Sodium glucose co-transporter inhibitors – A new class of old drugs

Aneeta Malhotra, Surbhi Kudyar[1], Anil K. Gupta[2], Rattan P. Kudyar[3], Pavan Malhotra[4]

Departments of Pathology, [1]Surgery, [2]Medicine, [3]Endocrinology and [4]Pharmacology and Therapeutics, Acharya Shri Chander College of Medical Sciences and Hospital, Sidhra, Jammu, Jammu and Kashmir, India

Abstract

Sodium glucose co-transporter (SGLT) inhibitors are a new class of drugs which are used in the pharmacotherapy of Type-II diabetes, which happens to be a major risk factor for developing both micro as well as macro-vascular complications. These drugs inhibit the glucose reabsorption by inhibiting SGLT, which exhibits a novel and promising mechanism of action by promoting the urinary glucose excretion hence providing a basis of therapeutic intervention. Results of SGLT-II inhibitors are very encouraging as there is a significant elevation of GLP-1 level, which forms the basis of relevance in treatment of diabetes. It targets the HbA1C and keeps a check on its levels. It also exerts other positive benefits such as weight loss, reduction in blood glucose levels, reduction in blood pressure and improvement in insulin resistance and β-cell dysfunction: All contributing to effective glycemic control. SGLT inhibition will develop as effective modality as it has the capability of inhibiting reabsorption of greater percentage of filtered glucose load.

Key words: Canagliflozin, glucose reabsorption, glucosuria, HbA1C, phlorizin, proximal renal tubule, sodium-glucose co-transporter inhibitors

Submission: 19-07-2014 **Accepted:** 24-03-2015

Introduction

Diabetes mellitus, is a metabolic disorder caused by dysfunction of pancreatic β-cells resulting in a state of hyperglycemia and glucosuria. Defronzo while giving a fresh look to pathogenesis of Type-II diabetes mellitus in his ominous octet described that kidneys play an important role in both causing and maintaining the hyperglycemic state.

The idea was developed to lower the serum sugar levels in Type-II diabetes by inhibiting the reabsorption of sugar from the kidney generally mediated by sodium glucose co-transporter (SGLT), which has six active variants SGLT-1 to SGLT-6 [Figure 1]. SGLT-2 is responsible for 90% of glucose reabsorption, whereas SGLT-1 is responsible for remaining 10% of the reabsorption in kidneys.

Hence, the primary target of glucose reabsorption inhibition is in the early proximal tubule where this action is mediated by SGLT-2. This action is insulin independent as the elevated serum sugar levels are lowered by promoting glucosuria.

Historical Background

This new class of old drugs has a very long history. The prototype compound in this category "phlorizin" (O-glucoside phlorizin dihydrochalcones, a type of flavonoid) is a bitter white glycoside isolated 179 years ago, way back in 1835 by French chemist from the apple tree bark and later on in 1886 the famous diabetologist Joseph Vas Mering first described pharmacological role of SGLT inhibitor ingestion causes glycosuria.

Phlorizin was found to improve glycemic control in diabetic animals. The key factor precluding its use in humans was the dosage. Since the majority of phlorizin gets converted into an intermediary before it can be of any use, thereby requiring an increase in dose to achieve desired hypoglycemic effect.

Address for correspondence: Dr. Pavan Malhotra,
Department of Pharmacology and Therapeutics, Acharya Shri Chander College of Medical Sciences and Hospital, Sidhra, Jammu, Jammu and Kashmir, India.
E-mail: pavanmalhotra@yahoo.com

Access this article online	
Quick Response Code:	Website: www.ijabmr.org
	DOI: 10.4103/2229-516X.165363

Beta-glycoside, phlorizin could not see the light of the day as a potent oral anti-diabetic agent as it was poorly tolerated in GIT thereby producing series of unpleasant adverse drug reactions. The renal glucose handling occurs at two main sites, proximal convoluted tubule accounts for 90% of reabsorption through SGLT-2 and remaining 10% through SGLT-1. The interpolation of this effect gave birth to new class of drugs "the SGLT inhibitors." The search for a molecule, which has the quality of phlorizin and simultaneously eliminating the dosage issues ushered in bringing the molecules such as canagliflozin, empagliflozin, ipragliflozin and dapagliflozin [Table 1].

Pharmacology of Sodium Glucose Co-transporter Inhibitors

Under normal physiological conditions, 180 g of glucose is filtered in kidneys daily and 100% of it is of reabsorbed into the circulation via SGLT's. SGLT transports sodium and glucose into the cells using sodium gradient created by Na^+/K^+ ATPase pumps at the basolateral border of the cell membranes. Glucose is then transported passively by GLUT-2 along its concentration gradient into the interstitium[1,2] [Figure 2]. The affinity of phlorizin, the prototype drug of the group, is about 1 uM for hSGLT-1 and 20 nM for hSGLT-2. It was also found that the affinity of phlorizin congeners mirrored the stereospecific requirements for sugar translocation, supporting the view that interaction of phlorizin with the transporter occurs at the sugar binding/translocation site of transporter in microperfused rat renal tubules.[3] Thus, it was observed that phlorizin binds to the outside of SGLT at two domains one representing the sugar binding site and the other one as a glucose binding site. Hence, this double interaction describes the high affinity of phlorizin when compared to D-glucose.

