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Transport of Sugars

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Keywords

glucose, sucrose, carrier, GLUT, SGLT, SWEET

Abstract

Soluble sugars serve five main purposes in multicellular organisms: as sources of carbon skeletons, osmolytes, signals, and transient energy storage and as transport molecules. Most sugars are derived from photosynthetic organisms, particularly plants. In multicellular organisms, some cells specialize in providing sugars to other cells (e.g., intestinal and liver cells in animals, photosynthetic cells in plants), whereas others depend completely on an external supply (e.g., brain cells, roots and seeds). This cellular exchange of sugars requires transport proteins to mediate uptake or release from cells or subcellular compartments. Thus, not surprisingly, sugar transport is critical for plants, animals, and humans. At present, three classes of eukaryotic sugar transporters have been characterized, namely the glucose transporters (GLUTs), sodium-glucose symporters (SGLTs), and SWEETs. This review presents the history and state of the art of sugar transporter research, covering genetics, biochemistry, and physiology—from their identification and characterization to their structure, function, and physiology. In humans, understanding sugar transport has therapeutic importance (e.g., addressing diabetes or limiting access of cancer cells to sugars), and in plants, these transporters are critical for crop yield and pathogen susceptibility.

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Contents

Permease: does not indicate permeation; not specifically used for uniporters or facilitators but for transporters, except for pumps

Transporter or transport protein: carrier, pump, or channel

Symporter: couples transport of a substrate to cotransport with an ion in the same direction; thus, a proton symporter transports a substrate against a concentration gradient by exploiting both the pH gradient and a membrane potential

INTRODUCTION

Quantitatively, sugars represent the most important organic compounds that are taken up by living organisms. Sugars can be used as carbon skeletons for the biosynthesis of many other cellular compounds, are used to generate energy, and are key players in osmotic processes. Before reaching their consumers, however, sugars and their various oligo- and polymers have to be produced by photosynthesizing plants. Here, the carbohydrates get transported from the leaves to all plant tissues, and—after depolymerization—they have to enter the cells of all other organs, especially those of roots, seeds, and fruits. The uptake of sugars into a multitude of cells has been the most intensely studied membrane transport process in physiology and biochemistry. According to the authors' personal perspective, it started with Cori's studies of intestinal sugar absorption (1, 2; also see the section titled From the Lipid-Filter Theory to Permeases: A Historical Account), and was followed by Crane and colleagues' finding that this uptake is energized by sodium gradients (3, 4); a major input came from the lactose permease of *Escherichia coli* (5), which together with other bacterial transporters led to a formidable understanding of structural details of sugar transport proteins (**Supplemental Table 1**; follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

This prototype transporter, LacY, has been a starting point for many new developments and discoveries (**Supplemental Table 1**) (6, 7). The mammalian Na^+/glucose symporters, also known as sodium-glucose symporters (SGLTs) (8), as well as the glucose facilitators, the glucose transporters (GLUTs) (9), attracted much attention, not least because of their medical relevance. Numerous reviews dealing with these sugar transport systems have been published (7–11), and they have

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focused more or less exclusively on the *E. coli* lactose permease and on mammalian sugar transport. To avoid repetition, we concentrate on sugar transport in a broader way, although we discuss major points from studies of these well-established systems. We mention only briefly the special case of the bacterial phosphotransferase system (PTS) (12), also extensively reviewed elsewhere (13, 14). Instead, we review the current state of knowledge of the eukaryotic GLUTs, SGLTs, and SWEETs—the most recently discovered sugar transport family, which is responsible for cellular export (15). The exciting sequence of investigations and discoveries is likely to continue.

Facilitator: a carrier that transports its substrate down a concentration gradient, which determines the direction of transport

FROM THE LIPID-FILTER THEORY TO PERMEASES: A HISTORICAL ACCOUNT

Plant biologists have contributed two major discoveries to general cell biology: the plasma membrane and the principles of heredity. The plasma membrane was, in a way, reserved for discovery by botanists, given that in plant cells the cytoplasm retracts from the cell wall when the cell's external solution is more concentrated than the cell interior one, an osmotic phenomenon termed plasmolysis. During this process, intracellular compounds, such as anthocyanin, become visibly concentrated. To explain this behavior, investigators postulated the existence of a semipermeable membrane (16, 17): Water leaves the cell, whereas other substances, such as anthocyanin, have to remain inside. A hundred years before the postulated membrane was eventually visualized by electron microscopy (18; reviewed in Reference 19) it had already been characterized in some detail. Due to this historic start, it is not surprising that mainly botanists studied membrane permeability, typically in large cells such as those of Characean algae (for more details on the structure of membranes, see Reference 20). The main questions were: How do molecules get through plasma membranes, either entering or exiting a cell? And what determines selectivity? Overton's[1] careful studies (21) clearly showed a correlation between the oil/water partitioning of a compound and its ease in entering a cell (22). Overton was the first to suggest that the main components of the membrane are lipids (he mentioned cholesterol and phosphatidylethanolamine, among others). Exceptions to Overton's rule of membrane permeability led to the lipid-filter theory of permeation, given that the size of molecules also seemed to matter (23).

It has been frequently stated that Cori was the first to present evidence for the existence of catalyzed transport (**Supplemental Table 1**). This statement is technically correct because he showed that sugars supplied to the intestine of rats were taken up from the lumen at rates that are specific for different types of sugars, and he observed saturation behavior as well as competition between glucose and galactose (1, 2). However, Cori did not dare to postulate catalyzed membrane transport; the lipid-filter theory obviously dominated the field. Instead, he wrote: "What can be learned from this fact in regard to the mechanism of absorption in general it would be too early to discuss... nor has the absorption of lipid-soluble substances and of electrolytes been studied with this method. For these reasons, it seemed advisable to postpone a discussion of the mechanism of absorption" (1, p. 710). Even 10 years later, Höber & Höber (24) reported that the permeation behavior of physiological substances such as amino acids and sugars did not follow the straightforward rules of physical chemistry; somewhat irritated, these authors concluded that "a process complicated by the presence of an accelerating factor" must exist.

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[1]Overton, although a botanist, also studied the permeability of nerve and muscle cell membranes, and implicated an exchange of Na^+ entering the cells for K^+ loss in nerve excitation. The general neglect of this fundamental concept for the nerve excitation process provoked a comment by Huxley (21, p. 52): "If people had listened to what Overton had to say about excitability, the work of Alan [Hodgkin] and myself would have been obsolete."

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Table 1 Timeline of lactose permease discoveries

Year	Discoveries	Reference(s)
1956	The Y gene product as a transport protein for lactose and analogs	5
1958	Proof obtained for transport against a concentration gradient ("active" transport); accumulated sugar is freely soluble and osmotically active	30
1965	M protein corresponding to lactose permease detected	29
1966	K_m values differ by a factor of 60 for influx and efflux; first partial explanation for accumulation	43
1970	First experimental evidence for proton symport (based on the prediction in Reference 33)	35
1980	The first gene of a transport protein cloned and sequenced; the Y gene codes for a 46-kD protein	44
1981	Purified lactose permease in vesicles catalyzes transport and accumulation	51
1984	Phosphatidylethanolamine required for full activity	140, 141
1998	Cysteine-scanning mutagenesis described; a detailed mechanism of lac/H^+-symport proposed	89, 92
2003	Crystal structure of the lactose permease reported	88

Thus, here they were: the transport-catalyzing factors in the plasma membrane. Obviously, the next question to resolve was whether these factors were proteins. Proteins had been implicated in membrane transport whenever sizing of molecules seemed to play a role in permeability, but real evidence for proteins appeared only when inhibition of glycerol, as well as of glucose uptake with heavy-metal ions, was observed in erythrocytes (25, 26). For instance, a concentration of copper that could cover only 1% of the erythrocyte surface inhibited glycerol uptake by 90% (25). At this point, LeFevre (26, p. 505) stated that the entrance of substrates "involves the activity of sulfhydryl-containing enzymes."[2] **Supplemental Table 1** summarizes the discoveries that led to characterization of carrier-mediated transport.

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Final proof, however, that specific proteins catalyze transmembrane (TM) transport of cellular substrates had to await Monod and colleagues' (5) discovery of the Y gene coding for the lactose permease (**Table 1**) (**Figure 1**). A major milestone was the identification and purification of the corresponding protein, named the M (membrane) protein, by Fox & Kennedy (29), who used a combination of radiolabeled inhibitor-binding studies and anion-exchange chromatography. This study was the first investigation of a defined protein that catalyzes membrane transport.

