Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/focus-on-heart-health/can-viagra-protect-the-heart/4166/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Can Viagra Protect the Heart?

Can Viagra also protect the heart? Welcome to our Focus on Heart Health. I'm Dr. Larry Kaskel, your host. Recent research shows that sildenafil, an ingredient in Viagra may actually shield the heart from damage caused by high blood pressure. My guest today is Dr. David Kass in Abraham and Virginia Weiss Professor of Cardiology at Johns Hopkins University School of Medicine and we're going to talk a little bit about his findings of recent research published in the Journal of Clinical Investigation, which suggests that Viagra may actually prove useful and the treatment of and/or prevention of heart damage due to chronic high blood pressure.

DR. LARRY KASKEL:

Dr. Kass, welcome to the show.

DR. DAVID KASS:

Thanks very much, it's a pleasure to be here.

DR. LARRY KASKEL:

Let's go back in time to when Viagra was in clinical trials, what were they actually looking for Viagra to do?

DR. DAVID KASS:

Well, Viagra, as many of the listeners may or may not know is a drug that inhibits an enzyme called PDE5 stands for phosphodiesterase type 5, this is an enzyme that would normally degrade molecule cyclic GMP, one of the second messenger molecules, and the enzyme had been discovered in platelets where it was thought to play a role in clotting instead of coagulation. It had been discovered in smooth muscle, so inhibiting it led to dilation.

DR. LARRY KASKEL:

So, really it had its effect on nitric oxide.

DR. DAVID KASS:

Right. Nitric oxide stimulates the enzyme that produces cyclic GMP, so called soluble guanylate cyclase and PD5 is getting rid of the cyclic GMP that is being produced. So, either end of it, either you likely turn off the vacuum cleaner or you make more dust and it's the same effect. So they knew is in platelets and they knew is in blood vessels and they initially started after ischemic heart disease, so the original trials were looking at an angina model that seemed like a reasonable combination where you want to do vasodilate and prevent clotting and the trial that Pfizer had initiated didn't end up proving terribly positive for angina. For one thing, it turns out these drugs are not really very potent coronary vasodilators. We've learnt what are the organs they do more potently dilate. So the patient's chest pain really wasn't affected, but the side effect, which was sort of a standard question on a forum you know they ask for all sorts of side effects including how is your sex life, and what I understood the story, all these forms ended up on someone's desk we can, where the rest of the group was away and a little posted note on the top saying it might want to check out the answer to #14 whether it was it, that's very interesting.

DR. LARRY KASKEL:

I had heard that a lot of the study candidate did not return the trial drug.

DR. DAVID KASS:

That's what I heard too. They like the side effect and so in an interesting way it's very rare really I think historically that you have a drug that was initially being developed because of cardiovascular potential ends up being found to have a side effect that doesn't involve the cardiovascular system directly and that drug development and the studies to follow for quite sometime becomes effectively hijacked away from the heart or any other cardiovascular organ and up until very recently, when we got back to the lung, we knew within the lung and it was highly expressed in the lung and it could produce vasodilation of the lung. But it took almost a decade after the erectile dysfunction indication or the drug to now be approved for the use in forms of pulmonary hypertension, in and out kind of context, it may be less surprising that it's taken us even a bit longer to get back to the heart and realize that this enzyme can have effects on the myocardium itself.

DR. LARRY KASKEL:

Well, let's talk a little bit more about the effect on vasodilatation because you said it wasn't a great vasodilator, but why does it potentiate the effect of nitrates that much, so that we are warned not to take it with nitrates if it doesn't have its own vasodilatory properties in the heart.

