CHAPTER 7
Diseases of Renal Glucose Handling

ERNEST M. WRIGHT

INTRODUCTION

Blood glucose is normally maintained within narrow limits, 4–12 mM, in the face of variable inputs and outputs. On average 125 grams of glucose are absorbed each day from digested food in the gut, but the amount consumed can vary from none to much greater than 300 grams/day. The body uses about 250 grams to fuel normal daily activity, but this amount varies widely depending upon the individual's workload. Irrespective of the amount of glucose in the diet and the level of physical activity the brain requires 125 grams to sustain neuronal function. The gap between the amount of glucose needed as fuel and the amount consumed is bridged by the use of glucose stores (glycogen) and gluconeogenesis. Surprisingly, glucose is not an essential nutrient and this is best exemplified by people who are intolerant of glucose (and galactose) in their diet. These individuals thrive on a high-fat and -protein diet (see below). The kidneys play two important roles in glucose homeostasis, i.e. salvaging glucose from the glomerular filtrate and by gluconeogenesis. Each day the kidney filters 180 liters of plasma and this could potentially result in the loss of 180 grams of glucose to the urine. Virtually all of the filtered glucose is reabsorbed in the proximal tubule and less than 0.5 grams are lost. Thus greater than 99% of the filtered load is reabsorbed.

This chapter summarizes the normal mechanisms of renal glucose reabsorption and their genetic disturbances. Glucose transporters were among the first to be cloned and genetic disorders of glucose transporters were among the first to be identified. The study of patients with specific defects in glucose transporters has clarified, but not completely resolved, how the kidney handles glucose. Furthermore, the benign nature of familial renal mutations in the transporter gene but a through genotyping and phenotyping rnal Tmal oral glycosuria and the advances in the molecular biology have stimulated the pharmaceutical industry into targeting renal glucose transporters in the fight against hyperglycemia in diabetes (Yasuda et al 2002).

PHYSIOLOGY OF RENAL GLUCOSE TRANSPORT

Glucose is freely filtered at the glomerulus and so the concentration in the glomerular filtrate is close to that in plasma. Given a GFR of ~180 liters/day/1.73 m² and plasma glucose concentration of 4 mM, the filtered glucose load is ~180 grams (1 mole/day/1.73 m², but only (0.1–0.3 grams)/day/1.73 m² are excreted in the urine (Keller 1968, Maddox & Gennari 1987). Renal glucose titration studies provide an estimate of the maximal reabsorptive capacity (T_max ~425 grams/day) and the minimum filtered load (F_min ~325 grams/day) at which significant amounts of glucose (>1.4 grams/day) appear in the urine. That is, significant amounts of glucose are excreted when the plasma glucose concentration exceeds 9 mM and the maximum reabsorption capacity is reached when the plasma glucose concentration reaches 15 mM. Above 15 mM the rate of excretion is directly proportional to the filtered load.

Our present understanding of the physiological mechanisms involved in glucose reabsorption in the nephron comes largely from animal studies and analogy to glucose absorption from the small intestine. Micropuncture studies of amphibian and mammalian nephrons demonstrated that glucose is reabsorbed in the proximal tubule. In the rat the concentration of glucose in the glomerular filtrate falls by more than 50% within 1 mm and 90% within 2 mm of the glomerulus (see Figure 7.1). This leads to the conclusion that more than 98% of the filtered glucose is reabsorbed.

The kinetics of glucose absorption in the ‘early’ and ‘late’ segments of rabbit proximal tubule was examined in isolated, perfused nephron segments (Barfuss & Schafer 1981). The capacity of the ‘active’ component of glucose absorption decreases from 83 pmoles/min/mm in the proximal convoluted tubule to 8 pmoles/min/mm in the late proximal straight tubule. The apparent affinity for active glucose transport increased along the tubule: the K_m values...
decreased from 1.6 to 0.35 mM. It should be noted that the perfused tubules were isolated from the superficial cortex and little is known about the heterogeneity of glucose transport among superficial and deep nephrons. Indirect support for differences in kinetics of glucose reabsorption along the proximal tubule was obtained by Turner & Moran (1982) in their study of brush border membrane vesicles from the rabbit outer cortex and outer medulla. They found that the $K_m$ for glucose transport was 6 mM in the outer cortex and 0.3 mM in the inner medulla, and that the outer medulla glucose transporter was more sensitive to competition by galactose than the outer cortex transporter.

