Behavioral origins of metabolic syndrome disorders

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The burden of history

Insulin and IR

Brain-cognitive functions

Sex and reproduction

Growth and development

Skin

Energy homeostasis

Innate immunity

Anything primary?

Badly needed: a theory for all
Inadequacies of thriftiness paradigm

Thrifty gene

- Who is thrifty? Measurements of resting metabolic rates not in support
- Obesity more due to defective fat oxidation than metabolic frugality
- Are fat people more likely to survive famines? ... No data in support

Thrifty phenotype

- Majority of T2D have normal birth weight
- Exercises often reduce insulin resistance without changing BMI
The adipokine paradox

**Adipocyte**

- Adiponectin
- Sfrp5
- Anti-inflammatory
- Anti-obesity
- Insulin sensitizing

- TNF-alpha
- IL-6 & Other
- Pro-inflammatory
- Pro-insulin-resistance
What matters? Obesity or perception of obesity?

1. Perception of calories affects life span in Drosophila (Libert et al. 2007)

2. Malnourished rats had low body weight and higher IR, positive correlation within malnourished colony (Hardeekar 2001)

3. Slope of regression greater in populations with low mean BMI

4. Optimum BMI increases with mean BMI (Su 2005)
The hawk and dove game

<table>
<thead>
<tr>
<th>Opponent</th>
<th>Hawk</th>
<th>Dove</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal Strategy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawk</td>
<td>-25</td>
<td>+50</td>
</tr>
<tr>
<td>Dove</td>
<td>0</td>
<td>+15</td>
</tr>
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No single strategy is evolutionarily stable.

The hawk (aggressive) and dove (non-aggressive) strategies co-exist in a stable polymorphism owing to negative frequency dependence.
Real life Hawk and Dove situations

- **Survival of the mightiest?**

  While dominant males have greater access to females, subordinate males are not outright losers. They remain submissive but ‘sneak-mate’ opportunistically. Similar behaviors seen in amphibians, fish and even invertebrates.

- **No... ... Survival of the fittest.**
Accompanying physiology

**Dominant**
- High testosterone/estradiol. High sexual activity
- Low extracellular brain serotonin, plasma cholesterol, cortisol
- Greater access to calorie rich food (snatcher)

**Subordinate**
- Low testosterone/estradiol. Restrained sexual activity
- High brain serotonin, plasma cholesterol, insulin, cortisol
- Less access to calorie rich food (sneaker).
  More fibrous food
Serotonin: a key player

- Manipulated serotonin elevation makes dominant individuals submissive (Larson 2001)
- 5-HT 1B receptor knockout mice become more aggressive (Baxter 2001)
- Serotonin necessary for control of impulsive aggression (Linnoila et al 1992, Seo et al 2008)
- Chronically elevated extracellular serotonin signaling in hypothalamus induces peripheral insulin resistance (Luo et al 1998)
- A long known and strong but ignored association: Diabetic rats lose aggression (review Leedom et al 1987)
Natural causes of aggression: food and sex

Aggression suppression: food satiety, stored fat, sexual satiety, loss of sexual/reproductive potential, being weaker than the opponent.
Why is aggression control accompanied by IR

- Alternative strategy (dove) needs less of physical activity, more social manipulation skills (Bernstein et al, 2008)
- A shift from muscle dependent to brain dependent life, altered budget allocation to tissues
- Insulin’s main job is energy budget allocation and insulin resistance changes the budget allocation
Insulin: a budget allocation mechanism

Increase

Insulin independent

Decrease

Insulin Resistant

Glucose & Nutrients in blood

Brain

GUT

Muscle
Insulin and Brain

Insulin infusion

1.5 mU/Kg.min

15 mU/Kg.min

Insulin infusion with controlled blood glucose levels enhances memory function
Hawk-Dove versus Soldier-Diplomat

(Watve and Yajnik 2007)

Similarities

• Avoidance of physical aggression
• Social manipulation skills

Differences

• Doves are subordinate and have less access to calorie-rich food. Diplomats can have high social ranking and access to calorie-rich foods
• Distinct physical, verbal and political types of aggressions in humans. Only physical in animals.
Association between aggression signals and obesity/IR signals

<table>
<thead>
<tr>
<th></th>
<th>Pro aggression</th>
<th>Antiaggression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro obesity/IR</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Antiobesity/IR</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

Chi- square = 14.28, p = 0.0002

Metabolic syndrome = Aggression control gone out of control

(Belsare et al 2010)
Are there detectable behavioral differences?

Ultimatum game offers:
- Metabolic syndrome vs age matched healthy control
- Diabetic vs non-diabetic

(Joshi et al. 2010)
Behavioral deficiency disorders

Type 2 diabetes, hypertension, high cholesterol, CVD, osteoporosis, PCOS

• We evolved as hunter-gatherers
• A number of behaviors evolved with us
• Every behavior linked to a neuro-endocrine pathway
• Deficiency in certain behaviors can cause problems with specific neuro-endocrine mechanisms
• Behavioral deficiencies can be treated with behavioral supplementation
How does it work?

- The serotonin pathway
- The EGF pathway
- The adipokine pathway

More mechanisms relating behavior to metabolism being discovered.

Physical aggression

Salivary EGF

Injuries.

Insulin

Healing

Beta cell regeneration
Behavioral intervention

Volunteer trials: (16 m 20 f)
• Volunteer diabetics with stable medication on a recommended games/activities/exercise regime
• No change in diet & medication
• Reduction in CRP and HOMA R without weight loss.