

Sodium-glucose co-transporter inhibitors

Mechanisms of action

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SUMMARY

Sodium-glucose co-transporter 2 inhibitors are a new class of drug for the treatment of type 2 diabetes. They lower plasma glucose concentrations by increasing renal excretion of glucose.

This class of drugs reduces glucose reabsorption in the kidney and lowers plasma glucose independent of changes in insulin concentrations or peripheral insulin resistance. They have a low risk of hypoglycaemia when used as monotherapy.

The known adverse effects of the sodium-glucose co-transporter 2 inhibitors are related to their mechanism of action. They include an increased risk of dehydration and genital and urinary tract infections because of the increase in urinary glucose.

Introduction

Current treatment options for type 2 diabetes focus on reducing insulin resistance, enhancing insulin secretion or providing exogenous insulin. However, the kidneys play an important role in glucose homeostasis. Increasing the excretion of glucose could lower blood glucose. This can be achieved by inhibiting the sodium-glucose co-transporter (SGLT).

Physiology of renal glucose reabsorption

At normal concentrations of plasma glucose, the kidneys actively reabsorb almost all filtered glucose (approximately 180 g/day) with less than 1% excreted in the urine.¹ Glycosuria occurs when plasma glucose concentrations exceed the glucose reabsorbing capacity of the proximal tubules. This renal threshold for glucose is about 11 mmol/L.

Glucose is a hydrophilic molecule which needs to be transported across cell membranes to enter cells. Glucose transport can either be facilitative or active. Facilitative transport is driven by the concentration gradient across the cell membrane. Active transport is driven by sodium co-transport. Uptake of glucose in the intestine and kidneys is by active transport, mediated by members of the SGLT family. SGLT1 and

SGLT2 are responsible for glucose reabsorption in the proximal tubules of the kidneys (Fig. 1).²

SGLT2 is a low-affinity, high capacity glucose transporter located in segment 1 of the proximal tubule (in the apical membrane of the tubule cells). Under normal circumstances SGLT2 reabsorbs about 90% of the filtered glucose (Fig. 2). SGLT2 is minimally expressed in other tissues.³

SGLT1 is a high-affinity, low capacity glucose transporter predominantly found in enterocytes of the small intestine where it transports glucose and galactose from the gut lumen across the gut wall. In the kidney SGLT1 is located in segments 2–3 of the proximal tubule. Following glucose reabsorption by SGLT2 early in the proximal tubule the remaining 10% of filtered glucose is reabsorbed by SGLT1 later in the proximal tubule.

SGLT2 as a therapeutic target

Familial renal glycosuria is a rare renal tubular disorder caused by a mutation in the SLC5A2 gene which encodes for SGLT2. It is characterised by persistent glycosuria with urinary glucose excretion up to 100 g/day in the absence of hyperglycaemia.⁴ Familial renal glycosuria therefore acts as a model for therapeutic SGLT2 inhibition and, reassuringly, it is a benign condition. Despite chronic glycosuria, it is not associated with chronic kidney disease or urinary tract infections.

Phlorizin, a glucoside isolated from the bark of apple trees in the 19th century, was recognised in the 1950s as an inhibitor of glucose uptake by erythrocytes and of glucose transport in the kidneys and small intestine. In the 1990s phlorizin was shown to inhibit SGLT1 and SGLT2.⁵ Further development of phlorizin was limited by its low bioavailability, lack of specificity and its adverse effects.

Pharmacology of SGLT2 inhibitors

The first two SGLT2 inhibitors approved in Australia, dapagliflozin and canagliflozin, have high bioavailability. They have a half-life of about 12 hours and are taken once a day. Dapagliflozin can be taken with or without food, while it is recommended that canagliflozin is taken before the first meal of the day. Both drugs are highly protein bound in plasma and are metabolised in the liver via glucuronidation.

With these characteristics there is a low propensity for pharmacokinetic drug–drug interactions. However, inducers of glucuronidation can cause a modest increase in the metabolism of SGLT2 inhibitors. When inducers of glucuronidation (e.g. rifampicin, phenytoin or ritonavir) are prescribed, the product information for canagliflozin recommends a higher dose of 300 mg daily (usual starting dose 100 mg daily) or using an alternative blood glucose-lowering drug. The product information for dapagliflozin does not recommend a dose increase. Inhibition of metabolism by other glucuronidated drugs, for example mefenamic acid, is possible.⁶ The clinical significance of these potential interactions with either drug is likely to be low. Canagliflozin may increase the plasma concentration of digoxin so digoxin concentrations should be monitored when starting or stopping canagliflozin.

