Stimulating brown fat: a potential future therapeutic approach for obesity and insulin resistance?

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Abstract

The failure of current strategies aimed at the containment and treatment of the obesity epidemic has prompted the search for novel targets for therapeutic intervention. The recent discovery that brown adipose tissue (BAT) activity can be detected in a substantial proportion of the adult population has generated a renewed interest in the study of this tissue. As the physiologic activation of BAT can rapidly increase intracellular tri-iodothyronine (T3), generating a local, tissue-specific "thyrotoxicosis" and a substantial increase in energy dissipation in the form of heat, this tissue can be considered a potential therapeutic target for the development of treatments for obesity.
■ *Heart Metab.* 2010;48:19–22.

The obesity epidemic, with its prohibitive health care and societal costs [1], and the poor success record of available interventions, either behavioral or pharmacological, have prompted the search for novel therapeutic targets and modalities. The past two decades have seen a major push towards obesity research, as demonstrated by an almost 10-fold increase in scientific output in this area over the past 20 years: a simple PubMed search for the topics "obesity" and "therapy" produced 673 results for the year 1989, 1601 for the year 1999, and 5758 for the year 2009.

Besides reducing energy intake through dietary, pharmacological, or surgical means, interventions aimed at increasing energy expenditure would appear to provide a logical method of producing a sustained negative overall energy balance, ultimately resulting in weight loss. Even a small but sustained increase in the resting energy expenditure, which represents approximately 65–85% of total energy expenditure in individuals not engaging in high-intensity manual work, would produce a significant dispersion of calories over time and, in the absence of significant counter-regulatory mechanisms, clinically relevant weight loss. Several pharmacologic approaches have been explored [2–7]; adrenergic stimulants and high doses of thyroid hormone generate a significant increase in resting energy expenditure, but unwanted side effects relating to the neurologic, cardiovascular, and skeletal systems (in the case of thyroid hormone) preclude their clinical use. In contrast, thyrotoxicosis is a model of increased resting energy expenditure, and the use of selective thyroid hormone receptor subtype or target tissue agonists, which retain the ability to increase overall energy expenditure without

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causing organ-specific toxicity, have been considered as targets for drug development [8].

Brown adipose tissue (BAT), by virtue of a high endogenous expression and activity of intracellular type-2 5′-deiodinase (D2), has the unique ability to increase substantially the intracellular concentrations of tri-iodothyronine (T3), the active form of thyroid hormone, without affecting its circulating concentrations [9]. The resulting high intracellular concentrations of T3 positively regulate the transcription of uncoupling protein-1 (UCP-1), which causes the mitochondrial membrane to become ''leaky'' to protons, rendering the respiration process inefficient [10]. In other words, BAT has the ability to generate a local, tissue-specific thyrotoxicosis, which in turn leads to a net increase in ''inefficient'' substrate utilization, with consequent energy dispersion in the form of heat aimed at assuring the maintenance of core temperature in small rodents and in human newborns. This mechanism is positively regulated by the sympathetic nervous system via the norepinephrine-mediated activation of BAT β_3-adrenergic receptors [11], whereas substrate-dependent proteasome-mediated degradation of D2 allows rapid switch-off of this enzymatic reaction [12]. The ability to inactivate this D2-mediated process rapidly is particularly important evolutionarily, as BAT activation comes at an exorbitant cost, from an energy conservation standpoint, when energy (food) availability is the limiting factor for survival and propagation of the species. A notable exception to this rule is represented by ''*homo technologicus*'', which has at his disposal virtually unlimited access to food, without the need to expend significant amounts of energy in order to gather food, evade or defend himself from predators, or maintain core body temperature.

An increase in sympathetic nervous system tone mediated by exposure to cold is not the exclusive pathway of BAT activation. The thermic effect of food – that is, the increase in energy expenditure associated with food intake not explained by the digestion and absorption of nutrients [13], has been attributed to BAT [14]. Recently, Watanabe and co-workers [15] have mechanistically demonstrated that, in mice, bile acids* act as endocrine signalers for the activation of D2 in BAT via interaction with the transmembrane G-protein coupled receptor*, TGR5, and that administration of pharmacologic doses of bile acids prevents the development of diet-induced obesity. One could thus hypothesize that bile-acid-mediated activation of BAT represents a short-loop feedback system for dispersing sudden excesses of energy intake.

The potential role of human BAT in the pathophysiology of obesity, or as a target for therapeutic intervention, has been considered for several decades [16], but this line of research has not been fully pursued, as human intrascapular BAT disappears during the early postnatal period, and the few nests of multiloculated adipocytes resembling BAT that persist have been considered too small to have a significant impact on metabolism. Until recently, the occasional finding of diffuse BAT in individuals chronically exposed to cold [17] or in patients affected by pheochromocytoma [18], and of occasional bilateral tracer uptake in the neck region of patients undergoing positron emission tomography (PET) scans [19], especially during the winter months, have been considered incidental findings devoid of clinical relevance.

Very recently, a series of manuscripts have clearly demonstrated that active BAT can be detected by PET in a substantial proportion of the population [20,21], that, in humans (similarly to rodents), BAT is activated by exposure to cold [22,23], and that the presence of active BAT demonstrated by PET is inversely associated with obesity and traits of the metabolic syndrome [20]. A recent case report further illustrated the potential metabolic role of BAT in humans: the reversal of poorly controlled diabetes in a patient affected by a severe form of insulin resistance (secondary to a mutation in the alpha subunit of the insulin receptor) was linked to the presence of diffuse deposits of BAT, possibly stimulated by supraphysiologic doses of thyroid hormone required for treatment of thyroid cancer. Interestingly, when levothyroxine treatment was suspended for a diagnostic iodine-131 scan, glycemic control deteriorated acutely, concomitant with a loss of BAT activity on PET scan [24]. The clinical data from this very unusual case illustrate the ability of BAT to generate insulin-independent glucose disposal. Taken together, these findings have contributed to a renewed interest in this tissue as a target for the development of pharmacologic intervention for the treatment of obesity, insulin resistance, and their complications [25].

