

**PUBLIC RELEASE DATE: 31-OCT-2002**

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## 'Control valve' within heart cells could protect body during heart attacks

"We're at a new frontier of discovery." – Brian O'Rourke, Ph.D.

A Johns Hopkins-led research team has identified a type of control valve within heart cells that can be switched on to help the organ survive injury during a heart attack. The work is published in the Nov. 1 issue of *Science*.

The valve, actually an ion channel on the walls of heart cells' energy-producing structures, offers new information about how energy supplies are maintained in the heart. This could lead to new therapies for heart disease.

"Our results suggest that activating this channel optimizes energy production to improve the heart's overall strength," says senior author Brian O'Rourke, Ph.D., associate professor of medicine at Hopkins. "Interestingly, this beneficial effect can be activated by a drug to help the heart cell resist stumbling down the slippery slope to cell death when the blood supply is cut off, reducing the damage caused by a cardiac arrest."

Energy that the heart needs to continuously pump is provided by mitochondria, tiny powerhouses packed inside the cell that produce ATP, a chemical storage form of energy. ATP can be used by other parts of the cell to make the muscle contract. The mitochondria's engine is finely tuned to adapt to changes in workload, like when a person needs to run up the stairs, or to respond to physiological emergencies, like losing blood supply during a heart attack. Ultimately, the ability of the mitochondria to cope with such environmental stress determines whether the individual heart cells, and eventually the person, lives or dies.

The newly found channel, called mitoKCa (a calcium-activated potassium channel), resides in the mitochondria's inner membrane and allows potassium ions to flow, especially when cellular calcium levels rise. The researchers observed its function through four types of experiments. First, lead author Wenhong Xu, Ph.D., isolated mitochondria from guinea pig heart cells and used fine-tipped glass pipettes and a high-magnification lens to record the electrical activity of the channel in tiny patches of mitochondrial membrane. When the scorpion-derived poison charybdotoxin, a potassium channel inhibitor, was added to the pipette, the channel's activity stopped. The channel's activity increased when calcium was added.

Next, using fluorescent indicators in whole cardiac cells, researchers confirmed that the potassium channel contributed to mitochondrial potassium uptake. With help from Canadian collaborators, they found the channel protein in purified mitochondrial membrane preparations.

Finally, researchers at the Otsuka Maryland Research Institute tested whether an opener of mitoKCa could protect against a blood flow blockage similar to that during a heart attack. Rabbit hearts that received the drug had heart attacks that were half the size of untreated hearts.

"We're at a new frontier of discovery," O'Rourke says. "If we can determine how mitochondrial ion channels regulate energy in heart cells, we may be able to protect the heart against life-threatening arrhythmias and other cardiac diseases."

Study co-authors were Xu and Agnieszka Sidor of Hopkins; Yongge Liu and Sheng Wang of the Otsuka Maryland Research Institute, Rockville; and Todd McDonald and Jennifer E. Van Eyk of Queen's University, Ontario, Canada.

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Xu, Wenhong et al, "Cytoprotective Role of Ca<sup>2+</sup>-activated K<sup>+</sup> Channels in the Cardiac Inner Mitochondrial Membrane," Science, Nov. 1

Related Web sites:

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