Mice lacking the thyroid hormone receptor-alpha gene spend more energy in thermogenesis, burn more fat, and are less sensitive to high-fat diet-induced obesity.

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SUMMARY

Background: Unable to activate brown adipose tissue (BAT) thermogenesis, alphaT3-receptor-deficient mice (Thra-0/0) are cold intolerant.

Objective: The objective of the study was to investigate the impact on energy economy and mechanisms of the alternate facultative thermogenesis developed.

Results: Energy expenditure (oxygen and food consumption) was elevated in Thra-0/0 mice reared at room temperature. Such difference disappeared at thermo-neutrality (30°C) and expanded as ambient temperature became colder (P < 0.001). Despite eating more, Thra-0/0 were leaner than wild-type (WT) mice, whereas the latter, whether on chow or high-fat diet, gained more weight and adiposity than Thra-0/0 mice (P < 0.001). The respiratory quotient was lower in Thra-0/0 than WT mice (P < 0.001), after feeding or fasted, on chow or high-fat diet, indicating a preference for fat as fuel, which was associated with increased lipoprotein lipase (LPL) expression in skeletal muscle of Thra-0/0 mice but with no differences in gene expression in white adipose tissue. Type-2 deiodinase (D2) was increased in brown adipose tissue (BAT) and aerobic muscle of Thra-0/0 mice. This and liver D1 were increased by a high-fat diet in both genotypes, as also were serum T3 and the T3/T4 ratio, but more in Thra-0/0 than wild type mice (P < 0.001). Remarkably, when studied at thermo-neutrality, genotype differences in weight and adiposity gain, respiratory quotient, D2, and LPL disappeared.

Conclusions: Disruption of BAT thermogenesis in Thra-0/0 mice activates an alternate facultative thermogenesis that is more energy demanding and associated with reduced fuel efficiency, leanness, increased capacity to oxidize fat, and relative resistance to diet-induced obesity, in all of which muscle LPL and iodothyronine deiodinases play a key role.

COMMENT

Thyroid hormone regulates thermogenesis via complex mechanisms that have been dissected since many years by Enrique Silva and his group. Evolutionary development of homeothermy was an important biological advance because it allowed animal life to expand into environments with temperatures markedly different from those of the body. Thermogenesis (both obligatory and facultative) corresponds to heat production and thyroid hormones (TH) play an essential role in warm-blooded species, both via the basal metabolic rate and TH action in different tissues, such as BAT (brown adipose tissue). The mechanisms involved are the synthesis of ATP and the role of a unique protein called thermogenin (or uncoupling protein, UCP). For further reading on this subject, see the remarkable review article by Enrique Silva in the

Deletion of thyroid hormone nuclear receptors (TRs) is not associated with flagrant disruption of temperature homeostasis. TRβ-deficient mice have no apparent problem in regulating body temperature, but TRα1-deficient mice show a phenotype that is constantly associated with a 0.5-1°C lower body temperature.

In this study, the authors investigated, using an experimental model of transgenic mice lacking all TRα (TRα-0/0), the impact of the lack of TRα gene products on energy balance.

The main result was to show an inability of BAT to produce heat in response to the adrenergic stimulation induced by exposure to cold in TRα-0/0 mice. These knock-out animals activated an alternate form of facultative thermogenesis that made them spend more energy which, in turn, rendered them leaner, less fuel efficient, and more dependent on continuous food supply for adaptation to cold. Alternative thermogenesis in such animals was geared by higher levels of deiodinases type 1 & type 2, as well as by increased LPL expression. Thus, this led to increased T4 to T3 conversion, and increased LPL in muscle diverted fat from white adipose tissues to the muscle where its oxidation was stimulated by higher levels of circulating and local T3.

The authors concluded that BAT thermogenesis has evolved as a highly efficient pathway to produce heat for the homeostasis of body temperature. When this pathway is disabled, evolutionary older – and less efficient mechanisms – are activated by recall. These older mechanisms are more energy demanding and make the regulation of temperature much more dependent upon a constant food intake. These findings therefore open new avenues to explore, as potential risk factors for development of obesity.

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See Figure below

**Fig. 2.** Cold adaptation increases food demands more in Thra-0/0 than in WT mice. Experiments were performed in Massachusetts, with the WT and Thra-0/0 genotypes in the C57BL genetic background. A. Food consumption in mice exposed to 22, 11, and 4°C for 24 h and fed standard diet (chow, as defined in Materials and Methods). All mice were 3–4 months old, did not differ in weight, and had been reared at 31°C, eating chow at all times. Reducing ambient temperature is associated with increased food consumption, but the increment is greater in Thra-0/0 than in WT mice. B. Weight loss in response to a 16-h exposure to 10°C without food: left pair of bars and left y-axis show absolute weight loss (grams), whereas the right bars and right y-axis show the relative loss (percent). Initial weights were not significantly different. Statistical significance is as in Fig. 1.