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The role of the kidneys in glucose homeostasis in type 2 diabetes: Clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors

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ABSTRACT

The kidneys play an important role in regulating glucose homeostasis through utilization of glucose, gluconeogenesis, and glucose reabsorption via sodium glucose co-transporters (SGLTs) and glucose transporters. The renal threshold for glucose excretion (RT_G) is increased in patients with type 2 diabetes mellitus (T2DM), possibly due to upregulation of SGLT2 and SGLT1 expression. The resulting increase in renal glucose reabsorption is thought to contribute to the maintenance of hyperglycemia in patients with T2DM. Selective SGLT2 inhibitors reduce the RT_G, thereby increasing glucosuria, and have demonstrated favorable efficacy and safety in patients with T2DM inadequately controlled with diet and exercise and other glucose-lowering treatments.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease that is associated with obesity and the progressive development of hyperglycemia [1]. Increased body fat is associated with the development of insulin resistance in muscle and in the liver, particularly if excess fat is deposited in these tissues (ie, ectopic fat). Initially, the pancreas is able to overcome this insulin resistance by producing more insulin, but in diabetes there is a progressive failure of β-cell output, resulting first in glucose intolerance and then overt T2DM. In addition to these established factors, it is now known that multiple defects, involving numerous metabolic pathways and organ systems, contribute to the progression of hyperglycemia in T2DM. These include adipocytes (accelerated lipolysis), the gastrointestinal tract (incretin deficiency/resistance), pancreatic α-cells (hyperglucagonemia), the brain (insulin resistance), and the kidneys (increased glucose reabsorption) [1].

With this further elucidation of the key mechanisms underlying the pathology of T2DM, understanding the role of the kidneys in glucose homeostasis under normal and pathological conditions has increased [2]. This review article explores the role of the kidneys in regulating gluconeogenesis and glucose utilization, and how this is disturbed in T2DM.

Abbreviations: ATPase, adenosine triphosphatase; eGFR, estimated glomerular filtration rate; EGP, endogenous glucose production; FPG, fasting plasma glucose; FRG, familial renal glucosuria; GFR, glomerular filtration rate; GGM, glucose-galactose malabsorption; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RT_G, renal threshold for glucose excretion; SGLT, sodium glucose co-transporter; T_mG, tubular maximum glucose reabsorptive capacity; T2DM, type 2 diabetes mellitus; UGE, urinary glucose excretion.

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2. Renal gluconeogenesis in the postabsorptive state

In the fasting (postabsorptive) state in healthy individuals, the kidneys contribute about 20% to 25% of the glucose released into the circulation via gluconeogenesis (15–55 g per day), with the liver responsible for the remainder via both glycogenolysis and gluconeogenesis [2–4]. Renal gluconeogenesis occurs predominantly within proximal tubule cells in the renal cortex, and is chiefly regulated by insulin and catecholamines (eg, adrenaline). Insulin reduces renal gluconeogenesis directly, and also reduces the availability of gluconeogenic substrates, such as lactate, glutamine, and glycerol [5], thus reducing glucose release into the circulation [4,6,7]. Adrenaline stimulates renal gluconeogenesis [3,8], stimulates renal glucose release, inhibits insulin secretion, increases the supply of gluconeogenic substrates, and reduces renal glucose uptake [2,9].

In patients with T2DM, both renal and hepatic glucose release are increased as a result of increased gluconeogenesis. The relative increase in renal gluconeogenesis is thought to be substantially greater than in hepatic gluconeogenesis (300% vs 30%) [2]. Renal glycogenolysis is minimal in healthy individuals but may play a role in increased renal glucose release in patients with T2DM, due to accumulation of glycogen in diabetic kidneys [5].

3. Renal glucose release in the postprandial state

Renal gluconeogenesis increases during the postprandial state relative to the postabsorptive state. Studies using stable isotopes to estimate renal glucose balance have shown renal glucose release increases more than 2-fold during the 4.5-hour postprandial period [5,10]. It is thought that this increase in renal glucose release allows for repletion of hepatic glycogen stores by permitting suppression of hepatic glucose release. The mechanisms for this are not known, but may include the postprandial increases in lactate and amino acids that are precursors for gluconeogenesis, as well as an increase in sympathetic nervous system activity. Indeed, renal glucose production accounts for ~60% of endogenous glucose release during the postprandial period (4–6 hours after meals) [5,10].

