Chymase inhibitors could enhance treatment for damaged hearts

25 March 2010

Millions of patients with high blood pressure and heart failure take a class of drugs known as ACE (angiotensin-converting enzyme) inhibitors. These drugs prevent the body from processing angiotensin II, a hormone that constricts blood vessels.

Scientists at Emory University, University of Alabama, Birmingham, and Fukuoka University in Japan have shown that another enzyme present in the heart called chymase is also capable of processing angiotensin II. Adding drugs that interfere with chymase to ACE inhibitors significantly boosted recovery of heart function in animals after heart attack, the researchers found.

The results, to be published in the April 2010 issue of the Journal of Clinical Investigation, could lead to improved treatments for people with high blood pressure, heart failure and other conditions.

"The development of ACE inhibitors was a major advance in the treatment of hypertension and heart failure, and they have become the standard of care," says senior author Ahsan Husain, PhD, professor of medicine (cardiology) at Emory University School of Medicine. "But ACE inhibitors don't work for everyone, and we think we have found a way to make them more effective."

Doctors have reported for years that taking an ACE inhibitor usually reduces a patient's blood pressure, but angiotensin II often returns to high levels over several months, a phenomenon called "ACE inhibitor escape." This is bad news because angiotensin II drives the release of other hormones, leading to fluid retention, and also has direct effects on the heart. For example, after a heart attack, it promotes scarring and enlargement of the heart. In addition, ACE inhibitors have been reported to be less effective for some population groups such as African Americans.

Sometimes an inadequate response to ACE inhibitors leads doctors to add drugs that can block some of angiotensin II's effects (angiotensin II receptor blockers), but the clinical evidence for an additional benefit from these drugs is still up for debate, Husain says.

Much of Husain's laboratory's research over the last 20 years has been aimed at understanding the production of angiotensin II in the heart. In 2008, Husain came to Emory from University of Alabama, Birmingham, where he had been working with the first author of the paper, assistant professor Chih-Chang (Kevin) Wei, PhD, and professor Louis Dell'Italia, MD. Naoki Hase at Teijin Pharma and Yukiko Inoue and Hidenori Urata, MD at Fukuoka University in Japan also contributed to the paper.

Wei, Husain and colleagues showed that chymase in the heart comes from mast cells, inflammatory cells that play a central role in allergies and asthma. Mast cells are missing in mice with mutations in the gene for the blood cell growth factor receptor c-kit. In these mice, angiotensin II almost disappears after treatment with ACE inhibitors. But giving normal mice ACE inhibitors induces mast cells to release chymase, restoring their ability to produce angiotensin II.

Previous research by Husain and Urata demonstrated that chymase activity is especially abundant in heart tissue from patients with heart failure. Inflammation arising from atherosclerosis or myocarditis may be attracting mast cells to the heart, Husain says.

To test whether chymase makes a difference in recovery after a heart attack, Wei, Husain and colleagues compared the effects of an experimental chymase inhibitor (provided by Teijin Pharma) to a standard ACE inhibitor on hamsters that had a simulated heart attack.

Combining the ACE inhibitor and the chymase inhibitor improved ejection fraction, a measure of

heart function, and reduced the amount of dead tissue and scarring more than either drug by itself. The experiments on recovery after heart attack were performed on hamsters because mouse heart cells do not respond as much to angiotensin II as human or hamster heart cells do.

Chymase inhibitors are not available for clinical use, although pharmaceutical companies have begun investigations of their usefulness for conditions such as inflammatory bowel disease and asthma.

"Now, cardiovascular studies of chymase inhibitors in humans need to be done," Husain says. "Our hope is that pharmaceutical companies will see this as an opportunity to address a significant need."

More information: C.C. Wei et al Mast cell chymase limits the cardiac efficacy of Ang I-converting enzyme therapy in rodents J. Clin. Invest. 120, 1-11 (2010).

Provided by Emory University