In the years following 1956, the field of membrane transport flourished, and the uptake of sugars was studied in numerous organisms: bacteria, yeasts, algae, and plants, and of course in erythrocytes, as well as other mammalian cells. In 1958, Sistrom (30) showed that analogs of β-galactosides can indeed be transported against a concentration gradient and intracellularly are not simply "removed" from equilibrium, for example, by adsorption to some polymers. This result led to the most pertinent question of how this active transport is energetically achieved. First, it renewed a long-lasting discussion about whether sugars might be modified—for example, phosphorylated—during the transport step. This hypothesis was considered almost proven when the first papers on the PTS appeared (12). Investigators took a considerable amount of time to experiment with glucose analogs such as 1-, 2-, and 6-deoxy glucose (31, 32) until it became clear

Carrier: member of a subclass including uniporters and cotransporters but not channels; turnover rates are often only a few to a few hundred per second

Active transport: describes a transport process that directly consumes energy (e.g., by hydrolysis of ATP or phosphoenolpyruvate)

[2]The same experimental approach led to the discovery of water channels, the aquaporins, more than 20 years later (27). The glycerol transporter was eventually found to belong to the family of aquaporins, too (28).

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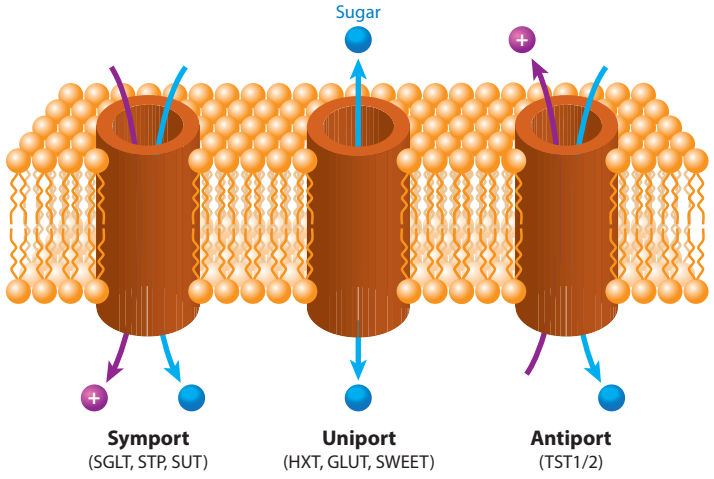

Figure 1

Transport mechanisms in eukaryotes. Cotransporters (76) can be divided into symporters (here a purple cation coupled to transport of a sugar; examples are SGLTs, STPs, and SUTs) and antiporters (shown here is the vacuolar H^+/glucose antiporter). Uniporters facilitate sugar transport along the sugar gradient (examples include HXTs, GLUTs, and SWEETs). Abbreviations: GLUT, glucose transporter; HXT, hexose transporter; SGLT, sodium-glucose symporter; STP, sucrose/H^+ cotransporter; SUT, sugar transporter in plants; TST, tonoplast sugar transporter.

that phosphorylation is not a prerequisite for active transport in eukaryotes and that the PTS is exclusive to bacteria (it is not present even in archaea) (14).

Completely new concepts were formulated after Mitchell (33) postulated a proton gradient as an energy source both for the formation of ATP and for galactoside transport. At the same time, Bihler & Crane (34) modified an earlier theory of a sodium-dependent transport into a sodium gradient–dependent one (3, 4). The first experimental evidence for proton cotransport—again with the lactose transport system (35)—was published in 1970 and, for the first eukaryotic cell, in 1973 (36, 37). Subsequently, it rapidly became clear that H^+ symport or cotransport is a major transport mechanism for bacteria, fungi, and plants (38–40), whereas in animals, sodium is the cotransported ion (41, 42). Responsible for maintaining the gradient are the H^+- and Na^+/K^+-ATPases. From that time onward, a new nomenclature was used to define transport against a concentration gradient or, more precisely, against an electrochemical potential, either as primary (ATP-involving) or as secondary active transport.

As far as we know, the first experimentally based explanation of how accumulation of a substrate may come about was published by Winkler & Wilson (43). They showed that the affinity of the lactose permease for lactose influx versus that for efflux differed by a factor of 26, and that for NPG (*O*-nitrophenyl-galactoside) the difference was more than a factor of 40, whereas V_{max} (maximal velocity) values were not significantly different. Thus, a steady state of influx equaling efflux should be reached at a correspondingly higher concentration inside the cells. However, the measured accumulation rate was considerably higher than the one predicted by the two K_m (substrate concentration at 1/2 V_{max}) values, indicating a missing link. Subsequently, this discrepancy was postulated to arise from the membrane potential, $\Delta\Psi$ (see the discussion in the supplemental material).

Secondary active transport: symport or antiport, exploiting gradients that are built up by primary active transport (i.e., by pumps)

The 1970s saw a race to learn more about the mystique of transport proteins. Once molecular cloning became available, the lac permease gene, as expected, became the first to be cloned and sequenced in Müller-Hill's laboratory in 1980 (44). Within the next decade, the first sugar

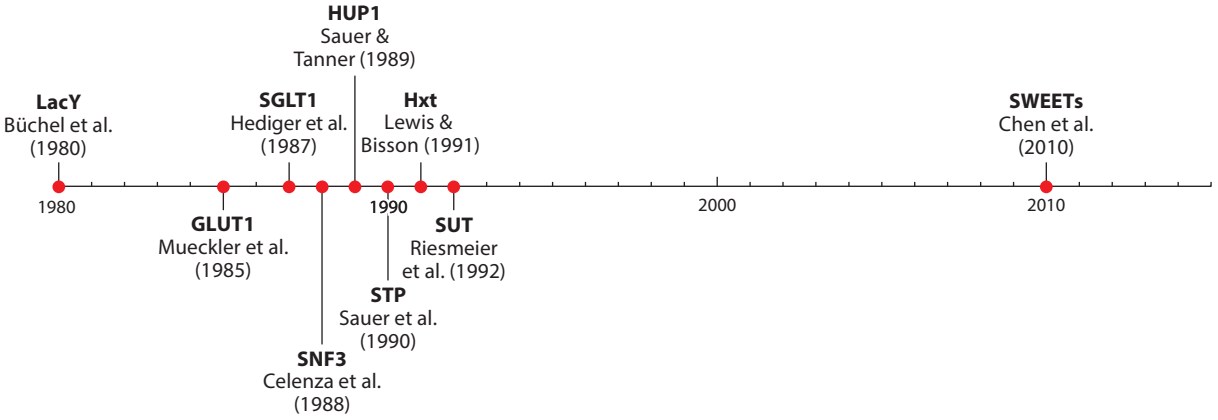

Figure 2

Timeline of the identification of sugar transporters. Details of the transport mechanism classification and associated references are provided in **Supplemental Table 1**. Abbreviations: GLUT, human glucose transporter; HUP, hexose uptake protein of *Chlorella*; Hxt, yeast hexose transporter; SGLT, human sodium-glucose symporter; SNF, sucrose nonfermenting; STP, plant sugar transporter; SUT, plant sucrose/H^+ cotransporter.

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transporter genes of other major families were cloned (46–50). These advances were followed by a period of relative quiet until the cloning of SWEETs in 2010 (**Supplemental Table 2**) (**Figure 2**). For the galactoside transport, in vitro experiments (51) showed that only the protein encoded by the *lacY* gene is required for catalyzing β-galactoside transport. When the vesicles used were supplied with an energy-generating system, the sugars were also transported in vitro against a concentration gradient. No *vis vitalis* remained for the mystics!

Each transport protein is embedded in the lipid matrix of its particular membrane. Although we describe mainly sugar transporters of plasma membranes, these transporters are also present in internal membranes, which we discuss briefly below (**Figure 1** illustrates the symport, antiport, and uniport mechanisms).

ANALYSIS OF TRANSPORT ACTIVITY

As opposed to enzymes, which typically can be assayed in vitro, transporters have to be embedded in membranes for functional analyses. Moreover, the biochemistry of intrinsic membrane proteins is more challenging to study due to their hydrophobicity. Typical approaches for monitoring transport include radiotracer studies, electrophysiology, and mass spectrometric analyses. These studies either are performed in native cells or tissues or involve heterologous expression systems to isolate the respective activity.

In a few cases, *E. coli* was used to study eukaryotic transporters (52, 53); however, expression in *E. coli* typically leads to toxicity, so tight control of expression is required (53, 55). Yeast has been a highly efficient system for both identification of plant transporters via growth assays and radiotracer studies, but it has been less successful for characterizing animal transporters. *Xenopus* oocytes are one of the best expression systems for both animal and plant transporters, and can be used for quantitative uptake and efflux studies. Moreover, oocytes are amenable to two-electrode voltage-clamp and even patch-clamp analyses, provided that the transporters are electrogenic (56), and they have also been used in combination with mass spectrometry to identify and verify transport activity (57). More recently, genetically encoded biosensor technology has been used

IN VIVO BIOCHEMISTRY

Förster resonance energy transfer (FRET) sugar sensors are used to measure the dynamics of sugars in cells and tissues with subcellular resolution. Sugar concentrations (ribose, glucose, sucrose, and maltose) can be determined in vitro and in vivo using genetically encoded FRET sensors, composed of a pair of spectral variants of fluorescent proteins fused to a protein that undergoes a sugar-induced conformational rearrangement (135).

