Five Transmembrane Helices Form the Sugar Pathway through the Na\(^+\)/Glucose Cotransporter*

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To test the hypothesis that the C-terminal half of the Na\(^+\)/glucose cotransporter (SGLT1) contains the sugar permeation pathway, a cDNA construct (C5) coding for rabbit SGLT1 amino acids 407–662, helices 10–14, was expressed in Xenopus oocytes. Expression and function of C5 was followed by Western blotting, electron microscopy, radioactive tracer, and electrophysiological methods. The C5 protein was synthesized in 20-fold higher levels than SGLT1. The particle density in the protoplasmic face of the oocyte plasma membrane increased 2-fold after C5-cRNA injection compared with noninjected oocytes. The diameters of the C5 particles were comparable with those of native SGLT1 in the absence of Na\(^+\). oocytes. It behaves as a specific low affinity glucose uniporter with properties comparable with those of native SGLT1 in the absence of Na\(^+\).

MATERIALS AND METHODS

**Molecular Biology Methods**—The recombinant construct of plasmid pGEM3Zf+ containing the full-length coding sequence of rabbit SGLT1 (7) was digested with Nol to remove a ~1200-base pair DNA fragment. The fragment encodes amino acids 1–406, which cover the nine N-terminal α-helices of the SGLT1 transporter in the secondary structure model. Recirculation of the remaining large fragment (C5 construct) re-created the methionine start codon in frame. The truncated protein consisted of amino acids 407–662, which include transmembrane helices 10–14. A human equivalent of C5 (hC5) was made by the same strategy. A second human SGLT1 truncation lacking only the 14th transmembrane span (hN13) was made by mutagenic incorporation of a stop codon after Asn-648, which thereby deleted the 16 C-terminal hydrophobic residues, and the mutated domain was verified by sequencing. A BstXI fragment of hN13 bearing the new stop codon was swapped into construct hC5 to produce a third truncated human construct, hC6, amino acids 407–662 (see Fig. 1). Template DNA was linearized with EcoRI (C5) or XbaI (hC5, hC6, hN13) and used for in vitro transcription and capping with SP6 RNA polymerase (MEGAscript transcription kit, Ambion, Austin, TX).

**Oocyte Preparation, Western Blot Analysis, Freeze Fracture, and Functional Assays**—Mature Xenopus laevis oocytes were manipulated as described (7). All experiments were repeated 2–3 times on oocytes from different donors, usually 3–5 days after cRNA injection. Incubation of the oocytes for western blot analysis, SDS-polyacrylamide gel electrophoresis, and immunoblotting were done as described (8), using antibody 8821 (9) at a 1:3000 dilution. Immunoreactive proteins were detected by chemiluminescence (SuperSignal™ Kit, Pierce) and exposure on Hyperfilm ECL (Amersham Life Science Inc.). Freeze fracture of oocyte plasma membranes and sugar influxes were performed by standard procedures (10, 11). 7–10 control or cRNA-injected oocytes were incubated in the presence of \(^{14}C\)MDG\(^2\) (specific activity, 293 mCi/mmol; Amersham Life Science Inc.) alone or in the presence of different nonradioactive substrates/inhibitors. Sugars, phloretin, and phlorizin were from Sigma. Two-electrode voltage clamp measurements were performed as described (7).

**RESULTS**

**C5 Expression**—The truncated rabbit SGLT1 transporter (C5) includes the last five transmembrane domains of wild-type SGLT1 (Fig. 1). Western blot analysis (Fig. 2A) showed that oocyte expression of C5 was 20-fold higher than that of SGLT1. C5 appeared as a major band at ~29 kDa and a minor band at ~50 kDa. Full-length SGLT1 appeared as two bands; the lower band

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‡ This abbreviation used is: αMDG, α-methyl-D-glucopyranoside.
Signals were completely blocked with the antigenic peptide. The higher band corresponds to the complex glycosylated protein. All proteins were expressed in oocytes.

Secondary structure model for SGLT1 with 14 transmembrane spans. Rabbit and human SGLT1 hemi-transporters C5 and hC5 (amino acids 407–662, helices 10–14), human hC4 (amino acids 407–648, helices 10–13), and human hN13 (amino acids 1–648, helices 1–13) were separated on an 8% polyacrylamide gel electrophoresis gel and transferred to nitrocellulose. Immunoreactivity was visualized by a 5-s exposure to Hyperfilm. The calibration bar is 100 nm.

