The Other Glucose Transporter, SGLT1 – Also a Potential Trouble Maker in Diabetes?

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Diabetes mellitus, characterized by abnormal insulin secretion or resistance accompanied by hyperglycemia is an increasing problem worldwide, which results in various vascular pathologies, including diabetic nephropathies, and increased risk of developing CKD and ESRD.1 Hyperglycemia-induced glomerular hyperfiltration, which has been hypothesized to predispose to irreversible nephron damages, is observed early in the history of as many as 70% of all patients with type 1 and type 2 diabetes.2 The mechanism(s) contributing to glomerular hyperfiltration in diabetes have not been fully clarified, but hyperglycemia-associated ultrastructural, vascular, and tubular changes affecting renal autoregulation within the juxtaglomerular apparatus have primarily been discussed.2,3 The ultrastructural theory has been difficult to prove because it is not trivial to distinguish between cause and consequence regarding the glomerular hypertrophic changes after alterations in metabolic profile, growth hormones, and cytokines production. According to the vascular theory, hyperfiltration results from imbalance between various vasoactive humoral factors modulating the tone of the afferent arterioles (i.e., dilation) and the efferent arterioles (i.e., constriction), resulting in increased glomerular net filtration pressure and GFR. As proposed by Vallon and others,4 the tubular theory suggests that increased expression of the sodium-glucose cotransporter-2 (SGLT2) in the proximal tubule enhances reabsorption, leading to reduced delivery of sodium to the macula densa (MD) cells in the thick ascending limb. This inhibits tubuloglomerular feedback response and results in dilation of the afferent arterioles, increased glomerular hydrostatic capillary pressure, and increased GFR.

Renal autoregulation encompasses two distinct mechanisms, i.e., the fast myogenic response which is intrinsic to the afferent arteriole and the somewhat slower-acting MD-tubuloglomerular feedback response that regulates preglomerular vasomotor tone primarily of the afferent arteriole.5 Sophisticated interaction between vascular and tubular mechanisms, novel to the kidney, contributes to the regulation of tubuloglomerular feedback, which provides high autoregulatory efficiency that maintains both renal blood flow and GFR despite great physiologic and metabolic demands.5 However, abnormal renal autoregulation has been proposed to contribute to the development of renal damages in several models of renal, diabetic, and hypertensive diseases.5 The underlying pathologic mechanisms are not yet fully defined, but imbalance between the production of the modulating agents’ reactive oxygen species (i.e., hydrogen peroxide and superoxide), nitric oxide (NO), and angiotensin II within the juxtaglomerular apparatus is considered to be an important contribution. It should be noted that in several experimental models of type 1 and 2 diabetes, the tubuloglomerular feedback response has been reported to be blunted; however, how or if elevated tubular glucose levels per se contributed to this effect remained unclear. Neuronal nitric oxide synthase (nNOS or NOS1) is the predominant source of NO generation in the MD, and numerous studies, using pharmacologic or genetic approaches, have suggested its decisive role in dampening tubuloglomerular feedback (Figure 1A).2 More recently, it was demonstrated that mice with MD-specific deletion of nNOS display exaggerated tubuloglomerular feedback responses and develop salt-sensitive hypertension.6 Although the focus of many previous studies, its role in hyperglycemia-associated hyperfiltration and development of diabetic nephropathies remains elusive.

