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Mini review

Sodium-Glucose Transporter Type 2 (SGLT2) Inhibitor for Diabetic Kidney

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Abstract

In diabetes, both activation of renin-angiotensin system and glomerular hyperfiltration are seen even before the development of diabetic nephropathy. Glomerular hyperfiltration depends on glomerular hypertension sue to pathophysiological afferent arteriolar dilation. Tubular hypothesis has been proposed more than a decade ago to explain the above in type1 diabetes. Recently, clinical evidences have been accumulated to support tubular hypothesis functioning in type2 diabetes. In addition to intrinsic renal hemodynamic physiology, the key molecule for tubular hypothesis is sodium glucose co-transporter in proximal tubules. Thus, application of sodium glucose co-transporter for diabetes may provide a break-through for the management of diabetes in preventing the development of nephropathy.

Recently, SGLT2 inhibitors, a new anti-diabetic drug, have become available for clinical use. This drug is superior to classical anti-diabetic medications such as sulfonyl urea and metoformin, facilitating weight loss and decreasing systolic blood pressure [1]. In addition to their excellent anti-diabetic actions, they could prevent the development of diabetic nephropathy. Potential renal hemodynamic mechanisms for renal protection by this medication are reviewed.

TUBULOGLOMERULAR FEEDBACK (TGF)

Macula densa cell releases ATP into the interstitium when it reabsorbs sodium chloride delivered by tubular flow [2]. On the one hand, ATP released from macula densa binds to ATP receptor located on extraglomerular mesangial cells to induce membrane depolarization and/or an increase in cytosolic calcium. These signals travel to neighboring mesangial cells through gap junctions, and finally the signals are transduced to afferent arteriolar myocytes through gap junction. Gap junction constitutes an important intercellular communication tool. Indeed, the inhibiting the function of connexin (Cx37 or Cx40), which compose of gap junction, elicits both suppression of TGF-dependent autoregulation and RAS activation. There is a possibility that ATP secreted from macula densa diffuses to afferent arteriolar myocytes and directly interacts with ATP receptors to induce afferent arteriolar constriction. On the other hand, ATP is degraded to adenosine by nucleotidase on extra glomerular mesangial cells, and subsequently adenosine binds to its specific receptor on afferent arteriolar myocytes to induce constriction.

TUBULAR HYPOTHESIS

From the renal hemodynamic point of view, diabetic nephropathy is characterized by glomerular hypertension and hyperfiltration from its early stage. Abnormal afferent arteriolar dilation is the basis for experimental diabetic nephropathy [3]. In non-diabetic chronic kidney disease, single nephron glomerular hypertension and hyperfiltration occur in remnant nephrons to suffice the function of lost glomeruli due to its underlying renal disease. Thus, glomerular hyperfiltration starts when renal injury has progressed to some extent in non-diabetic chronic kidney diseases. However, all nephrons in diabetes show glomerular hypertension and hyperfiltration before microalbuminuria will be developed [4]. Tubular hypothesis is based on physiological responses to hyperglycemia and its mechanisms are following [5]. In diabetes, hyperglycemia results in high glucose concentration in ultrafiltrate in Bowman capsule. Although proximal tubules reuptake most amounts of filtered glucose, glucose exceeding the capacity of tubular reuptake excretes into urine (glycosuria). Since proximal tubule possesses sodium glucose co-transporter type 1 (SGLT1) and SGLT2, glucose is up-taken together with sodium through these transporters. Then, the reuptake of sodium chloride is increased in hyperglycemic condition, which is considered as a cause of salt sensitive hypertension in diabetes. Furthermore, the delivery of sodium and chloride to macula densa is decreased by enhanced reuptake by proximal tubules (figure 1). A reduced delivery to macula densa dilates the afferent arteriole by removing constrictor signals from tubuloglomerular feedback (TGF), thereby inducing glomerular hypertension and hyperfiltration. Moreover, TGF signal from macula densa inhibits

