Journal of the American Society of Hypertension 10(3) (2016) 271–278

Review Article

Importance of inhibiting sodium-glucose cotransporter and its compelling indication in type 2 diabetes: pathophysiological hypothesis

Genjiro Kimura, MD[a,b,*]

[a]*Asahi Rosai Hospital, Japan Labour Health and Welfare Organization, Owariasahi, Japan; and*
[b]*Nagoya City University Medical School*

Manuscript received November 9, 2015 and accepted January 5, 2016

Abstract

Primarily the sodium-glucose cotransporter 2 (SGLT2) inhibitors suppress the cotransport of glucose and sodium from the tubular lumen of proximal tubules to the blood and enhance the glucose excretion into urine. Therefore, glucose and caloric balances become negative, making the blood glucose level as well as insulin secretion both reduced. On the other hand, the proximal tubular fluid, constituting with low chloride concentration because of SGLT2 inhibition, is transferred to the loop of Henle. On the low chloride conditions, the reabsorption mechanisms in the loop of Henle do not work, as if loop diuretics are given. Finally, blood pressure is also lowered secondarily due to the loop diuretic action by SGLT2 inhibitions. Thus, the metabolic and hemodynamic combined systems synergistically interact further to suppress the risks leading to atherosclerosis and organs damage. Precise mechanisms for SGLT2 inhibitors to work in various aspects especially in preventing organ damage and cardiovascular events must be clarified further. J Am Soc Hypertens 2016;10(3):271–278.

Keywords: Diuretics; glucose handling; hypertension; sodium balance.

Introduction

Conventional therapies for diabetes mellitus usually activate insulin secretion, resulting in blood glucose (P_S) lowered and controlled. To achieve this end in precise and safe manners, it has been important to understand the glucose metabolism and insulin regulation system. On the other hand, newly introduced sodium-glucose cotransporter (SGLT) 2 inhibitors are drugs capable to lower P_S independently of insulin because they inhibit glucose reabsorption in renal tubules and excrete glucose into urine.[1–4] In this way, SGLT2 inhibitors are different from other antidiabetic agents. The former lowers P_S independently of insulin, resulting in insulin secretion reduced, while the latter does dependently on insulin system. Therefore, there are remarkable differences between two in terms of the mechanisms to lower P_S as well as the effects on renal and cardiovascular benefits.

In this review, mainly based on personal hypothesis about pathophysiology of kidney and hypertension, I will discuss the significance and characteristics of SGLT2 inhibitors and recommend the types of patients who are compelling indicated for SGLT2 inhibitors.

SGLT2 Inhibitors Directly Suppress Glucose Reabsorption in Renal Proximal Tubules

In the kidneys, first, not only waste products but also essential nutrients such as glucose and amino acids are filtered at glomeruli without using energy in a nonselective manner. Then, in proximal tubules, connected to glomeruli, only essential nutrients are transported from glomerular

This study was supported in part by Research Grants from Japan Labour Health and Welfare Organization as well as by an honorarium for scientific presentations from Takeda, Daiichi-Sankyo, Novartis, and Taisho-Toyama companies.

Conflict of interest: None.

*Corresponding author: Genjiro Kimura, MD, Asahi Rosai Hospital, Japan Labour Health and Welfare Organization, 61 Hirako-cho, Owariasahi City, Aich Prefecture, 488-8585, Japan. Tel: +81-561-54-3131; Fax: +81-561-52-2426.

E-mail: genki@asahih.rofuku.go.jp

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2016.01.009

filtrate to blood in selective manner based on the active transport using energy. This transport process is referred as tubular reabsorption. In healthy subjects, neither glucose nor amino acids are detected in the urine because of the complete reabsorption in proximal tubules.

Figure 1 illustrates the cellular mechanisms of glucose reabsorption by proximal tubules. There is a universal sodium pump (Na-K ATPase) in the basolateral membrane on the blood side, which plays an important role to pump out sodium (Na) from the intracellular to extracellular compartments. This active Na transport does not only maintain the intracellular Na concentration at low level, but also plays the crucial role to transports Na from the tubule to blood, resulting in reabsorption of Na. SGLT2 is located in the brush border of the luminal membrane and is involved in glucose reabsorption. When SGLT2 is bound to Na, its affinity with glucose becomes high. Na is released from SGLT2 binding, on the other hand, the affinity become weak. Therefore, SGLT2 binds to glucose on the luminal side because Na concentration is high similarly as serum. When it moves to the intracellular compartment, however, it cannot bind to glucose because of the low Na environment within cells. As a result, glucose is continuously transported into cells, and the intracellular glucose concentration increases. This process is referred to as ‘‘secondary active transport’’ because it does not directly require energy if the intracellular Na concentration is maintained low. As the intracellular glucose concentration increases, glucose is passively transported into blood through another transporter (glucose transporter) present in the basolateral membrane on the blood side. Eventually, glucose is reabsorbed from tubule to blood. Of course, the uptake by SGLT2 from tubular lumen is the rate-limiting step in this glucose reabsorption process and determines the amount of glucose reabsorption.

