Rare genetic syndrome may hold key to cure for heat stroke

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A genetic disorder that can cause a fatal rise in body temperature in some patients undergoing general anesthesia may hold the key to a cure for heat stroke, according to research published in the April 4 edition of the journal *Cell*. The findings further suggest that antioxidants, like those currently being tested to protect the lungs of cystic fibrosis patients, may also protect those genetically prone to suffer heat stroke.

According to the current study authors, all U.S. operating rooms should, but do not always, have a supply of a drug called dantrolene on hand, which causes muscles to relax by a unique mechanism. Dantrolene is a must in the rare cases where patients receiving general anesthesia unexpectedly go into whole-body muscle contractions as part of an inherited condition called malignant hyperthermia (MH).

Occurring in one in about 10,000 adult patients undergoing general anesthesia, and more frequently in children, MH reactions alter the acid content of blood and tissues, increase heart rate, cause muscle rigidity and trigger a rapid rise in body temperature up to 112° F. Kidney failure and potentially fatal heart arrhythmias can result in the worse cases. MH received national news coverage recently because of the unfortunate case of an 18-year-old Florida high school senior, Stephanie Kuleba, whose death was apparently caused by a fatal reaction to anesthesia during corrective surgery.

Researchers are also interested in MH because it may be caused by the same biochemical pathways as heat stroke, a much more common

condition that has caused more U.S. deaths than hurricanes, tornadoes, floods and earthquakes (8,000) together since 1979, according to the Centers for Disease Control and Prevention. Given the number of troops currently operating in deserts, the U.S. military has a keen interest in the work. For the first time, researchers at four universities and in the U.S. Army have provided strong evidence that the genetic and protein defects that cause MH also contribute to the development of heat stroke. They have also identified mechanisms by which both conditions may damage cells.

”Along with cardiac abnormalities, heat stroke is a major culprit in unexpected sudden deaths of otherwise fit, young athletes and soldiers,” said Robert T. Dirksen, Ph.D., associate professor of Pharmacology and Physiology at the University of Rochester Medical Center. “With a better knowledge of these mechanisms, we can begin to better diagnose and treat both disorders, and hopefully, save some lives,” said Dirksen, a co-author on the study.

The Perfect Switch

To drive life processes, human cells expend tremendous energy to continually push positively charged calcium ions both out of cells, and into internal calcium storage compartments. This creates charge/calcium gradients across cell membranes, a powerful source of potential energy. Cells harness this energy to send nerve signals, regulate genes and trigger muscle contraction. Muscle movement in the body is regulated by precisely controlled increases in calcium ion concentration acting as a biochemical switch.

Going into the current study, the team knew from the literature that a genetic mutation – a small, random mistake in the genetic code – causes MH susceptibility in humans. They also knew that the mutation was located in a gene that codes for ryanodine receptor proteins. These

calcium channels provide a pathway for calcium in the internal storage compartment, the sarcoplasmic reticulum, to be released into the muscle cell to cause contraction.

For the current project, researchers genetically engineered mice with a mutation seen in human MH disease. They found that these mice indeed exhibited full-body contractions that lead to death during exposure to anesthesia (e.g. halothane), a hallmark of malignant hyperthermia. Unexpectedly, the mice were also found to experience similar, life-threatening episodes during brief exposure to environmental heat stress (105F). These results establish a surprising connection between altered ryanodine receptor activity and heat stroke, with the mutated calcium channel being more likely to exhibit uncontrolled calcium release and muscle contraction in response to heat.

Furthermore, the team demonstrated that increased calcium ion leakage from mutated ryanodine receptors during heat stress caused a profound increase in free radical production. Also called reactive oxygen species (ROS) and nitrogen species (RNS), free radicals are highly reactive molecules that can destroy sensitive cell components and hasten cell death. Free radicals are largely created as a side effect when structures within all human cells, the mitochondria, use oxygen to turn food into an energy-storing molecule called adenosine triphosphate (ATP). To drive ATP production, electrons are passed along a chain of enzymes within the mitochondria. When some of these electrons are not passed along effectively, they combine with oxygen and nitrogen to form free radicals. Disease processes tend to create far higher levels of free radicals than the body's naturally occurring antioxidants can mop up.

In the current study, results showed that free radical production in muscle nearly doubled in the genetically altered mice, and that it rose even more during heat stress. Researchers also found that the increase in free radicals results from increased calcium leak from the mutated

calcium channels in the sarcoplasmic reticulum, potentially driving increased ROS/RNS production by nearby mitochondria. In addition, the increase in ROS/RNS levels were in turn found to travel back to, and further alter, mutated ryanodine receptor calcium channels.

This “vicious feed-forward cycle” caused the calcium leak to further worsen, the calcium channels to become extremely heat sensitive and muscles to contract uncontrollably in response to both anesthesia and heat. Uncontrolled contractions can break apart muscle cells, releasing toxic cellular metabolites into the bloodstream that ultimately trigger kidney failure and throw the heartbeat out of rhythm. Even in the absence of such acute events, increased oxidative stress in the muscle of mutant mice over the long term was also found to distort the shape of mitochondria and weaken muscle contraction (myopathy).

Most importantly, simply including an antioxidant, N-acetylcysteine (NAC), in the animal’s water supply resulted in a marked reduction in sensitivity to heat stress, improved mitochondrial health and restoration of muscle function in aged mice. NAC is currently in phase 2 human clinical trials for patients with cystic fibrosis, where disease creates free radicals that damage lung tissue.

Researchers from the Medical Center, the Baylor College of Medicine and CeSI Centro Scienze dell'Invecchiamento Universit degli Studi G in Italy collaborated on the paper. Along with Dirksen, the Rochester effort was led by Ann Rossi and Sanjeewa Goonasekera, Ph.D. in the Department of Pharmacology and Physiology. Susan L. Hamilton, Ph.D., chair of the Department of Molecular Physiology & Biophysics at Baylor, was the corresponding author. Although not authoring institutions on the current paper, the Uniform Services University of the U.S. Army and Harvard University also participated in the work through a related grant from the National Institutes of Health.

“We found that destructive cycles of calcium leakage and excess free radical production damage mitochondria and contribute to the deterioration of muscle function in aged animals,” Dirksen said. “In successfully constructing the first mouse model of human MH, we unwittingly generated the first animal model of heat stroke that will undoubtedly be tremendously useful in better understanding these disorders and in accelerating the design of safe and effective treatments for both conditions.”

“Malignant hyperthermia syndrome, a potentially fatal inherited disorder, is most often ‘triggered’ by certain gas anesthetics and the paralyzing drug succinylcholine,” said Henry Rosenberg, M.D., president of the Malignant Hyperthermia Society of the United States and professor of anesthesiology at Mount Sinai School of Medicine, N.Y. “In the naturally occurring animal model, certain breeds of swine, the syndrome is also precipitated by environmental conditions. It has long been debated as to whether some cases of heat stroke and exercise-induced muscle breakdown in humans are related to malignant hyperthermia as well.

This study defines a biochemical pathway that might very well clarify the relationship between anesthesia-induced malignant hyperthermia and heat stroke. This elegant study, using modern molecular techniques, opens new avenues for the study of the not-uncommon problem of heat stroke and exercise-induced muscle breakdown and the risk for malignant hyperthermia.”

Source: University of Rochester