Brown adipose tissue: a novel target to comBAT cardiovascular disease?

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Brown adipose tissue (BAT): a ‘novel’ player in lipoprotein metabolism

- ATP production
- Storage
- Heat

Dyslipidemia:
- TG↑ LDL-C↑ HDL-C↓

Atherosclerosis
- Cholesterol

Intestine

Liver

Heart

Muscle

BAT

NAFLD

Bartelt, Nat Med 2011
Brown fat is essential for heat production by ‘non-shivering’ thermogenesis in neonates.
2009: BAT is present and active in adults

Van Marken-Lichtenbelt, NEJM 2009; Cypess, NEJM 2009; Virtanen, NEJM 2009

Enerbäck, Cell Metab 2010
South Asians have unfavorable metabolic phenotype: Involvement of BAT?

- unfavorable metabolic phenotype (e.g. obesity, dyslipidemia)
- 6-fold higher risk to develop T2D (at lower BMI and at 10 years earlier)
- increased risk to develop CVD (at lower age)

South Asians have reduced BAT volume and activity

- South Asians have decreased BAT volume that correlates with decreased REE
- Decreased BAT activity may underlie unfavorable metabolic phenotype

*Bakker & Boon, Lancet Diabetes Endocrinol 2014*
BAT is physiologically activated by cold via β3 adrenergic receptors.

Transcript receptor potential channels TRP (M8, A1, V1)

Hypothalamus

SNS

Sensory nerves

Cold

Noradrenalin

Sympathetic neuron

β3 receptor

cAMP

Boon, Ned Tijdschr Geneeskd 2013
Brown adipose tissue activation: mechanism and consequences

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Does brown fat activation reduce atherosclerosis?

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Western-type diet (0.1% cholesterol)

APOE*3-Leiden.CETP mice

n=13-19 per group

CL316243 (20 µg; 3x/week s.c.)

Berbée, Nat Commun 2015
β3 receptor activation enhances fat oxidation

Berbée, Nat Commun 2015
β3 receptor activation increases uptake of triglycerides by brown fat and uptake of cholesterol by liver

Rensen, Nat Med 1995

Berbée, Nat Commun 2015
β3 receptor activation reduces plasma cholesterol and inhibits development of atherosclerosis

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Berbée, Nat Commun 2015
β3 receptor activation does not reduce atherosclerosis development in Apoe\(^{-/-}\) mice and Ldlr\(^{-/-}\) mice.

**ApoE-deficient mouse**

- **A**
  - Plasma triglycerides (mg/dl)
  - Time of treatment (weeks): 6, 12
  - **B**
  - Plasma total cholesterol (mg/dl)
  - Time of treatment (weeks): 6, 12

**LDL receptor-deficient mouse**

- **G**
  - Plasma triglycerides (mg/dl)
  - Time of treatment (weeks): 6, 12
- **H**
  - Plasma total cholesterol (mg/dl)
  - Time of treatment (weeks): 6, 12

**C**

- Vehicle
- CL316243

**D**

- Atherosclerotic lesion area (x10^4 μm² cross section)

**I**

- Vehicle
- CL316243

**J**

- Atherosclerotic lesion area (x10^4 μm² cross section)

*Berbée, Nat Commun 2015*
β3 receptor activation inhibits atherosclerosis dependent on a functional apoE/LDLr clearance pathway

Berbée, Nat Commun 2015
β3 receptor activation inhibits atherosclerosis dependent on a functional apoE/LDLr clearance pathway

Berbée, Nat Commun 2015
β3 receptor activation inhibits atherosclerosis dependent on a functional apoE/LDLr clearance pathway.
β3 receptor agonist also activates BAT in humans
BAT activity under control of hypothalamus

- CB1R antagonism
  - FASEB J 2014
- Metformin
  - Diabetes 2014
- Salsalate
  - Diabetes 2015

Ghrelin, GLP-1, AgRP/NPY, POMC (αMSH), MC3R/MC4R, PVN, ARC, SCN, Hypothalamus, IML, sympath. ganglia, NE, adrenergic receptors, BAT, Insulin, Leptin.
Central GLP-1 receptor activation increases fat oxidation and uptake of fatty acids and glucose by BAT

Kooijman, Diabetologia 2015
Central GLP-1 receptor activation activates BAT

TH

UCP1

droplet

Control  Exendin-4  Pair fed control

TH expression (relative to control)

UCP1 expression (relative to control)

Lipid droplet content (% area)

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Kooijman, Diabetologia 2015
GLP-1, leptin and insulin increase energy expenditure by activating BAT via MC4R

Kooijman, Diabetologia; Enriori, J Neurosci 2011; Müller, Int J Obes 1997
BAT activity under control of hypothalamus
Circadian disturbance is associated with obesity

- Short sleep is associated with obesity
  Watanabe, Sleep 2010; Hairston, Sleep 2010; Nishiura, Sleep 2010

- Shift work is associated with obesity
  Karlsson, Occup Environ Med 2001; Di Lorenzo, Int J Obes 2003; Barbadoro; PloS One 2013

- Light at night associated with obesity
  Obayashi J Clin Endocrinol Metab 2013; McFadden Am J Epidemiol 2014
Prolonged photoperiod induces adiposity

C57Bl/6J mice on chow diet
5 weeks photoperiod regime
21°C

Kooijman & Van den Berg, PNAS USA 2015
Prolonged photoperiod decreases sympathetic activation of BAT and decreases uptake of fatty acids by BAT.
Prolonged photoperiod decreases causes adiposity by decreasing BAT activity

Kooijman & Van den Berg, PNAS USA 2015
Brown adipose tissue is under sympathetic, endocrine and pharmacological control

- GLP1R agonism  
  Diabetologia 2015  
- BMP7  
  PloS ONE 2013  
- MC4R agonism  
  J Lipid Res 2014  
- CB1R antagonism  
  FASEB J 2014  
- Metformin  
  Diabetes 2014  
- Salsalate  
  Diabetes 2015

- β3R agonism  
  Nat Commun 2015

Adapted from: Yoneshiro & Saito, Ann Med 2015
Conclusions

• Brown fat plays a role in metabolism of glucose, triglycerides and cholesterol

• Brown fat activation attenuates dyslipidemia, obesity, hepatosteatosis, insulin resistance and atherosclerosis

• Brown fat can be activated directly and via central mechanisms

• Disturbance of circadian rhythm reduces brown fat activity

→ Brown fat is a target for the treatment of obesity and associated diseases including type 2 diabetes and cardiovascular disease