Fig. 1. Membrane topology of SGLT1. Secondary structure model for SGLT1 with 14 transmembrane spans. Rabbit and human SGLT1 hemi-transporters C5 and hC5 (amino acids 407–662, helices 10–14), human hC4 (amino acids 407–648, helices 10–13), and human hN13 (amino acids 1–648, helices 1–13) proteins were expressed in oocytes.

Sugar Transport and Specificity by C5—Can the truncated protein function as an active sugar transporter? Electrical properties of C5 expressed in oocytes were examined by the two-electrode voltage clamp technique. In experiments over several months on C5 expressing oocytes from different donors, none of the following currents characteristic of full-length SGLT1 (12) were observed: 1) transient currents in the voltage range −150 to +50 mV; 2) phlorizin-sensitive “leak” currents in the absence of sugar; or 3) Na+-specific sugar-induced currents, even at high (100 mM) sugar concentrations. The sugar uptake in 50 μM [14C]αMDG mediated by C5 was Na+-independent; there was no difference in transport between C5-expressing oocytes incubated for different time periods in 100 mM Na+ or choline chloride. Therefore all following experiments, unless indicated, were in 100 mM choline chloride. To estimate the initial rates of αMDG transport, noninjected and C5-expressing oocytes were incubated for different times in 100 mM choline chloride. Where the 50 μM [14C]αMDG sugar uptake by noninjected oocytes increased linearly with time (3 ± 1 pmol/oocyte/h), C5 uptake increased linearly for 5–10 min, plateaued in 15–20 min, and amounted to 27 ± 3 pmol/oocyte after 1 h. Therefore, sugar uptakes of C5 were measured after 7 min in subsequent experiments. C5 transported 15 ± 1.4 pmol/oocyte in choline chloride and 13 ± 1.6 pmol/oocyte in Na+, where control uptakes were 1.7 ± 0.1 pmol/oocyte in choline and 2.4 ± 0.1 pmol/oocyte in Na+. In general, C5 initial uptake rates in

3.2 nm (2%), and a third with a diameter of 10.3 ± 0.8 nm (8%). In contrast, noninjected oocytes showed a homogeneous distribution with diameter of 7.6 ± 1.2 nm (n = 875).

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at −55 kDa corresponds to the core glycosylated protein, and the higher band corresponds to the complex glycosylated protein. All signals were completely blocked with the antigenic peptide.

Fig. 2. Expression of C5, A. Western blot. Proteins from oocyte homogenates corresponding to one control oocyte, one oocyte expressing rhSGLT1, or 1/16 of a C5-expressing oocyte were separated on an 8% polyacrylamide gel electrophoresis gel and transferred to nitrocellulose. Visualization of the immunoreactive proteins was achieved by a 5-s exposure to Hyperfilm. The arrows indicate molecular mass standards in kDa (Novex, San Diego, CA). The fine band in the C5 lane at −50 kDa represents less than 10% of the intense signal at 29 kDa. B, freeze fracture. Electron micrographs of the protoplasmic face of the plasma membrane of a control (NI) and a C5-expressing oocyte. Intramembrane particle density of the control was 353 ± 54 particles/μm² (mean ± S.D., n = 2990), from an area of 7.3 μm², while the C5-expressing oocyte increased to 726 ± 292 μm⁻² was twice as high as in noninjected oocytes (353 ± 54 μm⁻²). In contrast, particle density in the plasma membrane of oocytes expressing SGLT1 was ~5000 μm⁻². Electron micrographs showed heterogeneity in the size of C5 intramembrane particles: analysis of 916 particles revealed three populations: one with a diameter of 7.1 ± 1.2 nm (mean ± S.D.), representing 90% of all C5 particles, a second with a diameter of 4.8 ± 0.3 nm (2%), and a third with a diameter of 10.3 ± 0.8 nm (8%). In contrast, noninjected oocytes showed a homogeneous distribution with diameter of 7.6 ± 1.2 nm (n = 875).
The uptake in the presence of 50 μM cold substrate ([S]). At any time, the amount of radioactivity recovered by the addition of radioactive substrate in control oocytes was 1.1 pmol/oocyte. Uptake in controls linearly increased to 3 ± 1 pmol/oocyte in 60 min. Similar results were obtained in one additional experiment. B, SGLT1 uptake in choline. SGLT1 uptake of 50 μM [14C]αMDG measured over 7 min (6 ± 2 pmol/oocyte) was completely inhibited by the addition of 100 mM D-glucose (0.6 ± 0.01 pmol/oocyte) or αMDG (0.9 ± 0.1 pmol/oocyte). 100 mM αMDG decreased the signal to 4 ± 1 pmol/oocyte. The Na+-dependent SGLT1 uptake for the same time measured 74 ± 8 pmol/oocyte. Noninjected oocytes transported 2 ± 1 pmol/oocyte. Similar results were obtained in one additional experiment. C, apparent affinity of C5 for αMDG. Uptake of 50 μM [14C]αMDG into control oocytes (NI) and oocytes expressing C5 was followed for 7 min by the addition of different concentration of nonradioactive αMDG (in mM: 0, 50, 100, and 150). The transport rate was reduced from 11 ± 1 pmol/oocyte in 50 μM [14C]αMDG to 3 ± 1 pmol/oocyte at 100 mM αMDG and 0.9 ± 0.2 pmol/oocyte at 150 mM αMDG. 50% inhibition of the uptake rate was reached by the addition of ~50 mM αMDG. Endogenous αMDG transport in control oocytes was 0.7 ± 0.1 pmol/oocyte. D, stereoselectivity. The 7-min uptake of 50 μM [14C]MDG into oocytes expressing C5 was reduced by 50% with 100 mM l-glucose (from 7.5 ± 1.2 pmol/oocyte to 4.2 ± 0.2 pmol/oocyte), whereas 100 mM D-glucose (7 ± 1 pmol/oocyte) left the protein transport rate unaffected. These results were confirmed in three additional experiments. Endogenous sugar transport in control oocytes was 1.1 ± 0.01 pmol/oocyte.

