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Glucose transporters in the kidney in health and disease

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Abstract

The kidneys filter large amounts of glucose. To prevent the loss of this valuable fuel, the tubular system of the kidney, particularly the proximal tubule, has been programmed to reabsorb all filtered glucose. The machinery involves the sodium-glucose cotransporters SGLT2 and SGLT1 on the apical membrane and the facilitative glucose transporter GLUT2 on the basolateral membrane. The proximal tubule also generates new glucose, particularly in the post-absorptive phase but also to enhance bicarbonate formation and maintain acid-base balance. The glucose reabsorbed or formed by the proximal tubule is primarily taken up into peritubular capillaries and returned to the systemic circulation or provided as an energy source to further distal tubular segments that take up glucose by basolateral GLUT1. Recent studies provided insights on the coordination of renal glucose reabsorption, formation, and usage. Moreover, a better understanding of renal glucose transport in disease states is emerging. This includes the kidney in diabetes mellitus, when renal glucose retention becomes maladaptive and contributes to hyperglycemia. Furthermore, enhanced glucose reabsorption is coupled to sodium retention through the sodium-glucose cotransporter SGLT2, which induces secondary deleterious effects. As a consequence, SGLT2 inhibitors are new anti-hyperglycemic drugs that can protect the kidneys and heart from failing. Recent studies discovered unique roles for SGLT1 with implications in acute kidney injury and glucose sensing at the macula densa. This review discusses established and emerging concepts of renal glucose transport, and outlines the need for a better understanding of renal glucose handling in health and disease.

Keywords

Glucose transport; Gluconeogenesis; SGLT1; SGLT2 inhibition; Diabetic nephropathy; GLUT1

The kidneys continuously filter large quantities of glucose. Glucose is a valuable energy substrate and the tubular system of the kidney, particularly the proximal tubule, has evolved to reabsorb and retain basically all the filtered glucose. As a consequence, the urine in a

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healthy individual is nearly free of glucose. This may change in patients with diabetes mellitus, when hyperglycemia may enhance filtered glucose and overwhelm the tubular transport capacity for glucose. The glucose reabsorbed by the proximal tubule is primarily taken up into peritubular capillaries and returned to the systemic circulation or provided as an energy source to further distal tubular segments. Moreover and in addition to the liver, the kidneys generate new glucose through gluconeogenesis thereby contributing to systemic glucose homeostasis. The renal formation of glucose is also important for acid-base balance as it is linked to the generation of new bicarbonate in the proximal tubule. Gluconeogenesis also resides in the proximal tubule. Proximal tubule cells, which reabsorb most of the filtered glucose and in addition generate glucose, do normally not use glucose themselves as an energy source, possibly to prevent a futile cycle. Thus, distal tubular segments use glucose as fuel whereas the proximal tubule by reabsorbing all filtered glucose and generating new glucose contributes to maintaining blood glucose levels and overall metabolic balance.

The role of the proximal tubule in glucose handling is relevant in healthy individuals, in particular in the fasting state and during an acid load, and gains pathophysiological importance in disease states. This includes states of kidney injury as well as diabetes or hyperglycemic conditions. In the latter situation, renal glucose retention is maladaptive and contributes to hyperglycemia. As a consequence, new anti-hyperglycemic drugs have been developed to inhibit proximal tubular retention of glucose and induce urinary glucose loss, thereby lowering blood glucose levels. Moreover, these drugs have shown protective effects on the kidney and cardiovascular system in large clinical outcome trials [168]. The unexpected logic of glucose transport inhibition in the kidney goes beyond glucose homeostasis and is related to the integrated renal physiology of glucose handling, which includes the coupling of glucose reabsorption to the cellular uptake of sodium [185]. The interested reader is referred to recent reviews on the topic by the author, forming the basis for the current work [43, 117, 180, 185, 196] as well as by other authors [33, 157, 165, 166, 208].

The physiology of renal glucose transport

The cellular uptake and metabolism of D-glucose provides an important energy source [85, 215]. The brain depends on continuous glucose uptake, and alone requires ~ 125 g of glucose every day. To provide a constant supply, blood glucose is highly regulated and maintained in a range of 70–160 mg/dL. This involves many hormones, including insulin and glucagon that regulate cellular glucose uptake as well as glucose storage and endogenous glucose production [85, 215].

Glucose is an uncharged small molecule with a molecular mass of 180 that is freely filtered by the kidneys. In healthy individuals with normal glomerular filtration rate (GFR, ~ 180 L/day) and blood glucose levels (~ 100 mg/dL), the kidneys filter 160–180 g of glucose every day. This is equivalent to approximately one third of the daily energy expenditure that would be wasted in the urine. Instead, the healthy tubular system reabsorbs more than 99% of the filtered glucose in euglycemic conditions, primarily in the proximal tubule (Fig. 1). As outlined in the following sections, glucose is taken up from the tubular fluid in the proximal

tubule by two Na^+- glucose cotransporters, SGLT2 and SGLT1, which are expressed in the brush border membrane of the early and later proximal tubule, respectively. Na^+-glucose cotransport is a saturable process. The maximum renal transport capacity (T_{max}) for glucose averages around 300 and 350 mg/min or 430 and 500 g/day in female and male healthy individuals, respectively [30, 110], which equals approximately threefold the typical tubular glucose load. In other words, the renal glucose reabsorption machinery is not saturated under normal conditions. The T_{max} varies between individual nephrons and, therefore, low level spilling of glucose into the urine initiates at modestly elevated plasma glucose levels of ~ 180–200 mg/dL in a healthy adult. A consistent and linear increase in glucosuria is observed when blood glucose exceeds 270–290 mg/dL (Fig. 2). Glucosuria may require higher blood glucose levels when GFR is diminished (e.g., in kidney disease) or may occur at lower plasma glucose concentrations when GFR is increased (e.g., in diabetes or pregnancy).

Renal glucose reabsorption is largely mediated by SGLT2 in the early proximal tubule

In the early 1980s, studies in isolated rabbit proximal tubule segments indicated that the uptake rate and affinity for glucose differ between the early and late proximal tubule, respectively [6]. Subsequent experiments confirmed that these differences were attributed to the presence of two different glucose transporters in the brush border membrane [174]. These findings and follow-up studies identified the Na^+-glucose cotransporters SGLT2 (SLC5A2) and SGLT1 (SLC5A1) as key genes and pathways mediating glucose reabsorption in the kidney. This included analyses of mRNA expression in nephron segments of rat and rabbit kidneys and transport studies in membrane vesicles, as well as the cloning of the responsible genes, largely performed between 1981 and 1995 [6, 62, 76, 93, 138, 174, 202, 205, 207, 210]. The findings indicated that the *bulk* of tubular glucose uptake takes place in the *early* proximal tubule (S1/2 segment) and is mediated across the apical membrane by the low-affinity and high-capacity SGLT2. In comparison, SGLT1, which has a higher-affinity and lower-capacity for glucose transport than SGLT2, was proposed to reabsorb most of the remaining luminal glucose in *later* parts of the proximal tubule (S2/S3 segment) (Fig. 1). Using well-validated antibodies on rodent and human kidney sections, the primary expression of SGLT2 and SGLT1 has been confirmed in the brush border membrane of the early and late proximal tubule, respectively [4, 144, 193, 197]. In the mouse, SGLT1 protein expression was higher in S2 segments than in the S3 segments in medullary rays and the outer stripe [101]. In comparison, the strongest expression of SGLT1 in the human kidney was found in the S3 segment [197]. More recent studies established that SGLT1 is also expressed in the luminal membrane of the thick ascending limb (TAL) as well as the macula densa (MD), as shown in mouse and human kidneys [101, 197, 214]. Consistent with the expression profiles for SGLT2 versus SGLT1 along the proximal tubule, free-flow renal micropuncture demonstrated that glucose reabsorption was absent in the early proximal tubule in mice lacking SGLT2 [193] (Fig. 3a), whereas fractional glucose reabsorption up to the accessible late proximal convoluted tubule (S2 segments) was only reduced from 97 to 94% in mice lacking SGLT1 [54].

Humans carrying mutations in the genes for SGLT1 (*SLC5A1*) and SGLT2 (*SLC5A2*) show distinct renal pheno-types. Mutations in SGLT1 cause “Intestinal Glucose Galactose Malabsorption” (Online Mendelian Inheritance in Man [OMIM] 182380) due to the critical role of SGLT1 in active intestinal glucose reabsorption [105, 208] (Koepsell H. Pfluegers Archives 2020). As a consequence, dietary exposure to galactose or glucose of newborns with mutations in SGLT1 or gene-targeted mice lacking SGLT1 [54] can induce life-threatening diarrhea, but they show little or no glucosuria. In comparison, individuals with mutations in SGLT2 present with “Familial Renal Glucosuria” (OMIM 233100) ranging from 1 to > 100 g per day, whereas intestinal glucose handling is normal [147]. Notably, no other complications (such as impaired kidney function or urinary tract infections) have been consistently observed in individuals with loss-of-function mutations in SGLT2 [147, 208]. While these mutations are rare, this information was taken into account for the rationale to develop SGLT2 inhibitors as a potentially safe therapeutic strategy to lower blood glucose levels (see below). In alignment with the human phenotypes, genetic and pharmacologic inhibition in mice indicated that SGLT2 reabsorbs ~ 97% of the filtered glucose, whereas SGLT1 mediates the reabsorption of the remaining ~ 2–3% under normal conditions [54, 142, 193] (Figs. 1 and 3c).

SGLT2 inhibition unmasks the renal glucose transport capacity of SGLT1

SGLT2 reabsorbs almost all the filtered glucose, yet fractional renal glucose reabsorption is maintained at 40–50% following application of a selective SGLT2 inhibitor in humans and rodents [64, 84, 155] (Figs. 1 and 3). Similarly, fractional renal glucose reabsorption varied between 10 and 60% in normoglycemic mice lacking *Sglt2*, inversely with the amount of filtered glucose, with a mean fractional renal glucose reabsorption of ~ 40% [193] (Fig. 3a). Follow-up studies demonstrated that SGLT2 inhibition unmasked the transport capacity of downstream SGLT1 (Figs. 1 and 3). First evidence was obtained in micropuncture studies in mice lacking *Sglt2*, which showed prominent glucose reabsorption in the later parts of the proximal convoluted tubule, where SGLT1 is expressed in S2 segments [193] (Fig. 3a). Experiments in metabolic cages revealed that the dose-response curve for glucosuria of a selective SGLT2 inhibitor was shifted leftward in mice lacking *Sglt1*, i.e., glucosuria initiated at lower doses since SGLT1 did not compensate. Moreover, the maximum glucosuric response to the SGLT2 inhibitor doubled in the absence of SGLT1 [142] (Fig. 3b). Renal clearance studies showed that a high dose of the SGLT2 inhibitor reduced fractional renal glucose reabsorption to 44% in WT and abolished net renal glucose reabsorption in mice lacking SGLT1 (Fig. 3c). Thus, SGLT1 and SGLT2 together accounted for all net renal glucose reabsorption under euglycemic conditions [142]. In accordance, absence of net renal glucose reabsorption was also demonstrated in both female and male mice carrying a double knockout of *Sglt1* and *Sglt2* [142] (Fig. 3c). Thus, SGLT1 provides a sizable glucose transport capacity in the late proximal tubule, consistent with high maximal glucose transport rates of human SGLT1 observed in in vitro studies [69]. This transport capacity becomes engaged when inhibition of SGLT2 delivers more glucose to the downstream SGLT1 (Fig. 1). In accordance, dual inhibition of SGLT1 and SGLT2 approximately doubles glucosuria versus sole SGLT2 inhibition, as shown in non-diabetic and diabetic mice [134, 142, 161], and indicated by studies using a dual SGLT2/SGLT1

inhibitor in mice, rats, and dogs [135]. Based on these data, a 3:1 to 5:1 ratio has been estimated for the glucose reabsorption capacities of SGLT2 versus SGLT1 in a non-diabetic mouse kidney [43].

Molecular organization of renal glucose transport

Apical sodium-glucose cotransport

The Na^+/K^+ ATPase, which is located on the basolateral membrane, is the primary active and ATP-consuming transport step for Na^+ reabsorption in the tubular system of the kidney. The Na^+/K^+ ATPase lowers cytosolic Na^+ concentrations, which generates the concentration gradient that drives Na^+ uptake and the secondary uptake of other molecules from the tubular lumen into tubular cells (Figs. 1 and 4). In 1960, Crane proposed the Na^+ glucose cotransport hypothesis, which stated that the Na^+ gradient across cell membranes energized active glucose transport in the intestinal epithelium (which expresses SGLT1) (for review, see [208]). This concept was rapidly extended to other molecules and ions including Na^+ glucose cotransport in the kidney [208].

The human SLC5 solute carrier family includes 12 members of which SGLT1 and SGLT2 have been intensively characterized. Six members are termed as SGLTs, and they vary in their preferences for binding of glucose, galactose, fructose, mannose, myoinositol, choline, short-chain fatty acids, and other anions [208]. All SGLTs have 15 exons that code for proteins with molecular weights of 60 to 80 kDa and 580 to 718 amino acids [208]. Wright, Hediger, and their group have largely pioneered studies on the molecular nature of SGLTs including the cloning of SGLT1 and SGLT2 (for review of the SLC5 family, see [208], [Hediger. Pfluegers Archives 2020], and [Wright. Pfluegers Archives 2020]). The amino acid identity between human SGLT1 and SGLT2 is 59% [207]. To characterize how Na^+ and sugar transport is coupled, Wright's group also described the crystal structure of a sodium galactose bacterial isoform in *Vibrio parahaemolyticus*. According to this work, Na^+ binds first to the outside of the transport protein to open the outside gate. This allows outside sugar to bind and be trapped, which is followed by a change in conformation and opening of the inward gate and Na^+ and sugar are released into the cell cytoplasm. A subsequent change in conformation from a ligand-free inward facing state to a ligand-free outward facing state completes the transport cycle [29, 208].

Electrophysiological techniques were applied to various expression systems in order to determine the sugar selectivity and transport kinetics of cloned SGLTs. SGLT1 has a similar affinity for glucose and galactose, whereas SGLT2 transports glucose but not galactose, and neither transports fructose [208]. The apparent affinities (K_m) for D-glucose are rather similar for human SGLT2 and human SGLT1 with values of 5 and 2 mM, respectively, as determined in transfected human embryonic kidney (HEK) 293T cells [69]. Sugar binding is Na^+-dependent and the K_m for Na^+ transport by human SGLT2 and human SGLT1 are 25 and 70 mM, respectively [69]. Thus, under conditions of normal blood glucose levels, glucose concentration in the glomerular filtrate is in the range of the K_m of SGLT2. In comparison, the luminal Na^+ concentration of 140 mM is not rate-limiting since it is much higher than the K_m of SGLT2.

