Common antidepressant may hold the key to heart failure reversal
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A normal human heart. Heart failure occurs when the heart muscle’s ability to pump blood is impaired. Credit: C. Bickel/ Science Translational Medicine

A team led by researchers at Temple University School of Medicine (TUSM) found that a commonly prescribed antidepressant restored heart function in mice with heart failure, a finding that could lead to clinical trials for a disease long considered irreversible.

The team, which was led by Walter J. Koch, PhD, the William Wikoff Smith Endowed Chair in Cardiovascular Medicine and Director of the Center for Translational Medicine at TUSM, found that the antidepressant paroxetine (also known as Paxil), reversed heart failure in mice. The findings were published in the March 4 issue of the journal Science Translational Medicine. The effect of paroxetine was not because of its antidepressant properties, but the inhibition of a specific enzyme that is a side-effect of the drug.

"This may open the way for a new class of therapies for a disease for which we lack effective interventions," Koch said. "At a minimum, the research suggests that physicians may want to consider prescribing paroxetine for heart failure patients who also suffer from clinical depression. If you have to give these patients an antidepressant, why not give them this one, which may improve heart function?" Koch asked.

The disease reversal occurred at concentrations of paroxetine similar to those found in the blood of people treated for depression, although Koch cautioned that what happens in mice is no guarantee of the same response in humans.

More than a half million Americans are diagnosed with heart failure every year, and 5.1 million live with the disease. That number is projected to increase 25 percent by 2030, according to the American Heart Association. The cost of treating the disease will more than double, from $30.7 billion in 2012 to nearly $70 billion in 2030. While treatment has improved significantly in recent years with the use of beta blockers and angiotensin-converting enzyme inhibitors, once the deterioration of the heart muscle begins, there has been no way to reverse it without having a heart transplant. About half the people diagnosed with heart failure die within five years.

The current study grows out of Koch's two decades of investigation into an enzyme called GRK2, which stands for G protein-coupled receptor kinase-2. Levels of this enzyme rise when the heart is failing. Previous research by Koch and his colleagues has demonstrated the role of GRK2 in heart failure. That research relied on genetic manipulation to control GRK2 levels and, when GRK2 is lowered in various animal models, heart failure is reversed. Koch said he hopes next year to begin clinical trials of a gene therapy approach to lowering GRK2 levels.

But paroxetine is the first small molecule shown to successfully and selectively turn off GRK2's
enzymatic activity, and it is a small molecule already known to be safe in humans, which has a real advantage. John J.G. Tesmer, at the Life Sciences Institute at the University of Michigan, a co-author on the current work, stumbled onto paroxetine. He was testing a procedure for screening compounds that affect GRK2 using a series of FDA-approved compounds. But the test run discovered that the antidepressant both bound GRK2 and inhibited its activity. Tesmer sent Koch an unlabeled sample of the compound and Koch tried it on isolated cardiac myocytes - heart cells —and found they beat stronger.

"I was excited. I've been trying to find a GRK2 inhibitor for 20 years. I've talked to drug companies for years trying to get them interested in producing small molecules to inhibit GRK2. Now we have our small molecule." Tesmer is now working to create a derivative of paroxetine that can shut off GRK2 at lower doses without the antidepressant effect, Koch said.

In the current paper, Koch's team tested paroxetine against a placebo and a second antidepressant - fluoxetine (also known as Prozac). Mice were given myocardial infarctions—heart attacks—and developed heart failure over the next two weeks. When the heart failure was well developed, they were treated with placebo, paroxetine, or fluoxetine. Only paroxetine-treated mice showed the reversal of heart failure. Many antidepressants, including Prozac and Paxil, work by affecting levels of the brain signaling chemical, serotonin. Fluoxetine's failure to restore heart function demonstrates that the paroxetine's effect on the heart is unrelated to the serotonin system. The researchers also tested paroxetine against the beta-blocker metoprolol, a current standard of care for heart failure. "The beneficial effects of paroxetine were far greater than beta-blocker therapy," Koch said.

"We believe this validates that GRK2 is a viable therapeutic target for heart failure and paroxetine is the starting point for a novel small molecule," Koch said. When the heart muscle is damaged by a heart attack, the body attempts to compensate for its lost pumping power by increasing adrenaline levels to boost heart rate. This leads to a series of maladaptive adjustments, and the heart grows larger and less efficient as its contractile force weakens. GRK2 is a major player in this unfortunate remodeling, which leaves patients with a heart less able to supply blood to the entire body.
said. "We're looking at a totally new class of drugs for heart failure."


Provided by Temple University


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