MedicalXpress

Culprit found for increased stroke injury with diabetes

January 23 2011

Strokes are a leading cause of mortality and adult disability. Those that involve intracerebral hemorrhage (bleeding in the brain) are especially deadly, and there are no effective treatments to control such bleeding. Moreover, diabetes and hyperglycemia (high blood glucose levels) are associated with increases in bleeding during hemorrhagic stroke and worse clinical outcomes.

But Joslin Diabetes Center researchers now have identified one key player that contributes to this increased bleeding, a discovery that may pave the way toward treatments that minimize adverse stroke outcomes both for people with pre-existing diabetes and those with hyperglycemia identified at the time of stroke.

Studies in the lab of Joslin Investigator Edward Feener, Ph.D., pinpointed a new mechanism involving a protein called plasma kallikrein that interferes with the normal clotting process in the brain following blood vessel injury with diabetes. Their work is reported online in the journal *Nature Medicine*.

The scientists began by injecting a small amount of blood into the brains of rats with diabetes and of control animals without diabetes. The difference was dramatic—the diabetic animals bled over a much greater area of the brain.

Work in the Feener lab had previously implicated plasma kallikrein in diabetic eye complications. When the experimenters pre-treated the

diabetic animals with a molecule that inhibits the protein's effects, brain damage from the blood injections dropped to levels similar to that in the control animals. Conversely, when pure plasma kallikrein was injected into the brain, it produced little impact on the control animals but rapidly increased major bleeding in the animals with diabetes.

Further studies by the Joslin researchers showed that normalizing blood glucose levels in diabetic animals could block the effect from plasma kallikrein, and that rapidly inducing hyperglycemia in control animals mimicked the effects of diabetes on brain hemorrhage. This suggests that high blood sugar at the time of brain hemorrhage, rather than diabetes per se, is responsible for the increased bleeding.

"Given the prevalence of strokes and the damage they inflict, these findings are exciting because they suggest the possibility that rapid control of blood sugar levels may provide an opportunity to reduce intracerebral hemorrhage, which is a clinical situation that has very limited treatment options," says Dr. Feener, who is also an associate professor of medicine at Harvard Medical School. "This work could have broad implications since about half of patients with acute hemorrhagic stroke have hyperglycemia, whether or not they have pre-existing diabetes."

The work also raises the possibility of developing drugs that target plasma kallikrein and may provide protective measures in people with diabetes or others at high risk for stroke. Such drugs might also prove useful for patients suffering from the more common ischemic strokes, which usually begin as blocked vessels in the brain but can transform into hemorrhages.

Surprisingly, while plasma kallikrein has been studied for decades, the Joslin scientists found that the protein boosts brain bleeding through a previously unknown mechanism—by blocking platelet activation near

damaged blood vessels.

Provided by Joslin Diabetes Center