Novel approach may protect against heart attack injury

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Researchers at The Children's Hospital of Philadelphia have manipulated cell activity that occurs during the interruption of blood flow to strongly protect heart tissue in animal studies. The finding has the potential to become an emergency treatment for heart attack patients, particularly since already existing drugs might be pressed into service to produce the protective effects.

"Reduced blood flow, or ischemia, is a major problem in many organs, where it can lead to cell death and tissue damage," said study leader Peter J. Gruber, M.D., Ph.D., a cardiothoracic surgeon at Children's Hospital and a faculty member of the University of Pennsylvania School of Medicine. "We decided to look for a global approach to protecting heart tissue by inhibiting enzymes that govern how cells respond to ischemia."

Gruber's team published their findings online July 7 in the journal of the Federation of American Societies for Experimental Biology (FASEB). The article will appear in the journal's October 2008 print issue.

The researchers made use of drugs called histone deactylase (HDAC) inhibitors that alter the way DNA is packaged within cells, as well as modifying the function of other proteins. Building on previous work by other researchers, who showed that HDAC inhibitors reduce ischemic injury in the brain, they used the same agents in mice with induced heart damage.

"We found significant and dramatic results in the mice," said Gruber. "The HDAC inhibitors reduced the area of tissue injury, even when delivered an hour after the ischemic event occurred." The size of the myocardial infarction—an area of dead tissue caused by obstructed blood flow, as occurs after a heart attack—was reduced by more than half.

In further investigating how the HDAC inhibitors acted, Gruber's team found they blocked gene pathways that led to cell death and ischemia-induced vascular permeability, the leakage of fluid through blood vessels. They also identified a specific molecule, HDAC4, as the likely HDAC enzyme with the most critical role in affecting how cells respond to ischemia.

An important advantage of their finding, said Gruber, is that a number of HDAC inhibitors are already used in medicine, for treating both cancer and epilepsy, and are well-tolerated. Although much research remains to be done, he added, this raises the possibility that existing drugs, or modified versions of them, might play an important new role in heart disease.

Because the protective effect of HDAC inhibitors may occur even after the initial blockage of blood flow, therapies based on Gruber's research may lead to an emergency treatment following a heart attack. In addition, because open-heart surgery for both children and adults requires a period in which the heart is stopped, such treatment might also protect tissues from the adverse effects of interrupting blood flow during surgery.

For now, said Gruber, the next step for his study team will be to test how HDAC inhibitors work in protecting against ischemic injury in larger animals.

Source: Children's Hospital of Philadelphia