# Scientists discover compound that could lead to new blood pressure drugs

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University of Florida researchers have identified a drug compound that dramatically lowers blood pressure, improves heart function and — in a remarkable finding — prevents damage to the heart and kidneys in rats with persistent hypertension.

The findings, which appear in today's (May 1) edition of the American Heart Association journal *Hypertension*, could lead to a new class of antihypertensive drugs designed to address two major problems associated with cardiovascular disease: high blood pressure and the tissue damage associated with it, known as fibrosis.

"When people have heart attacks (or suffer from hypertension) the blood vessels get more rigid," said study author David Ostrov, Ph.D., an assistant professor in the UF College of Medicine's department of pathology, immunology and laboratory medicine. "We discovered a compound that reverses the fibrosis that makes the blood vessels more rigid."

The American Heart Association estimates that 72 million people in the United States have high blood pressure, a major risk factor for stroke, heart attack and death.

Angiotensin-converting enzyme plays a key role in the development of high blood pressure. It produces angiotensin II, a potent hormone that triggers the condition and contributes to the development of cardiovascular disease by constricting blood vessels, causing blood

pressure to rise. That's why millions of Americans with hypertension and cardiovascular disease take ACE inhibitors. But these drugs have limited capacity to repair heart function and to reverse tissue damage.

In contrast, the enzyme ACE2 not only lowers levels of angiotensin II but also converts it to a hormone that helps protect the cardiovascular system.

"Only recently has it come to be appreciated that ACE and ACE2 play a very important role in balancing the activity of the other one to maintain normal blood pressure," Ostrov said. "They work in harmony."

Hypothesizing that activating ACE2 could be beneficial, UF scientists set out to discover a compound that enhances the enzyme's activity.

Researchers used one of the world's most powerful supercomputers to process 140,000 prospective drug compounds in a matter of weeks. The computer predicted which molecules would be most likely to enhance the activity of ACE2, rotating them in thousands of different orientations to see how they would bind to certain pockets on the enzyme's surface.

"This project had a very small likelihood of succeeding because it's much easier to inhibit activity rather than to enhance it. By analogy, it's easier to break something than to build it," Ostrov said. "If you consider the structure of an enzyme's active site it's easy to see that if you plug up the active site it's not going to work. But how can one make the enzyme actually work better" This seemed to be a very significant challenge we were probably not likely to overcome. We tried anyway."

And it worked.

"That in itself is a significant accomplishment because no one has ever

specifically identified a compound that enhances the activity of an enzyme using a rational structure-based approach," he said. "In other words, no one has ever done this before on purpose. People have discovered molecules that enhance the activity of enzymes by trial and error, but no group has ever done it in a specifically pointed way like this."

Ostrov said the enzyme exists in two forms: like a Pac-Man with a mouth that has chomped closed, and like a Pac-Man with a mouth that remains wide open. The molecule that worked best fit in a structural pocket in the enzyme's open conformation.

"So in other words, stabilizing the open conformation may be the reason why we enhance the activity of the enzyme," he said.

After hitting on the "lead" compound, UF researchers then tested it in hypertensive rats that had developed fibrosis of the heart and kidney. The animals received the drug for two weeks. Tissue samples from treated animals revealed a significant decrease in fibrosis of the heart, kidney and blood vessels, said Ostrov, who described the findings as "striking and reproducible."

The study was funded by grants from the National Institutes of Health and the American Heart Association and was a collaborative effort of the UF colleges of Medicine, Pharmacy and Liberal Arts and Sciences. Researchers also included Mohan Raizada, Ph.D., distinguished professor of physiology and functional genomics, Michael J. Katovich, Ph.D., a professor of pharmacodynamics, and Ronald K. Castellano, an assistant professor of chemistry, among others.

Early results also show the compound inhibits inflammation, which has significant implications for a number of human diseases, including autoimmune diseases such as type 1 diabetes and rheumatoid arthritis as

well as other diseases involving fibrosis, such as Alzheimer's, Ostrov said.

Additional research will continue to explore the compound's effectiveness in animals and humans.

Source: University of Florida