Is Brown Adipose Tissue-Mediated Adaptive Thermogenesis the Missing Component of the Constrained Total Energy Expenditure Model?

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In simple terms, obesity is the result of chronic excess of energy intake over energy expenditure. However, the obese phenotype is likely to be the result of complex interactions between the individual’s genetic background, environmental, behavioral and socioeconomic factors. Although much has been done, it is evident that our current knowledge about energy balance is insufficient to combat the obesity pandemic and new approaches have to be harnessed and exploited.

Recently, in an outstanding study, Pontzer et al. [1] showed evidence supporting the constrained total energy expenditure (TEE) model [2], by objectively measuring TEE and physical activity (PA) in free living humans. The constrained TEE model proposes that TEE increases linearly with PA until it reaches a plateau above which the effect of PA on TEE is negligible. Free-living PA influences energy balance in a different manner than what structured exercise training does. It remains to be investigated in a longitudinal design whether the constrained model hypothesis also applies to long-term exercise training. Pontzer et al. [1] also showed that the plateau in the PA-TEE relationship is not explained by a decrease in resting energy expenditure [2], but by a decrease in the activity energy expenditure component itself. Besides an obvious reduction in non-exercise activity thermogenesis, the magnitude of the reduction of activity energy expenditure component points out to an additional reduction in non-muscular energy expenditure (e.g. reproductive activity or somatic maintenance) [1]. Clarifying the mechanism for the decrease in non-muscular energy expenditure is crucial to fully understand the PA-TEE relationship. Here, we hypothesize that the adaptive thermogenesis mediated by brown adipose tissue (BAT) might account for a large proportion of the exercise-induced decrease in non-muscular energy expenditure.

There are 2 types of thermogenic BAT: classical brown and beige adipose tissues. The main function of both tissues is to burn glucose and lipids to produce heat (by uncoupled respiration). Although sharing its main metabolic role, classical brown and beige adipocytes have distinct developmental origins as well as gene expression patterns [3]. A huge interest in human BAT physiology emerged in 2009 due to its potential role in energy balance, as well as in glucose and lipid metabolism [3, 4]. Activated BAT influences energy expenditure in animal models, increasing both resting energy expenditure and adaptive thermogenesis (i.e. diet- and cold-induced thermogenesis). In humans, the influence of activated BAT on resting energy expenditure in thermoneutral conditions seems negligible, and its role on diet-induced...
thermogenesis remains to be confirmed [5]. However, human-activated BAT increases the resting energy expenditure when it is fully activated and exposed to cold temperatures up to \( \approx 200-400 \text{ kcal/day} \) [4]. Therefore, enhancing BAT activity could be a promising strategy to increase energy expenditure (through adaptive thermogenesis) in humans.

Sympathetic nervous system, through noradrenaline action, is the classical activator of BAT. Additionally, a set of non-sympathetic-dependent molecules also increases BAT activity. Interestingly, both sympathetic and non-sympathetic pathways (e.g. irisin, BAIBA, IL-6, FGF21, cardiac natriuretic peptides, myostatin, meteorin-like, lactate, and leptin) are sensitive to exercise [6, 7]. It was therefore suggested that exercise could be an activator of BAT [6–13]. Several studies reported that exercise induces beige activation and recruitment in murine models [6, 10, 11]. In contrast, although available results are not yet conclusive, murine classical BAT seems to be inhibited in response to long-term exercise [10]. As exercise is a thermogenic stimulus (a large amount of heat is produced as a consequence of muscle contractions), there is a debate about the physiological meaning of exercise-induced beige stimulation. Classical BAT is located near the core areas and thus is more effective on whole body warming than beige. Therefore, exercise-induced reduction of classical BAT activity would result in an impaired capacity to generate heat, as expected. However, BAT function is not only to generate heat but also to participate in the energy metabolism regulation (e.g. adjusting the metabolic rate according to energy availability). It has been suggested that the impaired classical BAT thermoregulatory function as a consequence of exercise, might be compensated by beige stimulation, which would exert the same metabolic regulation but a lower heat-generating role (and possibly lower energy consumption than BAT) [11].

The exercise-induced sympathetic nervous system, myokines and adipokines responses related to BAT physiology observed in animals are also present in humans [6, 13]; it is therefore biologically plausible that exercise also stimulates human’s BAT activity [7]. Dinas et al. [8] reported, in a cross-sectional study, a positive association between PA and BAT activity in cancer patients who were unfit and inactive. On the other hand, 2 case-controlled studies [9, 10] showed much lower BAT activity in highly trained endurance athletes than in sedentary counterparts. Despite some limitations inherent to the studies’ methodology [14, 15], these contradictory findings might be partially explained by the vast differences in both training status and PA levels of the participants (i.e. unfit and inactive versus fit and active individuals, respectively). Regarding beige induction in response to exercise, there is still no convincing evidence to determine whether it also exists in humans [10, 16].

In summary, there is epidemiological evidence [8] and biological base [6, 7] to believe that human BAT activation takes place in response to exercise at low training status or PA level. However, based also on observational data [9, 10] and animals studies [11], it is plausible that human BAT activity is reduced in response to exercise in fit or very active individuals, which might be explained by a decrease in classic brown adipocytes activity not completely compensated by an increase in beige adipocytes activity [11]. Therefore, BAT adaptation to exercise could partially explain, by means of a reduced adaptive thermogenesis, the observed decrease in non-muscular energy expenditure hypothesized by Pontzer et al. [1]. Indeed, in a different study, Pontzer et al. [17] reported that the PA–TEE relationship in a group of Bolivians farmers was less concordant with the constrained model than in Tanzanian hunter-gatherer and US. people. Farmers from the altiplano of Bolivia are likely to be exposed to low temperatures, and thus, it could be that cold-induced BAT activation (i) counteracts the reduction in non-muscular energy expenditure and (ii) enhances TEE in highly active individuals.

More studies are needed to test these hypotheses [18], and if confirmed, new strategies have to be designed to counteract the BAT ‘side effect’ of exercise-based therapies for preventing and treating obesity and related comorbidities.

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References