Studies of the molecular mechanisms of active glucose transport across the proximal tubule were advanced in the mid-1970s by the introduction of isolated brush border and basolateral membrane vesicle preparations (Kinne et al 1975). As in the small intestine, glucose uptake across the brush border membrane was concentrative, sodium-dependent, and phlorizin-sensitive, i.e. occurred by $\text{Na}^+$/glucose-cotransport. Glucose transport across the basolateral membrane was neither concentrative, nor sodium-dependent, nor phlorizin-sensitive, i.e. occurred by facilitated diffusion. A model for glucose transport across the proximal tubule is shown in Figure 7.2 where the basolateral Na/K-pump maintains the low intracellular sodium in the face of sodium entry across the apical membrane through the $\text{Na}^+$/glucose cotransporter.

The quest for the molecular identity of the brush border and basolateral membrane glucose transporters was advanced further in the mid-1980s by the cloning of membrane proteins, specifically the red cell facilitated glucose transporter (GLUT1, Mueckler et al 1985) and the intestinal brush border sodium/glucose cotransporter (SGLT1, Hediger et al 1987). With further advances in cloning, especially homology and expression cloning, and the completion of the human genome project, a clear picture has emerged about the two major families of human glucose transporters, the GLUT (SLC2) and SGLT (SLC5) families (Uldry & Thorens 2004, Wright & Turk 2004). The SLC2 family is comprised of 13 members in three classes: Class I GLUT1–4; Class II GLUT 5, 7, 9, and 11; and Class 3 GLUT 6, 8, 10, 12 and HMIT. All are postulated to have similar secondary structures with 12 transmembrane-spanning helices and a large number of conserved motifs. High-resolution structural models of the GLUTs are lacking but X-ray crystal structures of two members of the larger gene superfamily (MFS) have been solved, for lac permease (Abramson et al 2003) and GlpT (Huang et al 2003).

Initially, GLUTs 1–4 were functionally expressed and characterized as glucose transporters, and efforts are continuing to
document the functions of the other family members. Human GLUT1, 3, and 4 are high-affinity glucose transporters, K_m 1–5 mM. Of these three only GLUT1 appears to be expressed in the kidney, where it is found all along the nephron. GLUT2 is a low-affinity glucose transporter, K_m 17 mM, and this protein is found in the basolateral membranes of the proximal tubule and in the small intestine amongst other places. GLUT2 transports galactose and 2-deoxy-glucose, but not alpha-methyl-glucopyranoside.

The SLC5 family is comprised of 11 genes and two code for sodium/glucose cotransporters expressed in the kidney, SGLT2 and SGLT1 (Wright & Turk 2004). Other genes in the family with high sequence similarity to SGLT1 and two code for a glucose sensor (SGLT3), a mannose transporter (SGLT4, Tazawa et al 2005) and a myo-inositol transporter (SGLT6 or SMIT2). The function of SGLT5 is not yet known. All are expressed in the kidney, but the level of expression relative to that in the small intestine varies: SGLT1 K/I 0.05; SGLT2 Kid/Intest ~ infinite; SGLT3 Kid/Intest ~ 6; SGLT4 Kid/Intest ~ 1.25; SGLT5 Kid/Intest ~ infinite; and SGLT6 Kid/Intest ~ 9 (Bing, Martin, Turk & Wright, unpublished). There is no homology of the SLC5 genes with the SLC2 family. The SGLTs have 14 transmembrane helices (see Figure 7.3) and there are no structural motifs in common with those in the GLUT family. The crystal structure of a bacterial SGLT has just been reported (Faham et al 2008).

