Missing Molecule Raises Diabetes Risk in Humans

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Researchers at the University of California, San Diego School of Medicine and Rady Children's Hospital-San Diego say an evolutionary gene mutation that occurred in humans millions of years ago and our subsequent inability to produce a specific kind of sialic acid molecule appears to make people more vulnerable to developing type 2 diabetes, especially if they're overweight.

The findings are published in the Feb. 24 online edition of *The FASEB Journal*, a publication of the Federation of American Societies of Experimental Biology.

Corresponding study author, Jane J. Kim, an assistant professor in the UCSD Department of Pediatrics, a member of the Pediatric Diabetes Research Center and Rady Children's Hospital-San Diego, said the findings represent the first documented evidence linking the non-human sialic acid production to insulin and glucose metabolism problems associated with diabetes.

"It opens up a new perspective in understanding the causes of diabetes," said Kim. "Given the global epidemic of obesity and diabetes, we think that these findings suggest that evolutionary changes may have influenced our metabolism and perhaps increased our risk of the disease."

Type 2 diabetes is caused by both genetic and environmental factors, such as a fatty diet and lack of exercise, that result in progressively dysfunctional pancreatic beta cells, elevated blood sugar levels due to insulin resistance and eventual health complications, sometimes fatally so. Diabetes is an expanding problem, nationally and globally. In the United States, more than 25 million adults and children – almost nine percent of the population – have diabetes, according to the American Diabetes Association. Another 79 million Americans are estimated to be prediabetic. Worldwide, roughly 285 million people are believed to have the disease.

Sialic acids are molecules found on the surfaces of all animal cells, where they act as vital contact points for interaction with other cells and with their surrounding environment. All mammals studied to date produce two types: N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc).

Humans are an exception. For reasons lost in the mists of evolution, a mutation in a gene called CMAH occurred about 2 to 3 million years ago, inactivating an enzyme in humans that catalyzes

production of Neu5Gc by adding a single oxygen atom to Neu5Ac. This discovery was made earlier by UCSD scientists, led by Ajit Varki, MD, professor of medicine and cellular and molecular medicine at UC San Diego School of Medicine. They then developed a mouse model with a human-like defect in the CMAH gene.

Kim's group compared mice with a functional CMAH gene to mice with a human-like mutation in CMAH. Both groups of mice were fed a high-fat diet. Mice in both groups became obese and developed insulin resistance. However, only mice with the CMAH gene mutation experienced pancreatic beta cell failure. Pancreatic beta cells normally make and release insulin, a hormone that controls blood sugar levels.

Kim said the findings help refine understanding of why obese humans appear to be particularly vulnerable to type 2 diabetes, and also suggest that current animal models used to study diabetes may not accurately mirror the human condition. In clinical terms, she said further research to determine how sialic acid composition affects pancreatic beta cell function may reveal new strategies to preserve the cells, improve insulin production and prevent diabetes.

"It's exciting to see the real-life significance of our discovery of the human CMAH mutation, said Varki, who is also co-director of the Glycobiology Research and Training Center and the Center for Academic Research and Training in Anthropogeny, both at UC San Diego. "This shows yet again that research in fundamental processes of biology and evolution can yield unexpected dividends for understanding human disease."

Co-authors of the study are Sarah Kavaler and Alice Jih, UCSD Department of Pediatrics and Rady Children's Hospital-San Diego; Hidetaka Morinaga and WuQuiang Fan, UCSD Department of Medicine; Maria Hedlund, UCSD departments of Medicine and Cellular and Molecular Medicine and UCSD Glycobiology Research and Training Center.

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