Carbohydrates pt. 2

Chapter 3

ABSORPTIONAND TRANSPORT

- Dietary monosaccharides to be absorbed into the bloodstream, they must twice cross the plasma membrane of enterocytes

1. First enter the cell on the brush border (apical) side
2. Exit on the basolateral side that faces a network of capillaries connected to the hepatic portal vein
3. The newly absorbed sugars are delivered directly to the liver where they will be metabolized according to the body's needs,

- The movement of molecules across cell membranes, including those of enterocytes is a highly regulated process
- Monosaccharides movement mediated by specialized transport proteins integrated in the cell membrane

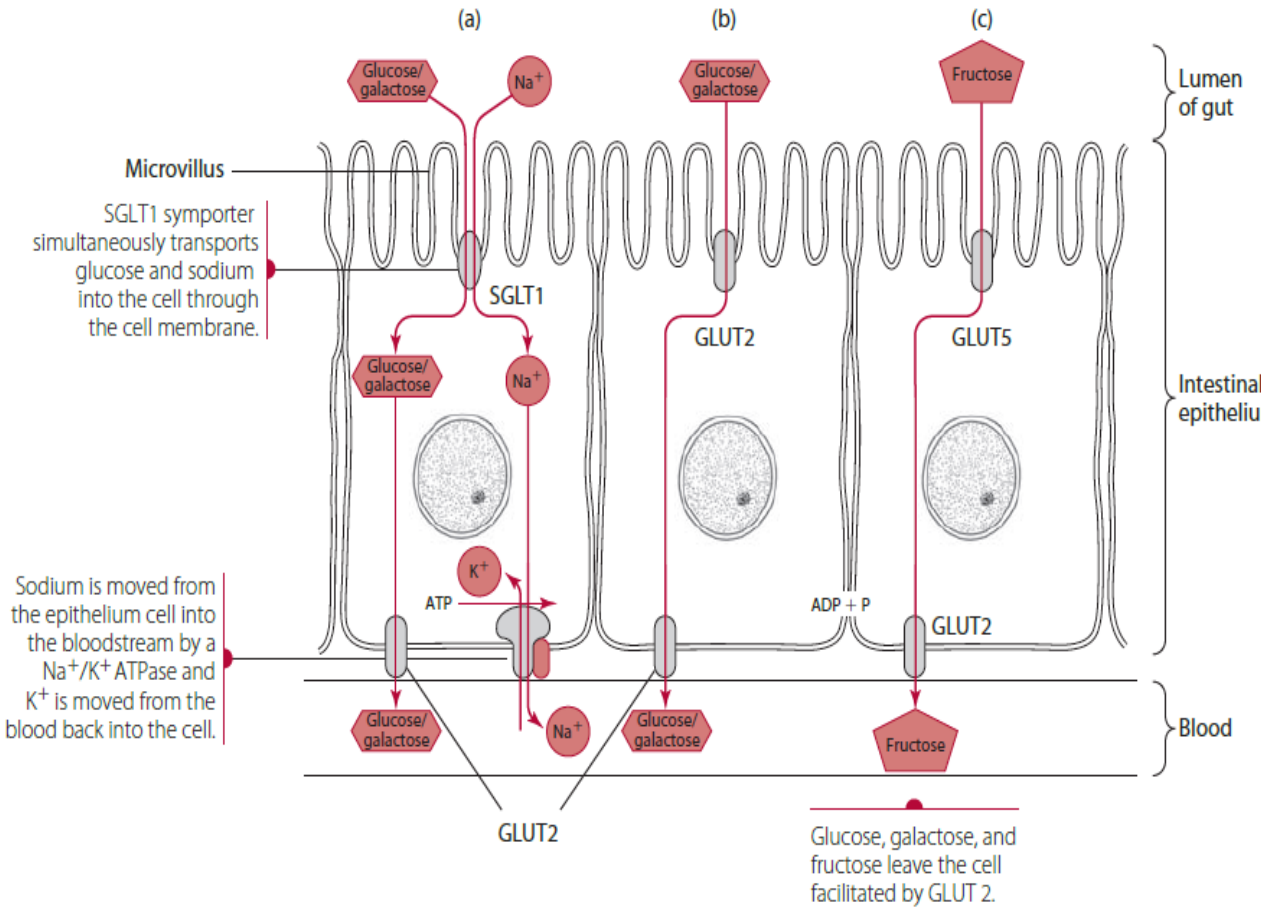
1. The energy-dependent *sodium- glucose cotransporters* (SGLTs)
2. The facilitated diffusion *glucose transporters* (GLUTs)

