S195. A tail of two torpors: insight from autonomic and behavioural thermoregulation

Saturday, April 25, 2026
4:30 PM - 7:00 PM
Room: MCC, PhysioHub, Posters

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Abstract:
Fasted mice readily enter daily torpor, a fascinating state of reduced: activity, heart rate, oxygen consumption, and body temperature. Chemoactivation of neurons in the preoptic area of the mouse hypothalamus (POA) using designer receptors exclusively activated by designer drugs (DREADDs) produces 'synthetic torpor', recapitulating key features of torpor even in fed mice. Several groups have noted that synthetic torpor in mice is accompanied by a flash of tail, vasodilation, suggesting an active attempt to lose heat into the environment. In contrast, during fasting-induced torpor vascular tone is increased, and a hunched posture taken, suggesting a drive towards heat conservation.
Methods: we investigated autonomic and behavioural thermoregulation during synthetic and fasting-induced torpor (FIT) using targeted recombination in active populations (TRAP) to selectively express DREADDs in POA neurons that were active during FIT (POA torpor-TRAP). We then recorded tail temperature using a thermal camera from below as the mice entered FIT or synthetic torpor. Next, we used a thermal ramp to measure thermal preference in mice entering synthetic torpor.
Results: injection of the DREADD activator clozapine-N-Oxide (CNO, 2mg/kg, i.p.) to trigger synthetic torpor reduced core temperature in POA torpor-TRAP mice (mean change -3.35±2.04°C, paired t-test, p =0.0023, n=8 mice). Tail temperature rose during entry into synthetic torpor compared to the tail temperature on entry into FIT (2-way repeated measures ANOVA time x condition interaction, p = 0.004, n = 6 mice). The observed changes were specific to the tail: there was no time x condition interaction for the temperature of the underside of the abdomen (p=0.3773). Finally, we investigated behavioural thermoregulation during synthetic torpor. Injection of CNO into POA torpor-TRAP mice resulted in a significant preference for the warm end of the thermal ramp compared to when the same mice received saline (2-way repeated measures ANOVA, time x treatment interaction, p=0.0094, n = 9). CNO treatment did not affect thermal place preference in wild type control mice (2-way repeated measures ANOVA, time x treatment interaction, p=0.2485, n = 6). The option to behaviourally thermoregulate prevented the previously observed core temperature reduction of synthetic torpor (mean change -0.3750±1.33°C, paired t-test, p = 0.45).
Discussion: we found important differences between fasting-induced torpor and synthetic torpor in terms of autonomic thermoregulation: tail vasodilation on entry into synthetic torpor indicates an attempt to lose heat into the environment. This response was not observed during entry into

fasting-induced torpor. We hypothesised that the torpor-TRAPed POA neurons might signal that the animal was too hot, hence triggering vasodilation. However, we found that chemoactivation of POA torpor-TRAPed neurons resulted in a strong preference for a warm environment. Indeed, these mice moved to a warmer zone than did control mice. In doing so, these mice were able to avoid any significant drop in core temperature, indicating that from a behavioural perspective thermoregulation was intact. These observations are in keeping with previous reports that fasted mice prefer a warmer environment and in doing so they prevent significant reductions in core temperature. Our data suggest that synthetic torpor is not a state of pathologically disturbed thermoregulation, Instead, as when fasted naturally, mice in synthetic torpor maintain the ability to thermoregulate. Future work will investigate whether neurons outside the POA provide a counter-regulatory signal to prevent the vasodilation observed when the POA neurons are activated in isolation.