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Calcium is spark of life, kiss of death for nerve cells

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Oregon Health & Science University research shows how calcium regulates the recharging of high-frequency auditory nerve cells after they've fired a burst of signals, and it may have implications for neurological disorders.

The study by scientists at OHSU's Vollum Institute and the University of Arkansas for Medical Sciences, which appears in the current issue of the journal *Nature Neuroscience*, shows that calcium ions play a greater role in keeping in check the brain's most powerful circuits, such as those used for processing sound signals, than previously thought.

A better understanding of that role could someday help prevent the death of neurons behind some diseases of the brain and spinal cord, such as stroke and multiple sclerosis, the scientists say.

The research, led by postdoctoral fellow Jun Hee Kim, Ph.D., and her advisor, Henrique von Gersdorff, Ph.D., both scientists at the Vollum Institute, found that calcium tempers the activity of a high-throughput sodium pump, located in the plasma membrane covering nerve endings, that controls how quickly and accurately a nerve cell continues firing after an initial burst of spiking activity.

"What's happening in the brain is you have all these action potentials (spikes) that are firing - the action potential is the way you transmit information quickly from neuron to neuron - and when you have an action potential, you have an explosive influx of sodium ions into the

cell," von Gersdorff said. "As a result, the cell is depolarized and it needs to be quickly repolarized."

To repolarize a cell so it can continue firing, and do so accurately and at high-input frequencies, the sodium pump ejects three positively charged sodium ions and imports two positively charged potassium ions. The net result is one positive charged is expelled from the cell, causing a hyperpolarization of the cell's membrane potential.

Quick repolarization of the nerve cell is essential. Mature auditory nerve cells fire at frequencies that are 10 to 100 times higher than most high-frequency cells in the brain - 1 kiloHertz, or 1,000 Hertz. Most brain synapses, the space between nerve cells through which impulses are transmitted and received, begin failing beyond 10 Hertz.

"In the last few years, we have been studying high-frequency firing cells in the auditory part of the brain. We found that these cells and nerve terminals are amazing because they can fire at 1,000 Hertz without failures and with high precision," von Gersdorff said. "That discovery in our lab prompted us to ask the question: How is it that these nerve cells can handle all this high-frequency firing?"

Enter calcium, which, by inhibiting the activity of the sodium pump, regulates signal firing, and may conserve energy and keep the high-frequency cells from burning out. But calcium in high levels within a nerve cell can be toxic, so the researchers discovered another purpose for the sodium pump: powering a protein located on the nerve terminal membrane called the sodium-calcium exchanger, which removes the calcium and replaces it with sodium. That action, in turn, triggers the sodium pump, and so on.

The sodium-calcium exchanger "can import high concentrations of sodium from outside the cell, and it uses the gradient of low internal

sodium in the cell as a form of energy to get rid of calcium. That energy comes, ultimately, from the sodium pump and its use of ATP, the cells' major fuel," von Gersdorff explained. The pump is "always keeping sodium concentration in the neuron low and that allows the sodium-calcium exchanger protein to constantly exchange sodium for calcium."

Otherwise, if allowed to get too high within the cell, the calcium shuts down the sodium pumps, creating a "vicious loop," von Gersdorff said.

"You then get a simultaneous build-up of calcium and sodium in the cell, and it's 'Goodbye to your neuron.' It goes at some point into an irreversible cycle of death," he said.

One potential therapeutic approach to preventing cell death caused by increasing calcium levels is making the sodium pump more insensitive to calcium. A potential new drug, for example, could "help the neuron to keep extruding sodium so it can help the sodium-calcium exchanger get rid of calcium, thereby not allowing calcium to reach toxic levels," von Gersdorff said.

For the time being, von Gersdorff's lab will continue studying how calcium regulates the sodium pump.

"Our hope is that these basic, fundamental issues will eventually lead to therapeutic strategies that alleviate neuronal damage from ischemia and stroke," he said.

Source: Oregon Health & Science University