The C5-mediated influx of 50 μM [14C]αMDG was reduced 50% by the addition of 50 mM αMDG (Fig. 3C), suggesting an apparent K_m for C5 of about 50 mM. The maximal velocity (V_max) for C5 was estimated from the net initial rates (v) of sugar uptake in the presence of 50 mM cold substrate (S). At any substrate concentration the initial velocity is related to V_max by the equation: v(V_max − [S]/(K_m + [S])). The calculated V_max was ~1500 pmol/oocyte/min. Knowing the number of C5 particles in the plasma membrane and the maximal velocity for αMDG, we estimated the C5 turnover number (V_max/number of particles). The number of C5 plasma membrane particles is approximately the product of the oocyte surface area (6 × 10^7 μm^2, Ref. 10) and the C5 particle density (375 μm^2; Fig. 2B). The difference in the particle density between C5-injected oocytes and noninjected oocytes (legend of Fig. 2B) was ~373 μm^2. Therefore the C5 turnover number is ~660 s^-1 (V_max/number of particles).

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pmol/oocyte/h) was 30% above the noninjected level of transport (3.4 ± 0.1 pmol/oocyte/h, p < 10⁻⁴).

**DISCUSSION**

Expression of the C₅ protein in Xenopus oocytes resulted in a 20-fold increase in the rate of Na⁺-independent glucose uptake; the half-time of sugar equilibration with the cell was 5–7 min for C₅ and 180 min for control oocytes (Fig. 3A), and the initial rate of sugar uptake was 10–20-fold greater than in controls (Figs. 3, C and D, and 4). Sugar uptake by C₅ was independent of the cation species (Na⁺ or choline) and was equilibrative, i.e. the steady-state uptake, 20 pmol/oocyte, was that expected for Na⁺. The apparent affinity of C₅ for αMDG (Kᵡ₅MDG) was ∼500 M⁻¹, and sugar transport was similar to the uptake mediated by SGLT1 in the absence of Na⁺. This includes: 1) the higher initial rate of sugar uptake than in control oocytes (Figs. 3 and 4); 2) the sugar specificity, αMDG > d-glucose > d-galactose >> L-glucose = d-mannose (Fig. 3); 3) the low sensitivity to phlorizin (Fig. 4), which is not unexpected as phlorizin inhibition of SGLT1 is Na⁺-dependent; and 4) the similar sensitivity to phloretin, Kᵡ₅ 500–5000 μM (Fig. 4). Because the facilitated sugar transport mediated by the GLUT family members also shows sensitivity to phloretin (13), it is possible that the GLUT family members and C₅ interact by a common mechanism with the sugar substrate. Our results suggest that the C₅ truncated protein retains sufficient tertiary structure to transport sugar in a fashion similar to the wild-type protein in the absence of Na⁺−consistent with the previous report (6) that affinity and substrate specificity of Na⁺/sugar cotransport are determined by the C-terminal half of the protein. Although it is perhaps surprising that the truncated protein retains function, it should be noted that a truncated lactose permease (helices 7–12) mediates downhill lactose transport (14), suggesting the localization of essential structures for high affinity binding and substrate translocation within the last six helices of lac permease.