Each tissue has a different distribution of SGLTs and GLUTs

SGLTs *The ene*

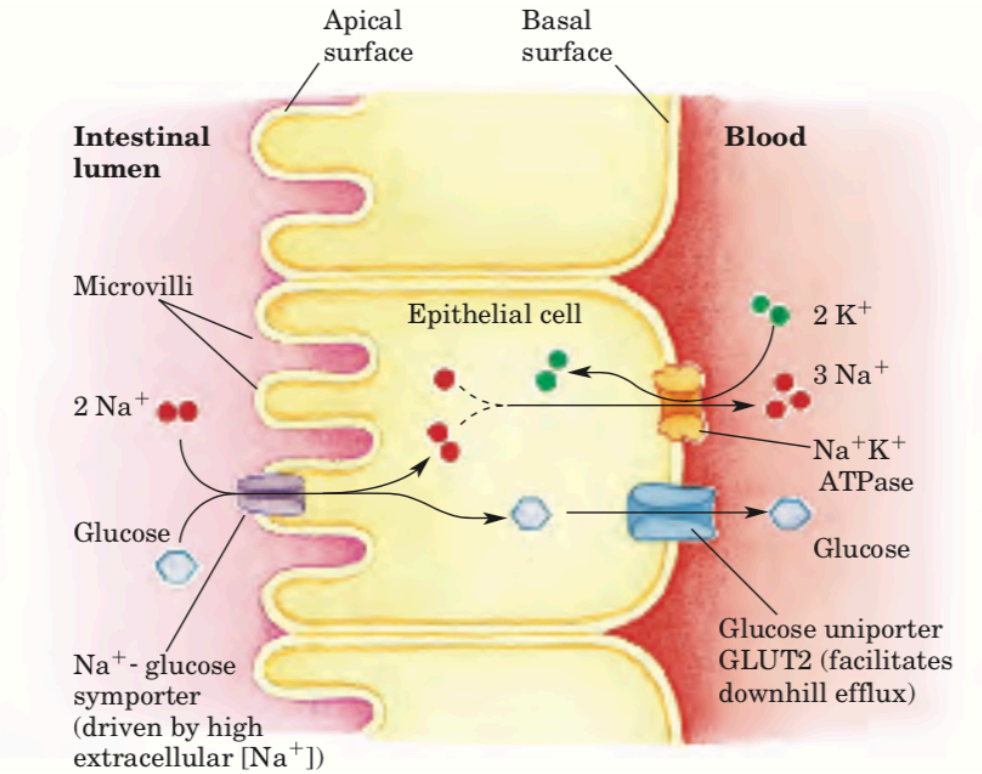
glucose cotransp

- Symporters
  - simultaneously transports two substances (Na+ and glucose or galactose) in the same direction and is thus a symporter.
- SGLTs are enzyme proteins that take up glucose into cells against an electrochemical gradient, and take up sodium ions down their concentration gradient.
- SGLT1 and SGLT2 play



SGLTs

- **SGLT's- secondary transport**
- Rely on the sodium concentration gradient generated by the sodium–potassium ATPase as a source of chemical potential to generate energy for taking up glucose against concentration gradient



The Na□K□ATPase continues to pump Na□outward to maintain the Na□gradient that drives glucose uptake.

- The transport protein of SGLT1 has two binding sites. The glucose binding site is not available unless the transport protein has already bound a Na+.
- Firstly, an Na+/K+ ATPase pump on the basolateral membrane of the proximal tubule cell uses ATP molecules to move 3 sodium ions outward into the blood, while bringing in 2 potassium ions
- The SGLT proteins use the energy from this downhill sodium ion gradient created by the ATPase pump to transport glucose across the apical membrane, against an uphill glucose gradient

SGLT1

- Expressed mainly in the brush border membrane of enterocytes where its primary role is the absorption of dietary glucose and galactose
- Mutations in the *SGLT1* gene causing the genetic abnormality called *glucose-galactose malabsorption.*
- Patients with the mutation experience severe diarrhea unless food sources of glucose and galactose are removed from the diet

SGLT2

SGLT2 is highly expressed in the proximal tubule of the kidney where it is responsible for reabsorbing glucose from the glomerular filtrate.

Important for glucose retention

In type 2 diabetes mellitus, SGLT2 may be upregulated, which can exacerbate **hyperglycemia**.