SGLT2 and SGLT1 transport Na^+ and glucose with a Na^+-glucose coupling ratio of 1:1 and 2:1, respectively [69]. This enhances the glucose concentration power of SGLT1 and thereby the ability of the late proximal tubule to reabsorb glucose in the face of falling luminal glucose delivery (Fig. 1). Na^+-glucose cotransport is electrogenic. Paracellular Cl^- reabsorption and transcellular K^+ secretion help to preserve membrane potential and driving force. This involves K^+ channels, like KCNE1/KCNQ1, in the luminal membrane of the proximal tubule [188, 191] (Fig. 1).

Beyond SGLT2 and SGLT1 and based on mRNA expression studies, three other members of the SLC5 family that are interacting with glucose have been detected in the kidney, namely SGLT3, SGLT4, and SGLT5 [206]. Glucose can depolarize the plasma membrane in the presence of SGLT3 (SLC5A4) in a saturable, Na^+-dependent, and phlorizin-sensitive manner. As such, SGLT3 may act as a glucose sensor, but its renal protein expression and function remain unclear [162]. In COS-7 cells, SGLT4 (SLC5A9) can transport glucose but the affinity of this transporter for mannose is much higher than for glucose (Ki 0.15 vs. 8 mM) [167]. Therefore, SGLT4 may primarily serve as a mannose transporter. SGLT5 (SLC5A10) is a Na^+-dependent sugar transporter that has a relatively high affinity and capacity for mannose and fructose relative to glucose and galactose [50, 55]. SGLT5 mRNA is highly expressed in kidney cortex [16, 55], and experiments in gene-targeted mice indicated that SGLT5 is the major luminal transporter responsible for renal fructose reabsorption [42].

Basolateral facilitative glucose transport

The healthy kidney takes up large amounts of glucose in the early proximal convoluted tubule (S1 segment). These cells, however, lack significant capacity for aerobic and anaerobic glycolysis and glucose does not considerably contribute to the cellular metabolism in this segment [56, 81, 175]. Therefore, glucose that is taken up across the luminal membrane or formed within proximal tubule cells (see below) exits across the basolateral membrane by concentration gradient-driven facilitative glucose transporters, primarily GLUT2 (Fig. 1). Glucose is subsequently taken up into peritubular capillaries through fenestrated endothelial cells, driven by convection. The “liver-type” transporter GLUT2 (SLC2A2) has a low affinity for glucose (K_m; 15–20 mM) and is strongly expressed in the proximal convoluted tubule (S1/S2 segments) and to a lesser extent in the proximal straight tubule (S3 segment) [18] (see [Holman. Pfluegers Archives 2020] for review of the SLC2 family). GLUT2 is primarily responsible for the basolateral exit of glucose in proximal convoluted tubules [24, 171, 204]. In comparison, the “erythroid/brain-type” transporter GLUT1 (SLC2A1), which has a higher glucose affinity (K_m; 1–2 mM), is expressed along the entire proximal tubule and has been proposed to support transcellular glucose transport in the S3 segments [24, 171, 204]. The strongest renal expression of GLUT1, however, is found in the basolateral membrane of further distal tubule segments. In the rat kidney, this includes the medullary thin and thick ascending limbs with the highest levels detected in connecting segments and collecting ducts, including principal cells and, even more so, in intercalated cells [171]. The correlation between GLUT1 expression and the glycolytic activity of nephron and collecting duct segments is consistent with the concept that in particular the more distal tubule segments are taking up glucose for energy supply via

basolateral GLUT1 (Fig. 1). In accordance with a more prominent role of GLUT2 versus GLUT1 for basolateral exit of glucose in mouse proximal tubules (Fig. 1), the use of positron emission tomography indicated that gene knockout of GLUT2 prevented renal glucose reabsorption [145]. In accordance, humans with loss of function mutations in GLUT2 present with the Fanconi-Bickel syndrome, which includes a proximal tubulopathy characterized by glycosuria, phosphaturia, aminoaciduria, proteinuria, and hyperuricemia [125, 148, 149]. The observed generalized proximal tubulopathy may reflect glucotoxicity due to accumulation of intracellular glucose when the main basolateral exit pathway for glucose is missing. In contrast, individuals with mutations in GLUT1 primarily present with neurologic problems, in the absence of a renal phenotype [125, 154].

Some other members of the SLC2 gene family have been detected in the kidney and implicated in glucose transport; however, little information is available regarding their functional relevance [113]. For example, the mRNA and protein expression of GLUT4 has been detected in the TAL. GLUT4 may play a potential role in local fuel control in this segment, inasmuch as GLUT4 was co-expressed with IGF-I, and vasopressin, a stimulator of Na^+ transport in this segment, increased GLUT4 expression [18]. GLUT5 is strongly expressed in the apical membrane of rat proximal straight tubule (S3 segment), but proposed to primarily serve as a fructose transporter [18, 164]. GLUT12 can transport glucose and has been detected in the apical membrane of distal tubules and collecting ducts; however, the functional contribution is unknown [95].

Coordination of tubular glucose transport and formation

The kidneys reabsorb large amounts of filtered glucose and, in addition, generate new glucose. Like glucose reabsorption, renal gluconeogenesis occurs along the entire proximal tubule [12, 22, 26, 56]. The proximal tubule generates glucose-6-phosphate from various precursors (see below). Glucose-6-phosphatase subsequently generates free glucose that can exit the cell, usually via GLUT2 across the basolateral membrane. This way, healthy human kidneys generate approximately 15–55 g of glucose every day, particularly in the fasting state. Notably, the gluconeogenesis in human kidneys generates similar amounts of glucose as the liver in the post-absorptive state (i.e., 12–16 h after the last meal) [46]. Epinephrine stimulates and insulin inhibits renal gluconeogenesis; thus, in the fasting state, the associated changes in epinephrine and insulin concentrations upregulate renal gluconeogenesis [46] (Fig. 4). Glucagon seems not to be a relevant regulator of renal gluconeogenesis, which is in contrast to the liver [46].

Starvation stimulates gluconeogenesis uniformly along the entire proximal tubule; in comparison, metabolic acidosis enhances gluconeogenesis primarily in S1 and S2 segments [12, 26, 56]. Whereas in the post-absorptive state, renal gluconeogenesis primarily uses lactate as substrate, followed by gluta-mine, glycerol, and alanine [47], gluconeogenesis induced by metabolic acidosis primarily uses glutamine. Lactate is provided to the S3 segments in the outer medulla by ascending vasa recta that carry lactate-rich blood due to anaerobic metabolism in the inner medulla, consuming glucose and producing lactate (see also discussion of Cori cycle below). Anaerobic glucose usage by the medullary TAL may provide an additional lactate source. Under acidotic conditions, the conversion of glutamine

to glutamate and alpha-ketoglutarate generates ammonium (NH_4^+), which is excreted into the urine as an acid equivalent. The generation of glucose from alpha-ketoglutarate is associated with formation of new bicarbonate that is transported across the basolateral membrane and provided as an acid buffer to the circulation (Fig. 4) [46, 47].

To prevent glucose overload of proximal tubular cells, particularly in the early proximal tubule, apical glucose uptake via SGLT2 and gluconeogenesis may be coordinated. Studies in mice and HK2 cells indicated that apical glucose uptake via SGLT1 or SGLT2 may have an inhibitory influence on gluconeogenic genes (Fig. 4) by a mechanism that involves glucose-induced and sirtuin 1-mediated deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1alpha) [151]. A recent study that characterized the consequences of tubular knockdown of the Na-H-exchanger NHE3 provided first evidence that the reverse may also be true, i.e., that enhanced gluconeogenesis suppresses SGLT2 [123]. NHE3 contributes to proximal tubular ammonium secretion and bicarbonate reabsorption (Fig. 4). To preserve systemic acid-base balance, mice lacking NHE3 in the tubular system strongly upregulate the renal expression of phosphoenolpyruvate carboxykinase (PEPCK) [123], the principal gluconeogenic enzyme [139]. This was associated with a robust downregulation of renal SGLT2 mRNA and protein expression, consistent with an intracellular negative feedback loop that regulates SGLT2 to limit excessive cellular accumulation of glucose (Figs. 4 and 5). In accordance, pharmacologic SGLT2 inhibition increases renal SGLT2 protein expression in non-diabetic mice [195]. Moreover, tubular NHE3 knockdown increases renal SGLT1 mRNA expression, possibly to compensate in part for the reduced upstream SGLT2 expression, indicating a coordinated response to assure effective glucose retention. In fact, urinary glucose excretion was not significantly increased in non-diabetic mice lacking tubular NHE3 despite a 50% downregulation of SGLT2; enhanced glucosuria in the absence of tubular NHE3, however, was induced by superimposing Akita type 1 diabetes mellitus (T1DM) and thereby increasing the tubular glucose load and overwhelming the compensation capacity of SGLT1 [123]. Notably, the increased glucosuria and thus the urinary loss of calories in diabetic mice with tubular NHE3 knockdown did not lower hyperglycemia or induce compensatory increases in food intake, as observed in response to an SGLT2 inhibitor [194, 195] (see below). This may be the consequence of greater glucose delivery to the systemic circulation by the upregulation of renal gluconeogenesis in these mice, consistent with the observed upregulation of renal mRNA of PEPCK, glucose-6-phosphatase, and GLUT2 [123]. Finally, the expression analysis of rate-limiting glycolytic enzymes supported the notion that the newly formed glucose is in part metabolized by glycolysis to drive ATP-consuming processes to facilitate renal ammonium secretion or bicarbonate reabsorption [123]. Potential transporters include the basolateral Na^+-K^+-ATPase and the luminal H^+-ATPase in proximal tubules or the luminal H^+-ATPase in type A intercalated cells (Fig. 4). Glucose may reach the latter cells by intercellular transfer, which includes basolateral exit via GLUT2 from proximal tubules and entry into intercalated cells through basolateral GLUT1 [171]. Upregulation of distal tubule glycolytic markers in mice with tubular knockdown of NHE3 may also reflect a shift in sodium reabsorption from proximal to more distal tubules [123]. This example illustrates the potential coordination between renal glucose transport, generation, and usage.

Bankir and Yang put forward the hypothesis of an intrarenal Cori cycle [5]. These authors propose that glucose generated from lactate in the medullary S3 segment is released into the lumen by reversed transport through SGLT1 [28]. Glucose is delivered to and taken up by downstream tubular segments that use glucose as an energy resource for glycolysis (particularly in the inner medulla, including thin segments of long looped-nephrons, inner medullary collecting ducts, and abundant interstitial cells), whereas the formed lactate is returned by ascending vasa recta to S3 segments for gluconeogenesis and closing of the cycle. Lactate appears to be a better gluconeogenic precursor than glutamine in human proximal tubule S2 and S3 segments [22]. Moreover, studies in mice, rats, and humans indicated that the luminal membrane of the TAL (including the MD) express SGLT1 [4, 101, 214]. Bankir and Yang also hypothesized tubular secretion via SGLT1 in the S3 segment of urea [5]. Notably, mice lacking SGLT1 that are fed a high protein diet, which enhances hepatic urea formation and the need for renal excretion, have increased plasma urea levels compared with wild-type mice despite similar GFR [119]. Additional studies are needed to demonstrate the secretion of urea and glucose via SGLT1. On the other hand, the author of this review envisions that it also seems possible that the glucose generated from lactate in the S3 segments of the proximal tubule reaches the neighboring TAL through the interstitium by intercellular transport (see above), and that anaerobic glycolysis in the medullary TAL generates lactate, which is then transported back through the interstitium to the S3 segments for gluconeogenesis and closing of the cycle.

Renal glucose transport in acute kidney injury

Acute kidney injury (AKI) is associated with high morbidity and mortality [2]. This includes the fact that recurring episodes of AKI contribute to the development of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [36]. Current therapies mainly consist of supportive care rather than effective prevention or curative treatments [15]. The outer medulla (OM) of the kidney is particularly vulnerable [8, 65]. This is due to high active solute reabsorption, including the S3 segment of the proximal tubule and the medullary TAL (mTAL) in combination with a relatively low blood supply [60, 143].

The high transport rates in proximal tubules require high turnover of ATP, which, under normal conditions, is primarily provided by mitochondrial oxidative phosphorylation [56, 201]. This may change in pathophysiological conditions that impair mitochondrial function. For example, a shift to glycolysis has been proposed in proximal tubules regenerating from AKI as well as proximal tubules undergoing atrophy [88]. This switch to glycolysis occurs early during proximal tubule regeneration and reverses during tubular recovery, but persists and becomes more severe in the tubular cells that fail to redifferentiate and recover. Tubular overexpression of HIF-1alpha in a murine model enhanced renal GLUT1 mRNA expression; this was associated with less oxygen consumption and increased glycolysis [31]. Thus, hypoxia may increase basolateral GLUT1-mediated facilitative uptake of glucose, which is then used for glycolysis. Hypoxia induction of GLUT1 likely applies to distal tubule segments, but may also be relevant for the proximal tubule including medullary S3 segments [88], and may occur in response to tubular injury and potentially in diabetic conditions (Fig. 5).

Renal ischemia-reperfusion (IR) injury is an important cause of AKI that can occur in shock, episodes of congestive heart failure decompensation, cardiac bypass surgery, or in kidney transplantation [11, 103]. A typical hallmark of IR injury is the rapid and reversible loss of proximal tubule brush border accompanied by a substantial decrease in fluid and solute reabsorption, both resulting from ischemic ATP depletion. Previous studies in rats demonstrated that renal ischemia is associated with a transient decrease in SGLT-mediated glucose transport activity in brush border vesicles of proximal tubules and a decreased SGLT2 expression at the apical membrane [73, 111]. In accordance, preliminary RNA sequencing data indicated that renal *Sglt2* and *Sglt1* mRNA expression was downregulated on day 1 of reperfusion after 15 or 25 min of bilateral renal artery clamping in C57BL/6J mice (notably, these studies showed upregulation of *Glut1* mRNA [32], see discussion above). Downregulation of SGLT2 expression may protect the early proximal tubule from further injury. Recent meta-analyses reported that SGLT2 inhibition is associated with a reduction in AKI in patients with type 2 diabetes mellitus (T2DM) [52, 120]. In accordance, treatment with the SGLT2 inhibitor dapagliflozin decreased urinary levels of markers of glomerular and tubular injury in patients with T2DM [23, 152] (SGLT2 inhibition in diabetes is discussed in detail below). Moreover, the SGLT2 inhibitor luseogliflozin prevented renal capillary rarefaction and reduced hypoxia and fibrosis in a non-diabetic murine model of renal IR [213]. For unclear reasons, SGLT2 gene knockout in mice, however, did not affect IR injury and subsequent glomerular and tubular recovery after bilateral renal artery clamping in non-diabetic mice [118].

