Understanding night blindness and calcium

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Congenital stationary night blindness, an inherited condition that affects one's ability to see in the dark, is caused by a mutation in a calcium channel protein that shuttles calcium into and out of cells. Now, researchers at the Johns Hopkins University School of Medicine have teased apart the molecular mechanism behind this mutation, uncovering a more general principle of how cells control calcium levels. The discovery, published in the Feb. 18 issue of *Nature*, could have implications for several other conditions, including neurodegenerative diseases such as schizophrenia and Alzheimer's, Parkinson's and Huntington's diseases.

"Calcium is so crucial for normal functions like heart contraction, insulin control and brain function," says David Yue, M.D., Ph.D., a professor of biomedical engineering and director of the Calcium Signals Lab at Hopkins. "If calcium levels are off at any time, disease can ensue. Our new approach, watching calcium channels in action in living cells, allowed us to tease apart how they behave and how they're controlled and find a new module that could be targeted for drug design."

The aberrant calcium channel protein that causes this type of night blindness is missing the tail end of the protein. Yue's team compared the ability of this protein to full length versions by examining how well they can maintain electrical current in cells. Normal channels show a decrease in current with an increase in calcium levels. "We and others initially believed that the missing piece of the protein might behave to simply switch off the ability of elevated intracellular calcium to inhibit this current," says Yue. "Without this module, there's no way to down-

regulate the calcium entering through these channels."

Yue's team found out, however, that in reality, this module functions in a far richer and nuanced manner. Calcium channels are known to be controlled by the protein CaM, which senses and binds to calcium, whereupon CaM binds to channels in a manner that inhibits their calcium transport function. To figure out how the tail module works in conjunction with CaM to control the calcium channel, the team used a molecular optical sensor tool that enabled them to see in live cells different levels of CaM, a controller of the channel protein. When CaM is abundant, the sensor glows cyan; when CaM is low, the sensor glows yellow.

The researchers found that the tail module doesn't simply turn off channel sensitivity to calcium; rather, the module smoothly retunes how sensitive channels are to CaM, and in turn how sensitive the transport function of channels is to intracellular calcium. In all, the tail module smoothly adjusts how much calcium enters cells. This manner of adjustment "may bear on many neurodegenerative diseases where calcium is dysregulated," says Yue.

With the optical sensor, Yue and his team next will examine other types of live cells, including nerve and heart cells, to measure whether changes in calcium channel behavior can lead to disease-like states.

More information: Nature paper: www.nature.com/nature/journal/ … ull/nature08766.html

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