New stroke clot-buster drug shows 'exciting potential' in mice

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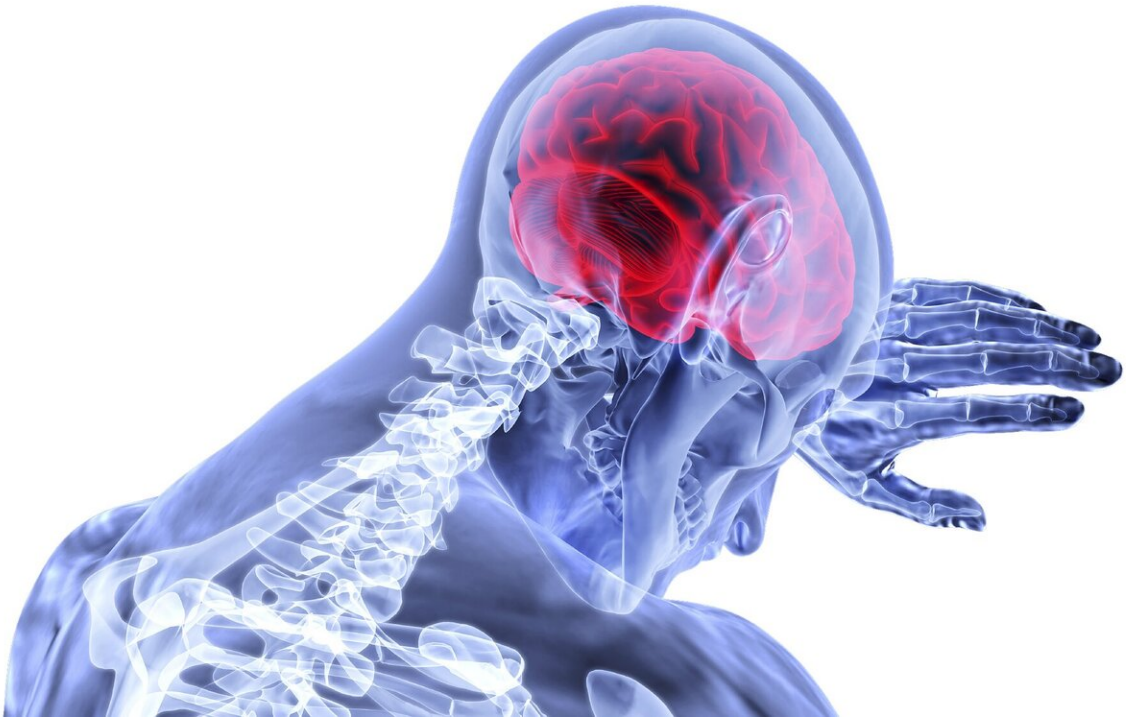

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A novel clot-busting drug formulated and tested by University of Manchester scientists is able to effectively restore blood flow in the brains of mice, opening the door for a safer and more effective stroke treatment.

The compound—an enzyme called caADAMTS13—could dissolve clots

in patients that are resistant to current treatment, according to the study published in the journal *Blood* today.

The study of the novel compound—which is patented by the team—was funded by the British Heart Foundation.

The treatment tPA—currently used by doctors in the acute phase of a stroke—works for many patients; however, it is not able to break down clots which are rich in Von Willebrand Factor (VWF), a large string shaped protein molecule which plays a crucial role in clot formation.

Around 50% of all clots are resistant to tPA and rich in VWF, which tethers circulating clotting cells called platelets at sites of clot formation.

The team examined the efficacy of the drug in mice and compared it with the wildtype variant of the enzyme—called wtADAMTS13—that occurs naturally in the body.

When given 1 hour after a stroke, the new drug significantly reduced VWF by dismantling its long chains—five times more quickly than the wildtype variant achieved.

The drug also prevented a type of white blood cell called a neutrophil from entering the brain tissue starved of blood supply and thought to be a cause of the damage to brain cells.

VWF is also implicated in the recruitment of neutrophils to the site of clot formation, which impacts on the stability of the clot and its likelihood of breaking down into smaller fragments.

Stroke is caused by a reduction in blood flow to the brain—which most frequently results in loss of movement, problems with speech and other symptoms in the patient.

The reduced blood flow is most often caused by a blood clot that lodges in the narrow blood vessels that supply the brain, which means the cells of the brain don't get the energy they need to work.

If blood flow is not quickly restored, the brain cells will die, leading to permanent brain damage, and in severe cases, death.

Current treatments for stroke are focused on removing the blood clot to restore blood flow to the brain. In many patients this treatment works well, and the patients recover function.

However, in many patients the blood clot is not broken down by the drug treatment and symptoms persist.

With tPA, there is an increased risk of hemorrhage occurring if it is given witin about 4.5 hours after the stroke occurred.

Co-author Professor Stuart Allan from The University of Manchester and Co-Director of the Geoffrey Jefferson Brain Research Centre said, "Our novel drug is able break down the blood clots that are resistant to the current treatment tPA. In doing so, more stroke patients could show recovery of function than at present.

"Clearly there is still some way to go, and we need to know if the drug is effective a period of time after the stroke has occurred—with less risk of hemorrhage.

"We are optimistic that we will be able to show this drug can to do that; once we have, we hope to move onto human trials. It's very exciting."

More information: Kieron South et al, Robust Thrombolytic and Anti-Inflammatory Action of a Constitutively Active ADAMTS13 Variant in Murine Stroke Models *Blood* (2021). DOI: 10.1182/blood.2021012787