Injection of C₅ cRNA into oocytes resulted in high levels of accumulation (10–20 times higher than SGLT1) of a protein with the expected molecular mass of ∼30 kDa (Fig. 2A). This higher synthesis may be due to a prolonged half-life of the cRNA or changed secondary structures of the cRNA favoring easier initiation of C₅ translation, or it could simply be a reflection of a more effective transfer to nitrocellulose of the smaller C₅ protein. Freeze fracture electron microscopy of the plasma membrane (Fig. 2B) showed that only a small fraction of the protein was inserted into the plasma membrane and that the density of the protoplasmic face intramembrane particles in C₅ expressing oocytes was about twice that of noninjected oocytes. The lower amount of C₅ molecules in the plasma membrane is probably due to inefficiency of C₅ trafficking to the plasma membrane (8). The estimated Vₘₐₓ for C₅ was 1500 pmol/oocyte/min, and the turnover of αMDG by C₅ was 660 molecules/particle. In contrast, the turnover of wild-type SGLT1 is 30–60 s⁻¹ (5), an order of magnitude lower. This lower turnover rate of Na⁺⁻driven sugar transport by SGLT1 presumably reflects constraints imposed on the conformational changes in the C₅ domain, which normally accompany sugar transit through intact SGLT1. These constraints are likely the natural consequences of the coupling of sugar transport with Na⁺ transport. Interestingly, the C₅ turnover number is in the range of the turnover of facilitated glucose carrier proteins (GLUTs), like the human erythrocyte glucose transporter (330–660 s⁻¹; Ref. 15). Although C₅ functions as a facilitated sugar transporter, it is not clear if the functional protein is monomeric or oligomeric. Our freeze fracture electron microscopic analysis of C₅ in the oocyte plasma membrane suggests that the protein exists as three populations of intramembrane particles with diameters of 4.8, 7.1, and 10.3 nm. The smallest particle is probably a C₅ monomer, and the larger particles are probably oligomers. Analysis of glucose/galactose malabsorption SGLT1 mutants provides additional evidence that sugar affinity and transport are determined by the last five C-terminal helices of SGLT1. In two naturally occurring mutations in patients with glucose/galactose malabsorption, sugar transport is compromised in the absence of major effects on Na⁺ binding. In one, R499H in helix 12, the sugar affinity was markedly reduced (16); in the other, Q457R in helix 11, sugar binding was reduced by an order of magnitude, and there was no sugar translocation (17). Moreover, mutations in the N-terminal half of SGLT1, e.g. K321A in helix 7, dramatically decreased the apparent Na⁺ affinity without changes in sugar affinity (18). These results, together with our observations that C₅, unlike SGLT1 (12), does not exhibit the Na⁺ leak pathway or voltage-induced fast current transients, may be taken as evidence that Na⁺ binding and translocation occur through the N-terminal half of the protein. Previous energy transfer measurements between extrinsic fluorescent probes covalently attached to the putative Na⁺ binding sites of the cotransporter indicated that the distance between the active sites was 35 Å (19).

Our conclusion is that five transmembrane helices (10–14) of SGLT1 retain sufficient tertiary structure to transport sugar downhill in a stereospecific, selective, phloretin-sensitive manner. Given that the 14th helix is absent from a number of functional SGLT family members (3, 20), e.g. the Na⁺/iodide and H⁺/proline cotransporters, and that partial function was retained by the human SGLT1 when the 14th helix was deleted (hN₅1₄), the present study suggests that the critical requirement for sugar transport pathway perhaps is formed by just four helices (10–13). The N-terminal region of SGLT1 (helices 1–9) may be required to couple Na⁺ and sugar transport, and studies are now in progress to test this hypothesis.

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