Should Brown Adipose Tissue be a Treatment Target?

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Conflict of Interest Disclosure

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I have no relevant relationships with industry to report
Objectives

1. Distinguish the structural and functional differences between brown and white adipose tissue.

2. Explain why brown adipose tissue has the potential to be a treatment target for obesity and metabolic dysregulation.

3. Identify which imaging modalities are available to study brown fat function.

4. List the interventions already shown to increase brown adipose tissue mass and activity.

5. Based on the currently available data, describe the likelihood that brown adipose tissue will be a treatment target for obesity and diabetes.
Too Much Fat is Highly Morbid

Obesity (BMI ≥30 kg/m²)

1994

2000

2007

Diabetes

1994

2000

2007

Two Types of Fat

White (WAT)

Energy storage
50g contains 300-500 kcal

Cold-induced [NST]
Diet-induced [DIT]

Brown (BAT)

Energy expenditure
50g consumes 100-300 kcal/day (max)

Thermogenesis via Uncoupling Protein-1 [UCP-1]


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What is Known About Adult Human BAT?

**Structure**
- Predominantly in one region of the body, but it is not a discrete organ.
- We can now use imaging to measure its volume and activity.

**Function**
- Protects against cold acutely and chronically [NST].
- People with detectable brown fat are more frequently younger, female, not taking beta-blockers, and leaner [DIT?].
- Most adult humans may have functional BAT
Pediatric BAT is More Frequently Active than in Adults, in both Girls and Boys

BAT Activity *Increases* Through Adolescence, Then Declines

**P=0.005**

Drubach LA et al. J Pediatr 2011;159:939
Pediatric BAT Activity Correlates Inversely with BMI%
We Measure BAT Mass and Activity with PET/CT

- CT = Computed Tomography, describes the tissue
- PET = Positron Emission Tomography, shows glucose uptake
- PET/CT = tells us the relative metabolic activity of each tissue
Human BAT is a Mix of White and Brown Adipocytes

Virtanen KA, et al. NEJM 2009;360:1518

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Human BAT has Extensive Neuronal and Vascular Connections as well as Numerous Mitochondria

Zingaretti MC et al. FASEB J. 2009;23:3113
How Brown Fat Generates Heat

Sympathetic Neurons
Norepinephrine

Endogenous Lipids

Plasma
Glucose
FFA

ΔμH⁺

H⁺

Intemembrane Space

Mitochondrial Inner Membrane

Matrix

H⁺

CO₂
H₂O

TCA

+ heat

+ heat

UCP-1
BAT May be Usable for Treating Metabolic Dysregulation

- BAT in cold-acclimatized mice consumed more than half of ingested lipids and glucose.
  
Adult Human Brown Fat is a Glucose Sink

- Cold-activated human BAT took up more glucose per gram of tissue than even insulin-stimulated skeletal muscle.

Orava J et al. Cell Metab. 2011;14:272-9
Uptake of Glucose and Fatty Acids Correlate with Oxidative Metabolism

- $^{18}$F-FDG tissue kinetics showed significant cold-induced activation of BAT oxidative metabolism.

- $^{18}$F-FTHA tissue kinetics showed significant cold-induced activation of BAT oxidative metabolism.

- $^{11}$C-acetate tissue kinetics showed significant cold-induced activation of BAT oxidative metabolism.

- BAT could account for the 250 ± 45 kcal expended during the 3-hour period of cold exposure.

Cold increased whole body energy expenditure by 300 kcal/day, but BAT thermogenesis accounted for only <20 kcal/day.

Cold exposure caused a significant increase in energy expenditure that correlated positively with the change in skeletal muscle mitochondrial uncoupling (state 4).

However...

There is no evidence for any alternative adaptive adrenergic thermogenesis to that mediated by UCP1, even though the existence of such mechanisms has been suggested.
Therapeutics – Increase BAT Activity and Induce Weight Loss

Cold

Hormone Ephedrine – ↑FDG uptake in BAT

Both Ephedrine and Cold Activated the SNS

Cypess AM et al. PNAS 2012, in press

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Ephedrine and Cold Increased Energy Expenditure and Fat Metabolism

Cypess AM et al. PNAS 2012, in press

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Ephedrine Had Many Unfavorable Effects on Metabolites – *Cold Did Not*

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Ephedrine</th>
<th>Cold</th>
<th>Ephedrine vs Saline</th>
<th>Cold vs Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td>83</td>
<td>95</td>
<td>83</td>
<td>&lt;0.001</td>
<td>0.88</td>
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<tr>
<td><strong>Lactic Acid</strong></td>
<td>6.9</td>
<td>11.5</td>
<td>8.5</td>
<td>&lt;0.001</td>
<td>0.015</td>
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<tr>
<td><strong>β-hydroxybutyrate</strong></td>
<td>0.16</td>
<td>0.31</td>
<td>0.11</td>
<td>0.045</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Free Fatty Acids</strong></td>
<td>0.59</td>
<td>0.76</td>
<td>0.57</td>
<td>0.16</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>2.95</td>
<td>6.79</td>
<td>3.41</td>
<td>&lt;0.001</td>
<td>0.28</td>
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<tr>
<td><strong>C-peptide</strong></td>
<td>1.37</td>
<td>1.98</td>
<td>1.67</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Norepinephrine</strong></td>
<td>120</td>
<td>205</td>
<td>365</td>
<td>0.010</td>
<td>0.004</td>
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<tr>
<td><strong>Epinephrine</strong></td>
<td>12.6</td>
<td>13.5</td>
<td>14.9</td>
<td>0.31</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Free T4</strong></td>
<td>1.13</td>
<td>1.19</td>
<td>1.12</td>
<td>0.014</td>
<td>0.62</td>
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<tr>
<td><strong>Total T3</strong></td>
<td>105.5</td>
<td>114.3</td>
<td>110.5</td>
<td>0.026</td>
<td>0.53</td>
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<tr>
<td><strong>Ghrelin</strong></td>
<td>117</td>
<td>78</td>
<td>90</td>
<td>0.007</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Only Cold Exposure Increased Brown Fat Activity

Cypess AM et al. PNAS 2012, *in press*  
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Brown fat can be found in a substantial proportion of adult humans (≤100%).

Multiple imaging techniques [PET/CT, MRI, U/S, IR] can measure brown fat activity that have both research and clinical applications.

Preliminary data suggest that brown fat could consume at least 100-200 kcal per day – and perhaps much more – with sustained activation.

In children, brown fat may play a significant role in energy balance.
Once activated, either via cold exposure or medications, the physiological response in BAT happens within seconds and increases with the following proportions:

- Treating obesity and diabetes by increasing brown fat mass and activity continues to have great potential.
Thank You!

Joslin Diabetes Center

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