Table 1: New SGLT inhibitors and their status and selectivity

Name of drug	Status	Mechanism of action
Canagliflozin	Available in USA	SGLT-2 and SGLT-1 inhibitor
Empagliflozin	Submitted	SGLT-2 inhibitor
Ipragliflozin	Submitted in Japan	SGLT-2 inhibitor
Dapagliflozin	Available in EU, USA, Australia	Selective SGLT-2 inhibitor
LX 4211	Phase-II clinical trials	Dual inhibitor

SGLT: Sodium glucose co-transporter

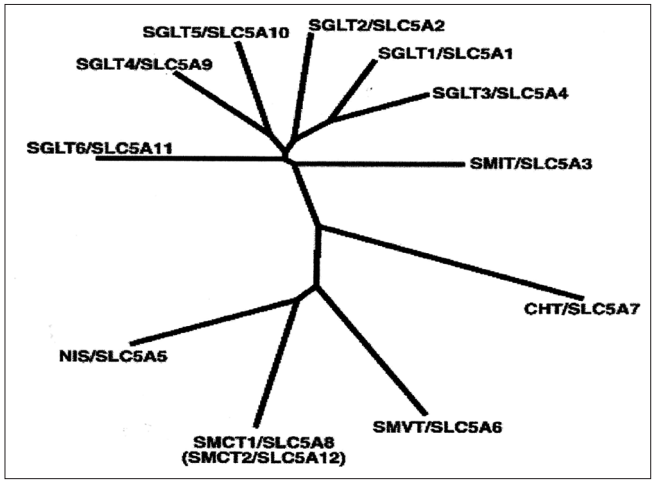

Figure 1: Sodium glucose co-transporter isozymes subtypes

Pharmacokinetics

The drug Canagliflozin, an oral SGLT-2 inhibitor, which is chemically a C-glucoside with a thiophene ring, can be considered as the prototype drug among the newer agents. The t½ of this group varies from 10 to 18 h, this effect is dose-dependent and peak steady state level are reached within 4–5 days. The Bioavailability of the drugs is >60% and the enzyme responsible for the metabolism is uridine diphosphate glucuronosyltransferase (UGT) 1A9 and UGT 2B4 to O-glucuronide metabolites, and also cytochrome P-450 enzymatic system causes minor metabolism. These drugs significantly improved the HbA1C especially in those who achieve a suboptimal control with lifestyle means alone and the best results are achieved, especially in those where it is used as an adjunct to metformin. The pharmacokinetic profile of the group is similar in diabetics and nondiabetics and the age, race, gender, body weight, food or mild renal dysfunction do not affect the pharmacokinetics. However, the dose adjustments are required for moderate renal dysfunction.

Pharmacological Actions of Sodium Glucose Co-transporter Inhibitors

Effects on plasma glucose levels

The effect of SGLT-Inhibitors on plasma glucose is dose-dependent[4] the effect is comparable to other anti-diabetics. In addition to improving the glycemic control it does reduce the glycated hemoglobin (HbA1C) levels; thereby preventing diabetic nephropathy in experimental animals.[5]

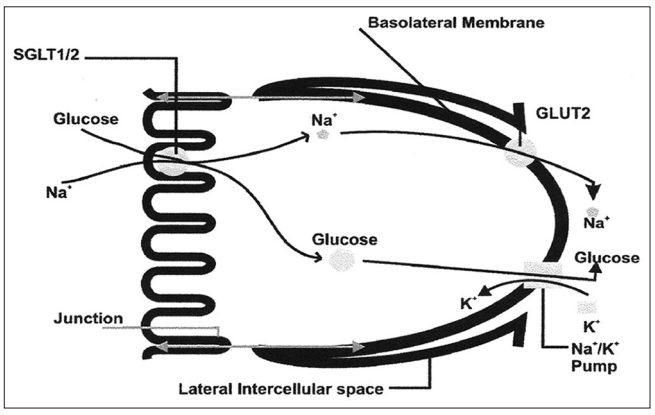

Figure 2: Glucose reabsorption in kidney using proximal tubule into central compartment

On fasting hypoglycemia

Hypoglycemia is the most potential side effect of most of the oral hypoglycemic agents. It was observed that sergliflozin, an SGLT inhibitor does not cause hypoglycemia.[6] Henceforth it was postulated that these pharmacological agents be used for SGLT-2 and not SGLT-1 inhibition. As evident, the complete absence of SGLT-2 does not lead to hypoglycemia.[7] The residual glucose reabsorption in the proximal tubule is mediated by SGLT-1, which suffices to maintain the plasma glucose level to near normal.

