This Week in The Journal

A $\text{Na}^+/\text{Ca}^{2+}$ Exchanger in Endoplasmic Reticulum

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(see pages 3152–3164)

Phototransduction in *Drosophila* begins when a photon activates rhabdomeric rhodopsin, a Gq-coupled receptor that activates phospholipase C (PLC). PLC hydrolyzes membrane phosphatidylinositol 4,5-bisphosphate (PIP₂), forming diacylglycerol (DAG), inositol 1,4,5-trisphosphate (InsP₃), and a proton. One of these products, through unknown mechanisms, opens TRP and TRPL channels, allowing influx of calcium and sodium to complete the phototransduction cascade.

Because cytoplasmic calcium levels in *Drosophila* photoreceptors also increase in response to light when extracellular calcium is removed, albeit more slowly and to a lesser extent, light is thought to trigger calcium release from intracellular stores. One might predict that this release is mediated by InsP₃ receptors in the endoplasmic reticulum (ER), because these trigger calcium release in many cell types. But mutating these receptors did not block light-induced increases in cytoplasmic calcium. Although the $\text{Na}^+/\text{Ca}^{2+}$ exchanger was shown to be required for light-induced calcium increases, this exchanger has only been reported in the plasma membrane, raising doubts about whether it could increase cytoplasmic calcium in the absence of extracellular calcium. Liu et al. now report that the $\text{Na}^+/\text{Ca}^{2+}$ exchanger is also present in the ER membrane and is responsible for light-induced calcium release from the ER.

Expression of a genetically encoded, low-affinity calcium indicator targeted to the ER confirmed that bright light triggered depletion of ER calcium levels in dark-adapted photoreceptors. This depletion persisted when InsP₃ receptors were mutated and when extracellular calcium was removed, but it was greatly reduced when the $\text{Na}^+/\text{Ca}^{2+}$ exchanger was mutated or extracellular sodium was removed. Conversely, overexpressing the $\text{Na}^+/\text{Ca}^{2+}$ exchanger increased and ac-

celerated light-induced depletion of ER calcium. Importantly, immunostaining revealed the presence of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger throughout the ER. Notably, light-induced depletion of ER calcium was attenuated in older flies *in vivo*, and low-intensity light increased, rather than depleted, ER calcium.

These results suggest that sodium influx through TRP/TRPL channels activates ER $\text{Na}^+/\text{Ca}^{2+}$ exchangers, leading to depletion of ER calcium. Because the resulting increase in cytoplasmic calcium is much smaller than that resulting from TRP/TRPL channel opening, and because depletion is minimal under natural lighting conditions, the authors suggest that the main function of the ER $\text{Na}^+/\text{Ca}^{2+}$ exchanger is to help remove cytoplasmic calcium to terminate the light response.

Expression of POMC (top), but not of AgRP (bottom), is reduced in *Prdm12*-deficient hypothalamus (right) compared with control (left). See Chen, Wyler, et al. for details.

Specification of Neurons that Promote and Inhibit Eating

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(see pages 3165–3177)

The drive to eat is controlled primarily by two populations of neurons in the arcuate nucleus of the hypothalamus. One population produces pro-opiomelanocortin (POMC), which is cleaved to form α -melanocyte-stimulating hormone (α -MSH); these neurons suppress feeding by activating neurons that express melanocortin 4 receptors (MC4Rs). The other population produces neuropeptide Y (NPY)

and agouti-related peptide (AgRP); these neurons promote feeding both by inhibiting POMC neurons and by opposing the action of α -MSH on MC4Rs. During development, POMC and NPY/AgRP neurons are generated from the same pool of POMC-expressing progenitors. The genetic programs that determine whether a cell continues to express POMC or switches to NPY/AgRP are poorly understood, however (Toda et al., 2017, *Ann Rev Physiol* 79:209). To tackle this question, Chen, Wyler, et al. performed whole-transcriptome RNA sequencing of genetically labeled neurons purified from mouse hypothalamus on embryonic day 15.5 (E15.5), just after POMC and NPY/AgRP populations have separated.

Unlike in adult brains, where nearly 700 genes are differentially expressed in POMC and NPY/AgRP neurons, only 120 genes were differentially expressed at E15.5. This included 29 transcription factors, which likely control cell phenotype. The differentially expressed transcription factors included several that were previously identified in developing POMC neurons, as well as two (*Prdm12* and *Prdm13*) proposed to regulate fate specification in sensory ganglia and spinal cord.

Prdm12 was expressed in POMC-expressing neurons as early as E10.5, when POMC first appears. Notably, knocking out *Prdm12* greatly reduced POMC expression in the arcuate nucleus, but did not affect expression of NPY or AgRP. Consistent with loss of POMC function, mice lacking *Prdm12* consumed more food and gained more weight than wild-type mice when fed a high-fat diet. But knocking out *Prdm12* selectively in adult POMC neurons did not affect POMC levels or food intake.

These results suggest that *Prdm12* is necessary for the expression of POMC in developing arcuate nucleus neurons, and thus is required for the proper development of circuits that control eating. Despite being required for POMC expression during development, however, *Prdm12* is not required in adult neurons. What drives expression of POMC in adults and how embryonic loss of *Prdm12* disrupts this regulation should be examined in future work.

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