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Review Article

Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications

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Abstract

Considerable data have accumulated over the past 20 years, indicating that the human kidney is involved in the regulation of glucose via gluconeogenesis, taking up glucose from the circulation, and by reabsorbing glucose from the glomerular filtrate. In light of the development of glucose-lowering drugs involving inhibition of renal glucose reabsorption, this review summarizes these data. Medline was searched from 1989 to present using the terms 'renal gluconeogenesis', 'renal glucose utilization', 'diabetes mellitus' and 'glucose transporters'. The human liver and kidneys release approximately equal amounts of glucose via gluconeogenesis in the post-absorptive state. In the postprandial state, although overall endogenous glucose release decreases substantially, renal gluconeogenesis increases by approximately twofold. Glucose utilization by the kidneys after an overnight fast accounts for ~10% of glucose utilized by the body. Following a meal, glucose utilization by the kidney increases. Normally each day, ~180 g of glucose is filtered by the kidneys; almost all of this is reabsorbed by means of sodium–glucose co-transporter 2 (SGLT2), expressed in the proximal tubules. However, the capacity of SGLT2 to reabsorb glucose from the renal tubules is finite and, when plasma glucose concentrations exceed a threshold, glucose appears in the urine. Handling of glucose by the kidney is altered in Type 2 diabetes mellitus (T2DM): renal gluconeogenesis and renal glucose uptake are increased in both the post-absorptive and postprandial states, and renal glucose reabsorption is increased. Specific SGLT2 inhibitors are being developed as a novel means of controlling hyperglycaemia in T2DM.

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Keywords gluconeogenesis, kidney, sodium glucose co-transporter 2, Type 2 diabetes mellitus

Abbreviations FFA, free fatty acid; FRG, familial renal glucosuria; GLUT, glucose transporter; SGLT1, sodium–glucose co-transporter 1; SGLT2, sodium glucose co-transporter 2; SGLTs, sodium–glucose co-transporters; T2DM, Type 2 diabetes mellitus; Tm, transport maximum

Introduction

The kidney's involvement in glucose homeostasis was first described in the 1930s [1]. Despite the large body of evidence amassed over the ensuing years, the kidney is still often overlooked as an important player in glucose metabolism. However, awareness of renal mechanisms of glucose homeostasis is likely to increase in the near future because novel glucose-lowering drugs are being developed that target one aspect of renal glucose handling, namely reabsorption of glucose from the glomerular filtrate [the sodium–glucose co-transporter 2 (SGLT2) inhibitors]. This article reviews our current understanding of the role of the kidney in normal glucose homeostasis and abnormalities in patients with Type 2 diabetes mellitus (T2DM). Medline was searched from 1989 to present using the terms 'renal gluconeogenesis', 'renal glucose utilization', 'diabetes mellitus' and 'glucose transporters'.

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Overview of renal glucose homeostasis

The human kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms: (i) release of glucose into the circulation via gluconeogenesis; (ii) uptake of glucose from the

circulation to satisfy its energy needs; and (iii) reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

Plasma glucose concentrations are determined by the relative rates of glucose entry into, and removal from, the circulation. Normally, despite wide daily fluctuations in the rate of delivery of glucose into the circulation (e.g. meal ingestion) and in the demands of tissues for glucose (e.g. during exercise), plasma levels are maintained within a relatively narrow range throughout the day. Maximal plasma concentrations following meal ingestion are usually < 9.0 mmol/l [2] and minimal concentrations, after moderate fast or exercise, are usually > 3.0 mmol/l [3,4]. This is in contrast to other substrates such as glycerol, lactate, free fatty acids (FFAs) and ketone bodies, for which daily fluctuation is much greater [5]. Teleologically, this can be explained by the fact that, on the one hand, the body must defend itself from hyperglycaemia, which is associated with both chronic effects (including retinopathy, neuropathy, nephropathy and premature atherosclerosis [6–9]) and acute effects (including diabetic ketoacidosis and hyperosmolar hyperglycaemic state, which have significant associated morbidity and mortality); on the other hand, the body must also defend itself against hypoglycaemia, which can cause cardiac arrhythmias, neurological dysfunction, coma, seizures and death [10]. Brain function is particularly dependent on having adequate levels of plasma glucose because the brain is unable to either store or produce glucose and alternative sources of energy are either in short supply (e.g. ketone bodies) or are unable to pass the blood–brain barrier (e.g. FFAs) [10].

