SGLT2 Inhibitors: A New Generation of Antidiabetic Drugs

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ABSTRACT

The incidence of type 2 diabetes is markedly increasing worldwide. Despite a plethora of therapeutic options available for the treatment of type 2 diabetes, the ability to effectively normalize blood glucose levels and prevent long-term complications of diabetes remains elusive. There is intense search for new drugs for diabetes. One novel therapeutic class of antidiabetic drugs is sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 is renal membrane transporter that plays an important role in glucose reabsorption within kidneys. Hence, inhibition of SGLT2 enhances renal glucose excretion, consequently lowers blood glucose levels in an insulin-independent manner. This article describes various SGLT2 inhibitors currently available in the market and also agents that are undergoing clinical trials for the treatment of type 2 diabetes. Currently three SGLT2 inhibitors are approved for clinical use and several others are still in development. The emerging data suggest that SGLT2 inhibitors hold great promise for the clinical management of type 2 diabetes. It remains to be seen whether this class of drugs offers additional advantages over the existing oral hypoglycemic agents.

KEYWORDS: Dapagliflozin; Canagliflozin; Empagliflozin; SGLT2; Kidney; Diabetes; Blood glucose.

Introduction

Diabetes mellitus is a metabolic disorder due primarily to insulin deficiency and it affects millions of people worldwide. The two forms of the disease, type 1 (T1DM, insulin-dependent or juvenile diabetes) and type 2 (T2DM, non-insulin dependent) diabetes mellitus are essentially caused by a decrease in plasma insulin (insulin deficiency) and/or a decrease in the response of peripheral tissues to insulin (insulin resistance). The prevalence of T2DM is alarmingly increasing across the world and is considered as one of the major non-communicable diseases affecting the humans. It is estimated that currently about 387 million people are affected by diabetes and the number is projected to reach 592 million by 2035 (International Diabetes Federation, 2013). Insulin resistance in muscle, liver and pancreatic β-cell failure secrete insulin are the core pathology of the defects in type 2 diabetes. In addition to muscle, liver and β-cell (triumvirate) the fat cell, gastrointestinal tract, pancreatic α-cell, kidney and brain all play an important role in the development of glucose intolerance in type 2 diabetic individuals. Collectively, these eight players comprise the ominous octet according to Ralph DeFronzo’s Banting Lecture (DeFronzo, 2009). Management of type 2 diabetes consists of lifestyle interventions such as diet and exercise and use of antidiabetic medications which help to reduce the plasma glucose and improving insulin resistance (Nathan et al., 2006).

There are several classes of anti-diabetic agents that are in use as monotherapy or combination therapy to treat hyperglycemia. These included biguanides, sulphonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitor, incretin mimetic and dipeptidyl dipeptidase-4 inhibitors (Tang and Zhu, 2012). The currently available drugs for the treatment of T2DM are often limited by their potential to induce significant adverse effects and moreover the glycemic control is difficult to attain at times even with combination therapy. Long-term blood glucose control becomes difficult when the treatment is accompanied by weight gain during the drug therapy (Katsuno et al., 2009). Hence, the search for newer agents with different mode or site of action in the management of T2DM continues. The key goal of therapy is to provide better glycemic control and improve quality of life in diabetes.

This article describes novel drugs targeted to kidney for treatment of diabetes. Three SGLT2 inhibitors are currently available in the market and many other similar agents are undergoing clinical trials for the treatment of type 2 diabetes.

Sodium-Glucose Cotransporter 2 (SGLT2): New target for diabetes: In 1951, it was demonstrated that renal tubular reabsorption was increased in both T2DM as well as T1DM (Farber et al., 1951; Bakris et al., 2009).