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Review

Manipulating molecular switches in brown adipocytes and their precursors: A therapeutic potential

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ABSTRACT

Brown adipocytes constitute a metabolically active tissue responsible for non-shivering thermogenesis and the depletion of excess calories. Differentiation of brown fat adipocytes *de novo* or stimulation of pre-existing brown adipocytes within white adipose depots could provide a novel method for reducing the obesity and alleviating the consequences of type II diabetes worldwide. In this review, we addressed several molecular mechanisms involved in the control of brown fat activity, namely, the β_3-adrenergic stimulation of thermogenesis during exposure to cold or by catecholamines; the augmentation of thyroid function; the modulation of peroxisome proliferator-activated receptor gamma (PPARγ), transcription factors of the C/EBP family, and the PPARγ co-activator PRDM16; the COX-2-driven expression of UCP1; the stimulation of the vanilloid subfamily receptor TRPV1 by capsaicin and monoacylglycerols; the effects of BMP7 or its analogs; the cannabinoid receptor antagonists and melanogenesis modulating agents. Manipulating one or more of these pathways may provide a solution to the problem of harnessing brown fat's thermogenic potential. However, a better understanding of their interplay and other homeostatic mechanisms is required for the development of novel therapies for millions of obese and/or diabetic individuals.

Contents

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1. Introduction

Many of the 21st century's complex diseases stem, in one form or another, from obesity. The healthcare cost, rising due to the complications of obesity, has become a major challenge even in the most developed and prosperous nations. Increasingly, obesity is recognized as the central player in the development of hypertension, diabetes, dyslipidemia, fatty liver disease, insulin resistance and cardiovascular diseases. All these disorders are often associated with metabolic disturbances commonly recognized as metabolic syndrome [1].

The last decade has brought increasing interest in the study of adipose tissue that is now unequivocally recognized as an active endocrine organ, releasing adipokines and cytokines that act upon the brain, liver, muscle and other tissues, and affecting numerous metabolic processes [2,3]. Diet, genetics and lifestyle influence both energy intake and expenditure levels, which, in turn, regulate the adipose depot size and, consequently, an extent of its pathophysiological activity. Importantly, metabolic outcomes associated with increased adiposity are highly variable. Some morbidly obese patients with substantial BMIs remain relatively healthy, with normal insulin sensitivity and no detectable cardiovascular diseases [4–6]. On the other hand, some simply overweight individuals develop insulin resistance and subsequent type II diabetes [7]. This variance is typically explained by gene-environment interactions [8,9]. Unfortunately, unraveling the details of these interactions

Table 1
Cellular and molecular characteristics of white and brown adipose tissue. DIO2 (deiodinase, iodothyronine, type II), ELOVL3 (ELOVL fatty acid elongase 3), COX8b (cytochrome c oxidase subunit VIIIB, pseudogene), LSDP5 (Lipid storage droplet protein 5), PGC-1α (peroxisome proliferator-activated receptor gamma, coactivator 1α), TR3 (Orphan nuclear receptor TR3), PPARα (peroxisome proliferator-activated receptor gamma, coactivator 1α), PPARγ (peroxisome proliferator-activated receptor gamma), CEBPα (CCAAT/enhancer binding protein (C/EBP), α) and CEBPβ (CCAAT/enhancer binding protein (C/EBP), β).

White adipose tissue	Brown adipose tissue
Cells are 70–80 nm in diameter	Cells are 30–40 μm in diameter
Cells contain a single large lipid droplet	Cells contain numerous smaller droplets
Few mitochondria	Relatively large number of mitochondria
Low iron content	Abundant iron
Enriched in monoenic acids	Enriched in free cholesterol and phospholipids. Contains substantial amounts of linoleic acid
Little vascularization/capillaries	Abundant vascularization/capillaries
Number of WAT cells positively correlates with insulin resistance	Number of BAT cells negatively correlates with insulin resistance
No UCP1 expression	Express UCP1
Do not produce heat	Produce heat
Differentiate from Myf− preadipocytes in the absence of PRDM16 signaling	Differentiate from both Myf+ and Myf− preadipocytes in the presence of PRDM16 signaling
DIO2, ELOVL3, COX8b, LSDP5, PGC-1α, TR3, PPARα, PPARγ, CEBPα and C/EBPβ genes are downregulated	DIO2, ELOVL3, COX8b, LSDP5, PGC-1α, TR3, PPARα, PPARγ, CEBPα and CEBPβ are upregulated

