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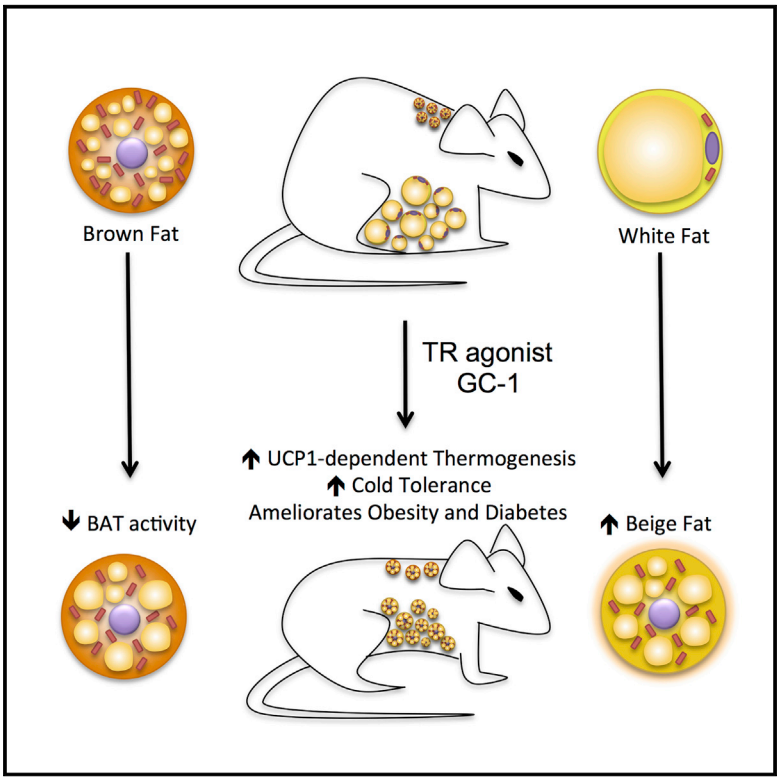
Pharmacological Activation of Thyroid Hormone Receptors Elicits a Functional Conversion of White to Brown Fat

Graphical Abstract



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In Brief

Lin et al. demonstrate that activation of the thyroid hormone receptors by a synthetic agonist strongly induces a brown-fat-like program of adaptive thermogenesis and increased metabolism in white adipocytes both in vivo and in vitro.

Highlights

- TR activation elicits a program of thermogenesis in subcutaneous white adipocytes
- TR-mediated browning coincides with anti-obesogenic and anti-diabetic effects
- TR-agonist-induced browning of white adipocytes is cell autonomous
- TR-mediated browning dissociates activation of WAT from classical BAT

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Report

Pharmacological Activation of Thyroid Hormone Receptors Elicits a Functional Conversion of White to Brown Fat

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SUMMARY

The functional conversion of white adipose tissue (WAT) into a tissue with brown adipose tissue (BAT)-like activity, often referred to as "browning," represents an intriguing strategy for combating obesity and metabolic disease. We demonstrate that thyroid hormone receptor (TR) activation by a synthetic agonist markedly induces a program of adaptive thermogenesis in subcutaneous WAT that coincides with a restoration of cold tolerance to cold-intolerant mice. Distinct from most other browning agents, pharmacological TR activation dissociates the browning of WAT from activation of classical BAT. TR agonism also induces the browning of white adipocytes in vitro, indicating that TR-mediated browning is cell autonomous. These data establish TR agonists as a class of browning agents, implicate the TRs in the browning of WAT, and suggest a profound pharmacological potential of this action.

INTRODUCTION

Obesity is an accelerating worldwide health crisis associated with co-morbidities that include diabetes, hyperlipidemia, and hypertension. Obesity is caused by chronic intake of excess energy relative to expenditure, which becomes stored as lipid in white adipose tissue (WAT) and leads to its expansion (Trayhurn and Beattie, 2001). While nearly everyone is familiar with WAT, typically referred to simply as "fat," there is less appreciation for brown adipose tissue (BAT), which has the unique capacity to conduct non-shivering adaptive thermogenesis (NSAT), the conversion of excess energy to heat.

Since BAT-mediated adaptive thermogenesis is inherently anti-obesogenic (Lowell et al., 1993), there has long been an interest in harnessing this action to treat obesity. However, until recently, it was generally accepted that adult humans did not possess brown fat (Cannon and Nedergaard, 2004). Instead, it was questioned whether WAT could be induced to become more BAT-like (Tiraby and Langin, 2003) to increase energy expenditure. The prospect of achieving this was bolstered by the appearance of BAT-like, or "beige," cells in WAT depots in response to cold exposure or treatment with β-adrenergic agonists (Guerra et al., 1998; Cousin et al., 1992). Although tantalizing, the physiological relevance of beige cells was unclear, and it was not apparent how to exploit this effect clinically (Arch, 2008).

Two events renewed interest in utilizing adaptive thermogenesis to combat obesity. First, several studies have established the existence of active brown fat in adult humans (Sidossis and Kajimura, 2015; Nedergaard et al., 2007). Second, several contemporary reports demonstrated the ability to impart BAT-like function to WAT depots in rodents, a process often referred to as "browning" (Harms and Seale, 2013). While these examples established induction of BAT-like adaptive thermogenesis in WAT can have anti-obesogenic and anti-diabetic effects, the magnitude of these effects have generally been modest despite the use of genetically engineered mice, leaving the pharmacological potential of browning (Nedergaard and Cannon, 2014) unclear.

It is well established that thyroid hormone receptor (TR) signaling regulates thermogenesis, body temperature (Silva, 1995), and energy balance (Grover et al., 2004). In both humans and mice, hypothyroidism is associated with hypersensitivity to cold, while hyperthyroid individuals have difficulty tolerating heat (Melish, 1990). Although TR signaling has been linked to BAT development (Hall et al., 2010), the relationship between TR activation and thermogenesis is complex and has not been fully resolved. Here, we report TR activation by the synthetic agonist GC-1 elicits a BAT-like program of adaptive thermogenesis in subcutaneous WAT (scWAT). This action, which is accompanied by a marked increase in metabolism, fat loss, and increased cold tolerance, suggests browning of WAT may represent an unappreciated component of TR-induced thermogenesis.