Researchers clarify function of glucose transport molecule

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Researchers at the David Geffen School of Medicine at UCLA have solved the structure of a class of proteins known as sodium glucose co-transporters (SGLTs), which pump glucose into cells. These transport proteins are used in the treatment of chronic diarrhea via oral rehydration therapy, saving the lives of millions of children each year. The solution of the SGLT structure will accelerate development of new drugs designed to treat patients with diabetes and cancer.

Led by Jeff Abramson and Ernest Wright of the UCLA Department of Physiology, the research team produced an "atomic snap shot" of an SGLT protein. Using a specialized technique known as X-ray crystallography, they and their team of post-docs and students generated the first high-resolution, three-dimensional picture of a glucose transport protein. The research is published in today's online edition of the journal *Science*.

"This was a very challenging study that required innovation at each step of the process," said Abramson. "We literally had to invent new approaches to entice the protein into a crystal and then spent years optimizing these crystals to reach a quality suitable for visualization by X-rays. This would not have been possible without high-throughput protein production and purification capabilities."

A tantalizing observation made during the determination of the glucose transporter structure was the possibility for structural similarities with a previously crystallized neurotransmitter transporter molecule. Exploiting

these similarities, along with computer modeling of structural dynamics, the researchers obtained the first atomic-level evidence for the mechanism underlying transport of glucose and neurotransmitters (such as serotonin) into cells. These results provide a fundamental understanding of how membrane proteins function in a dynamic manner.

Pharmaceutical companies already have extensive clinical trials underway to evaluate the use of inhibitors targeting SGLT1 and SGLT2 proteins to control blood glucose levels in diabetic patients by blocking intestinal glucose absorption and increasing glucose excretion into the urine. The UCLA findings will dramatically enhance the ability to rationally design these drugs.

In ongoing work, Wright and Abramson are examining the manner in which inhibitors of the transporter proteins modulate function with the goal of facilitating better drug design for the treatment of diabetes, obesity, and cancer.

Source: University of California - Los Angeles