'Preconditioning' helps protect brain's blood vessels from stroke

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Challenging brain tissue with a small noxious stimulus beforehand gives it a resilience that can lessen damage to blood vessels during a stroke, report researchers at Weill Cornell Medical College in New York City.

"This preconditioning works along the theory of 'what doesn't kill me makes me stronger,'" explains senior researcher Dr. Costantino Iadecola, the George C. Cotzias distinguished professor of neurology and neuroscience and Director of Neurobiology at Weill Cornell, and attending neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"We already knew that preconditioning helps minimize damage to heart tissue -- it's a strategy cardiologists routinely use today. And we know it can help protect brain cells -- neurons -- against stroke damage," Dr. Iadecola says. "Now, besides illuminating mechanisms involved in this process, our new study in mice demonstrates that preconditioning also shields the brain's blood vessels from stroke injury," he explains.

"The hope is that by studying this natural means of self-defense, we might develop potent pharmaceutical means of either preventing stroke or minimizing stroke damage," he says.

The findings appear as a special highlighted paper in the *Journal of Neuroscience*.

According to the National Stroke Association, stroke is the third leading

killer of Americans and the number one cause of adult disability. And yet scientists have still not developed a truly effective means of treating these attacks.

"We knew that preconditioning -- giving the brain a slight noxious stimulus beforehand -- can strengthen brain cells against damage from a larger insult later on. This phenomenon occurs naturally in the human brain," explains lead researcher Dr. Alexander Kunz of the University of Dresden, Germany. Dr. Kunz worked on the study while at Weill Cornell.

But exactly how does preconditioning work, and can it come to the aid of the brain's vasculature, as well"

Based on their prior work, the researchers knew that the protective effect of preconditioning relies on a ubiquitous chemical in the blood called nitric oxide (NO). Injuries to tissues -- such as the ischemia that occurs in stroke -- activate certain enzymes that produce NO. This process also produces destructive, oxidative byproducts called free radicals.

According to the new study, NO combines with these free radicals to produce low levels of another molecule, called peroxynitrite.

"At higher levels, peroxynitrite is a very dangerous chemical for tissues," Dr. Iadecola explains. "But we discovered that at these lower concentrations, it's actually beneficial -- helping to preserve the function of blood vessels in the brain whenever a more toxic event occurs."

Normal mice given an inflammatory toxin called lipopolysaccharide (LPS) 24 hours before an induced stroke -- the preconditioning method used in this study -- had a 68 percent reduction in stroke intensity, the researchers found.

Preconditioning also boosted blood flow in areas of the brain unaffected by the stroke by 114 percent.

However, mice that were genetically engineered so that they could not produce NO gained no such advantage from preconditioning. This suggests that NO and its chemical offspring, peroxynitrite, are essential to this protective process.

"Our study also demonstrates that preconditioning makes blood vessels more resilient against the damage caused by cerebral ischemia, just as it does for neurons," Dr. Iadecola notes. "After preconditioning, the vessels of the brain are impervious to the effects of the stroke and continue to function at a nearly normal level. That's something no one had shown before."

He stressed that it's far too dangerous to give patients peroxynitrite, so the goal here is to figure out how low concentrations of the chemical work their protective magic.

"What cell signaling mechanisms does it activate, for example" If we could find that out, we might be able to create a pharmaceutical mimic that could protect stroke patients," Dr. Iadecola says.

"The real novelty here is that we are looking for a stroke treatment that simply replicates strategies the brain is already using to protect itself," the researcher says. "There's a large population out there at high risk for stroke, and we believe this approach could really help them. It might even help minimize brain tissue damage should any stroke occur."

Source: New York- Presbyterian Hospital