Venom makes a beeline through blood brain barrier, delivering medication

December 6 2021, by Gina Wadas

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The blood-brain barrier is an essential and meticulous protector of the human body. This highly selective gatekeeper of interlocking endothelial cells forms tight junctions, shielding vulnerable brains cells from toxins

in the bloodstream. However, this also means that the BBB blocks many compounds from entering the brain, making the delivery of drugs via the bloodstream challenging.

To address this, Johns Hopkins University researchers are testing melittin, the main protein compound in honeybee venom, to unlock these tight junctions and enable delivery of drugs into the brain.

"Our early results indicate that melittin can disrupt the integrity of the blood-brain barrier by reversibly opening cell junctions," said Peter Searson, core member at the Institute for NanoBioTechnology and a professor in the Department of Materials Science and Engineering. "This provides a novel approach for delivering drugs into the brain, particularly large therapeutics like antibodies and nanoparticles."

Study results were published in *Biomaterials*.

To explore melittin's use, Searson joined forces with research groups led by Kalina Hristova, core member at the INBT and materials science and engineering professor, and Piotr Walczak at the University of Maryland School of Medicine.

The team first tested melittin in a tissue-engineered BBB model developed by Raleigh Linville, a former biomedical engineering Ph.D. student who is now a post-doctoral associate at MIT. They identified the effects and mechanisms of junction disruptions across different melittin doses. Critical to the study was identifying doses that were not toxic to neurons and allowed reversible disruption of tight junctions. They then applied their findings in a mouse model using real-time magnetic resonance imaging to show reversible and safe opening of the BBB.

Melittin is a widely studied membrane active peptide, or MAP, that interacts with cell membranes. Researchers are interested in melittin and

other MAPs from animal venom because of their potential therapeutic applications, particularly for anti-cancer approaches as high concentrations of melittin can be toxic to cancer cells. Interestingly, given their short amino acid chemical composition, MAPs provide engineers with room to modify and optimize their design for specific applications.

"There is a lot of customization with MAPs, so we have a lot of design space to explore. We hope to further optimize peptide design with specific biochemical properties that may enable safe and reversible opening of the blood-brain barrier," said Linville.

The researchers are now looking ahead towards developing this technology. They hope to test optimal doses in larger models, as brain size and blood volume between mouse and human brains differ. Also, they hope to apply this approach in a diseased mouse model to demonstrate therapeutic benefit. Lastly, given the interdisciplinary approaches used, these studies hope to improve the relevance of tissue-engineered BBB model to better predict outcomes in mice and eventually human patients.

"Melittin has been studied for many decades. Researchers have long believed that melittin can be useful for drug delivery, and the current work vindicates this belief," said Hristova.

More information: Raleigh M. Linville et al, Reversible blood-brain barrier opening utilizing the membrane active peptide melittin in vitro and in vivo, *Biomaterials* (2021). DOI: 10.1016/j.biomaterials.2021.120942

Provided by Johns Hopkins University