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Brown fat and vascular heat dissipation
The new cautionary tail

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Current efforts to treat obesity and associated disorders focus on the stimulation of energy expenditure by increasing thermogenesis, for instance through activating brown adipose tissue or more recently “beige” or “brite” fat, a relatively novel type of adipose tissue with putative thermogenic potential.

In this commentary, we aim to provide an alternative perspective on the current trend of analyzing and manipulating thermogenesis, brought about by our recent publication, in which we investigated the unexpected hypermetabolic phenotype of an animal model with defective thyroid hormone receptor α1 signaling. These mice display elevated brown adipose tissue thermogenesis; surprisingly, however, their body temperature is lower, pointing to a defect in heat conservation. Using infrared thermography and wire myograph experiments, we revealed that the tail arteries of the mutant mice are less sensitive to contractile stimuli, which leads to insufficient peripheral vasoconstriction and heat loss over the tail surface. This heat loss in turn lowers body temperature and triggers the additional thermogenesis. Our findings add a new aspect to the role of thyroid hormone in thermoregulation, and encourage a more holistic view in future studies in the field of thermogenesis, including the often-overlooked heat dissipation and recordings of body temperature.

Introduction
To fight obesity and its associated disorders, current research aims to increase energy expenditure in humans by triggering thermogenesis. Several new approaches have been identified recently; however, the vast majority of the experiments were conducted in rodents at ambient room temperature. This paradigm constitutes a continuous cold challenge for rodents, requiring them to persistently expend energy to defend their body temperature by several different means. Consequently, the immediate translation to a human condition is questionable, as humans usually create their own thermo-neutral zone at room temperature by the use of clothing. Even more importantly, the majority of studies have focused solely on the aspect of thermogenesis, i.e., the activation of brown fat, while the other side of the coin—heat dissipation—has been largely ignored. Clearly, these two are not independent from each other, as heat generated from one tissue may trigger compensatory cooling in another, and vice versa.

The importance of a complete analysis is illustrated in our recent paper, where we studied thermoregulatory mechanisms in a mouse model with a mutation in thyroid receptor α1 (TRα1+m). These TRα1+m mutants display sympathetic overactivation of brown adipose tissue, which appears paradoxical at first as the animal model resembles impaired thyroid hormone signaling—a condition usually associated with reduced thermogenesis. Even more surprising was the observation that—despite the increased thermogenesis—body temperature was not elevated, and even lower during nighttime. Through the combination of in vivo infrared thermography studies and ex vivo wire experiments...
myograph experiments, we found that tail artery vasoconstriction was strongly impaired in the TRα1+m mice, leading to significant heat loss over the tail surface. When we used the α-adrenergic agonist midodrine to enforce tail vasoconstriction, this inappropriate heat dissipation was reversed and the facultative thermogenesis returned to control levels.

Our findings therefore reveal that the unexpected thermogenesis in TRα1+m mice is a secondary compensation of a defect in a different thermoregulatory system. Consequently, the study adds a new aspect to the thermoregulatory functions of thyroid hormone: impaired thyroid hormone receptor α1 signaling as in hypothyroidism can affect vasoconstriction and heat dissipation, which could explain the cold hypersensitivity of hypothyroid patients. More importantly, our study underlines that compensatory mechanisms in thermoregulation can be of major importance to fully understand the phenotype of animal models below thermoneutrality.

Getting into the Zone: The Use of Thermoneutral vs. Room Temperature

As previously mentioned, transferring mechanisms derived from cold-challenged rodents to therapeutic approaches in thermoneutrally-maintained humans may be problematic. This not only refers to the species-specific differences in the regulation of the thermogenic tissues, i.e., brown adipose tissue and skeletal muscle, but also other tissues such as the heart, which are subject to a different autonomic regulation at subthermoneutral temperatures. Consequently, additional studies at thermoneutrality are highly recommended to evaluate promising novel thermogenic molecules for exploitation in pharmacological paradigms. For example, bone morphogenetic protein 7 was suggested as a new therapeutic approach for the treatment of obesity due to its thermogenic properties in mice at room temperature; however, recent studies have shown that the effects are blunted at thermoneutrality, a situation where brown adipose tissue is not sympathetically activated.