Most functional studies have been carried out on SGLT1 expressed in oocytes, cultured mammalian and insect cells and in bacteria (Wright et al 2004). Transport of glucose is tightly coupled to sodium with a coupling coefficient of 2 and is driven by the sodium and electrical potential gradients across the brush border membrane. Under the maximal driving forces the K_m is 0.6 mM for glucose and 4 mM for sodium. Transport is competitively inhibited by phlorizin with a K_I of 0.6 mM. SGLT1 also transports galactose and alpha-methyl-glucopyranoside with identical kinetics to glucose, but does not transport fructose. Alpha-methyl-glucopyranoside is poorly transported by SGLT1 (K_m 110 mM). There is evidence that SGLT1 is located on the brush border membrane of the intestinal epithelium and the S3 segment of the proximal tubule.

Studies of SGLT2 have been severely limited owing to the poor expression of the clone in heterologous expression systems; e.g. *Xenopus laevis* oocytes and COS-7 cells. Na-dependent glucose uptake is barely above background and in oocytes we have been unable to detect SGLT2 in the plasma membrane, using electron microscopic methods. Nevertheless, it is reported that SGLT2 transports both glucose and alpha-methyl-glucopyranoside with a K_m of 2 mM, but galactose is not transported (Wright et al 2001, Pajor 2008). It is claimed the sodium to glucose coupling ratio is 1. These properties resemble those obtained on brush border membrane vesicles prepared from the rabbit outer cortex (see above). Direct proof for the expression of SGLT2 protein in the apical membrane of the human proximal tubule is lacking in the absence of SGLT2 antibodies.

What can we conclude about the identity of the glucose transporters in the brush border and basolateral membrane of the human proximal tubule other than that they are likely to be members of the SLC2 and SLC5 gene families? Some headway in answering this question comes from a comparison of the kinetic properties of the recombinant transporters and those in native membranes, and from studies of inherited disorders of glucose transport. Additional insights come from the study of rodent gene knockout models.

**INHERITED DISORDERS OF RENAL GLUCOSE TRANSPORT**

The urine from normal healthy subjects contains a small amount of glucose, ranging from 0.3 to 1.1 moles (or 100–300 mg)/day/1.73 m^2 (Keller 1968, Elsas & Rosenberg 1969). This is a small fraction of the normal filtered glucose
Glucose-Galactose Malabsorption (GGM)
(MIM 182380)

The primary carbohydrate present in breast milk is lactose and this is hydrolyzed by lactase on the intestinal brush border to glucose and galactose. The liberated sugars are then normally transported across the brush border membrane by SGLT1 and across the basolateral membrane by GLUT2 (see also Figure 7.2). In patients with GGM, glucose and galactose are not absorbed and diarrhea results from the osmotic load in the gut. The diarrhea resolves on eliminating lactose, glucose, and galactose from the diet, but promptly resumes on adding one or more of the sugars back. This forms the basis for the rapid diagnosis of the disease. GGM patients are subject to a life-long diet free of glucose, galactose, and lactose.

Arguably the most complete evaluation of GGM was carried out during the first year of life of an American patient in the late 1960s (Schneider et al 1966). Clinical tests showed that there was malabsorption of glucose and galactose, while there was normal absorption of fructose. The histology of duodenal biopsies was normal, but biochemical and electron microscopic studies revealed that there was a defect in glucose and galactose transport across the brush border membrane due to the reduction in the density of transporters (phlorizin binding) in the brush border. This child thrived on a sugar-free diet and even as an adult she is intolerant of carbohydrate; ingestion of as little as 6 grams of table sugar produce malabsorption symptoms. Our oldest GGM subject, a 54-year-old male, lives an apparently normal, healthy life on a sugar-free diet but malabsorption symptoms also return rapidly if he consumes a modest

load, ~180 grams/day and, given the volume of urine produced in 24 hours, ~950 ml, the glucose concentration in urine is generally only ~8% of the plasma concentration, i.e. barely sufficient to register on a dip-stick. There are two genetic disorders where glucose excretion ranges up to a high of 250 grams/day/1.73 m² i.e. in subjects with Fanconi-Bickel syndrome (MIM 227810) and with familial renal glucosuria (MIM 233100). A mild renal glucosuria may also occur in subjects with glucose-galactose malabsorption (MIM 182380). Familial renal glucosuria (FRG) is a rather benign condition whereas Fanconi-Bickel syndrome (FBS) subjects present with an array of other symptoms ranging from failure to grow to hepatomegaly. Glucose-galactose malabsorption (GGM) presents in newborn children as a massive life-threatening diarrhea and this is caused by variations in the SGLT1 gene (Turk et al 1991, Martin et al 1996, Wright et al 2001). This story will be presented first, followed by those for familial renal glucosuria (FRG) and the Fanconi-Bickel syndrome (FBS).

