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Calcium channels team up to activate excitable cells

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Voltage-gated calcium channels open in unison, rather than independently, to allow calcium ions into and activate excitable cells such as neurons and muscle cells, researchers with UC Davis Health System and the University of Washington have found.

The research defies earlier electrophysiology canon and undermines the previously held belief that calcium channels function independently. The study is published online in the journal *eLife*.

The finding is important, the researchers said, because understanding how these channels collaborate could lead to improved therapies that target aberrant calcium channels in malfunctioning cells. Dysfunctional calcium channels can be found in a variety of conditions, such as epilepsy and Parkinson's disease.

"In cardiac muscle, if these channels don't coordinate their firing, it will have detrimental repercussions on the reliability of the cardiac muscle contractions," said Luis Fernando Santana, professor and chair of the Department of Physiology and Membrane Biology at UC Davis. "In neurons, if they don't gang up, they don't get the potentiation they need to sustain repetitive firing.

"In a previous study we found that a bad channel paired with a good channel can turn both of them bad," Santana said. "So, you don't need a lot of bad channels to make a cell dysfunctional and show pathological behavior."

To study these tiny channels, the researchers used high-resolution microscopy, electrophysiological measurements and optogenetic technologies—light-sensitive probes that can stimulate neurons to fire electrical signals—to study rat hippocampal neurons. They found that when cells begin responding to calcium, channels start grouping in clusters of two or more and open cooperatively, allowing cells to fire more rapidly.

"This is a clear demonstration that voltage-gated calcium channels can couple to amplify the influx of calcium and control a cell's excitability," Santana added. "This coordination has a powerful influence on the behavior of neurons and other excitable cells."

The channels coordinate through a protein called calmodulin, which binds to calcium and helps carry it through the channel.

"Normally these channels don't touch each other," Santana said. "However, a little bit of calcium comes through and calmodulin serves as a bridge between neighboring channels. Influenced by the channel that opens first, they begin opening in unison, bringing channels together."

The researchers also found that these clusters dissolve much more slowly than the associated calcium. This "molecular memory" may allow cells to anticipate future firings, increasing their efficiency.

"It's always been a contradiction," noted Santana. "In a heart muscle, five to 10 channels have to open to activate calcium release reliably during the activation of contraction, but the chance of such a cluster of channels firing simultaneously is minuscule unless there is some cooperation."

More information: Claudia M Moreno et al. Caentry into neurons is facilitated by cooperative gating of clustered Ca1.3 channels, *eLife* (2016). DOI: 10.7554/eLife.15744

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