Identification of the First Human Glucose Sensor: A New Target for Treatment of Diabetes, Obesity, and Related Metabolic Disorders

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BACKGROUND

Energy intake, expenditure and storage in humans and other organisms are highly regulated and disturbances lead to severe problems such as obesity and diabetes. Glucose is a major unit of currency in energy metabolism and the body goes to great lengths to regulate the level of glucose in the blood to ensure adequate delivery to the brain, muscle and other cells and tissues of the body. The cells of the pancreas can directly sense variations in the blood glucose concentrations, but glucose sensors are distributed throughout the body to modulate pancreatic and other responses. Until now, the molecular identity of these glucosensors has largely been unknown.

INNOVATION

Dr. Ernest Wright of UCLA and his colleagues have molecularly characterized the first glucose sensor in mammalian cells. Unexpectedly, this sensor, hSGLT3, is present in the plasma membrane of cholinergic neurons. The glucosensor responds to variations in extracellular glucose concentrations through changes in the membrane potential, indicating that glucose acts as a signaling molecule. These glucose-induced electrical changes may, in turn, modulate the action of other cells via electrical or hormonal signals. Possibly the hSGLT3 glucosensor is signaling the hypothalamus, which is known to respond to a number of metabolic signals, including leptin, ghrelin, insulin, fatty acids and glucose. The identification of the hSGLT3 glucosensor in neurons supports the hypothesis that the hypothalamus not only regulates food intake and body weight, but also plays a primary role in regulating glucose homeostasis.

APPLICATIONS

Obesity and diabetes are two major interrelated health risks. New strategies and drugs are essential to manage these and other related metabolic disorders. Pharmacologic agents that specifically modulate the activity of the hSGLT3 glucosensor may be developed as novel therapeutic treatments.

In another application, the hSGLT3 glucosensor may represent a new target for the pharmacologic treatment of irritable bowel syndrome. In view of the well-recognized importance of glucose in regulating intrinsic enteric reflexes after a meal, the presence of the hSGLT3 glucosensor in enteric cholinergic neurons may represent a new target for influencing the motility of the gastrointestinal tract in disease states.

ADVANTAGES

The electrogenic activity of hSGLT3 provides a novel mechanism for glucose sensing by neurons, muscle and neuroendocrine cells. This previously unknown signaling pathway for the modulation of glucose homeostasis may now be exploited to develop new pharmacological agents to treat type II diabetes, obesity, insulin resistance and related metabolic disorders. As a membrane-bound protein, hSGLT3 would likely be an accessible drug target.

Potential lead compounds are available: the natural product phlorizin and other glucosides, e.g.rhapontin, are specific inhibitors of SGLT3 and other members of the sodium/glucose cotransporter gene family (SGLTs). Additional studies are in progress to identify specific blockers of SGLT3. Of particular interest, the investigators have synthesized a new high-affinity agonist for SGLTs with a 10-fold higher affinity than glucose.

STATE OF DEVELOPMENT

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OTHER INFORMATION

KEYWORDS

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CATEGORIZED AS

- **Medical**
  - Disease: Metabolic/Endocrinology
  - Therapeutics

RELATED CASES

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The UCLA researchers and their colleagues characterized the function and tissue distribution of a protein encoded by the SGLT3/SLC5A4 gene, which is a member of the sodium/glucose transporter gene family (SLC5). Expression studies indicate that human SGLT3 (hSGLT3) is expressed in human skeletal muscle and small intestine, particularly in cholinergic neurons in the submucosal and myenteric plexuses. Functional studies using the Xenopus laevis oocyte expression system showed that hSGLT3 was incapable of sugar transport, even though it is membrane-bound. Electrophysiological assays further revealed that glucose caused a specific, phlorizin-sensitive, Na+-dependent depolarization of the membrane potential. Uptake assays under voltage clamp showed that the glucose-induced inward currents were not accompanied by glucose transport. These results suggest that SGLT3, although a family member of glucose transporters, is a glucose sensor in the plasma membrane of cholinergic neurons, skeletal muscle, and other tissues.

RELATED MATERIALS

- A glucose sensor hiding in a family of transporters. Proc. Nat. Acad. Sci. USA 2003 Sep; 100(20): 11753-11758.
- News and Views: Rethinking the central causes of diabetes. Nature Med. 2003 Jun; 9(6): 645-647
- Common mechanisms of inhibition for the Na+/glucose (hSGLT1) and Na+/Cl-/GABA (hGAT1) cotransporters. 2001 British Journal of Pharmacology 2001 Oct; 134(3): 484-495.
- Glycoside binding and translocation in Na(+)-dependent glucose cotransporters: comparison of SGLT1 and SGLT3. J. Membrane Biology 2000 Jul 15;176(2): 111-117.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	7,238,708	07/03/2007	2004-096

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- A New PET Probe for Glucose Transport and Metabolism

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