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Rare disease provides clues about enzyme role in arrhythmias

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A University of Iowa study provides insight into a calcium-sensing enzyme already known to play a role in irregular heartbeats and other critical functions. The researchers showed that the enzyme, calmodulin kinase II (CaM kinase II), contributes to arrhythmia in an extremely rare disease called Timothy syndrome and that inhibiting the enzyme prevents irregular heartbeats.

The findings, which involved a new cellular model, could help with developing treatments for irregular heartbeat in people with this syndrome as well as in the general population. There also could be implications for understanding other conditions such as autism. The study results were published online Nov. 10 by the journal *Circulation*.

Timothy syndrome has been reported in only about 20 people worldwide. In addition to causing an irregular heartbeat, Timothy syndrome can cause a malformed heart, autism and other nervous system problems. Timothy Syndrome is a type of long QT syndrome, which can cause sudden death in people with normal-appearing hearts.

"We focused on the multisystem disease Timothy syndrome and showed that its hallmark fatal heart disease, which typically is fatal by age 3, involves activation of the enzyme CaM kinase II. We also showed that inhibiting this enzyme prevented irregular heartbeats in adult rat heart cells engineered to express the Timothy syndrome disease gene," said study author Mark Anderson, M.D., Ph.D., professor of internal medicine and molecular physiology and biophysics at the University of

Iowa Carver College of Medicine.

CaM kinase II was already known to play a role in arrhythmias but the study helps uncover the enzyme's interplay with calcium channels, which provide the main way for calcium to enter heart cells. Calcium is needed to trigger each heartbeat and to help regulate cell survival, metabolism and gene transcription. In Timothy syndrome, a mutation causes the calcium channel to be malformed. The heart muscle then takes longer to recharge between beats and can lead to irregular heartbeat.

"The findings raise the possibility that CaM kinase II is a 'missing link' that connects this calcium channel mutation to arrhythmia and possibly other problems, such as autism," said Anderson, who also holds the Potter-Lambert Chair in Cardiology and is a member of the University of Iowa Heart and Vascular Center. "Our findings add more evidence that by acting on CaM kinase II, you could directly affect pathways that cause unwanted developmental and neurological changes."

"In contrast to sodium channels or potassium channels, there are very few diseases that cause mutations in calcium channels. Experts believe calcium is too important to 'futz' around with, perhaps accounting for the very severe nature and early death associated with patients with Timothy syndrome," Anderson added.

While previous researchers had observed defects in calcium channels in other cells, those cells did not have the coordinated electrical function of a heart. The University of Iowa team, using the expertise of Bill Thiel, Ph.D., postdoctoral trainee, and Peter Mohler, Ph.D., associate professor of internal medicine and a Pew Scholar, developed and assessed a cellular model to more clearly reveal the function that helps drive heartbeats.

"By studying this mutant channel in an adult rat heart cell that had all the

proteins and machinery of a normal heart cell, we obtained a much more complete picture of how the disease works," Anderson said. "When CaM kinase II was turned on in the cellular model, the activation was responsible for the heart rhythm problems. In contrast, when we inhibited the enzyme using a peptide, the disease features healed, the electrical oscillations resolved and the action potential was corrected."

Even though the calcium channel defect in Timothy syndrome is relatively tiny, the defect seriously affects the ability of the heart to keep a regular beat, Anderson said.

"The defect causes the channel to close too slowly, and this in turn amplifies CaM kinase II, which in turn can cause disease," he said. "You can't completely block calcium channels because you need some function to initiate heartbeats. Ideally, we would find a way to allow the defective channel to operate but without allowing the CaM kinase II to be over activated."

Source: University of Iowa