In enzyme's isoforms, hope for developing heart drugs that improve contractility, prevent SCD

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Drugs known as PDE3 inhibitors save many lives by helping failing hearts do a better job of pumping blood. But those same medications come with a sometimes deadly cost when taken for long periods: an increased risk for sudden cardiac death.

The drugs work by inhibiting PDE3A, an enzyme that regulates how the heart pumps blood. When PDE3A is inhibited, the heart contracts more forcefully, pumping more blood.

Developing a medication that has the benefits of current drugs but doesn't increase the risk for sudden cardiac death associated has eluded researchers. But an international collaboration led by two Utah researchers is a key first step in finding out whether such a drug may one day be developed.

The research, funded by the Department of Veterans Affairs, was published in the *Proceedings of the National Academy of Sciences* (*PNAS*) online the week of Nov. 18, 2013. Matthew A. Movsesian, M.D., professor of medicine at the University of Utah School of Medicine and a cardiologist at the George E. Wahlen Department of Veterans Affairs Medical Center in Salt Lake City, is the senior author. Fabrice Vandeput, Ph.D., a postdoctoral fellow in cardiology at the University of Utah and the VA Medical Center, is first author.

PDE3A comes in three types, or isoforms. PDE3A inhibitors work by inhibiting all three isoforms of the enzyme. Working with colleagues from the United States and Scotland, Vandeput and Movsesian made an important discovery: two of those isoforms, PDE3A1 and PDE3A2, are regulated individually and interact with different proteins in a cell.

"If those isoforms are regulated differently, this tells us they probably are doing different things in cells. And if they interact with different proteins, this means there are molecules that bind to one isoform and not the other," Movsesian says.

That could make it possible to develop a drug that targets one or other of the isoforms to inhibit PDE3A without upping the risk of sudden cardiac death. Years of work must be done before such a drug could be developed and available to heart failure patients. Researchers need to learn much more about the isoforms to understand their roles in how the heart contracts to pump blood (called contractility). They also need to know whether either form of PDE3A contributes to sudden cardiac death in those taking current drugs.

It's also possible that research could determine neither of the isoforms would be a good target for drugs, according to Movsesian, also a professor of pharmacology and toxicology.

"We don't know for certain if these isoforms will ultimately prove to be good targets for drugs," he says. "But we now have reason to believe we could target one or the other."

About 5.7 million people in the United States have heart failure, according to the Centers for Disease Control and Prevention (CDC), with more than 55,000 deaths directly attributed to the condition annually. In 2008, heart failure was a contributing cause in 280,000 deaths, according to the CDC.

PDE3 inhibitors can be taken for shorter periods, when someone has a heart attack and needs help recovering, for example, or for a year or more, such as when a patient with heart failure waits for a transplant or can't survive without the drug. In patients who take them for longer periods, an

increase in the mortality rate from sudden cardiac death may outweigh the benefits of increasing cardiac contractility, according to Movsesian.

More information: Selective regulation of cyclic nucleotide phosphodiesterase PDE3A isoforms, www.pnas.org/cgi/doi/10.1073/pnas.1305427110

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