Effects of environmental chemicals on energy metabolism and insulin secretion

Barbara E. Corkey, Jude T. Deeney, Karel Erion, Nathan Burritt and Orian Shirihai

Obesity Research Center
Boston University School of Medicine
The Problem

- There is neither cure nor understanding of obesity and diabetes
- Many proteins and organs implicated - none sufficient
- Perhaps our current focus on insulin resistance is wrong
The Road from Hyperinsulinemia to Redox Regulation and ROS

- Is hyperinsulinemia the problem?
- Can any changes in our environment cause an increase in basal insulin secretion?
- What causes basal insulin secretion?
- Could these changes influence other organs to explain the multi-organ nature of diabetes?
T2DM Patients Have Insulin Levels 900% of Normal

10 Days Insulin Minipump in Rats

Plasma Glucose (mmol/l)

- Hyperinsulinemic
- Control

Glucose OK

Plasma Insulin (µU/ml)

- Hyperinsulinemic
- Control

Juan et al. Metabolism 48:465 1999
Body Weight Difference Between DZ and Placebo Groups

Weight Change (%) vs. Weeks

-15 -12.5 -10 -7.5 -5 -2.5 0 2.5

0 1 2 3 4 5 6 7 8 9 10

Lead-in Period

Placebo
Diazoxide

Glucose OK

Alemzadeh R et al. JCEM 1998;83:1911-1915
Is this Insulin Resistance or Hypersecretion?

Both! But which comes first?
Hyperinsulinemia: A Model

β-Cell Hypersecretion

Hyperinsulinemia

Insulin Resistance

Obesity and Diabetes
Interpretation

- Obesity, diabetes and FFA cause hypersecretion and insulin resistance
- Either can be primary. So why focus on resistance?
- Insulin infusion causes insulin resistance
- Inhibition of insulin secretion improves resistance and increases weight loss
- Normoglycemia is maintained
**Insulin Resistance may be Beneficial**

- Insulin resistance may be an adaptive response to maintain normoglycemia in the presence of high insulin.
- Improving insulin sensitivity, without diminishing hypersecretion, may cause hypoglycemia!
Hyperinsulinemia as Problem?

1. What might cause insulin secretion in the absence of a stimulatory fuel?

2. How do these agents stimulate secretion?

3. Is ROS essential and sufficient for secretion? Can secretion be stimulated by increasing redox?
Comparison of GSIS in Rat Islets Cultured in 11 mM Glucose ± Oleate

Comparison of GSIS in Rat Islets Cultured in 11 mM Glucose ± Oleate

\( S_{0.5} = 8.5 \)

\( S_{0.5} = 11.9 \)

Erion et al unpublished data
Food Today

- Processed food
- 4,000 new agents
- Almost none evaluated as causes of diabetes or obesity
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)
Hyperinsulinemia as Cause

- Factor X
- **β-Cell Hypersecretion**
  - Hyperinsulinemia
  - Insulin Resistance

- Obesity and Diabetes
HTS of Environmental Agents
Mono-Acylglycerides (MG)

- MG are formed in the gut by release of FFA in the 1 and 3 positions of TG
- In cells via release of a fatty acid from DG, by DGL or HSL
- LPL by release of FFA in positions 1 and 3.
- Commonly added to food products as emulsifiers and preservatives
MOG Stimulates Basal Secretion

MOG (µM)

Insulin (fmole/5000 Islet cells)

0 25 50 100 200 400

Saadeh et al PLOSone e30200. Epub 2012 Jan 17
Artificial Sweeteners Affect Insulin Secretion in Dissociated Rat Islets

Iron Induces Insulin Secretion in INS-1 Cells

1. 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
Hyperinsulinemia as Problem?