Pharmacodynamic drug interactions may occur with thiazides and loop diuretics, increasing diuresis and the risk of dehydration. Changes in renal tubular handling of potassium associated with SGLT2 inhibition may be significant in patients at higher risk of hyperkalaemia, for example those with baseline renal impairment, taking ACE inhibitors or taking potassium-sparing diuretics.

In patients with mild to moderate liver impairment, no significant increase in drug concentrations was seen with either drug. A lower starting dose of dapagliflozin (5 mg) is recommended in patients with severe liver disease. There are no published data for canagliflozin in severe liver disease.

Caution in renal impairment

The efficacy of SGLT2 inhibitors is dependent on:

- glomerular filtration sufficient to deliver a glucose load to the proximal tubule
- sufficient drug reaching the proximal tubule.

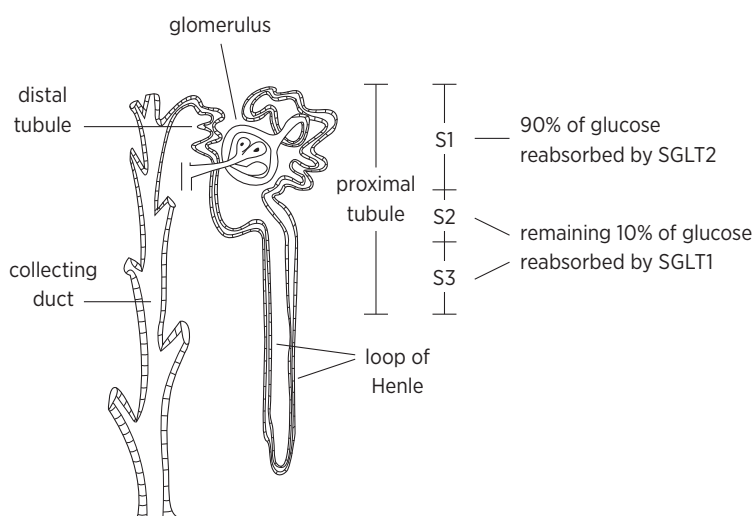
SGLT2 inhibitors are therefore ineffective, and consequently not recommended, in moderate to severe renal impairment (estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² or dialysis). There is limited experience in patients with eGFRs of 45–60 mL/min/1.73 m².

Concerns about the long-term renal effects of chronic inhibition of tubular glucose uptake have been raised. However, familial renal glycosuria is not associated with increased renal impairment, and in short-term trials SGLT2 inhibitors have not been associated with a decline in renal function.⁷ At this stage monitoring renal function at least annually is recommended and long-term studies are awaited.

SGLT2 inhibitors in type 2 diabetes

Treatment with an SGLT2 inhibitor causes dose-dependent urinary net glucose losses of 20–70 g

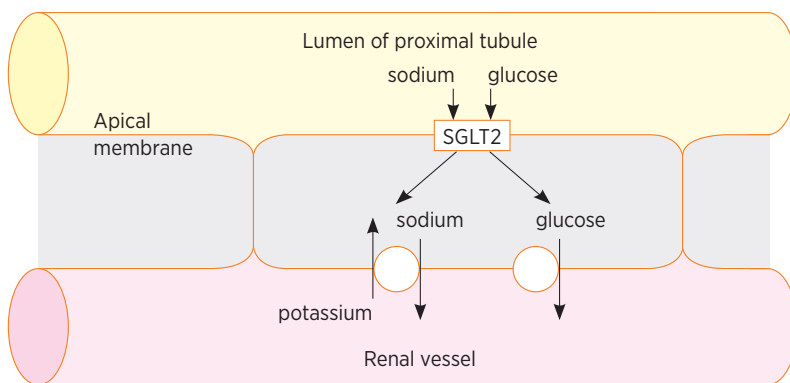
Fig. 1 Location of SGLT1 and SGLT2 in the proximal tubules of the kidney



