This Week in The Journal

Activation of Transducin by Free Opsin

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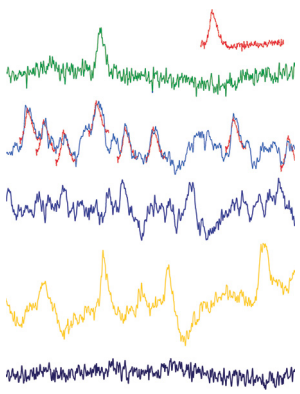
(see pages 212–224)

In darkness, photoreceptors are depolarized by a constant influx of cations through cGMP-gated channels. In rods, when photons strike the chromophore component of rhodopsin, chromophore isomerization induces a conformational change that produces Meta-II rhodopsin, which then activates a G-protein, transducin. Transducin activates a phosphodiesterase that hydrolyses cGMP, reducing cGMP levels. This causes closure of cation channels and transient hyperpolarization, constituting the photoresponse. Isomerized chromophore eventually detaches from rhodopsin, leaving free (bleached) opsin.

After a bright flash bleaches a substantial fraction of rhodopsin, rods' sensitivity to subsequent flashes decreases. This reduced sensitivity, called bleaching adaptation, persists for hours even in total darkness. Bleaching adaptation cannot be attributed solely to the loss of chromophore, but is thought to result from low-level activation of the phototransduction cascade by free opsin. How this occurs has been unclear, however. One possibility is that opsin constitutively activates transducin with low efficiency. Another possibility is that opsin occasionally, but spontaneously and in the absence of chromophore, transitions into an active conformation resembling that of Meta-II rhodopsin. A less likely possibility is that opsin directly activates phosphodiesterase.

To investigate these possibilities, Sato et al. measured the effects of single opsin molecules on membrane currents. To make these measurements possible, they bleached only a small fraction (~1%) of rhodopsin to prevent bleaching adaptation, and they knocked out a protein that blunts the photoresponse by promoting cGMP synthesis. Fully dark-adapted rods exhibited occasional events resembling single-photon responses, but the frequency of these events greatly increased after bleaching. Thus, the activity of bleached rods resembled that of dark-adapted rods exposed to dim light.

Bleaching-induced photoresponse-like events were absent in rods lacking transducin, ruling out direct activation of phosphodiesterase. The addition of chromophore to regenerate rhodopsin also reduced the number of photoresponse-like events. But when most bleached rhodopsin was regenerated with a chromophore analog that precludes photoactivation, the remaining free opsin still triggered photoresponse-like events, indicating that opsin does not act by transactivating rhodopsin. Altogether, the results suggest that single opsin molecules directly activate transducin sufficiently to induce membrane current fluctuations similar to those evoked by photons. This implies that opsin occasionally assumes a meta-II-rhodopsin-like conformation that activates the phototransduction cascade independently of chromophore and light.



Dark-adapted rods (green trace) show occasional current transients similar to the single-photon response (red inset and overlays). The frequency of these transients increases after bleaching, remaining elevated after 2 h (light blue) and 12 h (medium blue) in darkness. Activity in bleached rods resembles that of dark-adapted rods exposed to dim light (yellow). Transients disappear in rods lacking a transducin subunit (dark blue). See Sato et al. for details.

Model-Free and Model-Based Learning in Rodents

Stephanie M. Groman, Bart Massi, Samuel R. Mathias, Daniel W. Curry, Daeyeol Lee, et al.

(see pages 295–306)

When pursuing rewards, one can use various strategies. The simplest is to repeat actions that previously led to reward; but this strategy might prove unsuccessful when circumstances change. A more flexible approach is to construct a mental representation of how the world works and use this model to determine the best course of action. Because this strategy requires deliberation, however, it might be unsuccessful when rapid action is required. Switching between simpler, model-free strategies and more flexible, model-based strategies can therefore maximize reward.

The extent to which people use model-free and model-based strategies has been investigated using two-stage decision-making tasks. In Stage 1, players choose an option (A or X) that determines the choices available in Stage 2. In most cases, choosing A leads to a choice between B and C, whereas choosing X leads to Y versus Z. The value of B, C, Y, and Z differ. Therefore, if C is most valuable, one should pick A in Stage 1, making C available in Stage 2. Importantly, however, the Stage 2 options resulting from the Stage 1 choice are switched occasionally. For example, choosing X might lead to options B and C, making the most valuable reward available. In such cases, a model-free strategy would dictate repetition of the successful action—picking X—on the next turn. A model-based strategy, in contrast, would direct the player to pick A on the next turn, even after a rare disappointment. Previous work using this task has shown that people use a combination of model-based and model-free strategies (Daw et al., 2011 Neuron 69:1204), and the extent to which they use the model-based approach is correlated with dopamine levels in the striatum and prefrontal cortex.

Groman et al. have developed a similar two-stage decision-making task for rodents, and they show that rats, like humans, use a combination of model-free and model-based strategies. Moreover, like in humans, greater use of model-based strategies was associated with higher levels of dopamine in the ventral striatum and orbitofrontal cortex. Developing this task for rodents provides a valuable tool for identifying neural pathways involved in model-based and model-free learning and for determining how these pathways are altered in neurological conditions involving compulsive decision-making.

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