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Sea anemone venom-derived compound effective in anti-obesity studies

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Scientists at UC Irvine reported this week that a synthetic compound ShK-186, originally derived from a sea anemone toxin, has been found to enhance metabolic activity and shows potential as a treatment for obesity and insulin resistance.

The findings published the week of May 27 in the *Proceedings of the National Academy of Sciences* reveal that ShK-186 selectively blocks the activity of a protein that promotes inflammation through the Kv1.3 potassium channel. The study presents the first evidence that the drug candidate – which in March showed positive results in a Phase 1 safety clinical trial – may also work in an anti-obesity capacity.

UC Irvine licensed ShK-186 to Kineta Inc., a Seattle based biotechnology company in 2009; it is the company's lead drug candidate. Kineta is developing this compound to treat autoimmune diseases, such as multiple sclerosis, psoriatic arthritis and lupus. It has also licensed the use of ShK-186 for the treatment of metabolic syndrome and obesity.

Potassium channels regulate cell membrane potential and control a variety of cellular processes. Earlier studies using mice that lack Kv1.3, a potassium channel gene, suggested that Kv1.3 regulated body weight and the basal metabolic rate.

In the present study, Dr. George Chandy and his colleagues evaluated ShK-186 because it has high selectivity for the Kv1.3 target, a favorable pharmacokinetic profile, and meets the qualities of an industry-standard

drug. In tests on obese mice that ate a high-fat, high-sugar diet, ShK-186 therapy reduced weight gain, white fat deposits, fatty liver, blood cholesterol and blood sugar by activating calorie-burning brown fat, suppressing inflammation of white fat and augmenting liver function. The compound had no effect on mice that ate a standard chow diet, suggesting that the obesity-causing diet triggers the expression of the Kv1.3 target.

"This is a new twist in a sustained journey of discovery made over the 30 years that charts the course for expeditious translation to humans who suffer from potentially lethal consequences of metabolic syndrome and autoimmune diseases," said Chandy, professor of physiology & biophysics at UC Irvine and a Kineta scientific advisor. "We evaluated ShK-186 in an obesity model because it has high selectivity for the Kv1.3 target, a favorable pharmacokinetic profile, and meets the qualities of an industry-standard drug."

"These data are quite exciting and strongly support the notion that inhibition of the Kv1.3 channel provides a highly effective method for managing obesity and its associated metabolic abnormalities. The results obtained with ShK-186 are consistent with what one would expect to see with a potent inhibitor of this channel. While additional studies are needed, the potential clinical relevance of this work is enormous, since a significant number of people are afflicted with obesity and its associated complications, and no Kv1.3 inhibitor, as a drug candidate for obesity, has reached the clinic until now," said Dr. Gary V. Desir, professor of medicine at Yale University, and an expert on the Kv1.3 channel's role in renal potassium secretion and glucose metabolism. Dr. Desir was not involved with the study.

"Knowing that ShK-186's unique mechanism of action may have broad utilization across multiple therapeutic disciplines, such as autoimmune diseases and now obesity, further adds to the potential of this compound.

This study also shows how medical progress can be made through academic and private sector partnerships," added Charles Magness, Ph.D., President and CEO of Kineta.

According to the World Health Organization (March 2013), obesity worldwide has nearly doubled since 1980. In 2008, more than 200 million men and nearly 300 million women, or 11 percent, were obese. Diabetes is expected to affect roughly 300 million humans by 2030 with an economic cost of $260 billion annually.

Sanjeev Kumar Upadhyay, Kristin Eckel-Mahan, M. Reza Mirbolooki, Indra Tjong, Galina Schmunk, Briac Halbout, Brian Pedersen, Emiliana Borrelli, Ping H. Wang, Jogeshwar Mukherjee, and Paolo Sassone-Corsi with UC Irvine; Amanda Koehne and Stephen M. Griffey with UC Davis; and Shawn Iadonato with Kineta contributed to the study, which received support from the National Institutes of Health, a UC Irvine bridge grant, and the Ko Family Foundation.

More information: Selective Kv1.3 channel blocker as therapeutic for obesity and insulin resistance, www.pnas.org/cgi/doi/10.1073/pnas.1221206110

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