IR-induced downregulation of SGLT2 can enhance the transport burden on the S3 segment in the OM, which could worsen IR injury or the subsequent recovery [156, 181]. This may involve enhanced SGLT1-dependent glucose transport and oxygen consumption in the S3 segment. On the other hand, the glucose uptake associated with SGLT1 may provide glucose as a much needed energy substrate as glycolysis has been proposed to increase under these conditions in the proximal tubule (see above). To gain further insight, the bilateral renal artery clamping model of IR was performed in mice lacking SGLT1. It was observed that absence of SGLT1 did not affect the early tubular injury and impairment of kidney function after IR but improved the tubular and glomerular recovery as monitored over 16 days after IR [119]. As mentioned above, ischemic AKI leads to mitochondrial dysfunction and a metabolic shift of the recovering proximal tubules towards anaerobic glycolysis [3, 88]. This shift is characterized by increased activity of hexokinase in the kidney cortex and the outer stripe of the outer medulla at 14 days after IR injury [88]. Whole kidney mRNA expression of hexokinase 2, a key glycolytic enzyme, was similarly upregulated on day 16 after IR independent of SGLT1, suggesting that the transition to anaerobic glycolysis may not have been affected by the absence of SGLT1. However, the renal mRNA expression of the transcription factor *Ppargc1a*, a master regulator of mitochondrial biogenesis and function [97], was improved during recovery in mice lacking SGLT1. The study thus indicated a deleterious role of SGLT1 during recovery from renal IR (Fig. 6), which is reminiscent of the deleterious role of cardiac SGLT1 in heart IR injury [94].

Renal glucose transport is increased in the diabetic kidney

Diabetes mellitus enhances blood glucose levels and the amounts of glucose filtered by the kidneys, as long as GFR is preserved. In the early phase of diabetes, GFR is often enhanced (glomerular hyperfiltration; see below), thereby increasing the tubular glucose load further. This is associated with an increase in the transport capacity for glucose by ~ 20–30% to ~ 500–600 g/day in patients with T1DM [110] and T2DM [30]. Thus, glomerular filtration and tubular reabsorption of glucose are typically increased in the early diabetic kidney. Despite increased blood glucose levels, diabetes may also stimulate renal gluconeogenesis [46]. This can be due to diabetes-associated metabolic acidosis, activation of the sympathetic nervous system, or reduced insulin levels in T1DM (Figs. 4 and 5), as well as enhanced circulating fatty acids [46].

When the diabetic kidney reabsorbs the enhanced amounts of filtered glucose and makes more glucose, this can provide fuel for further distal segments to reabsorb the enhanced tubular load of salt and other compounds due to glomerular hyperfiltration. However, renal glucose retention and enhanced glucose formation also sustain hyperglycemia (Fig. 5). Upregulation of renal glucose transporter expression may explain the increased glucose transport capacity observed in diabetes. Available pre-clinical and human studies provided inconsistent results reporting reduced, unchanged, or increased renal glucose transporter expression and/or activity in response to hyperglycemia or diabetes [184]. These differences may reflect different diabetes models, metabolic states, and levels of kidney injury, or are due to other factors that regulate the expression of these transporters, the use of non-selective antibodies, or dissociation between mRNA and protein expression.

SGLT2 and GLUT2 expression in the diabetic kidney

Renal protein expression of SGLT2 was increased by 40–80% in the early stages of genetic mouse models of T2DM (db/db) and T1DM (Akita) [194, 195]. These studies used knockout mice as critical negative antibody controls. Consistent with a potential concerted regulation of luminal and basolateral glucose transport, upregulation of GLUT2 expression has been reported in renal proximal tubules in diabetic rats [19, 25, 39, 75].

In STZ-diabetic rats and mice, GLUT2 has also been detected on the brush border membrane of proximal tubules [53, 66, 104] (Fig. 5). This has been linked to protein kinase C PKCβ1 activation [53, 131, 132] and could implicate apical facilitated glucose diffusion into the cell if the luminal glucose chemical potential was to rise above that in the cell and interstitial space. On the other hand, net renal glucose reabsorption was eliminated when pharmacological SGLT2 inhibition was applied to genetic mouse models of T1DM (Akita) and T2DM (db/db) that lacked SGLT1, indicating that SGLT2 and SGLT1 can explain net renal glucose reabsorption also in the diabetic setting [161]. In the small intestine, increases in luminal glucose concentrations are sensed by SGLT1, which is required for the insertion of GLUT2 into the brush border membrane [79]. A similar role may apply to SGLT2 in the proximal tubule, and as a consequence, SGLT2 inhibition may lower renal glucose reabsorption in part by inhibiting apical GLUT2 translocation (Fig. 5). Alternatively, apical GLUT2 is leaking back glucose into the lumen. This would facilitate apical recycling of glucose and promote sodium reabsorption through SGLTs.

The available data on changes in glucose transporters in patients with diabetes is sparse and variable. Primary cultures of human exfoliated proximal tubular epithelial cells harvested from fresh urine of patients with T2DM showed increased protein expression of SGLT2 and GLUT2 associated with an increased glucose uptake [140]. An increase in SGLT2 protein expression was also detected in fresh kidney biopsies of patients with T2DM and advanced nephropathy [198]. On the other hand, the mRNA expression of SGLT2 and GLUT2 was slightly reduced in 19 patients with T2DM and preserved kidney function as compared with 20 non-diabetic patients matched for age and estimated glomerular filtration rate, all being subjected to nephrectomy [159]. Similar results were reported for SGLT2 and GLUT2 mRNA in another set of patients with T2DM but the results did not reach statistically significance [121].

An increase in SGLT2 expression may reflect overall growth and hypertrophy of the diabetic proximal tubule and the associated increase in transport machinery [179, 185] (Fig. 5). SGLT2 is phosphorylated at Ser624 in response to insulin; this was shown in HEK-293T cells and associated with increased Na^+-glucose transport [49]. Thus, insulin release may enhance SGLT2 activity in the proximal convoluted tubule to conserve the increased amounts of filtered glucose in the post-prandial phase (Fig. 4). Furthermore, the hyperinsulinemia associated with insulin resistance in obesity and T2DM may enhance renal SGLT2 activity [172] (Fig. 5). Upregulation of SGLT2 expression in diabetic rats has been linked to activation of Ang II AT1 receptors [124] and the transcription factor, hepatocyte nuclear factor HNF-1α [38], which may respond to basolateral hyperglycemia sensed through GLUT2 [176] (Fig. 5). HNF-1α and HNF-3β have also been implicated in renal GLUT2 upregulation [39] (Fig. 5). A potential negative feedback regulation of SGLT2 expression by intracellular glucose levels has been discussed above. Thus, reduced renal SGLT2 expression in the diabetic kidney may be the consequence of enhanced proximal tubular gluconeogenesis (Figs. 4 and 5) or reflect more severe tubular hypoxia or inflammation [153, 181, 211].

SGLT1 expression in the diabetic kidney

The renal protein expression of SGLT1 was increased in leptin-deficient ob/ob mice [45], a model of T2DM. Studies in Akita diabetic mice, a model of T1DM, indicated that the serum and glucocorticoidinducible kinase SGK1 may stimulate SGLT1 activity and glucose reabsorption in proximal straight tubules [1], and SGK1 can be upregulated in proximal tubules in patients with diabetic nephropathy [89]. On the other hand, renal protein expression of SGLT1 was reduced in another study in Akita mice that used knockout mice as negative antibody control [194]. In contrast to SGLT2 (see above), insulin stimulation slightly decreased SGLT1-mediated Na^+-glucose transport in HEK-293T cells [49], suggesting that insulin regulates these two transporters differently. In contrast to the increase in SGLT2, SGLT1 protein expression was not significantly changed in fresh kidney biopsies of patients with T2DM and nephropathy in comparison with non-diabetic controls [198].

Why should diabetes not increase renal SGLT1 expression or even reduce it? This would make the renal “glucose valve” to open earlier and make SGLT2 inhibitors more efficacious, see below. Lower renal SGLT1 protein expression was also found in other conditions of

enhanced glucose delivery to the late proximal tubule, namely in response to genetic or pharmacological SGLT2 inhibition in non-diabetic mice [193, 195]. In vitro studies in proximal tubule cells indicated that high glucose can reduce SGLT expression and Na^+/glucose cotransport activity through enhanced oxidative stress [59]. Studies in a model of pig epithelial tubular cells (LLC-PK1) found that hypoxia can diminish SGLT1 (and SGLT2) protein expression by activation of HIF-1alpha [211]. Thus, an increased glucose load to the S3 segment enhances net Na^+- glucose reabsorption by SGLT1, but the associated increased oxygen consumption may downregulate SGLT1 to limit hypoxia and glucotoxicity in this segment, which has a high sensitivity to acute injury [181] (Fig. 6). The role of SGLT1 in the MD is discussed below.

GLUT1 expression in the diabetic kidney

GLUT1 protein expression was downregulated in proximal tubules isolated from rat cortices at 2 and 4 weeks after STZ [25], but increased in kidneys of rats at 30 weeks after STZ [95]. A study in patients with T2DM and preserved kidney function reported that renal GLUT1 mRNA expression was slightly lower as compared with non-diabetic patients [159]. The meaning and relevance of the described findings in the diabetic kidney remain to be determined. Also in the setting of diabetes, GLUT1 in the proximal tubule and further distal segments may allow basolateral glucose uptake. Studies in the proximal tubular cell line LLC-PK1, which was cultured and polarized on porous tissue culture inserts, showed that basolateral exposure to 25 mmol/L D-glucose enhanced glucose uptake via GLUT1 and the subsequent intracellular metabolism of glucose enhanced TGF-beta 1 synthesis and secretion; this was not observed in response to apical glucose exposure [133]. These in vitro studies suggest that it may be the hyperglycemia-induced persistent uptake of glucose via basolateral GLUT1 (or GLUT2?), rather than the apical glucose uptake, that affects the tubular synthesis of TGF-beta 1 and thereby the development of tubulointerstitial fibrosis and tubular growth (Fig. 5). Clearly, there is a need for a better understanding of basolateral renal glucose transport and its implications in health and disease.

The pleiotropic effects of SGLT2 inhibition in the diabetic kidney

Current therapies for T2DM include drugs that target the liver, small intestine, adipose tissue, skeletal muscle, and/or pancreatic islets. Many of these therapies, including insulin, may not establish adequate glycemic control without relevant unwanted side effects, like hypoglycemia and weight gain, and may not reduce cardiovascular complications [48].

The following sections outline the logic of SGLT2 inhibition in the diabetic kidney. Long-term access to abundant exogenous energy resources is not part of human evolution, and, therefore, the body’s responses can be maladaptive. In contrast, the body’s ability to adapt to environments with scarce energy resources has been tested and refined throughout evolution for the survival of the organism. Therefore, targeting the body’s “periphery” by inhibiting renal glucose reabsorption and spilling glucose as an energy resource and extra calories into the urine, which then activates metabolic counterregulatory mechanisms similar to fasting, may provide unique benefits as an anti-hyperglycemic approach [185].

The logic of inhibiting SGLT2 in the diabetic kidney as a therapeutic strategy includes the role of tubular glucose reabsorption in maintaining hyperglycemia (Fig. 5). Multiple SGLT2 inhibitors have been approved as glucose-lowering agents for patients with T2DM and preserved kidney function [33, 185]. SGLT2 inhibitors act on their target in the luminal cell membrane from the extracellular surface [51], which is reached by glomerular filtration and, as indicated for empagliflozin, also by tubular secretion [41]. SGLT2 inhibition reduces the renal reabsorptive capacity for glucose to the capacity of SGLT1, which equals approximately 80 g/day. Thus, SGLT2 inhibition causes the renal “glucose valve” to open at a much lower threshold (Fig. 2). SGLT2 inhibitors cause a dose-dependent urinary glucose loss of up to 40–80 g/day, which in patients with T2DM is associated with a decrease in Hb A1C levels of 0.5–0.7% [185]. The higher the blood glucose level and GFR, the more glucose is filtered and reabsorbed and, as a consequence, will be excreted in response to SGLT2 blockade. The main side effect of SGLT2 inhibitors is an increased risk of genitourinary infections due to the glucosuric effect [44].

The observed small effect of SGLT2 inhibitors on blood glucose control alone appears insufficient to fully explain the rapid beneficial effect detectable within a few months in large cardiovascular outcome trials [168]. While other mechanisms are likely to contribute (see below), these other agents, in contrast to SGLT2 inhibitors, may have simultaneous countervailing effects that offset the benefits of better glycemic control, including gain in body weight and an increased hypoglycemia risk. SGLT2 inhibitors do not increase the incidence of hypoglycemia [112, 114, 199, 216] because they become ineffective at lowering blood glucose once the filtered glucose load falls to ~ 80 g/day, which can be handled by downstream SGLT1 (see above). In addition, SGLT2 inhibitors leave the metabolic counterregulation intact and increase plasma glucagon concentrations and subsequently endogenous hepatic glucose production (gluconeogenesis) in patients with T2DM [34, 109]. The mechanism by which SGLT2 inhibitors increase glucagon secretion in pancreatic alpha cells remains controversial [86, 150, 163]. Nevertheless, the intact metabolic counterregulation is potentially relevant for cardiovascular outcome, since episodes of hypoglycemia impair the cardioprotective effects of anti-hyperglycemic therapy [80]. Thus, SGLT2 inhibition is likely to tighten 24 h blood glucose profiles within the desirable range by preventing blood glucose lows and highs, which together may have little effect on HbA1C values, but induces significant benefits on renal and cardiovascular outcome.

