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Tests in mice identify compound that may keep survivors of brain aneurysms from succumbing to stroke

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Johns Hopkins researchers, working with mice, say they have identified a chemical compound that reduces the risk of dangerous, potentially stroke-causing blood vessel spasms that often occur after the rupture of a bulging vessel in the brain.

They say their findings offer clues about the biological mechanisms that cause vasospasm, or constriction of blood vessels that reduces oxygen flow to the brain, as well as potential means of treating the serious condition in humans.

When an aneurysm—essentially a blister-like bulge in the wall of a blood vessel—bursts, blood spills into the fluid-filled space that cushions the brain inside the skull. If a patient survives a ruptured aneurysm, between 20 and 40 percent of the time, this brain bleed, called a subarachnoid hemorrhage, will lead to an ischemic stroke within four to 21 days, even when the aneurysm is surgically clipped.

"We're a long way from applying this to humans, but it's a good start," says Johns Hopkins neurosurgery resident Tomas Garzon-Muvdi, M.D., M.Sc., one of the authors of the study led by Rafael J. Tamargo, M.D., and described in the October issue of the journal *Neurosurgery*.

To conduct their experiments, Garzon-Muvdi and his colleagues took blood from mouse leg arteries and injected it behind their necks to

mimic what happens in a subarachnoid hemorrhage. Then they gave the mice a compound called (S)-4-carboxyphenylglycine (S-4-CPG), a placebo or nothing at all. The mice given S-4-CPG developed less vasospasm, looked better and were more active than those in the other two groups.

The scientists also found concentrations of the drug in the brains of the mice, showing that it was able to cross the often impermeable blood-brain barrier. The researchers chose the compound because it is similar to drugs that have been used in stroke research in rodents. It is not approved for any use in humans.

Garzon-Muvdi explains that when blood vessels break anywhere but the brain, the body's immune cells easily clear the blood cells and their remnants from the area. This is what happens with a bruise, when immune cells rush to the area, and a chemical cascade scavenges and disperses the remnants of excess blood components.

When a blood vessel bursts in the space around the brain, however, the blood is trapped. A subsequent inflammatory response brings key immune system cells into the space, where they secrete the neurotransmitter glutamate outside of the blood vessels where it shouldn't be, promoting dangerous vasospasm in those blood vessels. This can lead to ischemic stroke, the most common type of stroke, caused by a blockage of a blood vessel in the brain. Death or serious disability may result.

The Johns Hopkins researchers say S-4-CPG keeps glutamate "in check," prevents or reduces vasospasm and allows oxygen-filled blood to continue flowing into the brain.

According to the National Institutes of Health, subarachnoid hemorrhage caused by a cerebral aneurysm that breaks open occurs in about 40 to 50

out of 100,000 people over age 30. Patients may die immediately, but those who survive are still at elevated risk for developing an ischemic stroke in the days afterward. These patients are often watched very carefully in the intensive care unit for one to two weeks to search for early signs of vasospasm so that doctors can take steps to prevent or limit damage from a stroke.

In the ICU, doctors can order regular angiograms or ultrasounds to measure blood flow in vessels. If need be, they can increase blood pressure to send blood through vessels faster in the hopes of counteracting the constriction.

A drug to prevent stroke after a serious subarachnoid hemorrhage that follows the rupture of an aneurysm would improve quality of life for patients, Garzon-Muvdi says, and could potentially save millions of dollars in health care costs if patients don't have to endure extensive hospital stays to monitor for a delayed stroke.

Provided by Johns Hopkins University School of Medicine

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