Fluorescent sensors are used to measure the activity of transporters in vivo. Whereas transporters can be characterized in heterologous systems, measuring their activity in their native environment (i.e., intact tissues or organs, or even intact organisms) has remained a major challenge. Recently, several transporters were successfully converted into genetically encoded transport activity sensors (62, 63). Insertion of a circularly permutated green fluorescent protein into a sensitive position of an ammonium transporter, or fusion of a fluorescent protein to a nitrate or peptide transporter, has been used to create such activity sensors. These sensors report the activity of the respective transporters, and their kinetics are indistinguishable from those of the wild-type transporters.

to monitor sugar fluxes in mammalian cells, brain slices (58), and intact plants (59, 60), and this technology was crucial for the identification of the SWEET family of sugar transporters (15, 61).

The most recent technological development involves transport activity sensors, which report the activity of a transporter in vivo as a change in intensity of fluorescence (62, 63). Such sensors will be essential for studying intracellular transport, but they are also expected to provide new insights into the regulation of transporter activity in vivo (see the sidebar). Although this platform has not yet been applied to sugar transport, we predict that it may be possible to expand it to the transporters discussed here.

FROM TRANSPORT BIOCHEMISTRY TO THE CARRIER GENES

The groundbreaking advance in carrier-mediated transport was the identification of *lacY*, the lactose permease gene, in 1980 (44). The protein encoded by the *lacY* gene is highly hydrophobic and is composed of 12 amphipathic α-helices. Lactose permease is the founding member of the MFS (major facilitator superfamily) of transporters. Between 1985 and 2000, most of the key eukaryotic sugar transporters were identified: the hexose transporters (HXTs) in yeast (45), the GLUTs (46) and SGLTs (47) in mammals, and the sugar transporters (STPs) (64) and sucrose/H^+ cotransporters (SUTs) (50, 65) in plants (**Supplemental Table 2**) (**Figure 2**). All except the SGLTs belong to the MFS. GLUT1 was identified through biochemical purification, development of an antiserum, and immunoscreening (46, 66). SGLT1 was identified using *Xenopus* oocytes as a functional expression system (47). In yeast, the process was much more complex: The first apparent GLUT with similarities to human GLUT1 was SNF3, which cannot transport glucose efficiently but serves instead as a glucose receptor that controls the activity of its sugar transporting paralogs, the HXTs (48). STPs were identified using a biological approach, which originally led to the identification of hexose uptake transporters (HUPs) from a green alga (49, 64). The HUPs were identified as differentially expressed genes in *Chlorella* through a comparison between photosynthetically grown and glucose-fed cells. The HUPs were then used to clone the *Arabidopsis* STP1 genes by homology-based hybridization. In animals, a novel sodium-dependent GLUT that belongs to the MFS, NaGLT1 (Na^+-dependent glucose transporter), has been identified as another potential player in glucose reabsorption in kidney (67, 68).

More recently, a new class of sugar transporters named SWEETs has been identified; SWEETs are conserved from archaebacteria to plants and humans (69). The first SWEET hexose and

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Cotransporters: encompass symporters (ion cotransporters) and antiporters (ions of substrate antiporters) but not uniporters or channels

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sucrose transporter genes were identified through the coexpression of genes encoding unknown membrane proteins by use of genetically encoded Förster resonance energy transfer sensors, in human cells (15, 61, 69). SWEETs are smaller than MFS and SGLT transporters, and they are built from only seven TM-spanning domains.

In essentially all cases, the eukaryotic genomes encode multiple transporter isoforms that often differ in regulation, transport kinetics, and substrate specificity. Whereas many of these transporter isoforms are targeted to the plasma membrane, others mediate transport across intracellular membranes.

Uniporter: facilitates transport of a substrate across the membrane, also called a facilitator

Countertransport or counterexchange: transport of one substrate against another one, or a radioactive species against the same one, but nonradioactive

Antiporter: couples the transport of a substrate to the countertransport of an ion or another substrate

***Trans* acceleration or *trans* stimulation:** acceleration of substrate transport in one direction due to the presence of the same or a related substrate on the other side (*trans*) of the membrane

INTRACELLULAR SUGAR TRANSPORTERS

Obviously, cellular uptake and release mediated by sugar carriers are crucial for the distribution of sugars among different cells, tissues, and organs of multicellular organisms. However, eukaryotic cells are highly compartmentalized; they require transporters that can take up and release sugars from these compartments. Thus, not surprisingly, members of the GLUTs (70); SWEETs (71–73); and plant VGT1 (vacuolar glucose transporter 1) (74), ERD-like (early response to dehydration–like) transporters (75), and TMTs (tonoplast monosaccharide transporters) (76) play important roles in sugar compartmentation. Moreover, transporter activity can be efficiently controlled through transporter delivery or endocytosis. The best-studied example is GLUT4, the activity of which is tightly controlled by trafficking (77–79).

TRANSPORT MECHANISM

Once transporter genes were identified, investigators were able to study the roles of the proteins by expressing them in heterologous systems, by analyzing mutants, and by purifying proteins and reconstituting them in artificial bilayers. Transporters can facilitate sugar transport or actively transport sugars against a concentration gradient into or out of cells or compartments (**Figure 1**).

Transport Mechanism for Hexose and Sucrose/H^+ Transporters

Yeast HXTs function as uniporters, as demonstrated by countertransport experiments (80). Individual paralogs differ mainly with respect to their glucose affinities, which allow yeast cells to optimally acquire sugars over a broad range of substrate availabilities (81). In contrast, plant STPs and SUTs function as proton cotransporters (82, 83). SUTs can work in reverse, as expected from thermodynamics (84). The plant vacuolar TMTs function as glucose/H^+ antiporters (76). Human GLUT1, one of the best-studied members of the MFS, functions as a uniporter. However, its activity is not simple, and it shows *trans* acceleration (85).[3] The underlying mechanism for the kinetic behavior of GLUT1 is not understood, and several models including geminate exchange have been proposed. Similar to the yeast HXTs, the human GLUT isoforms cover a wide range of affinities for glucose.

[3] *Trans* acceleration is generally explained by the observations that at zero *trans* concentration (e.g., inside the cell during net uptake), the unloaded carrier has to return to the outside (i.e., the internally exposed binding site of the transporter has to change to the externally exposed one) without substrate and that this reaction is slower than the return with bound substrate. Therefore, exchange transport is generally faster than net transport. *Trans* acceleration is especially pronounced for efflux, where the *trans* effect can amount to 100-fold.

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Transport Mechanism for Sodium-Glucose Symporters

With respect to their biochemistry, SGLTs are among the best-studied transporters. Extensive electrophysiological, kinetic and binding studies; analyses of the turnover rate; tryptophan scanning and mutagenesis studies; X-ray crystallography; and plasmon resonance spectroscopy experiments have led to a detailed understanding of the transport mechanism of SGLTs (for a comprehensive review, see Reference 8). SGLT1 functions as a Na^+/glucose symporter, coupling the transport of glucose to that of two sodium ions, whereas SGLT2 symports only a single sodium molecule (8). Most recently, conformational rearrangements were probed by single-molecule force spectroscopy (86).

Turnover rate: number of molecules transported per transport protein per second

Driving force: enthalpy; refers to uncharged substrates driven by a substrate gradient and charged substrates driven by an electrochemical gradient

Transport Mechanism for SWEETs

Common features of all SWEETs characterized to date are their ability to transport various mono- and disaccharides, their ability to mediate both cellular uptake and efflux, and their typically low affinities for sugars. This low affinity may be interpreted as a feature of transporters specialized in high turnover rates, rather than efficient movement at low substrate levels. Direct measurement of turnover numbers will be important to evaluate this hypothesis. SWEETs may function as uniporters, although this hypothesis remains unproven. Bidirectionality of sugar transport in radiotracer measurements in *Xenopus* oocytes as well as pH independence are consistent with a uniport mechanism. However, pH independence is a product of the properties of the transport protein and the driving force. For example, for electrogenic ammonium transporters, the driving force should increase with decreasing pH, yet these transporters' activity shows a steep optimum at pH ~7. Therefore, it will be important to perform more detailed experiments, including binding studies and analyses of the transporters' affinity for substrate supplied from the medium versus the cytosol, to confirm uniporter function. Molecular dynamics simulations that make use of the crystal structures (see the next section) may prove valuable for our understanding of the details of the transport cycle and mechanism (87).

SUGAR TRANSPORTER STRUCTURES

The first crystal structure of a sugar transport protein was published in 2003 (**Table 2**) (88). Earlier, many groups had attempted to obtain mechanistic insights by mutating transport proteins on the basis of educated guesses, random mutagenesis, or so-called cysteine-scanning mutagenesis (89–91). These endeavors provided the first indications of TM helices and/or individual amino acids, which were postulated to be involved in substrate binding. In many cases, insights into the atomic structures confirmed earlier predictions regarding overall topology and substrate interactions (92, 93). Over the past decade, more than 10 additional crystal structures of sugar transporters have been published (**Table 2**), and detailed mechanistic conceptions of the actual membrane translocation steps are now available (see the section titled Transport Mechanism). **Figure 3** shows sample structures for each of the three sugar transporter superfamilies, namely the SGLTs, GLUTs and SWEETs.

