A missing enzyme conveys major heart protection in pre-clinical work

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Mice born without a certain enzyme can resist the normal effects of a heart attack and retain nearly normal function in the heart's ventricles and still-oxygenated heart tissue, according to a study by researchers at Duke University Medical Center.

The findings raise the possibility of a therapy that could stimulate the growth of blood vessels and limit damage from a heart attack as well as prevent an attack from occurring at all, the scientists said.

Normal mice that went through the same experiment had full heart attacks, suffering damage to their heart pumps and a lack of oxygen in their heart tissues, which are typical effects of a heart attack.

The scientists found that in mice lacking the enzyme GNSOR (or S-nitrosoglutathione reductase) the blood was able to get around the blockage point that normally would cut off blood to the heart because of remarkable capillary growth in these animals.

"There were blood vessels everywhere in these mice born without the enzyme," said Jonathan Stamler, M.D., a Duke professor of medicine and biochemistry and author of the study published in the Proceedings of the National Academy of Sciences online on March 27. "The hope is that this discovery someday could result in a therapy for new blood vessel growth that could be a sort of natural bypass in humans. Perhaps it could also benefit patients with peripheral artery disease, who cannot walk, for example, but who might be able to grow new blood vessels in

their legs."

Stamler said his research group might look into the question of improving peripheral artery disease.

"Normally if you block the major artery to a heart, oxygen tension drops in the tissues - you can't get oxygen to the tissues and they die," Stamler said. "This appears to be a major step forward in the science of stimulating blood vessel growth around the heart, which many people have been trying to do."

"The remarkable aspect of this study is that we show that under conditions of elevated levels of nitric oxide, the heart can grow new blood vessels in the absence of chronic ischemia (inadequate circulation)," said Howard Rockman, M.D., Duke professor of medicine, chief of cardiology at Duke Heart Center and senior author of the study. Chronic ischemia usually occurs in people with severe coronary blockages, and who are at risk for heart attacks, he said.

"A therapy that can increase blood vessel growth in a person with only mild coronary artery narrowing would potentially decrease the amount of heart damage if a heart attack were ever to occur," Rockman said.

Stamler is an expert in nitric oxide (NO) chemistry and S-nitrosylation, a reaction perhaps as common in all cells as phosphorylation, a process that turns on enzymes for biological activity. Stamler's lab has been studying a class of compounds called S-nitrosothiols (SNOs) that regulate S-nitrosylation, and the most prevalent of these is GSNO (S-nitrosoglutathione). Rockman's group has been studying ways to protect the heart from failing, which has lead to a natural collaboration by these two investigators to study the role in S-nitrosylation in cardiac protection.

"We knew that NO had benefits in the heart and helped blood flow and blood vessel growth (angiogenesis), but we didn't know why, so that is what Dr. Rockman and I were exploring in this study," Stamler said.

The scientists also had discovered the enzyme in question, GSNOR, which breaks down GSNO and turns off the S-nitrosylation reactions in cells. Accumulating evidence suggests that the SNOs play various key roles in human health and disease.

"We wondered what the consequences would be if an animal did not have the GSNOR enzyme, so we created mice without the enzyme and studied heart function," Stamler said. "Lo and behold, there were clearly advantages to the animals, but there were no changes in their big blood vessels, no malformations. The answer was that small blood vessels - the capillaries - grew like crazy and established new pathways for blood flow." This was the case in six of the experimental animals studied compared with six normal mice.

Stamler said that the questions to ponder now are how long it takes to grow new blood vessels, and are there are dangerous or undesirable effects anywhere else in the animals?

Potentially, he foresees a day when people whose arteries are in the early stages of blockage could be treated so they can grow new blood vessels to preserve their heart function.

Source: Duke University Medical Center