Hostility, Adiposity and the Adrenal Medulla

*Psychological Factors And The Physiology of Glucose Regulation*

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Disclosure: This work is supported by R01HL076020 and P01HL36587.
• Exaggerated glycemic response to stress and to epinephrine (EPI) have been found in animals and humans predisposed to obesity and diabetes
C57BL6J Ob/Ob Mouse
Kuhn et al: 1987, PHARMACOLOGY, BIOCHEMISTRY & BEHAVIOR
Pima Indians
Serum glucose (mM)

Minutes post prandial

Stress Test Times

1 2 3

Caucasian
Pima

Personality Factors Have Also Been Related to Glucose Metabolism

• Depressed affect
• Hostility
Hostility

- Hostility is a personality construct that has been associated with increased risk of cardiovascular disease and all cause mortality.
Hostility is Commonly Measured By The 27 item Cook Medley Hostility Questionnaire (CMHOST)

Covers primary cognitive dimensions reflecting cynicism and mistrust

“I think most people would lie to get ahead.”

“People often disappoint me.”

“It’s safer to trust nobody”
The Mechanism of Hostility’s Relationship to Disease is Unknown

- Hostility has been related to increased neuroendocrine response to stress.
- Hostility has also been associated with increased food intake, BMI, and decreased insulin sensitivity.
Does Hostility Impact Glucose Metabolism?

- Fasting glucose and HbA1c are linearly related to risk for cardiovascular disease, even throughout the “normal” range.
Hostility Is Correlated with Fasting Glucose in African Americans

Surwit et al 2002, *Diabetes Care*
Relationship of Hostility to Fasting Glucose Was Repeatedly Found in African American Women

<table>
<thead>
<tr>
<th></th>
<th>Study A N=101</th>
<th>Replication Study B N=44</th>
<th>Replication Study C N=38</th>
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<tbody>
<tr>
<td>Fasting glucose</td>
<td>.22*</td>
<td>.34*</td>
<td>.34*</td>
</tr>
</tbody>
</table>

*p<.04

Georgiades, et al, 2009 *Psychosomatic Medicine*
How Does Hostility Impact Glucose Metabolism?

• Determine the variables which may mediate Hostility’s impact glucose metabolism in these populations
  – Sympathoadrenal activity
  – BMI
  – Physical Activity

• Determine the relationship between Hostility and glucose kinetics in healthy White and African American men and women

  Surwit et al, 2009, *Psychosomatic Med*
The Labeled IVGTT

- Enables modeling of glucose kinetics in vivo

- Enables separation of endogenous glucose (from liver and kidneys) from exogenous glucose
Method

• 115 African American and White male and female volunteers
• Glucose bolus (300mg/kg) containing 2mg/kg (0.7%) $^{13}\text{C}_6$-glucose administered by IV push (1 min)
• Specimens collected at t= -1, 2, 3, 4, 5, 6, 10, 12, 15, 20, 30, 40, 60, 80, 100, 120, 140, 150, 180, 210, 240 min.
• Total Glucose & Insulin assayed
• Glucose Isotope ratio by mass spec
Minimal Model of Glucose Kinetics

- **DI** = Glucose Disposition Index, reflects the ability of the beta cells in the pancreas to compensate for increased insulin resistance.
- **Sg** = Glucose effectiveness, is a measure of the ability of glucose to stimulate its own uptake independent of insulin.
- **AIRg** = Glucose-stimulated insulin release.
- **Si** = Insulin Sensitivity.
- **NEFA** = Non-esterified fatty acids.
- **EGP** = Endogenous glucose production, refers to glucose produced in the liver and kidneys through the process of gluconeogenesis.
• Hostility was related to metabolic parameters only in African American Women

• Hostility was unrelated to self-report of physical activity as measured by the IPAQ.
Hostility and BMI

Figure 1. Association of Hostility to BMI in women and men. Blue squares and lines represent African Americans and green circles and lines represent Whites.
Relationship of Hostility to BMI in African American Women

Relationship of Hostility to Epinephrine Change in African American Women

Relationship of Hostility to Fasting NEFA in African American Women

Surwit, R. S. et al. *Psychosomatic Medicine*
Relationship of Hostility to DI in African American Women

![Graph showing the relationship between CM HOST and LnDI with a correlation coefficient of r = -0.44, p = 0.01.]

