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The Vampire's Gift
Bat Saliva Yields a Promising Treatment for Stroke Victims
Robert Locke

Vampire bats are among the most reviled of nature's creatures. They really do feed on blood, and evolution has made them extraordinarily adept at it. Yet that propensity, which most people hate and fear, may well provide a powerful new drug that could save lives and limit brain damage among stroke victims.

An enzyme originally extracted from the saliva of the common vampire bat (*Desmodus rotundus*) has shown enormous potential in experiments with mice. It is more than 150 times more potent at dissolving blood clots, such as those that cause most strokes, than the only clot-busting treatment that is currently available.

More importantly, said Dr. Robert Medcalf, who led the research team at Australia's Monash University, the vampire enzyme focuses so tightly on blood clots that it appears to do virtually nothing in the body except dissolve clots. That means, he said, that it could be much safer than drugs used today and could be used over a much longer time. Those possibilities have yet to be demonstrated in humans, but clinical trials are under way in Europe and Australia and will begin soon in the United States. (Medcalf is not involved in the trials.)

The story was a media sensation. "For someone who's never had his name in a newspaper before, suddenly I was in just about every newspaper in the world. It was kind of scary in a way," Medcalf said. "Of course," he added, "it got all the publicity mainly because it came from the vampire bat."

The enzyme is called Desmodus rotundus salivary plasminogen activator, or DSPA. It is genetically related to t-PA, the human 'tissue-type plasminogen activator' that is very widely used to dissolve clots in heart-attack victims and is the only approved clot-buster for use against ischemic stroke. Such strokes, by far the most common type, occur when a blood clot or clogged artery keeps blood from reaching the brain.

T-PA has been proven effective against strokes, but only under such limited circumstances that it cannot be given to the vast majority of stroke victims. In fact, t-PA can only be administered within the first three hours of the stroke's onset. Later use can actually increase brain damage. DSPA may, based on these initial results, be given safely for an extended period after a stroke occurs. Current clinical trials with human patients are testing the effectiveness of DSPA up to nine hours after stroke onset.

Plasminogen activators are produced by all vertebrates. (Both human t-PA, approved for use against heart attacks in 1987, and DSPA are synthetic enzymes copied from the original with recombinant-DNA techniques.) These enzymes dissolve clots through a biochemical chain reaction. They convert plasminogen, an inactive enzyme circulating in the blood, into plasmin – the real clot buster. Plasmin attacks fibrin, a hair-like protein around which blood clots form: Destroy the fibrin, the clot dissolves, and blood flow is restored.

So far, so good. Medcalf said t-PA has been very effective against heart attacks. However, it works not just on the damaging blood clot but on the entire circulatory system and can cause bleeding elsewhere. With heart attacks, that generally is an acceptable risk. But for strokes, if you restore blood flow but initiate bleeding in the brain, you can kill more brain cells.

Several years ago, Medcalf said, scientists discovered some remarkable and unsuspected aspects of t-PA. Using a process called 'knockout technology,' they produced mice that had no t-PA. These mice, it turned out, 'lost their memory. T-PA has an important role in the brain: It promotes memory formation and visual processing.'

Then, however, they found 'the dark side to t-PA,' Medcalf said. Scientists used various chemicals to overstimulate the brains of normal mice, which caused the brain cells to die. In mice without t-PA, however, overstimulation did not kill brain cells. Inject those same mice with t-PA, and the cells die.

'We repeated these experiments that were done in the 1990s, and it demonstrates quite clearly that t-PA promotes this [brain-cell] death.' DSPA, the biochemical gift from the vampire, does not. 'That,' Medcalf said, 'is a pretty jolly good finding, actually.'

Wolf-Dieter Schleuning, chief scientific officer of the German biotech firm PAION GmbH in Berlin, is a co-author (with Medcalf, Gabriel Liberatore and Andre Samson of Monash and Chris Bladin of Eastern Melbourne Neuroscience at Box Hill Hospital) of the DSPA report published by the American Heart Association journal Stroke in February 2003. Schleuning has worked with DSPA since the 1980s, although he notes that it was identified as a plasminogen activator in 1966 by Christine Hawkey of the Zoological Society of London.

Schleuning was at Rockefeller University in New York about 20 years ago trying to genetically engineer a clone of t-PA, when a competitor beat him to it. So, he said, "I looked for alternatives to t-PA with an improved pharmacological profile and came across Hawkey's work."

Using DSPA genetic samples provided by researcher Alejandro Alagon of Mexico, he produced the synthetic enzyme and found the first strong hints of its medical potential.

The rather amazing ability of vampire bat saliva to dissolve blood clots was first noted, Schleuning said, by Brazilian researchers in the 1930s. "This bat," Medcalf said, "has figured out an amazing way of handling blood. It's a dramatic contrast to t-PA. It really needs fibrin to be present. If there is no blood clot, the DSPA doesn't do anything at all."

Once DSPA encounters fibrin, however, its clot-busting ability kicks in with a vengeance – far more powerfully than t-PA. Medcalf said DSPA's activity increases about 13,000-fold in the presence of fibrin, compared to a 72-fold increase in t-PA activity.

Based on the animal experiments, DSPA is a very effective clot-buster and does not promote brain-cell death. Whether DSPA also limits bleeding into the brain, however, must still be demonstrated in human stroke patients, Medcalf notes. But DSPA's ability to tightly target nothing except fibrin 'gives people a warm feeling that these clinical trials might turn out nicely.'

ROBERT LOCKE is Managing Editor of Bat Conservation International.

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