SGLT2 inhibitors: molecular design and potential differences in effect

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The physiological and pathological handling of glucose via sodium–glucose cotransporter-2 (SGLT2) in the kidneys has been evolving, and SGLT2 inhibitors have been focused upon as a novel drug for treating diabetes. SGLT2 inhibitors enhance renal glucose excretion by inhibiting renal glucose reabsorption. Consequently, SGLT2 inhibitors reduce plasma glucose insulin independently and improve insulin resistance in diabetes. To date, various SGLT2 inhibitors have been developed and evaluated in clinical studies. The potency and positioning of SGLT2 inhibitors as an antidiabetic drug are dependent on their characteristic profile, which induces selectivity, efficacy, pharmacokinetics, and safety. This profile decides which SGLT2 inhibitors can be expected for application of the theoretical concept of reducing renal glucose reabsorption for the treatment of diabetes. I review the structure and advancing profile of various SGLT2 inhibitors, comparing their similarities and differences, and discuss the expected SGLT2 inhibitors for an emerging category of antidiabetic drugs.

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Hyperglycemia is a characteristic of diabetes and a big concern because of its association with increased risks of microvascular and macrovascular complications promoting cardiovascular diseases in diabetic patients. Type 1 and type 2 diabetes are characterized by an autoimmune disease and by impaired insulin secretion and insulin resistance, respectively. Type 2 diabetes has been increasing progressively in incidence with lifestyle changes and is now referred to as a metabolic disorder.[1,2] Basic management of type 2 diabetes consists of lifestyle interventions such as diet and exercise, which modulate the energy balance in a negative direction. Because of the insufficiency of maintaining proper lifestyle changes, various antidiabetic drugs have been used for reducing plasma glucose and improving insulin resistance.[3] When our goal of the treatment of diabetes is set on preventing the progression of diabetes itself and reducing its consequent complications, optimal glycemic control and tolerable safety become key points, as shown in large randomized clinical trials.[4] Therefore, a new strategy for achieving optimal glycemic control, resulting in lower HbA1c levels, has been expected for management of the diabetic patient. Here, modulation of renal glucose handling has been highlighted as a promising approach for improving hyperglycemia and insulin resistance without intolerable adverse effects.[5]

In the handling of renal glucose,[6,7] the bulk of the filtered glucose is reabsorbed by the high-capacity low-affinity sodium–glucose cotransporter-2 (SGLT2),[8] which is a member of the solute carrier family 5A[9] and is distributed predominantly on the luminal surface of cells in the S1 segment of renal proximal tubules. The residual glucose is reabsorbed by the low-capacity high-affinity SGLT1 distributed in the S3 segment; SGLT4 may also participate in the reabsorption at least in part.[10]

SGLT2 inhibitors discard excess glucose into the urine by inhibiting renal glucose reabsorption, and may be referred to as a chemical inducer of familial renal glucosuria.[11,12] Consequently, they reduce the plasma glucose level and abolish glucose toxicity, resulting in improving the insulin resistance associated with diabetes.[13] At present, many SGLT2 inhibitors are being used in late-phase clinical studies to confirm their potency and safety for the treatment of diabetes.[14] In this review, the structure and advancing profile of various SGLT2 inhibitors are described, and the expected potential and positioning of SGLT2 inhibitors for an emerging category of antidiabetic drugs are discussed.

