Exploiting the body's own ability to fight a heart attack

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Scientists trying to find a way to better help patients protect themselves against harm from a heart attack are taking their cues from cardiac patients.

The work has its roots in a perplexing curiosity that physicians have long observed in their patients: When faced with a heart attack, people who have had a previous one oftentimes fare better than patients who have never had one. Scientists have been working for 25 years to understand one reason why - a process known as ischemic preconditioning, where a temporary restriction of blood flow somehow strengthens cardiac tissues down the road.

In the latest research, published online Feb. 25 in the journal *Circulation Research*, a group led by Paul Brookes, Ph.D., and graduate student Andrew Wojtovich at the University of Rochester Medical Center have developed new methods in the effort to track down one of the key molecular agents involved. That molecule, known as the mitochondrial ATP-sensitive potassium channel, or mKATP, is central to ischemic preconditioning, but it has proven elusive for scientists seeking to isolate and describe it.

The Rochester team has created a new way - faster, less expensive, and easier than current methods - to measure the activity of mKATP. The team has also identified a molecule, known as PIP2, that can restore the channel's activity even once it has stopped working properly. The new work is expected to provide new clues about how the channel, which is

thought to be central to our heart health, is regulated in the heart.

The ultimate goal of ischemic preconditioning, of course, is not to condition the heart by purposely causing a lack of blood flow to it. Rather, scientists like Brookes hope to use their knowledge to develop a new medication or treatment to help all patients better resist heart damage should it occur.

"Preconditioning has been shown to be effective in a variety of models in the laboratory, but it hasn't made it to the clinic yet," said Brookes, associate professor of Anesthesiology and of Pharmacology and Physiology. "One would want to design a drug to get the benefit of ischemic preconditioning without actually impeding blood flow in any way."

Physicians like cardiologist Eugene Storozynsky, M.D., Ph.D., see the phenomenon of ischemic preconditioning play out in their patients. He says that it's not uncommon for a middle-aged heart attack patient who has had symptoms of heart disease to fare much better than a younger person with no history of heart disease who suddenly has a heart attack.

"The person with chronic heart disease who presents with a new heart attack does not appear nearly as disabled as the younger, healthier person with no history of heart disease, even though they present to the hospital with nearly identical blockages in their heart arteries," said Storozynsky, a heart failure expert who was not involved in the study.

"Of course, the ultimate goal for patients is to prevent heart disease wherever possible," added Storozynsky, assistant professor of Medicine in the Cardiology Division. "People need to make sure they eat a balanced, low-fat, reduced-salt diet, exercise regularly, and control their blood pressure - these actions will cut down one's risk for having a heart attack dramatically."

Brookes' team also discovered that mKATP is inhibited by fluoxetine, whose brand name is Prozac. It's the latest in a list of medications that have been shown in the laboratory to impede ischemic preconditioning, Brookes said. Others include painkillers known as cox-2 inhibitors, as well as beta-blockers that are used frequently to treat high blood pressure and heart problems.

Because medications like anti-depressants and beta-blockers are used so widely in patients who have had heart problems, scientists should take a close look at their possible effects on ischemic preconditioning, Brookes said, noting that the drugs have not been linked to any cardiac difficulties in people.

The new findings came about through a collaboration of several research groups at Rochester that allowed the team to address a problem that has dogged scientists for years. Brookes and a few other scientists had worked on mKATP, which shuttles potassium into and out of the mitochondria, for many years, but the laboratory work involved was so finicky that some other teams have not been able to reproduce the results, leading some scientists to question whether the channel truly exists.

Keith Nehrke, Ph.D., assistant professor in the Nephrology Division of the Department of Medicine, proposed a new way to measure the channel's activity. The new method involves measuring the movement of the element thallium into and out of mitochondria, as a surrogate for potassium. The new method is much faster and less expensive and should be much easier to reproduce by other scientists, Brookes said. He and Nehrke recently received funding from the National Institutes of Health to use the new method in the tiny roundworm known as C. elegans to identify the mKATP channel.

Then a retreat of the Department of Pharmacology and Physiology,

where Wojtovich is a graduate student, connected the group with other researchers who are experts on potassium channels - Daniel A. Gray, M.D., of the Department of Medicine and Coeli Lopes, Ph.D., of the Aab Cardiovascular Research Institute.

Provided by University of Rochester Medical Center