Drug therapy for PKU reverses heart damage

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A pricy drug used to treat a rare but well-known genetic disorder may hold wider promise as a treatment for millions of Americans with potentially lethal enlarged hearts, due mainly to high blood pressure, a study from Johns Hopkins shows.

The common denominator in both phenylketonuria (PKU) and cardiac hypertrophy is the chemical tetrahydrobiopterin (BH4). In PKU, this enzyme coworker helps break down the molecule phenylalanine whose buildup is toxic to the brain. In the heart, BH4 helps build the chemical nitric oxide, which is needed for normal heart function and neutralizing toxic chemicals, called oxygen free radicals.

Doctors have used BH4 and diets that exclude phenylalanine for almost a decade to treat PKU, a so-called inborn error of metabolism that if left untreated causes irreversible brain damage. It affects an estimated 15,000 newborns in the United States each year.

Building on what has been known about BH4's activities, the Hopkins team, working with mice, found that treatment with BH4 stabilizes the pumping function of failing, enlarged hearts and dramatically shrinks the muscle size in a relatively short timeframe of just over a month. The team's findings appear in the May 20 edition of the journal Circulation.

"Our results show for the first time the pivotal role played by BH4 in stopping and reversing the weakening and damage done – even in severe cases – to the heart muscle as a result of hypertension and subsequent hypertrophy," says study senior investigator David Kass, M.D., a

professor at the Johns Hopkins University School of Medicine and its Heart Institute. “This key evidence may help us develop new therapies that stop and reverse hypertrophy, preventing the disease from leading to end-stage heart failure and keeping affected individuals from needing heart-assist pumps or a treatment of last resort, the heart transplant.”

Specifically, Kass and Belgian scientist, An Moens, M.D., a postdoctoral cardiology research fellow at Hopkins, fed a daily dose of 5 milligrams of BH4 per 25 grams of body weight to 31 mice whose hearts had been subjected to prolonged experimental hypertension created by constricting their aortas for four weeks.

Before and after treatment, heart function was monitored by several key tests, such as echocardiogram and magnetic resonance imaging, as well as catheters placed within the heart. This was supplemented by post-treatment tissue analysis. Results from this group were compared to another group of 25 mice, also subjected to high blood pressure, who were given placebo instead of BH4 during the same timeframe.

After induced heart failure and five weeks of subsequent therapy, researchers found that BH4-treated mice showed “remarkable improvements,” according to Kass, when compared to placebo-treated animals. Ejection fraction measures of heart pumping function not only stabilized with BH4, but improved, from an average 87 percent before heart failure to roughly 48 percent at the start of therapy, then back to 59 percent at the end of study. Meanwhile, average pumping function in placebo-treated mice showed a perilous decline, from 87 percent to 48 percent, to 35 percent.

Heart weight, as measured by muscle mass, showed similar results. Pressure stress resulted in mice hearts growing from an average 100 milligrams to 290 milligrams before therapy, returning to an average 209 milligrams in the BH4-treated hearts, while placebo-treated hearts grew

increasingly worse, to an average 330 milligrams.

Improvements with BH4 therapy were almost as dramatic in at least three other measurements of organ health, including heart wall thickness, muscle cell size and fibrosis, and lowered chemical production of dangerous free radicals.

“Hearts clearly got better from administering the drug, and our results offer proof of principle that damage to the left ventricle from hypertrophy can be stopped and reversed, providing a potential therapy for the lethal implications of prolonged high blood pressure,” says Moens, now a cardiologist at the University of Antwerp in Belgium.

Kass expects clinical trials to start within a year.

Though no harmful side effects have been observed with BH4 therapy, Kass says, at present, the drug comes with a significant cost drawback. Technologically complex to manufacture, it is currently priced at $375 per 100 milligrams, and individual treatments for PKU have been estimated to cost as much as $33,000 per year. (The drug is currently sold as sapropterin dihydrochlorid, or Kuvan, by its manufacturer, BioMarin Pharmaceuticals.)

Researchers say that even before symptoms of heart failure emerge, such as chronic fatigue and shortness of breath, the heart muscle contracts more strongly to counteract high blood pressure. As muscle action increases, the heart grows and its walls becomes thicker, taking up space inside the heart’s chambers normally reserved for blood. And despite harder muscle contractions, pumping function becomes increasingly weak as the heart can no longer push sufficient blood around the body to meet its energy needs.

According to the American Heart Association, more than 65 million

American adults have high blood pressure, a major risk factor for developing larger-than-normal hearts. Experts say nearly a quarter of the adult population worldwide is estimated to have above- normal blood pressure. Hypertrophy increases by two to three times an adult's risk of suffering cardiovascular disease, including heart failure and sudden cardiac death.

For nearly two decades, Kass and his team have studied the nitric oxide pathway for clues to its overall role in causing heart failure, in the belief that improving its function or lowering its production of oxygen free radicals could prevent or reverse the course of disease.

The Hopkins team says that BH4, whose tissue levels are degraded in stressed hearts from hypertrophy and the muscle's weakened state, works by recoupling the enzyme nitric oxide synthase.

Researchers say this is the only form of the enzyme that functions normally, making more nitric oxide rather than free radicals. Testing of another potent antioxidant, Tempol, did not counter the effects of hypertrophy like BH4 and failed to recouple nitric oxide synthase. "This tells us that BH4's targeted action is key to its benefits," says Kass.

Researchers next plan to look at combined therapies that could improve upon the effectiveness of BH4. Add-on drugs include vitamin C or folic acid, both of which are known to interact with the so-called enzyme cofactor, and researchers plan to monitor closely for the effects of combined therapy on heart function, size and weight.

In related work, Kass and his team have studied Viagra as a possible treatment for hypertrophy in its early stages. However, Kass points out that the Viagra-based research focuses on a different route, the phosphodiesterase-5 chemical pathway, and how it is involved in the process of heart failure. But, he says, BH4 is known to have some effect

on this chemical pathway, so “there could be some combination from these two therapies,” which he also plans to study.

Source: Johns Hopkins Medical Institutions