Insights into the transporters' structure and the processes that take place during the transport cycle are valuable for understanding how transporters have evolved, but combining these data with analyses of naturally occurring variants and haplotypes will also help us understand the roles of the transporters in physiology and in disease. This knowledge will be valuable both for designing new disease treatments and for improving crop yield.

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Table 2 Crystal structures for sugar transporters[a]

Family	Transporter	Substrate	Cotransport	Sugar-binding site	Protein Data Bank identifier(s)	Reference(s)
MFS	lacY	TDG, MTS-gal	H^+ E269, R302, H322, E325	E126, R144, W151, D237, E269, N272, H322, K358, Q359	1PV6, 1PV7, 2CFP, 2CFQ, 2V8N, 2Y5Y, 4OAA	88, 142–145
MFS	Fuc	β-NG	H^+ D46, E135	E135, N162	3O7P, 3O7Q	146
MFS	XylE	Xylose, glucose	H^+	Q168, Q288, Q289, N294, W392, Q415, Y298, F24, Y298, W392, W416	4GC0, 4GBY, 4GBZ, 4JA3, 4JA4	55, 96
MFS	$GlcP_{Se}$	Glucose	H^+ D22, R102	Q137, Q250, Q251, N256, W357	4LDS	97
MFS (SLC2)	GLUT1	β-NG	Uniport	Q282, Q283, N288, N317, N415	4PYP	94
SSF (SLC5)	vSGLT1	Galactose	Na^+ A62, I65, A361, S365	Q69, Y87, E88, S91, N260, Y263, K294, Q428	3DH4, 2XQ2	98, 100
ABC	$MalFGK_2$	Maltose	ATP hydrolysis	MalF: Y325, S329, N376, L379, G380, Y383, S433, F436, N437, N440	2R6G, 3FH6, 3PV0, 3PUV, 3PUW, 3PUX, 3RLF, 3PUY, 3PUZ, 4JBW	107–110
PTS	EIIC	$(GlcNAc)_2$	PEP-dependent phosphorylation	W245, H250, D290, G297, N333, E334, W382	3QNQ	147
SWEET	*Vs*SemiSWEET	Unknown	Unknown	W59, N75	4QNC	53
SWEET	*Lb*SemiSWEET	Glucose	Unknown	W48, N64	4QND	53
SWEET	*Ty*SemiSWEET	Unknown	Unknown	Not tested	4RNG	54

[a]Red text represents hydrogen bonds; green, water-mediated hydrogen bonds; blue, π-stacking; and purple, cation interactions. Abbreviations: $(GlcNAc)_2$, *N*,*N*′-diacetylchitobiose; GLUT, glucose transporter; *Ls*, *Leptospira biflexa*; MFS, major facilitator superfamily; MTS-gal, MTS-galactoside; PEP, phosphoenolpyruvate; PTS, phosphotransferase system; *Se*, *Staphylococcus epidermidis*; SGLT, sodium-glucose symporter; TDG, β-D-galactopyranosyl 1-thio-β-D-galactopyranoside; *Ty*, *Thermodesulfovibrio yellowstonii*; *Vs*, *Vibrio* sp.; β-NG, *n*-nonyl-β-D-glucopyranoside.

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Evolution and Structure of Glucose Transporters

After years of intense research, several structures of bacterial homologs of GLUTs have been resolved, but only recently was the structure of human GLUT1, the first cloned member of this family, resolved to 3.2 Å (**Figure 3**) (94). GLUT1 has the canonical 12-TM fold of the MFS. MFS transporters are organized into two pseudosymmetrical halves, each composed of a pair of antiparallel triple-helix bundles (THBs). This common [3+3+3+3] configuration for members of the MFS suggests that they may have resulted from an intragenic multiplication of the THBs (95). Like other MFS transporters, GLUT1 works by an alternating access mechanism, which is best understood through a comparison to the structure of the xylose/H^+ *E. coli* symporter XylE

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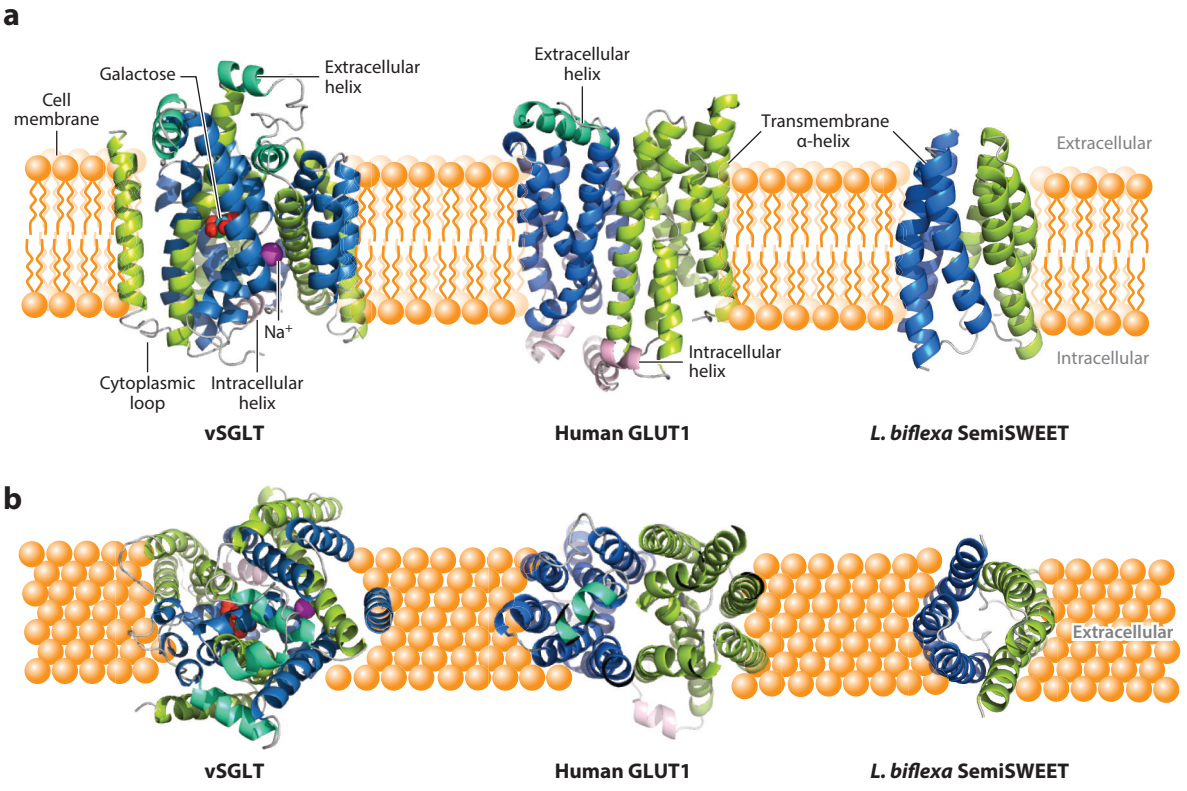

Figure 3

Structures of three classes of sugar transporters in eukaryotes. (*a*) Side views of a model of *Vibrio parahaemolyticus* SGLT [Protein Data Bank (PDB) identifier 3DH4] (98), a homolog of the human SGLTs, human GLUT1 (PDB 4PYP) (94), and the SemiSWEET from *Leptospira biflexa* serovar Patoc, a bacterial homolog of the SWEETs (PDB 4QNC) (53). (*b*) Extracellular view of the same structures. Blue and light green represent the N-terminal and C-terminal parts of the protein, respectively, for vSGLT and human GLUT1, or represent one of two protomers for SemiSWEET. The extracellular helix, intracellular helix, and cytoplasmic loop are colored green, light pink, and gray, respectively. Bound galactose is shown as red spheres, and green spheres represent the carbon and oxygen atoms. The tentative sodium ion is shown as a magenta sphere. Images were prepared with PYMOL. Abbreviations: GLUT, glucose transporter; SGLT, sodium-glucose symporter.

(55), the only MFS transporter for which three different states (outward-facing partially occluded, inward-facing partially occluded, and inward-facing open) are available (96).

GLUT1 has an intracellular helical (ICH) domain composed of four α-helices that it shares with its bacterial homologs, namely XylE and the glucose/H^+ *Staphylococcus epidermidis* symporter GlcP (97), but not with other MFS transporters with known structures. Residues that mediate the ICH interaction with the rest of the protein are conserved between the human GLUTs and the bacterial XylE. This ICH domain is proposed to be a unique feature of the sugar transporter family that facilitates the closure of the intracellular gate in the outward-facing conformation.

