Scientists identify a key to body's use of free calcium

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Scientists at Johns Hopkins report they have figured out a key step in how "free" calcium—the kind not contained in bones—is managed in the body, a finding that could aid in the development of new treatments for a variety of neurological disorders that include Parkinson's disease.

Appearing online this week in *Nature Chemical Biology*, the researchers describe their use of tiny "lights" and chemical "leashes" to unveil how calcium is controlled.

Electrical signals carried by free-floating calcium ions are "wildly important to keeping the second-by-second functions of the body going," says David Yue, M.D., Ph.D., professor of biomedical engineering and neuroscience at The Johns Hopkins University.

Yue, who led the research team of graduate students Philemon Yang and Manu Ben Johny, explains that large proteins called calcium channels are the gatekeepers that determine when calcium enters cells. Embedded in cell membranes, these channels open and shut to regulate calcium flow into the cell. When calcium goes into cells, it sets off a cascade of vital activity, but just the right amount of calcium must enter—otherwise, problems arise.

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In their research, Yue and his colleagues examined specific calcium channels embedded in the membranes of nerve cells in the brain to see how calmodulin and CaBP4, a particular calcium-binding protein, latch onto the channels.

They rigged the odds in favor of calmodulin binding by genetically engineering calcium channels that were tethered to calmodulin by a short, flexible strand of amino acids. But to their surprise, Yue says, calcium-binding proteins stuck to the calcium channels at the same time, suggesting that each regulator has its own parking space on the channel, whereas previous theories suggested a single space.

To further examine the relationships among these regulators of calcium, the scientists used markers that glow in different colors and attached them to calcium channels, calmodulin and CaBP4. When two molecules locked together, the color changed. By measuring color changes, the researchers could then tell which molecules bound to each other.

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"Our experiments established that calmodulin and calcium-binding proteins work by binding to distinct parts of the calcium channel," Yue says. "More generally, we have been able to investigate how large molecules such as these function in living cells."

The "live light show" permitted by the use of light markers should help scientists develop new drugs that target calcium channels, Yue adds. Some such drugs already exist, including calcium channel blockers that lower blood pressure by targeting a particular kind of calcium channel found in blood vessels.

Blocking calcium channels might help with other diseases, too, Yue says. For example, researchers have found that an overload of calcium in certain parts of the brain may drive some neurodegenerative diseases, such as Parkinson's. Blocking the calcium channels found in those trouble spots—the kind of calcium channels in Yue's study—could be a way to fight the debilitating brain disease.

More information: dx.doi.org/10.1038/nchembio.1436