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A New Handle for a Hot Topic: Genetic Markers for Warm-Sensing

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Stepping out of an aggressively air-conditioned building into the sweltering heat evokes a number of thermoregulatory responses, both autonomic (sweating) and behavioral (peeling off a layer of clothing or seeking an iced beverage). Just as we come out of the hottest part of the summer, a study by Tan and colleagues provides an exciting breakthrough in our ability to study the neural mechanisms of keeping cool when it's hot.

The medial preoptic area (POA) has been a candidate region for behavioral thermoregulation for decades, though its candidacy has been volatile. In this issue of *Cell*, Tan and colleagues (Tan et al., 2016) use an approach called "phosphoTRAP" wherein neural activation induces phosphorylation of ribosomal protein S6 (pS6) to reveal the molecular profile of neurons activated by exposure to a warm environment. The authors then identify two highly-enriched neuropeptides within this population, pituitary adenylate cyclase-activating polypeptide (PACAP) and brain-derived neurotrophic factor (BDNF). The majority of activated neurons (~2/3) co-expressed both PACAP and BDNF, whereas only half of these largely overlapping markers co-localized with pS6 (Figure 1)—leaving some questions about what other populations outside of this intersectional set may do.

This molecular approach led the authors to reopen the case of the POA in contributing to behavioral thermoregulation, one that had recently been put to rest (Almeida et al., 2015). This century-old debate began in 1914 with the finding that hypothalamic lesions impaired thermoregulation (Isenschmid and Schnitzler, 1914). Subsequent lesion studies refined the localization to the anterior hypothalamus, particularly highlighting the ventral portion of the medial POA (referred to as VMPO in this study), dubbed the "shivering suppression center" or "heat-loss center." A finer role for the POA was carved in the broad swath of thermoregulatory responses that included autonomic thermoregulation (sweating, brown adipose tissue activation), but not behavioral thermoregulation (nesting, heat/cold-seeking), as rats with POA lesions actually increased operant heat-seeking in a cold environment (Carlisle, 1969; Satinoff and Rutstein, 1970). Cold-seeking was also preserved in POA-lesioned animals, while autonomic thermoregulatory responses were impaired in animals with a lipopolysaccharide-induced fever (Almeida et al., 2006).

In summary, the possibility of the POA playing a role in behavioral demonstration of thermal preference was explicitly excluded (Almeida et al., 2015), based on the preservation of this ability upon loss-of-function manipulations. Here, Tan and colleagues demonstrate the sufficiency of PACAP/BDNF neurons in the POA for behavioral thermoregulation, including temperature preference. It remains, however, possible that the role of the POA in behavioral thermoregulation relies purely on its input to the dorsal medial hypothalamus (DMH) and that the POA may not be unique in that any region driving activity in the DMH might be sufficient to support behavioral thermoregulation.

Tan and colleagues reveal that the sensitivity of these neurons is restricted to a narrow range of temperatures, within the range of innocuous warmth (~30–42°C). This begs the question: which neurons are sensitive to temperatures outside of this range, and how are the appropriate thermoregulatory responses orchestrated under more extreme conditions? At almost the same time, a complementary paper identified a population of POA neurons expressing the temperature-sensing ion channel TRPM2, which also promote hypothermia when activated. These neurons display sensitivity to temperatures above 37°C, suggesting a more prominent role in initiating thermoregulation in response to heat stress and/or fever (Song et al., 2016). Another study that was published a few months ago demonstrated differential encoding of warm and cold temperature signals detected from the skin in the dorsal horn of the spinal cord (Ran et al., 2016), further supporting the idea that discrete pathways signal and initiate hyperthermic/hypothermic responses. How might environmental heat compare to inflammation-induced heat (why might a fever come with chills)?

