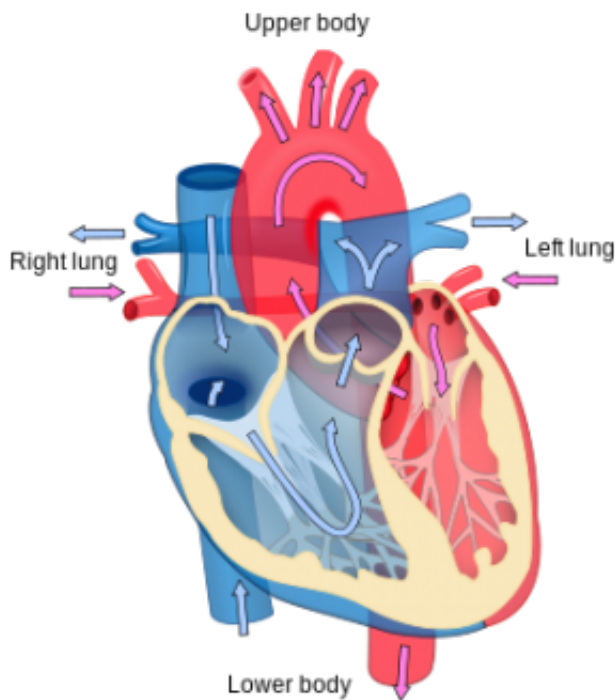


# 'Fight or flight' response control center for the heart found

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Heart diagram. Credit: Wikipedia

An animal study led by Johns Hopkins investigators has uncovered what controls the ability of healthy hearts to speed up in response to circumstances ranging from fear to a jog around the block.

The key to the heart's "fight or flight" response, they report, is a channel in cells' energy factories, known as mitochondria, which appear to drive

the heart to beat beyond its resting rate. Better understanding of this channel, called the mitochondrial calcium uniporter (MCU), could lead to new treatments for people whose heart rates needlessly accelerate, they say.

"Although researchers have long suspected that something in heart cells' mitochondria was responsible for changing heart rates, there really was no proof," says Yuejin Wu, Ph.D., an assistant professor at the Johns Hopkins University School of Medicine, who co-led the research team. "Our study is the most direct proof produced thus far." Because there are so many cardiovascular similarities between mice and humans, the investigators believe their findings may reflect what occurs in people.

To investigate the function of the MCU, the research team, also led by Mark E. Anderson, M.D., Ph.D., the William Osler Professor of Medicine and director of the Department of Medicine at the Johns Hopkins University School of Medicine, used a variety of methods to block its function in cells, isolated animal hearts and hearts in living animals.

Working first with isolated mouse "pacemaker" cells, which set the heart's rhythmic pulse rate, the researchers injected a chemical called Ru360, which clogs the MCU. These cells beat at a normal resting rate compared to cells that weren't injected with Ru360. However, when the researchers exposed the Ru360-injected cells to isoproterenol, a chemical that normally stimulates these cells to beat faster, they showed only a minimal increase in beating frequency.

The researchers prompted these cells to display a normal response to isoproterenol by injecting them with adenosine triphosphate, a molecule that provides energy for cells, suggesting that [pacemaker cells](#) need functioning MCUs to produce it.

Next, the researchers inactivated the MCU in whole mouse hearts by painting them with a virus that inserted an MCU-blocking gene into cells. These organs also lacked a normal heart rate increase in response to isoproterenol compared to large heart rate increases in healthy hearts, suggesting that the MCU plays a critical role in regulating the heartbeat in the whole organ.

Finally, the team bred mice with a deactivated MCU gene in their hearts. By continuously monitoring the animals' heartbeats as they went about their days, the researchers found that the mutant rodents had normal resting heart rates, but their heart rate barely increased, even during high spontaneous activity.

Together, these findings, reported in the Jan. 20 edition of *Nature Communications*, suggest that the MCU is critical for boosting heartbeat frequency above a resting rate, the researchers say.

Having a way to target the MCU could lead to a better way to prevent an uncomfortable and potentially harmful "racing" heart in people whose pulses accelerate unpredictably and without apparent cause, the researchers say. Though currently available drugs, such as beta blockers, can slow heart rate, they tend to do it uniformly, says Anderson, depressing even the resting heart rate, which can lead to undesirable side effects, including fatigue.

"The finding that the recently discovered MCU channel is required for physiological heart rate increases suggests the potential for a new therapeutic approach to selectively reduce inappropriately high heart rates without slowing resting [heart rates](#), which is an adverse side effect of currently available drugs," Anderson says. "Heart rate is a major determinant of whole-body metabolism, and our study suggests that heart pacemaker [cells](#) orchestrate heart rate by a metabolic mechanism involving the MCU."

Provided by Johns Hopkins University School of Medicine

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