SGLT2 inhibition lowers body weight initially due to the diuretic effect and subsequently due to the renal calorie loss, which shifts substrate utilization from carbohydrates to lipids and reduces body fat, including lesser visceral and subcutaneous fat [185]. The enhanced release of free fatty acids drives formation of ketone bodies, which can be used as an additional energy substrate, including in cardiac and kidney cells [35, 137]. On the other hand, SGLT2 inhibitors can increase the risk of diabetic ketoacidosis [137], particularly when the drugs are used off label in patients with T1DM [137]. By improving blood glucose control and lowering body weight, SGLT2 inhibitors improve beta-cell function and sensitivity to insulin as shown in patients and rodent models with T2DM [34, 61, 74, 100, 109]. By lowering hyperglycemia, SGLT2 inhibitors can attenuate the deleterious effects of glucotoxicity on the kidney and extrarenal organs [116]. Importantly, the logic of inhibiting

SGLT2 in the diabetic kidney relates to the role of the transporter in the “tubular hypothesis” of glomerular hyperfiltration and nephropathy [184, 190], as discussed in the following.

SGLT2 inhibition initially lowers GFR and preserves kidney function in long term

Less than 1% of filtered Na^+ is excreted in normal individuals to match urinary excretion to dietary Na^+ intake. As a consequence, almost all filtered Na^+ needs to be reabsorbed. Tubular transport, however, determines renal oxygen consumption. Therefore, glomerular hyperfiltration increases renal transport work and oxygen requirement, and lowering GFR has opposite effects [92]. Furthermore, glomerular hyperfiltration, which is observed in a subset of patients at the onset of T1DM and T2DM, is a risk factor for developing diabetic nephropathy [102].

According to the “tubular hypothesis,” glomerular hyperfiltration in diabetes is explained by a primary increase in tubular reabsorption (for review, see [184]). Moderate levels of hyperglycemia increase proximal tubular reabsorption by providing more substrate for Na^+-glucose cotransport via SGLT2 and SGLT1 and by causing the tubule to grow, which enhances the transport machinery and capacity. The increased reabsorption reduces the NaCl and fluid delivery to the downstream MD, which senses this reduction and subsequently increases GFR through the normal physiology of tubuloglomerular feedback (TGF) (Figs. 7 and 8). The TGF mechanism is mediated by basolateral release of ATP from MD cells, which occurs in proportion to the luminal NaCl concentration and delivery, and the subsequent extracellular conversion of ATP to adenosine; adenosine then adjusts the tone of the afferent arteriole (constriction via A_1 receptor) and under some condition of the efferent arteriole (vasodilation via A2 receptors) (Fig. 8) and thereby alters GFR of the same nephron such that the NaCl and fluid delivery downstream of the MD is stabilized [192]. This way, the TGF facilitates fine regulation of NaCl and fluid balance, which occurs in the distal nephron by neurohumoral control. A secondary consequence of TGF physiology is that the mechanism contributes to the autoregulation of GFR and renal blood flow. Moreover, the TGF makes GFR responsive to primary changes in tubular transport upstream of the MD, as proposed for the diabetic kidney. A primary increase in proximal reabsorption also reduces distal tubular flow rate, which increases GFR by lowering tubular back pressure, i.e., the hydrostatic pressure in Bowman space, and thereby increasing the effective glomerular filtration pressure (Fig. 7). Mathematical modeling indicates that TGF and the changes in tubular back pressure may contribute equally to the increase in GFR in diabetes [58].

Consistent with a prominent role of SGLT2 in the tubular hypothesis of glomerular filtration, SGLT2 inhibition attenuates proximal tubule hyperreabsorption in the diabetic kidney and thereby lowers diabetic glomerular hyperfiltration (Figs. 7 and 9). Micropuncture studies were done in hyperfiltering STZ-diabetic rats with superficial glomeruli that allowed for tubular fluid collection from sites close to the MD [187] (Fig. 7). Concentrations of Na^+, Cl^-, and K^+ at the MD were lower by ~ 25% compared to non-diabetic controls, consistent with a primary increase in reabsorption upstream of the MD. When SGLT2 and SGLT1 were inhibited by perfusing phlorizin into Bowman’s space of the same nephrons, the electrolyte concentrations at the MD increased to normal and SNGFR declined to normal in diabetic rats. Phlorizin had a much lesser effect in nephrons of non-diabetic animals (Fig. 7). Similar

results were obtained in micropuncture studies in rats by acute or chronic systemic application of a selective SGLT2 inhibitor [170]. Moreover, pharmacologic or genetic inhibition of SGLT2 reduced hyperfiltration on the whole-kidney level in diabetic mice [161, 194, 195]. The suppression of diabetic hyperfiltration in response to SGLT inhibition was associated with an increase in the hydrostatic pressure in Bowman space [187], and was independent of effects on blood glucose [170, 187, 194]. These results are consistent with diabetic hyperfiltration resulting from a primary increase in proximal tubular reabsorption that depends on sodium-glucose cotransport (Fig. 7).

Studies in humans confirmed this GFR-lowering effect of short-term SGLT2 inhibition. Moreover, a biphasic GFR profile has been established in long-term studies, i.e., an initial GFR reduction is followed by improved GFR preservation. Treatment with the SGLT2 inhibitor empagliflozin for 8 weeks decreased GFR in T1DM patients with baseline hyperfiltration independent of lowering blood glucose levels [17]. Estimation of glomerular hemodynamics in the latter study suggested a dominant effect on the afferent arteriole, whereas a preliminary study in patients with T2DM proposed that the SGLT2 inhibitor dapagliflozin reduced measured GFR by reducing efferent arteriolar resistance [10]. As indicated above, TGF-induced adenosine formation can constrict the afferent arteriole and dilate the efferent arteriole, and thus explain both effects (Fig. 8). In the EMPA-REG OUTCOME trial in patients with T2DM and preserved kidney function, empagliflozin initially reduced estimated GFR (eGFR) versus placebo when measured at week 4 of treatment, consistent with the above short-term studies. During subsequent follow-up until week 192, eGFR remained stable in SGLT2 inhibitor-treated participants while placebo treatment was accompanied by a progressive decrease in eGFR, such that kidney function was better preserved with the SGLT2 inhibitor [199]. A similar GFR time course was observed in clinical studies with canagliflozin [63, 127, 128] and dapagliflozin [82]. Most importantly, after treatment discontinuation, eGFR increased to baseline in the SGLT2 inhibitor groups while eGFR remained unchanged at reduced levels in placebo groups [127, 199]. Even though the blood glucose-lowering effect of SGLT2 inhibition was attenuated in T2DM patients with CKD2 and CKD3 due to lesser total glucose filtration, the short-term GFR lowering effect [7, 128, 209], the long-term GFR preservation [128] and the full reversibility of the GFR lowering effect after discontinuation of the SGLT2 inhibitor [7] remained.

Thus, SGLT2 inhibition initially induces a reversible GFR reduction, indicating a functional rather than structural cause, consistent with the tubular hypothesis of glomerular hyperfiltration. In the long term, and as shown in large clinical outcome trials, SGLT2 inhibition preserves eGFR and renal function in T2DM patients when compared with placebo treatment [114, 199, 212], including in patients with kidney disease [128] (Fig. 9). See [168] for further review of the CANVAS, EMPA-REG, DELCARE as w ell as CREDENCE trial, respectively. Lowering single nephron glomerular hyperfiltration and thereby the oxygen-consuming transport work may help to preserve the integrity of the remaining nephrons in CKD and in that way overall kidney function in the long term (Fig. 9). This has been proposed for blockers of angiotensin II [67] and may also apply to SGLT2 inhibitors. Most patients in the large outcome trials with SGLT2 inhibitors were also treated with a form of angiotensin II blockade, indicating additive effects, which is consistent with

the concept that angiotensin II blockade is primarily dilating the efferent arteriole, whereas SGLT2 inhibition primarily results in constriction of the afferent arteriole.

SGLT2 inhibition protects heart function

SGLT2 inhibition causes a modest osmotic diuresis (100–470 mL/24 h) and natriuretic effect and reduces body weight, thereby decreasing systolic blood pressure by 3–6 mmHg [185], an effect expected to have cardiovascular protective consequences, particularly in high-risk patients [37] (Fig. 9). In clinical studies, reduced proximal tubular sodium reabsorption in response to SGLT2 inhibition is indicated by enhanced fractional lithium excretion [27]. SGLT2 inhibition enhances renin levels [27, 193] and vasopressin (or copeptin) levels [27, 99, 106, 107] and reduces renal free-water clearance [27, 107] in rodents and humans, associated with increased renal protein expression of vasopressin V_2 receptors and phosphorylated aquaporin-2 in rats [107], indicating active compensation to counter the diuretic and natriuretic effects. Further homeostatic mechanisms to stabilize body fluid volume can include compensatory increases in fluid and food/carbohydrate intake [106, 107, 126, 195]. The blood pressure-lowering effect of SGLT2 inhibition and modest reduction in plasma volume [87] may quickly reduce cardiac pre- and afterload and thereby contribute to the rapid beneficial effects observed in larger outcome trials in heart failure patients [78, 114, 128, 216]. Beneficial renal and cardiovascular effects of SGLT2 inhibition can also be due to a uricosuric and plasma uric acid-lowering effect [77] that may be related to increased tubular or urinary glucose delivery [20, 98] and interactions with the luminal urate transporter URAT1 [122].

Many of the described effects of SGLT2 inhibition can occur independent of lowering blood glucose levels. For example, the anti-hyperglycemic effects of SGLT2 inhibitors are attenuated in diabetic patients with reduced GFR (since less glucose is filtered), yet the blood pressure-lowering and heart failure protective effects are preserved in patients with CKD and reduced GFR (estimated GFR ≥ 30 mL/min/1.73 m^2) [130, 200]. Modeling studies of diabetes, CKD, and nephron loss predicted that the gluco-osmotic effect of inhibiting SGLT2 in remaining hyperfiltering nephrons that are exposed to sustained hyperglycemia induced paracellular Na^+ secretion in the proximal tubule [90]. Thus, the model predicted that the chronic natriuretic and diuretic effects of SGLT2 inhibition persist in diabetic CKD.

Furthermore, ongoing trials test SGLT2 inhibitors in non-diabetic patients with heart failure and/or CKD [177]. A first completed study, the DAPA-HF trial, revealed that among patients with heart failure and reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was reduced by the SGLT2 inhibitor dapagliflozin versus placebo, regardless of the presence or absence of diabetes [108]. Also a secondary analysis of the CREDENCE trial indicated that canagliflozin reduced the risk of both cardiovascular and renal events in patients with T2DM and CKD without a significant interaction across the spectrum of baseline HbA1c values, which included patients with baseline HbA1c between 6.5 and 7% [13].

SGLT2 may be functionally coupled to NHE3 in the proximal tubule, such that pharmacological blockade of SGLT2 can partially inhibit the activity of NHE3 [21, 40, 68, 129]. Vice versa, tubular knockdown of NHE3 can reduce SGLT2 expression [123]. A

coordinated regulation of apical transporters in the early proximal tubule that are involved in Na^+, bicarbonate, and glucose reabsorption may facilitate appropriate up- and downregulation of tubular reabsorption in response to changes in GFR, e.g., in the post-prandial phase (Figs. 4 and 5). A similar co-regulation in the post-prandial phase has been proposed for SGLT1 and NHE3 in the small intestine. Thus, an interaction with NHE3 may contribute to the diuretic and natriuretic effect of SGLT2 inhibition. Such an interaction could enhance the natriuretic potential of SGLT2 inhibition, potentially independent of diabetes and the filtered glucose load. While renal NHE3 can be upregulated in heart failure [70], further studies are needed to test these hypotheses and any involved molecular mechanisms.

SGLT2 inhibition lowers and distributes the transport burden along the tubular system

The highest transport burden in response to hyperglycemia and hyperfiltration is on the early proximal tubule. Mathematical modeling predicted that inhibition of SGLT2 in the diabetic kidney reduces oxygen consumption in the proximal convoluted tubule and renal cortex, in part by lowering GFR [91, 92] (Fig. 9). The predicted increase in cortical O_2 pressure and availability has been observed in a diabetic rat model using phlorizin, a dual SGLT1/SGLT2 inhibitor [115]. Interestingly, renal cortical oxygenation has been linked to better preservation of kidney function in patients with CKD [136].

Some of the effects of SGLT2 inhibition on the kidney go beyond reversing the hyperreabsorption of glucose in the early proximal tubule. This includes the enhanced glucose and sodium load to downstream nephron segments (Fig. 9). By partially shifting sodium and glucose reabsorption downstream, SGLT2 inhibition more equally distributes the transport burden along the tubular and collecting duct system, which may help to preserve renal integrity and function. On the other hand, shifting more transport to the S3 segment and medullary TAL may reduce the already physiologically low O_2 availability in the renal outer medulla [91, 92, 115] (Figs. 6 and 9). This includes enhanced glucose transport via SGLT1, which, as discussed above, uses double the energy per glucose compared with SGLT2 [208].

Mathematical modeling predicted that the increase in medullary transport and oxygen consumption in response to SGLT2 inhibition is significantly attenuated by its blood glucose- and GFR-lowering effect [91, 92] (Fig. 9). Furthermore, the reduction in oxygen pressure in the deep cortex and outer medulla may stimulate hypoxia-inducible factors HIF-1 and HIF-2. Gene knockout of SGLT2 increased the renal mRNA expression of hemoxygenase 1 [194], a tissue protective gene that is induced by HIF-1-alpha. Moreover, activation of HIF-2 may explain enhanced erythropoietin release from renal interstitial cells in response to SGLT2 inhibition [146]. Together with the diuretic effect, the latter may contribute to the observed modest increase in hematocrit and hemoglobin in response to SGLT2 inhibition (Fig. 9); this may improve oxygenation not only in the renal outer medulla and cortex but enhance oxygen delivery to the heart and other organs [90]. Notably, 52 and 49% of the effect of the SGLT2 inhibitor empagliflozin on the risk of cardiovascular death was explained by changes in hematocrit and hemoglobin from baseline, respectively [71]. Thus, SGLT2 inhibition may mimic systemic hypoxia at the oxygen sensor in the

corticomedullary junction of the kidney, with the induced response helping the kidney and failing heart [90] (Fig. 9). Modeling studies indicate that these effects and the natriuretic effect of SGLT2 inhibition will be preserved in CKD [90].