The precise regulation of plasma glucose concentrations is mainly determined by hormonal and neural factors, which regulate endogenous production of glucose [10]. Acute glucoregulatory mechanisms involve insulin, glucagon and catecholamines, which can effect changes in plasma glucose levels over a matter of minutes. Insulin suppresses glucose release in both the liver and kidney by direct enzyme activation/deactivation, as well as by reducing the availability of gluconeogenic substrates and actions on gluconeogenic activators [11]. Glucagon has no effect on the kidney, but increases both gluconeogenesis and glycogenolysis in the liver [12]. Catecholamines have multiple acute actions, including stimulation of renal glucose release, inhibition of insulin secretion, stimulation of glucagon secretion, and increases in gluconeogenic substrate supply, stimulation of lipolysis and reduced tissue glucose uptake.

Growth hormone, thyroid hormone and cortisol influence glucose levels over a period of hours by altering the sensitivity of the liver, kidney, adipose tissue and muscle to insulin, glucagon and catecholamines, and by altering the activity of key enzymes, which effect glycogen stores and availability of gluconeogenic precursors (lactate, glycogen and amino acids) [10]. In the post-absorptive state, glucose uptake by tissues is largely dependent on tissue needs and the mass-action effects of the ambient plasma glucose concentration and, to a lesser extent, on the permissive actions of insulin and counter-regulatory hormones (e.g. thyroid hormones, growth hormone, catecholamines and cortisol). In these circumstances, most uptake of glucose occurs in tissues that do not require insulin (e.g. brain, gastrointestinal tract, renal medulla). However, in the postprandial state, although insulin and other hormones exert greater influence on tissue uptake of glucose, changes in hepatic and renal glucose release into the circulation are still quite important (Table 1) [10].

Renal gluconeogenesis

The post-absorptive state

After a 14- to 16-h overnight fast, glucose is released into the circulation at a rate of approximately 10 μmol/(kg min) [10,13,14]. Approximately 50% of this is the result of the breakdown of glycogen (glycogenolysis) stored in the liver and the other half is because of the production of new glucose molecules from precursors such as lactate, glycerol, alanine and other amino acids (gluconeogenesis) by liver and kidneys (Table 2) [10,13,14]. The kidney is unable to release glucose through glycogenolysis because it contains very little glycogen and those renal cells that are able to synthesize glycogen lack the enzyme glucose-6-phosphatase and therefore cannot release glucose [14]. In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Research over the last 15–20 years has established that the human liver and kidneys provide about equal amounts of glucose via gluconeogenesis in the post-absorptive state (Table 2). Consequently, after an overnight fast, 75–80% of glucose released into the circulation derives from the liver and the remaining 20–25% derives from the kidneys. As the duration of fasting increases, glycogen stores in the liver become further depleted until, after 48 h, virtually all the glucose released into the circulation is derived from gluconeogenesis [4,13]. Consequently, as the length of fast increases, the proportion of

Table 1 Proportion of glucose utilization as a result of specific tissues in the fasting and postprandial state [5,57]

Tissue/organ	Post-absorptive state, ~11.1 μmol/(kg min) (mainly insulin-independent) % of total	Postprandial state, ~55 μmol/(kg min) (mainly insulin-stimulated) % of total
Brain	40–45	~10
Muscle	15–20	30–35
Liver	10–15	25–30
Gastrointestinal (GI) tract	5–10	10–15
Kidney	5–10	10–15
Other (e.g. skin, blood cells)	5–10	5–10

Table 2 Mechanisms and sources of glucose release into the circulation in the post-absorptive state [10,13,14]

Overall rate [~μmol/(kg min)]	10
Hepatic contribution [~μmol/(kg min)]	7.5–8.0 (75–80%)
Glycogenolysis [~μmol/(kg min)]	4.5–5.0 (45–50%)
Gluconeogenesis [~μmol/(kg min)]	2.5–3.0 (25–30%)
Renal contribution [~μmol/(kg min)]	2.0–2.5 (20–25%)
Glycogenolysis [~μmol/(kg min)]	0
Gluconeogenesis [~μmol/(kg min)]	2.0–2.5 (20–25%)

overall glucose release accounted for by renal gluconeogenesis increases [15].