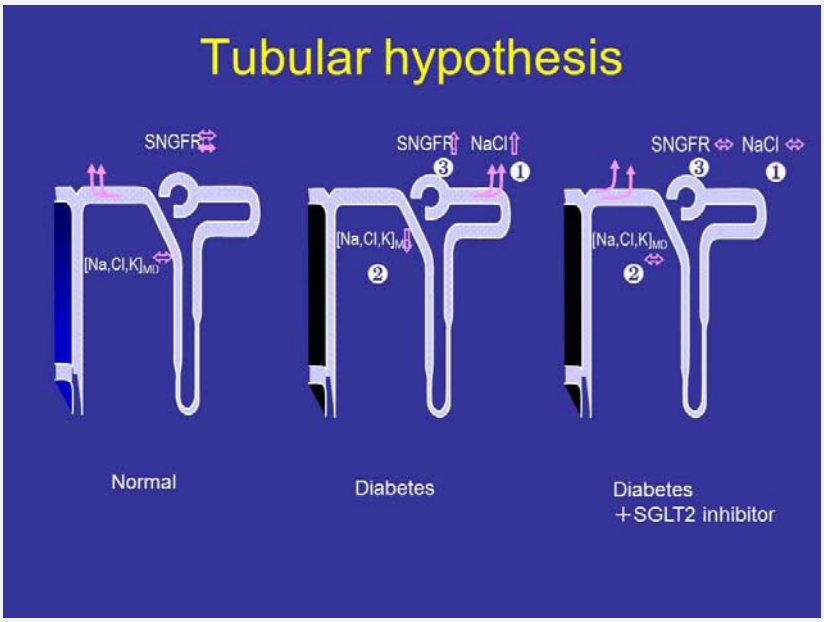

Figure 1 Compared to normal condition (left), ultrafiltrate in Bowman capsule contains significant amount of glucose in diabetes (middle). Because proximal tubules reabsorb more sodium with glucose through sodium glucoseco-transporter (SGLT) in diabetes [1], the delivery to macula densa is decreased [2]. This weakens tubuloglomerular feedback (TGF) signals to increase glomerular filtration rate [3], accounting for hyperfiltration in early stage of diabetes. SGLT inhibition (right] inhibits proximal tubular reabsorption [1], restoring sodium chloride delivery to macula densa even under hyperglycemic condition [2]. This would have TGF work and normalize glomerular filtration rate [3], ameliorating glomerular hyperfiltration.

renin release. Again, a reduced delivery to macula densa during hyperglycemia (due to increased proximal tubular absorption) removes TGF signal, thereby releasing renin and activate renin-angiotensin system (RAS) which constricts efferent arterioles, further worsening glomerular hypertension [2].

RAS

There are compelling evidences that RAS play an important role in the development of diabetic nephropathy. Why is RAS activated even in the early course of diabetes? Many experimental hypotheses for an overproduction of angiotensinogen by hyperglycemia and pathological activation of pro-renin in diabetes have been proposed [6,7]. Clinical trials have demonstrated that the inhibitors of RAS are effective to decrease new onset of diabetes and to prevent the development and progression of diabetic nephropathy. As discussed, tubular hypothesis can also explain both glomerular hyperfiltration and RAS activation [5]. Acetazolamide decreased glomerular filtration rate and albuminuria in patients with diabetic nephropathy, though RAS was not examined in this study [8]. Thus, normalization of proximal tubular reabsorption and restoration of the delivery to macula densa and TGF in diabetes would ameliorate both RAS activation and glomerular hypertension.

SGLT INHIBITOR: BEYOND GLUCOSE LOWERING AND BLOOD PRESSURE LOWERING EFFECTS

According to tubular hypothesis, SGLT2 inhibitors suppress proximal tubular reabsorption, which is enhanced in diabetes, suggesting that SGLT2 inhibitors possess blood pressure lowering and renal protective actions through beneficial effects on renal hemodynamics beyond its blood glucose lowering effects [1]. Indeed, one of adverse actions of SGLT2 inhibitors is hypotension as well as urinary tract infection. Furthermore, at least experimentally SGLT2 inhibitor showed protective effects on diabetic nephropathy [9]. SGLT2 inhibitors can suppress renin release by increasing the delivery to macula densa in diabetes. However, the influences on RAS and/or albuminuria of SGLT2 inhibitors have not been examined in diabetic nephropathy yet. Many clinical studies with SGLT2 inhibitors are required to clarify these issues.

Collectively, inhibitors of SGLT2 as well as RAS may prevent the development of diabetic nephropathy. Of importance, SGLT2 inhibitors can be used for diabetic patients without hypertension. Thus, total medical cost for a diabetic patient may be decreased by using SGLT2 inhibitor in its early clinical course to prevent nephropathy, which provides socio-economical problems in many countries [10]. Last but not the least, kidney disease and/or albuminuria is significant cardiovascular risk. Thus, SGLT2 inhibitors shall improve cardiovascular events and death in diabetes, provided that they prevent the development of nephropathy.

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