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## Fine-Tuning a Blood Pressure Regulator

Researchers have found that deleting a component of a protein found in smooth muscle cells that surround the arteries can cause a dangerous and prolonged increase in blood pressure. The researchers believe that defects in this ion channel protein may underlie some forms of hereditary hypertension, thereby making the channel an attractive target for new types of blood pressure medications.

Calcium and potassium ions play important roles in regulating blood pressure. In the smooth muscle cells surrounding arteries, calcium-activated BK ion channels control the flow of potassium out of smooth muscle. When a burst of calcium is released within smooth muscle cells, the BK channels in those cells open, potassium floods out, the smooth muscle relaxes and blood pressure is lowered. But calcium can also induce blood vessel constriction, and cause high blood pressure, so researchers wanted to understand more about how these important channels are regulated.

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— **Richard W. Aldrich**

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"BK channels have been known for quite some time as important in blood pressure regulation," said Howard Hughes Medical Institute investigator Richard W. Aldrich, who is at Stanford University. "However, calcium has a paradoxical effect. It not only acts on these channels to produce arterial dilation, but it can also act on the contractile machinery, which leads to blood vessel constriction. Thus, there's a balance involved in regulating blood pressure, and we are hoping to learn how the BK channel acts to tip that balance toward dilation."

BK channels are found in many types of cells, including neurons, smooth muscle cells and skeletal muscle cells. The diversity of cell types that contain BK channels is matched by the architectural diversity exhibited by the

building blocks, or subunits, that compose these channels. For example, earlier studies had shown that the various tissue-specific BK channels had only one basic type of  $\alpha$  subunit, but each had a slightly different  $\beta$  subunit. The difference in the  $\beta$  subunit may allow BK channels from different types of tissue to respond differently to calcium and voltage signals, says Aldrich.

In a research article published in the October 19, 2000, *Nature*, Aldrich, Mark T. Nelson of the University of Vermont, and their colleagues created knockout mice that were missing the  $\beta 1$  subunit of the BK channel that is contained in smooth muscle cells. By knocking out the gene for the  $\beta 1$  subunit in mice, they targeted the properties of BK channels in smooth muscle without affecting the channels in skeletal muscle or other tissues. The mice lacking the  $\beta 1$  subunit displayed high blood pressure and other abnormalities caused by prolonged hypertension.

In looking closer at the smooth muscle cells of the knockout mice, the scientists found that the BK channels in those cells showed reduced sensitivity to calcium and were unable to be opened by a drug that interacts with the  $\beta 1$  subunit. The studies also revealed that the BK channels of the knockout mice were much less able to open in response to calcium release.

Physiological studies of the  $\beta 1$ -subunit-knockout mice revealed that their arterial blood pressure was chronically elevated and they had enlarged hearts, like humans with chronic hypertension. "The finding of elevated blood pressure was important because it showed us that the pressure regulatory system was as simple as we had predicted it to be," said Aldrich.

Altering the  $\beta 1$  subunit showed such straightforward physiological effects that the subunit may be a promising target for new anti-hypertension drugs. "These findings suggest that drugs that change  $\beta 1$  subunit function by altering the channel's calcium sensitivity could allow control of blood pressure up or down with fewer side effects than current treatments," he said.

The  $\beta 1$  subunit's effects on calcium sensitivity offers a new model for researchers who are investigating the molecular basis of hypertension, said Aldrich. "Since we can alter this subunit to affect blood pressure without affecting other systems, we can use it as a model to study hypertension beginning at the molecular level, through cellular physiology and to the pathology and long-term ramifications of hypertension," he said.

Finally, the effects produced by knocking out the  $\beta 1$  subunit gene suggest that the gene may be involved in inherited forms of hypertension, he said. "Some forms of inherited hypertension so far have not been pinpointed to specific genes, so these findings suggest that this is a good candidate gene to examine to see if humans with hypertension have mutations in this gene," said Aldrich.

Further studies of the various  $\beta$  subunits will also reveal how they function in different tissues. "The organizing principle with these subunits is that they act to fine-tune the BK channels to function in specific tissues," said Aldrich. "For example, studying BK channels in neurons might reveal how the

channels limit the duration of neurotransmitter release in controlling nerve impulses."