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Calcium Channels Control Coronary Artery Relaxation

Researchers have discovered that a specific type of calcium channel—a pore-like protein that nestles in the cell membrane and controls the flow of calcium into the cell—regulates the relaxation of coronary arteries.

The studies showed that mice engineered to lack these calcium channels had constricted coronary arteries and had fibrous tissue in their hearts, which was evident when the animals' hearts reacted to chronic blood restriction. The researchers hypothesize that drugs targeting this calcium channel might one day be used to treat cardiovascular disease by opening arteries.

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— **Kevin P. Campbell**

The researchers, led by Howard Hughes Medical Institute investigator Kevin Campbell, published their findings in the November 21, 2003, issue of the journal *Science*. Campbell and his colleagues at the University of Iowa collaborated with researchers from the Veterans Administration Medical Center in Iowa City, Loyola University Medical Center and the University of Texas Southwestern Medical Center.

The calcium channel under study is triggered by voltage differences across the cell membrane that cause it to open, allowing calcium to flow into the cell. The operation of calcium channels is crucial to a wide array of physiological functions, including transmission of nerve impulses, muscle contraction and activation of genes. Although one type of calcium channel, called the L-type, had been shown to control muscle contraction, the action of the other type, called the T-type, remained largely unknown, said Campbell. The L-channel opens in response to large voltage differences across the cell membrane, while the T-channel responds to a weaker "depolarization," he said.

Campbell and his colleagues first became interested in exploring the T-channel because research by other scientists hinted that it might be involved in the fusion of muscle cells, or myoblasts, to one another during the

development and repair of muscles. Campbell's laboratory concentrates on muscular dystrophies, and the scientists reasoned that better understanding of the muscle-formation machinery would aid that effort.

To study the T-channels, the researchers created a knockout mouse lacking one type of T-channel, called the α_{1H} channel. "Although our main interest was initially to look at how the myoblasts would function and fuse, we found that myoblasts looked completely normal in these animals," said Campbell. "We then realized that another type of channel, the α_{1G} , could upregulate to compensate for the loss." However, when the scientists studied the structure of the various muscle tissues, they found a striking accumulation of fibrous tissue in heart muscle.

"We believed that this fibrosis was probably not due directly to the cardiac muscle abnormality, because we knew that a T-channel was not present in adult ventricular muscle," said Campbell. "So, it must have been caused by another abnormality, maybe in the blood vessels."

When the researchers performed visual studies of the coronary arteries of the mice and measured their contractility, they found the arteries to be irregularly shaped and constricted, although the vessels contracted normally. Such aberrations would have starved the heart of blood, inducing fibrosis, said Campbell.

To test the ability of the coronary arteries of the knockout mice to relax, the researchers administered drugs that in wild-type mice caused arterial dilation. However the drugs produced no such effect in the knockout mice.

"So, this impaired relaxation strongly suggested that this channel was involved in arterial relaxation, which was a surprise because calcium channels had been implicated in contraction, but not in relaxation," said Campbell.

Sure enough, when the researchers administered nickel—which blocks T-channels—to wild-type mice, dilation of their arteries was decreased.

Other research had shown that an entirely different channel, a potassium channel, plays a key role in regulating muscle relaxation. Campbell and his colleagues theorized that calcium ions flowing through T-channels might somehow "fine-tune" potassium channels.

Findings from two of their experiments supported this idea, said Campbell. A drug that opens potassium channels caused arterial dilation in both wild-type and T-channel knockout mice, they found. Also, when they isolated the potassium channel, they found it to be physically associated with the T-channel.

A great many puzzles remain concerning how the T-channel functions in coronary artery relaxation, said Campbell. One puzzle arises from the scientists' finding that an artery-relaxing drug, called sodium nitroprusside, produced some arterial relaxation in the knockout mice. This drug releases

the artery-relaxing chemical nitric oxide, leading the scientists to believe that only nitric-oxide-mediated relaxation is defective in the knockout mice.

A better understanding of T-channels function could lead to new treatments for cardiovascular disease, said Campbell. “Our current findings indicate that blocking this channel causes coronary artery constriction, which is clearly something you don't want to do in treating heart disease,” said Campbell. “However, if drugs could be developed that would open the channel, it might lead to relaxation and opening of the arteries. There are currently a number of treatments for opening blood vessels, but it's possible that understanding this process could lead to new approaches to causing vasorelaxation,” he said. “We're very excited about the potential for this work.”