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Temperature matters with rodent metabolic studies

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An illusory goal in obesity therapeutics is to increase energy expenditure without provoking a compensatory rise in food intake. With the (re)discovery that functional and inducible brown fat exists in adult humans, studies aimed at understanding the physiology and activation of brown adipose tissue (BAT) have proliferated. Yet, intermittent cold exposure alone is often accompanied with an increase in food intake. Cold and β-adrenergic specific agonist treatments have both been shown to activate brown fat in adult humans, suggesting the feasibility of therapeutic activation of this tissue.

Accordingly, Xiao et al. tested the physiologic and metabolic effects of a one-month subcutaneous infusion of CL316243, a specific β3 adrenergic agonist that activates lipolysis in white adipose tissue and heat generation in brown adipose tissue. The authors tested this thermogenic molecule in mice fed standard chow and a high fat diet, housed at normal ambient housing temperatures (22°C) as well as at thermoneutrality (30°C). The authors found – as expected – that housing mice at thermoneutrality (30°) was associated with increased deposition of adipose tissue, impaired insulin sensitivity and a deactivation of BAT when compared to control mice housed at 22°C. At 22°C ambient, the CL316243-treated mice maintained body weights similar to saline-treated animals by a compensatory increase in food intake whereas at 30°C ambient, CL316243-treated mice lost body fat due to uncompensated (by food intake) increases in metabolic rate. These effects of ambient temperature on what constitutes therapeutic efficacy of CL316243 are important. Although cogent arguments have been made for using thermoneutral housing conditions to test metabolic parameters in rodents[1], very few groups do so[2].

Rodent studies at both ambient room temperature and thermoneutrality have – not surprisingly – often shown opposite results. For example, *Ucp1-/-* mice are resistant to diet-induced obesity (DIO) at 22°C [3] but highly susceptible to the same diet when housed at 30°C [4], a reflection of the greater (~40% higher) thermogenic stress imposed at 22°C. Likewise, mice lacking type 2 deiodinase (*DioII-/-*), a protein involved in the conversion of T4 to T3 in BAT and other tissues, are susceptible to DIO at 30°C but not at 22°C [5]. The same group tested 2-4 dinitrophenol (DNP) – another molecule capable of uncoupling

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oxidative phosphorylation, thereby producing heat – in mice at both ambient 22C and 30C temperatures and observed discordant phenotypes. Thus, ambient temperature clearly affects phenotypes related to energy homeostasis in rodents [1].

By virtue of their clothing and room thermostats, humans generally live at near thermoneutrality. Rodent housing at 22 degrees is comfortable for personnel, but imposes a major thermal stress on rodents – the degree depending upon airflow rates and numbers of animals per cage. If relevance to human physiology or therapeutics is a concern, housing at thermoneutrality (∼30°C for rodents) is likely to be important. Xiao would have missed the uncompensated (by food intake) increase in metabolic rate in animals treated with CL316243 if the experiments had been conducted only at 22 degrees, because at the lower ambient extant metabolic stress masked the metabolic increment that CL316243 delivers in animals housed at thermoneutrality.

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