FIGURE 7.3 A secondary structure model of SGLT1 showing the location of the missense mutations identified in patients with glucose-galactose malabsorption (GGM). The 664 amino acid protein is predicted to contain 14 transmembrane helices and one external N-linked glycosylation site. Both the N- and C-termini are shown on the extracellular side of the membrane. (see also Plate 6)
amount of food containing the offending sugars (Phillips & McGill 1973). The only other symptom that we are aware of is that patients frequently have a mild renal glucosuria. This is consistent with a low level of SGLT1 expression in the proximal tubule.

In our genetic studies we have only screened patients with a clear diagnosis of GGM, i.e. patients with diarrhea who: (1) fully respond to removal of glucose and galactose (and lactose) from their diet; (2) show the diarrhea returning on the introduction of glucose; (3) exhibited flat oral glucose tolerance tests; (4) test positive with glucose hydrogen breath tests (>100 ppm); and (5) have a normal intestinal biopsy. Although GGM is a rare disorder, about 10% of the normal adult population in the USA and the UK (first-year medical students) test positive on glucose hydrogen breath tests (Montes et al 1992, BH Hirst, personal communication). As yet we have not been unable to screen these subjects for SGLT1 mutations.

This rare autosomal recessive disorder is caused by variations in the gene coding for SGLT1 (Turk et al 1991, Martin et al 1996, Wright et al 2001). We are aware of some 300 patients worldwide and have carried out genetic testing on 83 patients in 75 unrelated families. About 65% of our patients are the products of a consanguineous union as revealed by the fact that they have the same mutation on each allele. The remainder are compound heterozygotes, i.e. they have inherited different mutations from their mother and their father. Only one mutation was found in multiple (three), unrelated families, and there are several instances where the same mutation was found in two unrelated families with similar racial and ethnic backgrounds. This may signal an increase in the frequency of these variants in these populations. No mutations have been found in one patient with a clear diagnosis of GGM. It is unclear if mutations lie outside of the DNA sequenced (the coding regions, the exon/intron boundaries and the 527bp of the promoter) or if mutations in another gene cause the defect.

There are 34 missense mutations (Figure 7.3) and these are highly conserved residues in the 18 closely genes in the SGLT gene family including SGLT1 genes in eight different species. We have tested 24 of these in the Xenopus laevis oocyte expression system and all but three showed a serious defect in Na/glucose cotransport (<10% of wild-type activity). Using a combination of electrophysiological and electron microscopic methods we have established that the defect in transport is due to miss-sorting of the transporter in the cell, i.e. the protein is produced but is not delivered to the plasma membrane. In six patients we have been able to examine the distribution of the transporter in duodenal biopsies and have confirmed that the mutant proteins fail to reach the enterocyte brush border membrane. Five of the six patients with the three missense mutations with unimpaired transport in the oocyte assay have other mutations that cause the transport defect. In addition to the missense mutations, three nonsense, seven frame-shift and seven splice site mutations have been identified. These produce nonfunctional truncated transporters.

Overall, we have identified mutations on both alleles that account for the severe glucose (and galactose) malabsorption in 35 out of 39 patients. This leads to the conclusion that SGLT1 is the primary mechanism for glucose transport across the brush border of enterocytes. Other potential brush border glucose transporters include SGLT4, 5, and 6, but not SGLT2 which is poorly expressed in the human small intestine and not SGLT3 which is a glucosensor and not a transporter (Diez-Sampedro et al 2003).

