Novel peptide shows promise in penetrating heart attack scar tissue to regenerate cardiac nerves

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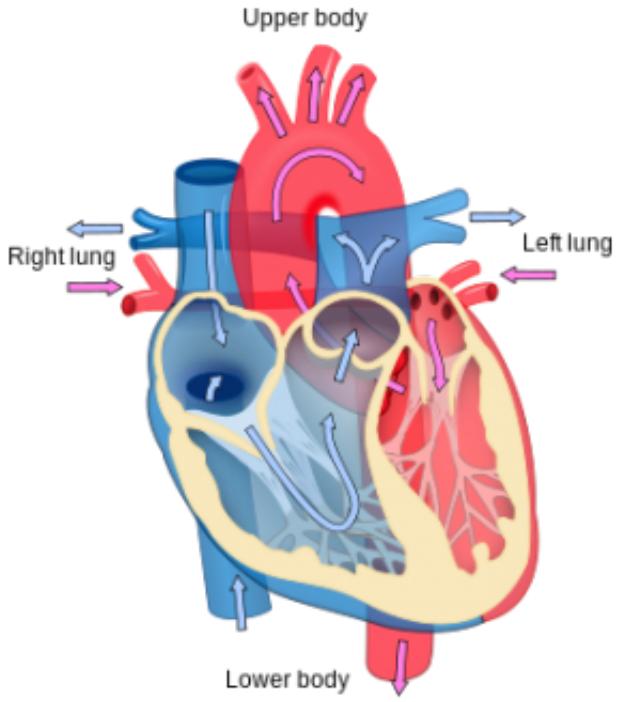

Heart diagram. Credit: Wikipedia

Case Western Reserve's chemical compound aimed at restoring spinal cord function may have an additional purpose: stopping potentially fatal arrhythmias after heart attack.

Case Western Reserve neurosciences professor Jerry Silver, PhD, long

has believed that lessons learned over decades from spinal cord research could someday apply to other areas of the body. He got the chance to test his theory when a colleague from another campus realized that his new compound - intracellular sigma peptide (ISP) - could address a critical cardiac issue.

The results of the project, led by Oregon Health & Sciences University (OHSU) researcher Beth A. Habecker, PhD, exceeded even Silver's greatest hopes: 100 percent success in animal models. Details can be found in the Feb. 2 edition of *Nature Communications*.

"Essentially, the OHSU group cured arrhythmia in the mouse using ISP," Silver said. "They observed true regeneration right back into the scar within the infarct area. This is pretty exciting."

Habecker, professor and interim chair of OHSU's Physiology and Pharmacology Department, is similarly enthusiastic about the findings. "Patients who survive a heart attack remain at high risk for cardiac arrest and severe arrhythmias," explained Habecker, the paper's senior author. "Recent clinical studies suggest sympathetic denervation predicts the risk for cardiac arrest. Our study shows that this risk can be decreased by intervening with ISP to promote axon regeneration into the cardiac scar."

At first, the idea sounds counterintuitive: a peptide shown to restore function in spinal cords could help stop an active malfunction in hearts. But once researchers looked more carefully at the reasons for the respective problems, ISP's benefits to both became clear. Spinal paralysis and denervation in the heart each stem from failed nerve regeneration caused by a family of inhibitory molecules called proteoglycans that form in scar tissue following injury or even the trauma of a cardiac procedure. ISP's role is to revive those nerves by allowing them to ignore the repulsing scar molecules.

Habecker's work with Case Western Reserve's compound emerged from a combination of history and happenstance. She knew Silver from her time as a postdoctoral fellow in neurosciences here in the early 1990s, and had followed his work with proteoglycans, the inhibitory protein molecules that engulf nerves during scarring. Habecker had found that proteoglycans played a similarly problematic role after heart attacks, and invited him to lecture on his most current research. As part of the visit, the pair compared notes on their respective projects.

"When she discussed her work with me, I almost fell out of my chair," Silver recalled. "I realized how similar our work was, and I said, 'we have to send you our peptide.' When I described the peptide, she said she wanted to give it a try in heart attack research in animal models."

The *Nature Communications* paper reflects work done entirely at OHSU after Silver's lab provided enough of the compound for Habecker's team to perform their experiment. The effort involved simulating the impact of an actual heart attack in mice, and then "treating" it with the ISP, saline, or a non-therapeutic peptide (the control).

Two weeks later, the OHSU scientists found that all of the mice that received ISP regained normal levels of sympathetic cardiac nerve function throughout the left ventricle, including the heart attack-damaged areas. Additionally, telemeter readings on these animals showed no arrhythmia activity. In contrast, animals treated with saline or the control peptide had cardiac sympathetic denervation in areas of their hearts damaged by the myocardial infarction, and as a consequence, experienced arrhythmias.

"My role was that of a supplier," Silver said. "It was really important that this study of the peptide be conducted without my involvement. The study at OHSU provided independent validation that the peptide works in animals. And it confirmed the effectiveness of ISP in a completely

different model—heart attack. That kind of replication is rare."

The discovery has significant potential in heart attack treatment. Currently, 7 to 10 percent of people die within the first six months from sudden cardiac death due to arrhythmia. ISP shows promise in serving as the basis for prophylactic treatment to prevent arrhythmia within the first months of a heart attack.

"We are extremely fortunate to have the connection with Dr. Silver's lab, which allowed us to test a systemically available therapeutic in our heart attack model," Habecker explained. "The fact that giving ISP several days after injury can fully restore innervation and decrease arrhythmia risk is amazing, and is a key finding."

Next steps in moving ISP forward will be testing the peptide as a post-heart attack treatment in larger animals. Such tests would reveal maximum tolerated dose, any toxicity potential and the extent to which the peptide infiltrates scar tissues. Additionally through animal studies, investigators wish to learn whether ISP administered several months, or even years, after a heart attack would confer a similar benefit as treatment administered three days post-heart attack.

"We want to do clinical trials here at Case Western Reserve with ISP when it reaches clinical trial stage," Silver said. "We could conduct those trials in collaboration with OHSU and other centers throughout the country."

More information: *Nature Communications*, www.nature.com/ncomms/2015/150 … full/ncomms7235.html

Provided by Case Western Reserve University