This example also nicely illustrates another caveat of research aiming to exploit the catabolic potential of brown fat or a subset of cells within white adipose tissue depots called beige or brite cells: the presence of adipose tissue capable of thermogenesis does not immediately equal increased energy expenditure, the tissue needs to be activated to do so, usually by the sympathetic nervous system. However, the activity of the sympathetic nervous system controlling thermogenesis is tightly regulated by the brain, aiming principally to keep body temperature stable. One could therefore speculate that initially the increase in brown fat or beige fat thermogenic capacity could lead to elevated body temperature, which in turn would cause a reduction of sympathetic stimulation through central mechanisms in order to avoid hyperthermia (Fig. 1, left).

In the long-term, this would leave two possibilities: either the overall thermogenesis returns to normal with a new equilibrium of more thermogenic tissue but less sympathetic stimulation, or the thermogenesis remains somewhat elevated despite the reduced sympathetic activity, which would trigger excessive sweating, peripheral vasodilation and reduced motoric activity to avoid hyperthermia.

The Cautionary Tail

The risk of hyperthermia caused by pharmaceutical stimulation of energy expenditure is an old problem. The anti-obesity compound 2,4-dinitrophenol, a mitochondrial uncoupler, was very effective in achieving weight loss through converting energy to heat, but caused substantial side effects in patients when overdosed, ranging from mild hyperthermia to death.

To circumvent this problem, we believe that facilitating heat dissipation instead of thermogenesis might be a concept worth considering. It has long been known that heat dissipation in uncovered extremities plays an important role in mammalian body temperature regulation. In mice and rats, this includes first and foremost the tail. In our TRα1+m animal model, we demonstrate that a reduced ability for vasoconstriction in peripheral heat dissipating surfaces such as the tail can indeed lead to heat loss and reduced body temperature, which in turn activates compensatory thermogenesis. The situation is similarly achieved in wildtype mice treated with the α-adrenergic antagonist prazosin, which enforces tail vasodilation and subsequently heat loss, triggering a similar compensatory activation of BAT thermogenesis. In contrast to the direct BAT activation, this approach will lead initially to lower body temperature, with the final output being physiologically-driven thermogenesis (Fig. 1, right).

Conclusions

The activation of brown or beige fat thermogenesis has without doubt enormous therapeutic potential for obesity and related metabolic disorders. However, current studies are often one-sidedly focused on the thermogenic aspect at room temperature, and largely ignore heat dissipation or other thermoregulatory mechanisms. In our opinion, a more holistic approach is required for this type of studies in rodents, including the consideration of heat loss and body temperature, cardiovascular or behavioral adaptations, and experiments at thermoneutrality.

More importantly, while substances inducing brown or beige fat generation are generally promising, it should be kept in mind that the tissue also needs to be activated in order to cause elevated energy expenditure. In thermoneutral humans this might be hard to achieve, as even a minor increase in body temperature will trigger the brain to reduce sympathetic stimulation of thermogenesis. If thermogenesis is enforced pharmacologically, hyperthermia might be a dangerous side effect.

Consequently, mimicking mechanisms that activate thermogenesis in more physiological conditions seems a promising strategy to achieve this goal. Although there is currently compelling evidence that frequent mild cold exposure could do the trick, cost-effectively and with few side effects, the inherent aversion to even mild discomfort would probably cause human patients to still prefer a weight loss pill over shivering.

Recent studies have therefore aimed to imitate the effects of shivering on the
molecular level: the myokine irisin was found to be released from muscle upon shivering to induce thermogenesis in beige fat.17 Earlier studies linked the release of this molecule exclusively to exercise;18 however, this finding seemed counterintuitive as the induction of thermogenesis upon physical activity such as fleeing from predators might not make sense in the light of evolution. Consequently it remains somewhat controversial19-21 whether this molecule can bridge the uncomfortable shivering period on the road to higher energy expenditure.

Nevertheless, all strategies aiming to directly stimulate thermogenesis will have to deal with the aforementioned problems of sympathetic coactivation and possible hyperthermia. We therefore believe it might be worthwhile to have a look at mechanisms increasing heat loss instead. This approach would induce energy expenditure by a compensatory activation, initially by shivering and later by the activation of brown or beige fat thermogenesis, without the risk of hyperthermia. Whether the heat loss can be more effectively induced by pharmacology, as with prazosin in our study,4 or by natural means, such as thinner blankets at night or moving to a country with a strong winter tradition of evolution. Consequently it remains to be elucidated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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