It is important to note that kidney and liver differ in their use of gluconeogenic precursors and the effect of hormones on their release of glucose. As shown in Table 3, lactate is the predominant gluconeogenic precursor in both organs, but otherwise the kidney preferentially uses glutamine [16], whereas the liver preferentially uses alanine [17].

With respect to hormonal influences, insulin suppresses glucose release by both organs with roughly comparable efficacy [18], whereas glucagon normally stimulates hepatic glucose release only, mainly via an early action on glycogenolysis [12]. Catecholamines normally exert a direct effect on renal glucose release only [19,20], although they may indirectly affect both hepatic and renal glucose release by increasing availability of gluconeogenic substrates and by suppressing insulin secretion. Cortisol, growth hormone and thyroid hormones have long-term stimulatory influences on hepatic glucose release (over a period of days) [10]. Their effects on renal glucose release in humans have yet to be determined.

The postprandial state

Classically, metabolic studies have usually been undertaken in the post-absorptive state (i.e. 12–16 h after the last meal). However, most of the day people are in the postprandial state as this includes 4–6 h on three occasions during the day.

Postprandial plasma glucose levels are critically influenced by insulin and glucagon levels. Following ingestion of glucose, plasma glucose levels peak in 60–90 min and slowly return to post-absorptive levels after 3–4 h. This profile is mirrored by a fourfold increase in plasma insulin and a reciprocal suppression of plasma glucagon levels of ~50% [10]. Meyer *et al.* (2002) demonstrated that, after meal ingestion, overall endogenous glucose release decreases by ~61%, with hepatic glycogenolysis virtually ceasing in the 4- to 6-h period [21]. Teleologically, this is understandable because this period is responsible for replenishment of hepatic glycogen stores. Furthermore, suppression of endogenous glucose release limits postprandial hyperglycaemia. Hepatic gluconeogenesis also decreases by ~82% and glucose molecules generated through this pathway are not generally released in the circulation, but are largely directed into hepatic glycogen. Perhaps surprisingly, renal gluconeogenesis actually increases by approximately twofold and accounts for ~60% of endogenous glucose release in the postprandial period [21]. This has been hypothesized to facilitate efficient repletion of glycogen stores in the liver [21].

These differences in regulation and reciprocal change in renal and hepatic glucose release have led to the concept of hepatorenal glucose reciprocity [22]. This concept refers to the situations in which a physiological or pathological decrease in glucose release by kidney or liver is associated with a compensatory increase in glucose release by liver or kidney so as to prevent hypoglycaemia or to optimize homeostasis. Examples of this include the anhepatic phase after liver transplantation, prolonged fasting, acidosis, meal ingestion and insulin overdoses in diabetes mellitus [22–24].

Renal glucose utilization

In the post-absorptive setting after an overnight fast, the kidneys utilize approximately 10% of all glucose utilized by the body. After meal ingestion their glucose utilization increases in an absolute sense. In terms of whole-body glucose economy, normally approximately 45% of ingested glucose is thought to be converted to glycogen in the liver, ~30% is taken up by skeletal muscle and later converted to glycogen, ~15% is taken up by the brain, ~5% is taken up by the adipose tissue and ~10% is taken up by the kidneys [10,21]. The metabolic fate of glucose is different in different regions of the kidney. Because of its low oxygen tension, and low levels of oxidative enzymes, the renal medulla is an obligate user of glucose for its energy requirement and does so anaerobically. Consequently, lactate is the main metabolic end product of glucose taken up in the renal medulla, not carbon dioxide (CO_2) and water. In contrast, the renal cortex has little glucose phosphorylating capacity but a high level of oxidative enzymes. Consequently, this part of the kidney does not take up and use very much glucose, with oxidation of FFAs acting

Table 3 Utilization of substrates for gluconeogenesis [17]

	Lactate (n = 16)	Glycerol (n = 9)	Glutamine (n = 37)	Alanine (n = 9)
Overall gluconeogenesis [~μmol/(kg min)]	1.88 ± 0.15	0.53 ± 0.09	0.58 ± 0.04	0.68 ± 0.07
Renal gluconeogenesis [~μmol/(kg min)]	0.89 ± 0.09	0.17 ± 0.03	0.36 ± 0.02	0.02 ± 0.01
(% of overall gluconeogenesis)	(47 ± 8)	(32 ± 4)	(62 ± 3)	(3 ± 1)
Hepatic gluconeogenesis [~μmol/(kg min)]	0.97 ± 0.18	0.39 ± 0.8	0.23 ± 0.02	0.67 ± 0.08
(% of overall gluconeogenesis)	(53 ± 8)	(68 ± 4)	(38 ± 3)	(97 ± 1)

as the main source of energy. A major energy-requiring process in the kidney is the reabsorption of glucose from glomerular filtrate in the proximal convoluted tubule [25].