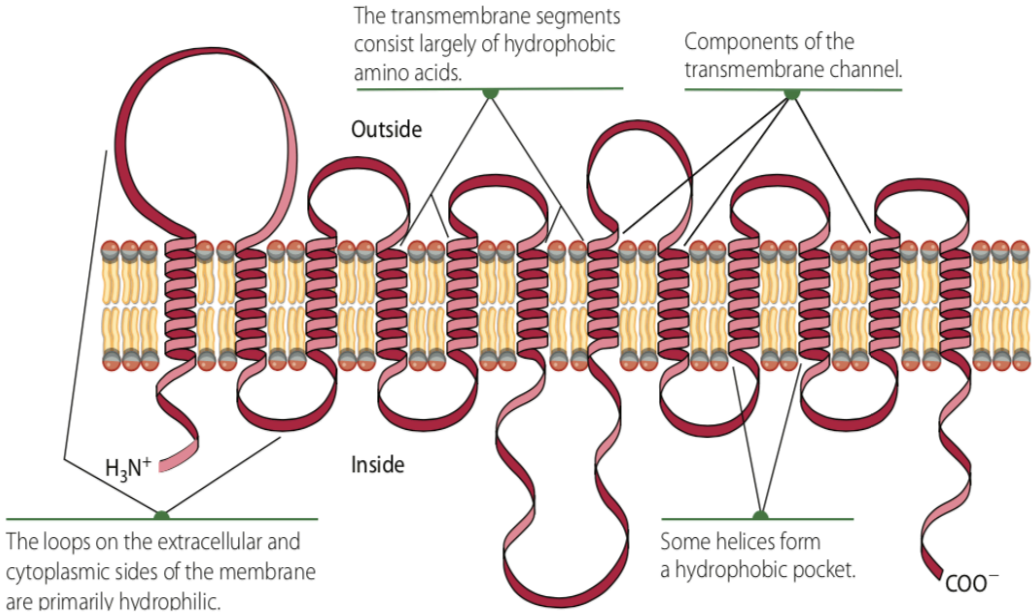
- Anti- hyperglycemic drugs called SGLT2 inhibitors are being used to promote the urinary excretion of glucose by blocking the glucose reabsorption in the kidney proximal tubule

GLUTs

- Facilitated diffusion
- Transport glucose across the plasma membrane. They are enzyme proteins that can also transport galactose and fructose
- GLUTs are expressed in a wide variety of cells, from red blood cells to liver to the brain
- Each GLUT is an integral protein, penetrating and spanning the lipid bilayer of the plasma membrane

GLUTs

- When glucose or other substrate attaches to the protein's binding site, it causes a conformational change in the protein, allowing the substrate to translocate to the other side of the membrane
- After the substrate is released, the conformational change is reversed and the GLUT protein can repeat the process.



GLUTs

- The GLUT family divided into three classes

GLUT1 :

- High Affinity for Glucose
- Insulin independent
- Allows glucose to cross the blood–brain barrier and supplies glucose to CNS
- Supply of glucose to erythrocytes, endothelial cells of the brain, and most fetal tissue.
- Patients with GLUT1 deficiency syndrome follow a ketogenic diet

GLUTs

GLUT2

- Insulin dependent
- Lowest-affinity glucose transporter
- Predominant expression in the b-cells of the pancreas, liver, small intestine, and kidney (only uptake when glucose concentration is high)
- Starts working when Glut 1 & 3 saturated
- Transport of most monosaccharides from enterocytes into the portal blood
- High insulin levels cause GLUT2 to leave the plasma membrane of the enterocyte and return to storage vesicles.

GLUTs

GLUT3

High-affinity glucose transporter (Saturated with glucose

- Dominant expression in brain and neurons that are highly dependent on glucose as a fuel

