This Week in The Journal

Rod HCN Channels Shape Cone-Mediated Signaling

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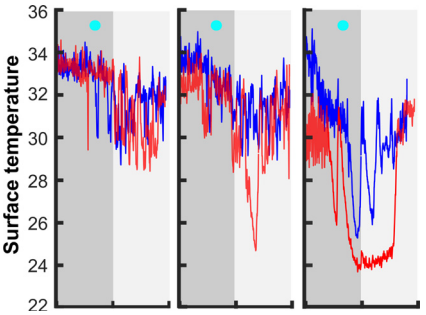
(see pages 4231–4249)

The presence of two types of photoreceptors—rods and cones—in the retina allows animals to see over a broad range of light intensity. In faint light (scotopic conditions), only rods are activated. As light levels increase to mesopic levels, cones become activated, and in bright light (photopic conditions), cone signaling dominates vision. Notably, rod and cone pathways interact and converge at multiple levels in the retina. For example, the two photoreceptor types can be directly connected by gap junctions or influence each other via horizontal cells. Moreover, the principal recipient of rod output—rod bipolar cells—transmits signals to retinal ganglion cells only indirectly, through amacrine cells and cone bipolar cells. Therefore, cone bipolar cells are driven by both rod and cone output.

Adaptation processes that decrease rod-mediated signaling are thought to prevent occlusion of cone-mediated signaling and saturation of cone bipolar cell responses when both cones and rods are active. Lankford et al. suspected that the hyperpolarization-activated cyclic-nucleotide-gated channel HCN1 contributes to this adaptation. Indeed, phototransduction involves hyperpolarization of photoreceptors, leading to opening of HCN1 channels, which, in turn, depolarize the cells and shorten the light response. As expected, therefore, knockout of HCN1 selectively in rods delayed recovery of the electroretinogram (ERG) b-wave—a measure of output from photoreceptors to bipolar cells—under scotopic conditions. In addition, knocking out HCN1 in rods eliminated visual responses to high-frequency flicker, which is thought to be mediated by cones, under high-mesopic conditions. More surprisingly, rod-specific knockout of HCN1 eliminated the cone-driven ERG b-wave under photopic conditions. In contrast, knocking out HCN1 selectively in cones had no apparent effect on the ERG at any light level.

These results confirm that HCN1 activation shortens the duration of rod signaling and suggest that this effect is essential for enabling the transmission of cone-mediated signaling, even in bright light. Future work should determine how rod output suppresses cone signaling in the absence of HCN1, how loss of rod HCN1 affects vision, and what role HCN1 plays in cones.



Recordings of mouse surface temperature over 24 h periods beginning after 1 (left), 2 (middle), or 5 (right) days of food restriction show that torpor (indicated by a drop in temperature) occurs sooner, and bouts last longer, when DMH neurons are exogenously activated (red) than when they are not (blue). See Ambler et al. for details.

Dorsomedial Hypothalamic Neurons Regulate Torpor

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(see pages 4267–4277)

Mammals must expend a large amount of energy to maintain normal body temperature when ambient temperatures drop. When food supplies are limited, some animals reduce this energy expenditure by slowing their metabolic, heart, and respiratory rates and letting their body temperature drop. This collection of changes is called hibernation or torpor, depending on the extent and duration of the changes.

When mice receive limited amounts of food, they begin to undergo daily bouts of torpor. The onset of each bout of torpor is associated with increased activity in a subset of neurons in the preoptic area of the hypothalamus, and exogenous activation of these neurons can initiate torpor even in well fed mice (Hrvatin et al., 2020, Nature 583:115). Because some of these neurons are thought to project to the dorsomedial hypothalamus (DMH), an area previously shown to regulate body temperature and energy expenditure, Ambler et al. sought to elucidate the role of DMH neurons in the initiation and maintenance of torpor.

The authors used transgenic mice in which the expression of Cre could be induced in neurons activated at a particular time, in this case, when the onset of a torpor bout was expected. As expected, more DMH neurons were activated in mice that entered torpor than in those that did not. Expressing designer receptors exclusively activated by designer drugs (DREADDs) in DMH neurons that were active during torpor allowed the authors to investigate how activating or inhibiting these neurons affected future torpor bouts. Activating the neurons did not induce torpor, but caused torpor to occur after fewer days of calorie restriction, increased the number of torpor bouts entered by each mouse, increased the duration of these bouts, and increased the depth of torpor, as indicated by how far the body temperature dropped. In contrast, inhibiting the neurons had no apparent effect on torpor.

These results indicate that DMH neurons have a modulatory effect on torpor, but do not on their own induce torpor. Future work should determine whether the DMH neurons activated during torpor receive direct input from the preoptic area, determine the targets of these neurons, and determine whether activation of DMH neurons that are not active during torpor play a role in inhibiting or terminating torpor.

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