SGLT1 in the macula densa serves as a glucose sensor that can contribute to diabetic hyperfiltration

The vasoconstrictor response of the TGF can be attenuated in diabetes [72, 182, 186]. Blantz et al. concluded that modest hyperglycemia reduced the vasoconstrictor TGF activity in non-diabetic rats by effects of glucose in the tubular fluid beyond the late proximal tubule [9]. Nitric oxide (NO), formed by neuronal NO synthase in the MD (MD-NOS1), shifts the TGF curve rightward and makes it less steep, which facilitates increased NaCl delivery to the MD and sodium excretion [96, 183, 189, 203]. MD-NOS1 has been implicated in the GFR increase in response to acute hyperglycemia and in STZ-induced diabetes in rats and mice [83, 169, 173, 214]. More recent studies demonstrated that the stimulus for increased MD-NOS1 activity in hyperglycemia and diabetes includes an enhanced glucose delivery to the MD, which is sensed by SGLT1 expressed in its luminal membrane [161, 214] (Figs. 8 and 10). In accordance, absence of SGLT1 prevented the Akita diabetes-induced increase in MD-NOS1 expression and attenuated hyperfiltration [161]. The two studies support the notion that increased tubular glucose delivery is sensed by SGLT1 in the luminal membrane of MD cells, which respond by increasing NOS1-dependent NO formation thereby reducing the vasoconstrictor tone set by TGF and contributing to glomerular hyperfiltration [161, 214] (Figs. 8 and 10).

Absence of SGLT1 not only lowers glomerular hyperfiltration in Akita mice, but also reduces kidney weight, glomerular size, and albuminuria [161]. These findings suggest that SGLT1 may have implications for renal integrity beyond the reabsorption of glucose. The MD and the juxtaglomerular apparatus may orchestrate single nephron function and structure. This involves the well-established regulation of renin, the adjustment of GFR by TGF, and TGF resetting to facilitate renal NaCl excretion, but it may do much more. E.g., sensing of increased glucose delivery at the MD may indicate the need for more upstream transport capacity and trigger tubular growth during development but also in response to hyperglycemia (Fig. 10). Further studies are needed to follow-up on these hypotheses.

Why should an increase in macula densa glucose increase GFR?

GFR rises in the diabetic kidney, at least in part, to stabilize body fluid volume when tubular growth and enhanced sodium-glucose-cotransport cause a primary increase in upstream tubular reabsorption of sodium, glucose, and fluid [58, 184] (Fig. 10). Glucose delivery to the MD indicates saturation of upstream SGLTs and thus hyperreabsorption of sodium, glucose, and fluid. The MD senses the increased luminal glucose via SGLT1, and the SGLT1-NOS1-GFR pathway enhances GFR in order to maintain urinary sodium and fluid excretion and volume balance (Fig. 10). Blunting this compensatory increase in GFR without significantly attenuating hyperreabsorption is expected to increase blood pressure, as a first-order mechanism for sodium homeostasis [57]. In fact, SGLT1 knockout blunted diabetes-induced hyperfiltration, but suppressed renal renin mRNA expression and increased

systolic blood pressure (Fig. 10). The response to SGLT1 knockout in diabetic mice resembled the effect of a selective NOS1 inhibitor in diabetic rats [83]—in both cases, GFR was reduced and accompanied by a mild increase in blood pressure. Thus, the MDSGLT1-NOS1-GFR pathway may complement the classic pathways of TGF and tubular back pressure in the compensatory adaptation of GFR to tubular hyperreabsorption in the diabetic kidney. In contrast to the MD-SGLT1-NOS1-GFR pathway, the two classic mechanisms primarily operate when tubular glucose reabsorption is below the transport maximum of glucose (Fig. 10). Deterioration of the MD-SGLT1-NOS1-GFR pathway could play a role in the transition from of a hyperfiltering and normotensive diabetic patient to later disease stages characterized by reduced GFR and hypertension [161, 214].

How does the MD-SGLT1-NOS1-GFR pathway affect the response to SGLT2 inhibition?

Studies in Akita mice indicated that inhibition of SGLT1 and SGLT2 can have additive effects on the early diabetic kidney, including the improvement of blood glucose control and the lowering of GFR, renal glucose reabsorption, kidney weight, and glomerular size [161]. SGLT2 inhibition lowers GFR by enhancing Na-Cl-K delivery to the MD (Figs. 8 and 9). This effect on GFR can be attenuated by increasing glucose delivery to the MD and engaging the MD-SGLT1-NOS1-GFR pathway. An increase in glucose delivery to the MD is expected when SGLT2 inhibition enhances glucosuria, which typically is observed in the clinical setting with no or only moderate hyperglycemia. In accordance, SGLT2 inhibition increased MD-NOS1 expression in non-diabetic mice, an effect that was prevented by the absence of SGLT1 [161]. SGLT2 inhibition in more severely hyperglycemic Akita mice did not induce a sustained increase in glucosuria and thus glucose delivery to the MD (due to the concomitant strong reduction in filtered glucose matching the inhibition of glucose reabsorption, as previously described [194, 195]), and actually reduced MD-NOS1 expression [161]. The latter could reflect the inhibitory influence of volume loss on MD-NOS1, induced by the diuretic effect of SGLT2 inhibition (Figs. 8 and 10). In other words, SGLT2 inhibitors may reduce hyperfiltration in part through inducing volume loss which impinges on the MD-NOS1 pathway. SGLT2 inhibition also prevented the blood pressure increase observed in Akita diabetic mice lacking SGLT1, potentially due to additive effects of SGLT2 and SGLT1 inhibition on renal glucose, Na^+, and fluid excretion [161]. Thus, these mouse studies provided supportive evidence for a combination of SGLT2 and SGLT1 inhibition. Further studies are required to define the nuances of MD glucose sensing and the therapeutic potential of dual SGLT2/SGLT1 inhibition, which also affects intestinal glucose handling and its consequences [14, 141, 158, 160].

Summary and perspectives

The quantitative roles of SGLT2, SGLT1, and GLUT2 for glucose reabsorption in the healthy kidney have been well established. The kidney has the ability to generate glucose and can also use it as an energy source. Little is known, however, about the coordination between renal glucose transport, glucose formation, and the intrarenal glucose usage. What molecular mechanisms are involved in this coordination? What is the quantitative role of intercellular glucose transfer within the kidney? Is there an intrarenal Cori cycle? Even less is known when it comes to kidney disease, including AKI or CKD. Is cellular glucose uptake

good or bad for an injured epithelial cell? Does it matter how glucose enters the cell? Does hyperglycemia alter cellular metabolism and integrity of renal epithelia primarily by basolateral glucose uptake through GLUT1 or GLUT2? In comparison, much has been learned about the role of apical SGLT2 an SGLT1 in diabetic glomerular hyperfiltration. The newly discovered role of SGLT1 as a glucose sensor in the macula densa that affects GFR may reflect the larger role of these cells in the orchestration of kidney function and structure. The tubular hypothesis of diabetic glomerular hyperfiltration and nephropathy illustrates the pathophysiological potential of SGLT2, which couples the retention of glucose, an energy source, to the reabsorption of sodium, which affects volume status. While this concept contributes to the unexpected logic of SGLT2 inhibition in the diabetic kidney [185], many aspects of their renal and cardiac protective effects remain to be established. Better understanding the protective effects of SGLT2 inhibitors provides an opportunity to better understand the needs of a failing kidney and heart.

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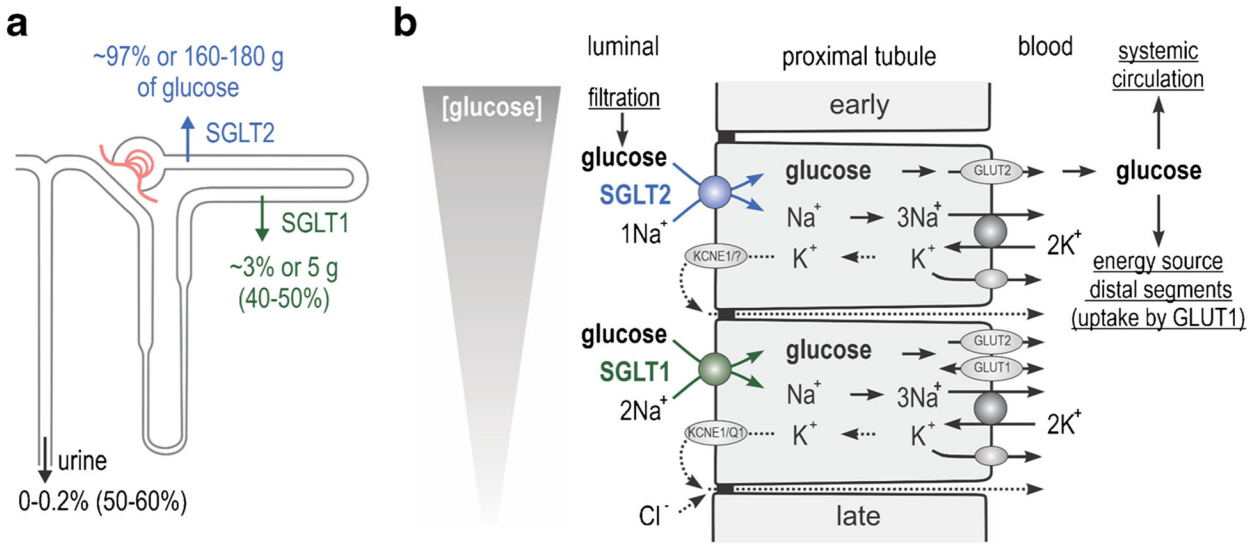

Fig. 1.

Glucose reabsorption in the kidney. **a** Under *normoglycemia*, SGLT2 in the early proximal tubule reabsorbs ~ 97% of filtered glucose. The remaining ~ 3% of glucose is reabsorbed by SGLT1 in the late proximal tubule, such that urine is nearly free of glucose. SGLT2 inhibition shifts glucose reabsorption downstream and unmasks the glucose reabsorption capacity of SGLT1 (~ 40% of filtered glucose, depending on glucose load; see numbers in parentheses). **b** Cell model of glucose transport: The basolateral Na^+-K^+-ATPase lowers cytosolic Na^+ concentrations and generates a negative interior voltage, thereby providing the driving force for Na^+-coupled glucose uptake through SGLT2 and SGLT1 across the apical membrane. The facilitative glucose transporter GLUT2 mediates glucose transport across the basolateral membrane down its chemical gradient. Basolateral GLUT1 may contribute to reabsorb glucose or take glucose up from peritubular space. Na^+-glucose cotransport is electrogenic and accompanied by paracellular Cl^- reabsorption or transcellular K^+ secretion to stabilize membrane potential; K^+ channels KCNE1/unknown α subunit and KCNE1/KCNQ1 in early and late proximal tubule, respectively. This figure was modified from [178]

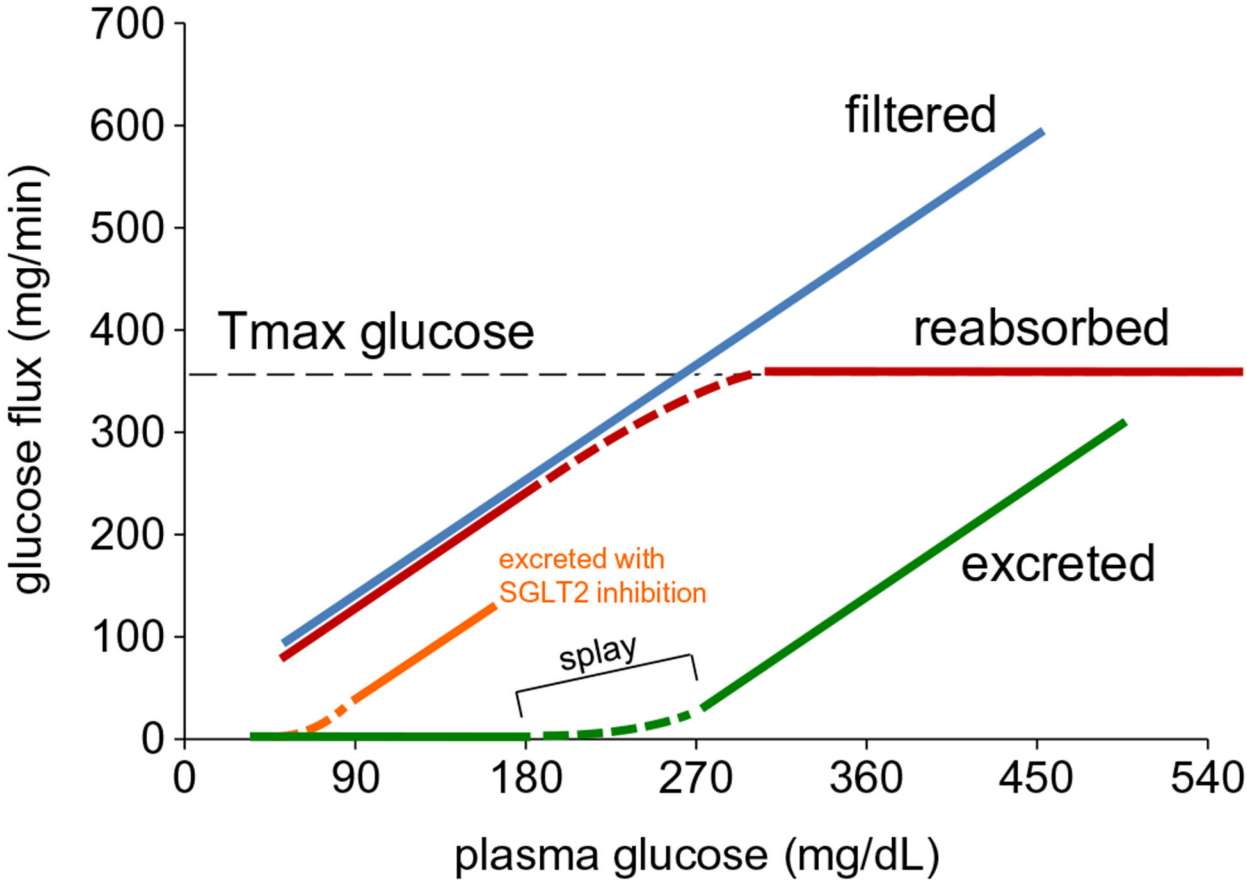

Fig. 2.

