Viagra relatives may shrink abnormally large hearts

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Compounds related to Viagra, which is already in clinical trials to prevent heart failure, may also counter the disease in a different way, according to a study published online today in the journal *Circulation Research*. The results hold promise for the design of a new drug class and for its potential use in combination with Viagra or beta blockers.

In heart failure, which affects about 5.7 million Americans, the heart gradually loses the ability to pump with enough force to supply the body with blood. One reason for lost pumping strength is the mass death of heart muscle cells seen in many heart diseases (e.g. heart attack). Fewer remaining muscle cells must then push around the same amount of blood, and hard working muscles grow. Unlike the healthy bulging of an athlete's bicep, abnormal muscle growth (pathogenic hypertrophy) in diseased hearts thickens chamber walls, slows the heartbeat and causes potentially fatal arrhythmias. Hypertrophy is a major risk factor for the development of heart failure as well.

Recent efforts to reverse hypertrophy include a clinical trial, sponsored by Viagra manufacturer Pfizer, and the National Heart, Lung, and Blood Institute (NHLBI), looking at whether Viagra (sildenafil) can treat moderate heart failure and reduce hypertrophy. Along with increasing blood flow in arteries, Viagra interferes with phosphodiesterases (PDEs), enzymes that break down the messenger molecule called cyclic guanosine monophosphate (cGMP), which would otherwise "put the brakes on" heart muscle cell growth.

Viagra shuts down the PDE5 family in particular, one of 11 PDE families in the body and that include more than 50 individual enzymes. They have proven to be famously good drug targets because each has a unique structure, tissue distribution and role, allowing them to be precisely targeted by drugs for fewer side effects. In the just-published experiments in heart muscle cells and live mice, researchers found that members of a second PDE family, particularly the PDE1a enzyme, also break up cGMP to control hypertrophy, but not in the same way as Viagra.

Where PDE5 breaks down cyclic nucleotides in response to the vital signaling molecule nitric oxide (NO), PDE1 affects cyclic nucleotide pathways sensitive to Calcium (Ca2+), another major player in cardiac disease, according to the authors.

"Our results suggest that a PDE1a inhibitor alone can shut down abnormal cardiac growth, and when combined with Viagra or beta blockers, may do so in more than one way," said Chen Yan, Ph.D., associate professor within the Aab Cardiovascular Research Institute (CVRI) at the University of Rochester Medical Center, and corresponding author for the study. "We found a new drug target, that if interfered with, prevents hypertrophy, and where compounds already exist that interfere with it. The compounds used in the study were experimental, but we are already developing drug candidates based on the discovery."

Whether combination treatments featuring PDE1 inhibitors will have value in heart failure will not become clear until further animal studies are completed, Yan said. Both PDE1 inhibitors and Viagra lower blood pressure, and may or may not lower it too much in combination. Viagra cannot be used with nitroglycerin for this reason. On the other hand, some patients with heart failure cannot use beta blockers, which also reduce hypertrophy, because the drugs make already weak hearts pump

with less vigor. Combining beta blockers with PDE1 inhibitors could potentially enable heart failure patients to take less beta blocker, protecting the contractile power of their heart muscle cells while still averting hypertrophy.

Study Details

PDEs, by degrading cGMP, control the strength of its signal. Normally, cGMP-dependent signaling suppresses abnormal growth in heart cells by restraining Ca2+ signals that drive hypertrophy. The research team believes that PDE signaling unbalanced by long-term strain on heart muscle distorts the "crosstalk" between Ca2+ and cGMP to promote abnormal growth. Past studies had shown at least five PDE families, PDE1-5, are present in the human heart, of which PDE1 and PDE5 are most responsible for limiting cGMP supply. Going into the current study, no one knew whether the PDE1 family was involved in hypertrophy.

Yan and colleagues found that levels of PDE1a were significantly increased in heart muscle cells in animal and individual cell models of hypertrophy. The study also confirmed that PDE1a inhibition reduces abnormal growth in heart muscle cells through their effect on cGMP.

PDE1 inhibitor IC86340 was found to reduce by at least 75 percent abnormal growth in studies of isolated rat heart muscle cells in the face of a chemical known to cause hypertrophy (phenylephrine). Yan had published in previous papers that IC86340 could inhibit the PDE1 family, but no one had ever used it to counter hypertrophy. In live mice, the study drug significantly reduced hypertrophy over control mice when both were exposed to the well established hypertrophic agent, isoproterenol.

Yan's team also found that the combination of IC86340 and Viagra in

studies of isolated heart muscle cells eliminated hypertrophy to a greater degree than either compound alone. Cell growth was measured by techniques that captured each cell's protein production (more protein equals more growth) and the size of cells in terms of their surface area. Studies already underway are looking at the effect on hypertrophy in live mice with the genes for various PDE1 enzymes removed.

Along with Yan, efforts at the University of Rochester Medical Center were led by Clint Miller, Masayoshi Oikawa, Yujun Cai, Haodong Xu, Burns Blaxall and Jun-ichi Abe within the CVRI; Andrew Wojtovich and David Nagel in the Departments of Pharmacology and Physiology; and by Xiangbin Xu and Jian-Dong Li in the Department of Microbiology and Immunology. Also leading the effort were Vince Florio of Omeris Corp. in Seattle; Sergei Rybalkin and Joseph Beavo in the Department of Pharmacology at the University of Washington and Yiu-Fai Chen in the Department of Medicine at the University of Alabama at Birmingham. This work was supported by the American Heart Association and the National Institutes of Health (NIH).

Also moving forward, Yan's lab is focused on revealing the role of various PDE enzymes in atherosclerosis and hypertension as well as in heart failure.

"Almost every signaling molecule involved in PDE-regulated hypertrophy in the heart - including nitric oxide, calcium and angiotensin II - are at the core of regulating blood pressure and disease-related structural changes in arteries," Yan said. "PDE1a levels appear to influence those pathways in return, which creates the potential for PDE1 inhibitors that treat both hypertrophy in the heart and vascular diseases like hypertension and atherosclerosis."

Source: University of Rochester Medical Center (news : web)