Medical Xpress

Heart arrhythmia can be acquired by people who are stressed, even with no genetic predisposition

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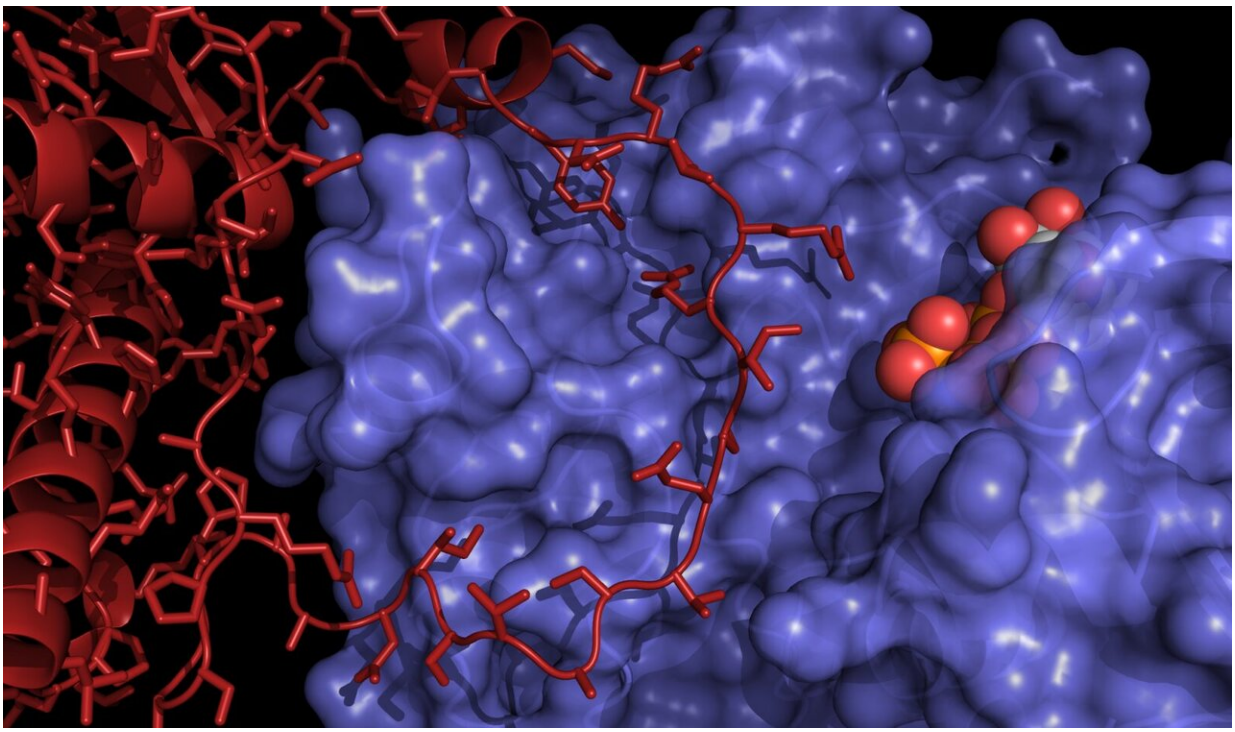


An enzyme known as 'Protein Kinase A' (blue), delivering the phosphorylation tag to the Ryanodine Receptor domain (red) - the protein that delivers the calcium required for contraction of the heart. Credit: Canadian Light Source

When encountering a charging predator or participating in a triathlon, the human heart responds by beating faster to increase blood supply to