1. What agents cause insulin secretion in the absence of a stimulatory fuel?
2. How do these agents stimulate secretion?
3. Is ROS essential and sufficient for secretion? Can secretion be stimulated by increasing redox?
Effect of MOG and Glucose on Rat Islet REDOX State

% increase in fluorescence

MOG

Glucose

% increase in fluorescence

15 mM Glucose

Time (min)

Time (min)

Saadeh et al PLOSone e30200. Epub 2012 Jan 17
ROS is Generated by MOG

![Graph showing the change in HyPer fluorescence ratio over time for Basal and MOG conditions.](Image)

**A.**
- **Time (min):** 0 to 30
- **HyPer fluorescence ratio:** Basal and MOG conditions

**B.**
- **HyPer Area Under Curve:** Basal and MOG conditions

Saadeh et al. PLOSone e30200. Epub 2012 Jan 17
2. How Do These Agents Stimulate Secretion?

- Through changes in redox
- Through changes in ROS
- Diazoxide does not inhibit
- Ca\(^{2+}\) does not change
Hyperinsulinemia as Problem?

1. What agents cause insulin secretion in the absence of a stimulatory fuel?
2. How do these agents stimulate secretion?
3. Is ROS essential and sufficient to cause secretion? Can Secretion be Stimulated by Increasing Redox?
Effect of ROS Scavengers on Insulin Secretion from INS-1 cells

Saadeh et al. PLOSone e30200. Epub 2012 Jan 17
### $H_2O_2$ Increases Insulin Secretion in INS-1 Cells

<table>
<thead>
<tr>
<th>Glucose (mM)</th>
<th>3</th>
<th>20</th>
<th>3</th>
<th>3</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2O_2$ (µM)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Insulin Secretion (ng/ml)

- 0
- 10
- 20
- 30

<table>
<thead>
<tr>
<th>DEM (mM)</th>
<th>3</th>
<th>20</th>
<th>3</th>
<th>3</th>
</tr>
</thead>
</table>

- 0
- 10
- 20
- 30

*Pi et al, Diabetes 2007*
3. Is ROS Essential and Sufficient? Can Secretion be Stimulated by Increasing Redox?

- Yes
Summary and Implications

1. Hyperinsulinemia can initiate insulin resistance

2. Environmental agents increase insulin secretion in the absence of a stimulatory fuel.

3. These agents stimulate secretion via changes in redox and ROS. ROS is essential and sufficient.

4. Agents are transported to cells via the circulation and can interact with all organs.

5. Agents could impact other organs similarly.
ROS Production in Hepatocytes

GSH / GSSG

CyS / CySS

Laura Nocito et al. PLoSone, in press
Do Changes in Redox or ROS Alter Function?
Hepatic Glucose Production

Laura Nocito et al. PLoS One, in press
Redox and ROS Affect Function

- Increasing extracellular SH, L/P or β/A decreases intracellular redox and ROS production.
- Decreases in redox increase ROS and inhibit hepatic glucose production and adipocyte lipolysis and TG synthesis.
Mitochondrion

$\beta$-Hydroxybutyrate ($\beta$) + NAD = Acetoacetate (A) + NADH

Blood Stream

Lactate (L) + NAD = Pyruvate (P) + NADH

$L / P = 10$

Muscle

Cytosol

SS(GSSG) + NADPH = SH(GSH) + NADP

Liver

Cytosol

Lactate + NAD = Pyruvate + NADH

$\beta$-Hydroxybutyrate + NAD = Acetoacetate + NADH

SS(GSSG) + NADPH = SH(GSH) + NADP

Muscle

Mitochondrion

SS(GSSG) + NADPH = SH(GSH) + NADP

Liver

Mitochondrion

SH(Cysteine) / SS(Cystine)
Eating too much and exercising too little causes 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 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 proton leak: increase energy expenditure

*Salans, Horton, Sims 1976
Variations in Energy Efficiency

- Can be induced by excess nutrients via a proton leak
- Current hypothesis is that ROS can control both energy efficiency and respiration
- Dysregulation of energy efficiency rather than overeating may cause obesity
Thank You