Blocking novel phosphodiesterase pathway can prevent cardiac hypertrophy

MedWire News: Researchers have demonstrated in laboratory experiments that cardiomyocyte hypertrophy can be prevented by treatment with a phosphodiesterase (PDE)1 inhibiting compound similar to sildenafil.

PDEs degrade cyclic guanosine monophosphate (cGMP), which suppresses abnormal cardiomyocyte growth via calcium signaling inhibition. Based on their findings, Chen Yan (University of Rochester, New York, USA) and co-workers believe that PDE levels are increased when there is long-term strain on cardiomyocytes, disturbing the cGMP-calcium pathway and thereby resulting in hypertrophy.

Using immunohistochemical techniques, the researchers found expression of PDE1A and PDE1C isoforms in normal human myocardial tissue explants, whereas only PDE1A was expressed in cultured rat cardiomyocytes. The expression of PDE1A was significantly increased in various rodent myocyte hypertrophy models and in isolated cardiomyocytes cultured with hypertrophic stimuli.

Blocking production of PDE1A expression in cultured rat ventricular myocytes by gene silencing and other loss-of-function techniques prevented phenylephrine-induced hypertrophy, a process that was dependent on cGMP-dependent protein kinase signaling.

Moreover, the PDE1-selective inhibitor IC86340 reduced myocyte hypertrophy in an isoproterenol-induced hypertrophy mouse model, Yan and team report in the journal *Circulation Research.*

The researchers also say that a combination of IC86340 and sildenafil, which inhibits PDE5 and is already in clinical trials for prevention of heart failure, resulted in greater reductions in hypertrophy than either compound alone.

“Our results suggest that a PDE1a inhibitor alone can shut down abnormal cardiac growth, and when combined with [sildenafil] or beta blockers, may do so in more than one way,” Yan commented. Some heart failure patients cannot tolerate beta blockers, so this could allow them to avoid the drugs, or to take them at more tolerable doses. It remains unclear whether a PDE1 inhibitor and sildenafil combination can lead to hypotension, however.

Commenting further, Yan added: “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.

“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 disease like hypertension and atherosclerosis.”

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