Demystifying Medicine Lecture Series

Obesity: Brown and Other Fat

Aaron M. Cypess, MD, PhD, MMSc

Investigator and Acting Chief, Translational Physiology Section
Diabetes, Endocrinology, and Obesity Branch, NIDDK, NIH

March 28, 2017
Conflict of Interest Disclosure
Aaron M. Cypess

The medication mirabegron (Myrbetriq®, Astellas Pharma) will be described in the context of trying to activate human brown adipose tissue and energy expenditure by using a dose of 200 mg, which is higher than the FDA’s highest-approved dosage of 50 mg for treating overactive bladder.

I have no relationship with Astellas Pharma.
Objectives

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

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

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

4. 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

At Least 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/d

- Uncoupling Protein-1 [UCP1]
- Thermogenesis

---

A. How Brown Fat Consumes Fuel to Generate Heat

Plasma
Glucose
NEFA

Sympathetic Neurons
Norepinephrine

Endogenous Lipids

ΔμH^+

H^+

Intermembrane Space

Mitochondrial Inner Membrane

Matrix

TCA

CO₂

H₂O

+ heat

H^+

Uncoupled

F₁F₀

UCP-1

H^+

+ heat

O₂
B. Brown Fat May be Used for Treating Metabolic Dysregulation

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

C. Endocrine Roles for Brown Adipose Tissue

- Nrg4
  - ErbB3/4
  - Liver
  - De novo lipogenesis
  - Hepatic steatosis
  - Insulin sensitivity
  - Obesity

Adipose tissue
- Inguinal
- Epididymal
- BAT
- Circulation
- Exosomal miRNAs
- miR-99b
- + others
- Liver
- FGF21
- Muscle
- Other

Ephx1/2 transcription
- Chronic
- Cold/Norepinephrine
- Fatty acid uptake
- Brown adipocyte
- 12,13-diHOME
- CD36c
- FATP1c
- CD36m
- FATP1m

Lipolysis & Ephx1/2 activity

Circa 2002: Adults Humans Have FDG-Avid Adipose Tissue = F-A-A-T

- CT = Computed Tomography → structure
- PET = Positron Emission Tomography (\(^{18}\text{FDG}\)) → function
- PET/CT = metabolic activity of each tissue
“You believe that there is no significant brown fat in adult humans and that what we see on PET/CT is not brown fat?”

-Cypess

“Yes, that's pretty much it.... I would be very surprised if those PET images were brown fat deposits.”

-KOL Endocrinologist

“In FDG-PET scans, you very often see false positive signals from brown fat....How do we know that it's brown fat?”

-Cypess

“Because everyone says so!”

-A Professor of Radiology
UCP1+ Benign Brown Fat Mass

H&E, 400X

αUCP1, 1:50, 400X
The Initial Understanding of Human Brown Fat

**Structure**
- Predominantly in specific regions of the body.
- We can measure it non-invasively via PET/CT.

**Function**
- Protects against cold acutely [NST].
- People with detectable brown fat are more frequently female, younger, leaner [DIT?], and not taking beta-blockers.
- Nearly every adult human has brown fat.

A. To what extent does adult human BAT contribute to increased energy expenditure?

B. How does BAT’s uptake of plasma glucose and triglycerides impact whole-body fuel metabolism?

C. How does activated human BAT interact with other organs in regulating metabolism?
Translational Approaches to Understanding BAT

Noninvasive Imaging
- Mass and Activity
  - PET/CT
  - MRI
  - Ultrasound

Integrative Physiology
- Human, Rodent, in vitro
  - Bioenergetics
  - Proteomics
  - Genomics

Therapeutics
- Cold
- Rx/Hormone – β3-ARA, etc.
BAT-based Therapeutics
Temperature can be used to increase – and then reduce – Human BAT activity
Cold Acclimation Improves Insulin Sensitivity in Patients with T2DM

• In eight subjects with T2DM, ten days of cold acclimation (14–15 °C) increased BAT activity
Why Pursue a Pharmacological Approach?

1. Potential for more specific targeting of human BAT.

2. Animal models show they are effective.

3. Likely greater adherence.

4. Combinations of approaches may be necessary.
The β3-AR is Expressed by Human BAT and WAT

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

Yu-Hua Tseng, Andrew White

Cypess AM...Tseng YH Nature Medicine 2013;19:635
Over 45 million are affected by overactive bladder (OAB) in the US (c.f. 26 million with DM).

Besides adipose tissue, there are β3-AR’s in the urinary bladder; activation relaxes the bladder.

Mirabegron is a β3-AR agonist approved by the FDA in 2012 for treatment of overactive bladder at 50 mg daily.

Proof-of-Concept Study Design

- Population: 12 young, lean, healthy men
- Each was treated acutely with placebo, mirabegron 200 mg, and exposed to mild cold (14 °C via vest / 20 °C room).
- Monitored vital signs, energy expenditure, drew blood prior to imaging, measured BAT metabolic activity via $^{18}$F-FDG PET/CT.
Mirabegron Agonist Increased Thermogenesis with Cardiovascular Stimulation

- **Change RMR (kcal/d):**
  - Placebo
  - Mirabegron 200 mg
  - Cold
  - +13%
  - 8%

- **Systolic BP:**
  - ***
  - Change (mmHg)

- **Diastolic BP:**
  - Change (mmHg)

- **Heart Rate:**
  - Change (bpm)
  - **
  - *

Cypress AM...Kolodny GM  Cell Metab 2015;21:33
The β3-AR Agonist Activated Human BAT

Placebo  Mirabegron  Cold
Brown adipocytes can be found in a substantial proportion of adult humans (≤100%).

Both cold and pharmacological activation of hBAT can substantially increase its mass and energy expenditure, but the extent is unknown.

Brown fat may impact human metabolism at three different levels – energy balance, glucose metabolism, and hormonal regulation – with much to be learned.

Coming up: “The Physiological Responses and Adaptation of Brown Adipose Tissue to Chronic Treatment with β3-Adrenergic Receptor Agonists.”
Thank You

NIH

Marc Reitman  Joyce Linderman
Monica Skarulis  Alison Baskin
Kong Chen  Cheryl Cero
Suzanne McGehee  Brooks Leitner
Rob Brychta  Courtney Duckworth
Shan Huang  Esti Anflick
Brent Abel  Natan Kelsey

CRC PET Department

Peter Herscovitch  William Dieckmann
Corina Millo  Craig Barker

CRC Radiology and Imaging Sciences

Ahmed Gharib  Brad Wood
Ron Ouwerkerk  Elliot Levy
Sheng Xu

Harvard University
Joslin Diabetes Center

Lauren Weiner  C. Ronald Kahn
Carla Roberts-Toler  Yu-Hua Tseng
Christie Sass  Alessandro Doria
Peter Kahn
Skyler Kessler

Beth Israel Deaconess Medical Center

Gerald M. Kolodny  Ilan Tal
Alina Gavrila  Per-Olof Hasselgren
Andrew White

Mass Spectrometry Core

Mass Spectrometry Core

NCI Surgery  NICHD  MDB

Electron  Karel  William Simonds
Kebebew  Pacak  Lee Weinstein

Grant support: NIH  DK087317, DK070722, DK46200, DK33201,
DK55545, DK46200, RR25758, DK81604, DK36836, CITP, the Eli Lilly
Foundation, Chugai Pharma, Ltd., Molecular Metabolism LLC.