METABOLISM

A point on thermoneutrality for mice

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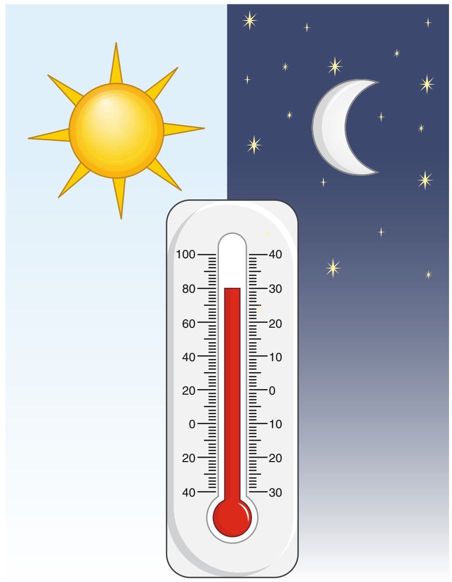
A comfortable temperature to humans runs a bit cooler than the average mouse may prefer. Mice housed in 'chilly' vivariums—typically 20 °C to 22 °C—can spend considerable energy maintaining their core body temperature—a third to a half of what they eat will go to cold-induced thermogenesis, a process in which brown fat in the body generates heat.

"Humans just don't do that," says Marc Reitman, a researcher at the National Institute of Diabetes and Digestive and Kidney Diseases who studies obesity and diabetes. "We maintain a thermoneutral microenvironment. Between our thermostats and our clothes, this is just not something we deal with." Rather, the human body more often needs to dissipate excess heat, rather than produce it.

Mice can't directly control the thermostat, but raise the thermostat to 30 °C—the long-agreed upon thermoneutral temperature for mouse—and the animals' metabolism will change. "You get some different physiology," says Reitman. "Some drugs work at 30 °C and not at 22 °C, for example. You can end up with more obesity [at 30 °C]…. Then the question is, which is a better model: a mouse at 30 °C or a mouse at 22 °C?"

That's a pressing question for metabolism-related research and drug development, given how complicated physiology can be and how expensive human clinical trials are to run. "If we could figure out how to use mice better, we could cut down the number of failed human trials because we would have a better predictive value from the mouse model," says Reitman. "That's the goal."

Conventional wisdom says that at 30 °C, mice no longer experience cold-induced thermogenesis and thus should make better models of metabolism-related human conditions such as obesity and diabetes. Many in the field have indeed been raising ambient temperatures in recent years, Reitman notes. But, the picture has been incomplete.



Night & day: the thermoneutral point for lab mice depends on whether they are in their active or resting phase. Credit: Marina Spence / Springer Nature

"People have really not studied the upper limit of thermoneutrality," says Reitman. Instead, much of our understanding of mouse thermal biology has been extrapolated from human studies. That assumes a flat thermoneutral zone, over which metabolism is constant and no attention is paid to body temperature. That detail is of little concern for large mammals such as ourselves, but one that becomes a more important variable for one as small as a mouse.

Reitman's latest work challenges that assumption of a thermoneutral zone for mice, with results even he and his team found surprising. They combined continuous mouse body temperature monitoring with continuous measurement of metabolic rate across several ambient temperatures below and above thermoneutral in four mouse strains with different thermal responses.

Rather than a thermoneutral zone spanning several degrees, the team found breakpoints—what Reitman and his coauthors termed thermoneutral points (TNPs). During the animals' active phase while it is dark, total energy expenditure decreases with constant body temperature until about 33 °C; above this ambient temperature, body temperature rises. When it is light and the animals are in a resting phase, however, the TNP occurred 4 degrees lower, at 29 °C. These results suggest that 'thermoneutral' in mice varies by the time of day.

"Mouse thermal biology is fundamentally different from human," says Reitman. "There is no magic solution." 30 °C, however, might be a touch too warm, at least for resting mice, and could actually be activating the immune system slightly. "I would really suggest people not use 30 °C when they want to study a mouse at thermoneutrality," he says. Better instead to set thermal cabinets to ~28 °C and let the mice use the thermoregulatory mechanisms they have evolved, which are better at handling cooler rather than warmer temperatures.

Group housing mice and/or providing the animals with nesting material may change these numbers, as can using mouse strains with different thermal biology from wildtype, such as ob/ob mice. But overall, Reitman says researchers conducting metabolic work with mouse models should be mindful of ambient temperature, and of any prior assumptions about the best range for their animals and their research questions. "I would argue we have to redefine thermoneutrality and include consideration explicitly of body temperature," he says.

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