DR. DAVID KASS:

It all depends upon where it's actually expressed, so levels of this enzyme PD5 are clearly high in the carpus cavernosum and as mentioned they are high in the pulmonary vasculature, and that's so high in the arterial smooth muscle. They are somewhat elevated; they are a little higher on venous side and depending again from where you are and where the nitric oxide is going to be acting, you can get differential effects. Remember that those warnings, which were based on some early almost ionic double experiences, I do not think there was a clear-cut clinical trial where people directly tested whether or not taking nitrates and PD5 inhibitor was always going to produce an adverse effect. They were just impatient to clearly have substantial blood pressure drops and then a warning came out, and it is sort of makes sense. But it's actually not entirely clear how that interaction is always going to work and the synergy really does require that the action of nitric oxide has to be in the same vascular bed where PD5 is expressed and where inhibiting it would then have this potentiating effect, so it's not an absolute given in ironically. We're coming back to this. We published a study as an animal study where we combined natriuretic peptide, which also increases cyclic GMP with a PD5 inhibitor and you might think sort of the same thing

that this would be not a good idea. This is a sort of like nature <_____> combining a synthetic natriuretic peptide with sildenafil, but actually the synergy that we saw on blood pressure was only in the lung. We didn't see any synergistic interactions in the arterial side. Systemic blood pressure really was not affected by the combination anymore than with either one lung. There was actually relatively modest effects on the arterial side. So, again exactly what happens to pressure depends really from where the enzyme is and that may even be changing in diseases. It seems to go up in some bed like the lung and in the heart failure. So, people with normal heart versus failing hearts might have different interactions of these drugs.

DR. LARRY KASKEL:

If you have just tuned in, you are listening to Focus on Heart Health on ReachMD, The Channel for Medical Professionals. I am Dr. Larry Kaskel, your host, and I am speaking with Dr. David Kass in Abraham and Virginia Weiss Professor of Cardiology at the John Hopkins University School of Medicine, and we're talking about some research that he has done that suggest that Viagra may increase effects of a heart protective protein.

So, tell me more about the trial you did and what you learnt?

DR. DAVID KASS:

Well, we have to go one more step down the path, why would an enzyme that prevents this molecule cyclic GMP and perhaps preventing hypertrophy, the sort of classic heart response to sustain high blood pressure and from hypertrophy often heart failure and for that we've an enzyme that cyclic GMP stimulates and that's called protein kinase-G and protein kinase-G like any kinase phosphorylates things and interacts with protein better than phosphorylase and number of those proteins have been suggested to be protective. PKG has been suggested to protect against ischemic damage and to improve sort of postinfarction, remodeling. It has been suggested to enhance the mitochondrial function, so energetics are better and there is data mostly coming from the natriuretic peptide side, which is another way of increasing protein kinase-G activities that it can be anti-hypertrophic. The issue of PD5 originally was people, who really think that it was made in the heart. It was so low; the expression level of the protein was so low when you measured it, but no one imagined it was ever really be important, but in work we actually first reported a couple of years ago when we first suggested that it is not only in the heart, but inhibiting it as anti-hypertrophic effect. What we found was that how much you have of this enzyme isn't so important as where it was; it is very strategic and it seemed to regulate a very strategic pool of cyclic-G and then protein kinase-G and indeed it had this anti-hypertrophic effect. So, the question is sort of a natural question that followed that study that was published in 2005 was how is it working? What is this target? Is it so strategic? What kinds of proteins might it be interacting with it that could have this protective effect? And that has been somewhat this brings us right up to this recent paper that reported in the Journal of Clinical Investigation, the basic science paper it's all done in mice and we do that obviously because we can knock things out and get rid of genes that we think are important signal in genes and in this case, we looked at mice that lacks the genes for protein known as RGS2. The RGS stands for Regulator of G-coupled signaling and there is all large family these protein is #2 and the thing the RGS2 is known to do in blood vessels that have been described do this in blood vessels is it acts as a inhibitor of the G protein signal that is normally triggered by hormones like angiotensin or endothelin or alpha agonists, all of those enzymes work on a receptor level interacting to let's call the Gq-protein and the RGS2 naturally when activated will inhibit that cascade and in essence turned it off, so that it can act to prevent long-term vasoconstriction and this was worked it, it was first reported <_____> a few years ago, and not much it had been known about this protein in the heart, the mouse that that doesn't have it has been around for a bit and doesn't develop any spontaneous heart problems that you can see. So, people are figuring that it couldn't be all that important. So, called knockout mouse and the proteins gone everywhere not just in blood vessels. What we found which was first was very striking is that if you take a mouse that doesn't have this RGS2 protein, they look fine. They look perfectly fine and you expose it to high blood pressure. To do that, what we do is put a little suture around the aorta, so the pressure that the heart confronts goes up; it is called aortic constriction, just like aortic stenosis from the band like coarctation. The mice died, they developed a lot of hypertrophy, they dilated within 48 hours and within a week, 40% of them were dead, where as in the controlled group that have this protein that didn't happen at all. We had to make our intervention even milder than usual because when we used our normal model, a 100% were dying. It's very interesting like the Achilles heel. We clearly identified this protein is very important, you wouldn't have known it just to look at the heart all the time, but you did a right thing and suddenly it's very damaging and why this protein because it's been known that protein kinase-G that protein that

