator of fuel excess
- Response to exogenous substances
- Stimulates flux thorough NNT and consequent leak
- Communicator via THIOLS in the blood stream
- Failure to metabolize ROS can cause obesity & T2D
- NNT is required to metabolize ROS

Energy Efficiency, ROS and Redox Respond to Altered Nutrient Supply

- Pancreatic β -cells regulate insulin secretion
- Adipose tissue controls lipid synthesis, breakdown, release of fatty acid and secretion of adipokines
- Liver controls gluconeogenesis and ketogenesis as well as lipid packaging and secretion
- Gut and brain control and integrate food consumption and satiety

Challenge: Test New Hypotheses

- Identify agents that alter energy efficiency.
- Inhibit excessive insulin secretion before β -cell failure occurs
- Prevent excess lipid accumulation by stimulating oxidation and lowering insulin with existing drugs and combinations.
- Consider that the metabolic state is communicated to all tissues regardless of site of initiation
- Choose animal and cell models well: not C57Bl6J

Unanswered Questions

- How do people who successfully defend their weight compared with those that gain weight more easily differ?
- Which comes first in patients that become obese? Obesity, HL, HI, or IR?
- What are the common weight trajectories over a lifetime? Not the average, individual patterns?
- Are there differences in insulin levels during over and underfeeding in easy gainers vs easy losers?

What Causes Metabolic Disease?

- Obesity, diabetes and FFA correlate with both hypersecretion and insulin resistance
- Insulin infusion causes insulin resistance
- Inhibition of insulin secretion improves resistance and increases weight loss-in a few small clinical trials
- Environmental agents may also cause hypersecretion

Should we seek single tissue defects to explain metabolic disease?

- β -Cells may secrete too much insulin
- Hepatocytes may produce too much glucose
- Fat cells may release too much FFA or not store efficiently
- Muscle becomes insulin resistant
- Neural cells may fail to sense satiety or hunger

Collaborators

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- Caroline Apovian
- Keith Tornheim
- James Hamilton
- Wen Guo
- Nawfal Istfan
- Lucia Rameh
- Ann-Marie Richard
- P.-O. Berggren

Marc Prentki

- Chris Rhodes
- James Kirkland
- Sheila Collins
- Karel Erion
- Amber Kleckner
- Tova Meshulam
- Laura Nocito
- Jingbo Pi

Orian Shirihai

Thank You