Renal glucose reabsorption

In addition to releasing glucose into the circulation by synthesizing new glucose molecules via gluconeogenesis and its utilization of glucose, the kidney can also influence glucose homeostasis by returning glucose to the circulation via the reabsorption of glucose from glomerular filtrate. Normally, approximately 180 l of plasma are filtered by the kidneys each day. As the average plasma glucose concentration throughout a 24-h period is ~5.5 mmol/l (100 mg/dl), ~180 g of glucose is filtered by the kidneys each day. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. To put this into perspective, in a given day, the kidneys produce 15–55 g glucose via gluconeogenesis and metabolize 25–35 g glucose. Therefore, in terms of glucose economy, it is clear that renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis. Alterations in renal tubular glucose reabsorption may therefore be expected to have a considerable impact on glucose homeostasis.

Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLTs) in the proximal convoluted tubulae. There are six members of this family (Table 4) [26]. In animal models, approximately 90% of glucose is reabsorbed by SGLT2, a high-capacity low-affinity glucose transporter (Km ~10 mmol/l; Vmax ~10 nmol/(min mg) protein [27]). SGLT2 is thought to be located exclusively on the luminal surface of the epithelial cells lining the S1 and S2 segments of the proximal tubule [28,29]. Transport of sodium and glucose by SGLT2 occurs in a 1 : 1 ratio [27,30]. The remaining ~10% of glucose reabsorption is mediated by SGLT1, a high-affinity, low-capacity glucose/galactose transporter (Km ~0.2 mmol/l; Vmax ~10 nmol/(min mg) protein; sodium:glucose coupling ratio = 2 : 1) located on the luminal surface of epithelial cells lining the S3 segment of the proximal tubule [27,30]. SGLT1 is also extensively expressed in the small intestine and in other tissues [30]. Glucose reabsorbed from the proximal tubules by SGLTs is then released into the circulation through the action of facilitative glucose transporters (GLUTs) at the basolateral membrane of the epithelial cells lining the proximal tubules (GLUT2 in the S1/2 segments and GLUT1 in the S3 segment) [31]. SGLT-mediated glucose transport is an active process, moving glucose against a concentration gradient, utilizing energy derived from the sodium electrochemical potential gradient across the brush border membrane and maintained by the transport of intracellular sodium into the blood via sodium:potassium adenosine triphosphatase (ATPase) pumps at the basolateral membrane [26]. In contrast, GLUTs facilitate passive transport (equilibration) of glucose across membranes and do not require an energy source [26].

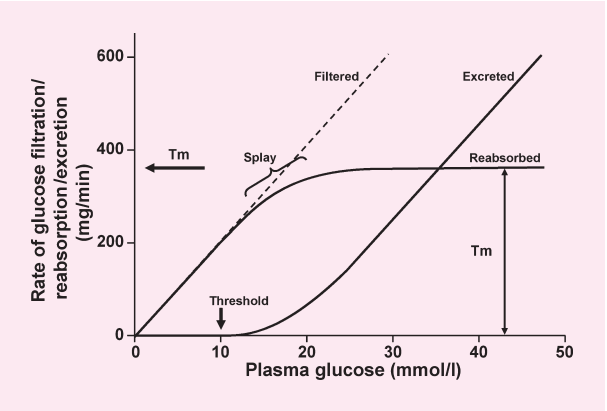

FIGURE 1 Renal glucose handling. Tm, transport maximum. Adapted with permission from Silverman & Turner (1992) [32]. Copyright © 1992 by the American Physiological Society. By permission of Oxford University Press Inc.