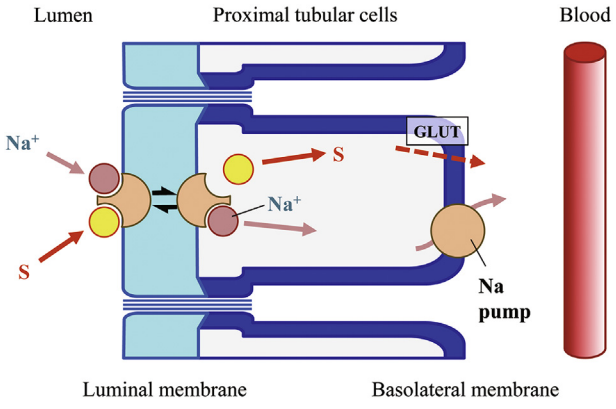

Figure 1. Secondary active transport of glucose in proximal tubules. Action mechanism of sodium-glucose cotransporter (SGLT) 2 inhibitors. SGLT2 inhibitors bind to glucose (S) sites of SGLT to inhibit the cotransport of glucose and sodium.

As discussed above, there is a limit in the amount of glucose reabsorption by SGLT2 and called as the maximum tubular reabsorption of glucose (T_{mS}). The relationship between glucose titration curve in kidneys and T_{mS} is illustrated in Figure 2. The amount of filtered glucose (F_S) in renal glomeruli is calculated by the following formula: $F_S = P_S \times GFR$, where GFR denotes the glomerular filtration rate. In healthy individuals, filtered glucose is completely reabsorbed in early proximal tubules, and therefore, no glucose is present in the urine. Glucose appears in urine when individuals develop diabetes, and their P_S level elevates because the glucose load applied to proximal tubules (F_S) exceeds T_{mS} (approximately 375 mg/min for males; 300 mg/min for females). Suppose GFR = 125 mL/min (a normal value for male adults) and the threshold P_S for glucose to appear in urine is simply calculated as 375/125 = 3 mg/mL = 300 mg/dL. The degree of glucose binding to SGLT2 does not linearly increase because the performance of each transporter may vary. This means that glycosuria gradually starts to be observed at approximately P_S = 170 mg/dL.

In the case of diabetes, it must be noted that T_{mS} threshold increases due to overexpression of SGLT2,[5] which causes hyperglycemia and increases renal glucose reabsorption. On the other hand, SGLT2 inhibitors reduce T_{mS} for glucose to be excreted into urine, resulting in increased glycosuria. Inhibition of the overexpression of SGLT2 becomes therefore a basic therapeutic strategy to normalize pathologic conditions

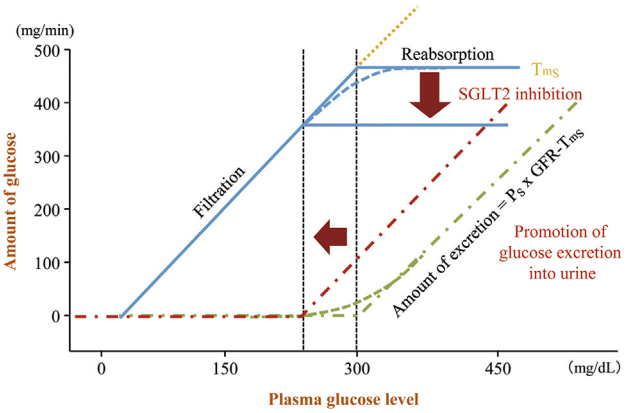

Figure 2. Maximum tubular reabsorption of glucose and glucose titration curve. Relationship between the amount of filtered glucose and the amount of excreted glucose. The amount of filtered glucose, corresponding to the amount of glucose loaded to proximal tubules from glomeruli, is expressed by glomerular filtration rate (GFR) × blood glucose (P_S). If it exceeds the maximum tubular reabsorption of glucose (T_{mS}), the excess amount is excreted in urine. In the case of diabetes, overexpression of SGLT2 causes elevation of the maximum tubular reabsorption. SGLT2 inhibitors reduce the maximum tubular reabsorption of glucose, resulting in glucosuria even at relatively low blood glucose levels.