What is this research about?
Blood clots are necessary to control bleeding; however, too much clotting can be harmful. Heart attacks and stroke, which are leading causes of death around the world, are often caused by clots blocking the flow of blood to the heart and brain.

Blood clots in the body are normally broken up by the clot-dissolving enzyme, plasmin. Plasmin is generated when its inactive form, plasminogen, is activated by an enzyme called tissue plasminogen activator (tPA). Nearly three decades ago, tPA produced in the lab (recombinant tPA; rtPA) was developed as a drug to treat and dissolve potentially harmful clots. Despite saving many lives, rtPA sometimes causes internal bleeding because to be effective it must be given at a very high dose compared to the amount of tPA that is normally in the body. As a consequence, plasmin gets generated throughout the body and not just at the clot location where it is needed.

Researchers at Canadian Blood Services have recently approached this problem from a new angle; instead of engineering better rtPA, they hunted for other molecules surrounding the clot that contribute to breaking it apart. They discovered that a molecule that helps clots form, factor Xa (FXa), can also help clots dissolve. This reversal of its function is triggered when clot-bound FXa is modified by enzymes surrounding the clot. As a result, the clot-busting activity of FXa is localized to the clot it’s bound to, rather than occurring throughout the body. This means that a drug based on FXa might not have the internal bleeding side effects associated with rtPA.

What did the researchers do?
To prolong the clot-dissolving properties of FXa, the group designed a drug called Xai-K by chemically linking FXa to a small synthetic molecule they invented.

To test the clot-dissolving performance of Xai-K, they measured its ability to enhance the clot-busting activity of rtPA. They also examined clot dissolution when Xai-K was added to clots formed in a test tube or given to a mouse in which a clot was induced in a major neck artery. To estimate the risk of bleeding side effects, they drew blood from the treated mice and searched for plasmin activation elsewhere in the body. To evaluate the ability of Xai-K to act as an anticoagulant, the researchers measured the time it took for a clot to form in two mouse models of bleeding with or without Xai-K treatment.

What did the researchers find?
- Xai-K promotes the generation of plasmin by rtPA to help dissolve clots.

In brief...
A novel drug that dissolves clots in mice faster than current drugs may lead to a new and improved clot-buster for patients.
Co-treatment with a modest dose of Xai-K reduced the dose of rtPA needed to fully dissolve a clot in mice by more than 97%.

When given separately, a higher dose of Xai-K dissolved clots in mice faster than rtPA.

Unlike in mice treated with rtPA alone, mice treated with Xai-K did not show signs of clot-dissolving activity throughout the body.

In a mouse model of bleeding, Xai-K also acted as an anticoagulant to slow clot formation.

How can you use this research?
Over the past three decades, heart and stroke patients have seen little progress toward the development of a safer and more effective drug that dissipates clots and restores blood flow. This study introduces an innovative approach to clot dissolution that avoids the detrimental effects of rtPA.

While the research was performed in small animal models and is promising, it needs to be tested in larger animals and in humans. If Xai-K was found to function similarly in humans, it could replace the current two-drug therapy (rtPA and an anticoagulant). Furthermore, clinical trials would be needed to evaluate whether Xai-K is a safe and effective clot-dissolving drug in humans. To that end, patents for Xai-K have been issued in the major global markets (U.S. and Europe).

In the meantime, more studies are underway to determine whether stubborn clots that are resistant to rtPA alone respond to Xai-K treatment, either alone or in combination with rtPA. If Xai-K has good results in clinical trials, it could one day be a breakthrough treatment for blood clots, solving the decades-old riddle of how to overcome the hazardous bleeding side-effect of rtPA.

About the research team: This research was conducted in the laboratories of Dr. Ed Pryzdial, Dr. Christian Kastrup and Dr. William Sheffield. Dr. Pryzdial is a Canadian Blood Services research scientist, an associate director of the Centre for Blood Research and a clinical professor in the department of pathology and laboratory medicine at the University of British Columbia. Dr. Kastrup is an assistant professor in the department of Biochemistry and Molecular Biology, University of British Columbia. Dr. Sheffield is a Canadian Blood Services associate director and senior scientist, and professor in the department of Pathology and Laboratory Medicine, McMaster University. Scott Meixner and Kimberly Talbot are research assistants in the Pryzdial lab at the Centre for Blood Research, and James Baylis and Frank Lee are graduate students in the Pryzdial and Kastrup research groups, respectively.

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