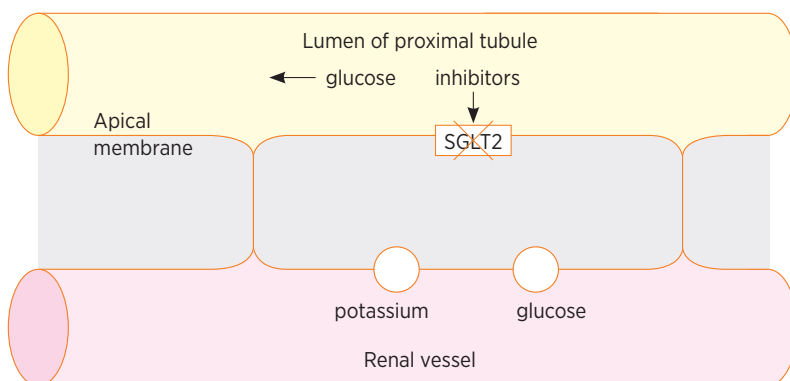
SGLT sodium-glucose co-transporter S segments of proximal tubule

Fig. 2 Action of SGLT2 in the proximal tubule

A Normal function



B SGLT2 inhibited



SGLT2 sodium-glucose co-transporter 2 (circle icon) sodium-potassium pump

per day. This varies with the degree of hyperglycaemia. The US Food and Drug Administration analyses of clinical trials found dapagliflozin reduces glycated haemoglobin (HbA1c) in patients with type 2 diabetes by 4–9 mmol/mol (0.4–0.8%), depending on the initial HbA1c.⁸ Similarly for canagliflozin there was a dose-dependent HbA1c reduction of 4–11 mmol/mol (0.4–1%).⁹ This is comparable to the effect of dipeptidyl peptidase 4 inhibitors, but less than that of metformin, sulfonyleureas or glucagon-like peptide-1 analogues.¹⁰ The reduction in blood glucose concentrations occurs independently of any increase in insulin concentrations or decrease in peripheral insulin resistance. In addition the glycosuria causes a caloric loss, which has been associated with an average weight loss of 2–3 kg over 6–12 months in clinical trials.¹¹

Mechanisms of potential harms

The mechanism of action of the SGLT2 inhibitors explains some of their reported adverse effects. The risk of hypoglycaemia is low when used as monotherapy or in combination with metformin. However, the risk of hypoglycaemia increases when SGLT2 inhibitors are combined with insulin or sulfonyleureas.¹¹

The glycosuria is accompanied by a small increase in urinary volume of about 100–500 mL/day due to osmotic diuresis. The consequent intravascular depletion may contribute to a small but consistent drop in blood pressure and a modest increase in postural hypotension.

The SGLT2 inhibitors are associated with a small increase in the rates of both genital infections and

urinary tract infections. This may be a consequence of induced glycosuria.

There are concerns about SGLT2 inhibition and bone health because of changes in the renal tubular handling of calcium, magnesium and phosphate, and preclinical reports of hyperostosis in rats. Calcium excretion can increase, but short-term studies (up to 24 weeks) have not shown a decline in bone mineral density with either drug compared to controls.^{9,12} Mild elevations of parathyroid hormone have been observed^{9,13} and the long-term safety of these drugs in regard to bone health and fracture risk is unclear.

There have also been concerns raised about a possible increase in the incidence of bladder and breast cancer. Continued surveillance for breast and bladder cancer with dapagliflozin, canagliflozin and future SGLT2 inhibitors will be required.

There are SGLT transporters in other tissues. Antagonism of these transporters may have long-term harmful or beneficial effects not detected by short-term studies.

Conclusion

SGLT2 inhibitors are a new class of drugs for lowering plasma glucose. They reduce the renal reabsorption of urinary glucose. The reduction in plasma glucose is independent of insulin secretion and insulin peripheral resistance. The long-term effects of SGLT2 inhibitors are unknown. ◀

Conflict of interest: none declared



SELF-TEST QUESTIONS

True or false?

5. Sodium-glucose co-transporter 1 is mainly found in the kidney.
6. Inhibition of the sodium-glucose co-transporter reduces urine volume.

Answers on page 35

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FURTHER READING

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