Insulin Independent

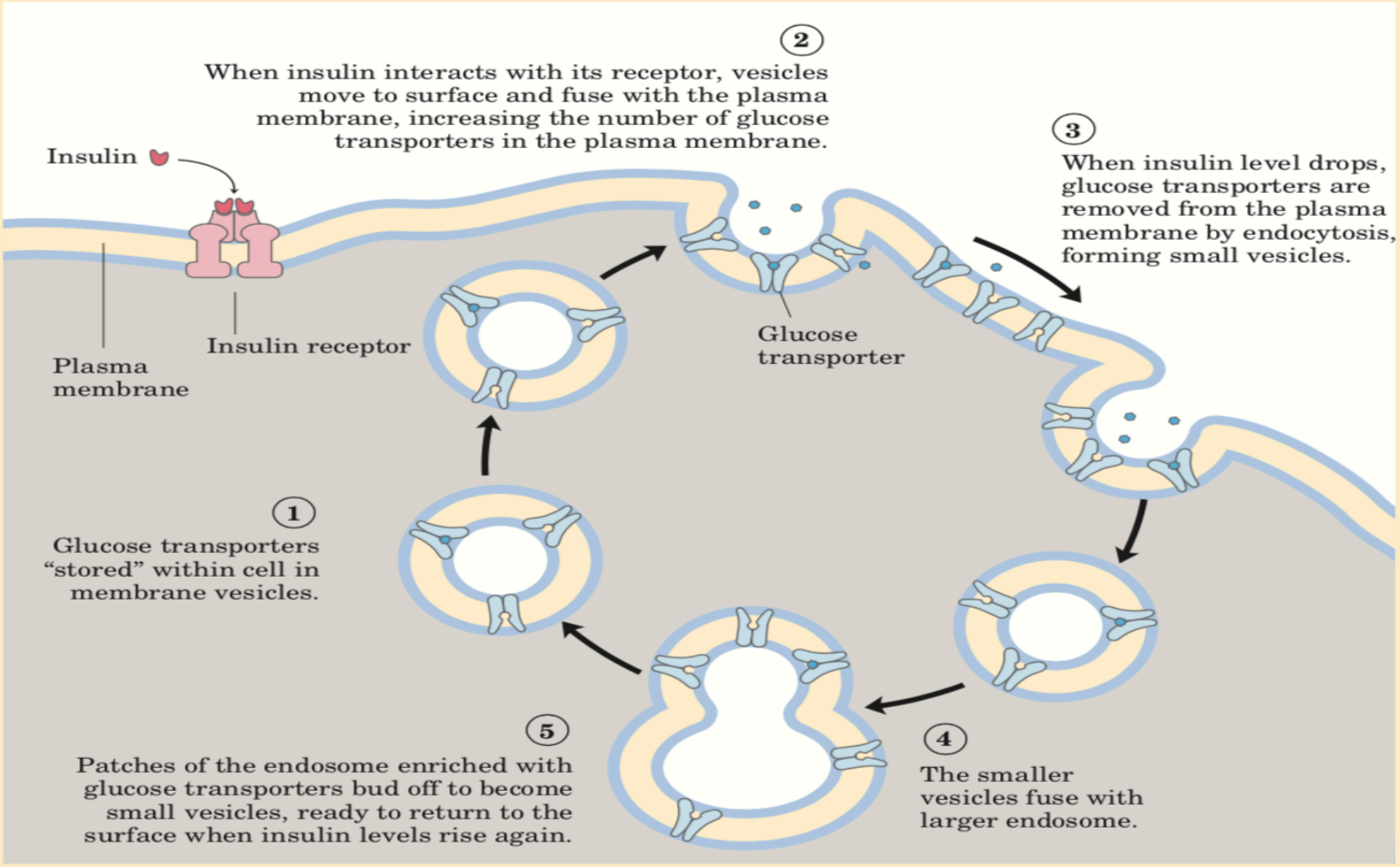
GLUTs

Glut 4

- Adipose tissue, muscle, heart
- Insulin dependent: insulin always uptake of glucose/ translocation of GLUT4 from intracellular storage vesicles to the plasma membrane
- Moderate affinity

