NONSHIVERING THERMOGENESIS: THE UNIQUE ROLE OF BROWN ADIPOSE TISSUE

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It has become generally accepted that the heat deriving from brown adipose tissue metabolism provides a quantitatively significant contribution to the total heat required to defend body temperature when a rodent is placed in a cold environment. However, it has remained unclear as to whether this tissue alone is responsible for all adaptive nonshivering thermogenesis or whether other tissues can also be induced to contribute. This has become particularly pertinent with the discovery of genes, the sequences of which demonstrate high homology with the brown-fat specific uncoupling protein UCP1. The question is also relevant in larger animals not demonstrating discrete depots of brown adipose tissue. It has, however, now become possible to address these questions because of the availability of mice with a genetic ablation in the UCP1 gene. Brown adipose tissue thermogenesis is activated by norepinephrine released from sympathetic nerve terminals within the tissue. Injection of norepinephrine (1 mg/kg, i.p.) can mimic this reaction. Using the UCP1-ablated mice, we have been able to show that the response to injected norepinephrine consists of two components, a UCP1-dependent response, the magnitude of which is recruitable, and a UCP1-independent response which is not recruitable and which presumably corresponds to the metabolic response of all tissues to a high dose of a catecholamine. It is unclear whether the UCP1-independent response can ever be considered as physiological. Although the UCP1-ablated mice are, as expected, sensitive to cold, they can, nonetheless, be acclimated to survive in cold by a preacclimation period at an intermediate temperature. We have shown that their ability to survive at low temperature is entirely due to the ability of the animals to maintain persistent shivering. They have not developed any nonshivering thermogenesis in any tissue or organ, and survive presumably because of an improved endurance to shivering in the skeletal muscles. Thus, no other protein can compensate for the loss of UCP1 and no other hormone or neurotransmitter can replace norepinephrine in inducing any nonshivering thermogenesis. This demonstrates unequivocally that UCP1 homologues such as UCP2 or UCP3 are unable to be recruited and activated to be thermogenic under conditions of cold stress. Since it is becoming increasingly clear that loci of brown adipocytes are found in white fat depots, it is not improbable that even mammals lacking large visible brown adipose tissue depots nonetheless can recruit brown adipose tissue thermogenesis when required.

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