Figure 1 describes the renal handling of filtered glucose [32]. Glucose is freely filtered in the glomerulus, so that, as plasma glucose levels increase, the amount of glucose in the glomerular filtrate increases linearly. Reabsorption of filtered glucose also increases linearly until the maximal reabsorptive capacity is exceeded. This is often referred to as the renal threshold and equates to a filtration rate of 260–350 mg/min per 1.73 m^2 [33], which occurs at plasma glucose concentrations of 11.0 mmol/l in healthy adults [34]. Above this plasma glucose concentration, the percentage of filtered glucose that is reabsorbed decreases and the percentage of the filtered load of glucose that is excreted in the

Table 4 The sodium glucose co-transporter family [26]

Co-transporter	Gene	Substrate	Tissue distribution
SGLT1	*SLC5A1*	Glucose, galactose	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2	*SLC5A2*	Glucose	Kidney, brain, liver, thyroid, muscle and heart
SGLT4	*SLC5A9*	Glucose, mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas
SGLT5	*SLC5A10*	Not known	Kidney
SGLT6	*SMIT2/SLC5A11*	Glucose, myo-inositol	Brain, kidney, intestine
SMIT1	*SLC5A3*	Glucose, myo-inositol	Brain, heart, kidney, lung

urine increases, resulting in glucosuria. The 'rounding' of the titration curve seen around the transition from complete reabsorption to urinary excretion of excess glucose (shown in Fig. 1 as 'splay') can be accounted for by heterogeneity in the glomerular filtration rate and glucose reabsorptive capacity of different individual nephrons [32].

The renal threshold for glucose is decreased in individuals with a rare condition known as familial renal glucosuria (FRG), caused by a range of mutations to the *SLC5A2* gene, which encodes SGLT2 [35]. Depending on the nature of the mutations, these individuals have varying degrees of glucosuria, but in the most severe form (so-called 'Type 0' disease) they can lose > 100 g glucose per day to the urine [35]. Interestingly, the large majority of patients exhibit no symptoms and their condition is only identified incidentally. Typically, they do not become hypoglycaemic or dehydrated and have no electrolyte imbalance or increased risk of urinary tract infections [35]. Even the most severe form of the condition appears to carry a favourable prognosis [36] (although it should be noted that only small numbers of patients have been described in the literature). In contrast, patients with SGLT1 gene mutations have low levels of glucosuria but suffer from glucose–galactose malabsorption in the gut, which can be associated with life-threatening severe diarrhoea and dehydration unless a glucose- and galactose-free diet is carefully followed [37].

The kidney in diabetes mellitus

All of the ways in which the kidney normally affects glucose homeostasis are altered in patients with diabetes mellitus.

Renal gluconeogenesis in the post-absorptive state

Consistent with numerous studies in diabetic animal models [38–44], patients with T2DM have an increased release of glucose into the circulation by the kidney in the fasting state [45]. Although the liver is commonly viewed as being largely responsible for increased release of glucose into the circulation in T2DM, the absolute increase in renal glucose release is comparable in magnitude (2.60 and 2.21 μmol/(kg min) for liver and kidneys, respectively; $P = 0.26$) [45]. In fact, the relative increase in renal gluconeogenesis is substantially greater than the increase in hepatic gluconeogenesis (300 vs. 30%). Similar to the liver, the increased glucose release by the kidney in the fasting state is solely, if not exclusively, a result of gluconeogenesis [45].

Postprandial renal glucose release

After meal ingestion, renal glucose release increases to a greater extent in people with T2DM than in people with normal glucose tolerance [46]. Meyer *et al.* (2004) found that over a 4.5-h period following ingestion of 75 g glucose, systemic glucose appearance was significantly greater in patients with T2DM than in normal individuals (100.0 ± 6.3 vs. 70.0 ± 3.3 g; $P < 0.001$). Much of this difference was as a result of an increase in endogenous glucose release because the systemic appearance of ingested glucose was only 7 g greater in the diabetic patients. Forty per cent of the increased endogenous glucose release was because of increased renal glucose release. This was primarily a result of impaired suppression of endogenous glucose release and to a lesser extent of reduced initial splanchnic sequestration of ingested glucose. Considering renal glucose release is regulated by insulin [11], this effect is not unexpected in diabetic patients for whom postprandial insulin release is reduced and insulin resistance is present. Other possible explanations could include a 'hangover' of the increased renal gluconeogenesis seen in the post-absorptive state [45], high FFA levels seen in patients with T2DM (because FFAs are known to stimulate renal and hepatic gluconeogenesis in animal models) [47,48] and an increased availability of gluconeogenic precursors seen in patients with T2DM [21].