The frequency of GGM is low due to the low frequency of SGLT1 mutations in the general population. As part of the Pharmacogenetics of Membrane Transporters project at UCSF (www.pharmacogenetics.ucsf.edu) we have found that none of the GGM mutations has been found in the SGLT1 gene in the 552 alleles in the Coriell Institute genomic DNA collection. Only 12 nonsynonymous mutations are found, and only six have a frequency greater than 1%. The frequency of three variants reaches 9% (Asn51Ser, Ala411Thr, and His611Gln) in the 160 alleles in the European-American population. The first two of these were found in our pool of GGM patients but on the basis of the oocyte expression assay these were judged to be polymorphisms (Martin et al 1996). GGM patients with these polymorphisms were found to have other SGLT1 mutations that caused the defect in sugar transport.

Patients with GGM frequently have a mild renal glucosuria. For example in one patient with SGLT1 mutations G426R and S159P that abolish Na/glucose transport (kindred #6, Martin et al 1996) careful analysis of renal glucose titration demonstrates a low minimal threshold (FminG) of 82 vs. a normal of 224 mg/min/1.73 m² and excretion of more than 1 mg of glucose/min/1.73 m² at all filtered loads above FminG (Elsas et al 1970). This suggests that SGLT1 only plays a modest role in the reabsorption of glucose from the glomerular filtrate. Finally, patients with type 0 renal glucosuria have no intestinal defect in sugar absorption suggesting that another SGLT gene is responsible for the bulk of glucose reabsorption in the kidney (see below).

**Familial Renal Glucosuria (FRG) (MIM 233100)**

FFG is an autosomal recessive renal tubular disorder characterized by urinary glucose excretion in the presence of normal blood glucose levels and normal oral glucose tolerance. This is an isolated renal tubular disorder, where the glomerular filtration rate (GFR) and reabsorption of salt, water, and other nutrients is normal. It is considered as a non-disease as the majority of affected individuals are otherwise asymptomatic. The level of glucose excretion ranges from 1 up to 169 grams/day/1.73 m² (Table 7.1). In the most severe cases there is no reabsorption of the filtered load of glucose. Three types of FFG have been defined, type A with a low threshold and low Tm, type B with a low threshold and
normal $T_m$, and type 0 with a complete absence of reabsorption (Elsas & Rosenberg 1969, Oemar et al 1987). These may be explained by different mutations in the transporter gene but a thorough genotyping and phenotyping of FRG patients is lacking. What is the effect of renal glucosuria on the subject? In the case of one type 0 patient the long-term follow up indicates that at age 31 he is normal, in good clinical condition, with no nephrologic complications (Scholl-Burgi et al 2004).

Since genetic defects in SGLT1 are not associated with severe renal glucosuria, SGLT2 is expressed in the S1 and S2 segments of rodent tubules, and severe renal glycosuria is considered a nondisease, it has been suggested that mutations in the SGLT2 gene caused the defect in glucose transport across the apical membrane of the early proximal tubule. This together with cloning of the SGLT2 cDNA (Wells et al 1992) and mapping of the SGLT1 gene (Turk et al 1994) facilitated genetic screening of the SGLT2 by several groups (Calado et al 2004, van den Heuvel et al 2002, Santer et al 2003b, Francis et al 2004, Kleta et al 2004, Magen et al 2005). To date the SGLT2 gene has been screened for mutations in 31 families with cases of FRG.

The SGLT2 mutations identified in FRG index cases in 26 families are summarized in Table 7.1 along with the glucose excretion rates. There are 12 FRG cases with homozygous mutations and seven who are compound heterozygotes, where the glucosuria is greater than 9 grams/day/1.73 m². No mutations were found in three index cases where the glucosuria ranged from 3 to 17 grams/day/1.73 m². Mutations on only one allele were identified in eight cases with glucosuria ranging from 0.75 to 6 grams/day/1.73 m². The mutations include 17 missense, three nonsense, three frame-shift, one abnormal splice site variant, and four deletions distributed throughout the gene (Figure 7.4). So far, virtually every FRG family has its own private mutation as few mutations occur in unrelated families. Exceptions include the missense mutation W440X in two unrelated families and the missense mutation K321R in three unrelated Israeli-Arab families.