In this issue of the Journal of the American Society of Nephrology, Zhang et al.7 identified a novel mechanism, whereby acute tubular hyperglycemia induced glomerular hyperfiltration via mechanism(s) that involve SGLT1 activation of nNOS in the MD cells, and subsequent dampening of afferent arteriolar tone, thus promoting a rise in GFR after tubular glucose loading (Figure 1B). The authors combined sophisticated in vivo and ex vivo approaches to characterize tubuloglomerular feedback, i.e., micro-puncture stop-flow pressure technique and isolated and double-perfused juxtaglomerular apparatus, respectively. Acute infusion of D-glucose induced hyperglycemia and glucosuria, which was associated with MD-derived NO release and blunted tubuloglomerular feedback response, promoting glomerular hyperfiltration. Single-cell RNA-sequencing profiling and immunofluorescence staining of MD cells from mouse and human kidney tissue suggested SGLT1, encoded by the SLC5A1 gene, as the primary glucose transporter on the apical membrane. Thereafter, the authors convincingly showed that in the presence of a selective SGLT1 inhibitor (KGA-2727; Kissei Pharmaceutical Co., Ltd., Nagano, Japan), the hyperglycemia-induced blunting of tubuloglomerular feedback via nNOS activation was blocked and the development of glomerular hyperfiltration was prevented (Figure 1B). In support of nNOS
being important in the development of hyperglycemia-induced hyperfiltration, the authors show that mice with targeted deletion of nNOS in the MD did not develop glucose-induced hyperfiltration. The authors speculate, on the basis of previous publications, that glucose and SGLT1 upregulate nNOS expression/activity via PI3K/Akt and/or cAMP/PKA pathways. Taken together, these novel findings by Zhang et al. suggest an important role of a SGLT1-nNOS-tubuloglomerular feedback pathway mediating glomerular hyperfiltration in response to acute hyperglycemia (Figure 1B). It should be noted that all experiments in this study were performed in nondiabetic animals. Future studies using diabetes mellitus models are warranted to determine the role of this pathway and the therapeutic value of inhibiting SGLT1-nNOS signaling in MD to prevent the development of hyperglycemia-associated hyperfiltration and later development of CKD and ESRD. Another limitation of the present investigation is the lack of functional tubuloglomerular feedback evidence in humans to demonstrate the clinical importance of the proposed interaction between SGLT1-NOS1 in MD during hyperglycemia.

It should be noted that much work has focused on the role of SGLT2 in development of hyperglycemia-induced hyperfiltration and associated nephropathies. In contrast to SGLT1, which is known to play an important role in intestinal absorption of glucose, SGLT2 located in the proximal tubule (S1/S2 segments) is considered the main glucose transporter (97% of glucose reabsorption) along the nephron during healthy normoglycemic conditions (Figure 1A). SGLT1 is also expressed in the proximal tubule (S2/S3 segment) but does not normally account for more than 3% reabsorption of filtered glucose. However, in conditions with hyperglycemia and especially during SGLT2 inhibition, SGLT1 may account for as much as 50% glucose reabsorption. The mechanism whereby SGLT2 dampens tubuloglomerular feedback is different from that of SGLT1, as proposed in the current study by Ruisheng Liu and his colleagues. Hyperglycemia is thought to increase glucose filtration and enhance expression and activity of SGLT2-mediated sodium-glucose reabsorption, which in turn reduces NaCl delivery to the MD cells and attenuates tubuloglomerular feedback–mediated vasoconstriction.
Piecing Together the Risk of Sudden Cardiac Death on Dialysis

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According to ESRD Death Notification forms, 40% of hemodialysis (HD) patient deaths with a known cause and 30% of all HD patient deaths in 2014–2016 were primarily due to cardiac arrest or arrhythmia.1 A decade earlier, corresponding shares were 36% and 27%.2 Amid a secular trend toward improving survival among patients on HD in the United States, proportionate mortality due to sudden cardiac death (SCD) has thus increased modestly. Very likely, the road to better survival on HD passes through the valley of SCD.

Prolongation of the QT-interval is associated with higher risks of torsades de pointes and SCD, and, importantly, prolongation may be drug-induced. Well known drug groups that prolong the QT-interval include macrolide antibiotics, class 3 antiarrhythmics, and antipsychotics. Another such drug is citalopram, a selective serotonin reuptake inhibitor (SSRI). In 2011, the US Food and Drug Administration warned that daily doses exceeding 40 mg should not be used3; in 2012, the US Food and Drug Administration warned that daily doses exceeding 20 mg should not be used in patients older than 60 years.4 Escitalopram, the S-enantiomer of citalopram, also prolongs the QT-interval, although to a lesser degree than citalopram.4

Against this backdrop, Assimon et al.5 have adeptly compared the risk of SCD in patients on HD who were dispensed either citalopram or escitalopram versus other SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline). Using Medicare claims data, the investigators identified over 65,000 patients who initiated SSRI exposure between 2007 and 2014. Slightly less than half were dispensed either citalopram or escitalopram, and with these drugs, the risk-adjusted hazard ratio of SCD was 1.18 (95% confidence interval, 1.05 to 1.31), relative to other SSRIs. This translates to an SSRI user population-attributable fraction of 7.8%. Provocatively, among 8% of patients with a diagnosed conduction disorder, the hazard ratio of SCD was 1.47, and among 48% of patients with use of at

See related article, “Macula Densa SGLT1-NOS1-Tubuloglomerular Feedback Pathway, a New Mechanism for Glomerular Hyperfiltration during Hyperglycemia,” on pages 578–593.