Renal glucose uptake

In addition to increased glucose production, renal glucose uptake is increased in both the post-absorptive and postprandial states in patients with T2DM [45,46]. Meyer *et al.* (1998) showed that, in the post-absorptive state, renal glucose uptake is significantly greater in patients with T2DM than in normal individuals (353 ± 48 vs. 103 ± 10 μmol/min; $P < 0.001$), actually exceeding increased glucose production to result in a net glucose uptake of 92 μmol/min. This contrasts with a net output of 21 μmol/min in non-diabetic individuals [45]. In the postprandial state, uptake of glucose by tissues is increased in patients with T2DM and its distribution and fate are altered [46]. Glucose uptake by the kidneys is raised by more than twofold [21.0 ± 3.5 vs. 9.8 ± 2.3 g in diabetic vs. non-diabetic individuals ($P < 0.03$) during a 4.5-h period following ingestion of 75 g of glucose [46]], whereas glucose uptake in muscle is not significantly altered [46]. Moreover, less glucose is oxidized [46].

Renal glucose reabsorption

It is well recognized that glucosuria in diabetic patients does not occur at plasma glucose levels that would normally produce glucosuria in non-diabetic individuals [49]. This is the result of increased glucose reabsorbtion from glomerular filtrate in people with diabetes mellitus. The transport maximum (Tm) for glucose is increased and glucosuria only begins to occur at higher than normal plasma glucose levels. In one study, the Tm increased from approximately 350 mg/min in normal individuals to approximately 420 mg/min in those with diabetes mellitus [49]. Studies of renal cells isolated from the urine of people with diabetes as well as cells from several animal models have demonstrated enhanced expression of SGLT2 transporters [50,51]. Hyperglycaemia, albumin and angiotensin II have all been reported to up-regulate expression of SGLT2 in T2DM [50]. The role of altered renal glucose

reabsorption in the pathogenesis of diabetic nephropathy is unclear.

Therapeutic implications

Inhibitors of SGLT2 are currently undergoing clinical trials in patients with T2DM as a novel means of reducing hyperglycaemia. Phlorizin, a non-specific SGLT1/2 inhibitor first isolated from the root bark of the apple tree in 1835 [52], was found to increase glucosuria and reduce hyperglycaemia and normalize insulin sensitivity in a partial pancreatectomized animal model of T2DM [53]. However, it has not been developed as a treatment for diabetes because of a number of practical shortcomings. It is non-selective and inhibits SLGT1 at the intestinal brush border, which is responsible for absorption of dietary glucose [26]. Inhibition of SGLT1, therefore, has the potential to result in glucose–galactose malabsorption and thus diarrhoea, as occurs in naturally occurring SGLT1 deficiency [54]. Furthermore, phlorizin is poorly absorbed in the intestine and is readily hydrolysed to phloretin, a compound that blocks the facilitative glucose transporter, GLUT1. This might lead to interference with glucose uptake in a number of tissues [55]. Highly-specific inhibitors of SGLT2 would overcome some of these shortcomings. However, this approach to lowering hyperglycaemia in T2DM has a number of attractions. For example, unlike the insulin secretagogues [e.g. sulphonylureas, glinides, glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors] and insulin sensitizers (metformin and thiazolidinediones), the action of SGLT2 inhibitors should not be dependent on pancreatic B-cell function, which deteriorates over time. The insulin-independence of their action may also mean that hypoglycaemic episodes are less likely. Furthermore, the glucosuric effects of these drugs mean that they may not cause weight gain and may even cause weight loss. Finally, SGLT2 inhibitors have an osmotic diuretic effect that may be beneficial for patients with elevated blood pressure. Theoretical safety and tolerability concerns include polyuria, electrolyte imbalance, urinary tract infection, genital fungal infection and impairment in renal function, although it is interesting to note that patients with FRG do not suffer from these adverse effects [35,36]. Clinical trials are underway to assess clinical efficacy and safety of several SGLT2 inhibitors [56].

Competing interests

JEG discloses the following: Advisory Boards/Consultant for Amylin, AstraZeneca, Bristol-Myers Squibb, Centocor, Eisai, Elixir, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Kowa, Lifescan, MannKind Corporation, Merck, Novartis, Novo Nordisk, Pfizer, Sankyo, Sanofi-Aventis, and Sitris; Speaker's Bureau for GlaxoSmithKline, Lifescan, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis; Grants/Clinical Trials from/for Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Kowa, Novartis, Novo Nordisk, Pfizer, Sankyo, Sanofi-Aventis, Takeda.

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