A number of other questions bubble to the surface: POA:PACAP→DMH activation inhibits brown adipose tissue (BAT) thermogenesis, but not tail vasodilation or behavioral thermoregulation—so what do the other projections from POA specifically do? What are the projections that give rise to motivated behaviors for thermoregulation? What are the inputs to these cells? The question of the origin of inputs to the POA$^{PACAP/BDNF}$ neurons is an especially intriguing one, particularly given the recent discovery that a novel set of TRPM2-expressing somatosensory neurons display a temperature sensitivity range similar to that of the POA$^{PACAP/BDNF}$ neurons (Tan and McNaughton, 2016). This hints at the possibility of a model in which these sensory neurons provide the necessary input to the POA$^{PACAP/BDNF}$ cells, directing heat loss and cold-seeking behavior.

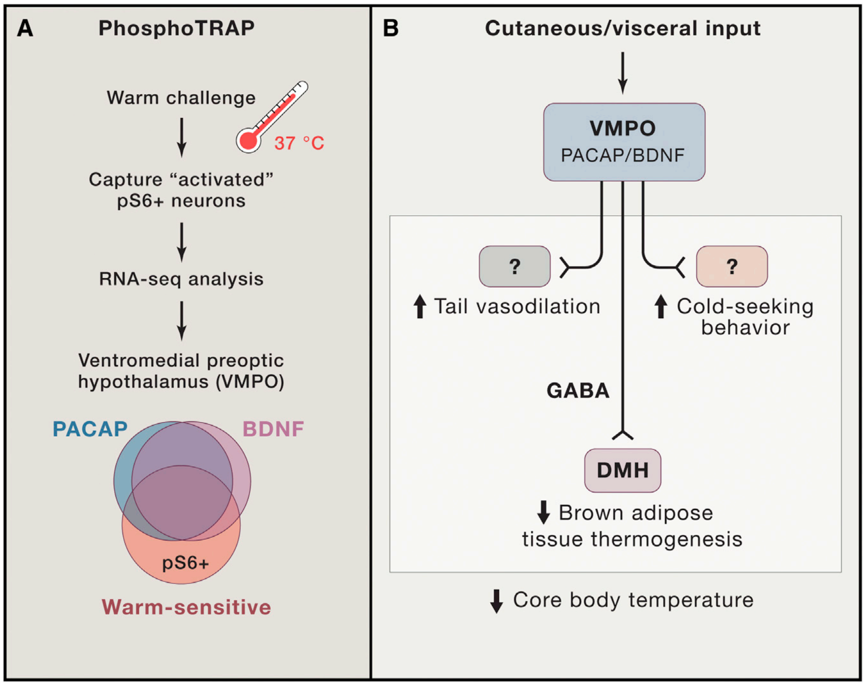

Figure 1. Characterizing Temperature-Sensitive Neurons and Their Role in Thermoregulation
(A) Warm-sensitive neurons were identified using "phosphoTRAP." Mice were subjected to environmental warmth followed by molecular profiling of activated (pS6+) neurons. This revealed a largely overlapping population of PACAP/BDNF+ neurons in the ventromedial preoptic area (VMPO), the majority of which were pS6+.
(B) Model indicating how the VMPO$^{PACAP/BDNF}$ neurons may integrate peripheral sensory temperature information and orchestrate a reduction in core body temperature via multiple downstream effector systems.

In conclusion, Tan and colleagues provide direct evidence supporting ideas reviewed by Shaun Morrison regarding the circuitry of warm-sensing POA projections to the DMH (Almeida et al., 2006; Morrison, 2016). They also provide a genetic handle that will enable study of these circuits, and an illustration of how this powerful "phosphoTrap" approach might be generalized to a vast array of functions. Indeed, this study promises to launch new research directions, characterizing anatomical targets downstream of these PACAP/BDNF neurons. Why might there be separable projections that contribute to different aspects? Perhaps the advantage of the parallel-effector organization within this homeostatic circuit is that contextual information can be integrated with motivated behaviors for thermoregulation. This study provides an exciting breakthrough that will heat up the field of thermoregulation as modern neuroscience approaches can now more easily be applied.

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