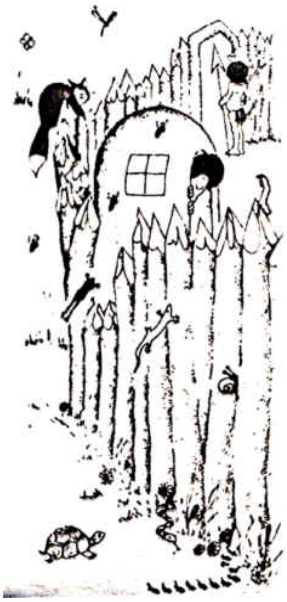
Glucose Transport Proteins

Sugar Transport over Cell Membranes



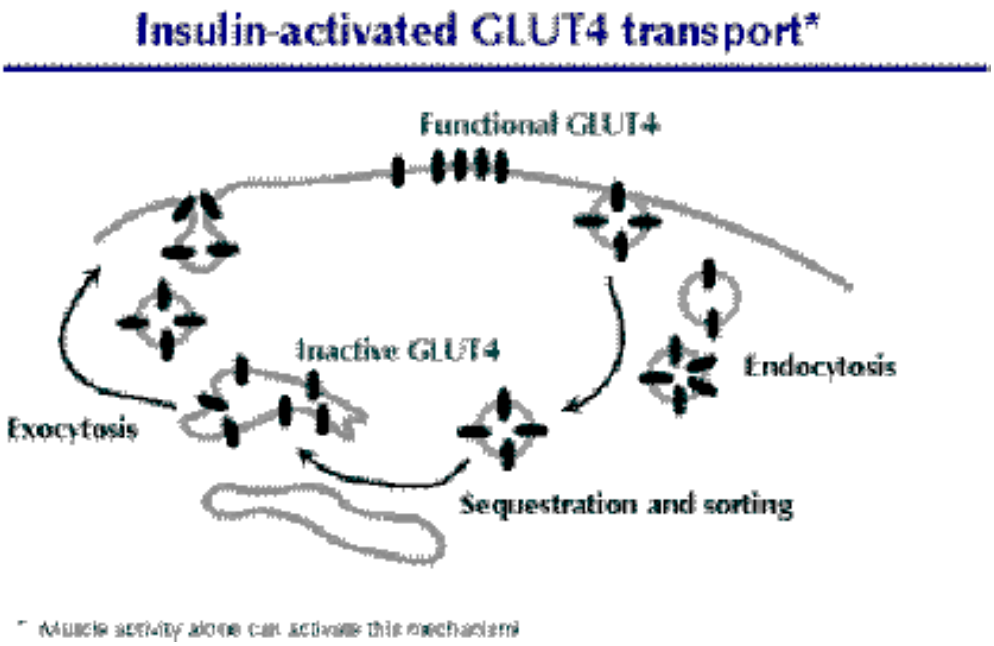
As you have certainly learned earlier, the outer membrane of eukaryotic cells has a lipid bilayer structure. Refer to a standard text book for a review of this. I will emphasize just one important point here; most metabolically active water-soluble materials are effectively hindered from crossing these membranes. Small channels are found in these membranes and these do allow low-molecular compounds (MW < 80) to diffuse into and out of cells. However, "simple" compounds such as sugars and amino acids are much larger. Carriers are necessary if these materials are to gain access to cells. These are usually large proteins that span the cell membrane. They are specific, transporting only the molecules they recognize. This is illustrated in the cartoon shown to the left (from Trends in Biochemical Sciences, ca 1980).

As the reader surely understands, transport of glucose is essential for life and is carefully regulated. A family of five proteins with a high degree of homology are involved in transport of glucose over cellular membranes. Each of these has special physiological functions and tissue distribution.

Properties of Glucose Transport Proteins		
Transporter	Tissue distribution	Special properties
GLUT 1	Most cells.	High capacity, relatively low K_m (2-3mM).
GLUT 2	Liver, beta cells, hypothalamus, basolateral membrane small intestine.	High capacity but low affinity (high K_m, ca. 5mM) part of "the glucose sensor" in ß-cells. Carrier for glucose and fructose!
GLUT 3	Neurons, placenta, testes.	Lowest K_m (ca. 1mM) high capacity.
GLUT 4	Skeletal and cardiac muscle, fat.	Activated by insulin.
GLUT 5	Mucosal surface in small intestine, sperm.	Fructose specific.

These transport proteins mediate facilitated transport, that is, they can only transport glucose (or fructose) from areas of high concentration to areas of lower concentration. The sugar is bound by the protein, a flip-flop mechanism reverses the membrane direction of the sugar-protein complex, the sugar is released and the protein flips around once more to initiate a new cycle. Transport activity is dependent upon the sugar concentrations and the number of transport proteins in the outer cell membrane. In principle the GLUT family can transport glucose both into and out of cells. In most tissues the internal glucose concentration is quite low; transport can only proceed from the extracellular area into the cell. In gluconeogenetic tissues (liver and kidney), intracellular glucose concentration can exceed blood glucose concentration in the post-absorptive or fasting states. Export of glucose from liver and kidney occurs through GLUT2.

The insulin-sensitive glucose transporter, GLUT4, is found bound to internal cellular membranes where it is inactive. Most researchers agree that GLUT4 is bound to the Golgi apparatus. GLUT4 is brought to the plasma membrane by an ATP requiring process. The



transport protein molecules that arrive at the surface membrane contribute to glucose transport. Another ATP-dependent mechanism transports GLUT4 back to the Golgi apparatus where these molecules are once more inactive. Insulin shifts the balance between exocytosis and endocytosis such that the number of functional GLUT4 molecules in the plasma membrane increases, thereby activating glucose uptake. I will come back to this under the discussion of insulin's mechanism of action.

Note that muscle activity can increase the number of GLUT4 molecules in the plasma membrane through the same mechanism. Muscle activity and depletion of intracellular glucose alone (without increased insulin levels) activates glucose uptake. For an up to date discussion of GLUT4 translocation see "Signals that Regulate GLUT4 Translocation", J.S. Elmendorf, Journal of Membrane Biology, 190(3), 167-174, 2002.

As mentioned previously, exhaustive physical work can lead to hypoglycemia and loss of consciousness. Evolution gave us a way to activate maximum speed to run from tigers and a simultaneous route to unconsciousness before being eaten.