Tubular glucose reabsorption can be saturated. Tubular reabsorption of glucose increases linearly with the filtered glucose load until reabsorption reaches the maximum tubular reabsorption (T_{max} glucose) and glucose starts to appear in urine. Theoretically in humans, a T_{max} of ~ 350 mg/min and normal GFR would result in a plasma glucose threshold of ~ 280 mg/dL. The T_{max}, however, varies between individual nephrons and, therefore, low level spilling of glucose into the urine initiates at modestly elevated plasma glucose levels of ~ 180–200 mg/dL in a healthy adult (see “splay”). Normoglycemia is defined as fasted plasma glucose levels < 100 mg/dL (< 5.5 mM). SGLT2 inhibition reduces the renal glucose reabsorption to the transport capacity of SGLT1, i.e., it reduces the renal glucose threshold (~ 55–65 mg/dL) and T_{max} (~ 60–80 mg/min)

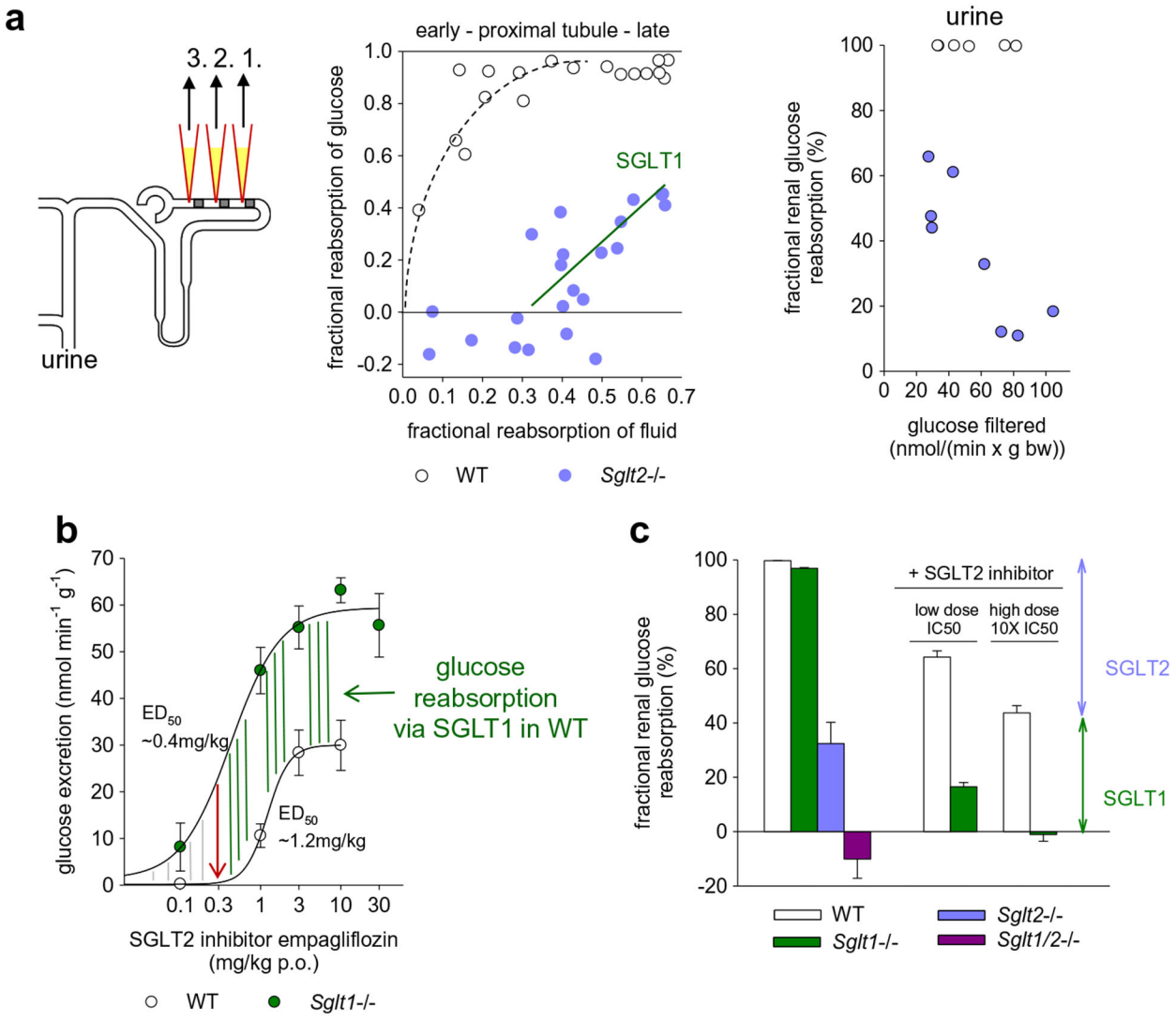

Fig. 3.

Defining the contribution of SGLT2 and SGLT1 to renal glucose reabsorption. **a** Left two panels: free-flow collections of tubular fluid was performed by micropuncture to establish a profile for fractional reabsorption of glucose versus fractional reabsorption of fluid along accessible proximal tubules at the kidney surface. Glucose reabsorption is prevented in the early proximal tubule in mice lacking SGLT2 (*Sglt2*−/−), but enhanced in the later proximal tubule, suggesting compensation by SGLT1. Right panel: in renal inulin clearance studies, the reduction in fractional renal glucose reabsorption in *Sglt2*−/− mice correlated with the amount of filtered glucose. **b** In metabolic cage studies, the SGLT2 inhibitor empagliflozin dose-dependently increased glucose excretion in WT mice. The response curve was shifted leftward and the maximum response doubled in *Sglt1*−/− mice. The difference between the 2 dose-response curves reflects glucose reabsorption via SGLT1 in WT mice. Glucosuria is initiated in WT mice when SGLT1-mediated glucose uptake is maximal (red arrow). The difference between curves was maintained for all higher doses (same length of vertical green lines), indicating selectivity of the drug for SGLT2 versus SGLT1 in this dose range. **c** Using

genetic knockout models and pharmacologic tools in renal inulin clearance studies indicated that the glucose reabsorption preserved during SGLT2 knockout or inhibition (~ 40%) is mediated by SGLT1. The SGLT2 inhibitor empagliflozin was applied at low and high doses to establish free plasma concentrations (similar to concentrations in glomerular filtrate) close to IC_{50} for mouse SGLT2 (~ 1–2 nM) or 10-fold higher. Data taken from [142, 193]

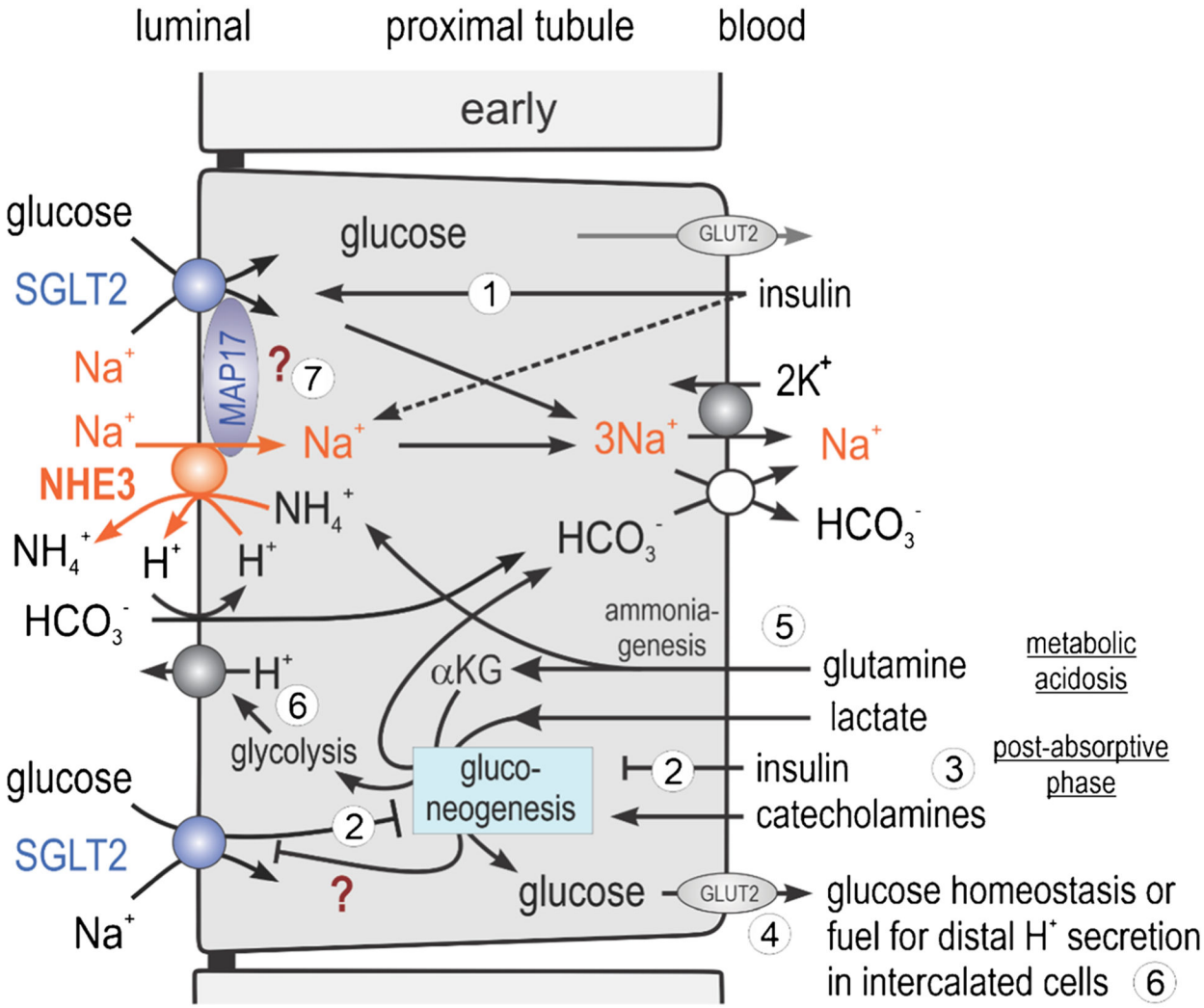

Fig. 4.

Coordination of glucose transport and gluconeogenesis in the proximal tubule. (1) Insulin is a physiological stimulator of SGLT2, which may serve to maximize renal glucose reabsorption capacity in situations of increased blood glucose levels, e.g., following a meal. (2) At the same time, enhanced Na^+-glucose uptake and insulin suppress renal gluconeogenesis. (3) The latter, in contrast, is stimulated in the post-absorptive phase (fasting) by increased catecholamine and reduced insulin levels, and involves primarily lactate as a precursor. (4) The newly formed glucose is delivered to the systemic circulation by basolateral GLUT2. (5) In metabolic acidosis, the increase in gluconeogenesis from glutamine is linked to the formation of (i) ammonium (NH_4^+), a renally excreted acid equivalent, and (ii) new bicarbonate, which is taken up into the circulation. The Na^+-H^+-exchanger NHE3 contributes to apical H^+/NH_4^+ secretion and Na^+/bicarbonate reabsorption. (6) The newly formed glucose can be used as fuel for proximal tubule H^+ secretion or, after intercellular transfer, for intercalated cell H^+ secretion. (7) SGLT2 and NHE3 are both stimulated by insulin to enhance Na^+ and glucose reabsorption and their functions may be positively linked through the scaffolding protein MAP17

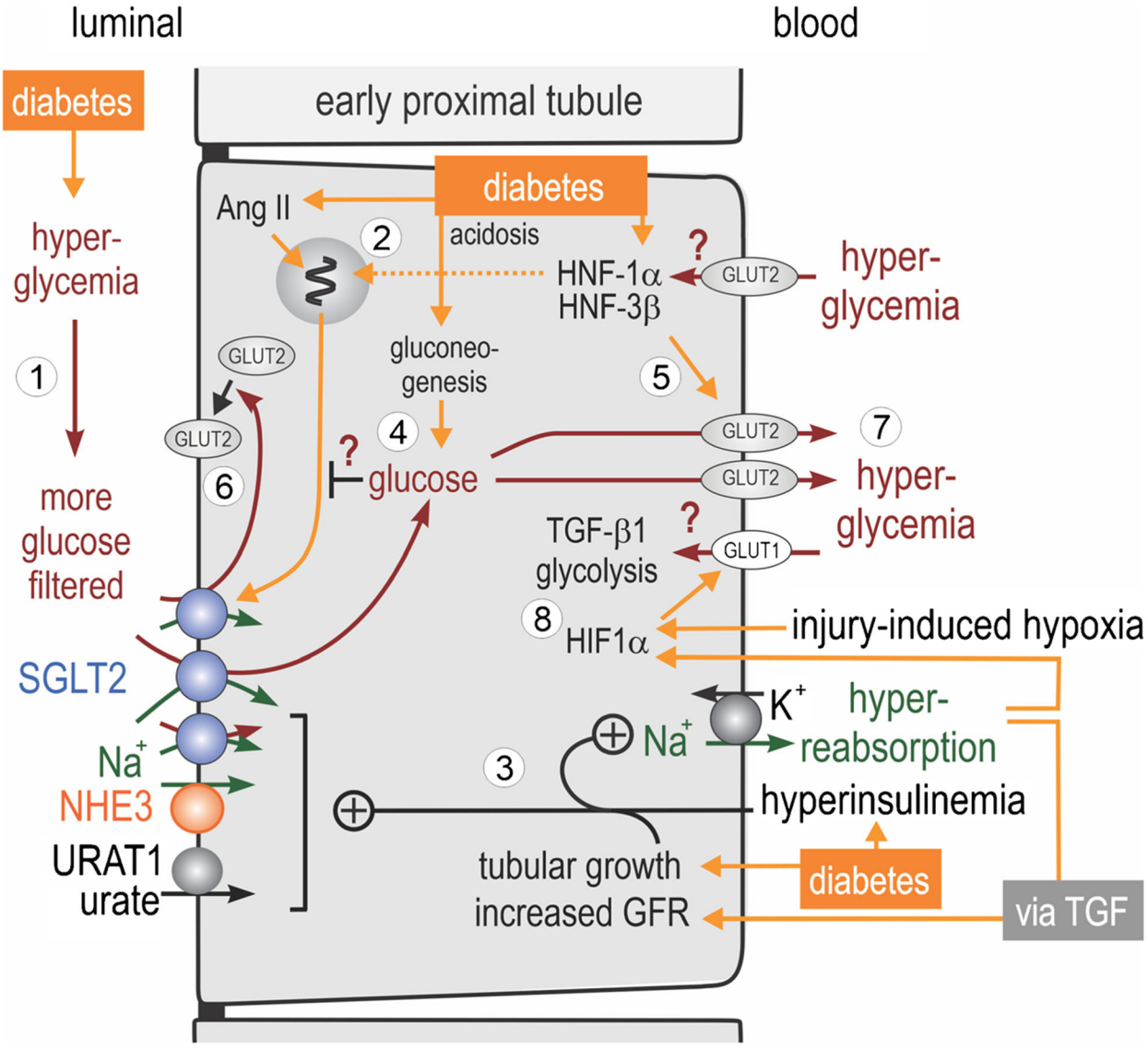

Fig. 5.