An important distinction between the uniporter GLUT1 and the proton symporters XylE and $GlcP_{Se}$ (where the subscript *Se* refers to *Staphylococcus epidermidis*) is the exchange between Asp22 and asparagine in the corresponding position in GLUT1; this substitution may help explain the difference in transport mechanism. The findings that TM1 is involved in H^+ binding and that D22N abrogates proton coupling and results in uniport (97) were reported first for $GlcP_{Se}$. Similar

results were later reported for Asp27 in XylE (93). At the structural level, the protonated aspartic acid is similar to asparagine, a finding that led Yan and collaborators to propose that "a uniporter can be regarded as a permanently protonated symporter" (94, p. 124).

Mapping of disease-related mutations onto the structure of GLUT1 has revealed three distinctive clusters: Cluster I maps to residues involved in sugar binding, whereas cluster II maps to residues at the interface between the ICH and the cytosolic portion of the TMs and cluster III to residues near the extracellular side of the transport path. Clustering mutations suggest the possibility of developing therapeutic agents for multiple mutations that may have similar mechanisms (94).

In both GLUT1 and XylE, glucose (or an analog) is bound between the N- and C-halves of the protein and is coordinated by polar and aromatic residues mainly from the C-terminal domain (**Table 2**). On the basis of a comparison between the outward-facing structure of XylE and the inward-open one of GLUT1, Yan and collaborators (94) proposed a translocation mechanism in which the C-terminal domain recognizes glucose while the N-terminal domain undergoes a rocking-type movement that exposes the substrate to alternate sides of the membrane.

Various lines of evidence support the hypothesis that GLUT1 forms a tetramer, a quaternary structure that is important for understanding the *trans* acceleration observed for GLUT1-mediated transport. So far, however, structural analyses have not provided further information about the unusual kinetics that have been observed.

Evolution and Structure of Sodium-Glucose Symporters

SGLTs belong to the large sodium-solute symport family (SSF) (8), which is responsible for coupled transport processes ranging from channeling water and urea to sensing glucose in cholinergic neurons. A bacterial homolog of the human SGLT1 from *Vibrio parahaemolyticus* (vSGLT) has been crystallized to 3.0-Å and 2.7-Å resolution in the inward-facing occluded and inward-facing open states, respectively (**Table 2**) (**Figure 3**) (98). vSGLT forms a 14-TM fold organized into two pseudosymmetrical inverted halves. Of these 14 TM helices, 10 (TM2–6 and TM7–11) make up the pore for galactose translocation. This topology is reminiscent of that of the leucine transporter (LeuT), which is apparently unrelated to that of GLUTs and SWEETs. This disparity indicates that SGLTs may have evolved independently from the other sugar transporters. The identification of two conformations indicates that SGLTs also function by an alternating access mechanism. This structural information is highly valuable, given that SGLT1 is among the best-characterized transporters (8, 86).

The substrate-binding site of vSGLT is located halfway through the membrane, where the pyranose ring of galactose forms stacking interactions with Tyr263, and its hydroxyl groups form hydrogen bonds with both charged and polar uncharged residues (**Table 2**) (98). Among these residues, Gln428 aligns with Gln457 of human intestinal SGLT1 and with Glu457 of the non-transporting glucose sensor SGLT3; Gln428 couples ion flux to sugar transport. Glutamate substitution of Gln457 in human SGLT1 uncouples sodium and glucose transport, whereas glutamine substitution of Glu457 in SGLT3 confers glucose transporter activity (99).

A sequence comparison between LeuT and vSGLT allowed the identification of a potential Na^+-binding site for vSGLT, away from the sugar-binding site (98). Mutation of a serine residue in this site abolished Na^+-dependent transport in proteoliposomes (**Table 2**). Release of sodium from this site may induce the transition from the inward-facing occluded to the inward-facing open state through rigid-body movements of subdomains. This conformational change may subsequently allow both entrance of water into the substrate-binding site and release of galactose (100).

Notably, each member of the SSF has a distinct substrate specificity including amino acids, neurotransmitters, and iodide. Careful phylogenetic analyses indicate that SGLTs fall into the

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amino acid/polyamine/organocation (APC) superfamily, covering an even wider spectrum of substrates (101). Members of the SSF are also interesting because there is evidence that they can transport water (8).

Evolution and Structure of SWEETs

Initially, several *Arabidopsis* and rice SWEETs were identified as glucose or sucrose transporters, and the *C. elegans* and human homologs, *Ce*SWEET1 and *Hs*SWEET1, were demonstrated to be as glucose transporters. Thereafter, additional isoforms and SWEETs from a variety of other plants were shown to transport sugars. Apart from their widespread occurrence in all eukaryotic kingdoms, including fungi, plants, and animals, homologs have also been found in prokaryotes. Both SWEETs and the bacterial SemiSWEETs homologs have been classified as members of the MtN3 saliva family (PFAM database code PF03083; see **http://pfam.xfam.org**). A key characteristic of the eukaryotic SWEETs is the presence of seven predicted TM-spanning domains; in contrast, the prokaryotic homologs are much smaller and contain only three predicted TMs, so they have been termed SemiSWEETs. Interestingly, the eukaryotic SWEETs consist of a direct repeat of a bacterial three-TM unit (TM1–3 and TM5–7), separated by an additional, less conserved TM (TM4). This configuration may suggest that eukaryotic SWEETs evolved from the ancestral prokaryotic SemiSWEETs by gene duplication and fusion, processes that have been observed for various eukaryotic transporters (e.g., ABC transporters). Thus, bacterial SemiSWEETs may have had to form at least a dimer to create a translocation pore, and the additional TM4 in the eukaryotic SWEETs may have served as an inversion linked domain that reoriented the second repeat and created a structure analogous to that in prokaryotic SemiSWEET dimers (102).

SemiSWEETs and SWEETs are predicted to have an extracellular N terminus and a cytosolic C terminus and to follow the "positive inside" rule, according to which excess positive charges in the loops face the cytosol. This proposed structure is supported by the observation that the C terminus of SWEET11 is phosphorylated in *Arabidopsis* (103). Despite the low sequence conservation, the prokaryotic SemiSWEETs can also function as sugar transporters. Specifically, *Bj*SemiSWEET1, from *Bradyrhizobium japonicum*, is capable of transporting sucrose (102), and *Lb*SemiSWEET, from *Leptospira biflexa*, can mediate glucose transport (53).

Three SemiSWEET structures have been resolved to 1.7 Å and 2.4 Å for *Vs*SemiSWEET (a *Vibrio* homolog), *Lb*SemiSWEET, and *Ty*SemiSWEET (from *Thermodesulfovibrio yellowstonii*) (**Figure 3**) (53, 54). The putative sugar translocation pore is formed by a dimer. Despite low overall sequence conservation, the structures of the protomers are highly similar; all are characterized by a basic unit consisting of a THB similar to that of MFS, in which TM3 is inserted between TM1 and TM2. This observation led Feng and collaborators (53) to propose that these families may have evolved from an ancestral THB into a parallel [3]+[3]/[3+1+3] configuration for SemiSWEETs/SWEETs and an antiparallel [3+3+3+3] configuration for MFS transporters or from convergent evolution. The two crystal structures show some remarkable differences, too; *Vs*SemiSWEET appears to represent an outward-facing open state, whereas *Lb*SemiSWEET and *Ty*SemiSWEET appear to have crystallized in an occluded state in which the protomers are tilted by ~10°. The presence of two different states indicates that SemiSWEETs, and by analogy SWEETs, are actual transporters (as opposed to channels) that undergo a rigid-body rocking-type movement during the transport cycle, similar to the movement that occurs in the other sugar transporters described above (**Figure 4**).

