Brown and Beige Adipose Tissue

Therapy for Obesity and Its Comorbidities?

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KEYWORDS

• Brown adipose tissue • Beige adipose tissue • Energy expenditure • Thermogenesis • Obesity • Type 2 diabetes • Lifestyle intervention

KEY POINTS

- Our understanding of the role of brown (BAT)/beige adipose tissues on body weight in obese humans is evolving.
- Unanswered questions include the abundance of beige adipocytes, "browning" of white adipose tissue, contribution of BAT thermogenesis to homeostasis, and the extent to which thermogenesis can be upregulated to have sufficient impact on weight loss.
- Resolution of these issues will determine the future for BAT as a therapeutic target in obesity and obesity-related comorbidities.

INTRODUCTION

Overweight and obesity are now among the greatest health challenges in both developed and developing countries. In 2013, worldwide estimates for the percentage of overweight/obese adults was 36.9% for men and 38% for women, and the prevalence in children and adolescents—23.8% for boys and 22.6% for girls is equally alarming.[1] The situation in the United States is even more dire, where 65% of US adults are overweight/obese, and 32.2% and 25.3% of children (aged 2–19 years) are overweight and obese, respectively. Obesity is associated with a number of comorbidities, including the metabolic syndrome, insulin resistance, cardiovascular diseases, type 2 diabetes, and cancer, all of which impact the social and economic burden on the population, and is contributing to the substantial increase in direct and indirect cost of health care. Thus, there is an urgent need to identify new therapeutic strategies to combat obesity and its comorbidities.

Disclosure: The authors have received funding for NIH, R01 DK089547.
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Endocrinol Metab Clin N Am 45 (2016) 605–621
http://dx.doi.org/10.1016/j.ecl.2016.04.010 **endo.theclinics.com**
0889-8529/16/$ – see front matter

Obesity is a chronic condition caused by excess energy intake relative to energy expenditure, creating positive energy balance and weight gain. Much of this extra energy is stored in the form of triacylglycerols in white adipose tissue (WAT). One of the strategies to reverse obesity is to generate "negative energy balance" with a focus on decreasing energy intake and increasing energy expenditure.[2] Understanding the physiologic, cellular, and molecular mechanisms of energy intake, storage, and expenditure to achieve whole body energy homeostasis may allow us to identify effective and durable (treatment) strategies for treating and managing obesity. One of the exciting possibilities of brown adipose tissue (BAT) is that it can oxidize fatty acids and glucose, and thus could in theory, dissipate energy in the form of heat via uncoupling mechanisms. This approach is supported by the strong negative association between BAT and body weight, body fat, and visceral fat.[3–5] Thus, further understanding of the genetic, molecular, and physiologic attributes of BAT may generate empirical data to support the idea that upregulation of BAT activity could lead to the discovery of a novel, effective, and durable therapy for treating and managing obesity. However, the significance and viability of this approach is the subject of some skepticism. In this review, we focus on how brown/beige fat cell activation may impact obesity therapy and its potential to mitigate obesity-related comorbidities.

FEATURE CHARACTERISTICS, AND PHYSIOLOGIC AND METABOLIC PHENOTYPE OF THERMOGENIC ADIPOCYTES

In mammals, thermogenic adipocytes are classified into BAT and the recently discovered "brownlike"/"beige"/"brite" adipocytes.[6] BAT is highly vascularized, is characterized by a light pink color, and is densely innervated by the sympathetic nervous system. Brown adipocytes are packed with multilocular small vacuoles that are rich in mitochondria that contain dense cristae.[7] In rodents and small mammals, the most classical brown fat presentation is around the upper back (interscapular), the kidney (perirenal), and heart (periaortic) regions. In humans, active BAT was traditionally thought to be restricted to newborns and the early childhood period, and was viewed as a natural defense mechanism against hypothermia.[8–10] More recently, several groups of investigators have reported functional active BAT in healthy adult humans using a combination of radiolabeled glucose tracers, 2-deoxy-2-[^{18}F]-fluoro-D-glucose ([^{18}F]-FDG), and PET and computed tomographic (CT) scanning technology.[3,4,11,12] These data show that BAT is present in the upper trunk, including the cervical, supraclavicular, paravertebral, and pericardial regions, and to a lesser extent in the mediastinal and mesenteric areas.[3,4,11] Glucose uptake and perfusion of the tissue are both increased in human BAT in response to cold, indicating active thermogenesis.[13] The amount of active BAT in humans is heterogeneous, but the exact mass has never been measured precisely. Estimates suggest that healthy humans have about 50 g of active BAT (approximately 0.1% of body mass).[14,15]

Beige adipocytes have similar morphologic features to classical brown adipocytes, with central nuclei, multilocular lipid droplets, and are rich in mitochondria.[16] Beige adipocytes arise upon external cues, such as stimulation of sympathetic activity during chronic cold exposure or administration of β3-adrenergic receptor agonists, or exercise. Unlike brown adipocytes, which seem to have a discrete anatomic location, beige adipocytes reside within the WAT depot, mainly in inguinal WAT in rodents. In humans, there remains uncertainty regarding the presence of both the precursor of white adipocytes committed to "browning" or functional beige adipocytes, and whether trans-differentiation of white into beige adipocytes is indeed a real physiologic phenomenon. Several reports suggest that human BAT, particularly from the