Regulation of proximal tubule glucose transporters in disease. (1) Hyperglycemia enhances filtered glucose and, via SGLT2 (and SGLT1, not shown), the reabsorption of glucose and Na^+ in the proximal tubule. (2) Diabetes can increase the renal membrane expression of SGLT2; proposed mechanisms include tubular growth, angiotensin II (Ang II), and hepatocyte nuclear factor HNF-1α, which may respond to basolateral hyperglycemia sensed through GLUT2. (3) Hyperinsulinemia and tubular growth may induce a coordinated upregulation of proximal tubular transport systems, including SGLT2, NHE3, URAT1, and Na^+/K^+-ATPase. The resulting increase in proximal tubular Na^+ retention enhances GFR via tubuloglomerular feedback (TGF), which by increasing brush border torque may further increase luminal membrane transporter density in the early proximal tubule. (4) Diabetes, in part due to the associated acidosis, can enhance gluconeogenesis in the early proximal tubule. The resulting increase in intracellular glucose may feedback inhibit on SGLT2 expression. (5) HNF-1α and HNF-3β upregulate GLUT2, the basolateral exit pathway of

glucose. (6) The relevance of apical translocation of GLUT2 in diabetes remains to be determined, but may be secondary to excessive SGLT2-mediated glucose uptake. (7) Increased glucose reabsorption maintains hyperglycemia. Induction of TGFβ1 and tubular growth may be particularly sensitive to basolateral glucose uptake via GLUT1. (8) Hypoxia induced by kidney injury or due to diabetes-induced hyperreabsorption may induce HIF1alpha, which inhibits apical transporters (not shown) and facilitates basolateral glucose uptake and a metabolic shift to glycolysis

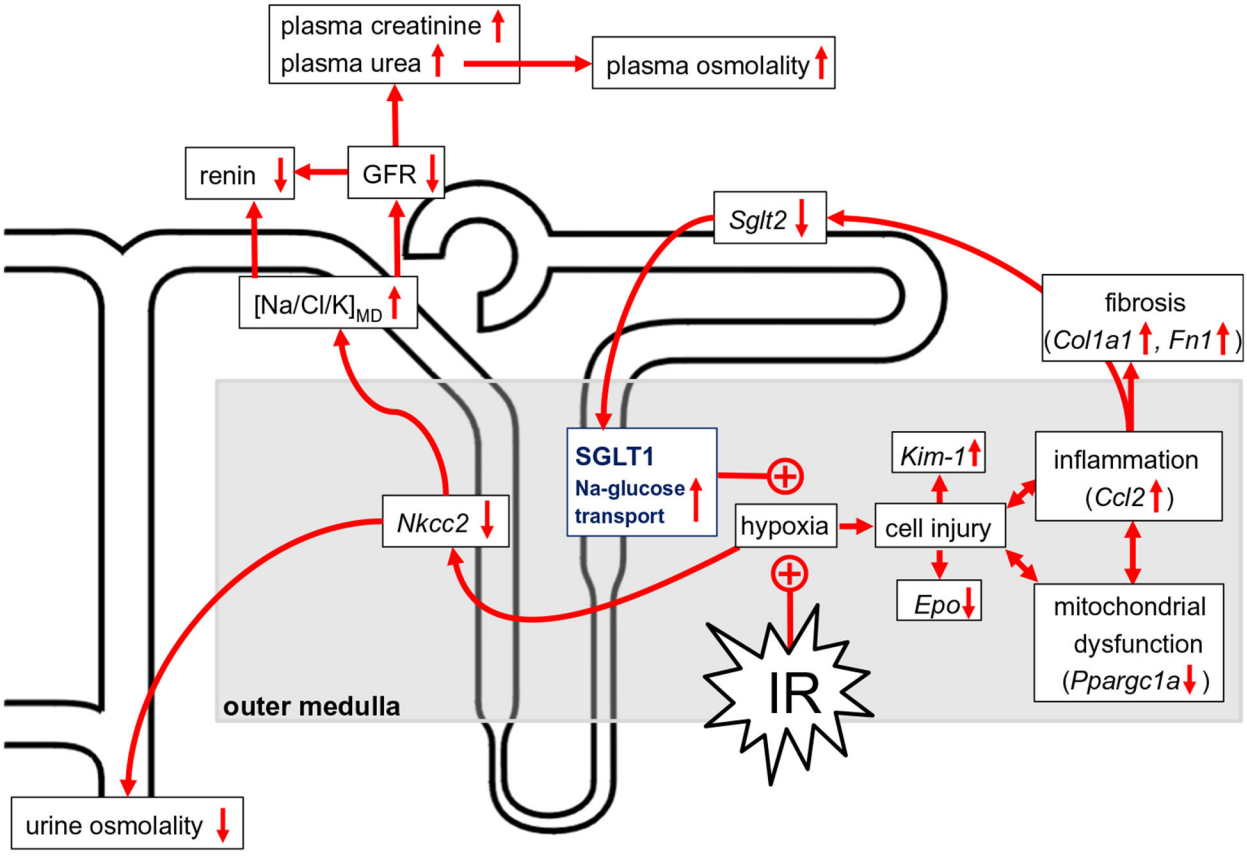

Fig. 6.

A proposed deleterious role for SGLT1-mediated reabsorption during recovery from IR-induced acute kidney injury. IR initially suppresses SGLT2- and SGLT1-mediated reabsorption in the early and later proximal tubule, respectively, which is associated with glucosuria. Early recovery of SGLT1 expression and SGLT1-mediated sodium reabsorption in late proximal tubule/outer medulla sustain IR-induced hypoxia. This sustains cell injury in the outer medulla and the inhibition of NKCC2-mediated NaCl reabsorption in the TAL, which impairs urine concentration and enhances Na-Cl-K delivery to macula densa ($[Na\text{-}Cl\text{-}K]_{MD}$). The latter reduces renin expression and lowers GFR via tubuloglomerular feedback. The reduction in GFR enhances plasma creatinine and urea, the latter contributing to enhanced plasma osmolality. The sustained hypoxia and cell injury further enhances mitochondrial dysfunction, inflammation, and fibrosis, which can spread to the cortex and further suppress tubular function. Sustained suppression of SGLT2 maintains a high glucose load to downstream SGLT1, which may enhance the detrimental influence of SGLT1. This figures was modified from [119]

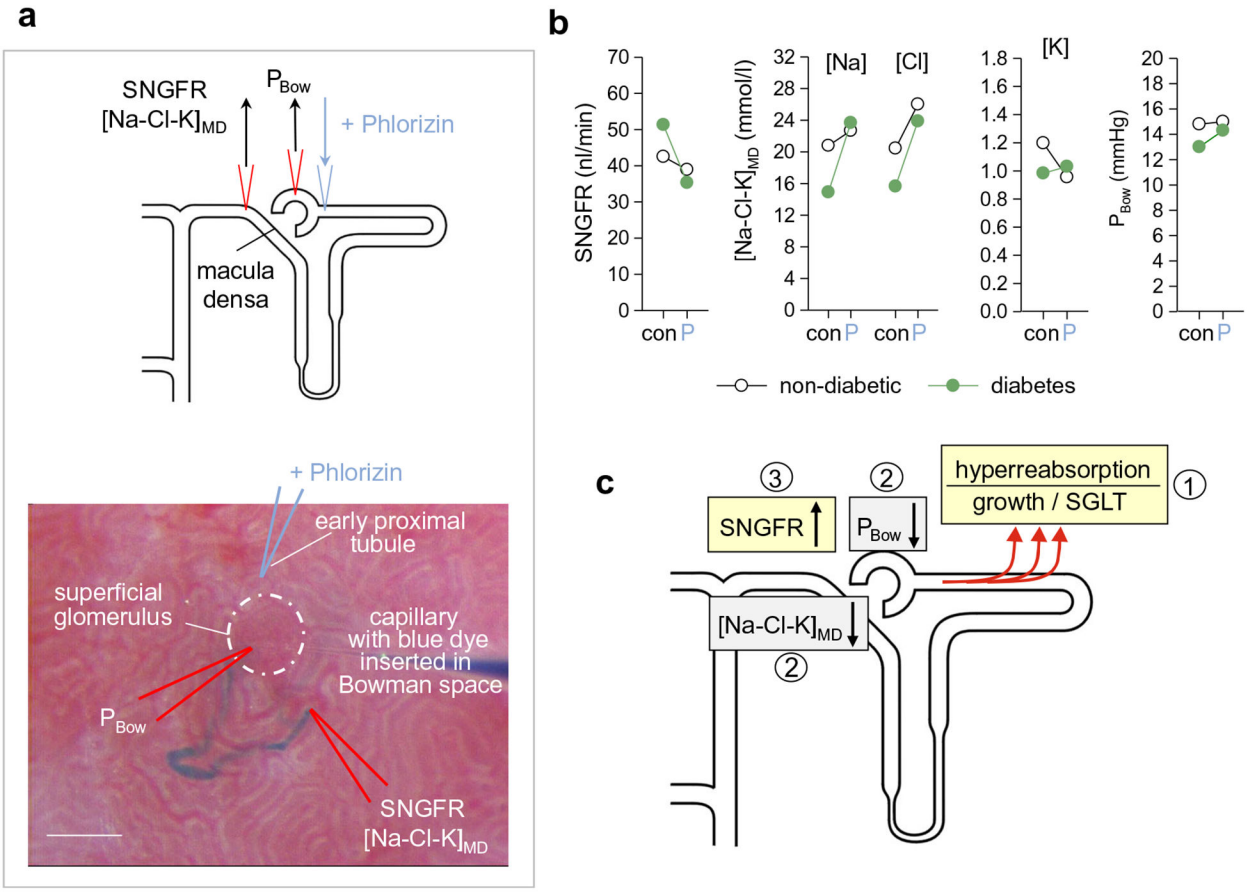

Fig. 7.

The tubular hypothesis of diabetic glomerular hyperfiltration. **a, b** In vivo micropuncture studies in rats with superficial glomeruli were performed in non-diabetic and streptozotocin diabetic rats [187]. Small amounts of blue dye were injected into Bowman space to determine nephron configuration, including the first proximal tubular loop and the early distal tubule close to the macula densa. Tubular fluid was collected close to the macula densa to determine the tubuloglomerular feedback signal ($[Na\text{-}Cl\text{-}K]_{MD}$) and single nephron glomerular filtration rate (SNGFR; by inulin clearance). Bowman space was punctured to determine the hydrostatic pressure (P_{Bow}). Measurements were performed under control conditions and following application of the SGLT2/SGLT1 inhibitor phlorizin into the early proximal tubule, i.e., without changing systemic blood glucose levels. Basal measurements (con) revealed that glomerular hyperfiltration in diabetes was associated with reductions in $[Na\text{-}Cl\text{-}K]_{MD}$ and P_{Bow}. Adding phlorizin (P) had a small effect in non-diabetic rats, but normalized $[Na\text{-}Cl\text{-}K]_{MD}$, P_{Bow}, and SNGFR in diabetes. **c** Kidneys are programmed to retain glucose. As a consequence, diabetes induces a primary hyperreabsorption in proximal tubules involving enhanced Na^+-glucose cotransport and tubular growth. The concomitant enhanced reabsorption of sodium causes glomerular hyperfiltration through tubuloglomerular feedback ($[Na\text{-}Cl\text{-}K]_{MD}$) and reducing tubular back pressure (P_{Bow}) thereby limiting sodium and volume retention. SGLT2 contributes to the tubular

hyperreabsorption, and as a consequence, SGLT2 inhibition mitigates these changes and lowers glomerular hyperfiltration. This figure was modified from [185]

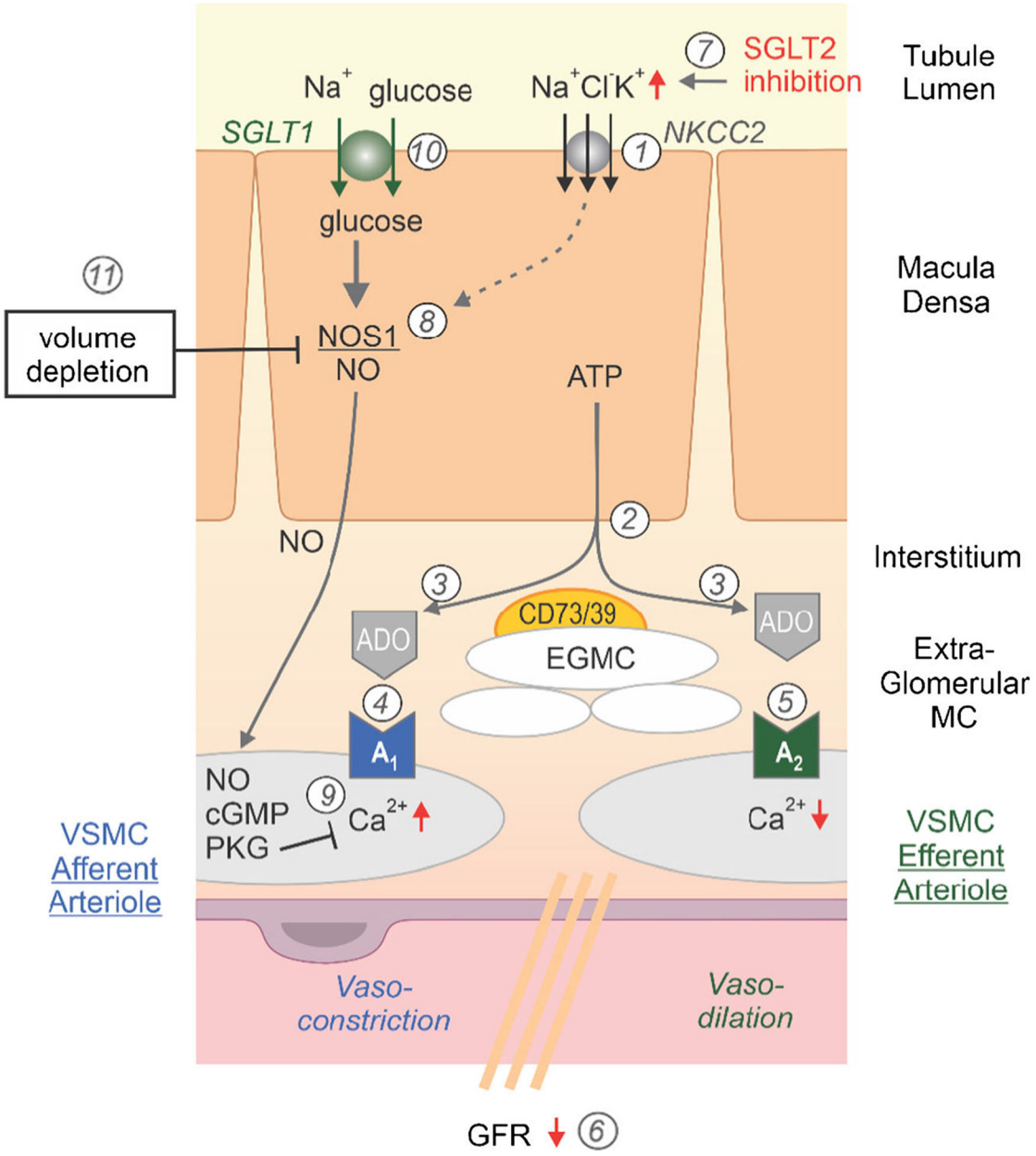

Fig. 8.

