Response

MOLECULAR METABOLISM

Response to *Leptin–deficient mice are not hypothermic, they are anapyrexic*

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To the Editor: The *Comment* by Fisher, Cannon and Nedergaard [1] on our recent paper [2] advocates use of the term 'anapyrexia,' which connotes a biologically defended decrease of body temperature; e.g., the opposite of a fever, to describe the subnormal core temperature of leptin-deficient *ob/ob* mice. Another option is the conjunction 'regulated hypothermia' [3], based on the Glossary of Terms for Thermal Physiology [4], which notes that *"hypothermia may be regulated (e.g., Torpor, Hibernation) or may be forced if heat loss exceeds the capacity for total heat production."* Crucial to these deliberations is that while *ob/ob* mice maintain normothermia when housed in a thermoneutral environment, and prefer such an environment when provided the option, they maintain a reduced core temperature when housed at sub-thermoneutrality, and the threshold at which they mount autonomic defenses against body heat loss is similarly subnormal. Leptin deficiency, therefore, gives rise to an unusual phenotype in which the biological defense of core temperature varies with external temperature. 'Pyrexia,' by contrast, involves a coordinated suite of autonomic and behavioral effector shifts reflective of a true regulated state (e.g., 'regulated hypothermia') that is largely insensitive to environmental temperature. Such terms do not accurately capture the unusual phenotype of *ob/ob* mice.

To better understand the biological underpinnings of what is observed, we propose that the *ob/ob* mouse brain responds to cold stress with a lowering of core temperature as part of an adaptive response to conserve energy, based on the widely accepted premise that lack of a leptin signal conveys a severe deficiency of stored fuel [5]. This "evolutionarily-based adaptive hypothermia model" proposes that when housed in a sub-thermoneutral environment, adaptive lowering of core temperature minimizes energy costs, thereby favoring survival, particularly given the increased susceptibility to heat loss of these mice. Given the opportunity to seek out a thermoneutral environment, however, they will do so [6]. This model is readily distinguished from 'regulated hypothermia,' which implies a coordinated set of effector responses to defend a sub-normal core temperature, including a preference for a sub-thermoneutral environment, which is not observed in *ob/ob* mice. Since leptin deficiency is ordinarily experienced only in the setting of severe food restriction, the 'adaptive hypothermia' model predicts that affected animals are motivated to achieve normal body temperature if this can be accomplished at minimal energy or predation cost; if not, the thermoregulatory system adjusts to defend a lower than normal body temperature and reap the associated energy savings.

From this perspective, the thermoregulatory phenotype of *ob/ob* mice is not so much a failure of thermoregulation as it is an adaptive downward re-setting of the thermoregulatory system in the face of reduced ambient temperature. Therefore, we agree that our original characterization of the *ob/ob* thermoregulatory phenotype as a "failure of thermoregulation" [2,6] is unjustified, although we note that in a sufficiently cold environment, the adaptive value of this arrangement appears limited. Specifically, *ob/ob* mice exposed to a sudden and dramatic decrease of ambient temperature are unable to stabilize their falling body temperature and can die [7]. The limited ability of *ob/ob* mice to adapt to acute cold stress may be related, in part, to their greater reliance on shivering to generate heat production, which itself increases convective heat loss. This is also consistent with the effect of leptin to decrease whole-body thermal conductance [2,6]. Nevertheless, when exposed to cold stress in a progressive, monotonic step-wise manner, such as the Scholander procedure, these mice can adapt effectively [6].

In the opening sentence of the *Comment* [1], the authors assert that *"…we are surprised by a recent paper in Molecular Metabolism, stating that we [authors of Comment] have shown that leptin functions by an "increase of the body temperature threshold for activating thermogenesis."* Our assertion was based on the author's publication [6] in which Supplemental Figure 5 reports that: "*leptin replacement results in an upward shift of the thresholds of heat-producing mechanisms.*" We suggest that whether leptin modulates the threshold for facultative thermogenesis warrants further study, and we appreciate the opportunity to re-think and clarify our perspectives on the *ob/ob* thermoregulatory phenotype.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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