Channel: typically minor conformational rearrangement during the transport cycle with resulting high turnover rates; under certain conditions, some transporters can function in channel mode

In the occluded state of *Lb*SemiSWEET, a cavity sealed from solvent is present right above the center of the protein. Within this cavity, a pair of Trp48 and Asn64 residues from both protomers

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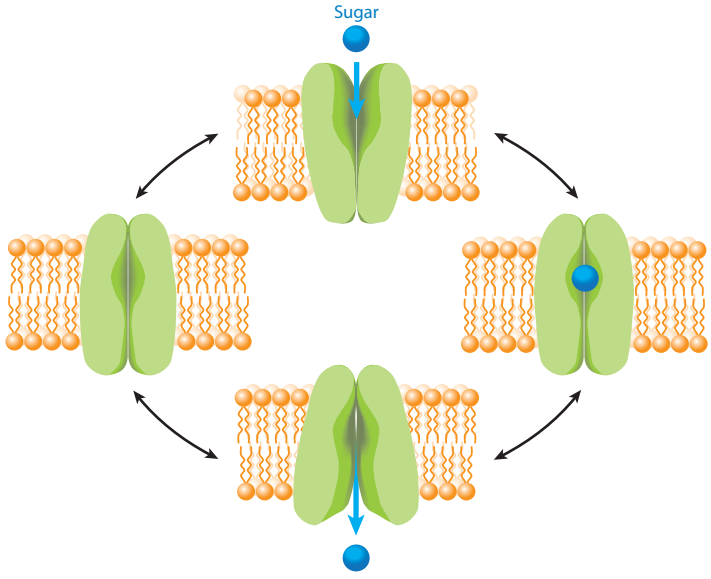

Figure 4

Predicted model of the transport cycle of SWEETs. If SWEETs function as uniporters, a glucose molecule present on the extracellular side of the membrane could bind to the open outward state of the SWEET. In this model, the transporter undergoes a conformational rearrangement, creating an occluded, substrate-bound state that, in turn, triggers a second conversion to an inward open state followed by release of the glucose. The transporter then returns to the outward open state. Alternatively, when the molecule is bound on the inside, the transporter exports the sugar in a series of similar steps.

is well positioned to form stacking interactions and/or hydrogen bonds with the substrate. Indeed, hydrogen bonding with positively charged side chains is a common feature of sugar-binding proteins (26–28), and alanine substitution of these residues, as well as the corresponding ones in *Arabidopsis* SWEET1, abolished the activity of the transporters (53). Ultimately, the crystal structure of a SemiSWEET dimer or a SWEET bound to its putative substrate will be necessary to reveal the actual sugar recognition process.

The crystal structures of SemiSWEETs clearly show that a dimer is sufficient to form the translocation pore, and analogously a SWEET monomer should be sufficient too. However, experiments using the split ubiquitin and split green fluorescent protein systems show that *Arabidopsis* SWEETs can form homo- and hetero-oligomers. Moreover, coexpression of wild-type *Arabidopsis* SWEET1 with a Gly58 mutant—which properly localized to the plasma membrane but could not transport glucose—resulted in loss of transport activity of the wild type, further supporting oligomerization (102). In the absence of structural information and more mutagenesis analyses of the eukaryotic SWEETs, the role of this process remains elusive. A possible explanation is that SWEETs can form higher-order oligomers as part of a more complex behavior, similar to that of GLUTs (104).

The transport mechanism of the SemiSWEETs and SWEETs has not been fully characterized, and although the current data are compatible with uniport/facilitated diffusion (15, 61, 105), more complicated mechanisms may be responsible. Apparently, in oocytes, sugar uptake by SWEET1 is largely insensitive to pH (a hypothesis tested only for *Arabidopsis* SWEET1), but the current data do not exclude the possibility that SWEETs are cotransporters.

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Another obvious feature of eukaryotic SWEETs is their long cytosolic C terminus, which carries multiple phosphorylation sites. The length of the C terminus varies between 16 and 120 amino acids, with an average of ~45 amino acids, derived from analyses of SWEETs from more than 80 plant proteins from 3 species. Otherwise, the C terminus is characterized by low apparent conservation between isoforms and even between closely related species. The cytosolic C terminus may act as a hub for binding of other proteins (e.g., regulatory components), or it could function in transmission of signals to the cell if SWEETs also work as sugar receptors (or transceptors). Thus, it will be important to determine the affinities and turnover rate of these transporters and their substrate spectrum, as well as whether sugar transport by SemiSWEETs and SWEETs is coupled or energized. If they are indeed uniporters, it would be interesting to learn whether they have physiological roles in cellular import and, furthermore, whether they exhibit *trans* acceleration or inhibition by extracellular, osmotic control.

When comparing the structures of MFS, SGLT, and SWEET classes of sugar transporters, it is interesting to note that their sugar-binding sites are configured differently but also have some common features. For instance, the binding sites are near the center of the membrane bilayer and are located at the interface between two repeats, and aromatic residues play critical roles by either providing stacking interactions with the substrate or constituting restrictions in the channel to prevent the substrate's escape.

Structures of Other Sugar Transporters

Although they are not a central topic of this review, we briefly discuss sugar transporters found in bacteria for comparison.

Sugar transporters belonging to the ABC transporter family. ABC transporters are primary active systems that use the energy derived from ATP hydrolysis to transport substrates against a concentration gradient. So far, no human or plant ABC transporter is known to transport sugars (106), yet numerous ABC transporter family members are still uncharacterized, so ABC sugar transporters may exist.

E. coli $MalFGK_2$, a bacterial ABC transporter involved in maltose transport, has been crystallized in an inward-facing state by itself both in (*a*) pretranslocation and outward-facing states in complex with the periplasmic maltose-binding protein (MBP) and (*b*) an inhibited state in complex with the cytoplasmic glucose-specific phosphotransferase system enzyme IIA ($EIIA^{Glc}$) (107–110). The $MalFGK_2$ system is composed of two membrane proteins, MalF and MalG, and two copies of the cytoplasmic ATP-binding cassette MalK. The TM pore is formed by the core region of MalG (TM2–5) and that of MalF (TM4–7). Transition from the inward- to the outward-facing conformations involves rigid-body movements, with a 22° rotation of the MalF core and a 23° rotation of the MalG core (108). Overall, alternating access is proposed to result from a rocking-type motion, as in MFS and SWEETs transporters (53, 88). In the pretranslocation state, maltose is bound by the MBP in the closed conformation, whereas the MalF–MalG cores adopt an occluded one. Formation of the outward-facing state is accompanied by transfer of maltose to the MalF–MaG core and positioning of ATP at the hydrolysis site. Upon ATP hydrolysis, the MalF–MaG core adopts the inward-facing open state with release of maltose to the cytoplasmic side (107). In the occluded state, no residues from MalG interact with maltose, and several residues from MalF make hydrogen bonds, van der Waals interactions, and stacking interactions with the sugar (**Table 2**) (107–110). This situation is similar to the case of GLUT1, in which residues responsible for sugar binding are located in only one half of the translocation pore, the C-domain half of the transporter, as described above.

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Phosphotransferase system–type transporters. Bacterial PTS systems (6) are responsible for the active uptake of a wide spectrum of mono-, di-, and oligosaccharides. So far, however, no homologs have been found in higher eukaryotes (111). The crystal structure of an EIIC transporter subunit involved in *N,N*-diacetylchitobiose uptake shows a two-domain structure in which each monomer consists of 10 TMs (112). The first five TMs form an N-terminal oligomerization domain, which is connected by an amphipathic helix with the second five-TM domain forming the translocation pore. This structure appears to be distinct from the eukaryotic sugar transporters reviewed here (for details, see References 6 and 112).

SIGNALING AND REGULATION

Sugar transport activity has to be tightly controlled to ensure sufficient supply to cells that depend on glucose delivered by other cells, most prominently the brain in animals and any nonphotosynthetic tissues in plants, such as the developing seeds. At the same time, overaccumulation needs to be avoided because it can cause toxicity. Animals have developed sophisticated control networks in which insulin and glucagon play key roles in adjusting blood glucose levels. The tongue, the intestine, and the pancreas contain specialized systems for monitoring external glucose levels, such as "sweet taste" sensors that regulate sugar transport activity (113). Human GLUT2 has been deemed a sugar sensor; however, although it is essential for the uptake of glucose into pancreatic β-cells, it does not appear to function directly as a sensor but rather is necessary for intracellular sensing mechanisms to operate. In this sense, transporters can affect cytosolic sugar levels, which in turn affect signaling networks. Moreover, cells can monitor conformational rearrangements that are induced by sugar binding or occur during the transport cycle, as in SNF3 and RGT2 from *Saccharomyces cerevisiae* (114). The yeast genome encodes 18 hexose transporters, as well as 2 homologous proteins that look like transporters but have never been shown to mediate transport. These transporter-like receptors appear to be one end of a contiguous spectrum of transport and sensing, which includes proteins that have dual function and have thus been termed transceptors (115). SGLT3 is apparently nonfunctional as a transporter and is thought to function as a sugar receptor, similar to SNF3 and RGT2 (99). However, more direct proof that SGLT3 acts as a sugar sensor, as achieved in the case of SNF3 through the identification of constitutive signaling mutants, would be valuable. Similarly, SUT2 had been considered to be a potential sucrose sensor, yet no direct evidence for this hypothesis has been presented (116). Extended loops or long C termini are certainly candidate platforms that could link to intracellular signaling cascades. Transporters undergo conformational rearrangements during their transport cycle, which can be detected in vivo with fluorescent protein fusions (62, 63). Thus, the cell may monitor these conformational rearrangements to provide information on sugar availability and/or flux rates.