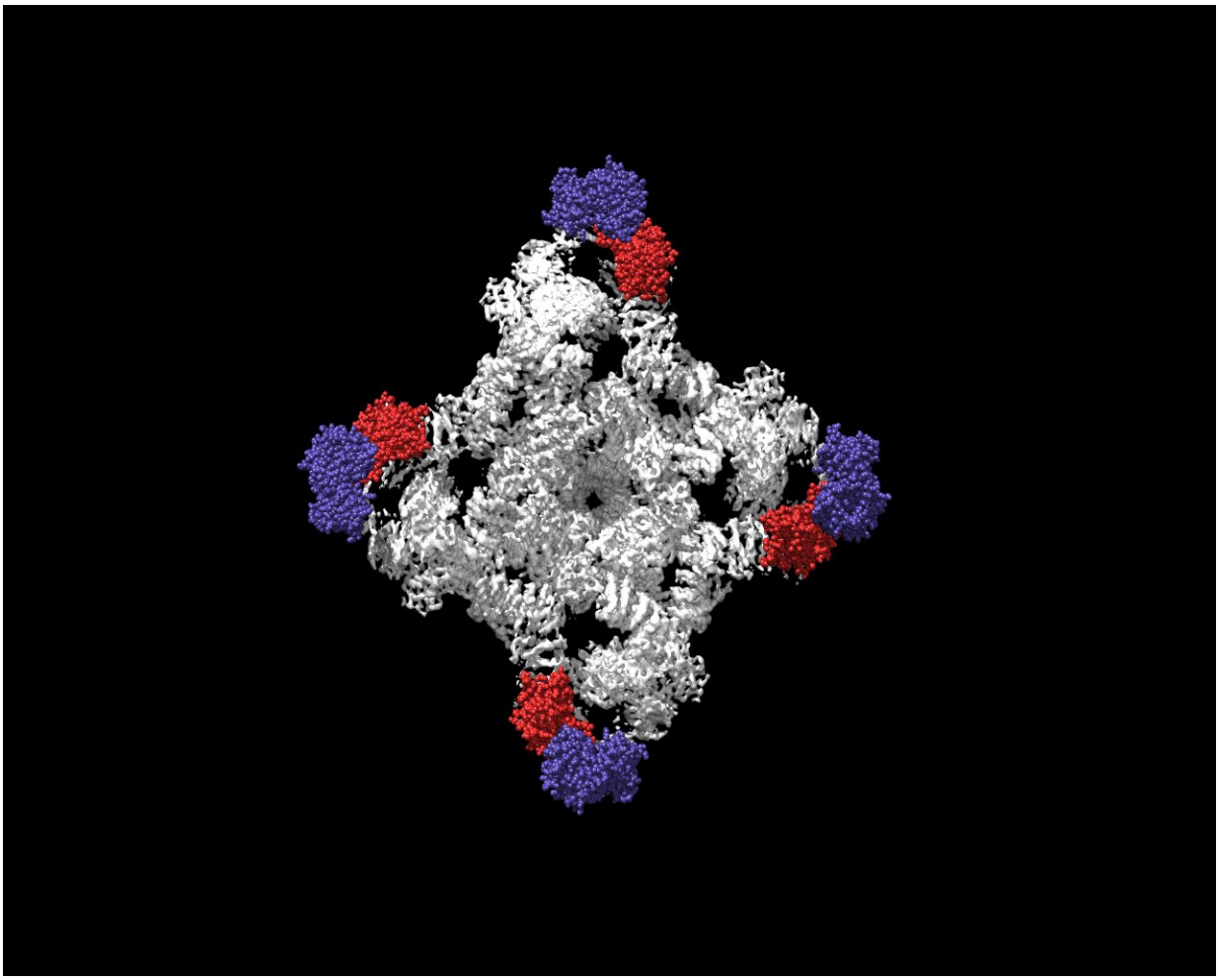
muscles. It is a natural and well-understood reaction to stress.

However, there are times when emotional or physical stress causes the heart to beat with an irregular or abnormal rhythm, a condition called arrhythmia that is the focus of research by Dr. Filip Van Petegem of the Department of Biochemistry and Molecular Biology at the University of British Columbia. In a paper published May 8, 2019 in *Molecular Cell*, Van Petegem sheds new light on how two proteins interact in the heart in cases of stress-induced arrhythmia, and on potential treatment.

"The big picture of our work is to understand how stress signals affect a protein in the heart muscle that is critical for heart contraction," said Van Petegem.

In a stress situation, that heart protein receives a tag from another protein, and the tag allows more efficient delivery of calcium, key to contraction. "Normally, the protein is tagged, the heart rate goes up, then the tag is removed and all is fine," he said. "This process allows the heart to adapt to the needs of the environment.

"But if the tags stay too long or there are too many tags, calcium can be delivered between heartbeats. That starts to affect the electrical signals in the hearts and can cause arrhythmia."



The full Ryanodine Receptor (grey) with the enzyme (blue) and the domain that receives the tag (red). Credit: Canadian Light Source

Arrhythmia in people with no genetic predisposition is an acquired condition, he explained, "and once you have it, it often progresses." It serves as a warning signal for more persistent forms of arrhythmia.

"Our research looked at the protein that delivers the tag—how it recognizes the protein on which it has to deliver the tag, and how that tag delivery happens."

To find the answer, Van Petegem and his colleagues created crystals from the proteins. They then used X-ray diffraction at the Canadian Light Source (CLS) at the University of Saskatchewan to produce 3-D images that revealed a structure that shows how the tag is delivered. "The structure was quite a surprise," he said. "We thought, this is weird, but we tested it in various ways and it was always there."

With this new understanding of the tag-delivery mechanism between proteins, "we've identified a lot of areas where we think a small molecule could be used to interrupt the excessive tagging. It's hypothetical but it's definitely an avenue worth pursuing."

In addition to identifying the structure between proteins, Van Petegem's research also found that the structure was subject to genetic mutation, and identified how the tag changes the properties of the protein.

Van Petegem pointed out the published research involved only one of two main proteins that deliver tags. The second "is equally as important if not more important, and they seem to interfere with each other." He hopes to repeat the study on the second protein if crystals can be produced, "but that can sometimes be very tricky."

More information: Omid Haji-Ghassemi et al. The Cardiac Ryanodine Receptor Phosphorylation Hotspot Embraces PKA in a Phosphorylation-Dependent Manner, *Molecular Cell* (2019). DOI: 10.1016/j.molcel.2019.04.019

Provided by Canadian Light Source