None of the SGLT2 mutations has been evaluated in a heterologous expression system and so it is difficult to relate the missense mutations to the severity of the renal glucosuria. However, it does appear that homozygous K321R mutations produced type 0 glucosuria in six patients (V–VII, Table 7.1). Excretion rates substantially less than the filtered loads do occur in homozygous and compound heterozygote subjects, e.g. G304K in subject III, G272R in 02-1, G449D in 05-1, R368W in 09-01, and T543P in 17-1. This could be due to retention of partial function by these mutant proteins. More perplexing are the excretion rates seen with homozygous stop codons. On one hand 347X is associated with the type 0 renal glucosuria (subject 01-1) but on the other hand much lower excretion rates are observed for two unrelated subjects with W440X (I and 06-1). In the absence of technical difficulties, this suggests that there are other transporters responsible for glucose reabsorption in the proximal tubule. Possibilities include SGLT4 and SGLT6 which appear to be low-affinity glucose transporters and SGLT5, that all expressed in the human renal cortex (Wright & Turk 2004). Yet another possibility is that a Na/glucose cotransporter in another gene family is involved, e.g. NaGLT1 (Horiba et al 2003).

**Fanconi-Bickel Syndrome (FBS) (MIM 227810)**

FBS is a rare autosomal recessive disorder characterized by failure to thrive, short stature, hepatomegaly, hepatorenal glycogen accumulation, and, most prominently, glucosuria ranging from 40 to 200 grams/day/1.73 m² (Fanconi & Bickel 1949, Manz et al 1987, Santer et al 1998). There may also be hyperaminoaciduria, moderate hyperphosphaturia,
hypercalciuria, and fasting hypoglycemia. Oral glucose tolerance tests appear normal and there may be mild glucose malabsorption.

In their 1998 review of 82 cases from 70 families Santer et al (1998) highlight that a massive renal glucosuria, typically 40–200 grams/day/1.73 m², is the most prominent observation. Glucose excretion ranges from a low of 12 to a high of 323 grams/day/1.73 m², but two ‘FBS’ patients have no glucose in their urine. FBS patients have a low fasting blood glucose level and normal to low-normal GFR. Given the symptoms of FBS, Santer and his colleagues reasoned that GLUT2 gene was a prime candidate for molecular genetic studies. In their 2002 review (Santer et al 2002) 34 novel mutations in GLUT2 were identified in 55 FBS patients. Homozygous mutations were found in 47 cases and this is consistent with the known consanguinity in the FBS families.

Of the 34 mutations identified, 24 of these result in truncated GLUT2 proteins (seven nonsense, 10 frame-shift, and seven splice-site mutations) and, as might be expected, FBS patients have a low fasting blood glucose level and normal to low-normal GFR. Given the symptoms of FBS, Santer and his colleagues reasoned that GLUT2 gene was a prime candidate for molecular genetic studies. In their 2002 review (Santer et al 2002) 34 novel mutations in GLUT2 were identified in 55 FBS patients. Homozygous mutations were found in 47 cases and this is consistent with the known consanguinity in the FBS families.

One of the 34 mutations identified, 24 of these result in truncated GLUT2 proteins (seven nonsense, 10 frame-shift, and seven splice-site mutations) and, as might be expected, FBS patients have a low fasting blood glucose level and normal to low-normal GFR. Given the symptoms of FBS, Santer and his colleagues reasoned that GLUT2 gene was a prime candidate for molecular genetic studies. In their 2002 review (Santer et al 2002) 34 novel mutations in GLUT2 were identified in 55 FBS patients. Homozygous mutations were found in 47 cases and this is consistent with the known consanguinity in the FBS families.

