Medical Xpress

Compound developed by scientists protects heart cells during and after attack

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Using two different compounds they developed, scientists from the Florida campus of The Scripps Research Institute (TSRI) have been able to show in animal models that inhibiting a specific enzyme protects heart cells and surrounding tissue against serious damage from heart attacks. The compounds also protect against additional injury from restored blood flow after an attack, a process known as reperfusion.

The study, which was led by Philip LoGrasso, a professor and senior scientific director of discovery biology at Scripps Florida, appears in the February 8, 2013 print edition of *The* Journal of Biological Chemistry.

A heart attack severely restricts blood supply, starving heart cells and surrounding tissue of oxygen, which can cause enormous damage in relatively little time—sometimes in just a few minutes. Known as an ischemic cascade, this drop-off of oxygen results in a sudden crush of metabolic waste that damages cell membranes as well as the mitochondria, a part of the cell that generates chemical energy and is involved in cell growth and death.

Unfortunately, restoring blood flow adds significantly to the damage, a serious medical issue when it comes to treating major ischemic events such as heart attack and stroke. Reperfusion re-invigorates production of free radicals and reactive oxygen species that attack and damage cells, exacerbating inflammation, turning loose white blood cells to attack otherwise salvageable cells and maybe even inducing potentially fatal cardiac arrhythmias.

The new study found that inhibiting the enzyme, c-jun-N-terminal kinase (JNK), pronounced "junk," protected against ischemic/reperfusion injury in rats, reducing the total volume of tissue death by as much as 34 percent. It also significantly reduced levels of reactive oxygen species and mitochondrial dysfunction.

In earlier studies, TSRI scientists found that JNK migrates to the mitochondria upon oxidative stress. That migration, coupled with JNK activation, they found, is associated with a number of serious health issues, including liver damage, neuronal cell death, stroke and heart attack. The peptide and small molecule inhibitor (SR3306) developed by LoGrasso and his colleagues blocks those harmful effects, thereby reducing programmed cell death four-fold.

"This is the same story," said LoGrasso. "These just happen to be heart cells, but we know that oxidative stress kills cells, and JNK inhibition protects against this stress. Blocking the translocation of JNK to the mitochondria is essential for stopping this killing cascade and may be an effective treatment for damage done to heart cells during an ischemic/reperfusion event."

In addition, LoGrasso said, biomarkers that rise during a heart attack shrink in the presence of JNK inhibition, a clear indication that blocking JNK reduces the severity of the infarction.

More information: "Inhibition of JNK Mitochondrial Localization and Signaling is Protective Against Ischemia-Reperfusion Injury in Rats," www.jbc.org/content/early/2012 … M112.406777.full.pdf

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