Sugar transporters are also targets of regulation. For example, the yeast hexose transporter HXT5 is subject to control by multiple signaling networks (117). Many transporters are highly regulated at the posttranscriptional and posttranslational levels. Surprisingly, however, little is known about the regulatory networks that control their activity. A notable exception is GLUT4, which is highly regulated at the level of trafficking (77). GLUT1, GLUT2, GLUT4, SGLT1, and SGLT2 may all be regulated by phosphorylation at various residues, and the glucocorticoid-induced kinase SGK1, as well as protein kinase A, has been implicated in phosphorylation, yet complete regulatory networks of posttranslational control of sugar fluxes are largely incomplete (118–120). Similarly, little is known about the regulation of the plant sugar transporters. New technologies, such as transporter activity sensors, may be a means to advance this critically important area (62, 63). The activity of transporters can also be tightly controlled by targeting; the most prominent example is muscle GLUT4 (78), which resides in

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Table 3 Pathophysiology of genetic defects related to glucose transporter (GLUT) genes

Gene	Syndrome	OMIM code	Symptoms	Reference(s)
GLUT1 (*SLC2A1*)	GLUT1 deficiency	606777	Reduced glucose transport across blood–brain barrier, infantile seizures, delayed development, and acquired microcephaly	148
GLUT2 (*SLC2A2*)	Fanconi–Bickel	227810	Fasting hypoglycemia and ketonuria, postprandial hyperglycemia, hypercholesterolemia, steatosis, hyperlipidemia, hepatorenal glycogen accumulation leading to hepatomegaly, proximal renal tubular dysfunction, small stature	149
GLUT9 (*SLC2A9*)	Renal hypouricemia	612076	Hypouricemia	150, 151
GLUT10 (*SLC2A10*)	Arterial tortuosity	208050	Connective tissue disorder with elongation and tortuosity of the major arteries (including aorta), skin and joint abnormalities (hyperextensibility, hyperlaxity), micrognathia, elongated face	152

Abbreviation: OMIM, Online Mendelian Inheritance in (hu)Man. Source: **http://omim.org/**.

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intracellular compartments and is released in response to stimulation by insulin. Further research will be required in all systems to obtain a more complete picture of sugar signaling networks.

PHYSIOLOGICAL ROLES OF SUGAR TRANSPORTERS

Physiology of Glucose Transporters

Human GLUT1–4 facilitate the uptake of glucose in a myriad of cell types, most notably erythrocytes, muscle and fat cells, endothelial cells of the blood–brain barrier, pancreatic β-cells, neurons, and multiple cancer cells (55). GLUT1 was originally identified in erythrocytes; it likely supplies these circulating cells with glucose. The gene was eventually cloned from HepG2 cells. The observation that GLUT1 deficiency can cause epilepsy suggests that GLUT1 also has an important role in supplying glucose to the brain. GLUT2 is essential for glucose uptake into the β-cells of the pancreas. Moreover, GLUT2 is induced in a sugar receptor–dependent manner in the intestine, where it likely plays a key role in glucose absorption at high levels of sugar supply. GLUT4 is well known for its central role in uptake into muscles and, thus, blood glucose homeostasis. GLUT9 is known as a urate/glucose antiporter; transport of glucose has also been observed in HepG2 cells (121). A detailed discussion of the pathophysiology of the GLUT family would go beyond the scope of this review; therefore, we refer readers to excellent reviews published elsewhere (**Tables 3** and **4**) (70, 122).

Physiology of Sodium-Glucose Symporters

SGLT1 is responsible for secondary active sodium-coupled uptake of glucose from the intestinal tract across the apical membrane into intestinal cells. It serves as a high-affinity transporter and is able to transport glucose against a concentration gradient. In conjunction with facilitative sugar transporters on the basal membrane, SGLT1 is thought to actively import sugars into the bloodstream. Mutations in SGLT1 lead to glucose-galactose malabsorption syndrome. SGLT2 is expressed in the kidney, particularly the proximal convoluted tubule cells, where it retrieves glucose that enters the lumen of the tubules. SGLT2 couples the transport of one sodium ion to the transport of one glucose molecule. Drugs that target SGLT2 are being used to treat type II

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Table 4 Overview of glucose transporter (GLUT)-deficient mouse models (122)[a]

Gene	Major phenotype	Reference(s)
GLUT1 (*SLC2A1*)	Homozygous: embryonic lethal Heterozygous: similar to human GLUT1 deficiency syndrome	153
GLUT2 (*SLC2A2*)	Homozygous: type II diabetes symptoms, early neonatal death	154
GLUT3 (*SLC2A3*)	Homozygous: embryonic lethal Heterozygous: autism spectrum disorders, adult onset of insulin resistance in males	155–159
GLUT4 (*SLC2A4*)	Homozygous: growth retardation, cardiomegaly, hyperglycemia, glucose intolerance and insulin resistance, development of diabetes in some patients, insulin resistance in liver and muscle. Heterozygous: diabetes, male mice with adult-onset adiposity and insulin resistance	160–164
GLUT5 (*SLC2A5*)	Fructose malabsorption	165
GLUT8 (*SLC2A8*)	Homozygous: embryonic lethal, increased proliferation of hippocampal cells, increased P-wave duration in heart, reduced sperm motility, reduced mitochondrial potential, behavioral alterations (hyperactivity)	166–168
GLUT9 (*SLC2A9*)	Homozygous: hyperuricemia, hyperuricosuria, nephropathy, inflammatory fibrosis of the kidney cortex, mild renal insufficiency	169
GLUT10 (*SLC2A10*)	Irregular vessel-wall shape of arteries; increased elastic fibers; intima endothelial hypertrophy, no vascular, anatomical, or immunohistological abnormalities of vasculature	170, 171
GLUT13 (*SLC2A13*)	Homozygous: neuronal inositol transport and homeostasis unaffected	172

[a]Source: **http://www.omim.org/.**

diabetes. Consistent with being a secondary guard against glucose losses, SGLT1, which is more potent because it couples the transport of two sodium ions to the transport of one glucose molecule, retrieves glucose in the more distal parts of the tubules. A detailed discussion of the pathophysiology of the SGLT family is beyond the scope of this review, so we refer readers to other excellent reviews (**Tables 5** and **6**) (8, 123).

Physiology of SWEETs

So far, SWEETs have been implicated mainly in cellular efflux and vacuolar transport processes in plants. SemiSWEETs have been found in bacteria, and several members of this family transport

Table 5 Human sodium-dependent solute transporters[a]

Gene	Substrate	Syndrome	Reference(s)
SGLT1 (*SLC5A1*)	Glucose, galactose	Glucose galactose malabsorption	173, 174
SGLT2 (*SLC5A2*)	Glucose	Renal glucosuria	175, 176
SGLT3 (*SLC5A4*)	Glucose sensor	Unknown	99, 177
SGLT4 (*SLC5A9*)	Mannose, fructose, glucose	Unknown	178
SGLT5 (*SLC5A10*)	Glucose, fructose	Unknown	179

[a]Source: **http://www.omim.org/**.

Table 6 Overview of sodium-glucose symporter (SGLT)-deficient mouse models[a]

Gene	Major phenotype	Reference
SGLT1 (*SLC5A1*)	Homozygous: glucose-galactose malabsorption syndrome; normal when fed a glucose- and galactose-free diet	180
SGLT2 (*SLC5A2*)	Homozygous: glucosuria; polyuria; increased food and fluid intake without differences in plasma glucose concentrations, glomerular filtration rate, or urinary excretion of other proximal tubular substrates (including amino acids)	181
SGLT5 (*SLC5A10*)	Homozygous: increased urinary fructose, hepatic steatosis, increased blood levels of insulin	179

[a]Source: **http://www.omim.org/**.

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sugars; however, their physiological role remains to be determined. Much more is known about the role of SWEETs in plants (**Table 7**). Plant genomes typically encode ~20 SWEET genes. Consistent with physiological roles in efflux, possibly by a uniport mechanism, SWEETs appear to play critical roles in the efflux component of cell-to-cell transport, as well as in secretion of sugars.

The plasma membrane sucrose transporters SWEET11 and -12 are expressed inside the leaf phloem, most likely in the phloem parenchymal cells involved in providing photosynthesis-derived sugars to the actual conduits, the so-called sieve element companion cell complex. A double-mutant *sweet11;12* in *Arabidopsis* shows all signs of reduced phloem loading, such as a backlog of starch in source leaf tissue, as well as delayed root development (61). SWEET11 and -12, as well as SWEET15, are expressed in developing *Arabidopsis* seeds, particularly the maternal tissues. A triple mutant shows a "wrinkled" phenotype that, together with starch backlog in the seed coat, demonstrates that their role in sugar efflux from maternal tissues is required for seed filling (124).

The plasma membrane sucrose transporter SWEET9 is specifically expressed in *Arabidopsis* nectaries, and mutation leads to loss of nectar secretion (105). Similar phenotypes have also been observed for *sweet9* mutants in *Brassica rapa* and tobacco (105). The male sterile phenotype of *sweet8/rpg1* and *sweet13/rpg2* mutants and expression in the tapetum and pollen are consistent with roles in sugar transfer from maternal tissues to the developing pollen (125).

