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FRONT MATTER: COMMENT

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Energy signaling in obese mice delays the impact of fasting on thermoregulation

Comment on: Solymár M, et al. The onset of daily torpor is regulated by the same low body mass in lean mice and in mice with diet-induced obesity. Temperature 2015; 2:129-134; http://dx.doi.org/10.1080/23328940.2015.1014250

I thank the editors of *Temperature* for the opportunity to provide an editorial comment on the recent article by Solymár et al.[1] We have known for some time that, when endothermic animals are fasted, their energy expenditure pathways are altered in a way that results in a decrease in core body temperature during the inactive phase of their daily activity cycle.[2] The decrease in body temperature generally is viewed as adaptive, since the closer the animal's body temperature is to ambient temperature, the less energy is required to defend body temperature. In the laboratory mouse, a few days of fasting takes body temperature to below 31°C, which, according to the definition employed in the paper under discussion, means that the mice enter torpor. There is no change (at least initially) in the core body temperature during the active phase of the daily cycle; that is counterintuitive but seems to be what occurs to the body temperature rhythm whenever mammals run low on energy.[3]

Mammals with normal body fat content run low on energy soon after starting to fast, and display heterothermy within a day or two of fast initiation.[4] What happens to obese animals, which have a store of energy in body fat? That is what Solymár et al.[1] have investigated, for the first time. In the face of a complete fast, mice previously made obese did not enter torpor until their body mass approached that of the normal-mass mice, a process that took several weeks; the obese mice started with a body mass more than double that of the control lean mice Figure. 2 of the paper by Solymár and colleagues shows, though, that less-dramatic but distinct changes in the temperature rhythm of the obese mice happened long before that, as do cardiovascular changes in fasted obese mice. Indeed, heart rate, blood pressure, and oxygen consumption fell more rapidly during a fast in obese mice than they did in lean mice, albeit from a higher baseline.[5]

Thermal physiologists certainly would want to know what signal to the thermoregulatory system differed, during the first days of fasting, between the obese and lean animals. Neither the obese nor the lean mice were eating, and so presumably the gut-derived peptides that have been implicated in the short- term control of appetite and energy expenditure did not differ. It would be valuable to test that hypothesis by measuring those peptides. A better candidate would be leptin, the adipose-derived cytokine that has been implicated in the hypothermia of fasting. Leptin replacement in underfed and ob/ob mice reduces the incidence of torpor, and mice without dopamine β hydroxylase (an enzyme in the pathway to epinephrine and norepinephrine production) show neither a fall in leptin nor torpor when fasted[6] Though Solymár and colleagues did not measure leptin concentrations in their mice, it seems quite possible that the obese mice, with surplus energy, had a delayed fall in leptin with fasting. There don't appear to be any long-term data on leptin concentrations during fasting in mice previously made obese, a surprising hiatus in the literature, but high fat feeding blunts the fall in plasma leptin during fasting, at least during the initial 48 hours.[7]

But leptin cannot be the only mediator of the torpor response to fasting. Other mediators must exist because ob/ob mice lack leptin, and db/db mice lack its receptor, and yet neither are permanently torpid.[2] An alternative signal for the entry into torpor might be falling glucose levels. Overton and Williams[2] summarise the evidence for a role

for glucose in torpor signaling: before animals enter torpor the respiratory quotient decreases to levels indicative of fat oxidation; treatment with 2-deoxyglucose (a glucose analog that is taken up by cells but that cannot be phosphorylated and so cannot enter the glycolysis pathway, causing functional glucose deficit in cells) induces torpor in hamsters; the injection of 2-deoxyglucose into the central nervous system makes mice go torpid; and the treatment of mice with gold aurothioglucose (a gold-containing analog of glucose that produces lesions in glucose-sensitive neurons) reduces the incidence of torpor.

Solymár and colleagues propose an interesting potential practical application of the underlying physiology that they have studied. To reduce mass, obese patients sometimes fast completely. Currently, there are no clear threshold symptoms or physiological measures to indicate when it is no longer safe to continue fasting, if irreversible pathology is to be avoided. Measuring plasma leptin itself would not be useful, because while a decrease in leptin is correlated with some pathology, it does not cause any known pathology. One suggestion is that the size of the protein pool available for gluconeogenesis would be a useful indication of when fasting should stop, but it is not easy to measure that protein pool in a family doctor setting. Could measuring body temperature alert doctors to an energy deficit compromising not only homeothermy but also glucose homeostasis, when obese patients fast?.

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