Viagra will increase the activity. It is important for stimulating the protein RGS2 to do this sort of protective thing. So, there's a interaction between these systems that we thought might turn out to be very important and indeed one of the other major findings of this paper was that if you take a mouse that has the protein, normal mouse, protein RGS2 and you expose it to this pressure load and they develop hypertrophy and they decompensate and you can give sildenafil, Viagra to these mice during that period of time and there is less hypertrophy very similar to what we had shown and published a few years ago. But if you don't have the RGS2 protein, then not only do you get more hypertrophy, but sildenafil don't do anything, it is ineffective. So, it really pinpoints in this kind of molecular experiment done in an intact heart, intact animal. Pinpoints this key interaction between sildenafil triggering, a kinase, protein kinase-G, this kinase activating this protective protein RGS2, turning off of signal that is damaging, that looks very much like an angiotensin or as I said an endothelin, a kind of stimulatory signal, but it's been triggered by pressure overload, so there is close interaction between these systems.

DR. LARRY KASKEL:

So, can you jump from the mouse to the human and tell me where you would like to see clinical investigations in different types of heart failure patients and where you think Viagra is going to be used prophylactically or even to treat heart failure patients. What do you see 3 to 5 years from now?

DR. DAVID KASS:

There are couple of things that we've done and there are things that are already going on and it <_____> interested and one thing we did early on was to test sildenafil in a just a normal volunteer group of folks here in Baltimore at Hopkins where we examined whether or it could inhibit another kind of stress in this case kind of catecholamine or sympathetic stress, we did that with giving people dobutamine and stimulating their hearts with dobutamine and in mice, we previously shown that you could inhibit that kind of a response with the beta-blocker effect with sildenafil also, and it worked in people. So it's really one of the first bits of evidence that they're really a heart effect, sildenafil in human being. This was published in circulation a few years back and accumulated series of studies from our lab and others, the NIH is now in fact, sponsoring a multicenter clinical trial called the relaxed trial, which people can find that the clinicaltrial.gov, that's multicenter kind of consortium trial and they're studying what we call patients with heart failure in the preserved ejection fraction, with some have called diastolic heart failure. This was really the other half of heart failure where the ejection fraction is over 50%, your heart usually are not dilated, hypertension is an extremely common component. People tend to be more elderly, it's more often in woman and this is the disease that's being first studied in this trial to see whether sildenafil will be effective in both reducing hypertrophy and a sort of secondary markers, but the primary endpoints are really an exercise test, exercise capacity, clinical symptoms, and things like re-hospitalization rates and stuff like that are important, I think clinical endpoint that are being targeted and we're going to get some answers I think fairly soon as to whether or not a hypertensive kind of heart failure much like our mice can be ameliorated by this therapy.

DR. LARRY KASKEL:

Well, Dr. David Kass, thank you very much for coming on the show.

DR. DAVID KASS:

It's my pleasure.

DR. LARRY KASKEL:

My guest was Dr. David Kass at Abraham and Virginia Weiss Professor of Cardiology at the Johns Hopkins University School of Medicine and he spoke to us from Baltimore today.

I'm Dr. Larry Kaskel. You've been listening to Focus on Heart Health on ReachMD, The Channel for Medical Professionals. Please visit our web site at reachmd.com, which features our entire library through on demand podcast, and thank you for listening.