SWEET16 and -17 are vacuolar fructose transporters that play critical roles in vacuolar storage of sugars (71–73). It is likely that the other SWEETs in the *Arabidopsis* genome also play important roles when apoplasmic sugar transfer is required. Research on the model plant *Arabidopsis* has laid the foundation for exploring the role of SWEETs in crop plants, as they may be key targets for improving crop yield.

Excitingly, SWEETs have been implicated in disease. Apparently, SWEETs can be hijacked by plant pathogens, possibly to provide sugars to the pathogen. OsSWEET from rice (originally named Os8N3) has been identified as an underlying recessive gene for susceptibility of rice to rice blight (126). Transcription activator–like (TAL) effectors produced by bacteria directly induce SWEET expression in infected cells and probably cause leakage of sugars that are then used by the pathogens for infection. This pathogenicity mechanism does not appear to be unique, as similar processes have been observed in cassava blight (127).

As described above, SWEET homologs are found in all metazoa analyzed to date, including humans (15). Because plant and animal SWEETs align well and bioinformatic analyses predict a duplication of the basic THB, connected via TM4 as an inversion linker, we hypothesize that the seven *C. elegans* SWEETs and the single human SWEET, *Hs*SWEET1, have a [3+1+3] structure similar to that of the plant SWEETs (15). Moreover, key residues, such as the tryptophan and asparagine pairs that are essential for plant SWEET1 function are conserved in *Hs*SWEET1 (15).

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Table 7 Role of *Arabidopsis* SWEET genes

Arabidopsis gene	Other names	Substrate	Cellular localization	Organ expression[a]	Function	Reference
SWEET1	None	Glucose, galactose (weak sucrose)	Plasma membrane	Dry seed and flower	ND	15
SWEET2	None	2-Deoxyglucose	Vacuolar membrane	Leaf and flower	ND	W.J. Guo, unpublished data
SWEET3	None	2-Deoxyglucose	ND	Flower	ND	W.J. Guo, unpublished data
SWEET4	None	Glucose	Plasma membrane	Flower	ND	15
SWEET5	VEX1	Glucose	ND	Pollen vegetative cell	Possibly feeding of germ cell	15, 182
SWEET6	None	Weak 2-deoxyglucose	ER	Dry seed	ND	15, 183; W.J. Guo, unpublished data
SWEET7	None	Glucose	ND	Flower and seed	ND	15
SWEET8	RPG1	Glucose	Plasma membrane	Tapetum and pollen	Tapetum efflux, pollen nutrition	15, 125
SWEET9	None	Sucrose (weak glucose)	Plasma membrane and TGN	nectary	Nectar secretion	105
SWEET10	None	Sucrose	ND	Flower and seed	ND	61
SWEET11	None	Sucrose	Plasma membrane	Leaf and seed	Embryo nutrition and efflux from phloem parenchyma/phloem loading	61, 124
SWEET12	None	Sucrose	Plasma membrane	Leaf and seed	Embryo nutrition and efflux from phloem parenchyma/phloem loading	61, 124
SWEET13	RPG2	Sucrose	ND	Tapetum, tetrads and in leaves of *sweet11;12* mutant	Tapetum efflux, pollen nutrition, primexine deposition, phloem loading?	61, 125
SWEET14	None	Sucrose	ND	Flower	ND	61
SWEET15	SAG29	Sucrose	Plasma membrane	Seed	Embryo nutrition, possibly leaf export during senescence	61, 124, 184
SWEET16	None	Glucose, sucrose, fructose	Vacuolar membrane	Leaf, root	Increased freezing tolerance	71–73
SWEET17	None	Fructose	Vacuolar membrane	Leaf, root	Vacuolar fructose content in leaves	71–73

[a]Entries in this column derived in part from public microarray data. Abbreviations: ER, endoplasmic reticulum; ND, no data; TGN, *trans*-Golgi network.

Both *C. elegans* SWT-1 and *Hs*SWEET1 transport glucose (15). Interestingly, *Hs*SWEET1 localizes to the Golgi apparatus (15). Whereas the physiological role of the human and *C. elegans* proteins remains elusive, mutation of the SWEET homolog [previously known as recombinase gene activator protein (RGA) or RAG1-activating protein 1 (RAG1AP1)] in the sea squirt *Ciona intestinalis* leads to defects in early development. Intriguingly, *Hs*SWEET1 is highly expressed in β-cells, according to public microarray data (**https://www.genevestigator.com/gv/**). Another suggestion that SWEETs play critical roles in animal and human physiology stems from the observation that a human lymphoid progenitor cell line is deficient in the activation of RAG1 activity due to deficiency in SWEET1 (RAG1AP1) (128). The RAG1–RAG2 complex is a lymphoid-specific endonuclease that catalyzes specific DNA cleavage during V(D)J recombination. RAG1 is directly activated by phosphorylation by the AMP-activated protein kinase (AMPK), thereby linking RAG1 to sugar signaling (129). A simple hypothesis is that SWEET1 sugar transport activity in human lymphoid progenitor cells affects sugar levels, which indirectly activate RAG1. Independently, SWEET1 (referred to as RGA in these studies) has also been implicated in assisting plasma membrane trafficking of the calcium-permeable cation channel TRPV2 (transient receptor potential cation channel subfamily V member 2) (130, 131). Also, glucose is known to induce translocation of TRPV2 to the plasma membrane (132). In this case, overexpression of SWEET1 may lead to altered glucose levels, which could affect TRPV2 targeting. SWEET1, which is expressed in β-cells, may contribute to glucose homeostasis and, thus, similar to GLUT2, may play a critical role in glucose-induced insulin secretion.

OUTLOOK

Over the past few decades, researchers have made massive progress in identifying important sugar transporters, characterizing their activities, determining structure–function relationships, and linking them to diseases—and, in some cases, even developing means of treating these diseases. These advances include drugs that affect transport activity and genomic editing-based engineering of disease resistance in plants. Yet many key questions remain: (*a*) Have we identified all of the sugar transporters, or are there still some that are unknown? (*b*) Do we understand how they work? (*c*) Do we understand their regulation and integration into organisms' physiology? (*d*) Have we exploited their full potential in the contexts of agriculture, medicine, and biotechnology?

The fact that only one new class of sugar transporters (the SWEETs) has been discovered recently suggests that we have identified most sugar transporter genes. Currently, more than 50 sugar transporters or close relatives are present in a single plant genome [~20 SWEET isoforms; ~5–10 SUTs; ~14 STPs; and 1 to several each of the TMTs, the ERD6-like transporters, AtpGlcT1 (plastidic glucose translocator 1), and the VGTs (133)], whereas the human genome contains more than 20 (7 SGLTs, 13 GLUTs, 1 NaGLT1, and 1 SWEET). Note that not all of the proteins listed are actual sugar transporters, and some transport other substrates. Yet both plant and animal genomes still contain many unknown membrane proteins, including uncharacterized members of known families, such as ABC and MFS. Thus, there may well be additional genes that we have not yet characterized as sugar transporters. Despite the undisputed importance of sugar transporters in the physiology of plants and humans, we might not even be close to a complete inventory, and most importantly, we do not have a complete map of the paths sugars take within a multicellular organism. For example, the lack of effect on glucose clearance in *GLUT2* knockout mice (complemented by *GLUT1* in pancreas) is puzzling, although one expects intestinal and liver functions to be severely affected. We also have a poor understanding of the path of sugar supply to the developing embryo in plant and humans. In plants, H^+/sucrose antiporters have been predicted to play a role in embryo nutrition on the basis of physiological evidence, yet the molecular identities

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of these proteins are elusive. Both plant and animal genomes encode vesicular transporters, giving rise to the possibility that both also use vesicular pathways for intercellular sugar transport.

Biochemically, some transporters are still only partially characterized. A major breakthrough has been the availability of atomic structures for all three classes of sugar transporters. However, except for GLUT1, eukaryotic structures remain to be determined. We do not yet understand substrate recognition in all of these sugar transporters, and their coupling to the proton-motive force is still speculative (see the supplemental material). Also, although we are beginning to understand the main states, there is still much to learn about the complex processes and rearrangements that occur during transport. Thus, new technologies, possibly NMR and single-molecule force spectroscopy (86), will help advance our knowledge and understanding. New tools such as fluorescent sensors for sugars and for transport activity will further expand the spectrum of possibilities for studying transport in vivo (63, 134, 135).

Sugar transporters are positioned strategically as the entry and exit guards of the cells in an organism. Surprisingly little is known about how these activities are regulated. Several groups have begun to model sugar fluxes mathematically, and careful biochemical studies of the transporters have provided core parameterization for these models. With the availability of Förster resonance energy transfer sensors for sugars, it is now possible to determine the subcellular concentrations and dynamics of these sugars (121, 136–139). We expect that all of this new knowledge will eventually enable us to integrate regulation and multicellularity into relevant modeling. With the revolutionary progress made in this field over the past few years, especially in the area of structural biology, we expect that it will be possible to develop drugs for treatment of diseases and to systematically engineer sugar flux in plants for a better future.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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