In contrast, the increased amount of subcutaneous fat present in obese individuals may provide natural insulation, dampening thermal dispersion, thus making obese individuals more ''energy efficient''; in this case the threshold for activation of BAT would seldom be reached. If this is true, it would represent yet another obstacle on the path toward weight loss. Moreover, current human studies have not yet proven that BAT per se has physiologic relevance in humans, and indeed this finding could be simple association rather than proof of causation. Nonetheless, it is important to note that, in humans, a diffuse ''BAT-like'' activity can be ascribed to skeletal muscle; such activity in skeletal muscle, well below the level of detection by PET, could play a significant metabolic role. In this regard, targeting whole-body adaptive thermogenesis, irrespective of the anatomical or tissue distribution, could be a viable intervention.

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Table I. *Potential molecular targets and strategies aimed at activation of brown adipose tissue.*

Target	Intervention	Potential untoward effects
Sympathetic nervous system	Central stimulation, catecholamine analogs	Generalized effects of sympathetic overactivity (e.g., cardiac toxicity, hypertension, anxiety)
Sympathetic nervous system	Cold exposure	Counter-regulatory mechanisms, poor tolerability
β_3-Adrenergic receptor	Selective agonist	Non specific effects on other adrenergic receptor subtypes
G-proteins, cAMP	Increase intracellular concentrations of cAMP	Generalized effects, cell proliferation
TGR5	Bile acids analogs	Not known
Type-2 5'-deiodinase	Stimulation of transcription, inhibition of degradation	Systemic effects of increased intracellular T3 concentrations (central nervous system, hypothalamus–pituitary–thyroid axis)
Thyroid hormone receptor	Tissue-selective agonist	Spill-over systemic thyrotoxic effects

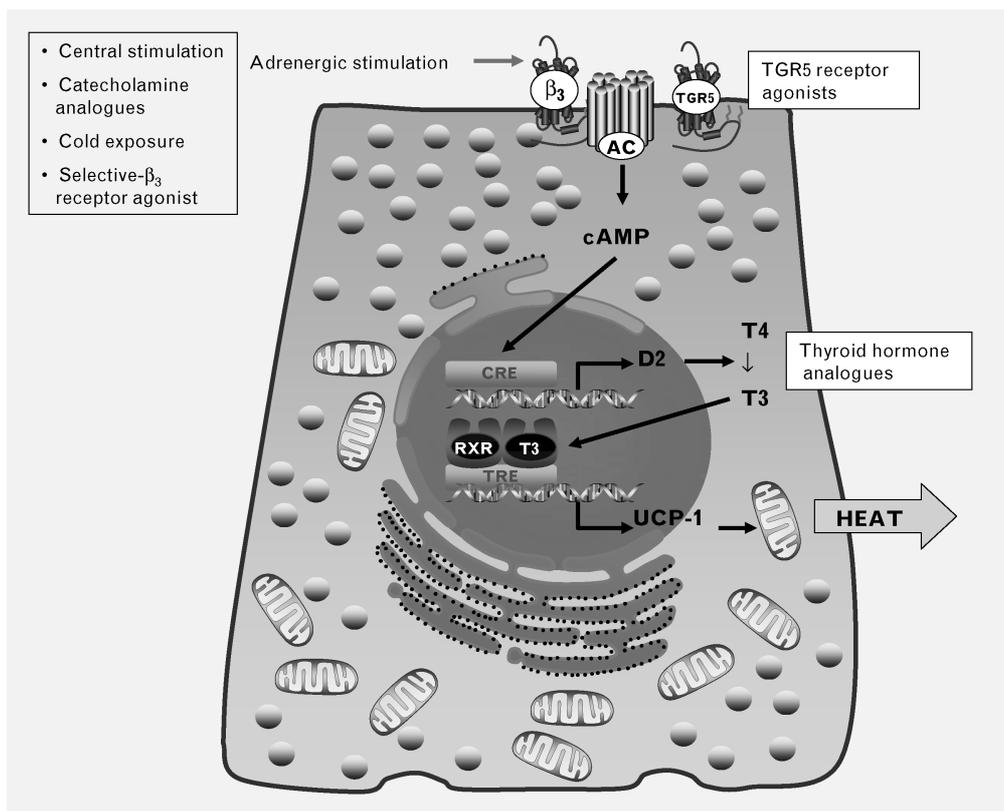T3, tri-iodothyronine; TGR5, transmembrane G-protein-coupled receptor 5.

Figure 1. *Schematic diagram of brown adipose tissue activation, showing potential therapeutic targets. AC, adenylate cyclase; β_3, β_3 adrenergic receptor; CRE, cAMP-responsive element; D2, type-2 5'-deiodinase; RXR, retinoid X receptor; T3, tri-iodothyronine; T4, thyroxine; TRE, thyroid-hormone-responsive element; TGR5, transmembrane G-protein-coupled receptor 5; UCP-1, uncoupling protein-1.*

Table I and *Figure 1* illustrate potential molecular targets and strategies aimed at the activation of BAT.

Conclusion

The demonstration that BAT is present and active in adult humans has renewed interest in the physiology of this tissue and its potential as a target for pharmacologic intervention. Conversely, a word of caution comes from the consideration that a chronic activation of BAT may generate a state of high-energy flux, and that compensatory mechanisms would probably ensue, mitigating the potentially beneficial effects on substrate metabolism and on the overall energy balance.

*see glossary for definition of these terms. ■

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