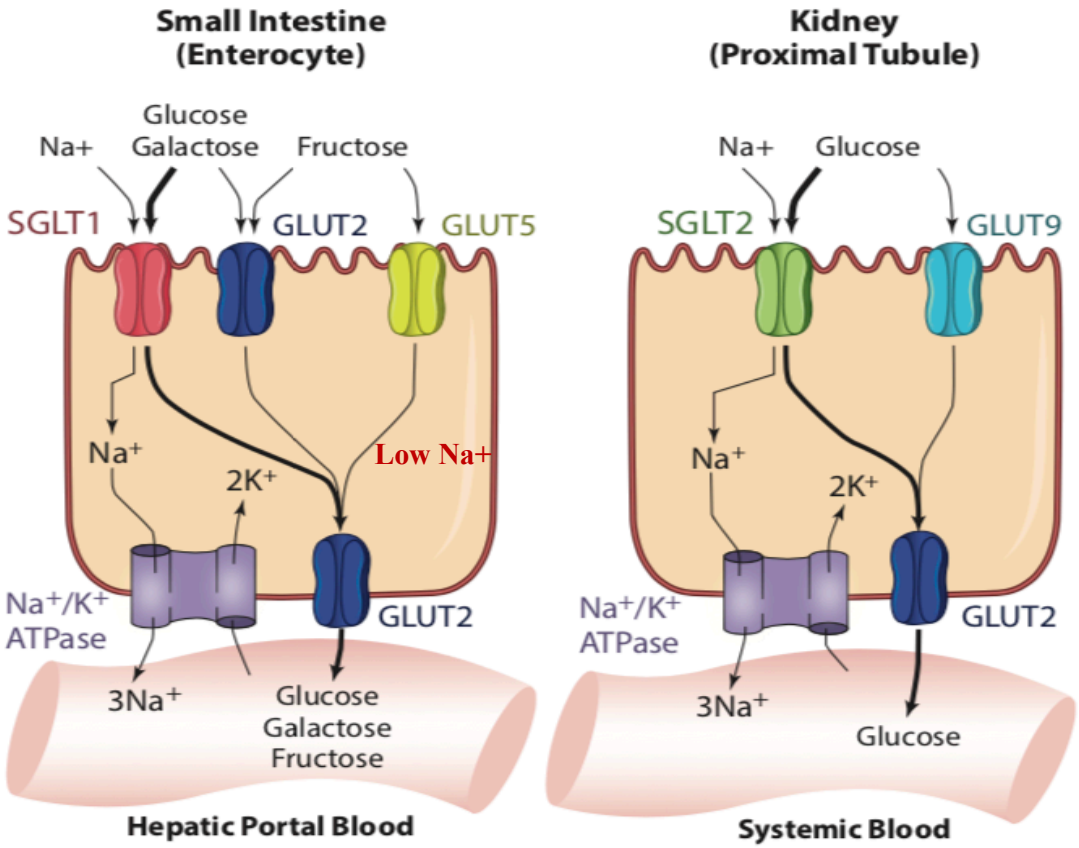
Glut 5

- Uptake of fructose/ does not recognize glucose
- expressed primarily in the small intestine and to a lesser degree in kidney, brain, skeletal muscle, and adipose tissue. Its main function is to transport dietary fructose across the brush border membrane of enterocytes.



IRE 1 Regulation by insulin of glucose transport by GLUT4 into a myocyte.

Transporters in the enterocyte encounter the greatest variety of monosaccharides derived from dietary sources.
In contrast, the kidney filters and reabsorbs primarily glucose because glucose is practically the only monosaccharide in the systemic circulation



Intestinal Absorption of Glucose and Galactose

- After carbohydrate digestion, glucose and galactose are transported into the enterocyte involving both active transport (SGLTs) and facilitated diffusion (GLUTs).
- **Active transport:** The attachment of Na+ to the carrier increases the transport protein's affinity for glucose
- After Na+ and glucose are transported into the enterocyte, they are released from SGLT1.
- When intracellular glucose concentration increases, glucose binds to GLUT2 in the basolateral membrane
- GLUT2 will facilitate exit of glucose and other monosaccharides from the enterocyte into the underlying capillaries for delivery into the hepatic portal vein

Facilitated Transport

- When glucose concentration in the intestinal lumen is high after a large carbohydrate meal, glucose is transported into the enterocyte by **GLUT2** ***(low affinity)*** in the brush border membrane
- After high-carbohydrate meals, more glucose is transported into the enterocyte by facilitated transport than by active transport via SGLT1.

Intestinal Absorption of Fructose

- GLUT5
- Facilitated diffusion
- GLUT5 has a high affinity for fructose and is not influenced by the presence of glucose
- Mainly in small intestine
- Absorption does not require energy
- When the intracellular concentration increases, fructose is transported out of the enterocyte into the hepatic portal vein by GLUT2 in the basolateral membrane
- The facilitated transport process can proceed only down a concentration gradient □ slower absorption rate compared to glucose

Hepatic Metabolism of Dietary Monosaccharides

- After intestinal absorption of glucose, galactose, and fructose, they enter the hepatic portal vein liver.
- All of the galactose and fructose is taken up by the liver through specific GLUTs and metabolized.
- Only 30–40% of glucose is taken up by the liver, with the majority passing through into the systemic circulation (only glucose is found in blood)
- Galactose glucose derivatives and stored as liver glycogen
- Fructose supplies liver with energy… excess is stored as triacylglycerol

BLOOD GLUCOSE CONCENTRATION

Maintaining normal blood glucose concentration

- Insulin inhibits hepatic gluconeogenesis and promotes glucose utilization
- Glucagon increases the breakdown of liver glycogen by glycogenolysis.
- Secretion of glucocorticoid hormones (stress hormones) primarily cause increased activity of hepatic **gluconeogenesis and** antagonize insulin response by skeletal muscle and white adipose tissue
- "In both mouse and human muscle cells, GC reduce insulin-stimulated glucose uptake attenuating insulin-induced GLUT4 translocation to the cell membrane.

Ruo H, McQueen A, Chen YC, Wang JC. Regulation of Glucose Homeostasis by Glucocorticoids. *Adv Exp Med Biol*. 2015;872:99-126.