The increase in glucose release over the 4.5-hour postprandial period has been shown to be roughly 30% higher (100 g vs 70 g) in patients with T2DM compared with healthy individuals, primarily due to increased endogenous glucose release. It is estimated that 40% of the increase in endogenous glucose release occurs via the kidney. Renal glucose release is regulated by insulin; thus, as insulin resistance increases, suppression of renal glucose release decreases [2]; an additional explanation may be an increase in renal glucose reabsorption due to upregulation of renal glucose transporters (GLUTs).

4. Renal glucose transport

The kidneys play a key role in glucose conservation, filtering 160 to 180 g of glucose per day in healthy individuals, which is all reabsorbed within the proximal tubules [1,11–14]. Glucose reabsorption occurs via both sodium glucose co-transporters (SGLTs) and GLUTs [12,15,16]. The energy for SGLT-mediated active transport of glucose (against its concentration gradient) across the cell membrane is derived from the sodium electrochemical potential gradient (Fig. 1). This is maintained by the transport of intracellular sodium ions into the blood via sodium-potassium adenosine triphosphatase (ATPase) pumps situated in the basolateral membrane [12,15]. GLUTs bind glucose, inducing a conformational change, and glucose is passively transported across the cell membrane from the intracellular compartment into the plasma [16].

Within the proximal renal tubule, 2 key subtypes of SGLT and GLUT are responsible for glucose reabsorption and are expressed at the luminal brush border and the basolateral membrane of the epithelial cells, respectively (Fig. 1) [15,16]. SGLT2 is a high-capacity, low-affinity co-transporter that is responsible for the majority of renal glucose reabsorption, coupling the active transport of sodium and glucose in a 1:1 ratio within the early proximal tubule [11,16,17]. Glucose is then reabsorbed into the circulation via GLUT2 [15]. Any remaining glucose is reabsorbed by SGLT1, a high-affinity

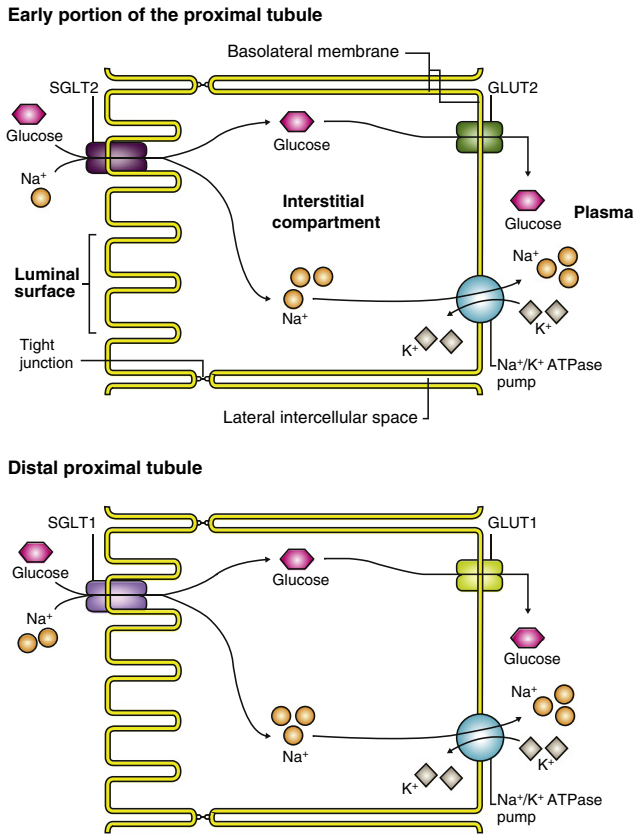

Fig. 1 – SGLTs and passive GLUTs in the proximal renal tubule [19]. Reprinted from *Trends in Pharmacological Sciences*, Vol 32 (2), Bailey CJ, Renal glucose reabsorption inhibitors to treat diabetes, pp. 63–71, Copyright (2011), with permission from Elsevier. SGLT, sodium glucose co-transporter; GLUT, glucose transporter; ATPase, adenosine triphosphatase.