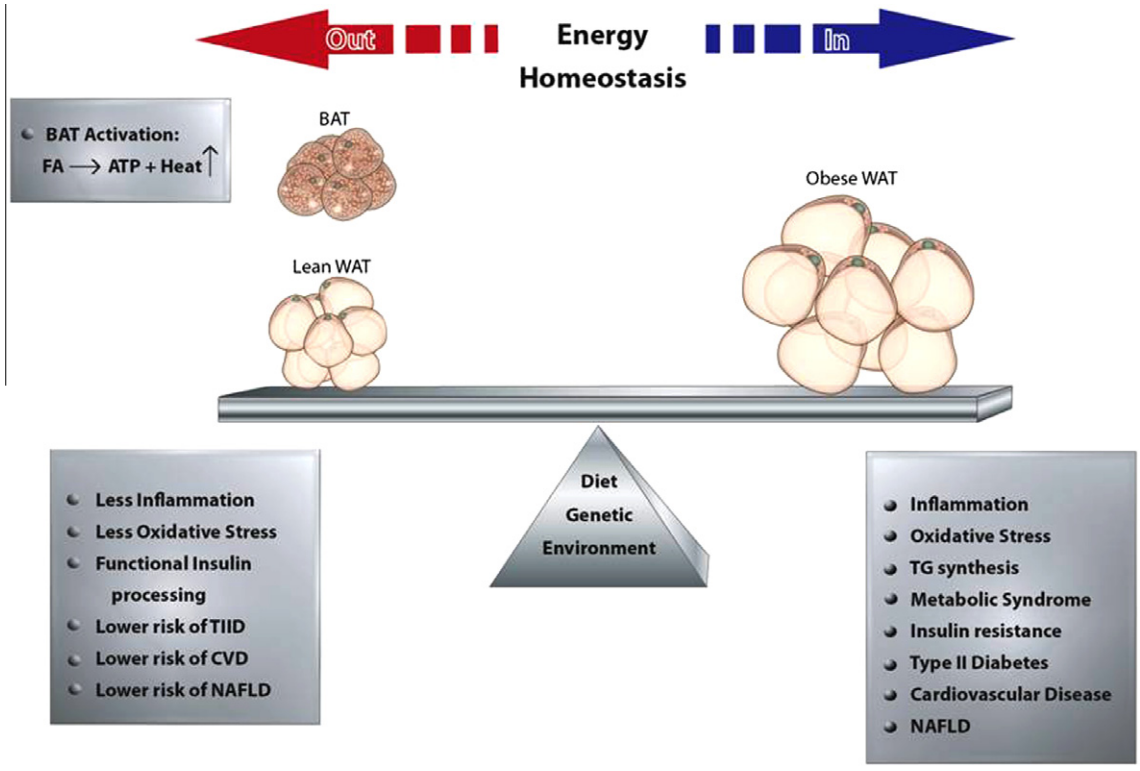

Fig. 1. The augmentation of the thermogenesis capacity of the human body may help obese and overweight individuals to shift their energy balance toward spending more and, consequently, to lose weight. Abbreviations: BAT (Brown Adipose Tissue); WAT (White Adipose Tissue); FA (Fatty Acids); ATP (Adenosine triphosphate); TG (Triglycerides); NAFLD (Non-Alcoholic Fatty Liver Disease); TIID (Type 2 Diabetes); CVD (Cardiovascular Disease).