FIGURE 7.4 A secondary structure model of SGLT2 showing the location of the missense, nonsense, and deletion mutations identified in patients with familial renal glucosuria (FRG). The 672 membrane protein is assumed to have the same secondary structure as SGLT1 (Figure 7.3). It should be noted that there are no functional data available for the SGLT2 mutants (see Table 7.1) as it has been difficult to express in heterologous expression systems. The boxed mutation R137W is the only residue that is found mutated in GGM patients (R135H). (see also Plate 7)
tests and no severe osmotic carbohydrate diarrhea, whereas these patients have renal glucosuria. Likewise mice lacking GLUT2 have normal oral glucose tolerance and severe renal glucosuria (Thorens et al 2000). In the intestine there is evidence for a transport pathway requiring glucose phosphorylation and transfer into the endoplasmic reticulum (Stumpel et al 2001, Santer et al 2003a). Essentially, glucose absorption may be fairly normal in FBS patients while absorption of the nonmetabolized sugar 3-O-methylglucoside is severely impaired. However, these same patients and GLUT2 knockout mice have severe renal glucosuria. Evidently, SGLT2 plays a much more important role in glucose transport across the proximal tubule than in the small intestine. The role of the exocytotic pathway could be tested in FBS subjects by comparing the clearances of glucose and a nonphosphorylated sugar that is a substrate for both SGLTs and GLUTs, 3-O-methyl-glucoside.

**SUMMARY AND OUTLOOK**

Studies of the rare genetic disorders of renal glucose transport have provided important insights into normal human renal physiology. It seems reasonable to conclude that SGLT2 and GLUT2 each play central roles in glucose transport across the apical and basolateral membranes of the proximal tubule as visualized in Figure 7.2. However, the less than perfect correlation between the genotyping and phenotyping of SGLT2 and GLUT2 in subjects with FRG and FBS suggest the presence of other glucose transporters. The clearest examples are those where subjects reabsorb substantial fractions of their filtered glucose loads despite having severely truncated SGLT2 or GLUT2 proteins. While it is unlikely that SGLT1 and SGLT3 fill the gap at the apical membrane, other potential candidates include SGLT4 and SGLT6, transporters that behave as low-affinity glucose transporters. SGLT5, which is expressed almost exclusively in the renal cortex, could be important but its function is not known. Potential candidates for glucose transport across the basolateral membrane include other members of the SLCA2 gene family. However, it is unlikely that GLUT1 is important as mutations in this gene (Brockmann et al 2001, MIM 606777) are not associated with renal glucosuria.

A number of technical advances could further our understanding of glucose transport in the human kidney: first, it is important to find methods to express SGLT2 and SGLT5 for functional studies; second, specific antibodies for SGLT1–6 are needed to determine the subcellular location of these proteins in the nephron; and third, noninvasive methods to visualize and quantitate the functional expression of SGLT and GLUT genes in the kidney would be an important step forward. One approach to the latter is to design specific positron emission tomography (PET) tracers for SGLTs and GLUTs: 2,18F-2-deoxy-glucose (FDG) is already in use as a general tracer for GLUT activity (Phelps 2004); and there has been some movement towards the development of 11C and 18F tracers for SGLTs (Borman et al 2003, de Groot et al 2003).

Finally, a comment is warranted about the employment of molecular diagnostics for genetic disorders of renal glucose transport. This is impractical due to the very low frequency of FRG, FBS, and GGM, the fact that FRG is a nondisease, and the autosomal recessive character of all three disorders. Virtually every kindred harboring a case of FRG, FBS, or GGM has a private mutation. Furthermore, given the relatively poor correlation between genotype and phenotype for FBS and FRG it would be both costly and of limited value to carry out genetic screening, especially since the diagnosis of each disorder is fairly simple and straightforward. One exception may be the value of prenatal screening for FBS and GGM in families at risk. Quite recently 21 additional cases of familial renal glucosuria have been reported (Calado et al 2008).

**ACKNOWLEDGMENTS**

The studies underlying this review were carried out by a very talented group of students, post-doctoral fellows, and collaborators who are the co-authors on many of the cited papers, and were made possible by grants from the National Institutes of Health (DK 19567, DK 44602, DK 44582 and GM 19567).

**References**


Van den Heuvel LP, Assink K, Willemens M, Monnens L. Autosomal recessive renal glucosuria attributable to a mutation...