Obesity, Fat, and Metabolism

Brown Fat: What You Need to Know Now and for the Future

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Conflict of Interest Disclosure
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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 – and Brown is “Good”

White (WAT)

- Energy storage
- 50g contains 300-500 kcal

Brown (BAT)

- Energy expenditure
- 50g consumes 100-300 kcal/day (max)
- Thermogenesis via Uncoupling Protein-1 (UCP1)

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

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How Brown Fat Generates Heat

Plasma
Glucose
FFA

Endogenous Lipids

Sympathetic Neurons
Norepinephrine

\[ \Delta \mu H^+ \]

H+ Intermembrane Space

Mitochondrial Inner Membrane

Matrix

H+ + heat

CO₂
H₂O

\[ \text{TCA} \]

\[ \text{O}_2 \]

\[ \text{ATP} \]

UCP-1

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Brown Fat May be Used for Treating Metabolic Dysregulation

- BAT in cold-acclimatized mice consumes more than half of ingested lipids and glucose.

Rodent Brown Fat Derives From Multiple Lineages

Mesenchymal Stem Cells

Commitment Phase
- Myf5- Progenitor
  - White Preadipocyte
  - Systemic Brown Preadipocyte

Myf5+ Progenitor
- Preformed Brown Preadipocyte
- Myoblast

Differentiation Phase
- White Adipocyte
- Systemic Brown Adipocyte
- Preformed Brown Adipocyte
- Myocyte


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How We Measure Human Brown Fat Activity

- **CT** = Computed Tomography, describes the tissue
- **PET** = Positron Emission Tomography, shows fluorodeoxyglucose uptake
- **PET/CT** = tells us the relative metabolic activity of each tissue

Cypess AM, et al. NEJM 2009;360:1509
Where is Normal Human Brown Fat?

One distinct region:
In the neck, shoulders, and chest, both sides.
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

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Adult Human Brown Fat is a Glucose Sink

- Cold-activated human BAT takes 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

11C-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.


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Pediatric BAT is More Frequently Active than in Adults, in both Girls and Boys


![Graph showing the prevalence of detectable brown adipose tissue in adults and pediatric patients at 21°C]

- **Adults**
  - Male: 3.1%
  - Female: 7.5%

- **Pediatric**
  - Male: 43.3%
  - Female: 45.3%

- **P-values**
  - For adults: P<0.001
  - For pediatric patients: P=0.88
BAT Activity *Increases* Through Adolescence, Then Declines

Drubach LA et al. J Pediatr 2011;159:939

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Pediatric BAT Activity Correlates Inversely with BMI%

$P = 0.01$, Kruskal-Wallis test

Drubach LA et al. J Pediatr 2011;159:939
Predominantly in one region of the body as a heterogeneous mixture of brown and white adipocytes.

We can measure its activity indirectly through non-invasive $^{18}$F-FDG PET/CT.

People with active brown fat are more frequently female, younger, and leaner, but cause and effect are not known.

Mild cold exposure is effective at stimulating it for prospective studies, but no pharmacological activators have been identified yet.

Its energy expenditure has great therapeutic potential.

Non-invasive Imaging
How do we currently quantify human BAT?

• Whole-body BAT mass or activity could not be measured in humans until 2002 with the discovery the $^{18}$F-FDG PET/CT could identify metabolically active adipose tissue.

• Problems with FDG PET/CT – ionizing radiation; expensive; detects an unknown and variable fraction of total BAT volume since you see only FDG-avid tissue.

• Options:
  (1) Infrared to detect BAT thermogenesis
  (2) MRI -- use water-to-fat ratio and high density of mitochondria and blood vessels.
Therapeutics
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;109:10001.  Confidential – Aaron M. Cypess, MD, PhD, Joslin Diabetes Center
Ephedrine and Cold Increased Energy Expenditure and Fat Metabolism


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Only Cold Exposure Increased Brown Fat Activity

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.

In children, brown fat may play a significant role in energy balance.

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