Effect on urinary glucose excretion

Inhibition of SGLT-2 activity reduces the tubular glucose reabsorption and due to reduction in transport maximum for glucose (TmG), more and more of glucose is excreted in urine, hence reducing hyperglycemic state even after glucose loading. Since the process is selective, a residual reabsorption of about 20–25% of the filtered load of glucose remains attributable to the operation of SGLT-1 in the last part of the proximal convoluted tubule. The effect of SGLT inhibitors on urinary glucose (UG) excretion has also been associated with reduction of body weight.[7] SGLT-2 inhibitor in clinical scenario inhibits only 30–50% of the filtered glucose load. Possible explanations are: (i) Although the renal secretions may deliver sufficient drug to achieve robust UG for a longer duration, it can saturate at high dose, thus limiting SGLT-2 inhibitors from maximally inhibiting renal glucose reabsorption. (ii) Relative to the renal secretion of SGLT-2 inhibitors, the SGLT-2 transporters are located upstream, and the expression levels of SGLT-2 in the renal proximal tubule may be much higher.

Effect on total body weight

In addition to improving on the glycemic control, these agents also lead to beneficial effects like reduction in weight. Glycosuria induced by these agents is generally associated with the net calorie loss of approximately 200–300 Kcal/day.[8]

Effect on blood pressure

This group of drugs exerts a therapeutic control over the high blood pressure. SGLT-2 inhibitors when used as monotherapy additionally exerts BP lowering effect, as well possibly by acting through net sodium loss without apparently changing the heart rate.[9]

Cardiovascular Safety and Benefits

Although the long-term cardio-vascular effects remain unknown, but recent studies reveal that these drugs also decrease the systolic blood pressure when hypertension is a co-morbid condition with diabetes. These drugs also have a low intrinsic propensity to cause hypoglycemia, also do not increase the incidence of serious infections or incidence of pyelonephritis, and reduces the elevated BP without significantly changing the heart rate. Although, the decrease in uric acid and increase in hematocrit is noticed as an additional beneficial effect, there is no impact on bone mineral density or fracture of any bone, liver toxicity or elevation of liver enzymes.[10]

Summary

Sodium glucose co-transporter 2 represents promising molecular targets for developing new alternatives in treatment of diabetes since SGLT-2 is expressed exclusively in renal proximal tubules, selective SGLT-2 inhibition should not affect other tissues and UG excretion leads to negative energy balance, a beneficial effect over existing pharmacological agents.

References

1. Nair S, Ewins JF, Wilding J, Goenka N. From history to reality sodium-glucose co-transportor inhibitor a novel therapy for type-II diabetes mellitus. Pract Diabetes Int 2010;27:311-6.
2. Pajor AM, Randolph KM, Kerner SA, Smith CD. Inhibitor binding in the human renal low- and high-affinity Na+/glucose cotransporters. J Pharmacol Exp Ther 2008;324:985-91.
3. Vick H, Diedrich DF, Baumann K. Reevaluation of renal tubular glucose transport inhibition by phlorizin analogs. Am J Physiol 1973;224:552-7.
4. Adachi T, Yasuda K, Okamoto Y, Shihara N, Oku A, Ueta K, *et al.* T-1095, a renal Na+-glucose transporter inhibitor, improves hyperglycemia in streptozotocin-induced diabetic rats. Metabolism 2000;49:990-5.
5. Kleta R, Stuart C, Gill FA, Gahl WA. Renal glucosuria due to SGLT2 mutations. Mol Genet Metab 2004;82:56-8.
6. Katsuno K, Fujimori Y, Takemura Y, Hiratochi M, Itoh F, Komatsu Y, *et al.* Sergliflozin, a novel selective inhibitor of low-affinity sodium glucose cotransporter (SGLT2), validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level. J Pharmacol Exp Ther 2007;320:323-30.
7. Ueta K, Ishihara T, Matsumoto Y, Oku A, Nawano M, Fujita T, *et al.* Long-term treatment with the Na+-glucose cotransporter inhibitor T-1095 causes sustained improvement in hyperglycemia and prevents diabetic neuropathy in Goto-Kakizaki Rats. Life Sci 2005;76:2655-68.
8. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32:650-7.
9. Baily CJ, Gross JL, Pieters A, Basiten A, List JF. Effect of dapagliflozin in patients with type-2 diabetes who have inadequate glycemic control with metform: A randomized, double blind, placebo controlled trial. Lancet 2010;375:2223-33.
10. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.

How to cite this article: Malhotra A, Kudyar S, Gupta AK, Kudyar RP, Malhotra P. Sodium glucose co-transporter inhibitors – A new class of old drugs. Int J App Basic Med Res 2015;5:161-3.

Source of Support: Nil. **Conflict of Interest:** None declared.