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Exercise in a pill may protect against extreme heat sensitivity

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We've all seen the story in the news before. Whether it's the death of a physically fit high school athlete at football training camp in August, or of an elderly woman gardening in the middle of the day in July, heat stroke is a serious, life-threatening condition for which there is no treatment beyond submersion in ice water or the application of ice packs to cool the body to a normal temperature.

But, in a new study published today in the journal *Nature Medicine*, scientists discovered what they believe is one of the first drugs to combat heat stroke. AICAR – an experimental therapy once dubbed the "couch potato pill" for its ability to mimic the effects of exercise in sedentary mice – protected animals genetically predisposed to the disorder and may hold promise for the treatment of people with enhanced susceptibility to heat-induced sudden death.

"There is a great need for the training staff of athletic teams, physicians in emergency rooms in places like Phoenix, and soldiers serving in the deserts of the Middle East to have a drug available to give to individuals during a heat stroke event," said Robert T. Dirksen, Ph.D., study author and professor of Pharmacology and Physiology at the University of Rochester Medical Center. "Our study takes an important first step towards developing a new drug therapy that may be part of the standard treatment regimen for heat stroke in the future."

The finding comes as heat stroke cases are on the rise. According to a recent study in the *American Journal of Preventive Medicine*, the number

of heat-related injuries in the U.S. more than doubled from 1997 to 2006. In that 10-year period, an estimated 55,000 people were treated for the condition in emergency rooms across the country.

The research team, led by Dirksen's long-time collaborator Susan L. Hamilton, Ph.D., from Baylor College of Medicine, tested the drug in mice with a mutation in the RYR1 gene. The mutation is associated with malignant hyperthermia, a life-threatening inherited disorder of skeletal muscle in which commonly used general anesthetics trigger uncontrolled muscle contractions and dangerous increases in body temperature. Unexpectedly, further work demonstrated that these mice exhibit similar uncontrolled muscle contractions – a classic heat stroke response – during exposure to high temperatures or when exercising under warm conditions.

The team found that AICAR administration protected the mice from experiencing such contractions under heat stress. If not stopped, the contractions cause muscles to break apart and release their contents, including potassium and proteins, into the blood. High levels of potassium in the blood are extremely toxic and, if not treated quickly, can cause cardiac arrhythmias and death.

Unfortunately, the drug didn't deliver the same positive result for anesthetic-induced malignant hyperthermia.

AICAR made a big splash in 2008 when a study published in *Cell*, a prestigious scientific journal, found that the drug built muscle and increased endurance in completely inactive mice. As additional studies further established AICAR's ability to improve muscle function, the team grew curious to test how it might influence the whole-body muscle contractions characteristic of RYR1-associated heat stroke in mice.

Not only did they discover the unanticipated protective effect of the

drug, but that it worked in a completely different way than they originally thought.

AICAR normally works by activating the body's metabolic "master switch," an enzyme called AMPK that, among other things, influences muscle activity. However, researchers found that the ability of the drug to protect the mice from heat stroke was unrelated to its effects on this master switch. Rather, it directly influenced RYR1.

RYR1, or the type 1 ryanodine receptor, is a protein that plays an essential role in muscle contraction. It is responsible for releasing positively charged calcium ions from storage compartments within cells, which then combine with muscle proteins to trigger contraction. In response to heat, mutations in RYR1 cause excessive amounts of calcium to leak from the storage compartment and trigger uncontrolled muscle contractions. The team found that AICAR reduces calcium leakage from RYR1, thus diminishing heat-induced contractions, muscle damage, and death.

In a separate but related article published in the journal *Anesthesiology*, Dirksen and colleagues reported cases of two children with RYR1 mutations who died following episodes triggered by either a viral fever or exposure to environmental heat stress. The team points out that while RYR1 mutations may only account for a small subset of heat stroke cases in the general population, they believe their finding that AICAR is protective against heat stroke is likely to apply more broadly.

"We think the fundamental process that occurs during heat stroke in individuals with RYR1 mutations is likely to be similar to what happens even in their absence. The difference may be that individuals with RYR1 mutations are more easily thrust into the process, whereas those without need to be pushed more – for example, by exposure to even greater temperatures or a longer time – in order to move beyond a critical

threshold," noted Dirksen.

The team plans to study the efficacy of AICAR in other models of heat- and exercise-induced disorders.

Though no couch potato pill has come to fruition yet, AICAR is currently under investigation for the treatment of certain muscle diseases and metabolic disorders where exercise is known to be beneficial.

Provided by University of Rochester Medical Center