MOLECULAR METABOLISM

Comment

Leptin-deficient mice are not hypothermic, they are anapyrexic

Having just published a paper with the explicit title "Leptin Raises Defended Body Temperature without Activating Thermogenesis" [1] we are surprised by a recent paper in Molecular Metabolism [2], stating that we have shown that leptin functions by an "increase of the body temperature threshold for activating thermogenesis." In contrast to what is implied, we are fully in agreement concerning essentially all relevant experimental data — indeed, given the differences in leptin administration, measurement techniques, etc., the data sets are scholarly examples of the reproducibility that is the hallmark of empirical science. Thus, we agree that the body temperature of ob/ob mice is lower than in wildtype mice when the mice are housed at subthermoneutral temperatures and that leptin treatment normalizes the body temperature. We also agree that this increase in body temperature following leptin treatment happens without any stimulation of thermogenesis and is instead due to a reduced heat loss (decreased conductance). Thus, both papers refute the common contention that leptin is thermogenic.

There are, however, differences between the two papers, but they relate to the interpretation of the data and are basically to be found in what is implied by the word "hypothermia". This may be considered a semantic discussion, but it forms the basis for the physiological interpretation of what is happening. Kaiyala et al. discuss the low body temperature as a "failure" in the thermoregulatory system and interpret it as an unintended imbalance between the rate of heat loss and the ability of the mice to produce sufficient heat. However, both Kaiyala et al. and we show very convincingly that e.g. at $\approx$22 °C, the animals are principally capable of producing much more heat than they do, because they increase their heat production very markedly when exposed to an even colder temperature. They thus do not to use their full, available thermogenic capacity at 22 °C. This is in contrast to a genuine hypothermic situation where the body temperature falls because the organism is no longer able to increase thermogenesis sufficiently to counteract heat loss (i.e. "freezing to death"). Rather, what we see in the ob/ob mice is that body temperature is maintained at a constant but lower than "normothermic" level. Thus, this is a situation akin to the circadian shift in body temperature between day and night, observed by e.g. both Kaiyala et al. and us and, of course, many others. Nobody would consider normal mice to be hypothermic during the day; yet, the decrease in temperature is similar to that seen between wildtype and ob/ob mice. Indeed, as compared to nighttime body temperature, daytime body temperature in mice should be considered an anapyrexic condition: a regulated condition similar to a fever, but in which body temperature is lowered not elevated.

In the classical interpretation of thermoregulation, a body temperature set-point was fixed, and when body temperatures increased above this point, cooling mechanisms were activated; when body temperatures decreased below this set point, warming mechanisms were activated. In a more contemporary analysis, promoted particularly by Romanovsky [3], the different thermoregulatory systems may have different threshold temperatures that may be differently affected by different mechanisms and, therefore, do not have to be synchronized. This opens the possibility of broader windows of acceptable body temperatures. In the ob/ob mice, we demonstrated that, in the absence of leptin, the threshold temperatures for behavioral thermoregulation are unchanged, but that the threshold for vasoconstriction is lowered. This means that the body temperature is allowed to be decreased more in the ob/ob mouse before vasoconstriction is activated. This lower body temperature is defended, however, and is therefore not a hypothermia. As we demonstrated, what leptin does is to affect the threshold for vasoconstriction, moving the threshold to a higher body temperature, thus causing vasoconstriction to be induced earlier and thus moving the resulting body temperature upwards.

Does it matter whether the lower body temperature is interpreted as hypothermia or anapyrexia? We believe it does, because if it is considered a hypothermia, the next step would be to look for failures in the peripheral vasoconstriction process, whereas if it is anapyrexia, the causes should be sought centrally, in the thermoregulatory system. Therefore, be not misdirected: leptin elevates the threshold temperature for certain energetically neutral thermoregulatory systems, e.g. conductance, resulting in a higher body temperature. Thus, leptin raises defended body temperature without activating thermogenesis.

REFERENCES

[1] Fischer, A.W., Hoefig, C.S., Abreu-Vieira, G., De Jong, J.M., Petrovic, N., Mittag, J., et al., 2016. Leptin raises defended body temperature without activating thermogenesis. Cell Reports 14:1621—1631.

[2] Kaiyala, K.J., Ogimoto, K., Nelson, J.T., Muta, K., Morton, G.J., 2016. Physiological role for leptin in the control of thermal conductance. Molecular Metabolism 5:892—902.

[3] Romanovsky, A.A., 2004. Do fever and anapyrexia exist? Analysis of set point-based definitions. American Journal of Physiolology: Regulatory Integrative and Comparative Physiology 287:R992—R995.

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