Energy Expenditure – the Great Unknown in Human Health and Disease

Matthias J. Betz – 2021-05-06
Outline

• Background: Components of energy expenditure
• How to assess energy expenditure
• Some implications of energy expenditure in health and disease
• Endocrine effects on energy expenditure
• Therapeutic targeting of energy expenditure
Energy Expenditure

1. Exercise thermogenesis
2. Cold induced thermogenesis
3. Non-exercise activity thermogenesis
4. Diet induced thermogenesis
5. Resting metabolic rate/
   Resting energy expenditure
Physiology of Cold Acclimation

Core temperature ~37°C

Cold → Temperature Sensors in Skin → POA

Vasoconstriction to Reduce Heat Loss

Increase Thermogenesis
- Muscle: Shivering
- BAT: Non-shivering Thermogenesis
BAT – a Thermogenic Organ

Molecular Heating System

Betz, M. J. & Enerbäck, S. (2017) Targeting thermogenesis in brown fat and muscle to treat obesity and metabolic disease

Nat. Rev. Endocrinol. doi:10.1038/nrendo.2017.132
How to Assess Energy Expenditure

In Humans
Lavoisier measuring the respiration of a subject at rest, as drawn by his wife. Adopted from: Wellcome Library London (Grimaux 1888)
Pettenkofer’s Repirationsapparat, the first human whole-room open-circuit indirect calorimeter. Adopted from: “Lehrbuch der Physiologischen Chemie” by Eugen von Gorup-Besanez (Gorup-Besanez 1867)
Indirect Calorimetry

Cooling System

Temperature sensors
Implications of Energy Expenditure

In Human Health and Disease
Mean Percent Weight Change during a 15-Year Period in the Control Group and the Surgery Group, According to the Method of Bariatric Surgery.
Obesity & Weight Loss – GLP1-Agonists

C. Mean percent change in body weight during the entire trial (weeks 0-68; observed in-trial data)

D. Proportion of participants achieving thresholds of weight loss during the entire trial (weeks 0-68; observed in-trial data)

Metabolic Adaptation

Fothergill E. et al.  
Mild Caloric Restriction

Cell Metabolism
Volume 27, Issue 4, 3 April 2018, Pages 805-815.e4
Endocrine Regulation
Of Human Energy Expenditure
Thyroid Hormone (1)

Maushart et al. Thyroid 2019.

Maushart et al. Thyroid 2019.

In preparation
Thyroid Hormone (2)

Maushart et al. Frontiers in Endocrinology, in press, 2021
"Experiments of Nature": Resistance to Thyroid Hormone

Table 1
Clinical observation influencing understanding of thyroid hormone action

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Mechanism</th>
<th>Key manifestations</th>
<th>Thyroid function studies</th>
<th>Treatment/reversibility</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTH</td>
<td>TAP heterozygous dominant-negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Variable, can include goiter; hearing deficit; hyperactive behavior; learning disability; developmental delay; tachycardia</td>
<td>Elevated serum T4 and T3; nonsuppressed TSH</td>
<td>No single treatment and should be individualized; high-dose T3 every other day can suppress TSH and reduce goiter; treatment to reduce T4 may be indicated during pregnancy to reduce miscarriage rate; other targeted treatment based on symptoms&lt;sup&gt;a&lt;/sup&gt;</td>
<td>63, 64, 85</td>
</tr>
</tbody>
</table>
Thyroid Hormone Receptor Resistance

J Clin Invest DOI: 10.1172/JCI38793
Metabolic (In-)Efficiency
On a Molecular Level
UPC1 - The Molecular Heating System

Betz, M. J. & Enerbäck, S. (2017) Targeting thermogenesis in brown fat and muscle to treat obesity and metabolic disease

Futile Cycling Beyond UCP1


Therapeutic Targeting
Of Human Energy Expenditure
Environment: Outdoor Temperature and Cold Induced Thermogenesis

Pharmacological Modulation of Cold Sensors

TRP M8


TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades.
Liedtke WB, Heller S, editors.
Central Activation of the SNS

Nicotine

Gut Hormones: GLP1 and Glucagon Receptor

https://doi.org/10.1038/nchembio.209

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<tr>
<th>PHASE 2</th>
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| **Bi 456906** | **Xentuzumab (Bi 836845)** | **cotadutide** |
| GLP1/GCGR agonist | IGF1/2 antibody | Type-2 diabetes, obesity and NASH, diabetic kidney disease |
| Obesity | |

| **Bi 1015550** | **Bi 730357** |
| Anti-fibrotic | RORγ antagonist |

**cotadutide - Phase II**

- **Mechanism:** GLP-1/glucagon dual agonist
- **Area under investigation:** Type-2 diabetes, obesity and NASH, diabetic kidney disease
- **Date commenced phase:** Q3 2018
- **Estimated Filing Acceptance:** US, EU, Japan, China
- **Additional information:**
  - **Molecule size:** Large molecule
  - **Status change:**
Conclusion

• Energy expenditure is an important component of human physiology.
• Complex regulation
• Potential target to ameliorate metabolic disease.