GLUCOSE TRANSPORT FACILITATORS (GLUT proteins) mediate the transport of glucose and other monosaccharides into and out of mammalian cells and thus play a pivotal role in maintaining blood glucose concentrations in a normal range between 4.5 and 6 mM (14). In addition, GLUT proteins are involved in the glucose-sensing machinery; e.g., in pancreatic β-cells, GLUT2 participates in the regulation of glucose-stimulated insulin secretion. Screening the literature results in a large number of publications on the insulin-regulated glucose transporter GLUT4 (7, 8), which is without question, together with GLUT2, a prominent transporter required for maintenance of glucose homeostasis and affected in diseases such as obesity and type 2 diabetes. However, since the late 1990s, we have known that the whole family of human GLUT proteins consists of 14 members (9, 14, 17, 18), indicating that glucose delivery into cells is a process of considerable complexity. The various transporters exhibit different substrate specificities, kinetic properties, and tissue expression profiles (Fig. 1). The fact that certain tissues and cells express two or even more glucose transporter isoforms indicates that the organism developed a backup system ensuring adequate energy supply. For instance, spermatozoa and their precursor cells express several transporters: GLUT3, -5, -8, and -9, which guarantees fuel supply and function of spermatozoa even when hexose transport via one of the GLUT proteins is impaired.

A series of minireviews in this issue on facilitative hexose transporters summarizes earlier and recent developments defining the specific roles of GLUT3, GLUT5, and GLUT7 in normal and morbid states. GLUT3 is a high-affinity glucose transporter, GLUT5 is a specific fructose transporter, while GLUT7 transports both glucose and fructose with high affinity.

Glucose is the obligate energetic source for the mammalian brain, and it is assumed that the majority of cerebral glucose utilization fuels neuronal activity via oxidative metabolism (15). GLUT1 is located in the microvascular endothelial cells of the blood-brain barrier and delivers glucose from the circulation to the brain, and GLUT3 mediates glucose transport into neurons. However, GLUT3 is also expressed in other cells (sperm and pre- and postimplantation embryo, circulating white blood cells, and carcinoma cells) where it triggers the specific requirements for glucose. The review by Simpson et al. (16) discusses the properties for GLUT3, its expression, subcellular distribution, and regulation and focuses on features that make GLUT3 unique within the GLUT family.

GLUT5 is the best-characterized fructose transporter and is expressed in several cell types and tissues (intestine, testis, kidney, skeletal muscle, fat, and brain). These days, GLUT5 is of tremendous interest because total fructose consumption has increased dramatically, e.g., in the United States from ~20 to ~80 g/day in the last 20–30 years (2). Increased fructose consumption, in particular as carbonated beverages, has been attributed to participate in the increased prevalence of obesity and type 2 diabetes. Fructose is absorbed in the jejunum and transferred (13) through the apical membrane of epithelial cells into the portal circulation (3). In the liver, fructose is phosphorylated to fructose 1-phosphate and converted to glycerol 3-phosphate for the synthesis of glycerol (6) or metabolized to acetyl-CoA and incorporated into fatty acids, while only a small portion is converted into glucose (1). Therefore, the preferential entry of fructose into lipogenesis might contribute to the effects of fructose to induce hyperlipidemia and to increased serum triglyceride levels (10). Several members of the GLUT family are able to transport fructose (GLUT2, -5, -7, -8, -9, -11, and -12), but only GLUT5 exclusively transports fructose. The review by Douard and Ferraris (5) focuses on alterations of GLUT5 expression and fructose uptake in diabetes, hypertension, obesity, and inflammation. It also gives important information on the role of GLUT5 during intestine development, metabolic disturbances, and cancer.

A closely related protein of GLUT5 is GLUT7, bearing 53% identity. It is a high-affinity transporter for glucose and fructose and is mainly expressed in the brush-border membrane of the small intestine and in the colon (11). Other intestinal glucose transporters, SGLT1, GLUT2, and GLUT5 are expressed in the jejunum, whereas the distribution of GLUT7 is limited to the distal region of the small intestine, the ileum, which does not contain high concentrations of glucose and fructose. This observation suggested that GLUT7 does not play a major role in taking up glucose and fructose from the diet but that it may be important toward the end of a meal when luminal concentrations of hexoses in the ileum are low (11). Comparison of sequence alignments and mutation studies on GLUT7 identified a specific hydrophobic residue in transmembrane domain 7 that determines the specificity for fructose (12). Several mutational studies mainly performed in GLUT1 and GLUT4 lead to the concept that GLUT proteins undergo specific conformational changes during the passage of the hexose. It is believed that its binding to the outward-facing binding site induces a conformational alteration that moves the substrate through the pore of the GLUT protein. Thereafter, the substrate is released from the inward-facing binding site to the cytoplasm, and the transporter undergoes the reverse conformational change (9). The review on GLUT7 by C. Cheeseman (4), who discovered GLUT7 as the latest member of the GLUT family, introduces the hypothesis that GLUT proteins may have a selectivity filter at the exofacial site which helps to determine which substrate is transported.

REFERENCES

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