Sea snail, human insulin hybrid could lead to better diabetes treatments

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Helena Safavi, left, helps her colleague, José Rosado from Maputo, Mozambique, sort cone snails collected by scuba divers near the Solomon Islands in the south Pacific. The scientists set up a mobile lab on the diving ship to dissect and preserve the biological samples. Credit: Adam

Nearly a century after insulin was discovered, an international team of researchers including University of Utah Health scientists report that they have developed the world's smallest, fully functional version of the hormone, one that combines the potency of human insulin with the fast-acting potential of a venom insulin produced by predatory cone snails. The finding, based on animal studies, could jumpstart the development

of insulin treatments capable of improving the lives of those with diabetes.

"We now have the capability to create a hybrid version of insulin that works in humans and that also appears to have many of the positive attributes of cone snail insulin," says Danny Hung-Chieh Chou, Ph.D, a U of U Health assistant professor of biochemistry and one of the study's corresponding authors. "That's an important step forward in our quest to make diabetes treatment safer and more effective."

The study appears in *Nature Structural and Molecular Biology*.

As cone snails slither across coral reefs, they are constantly on the prowl for prey. Some of these fish-hunting species, such as Conus geographus, release plumes of toxic venom that contain a unique form of insulin into the surrounding water. The insulin causes fish blood glucose levels to plummet, temporarily paralyzing them. As the fish flounders, the snail emerges from its shell to swallow the subdued victim whole.

In earlier research, Chou and colleagues discovered that this venomous insulin had many biochemical traits in common with human insulin. Plus, it appears to work faster than the swiftest-acting human insulin currently available.

Faster-acting insulin would diminish the risk of hyperglycemia and other serious complications of diabetes, says Helena Safavi, Ph.D., a study co-author and an assistant professor of biomedical sciences at the University of Copenhagen in Denmark. It also could improve the performance of insulin pumps or artificial pancreas devices, which automatically release insulin into the body as needed. "We want to help people with diabetes to more tightly and rapidly control their blood sugar ," she says.

In pursuit of their goal, the researchers found that insulin derived from cone snail venom lacks a "hinge" component that causes human insulin to aggregate or clump together so it can be stored in the pancreas. These aggregates must break up into individual molecules before they can begin to work on blood sugar, a process that can take up to an hour. Since cone snail insulin doesn't aggregate, it is in essence primed and ready to work on the body's biochemical machinery almost immediately.

Intrigued, the researchers began to investigate ways to transform the insulin that cone snails use as a weapon into a different form: one that people who have Type-1 diabetes could use to rapidly restore equilibrium in their bodies.

"We had the idea of making human insulin more snail-like," says Safavi, who is also an adjunct professor of biochemistry at U of U Health. "So, we sought to basically take some of the advantageous properties from the snail and graft them onto the human compound."

The researchers thought this was possible because cone snail insulin essentially has the same basic structure or "backbone" as human insulin. However, they faced a dilemma: the snail's insulin is far less potent than human insulin. In fact, the researchers suspect that humans would require 20 to 30 times more of the cone snail insulin to lower their blood sugar levels.

A scuba diver holds a live specimen of Conus geographus collected during a night dive. Scientists used insulin extracted from this snail's venom to produce a hybrid form of fast-acting insulin that could work in humans. Adam Blundell. Credit: Adam Blundell

In this new study, Chou and colleagues sought to overcome these problems. First, they used structural biology and medicinal chemistry techniques to isolate four amino acids that help the snail insulin bind to the insulin receptor. Then, they created a truncated version of a human insulin molecule without the region responsible for clumping.

The team integrated modified versions of these amino acids into the human molecule in hopes of creating a hybrid that does not clump and binds the human insulin receptor with high potency.

In tests with laboratory rats, this hybrid insulin molecule, which the scientists call "mini-insulin," interacted with insulin receptors in ways that cone snail insulin doesn't. These new interactions bound mini-insulin to insulin receptors in the rat's body just as strongly as normal human

insulin would. As a result, mini-insulin had the same potency as human insulin but acted faster.

"Mini-insulin has tremendous potential," Chou says. "With just a few strategic substitutions, we have generated a potent, fast-acting molecular structure that is the smallest, fully active insulin to date. Because it is so small, it should be easy to synthesize, making it a prime candidate for the development of a new generation of insulin therapeutics."

More information: A structurally minimized yet fully active insulin based on cone-snail venom insulin principles, *Nature Structural and Molecular Biology* (2020). DOI: 10.1038/s41594-020-0430-8 , www.nature.com/articles/s41594-020-0430-8

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