R Sq Linear = 0.19

Relationship of Hostility to Sg in African American Women

\[ r = .49, p = .008 \]

\[ R^2 \text{ Linear} = .24 \]

Hostility is Related to Hepatic Glucose Production

- Hepatic glucose production was estimated by assessing the ratio of labeled to unlabeled glucose and then measuring the latency of suppression of hepatic glucose following the IV bolus
Latency Time of Endogenous Glucose Suppression During the IVGTT
Hostility Was Associated with Increased Time to Suppression of Endogenous Glucose in African American Women

\[ r = 0.50, \ p = 0.001 \]

\[ R \text{ Sq Linear} = 0.25 \]
# Endogenous Glucose Latency Time in Relation to NEFA and Sg

<table>
<thead>
<tr>
<th></th>
<th>Spearman’s rho</th>
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<tr>
<td>NEFA</td>
<td>.50*</td>
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<tr>
<td>Sg</td>
<td>.50*</td>
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</table>

* $P<.01$
How Hostility Appears to Impact Fasting Glucose
Hostility, Metabolism and Serotonin

• Recent studies showed that AN SSRI (citalopram) successfully reduced hostility and improved metabolic parameters in high hostile individuals. Kamarck et al, Psychosomatic Medicine, 2009, Psychoneuroendocrinology, 2011).
Does Serotonin Metabolism Play a Role in the Relationship of Hostility to Metabolic Function?
Methods

Sample
37 healthy African American women. Mean age 32(9) years.

Measures
Hostility was assessed by a 27-item version of the Cook-Medley Hostility Scale. Tryptophan (TRYP), 5-OH-tryptophan (5HTP) and 5HIAA was assayed from cerebrospinal fluid drawn after lumbar puncture. Glucose and insulin were assayed from blood samples drawn after an overnight fast.
## Associations Among Study Variables

<table>
<thead>
<tr>
<th></th>
<th>TRYP</th>
<th>5HTP</th>
<th>5HIAA</th>
<th>Hostility</th>
<th>Glucose</th>
<th>Insulin</th>
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<tr>
<td>TRYP</td>
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<td>.37*</td>
<td>.01</td>
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<tr>
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<td>.41**</td>
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</table>

* P<.05, **P<.01

Boyle et al, 2010, *Psychosomatic Medicine*
Common Factor Analysis

A common factor analysis performed on age-adjusted hostility scores, fasting glucose and insulin, 5HTP and 5HIAA yielded a single factor (Eigenvalue = 2.31) in which all variables loaded above .55.
Hypothesized Interrelations Between Central Serotonin, Hostility and Glucose Metabolism
Do Central Adiposity and Epinephrine Interact to Determine Glucose Levels in African American Women?

Surwit et al, 2010, *Obesity*
DEXA scan

Standard regions of a DEXA scan:
1. head
2. trunk
3. right arm
4. left arm
5. right leg
6. left leg
Association between % Trunk Fat and Fasting Glucose in African American Women

\[ r = 0.45, \ p < 0.001 \]

R Sq Linear = 0.204
Association Between Plasma EPI Levels and Fasting Glucose in African American Women with High Central Adiposity

African American women, High Trunk fat (>32%) group

R Sq Linear = 0.361
Association Between Plasma EPI Levels and Fasting Glucose in African American Women with Low Central Adiposity

African American women, low trunk fat (<32%) group

Fasting Glucose vs. ln EPI mean

R Sq Linear = 6.57E-4
Fasting Glucose Levels by Trunk Fat Group (Low/High) and Epinephrine Group (Low/High)

Surwit et al. 2010, *Obesity*
NEFA levels by EPI and Obesity Group in African American Women
Conclusion

• Epinephrine interacts with central adiposity in determining fasting NEFA and fasting glucose in African American women
Does Adrenal Medullary Function Play a Role in Maintaining Euglycemia?
Method

We examined 445 healthy euglycemic individuals (159 white women, 156 white men, 75 AA women and 55 AA men) who had completed a DEXA scan as well as collection of both plasma and urine epinephrine measurements.
Plasma Epinephrine Levels In Men and Women With Fasting Glucose <95 mg/dl

![Graph showing mean resting EPI level (pg/ml) vs trunk fat level (%) for different percentage ranges.](image)
Urinary Epinephrine Levels in Men and Women With Fasting Glucose < 95 mg/dl
# Relationship of Urinary Epinephrine to BMI in Chinese Euglycemic Subjects

<table>
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<tr>
<th>BMI</th>
<th>16-20</th>
<th>21-23</th>
<th>24-25</th>
<th>26-28</th>
<th>28-38</th>
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<tbody>
<tr>
<td>Urinary EPI (nm/dl)</td>
<td>72</td>
<td>67</td>
<td>53</td>
<td>62</td>
<td>41</td>
<td>P&lt;.001</td>
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</table>

Lee et al, 2001, *Metabolism*
Several Smaller Studies Show the Same Phenomenon in Other Populations


EPI Does Not Decrease With Increasing BMI When Fasting Glucose > 95 mg/dl
Does Adipose Tissue Mass Feed Back to Limit Adrenal Medullary Function to Maintain Euglycemia?
Summary

• Hostility is related to body weight, adrenal medullary function, and CNS serotonin metabolism, and fasting glucose.
• Adrenal medullary function interacts with central adiposity to determine fasting NEFA and fasting glucose.
• Adrenal medullary function decreases with increasing adiposity in euglycemic individuals, but not in individuals with impaired fasting glucose.
• Abnormal glucose metabolism could be due, in part, to a failure of the adrenal medulla to adapt to increasing adiposity.
Collaborators

• Anastasia Georgiades
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