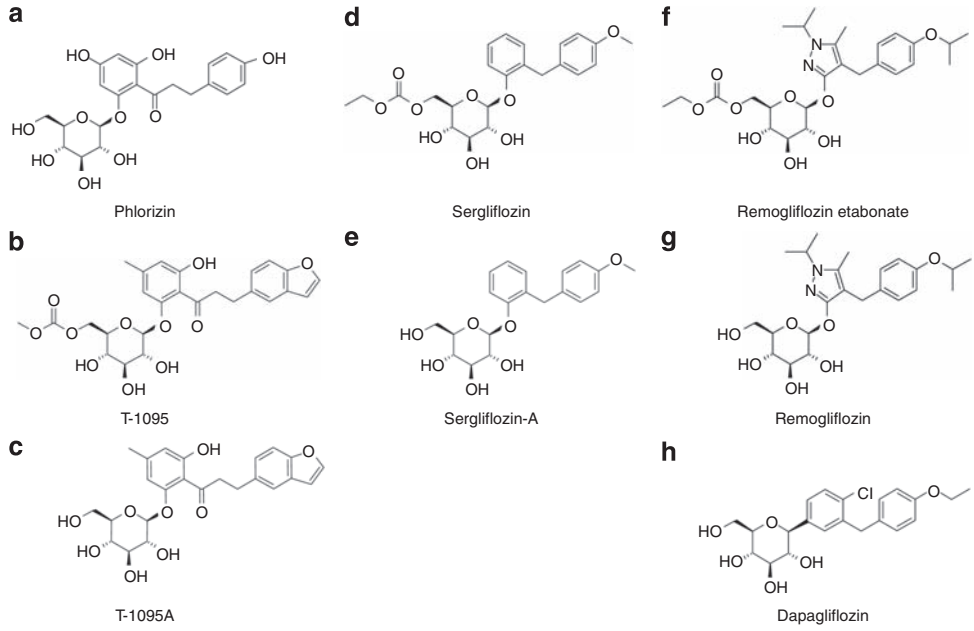

Figure 1 | Chemical structures of sodium–glucose cotransporter-2 (SGLT2) inhibitors.

STRUCTURE AND CLINICAL STAGES OF SGLT2 INHIBITORS

Diverse structures of SGLT2 inhibitors have been disclosed in some papers and in a number of patents.[9,15] Phlorizin, a β-D-glucoside, was the first non-selective SGLT inhibitor to be isolated from the root bark of the apple tree, and it consists of a glucose moiety and an aglycone in which two aromatic carbocycles are joined by an alkyl spacer (Figure 1a).[16] T-1095 is the prodrug of T-1095A, which is a non-selective SGLT inhibitor that is a derivative of phlorizin and categorized as an aromatic hydrocarbon *O*-glycoside (Figure 1b and c).[17] Thereafter, non-phlorizin *O*-glycoside derivatives inhibiting SGLT2 selectively were developed as the next generation. Sergliflozin, a prodrug of sergliflozin-A, is an aromatic *O*-glycoside (Figure 1d and e),[18] and remogliflozin etabonate, a prodrug of remogliflozin, is a heteroaromatic *O*-glycoside (Figure 1f and g).[19] Furthermore, fused aromatic *O*-glycosides have also been developed.[20] The next important structures are aromatic and heteroaromatic *C*-glycosides, in which the glucose moiety binds aglycone directly through a carbon–carbon bond.[21] Dapagliflozin is a representative compound of aromatic *C*-glycosides (Figure 1h) for enhancing the chemical stability of the glycosidic bond.[22] *C*-glycosides are more metabolically stable than *O*-glycosides because of their resistance to gastrointestinal β-glucosidases, and are rapidly absorbed in the gastrointestinal tract without modification of the prodrug form. Furthermore, *N*-glycosides, *S*-glycosides, and modified sugar rings have been developed for combination with various structures of aglycones. The structures of TA-7284, YM-543, ASP-1941, BI 10773, BI 44847, R-7201, TS-033, and TS-071 have not yet been disclosed.

Clinical development stages of SGLT2 inhibitors are shown in Table 1. Brystol-Myers Squibb/AstraZeneca have been codeveloping dapagliflozin at the Phase III stage. Canagliflozin and ASP-1941 follow at the Phase III stage and BI 10773, BI 44847, R-7201, TS-071, and LX4211 are being developed at the Phase II stage. The first-generation compounds of each company have now been discontinued; namely, T-1095, sergliflozin, AVE2268, TS-033, and YM-543 have been abandoned and taken over by next-generation compounds. Recently, GlaxoSmithKline discontinued the development of remogliflozin etabonate.

Table 1 | Clinical development of sodium–glucose cotransporter-2 (SGLT2) inhibitors for the treatment of diabetes

Drug	Development company	Phase of development
Dapagliflozin	Bristol-Myers Squibb/AstraZeneca	Phase III
Canagliflozin	JNJ/Mitsubishi Tanabe	Phase III
ASP-1941	Astellas/Kotobuki	Phase III (Japan)
BI 10773	Boehringer Ingelheim	Phase II
BI 44847	Boehringer Ingelheim/Ajinomoto	Phase II
R-7201	Roche/Chugai	Phase II
TS-071	Taisho	Phase II
LX4211	Lexicon	Phase II
Remogliflozin	GlaxoSmithKline	Discontinued
YM-543	Astellas/Kotobuki	Discontinued
TS-033	Taisho	Discontinued
AVE2268	Sanofi-Aventis	Discontinued
Sergliflozin	GlaxoSmithKline/Kissei	Discontinued
T-1095	Tanabe	Discontinued

ADVANCE IN PROFILE OF SGLTs INHIBITORS

Phlorizin

Phlorizin was the first non-selective SGLT inhibitor; it induces glucose excretion into the urine, so-called Phlorizin-induced glucosuria, by suppressing the renal glucose reabsorption system.[16] Phlorizin lowers plasma glucose by