Viagra's other talents: Help a 'signaling' protein shield the heart from high blood pressure damage

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Johns Hopkins and other researchers report what is believed to be the first direct evidence in lab animals that the erectile dysfunction drug sildenafil amplifies the effects of a heart-protective protein.

The team's findings, to be published in the *Journal of Clinical Investigation* online Jan. 5, helps explain why sildenafil, more widely known as Viagra, has already been shown to improve heart function and may one day have value in either treating or preventing heart damage due to chronic high blood pressure.

The key, investigators say, is sildenafil's effects on a single protein, RGS2, newly identified in the latest study as an essential link in the chain reactions that initially protect the body's main blood-pumping organ from spiraling into heart failure.

Experimenting in mice, the team of heart experts first established that after a week of induced high blood pressure, the hearts of animals engineered to lack RGS2, or regulator of G-protein signaling 2, quickly expanded in weight by 90 percent. Almost half the mice died of heart failure. In mice with RGS2, by contrast, the dangerous muscle expansion, known as hypertrophy, was delayed, growing only 30 percent, and no mice died.

Subsequent tests treating hypertensive mice that had RGS2 with

sildenafil showed enhanced buffering, with less hypertrophy, stronger heart muscle contraction and relaxation, and as much as 10 times lower stress-related enzyme activity compared to their untreated counterparts. In mice lacking RGS2, sildenafil had no effect.

"Sildenafil clearly prolongs the protective effects of RGS2 in mouse hearts," says study senior investigator and cardiologist David Kass, M.D.

According to Kass, a professor at the Johns Hopkins University School of Medicine and its Heart and Vascular Institute, RGS2 is stimulated by an enzyme, protein kinase G, whose action is, in turn, raised by countering the activity of another enzyme, phosphodiesterase 5 (PDE5A). Sildenafil's ability to block PDE5A was shown by Kass and his team in 2005 to be responsible for blunting hypertrophy due to high blood pressure in mice and offsetting similar, adrenaline-stimulated heart stress in people.

Kass says RGS2 "acts like a short-term reset mechanism in the heart," recoupling G proteins that if left alone stimulate the heart's response to high blood pressure. And without the "reset," a cascade of reactions known as Gq signaling leads to scar tissue formation, hypertrophy and heart failure.

Currently, physicians use so-called ACE inhibitor and ARB inhibitor drugs to block Gq signaling. These classes of drugs are the most common treatment for heart failure, which afflicts more than 5 million Americans, killing over a quarter million of them each year.

"The evidence is piling up that unbridled Gq signaling is driving a central biological chain reaction in heart failure," says Kass, "and that by extending the protective effects of RGS2 or by developing a test for its presence, researchers can develop new therapies or improve existing ones, including ACE inhibitors and possibly sildenafil, for people with

heart failure who will benefit most."

Until recently, scientists thought RGS proteins, which are found only in small quantities in the heart -- a thousand times less than other, more common proteins, such as myosin and metabolic proteins -- played no key role in heart function. Previous tests in mice, Kass says, had shown no harmful effects to the heart from knocking out production of RGS2, though the protein was known to have a role in maintaining smooth muscle function in blood vessels.

But studies by co-investigators at Tufts Medical Center in Boston had shown that RGS2 activity was upped by protein kinase G, leading Kass and others to look for stronger links between these biological pathways and hypertrophy.

The latest study involved more than a half-dozen experiments, all performed within the last three years and designed to zero in on the role played by RGS2 in stalling hypertrophy.

In one experiment for the current study, researchers artificially stimulated the Gq chemical pathway in mice lacking RGS2, worsening the effects of Gq signaling, including hypertrophy and widened heart chambers.

In another experiment in mice with and without RGS2, researchers analyzed the cardiac response to the physical stress of twice daily swimming exercises lasting 90 minutes each, a stress not known to affect Gq signaling. After six weeks of testing, both sets of mice showed similar increases, at 30 percent, in heart mass and no signs of impaired heart function.

Subsequent protein analysis for enzymatic action common to heart failure showed the same results for both sets of mice, confirming to

researchers that RGS2 proteins were responsible for protecting the heart from hypertrophy linked to Gq signaling.

More tests with pressure overload showed that when RGS2 was stimulated by protein kinase G, both proteins moved together from inside the cell to its outer cell walls. This effect was then stabilized in RGS2 mice treated with sildenafil, solidifying evidence of the biological chain reactions between the drug and the protein.

"Our results offer among the first insights into the biology of the RGS2 protein in heart cells during hypertrophy," says study lead investigator Eiki Takimoto, M.D., Ph.D. "This greatly expands our understanding of how high blood pressure affects the heart and helps break down the disease equation into its molecular components for subsequent clinical testing."

Takimoto, an assistant professor at Johns Hopkins, says the team's next plans are to look at other potential consequences of increased RGS2 activity within the cell and to zero in on what other proteins or factors boost its action.

PDE5A is involved in the breakdown of a key molecule, cyclic guanosine monophosphate, which helps control stresses and limit overgrowth in the heart. PDE5A is also the biological pathway blocked in the penis by sildenafil to promote the relaxation of blood vessels and maintain erections.

Source: Johns Hopkins Medical Institutions