Tubuloglomerular feedback, SGLT2 inhibition, and SGLT1 as a glucose sensor in the macula densa. The tubuloglomerular feedback (TGF) establishes an inverse relationship between the Na-Cl-K delivery to the macula densa and GFR of the same nephron. (1 + 2) The macula densa senses an increase in luminal Na-Cl-K delivery by a NKCC2-dependent mechanism, which then enhances the basolateral release of ATP. (3) ATP is converted by endonucleotidases CD73/39 to adenosine (ADO). (4) ADO activates the adenosine A_1 receptor in vascular smooth muscle cells (VSMC) of the afferent arteriole to increase cytosolic Ca^{2+} and induce vasoconstriction. (5) ADO can also activate adenosine A_2 receptors on VSMC of the efferent arteriole to reduce cytosolic Ca^{2+} and induce vasodilation. (6) Both effects contribute to the TGF mechanism and lower GFR. (7) Due to

upstream tubular hyperreabsorption, diabetes lowers Na-Cl-K delivery to the macula densa. SGLT2 inhibition attenuates the hyperreabsorption, increase Na-Cl-K delivery to the macula densa, and lowers GFR. (8) An increased Na-Cl-K delivery also activates nitric oxide synthase NOS1 in the macula densa. (9) The formed nitric oxide (NO) diffuses across the interstitium and dilates the afferent arteriole, thereby partially offsetting the afferent arteriolar vasoconstrictor tone of TGF. (10) When glucose delivery to the macula densa is increased (by hyperglycemia or SGLT2 inhibition), SGLT1 in the luminal membrane takes up glucose, a process that is linked to the phosphorylation, activation, and increased expression of NOS1 in the macula densa. The resulting NO tone dilates the afferent arteriole and enhances GFR. (11) Volume depletion (e.g., following SGLT2 inhibition) inhibits NOS1 activity. MC, mesangium cell

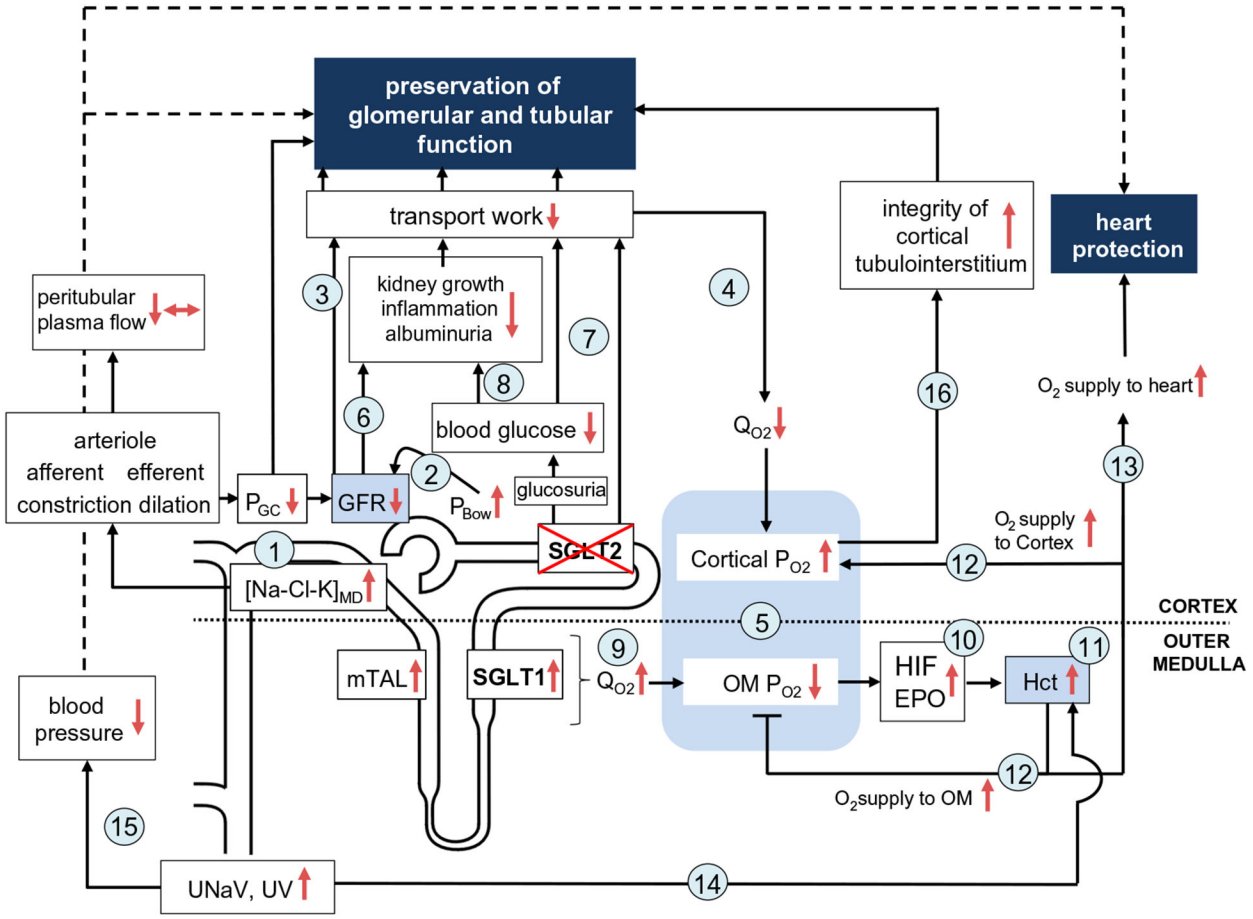

Fig. 9.

Proposed mechanisms of kidney protection by SGLT2 inhibition. SGLT2 inhibition reduces diabetes-induced hyperreabsorption of glucose and Na^+ in the early proximal tubule. This lowers hyperglycemia and increases NaCl and fluid delivery to the downstream macula densa. The latter reduces glomerular filtration rate (GFR) through the physiology of tubuloglomerular feedback (TGF) (1) and by increasing hydrostatic pressure in Bowman's space (P_{Bow}) (2). The TGF effect on GFR includes afferent arteriole constriction and potentially efferent arteriole dilation, which both reduce glomerular capillary pressure (P_{GC}). Reduction in GFR is the primary mechanism for reducing tubular transport work (3), particularly in the proximal convoluted tubule (PCT), thereby lowering cortical oxygen demand Q_{O2} (4) and increasing cortical oxygen tension P_{O2} (5). Lowering GFR attenuates tubular growth and albuminuria and consequently kidney inflammation (6). Tubular transport work is further reduced by lowering blood glucose and by cellular SGLT2 blockade itself (7). Less hyperglycemia causes less tubular growth, albuminuria, and inflammation (8). SGLT2 inhibition shifts glucose reabsorption downstream, particularly to the S3 segment where SGLT1 compensates and reduces the risk of hypoglycemia. Shifting glucose and Na^+ reabsorption to S3 and mTAL segments raises oxygen demand (9) and lowers P_{O2} in the outer medulla (OM) (5). On the other hand, lower medullary P_{O2} may stimulate pathways induced by hypoxia-inducible factor (HIF), including erythropoietin (EPO) (10), thereby increasing hematocrit (11), which improves O_2 delivery to kidney

medulla and cortex (12) and heart O_2 (13). The diuretic and natriuretic effects of SGLT2 inhibition further increase hematocrit (Hct) (14) and reduce circulating volume, blood pressure (15), and body weight, which all can help protect the failing heart. The overall reduced and better distributed renal transport activity increases cortical oxygen availability. This improves the cortical energy balance and tubular integrity, thereby allowing to maintain a higher tubular transport capacity and GFR in the long term (16). UNaV, urinary sodium excretion; UV, urinary flow rate. Adapted from [116]

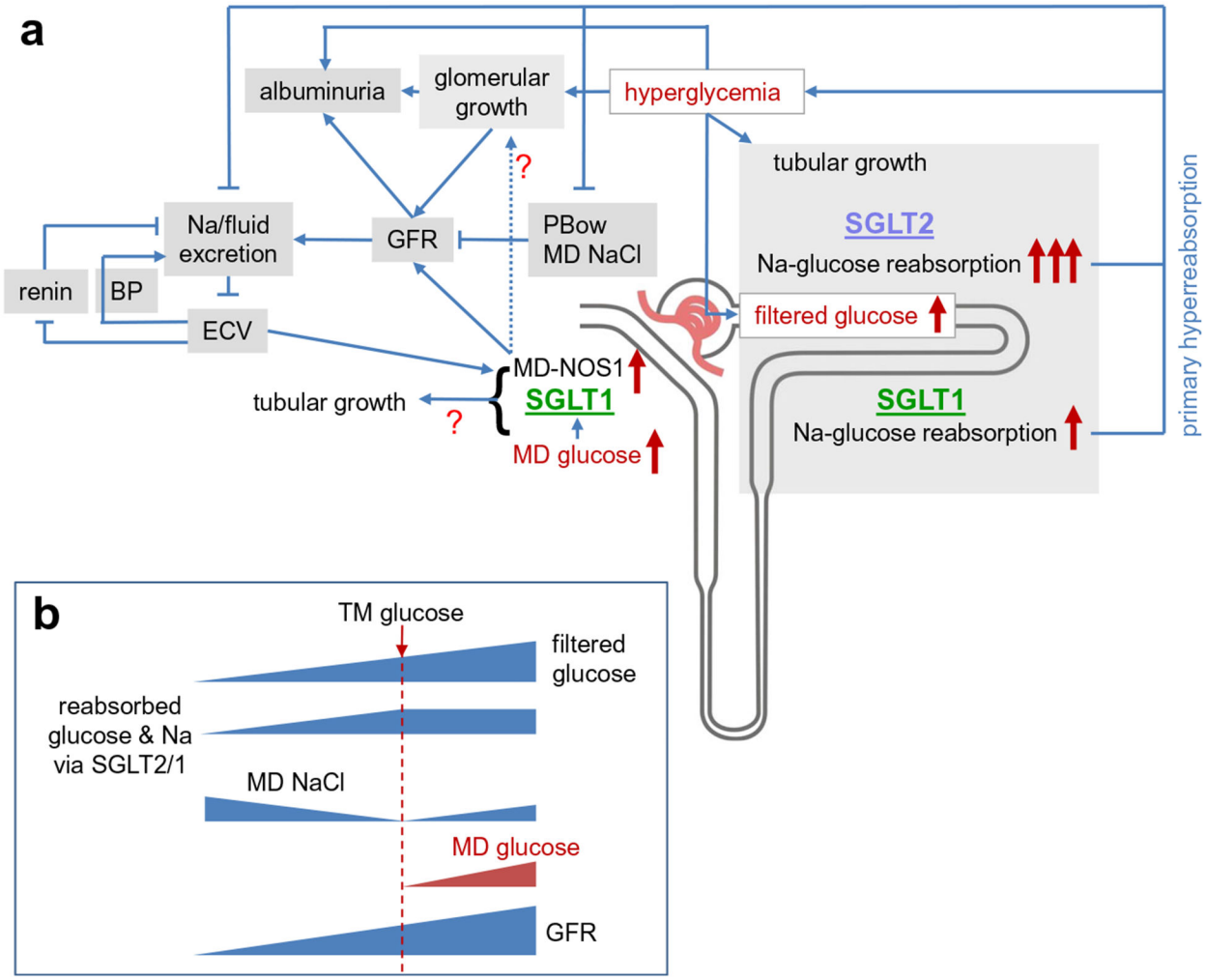

Fig. 10.

The integrated effects of SGLT1 in the diabetic kidney. **a** Blue arrows indicate positive interactions. Hyperglycemia enhances filtered glucose and induces tubular growth. This increases Na^+-glucose cotransport, thereby maintaining hyperglycemia and reducing urinary Na^+ and fluid excretion, with a larger contribution of SGLT2 versus SGLT1. Lesser urinary Na^+ and fluid excretion increases effective circulating volume (ECV) and blood pressure (BP). Tubular hyperreabsorption lowers tubular backpressure in Bowman space (P_{Bow}) and the NaCl delivery and concentration at the macula densa (MD), both increasing glomerular filtration rate (GFR) to restore urinary Na^+ and fluid excretion. An increase in glucose delivery to the MD indicates that upstream Na^+-glucose cotransport has been saturated. This is sensed by SGLT1 in the MD and, by stimulating MD nitric oxide synthase 1 (NOS1), further increases GFR to compensate for maximized Na^+-glucose cotransport. At the same time, SGLT1-mediated glucose sensing may trigger tubular growth to enhance the tubular glucose transport capacity. SGLT1 inhibition has a relatively small effect on diabetic tubular hyperreabsorption and thus induces little natriuresis and diuresis. Through inhibition of MD-NOS1 upregulation and lowering of hyperfiltration, however, SGLT1 inhibition induces a relatively larger antinatriuretic and antidiuretic effect. As a consequence, SGLT1 inhibition

can increase ECV with the resulting suppression in renin and increase in BP aiming to restore renal Na^+ and fluid excretion and ECV. Adapted from [161]. **b** Sensing proximal tubular hyperreabsorption via changes in both NaCl and glucose at the macula densa may allow adaptive increases in GFR over a wider range of filtered glucose. The abscissa refers to filtered glucose