The Mechanism and Some Controversies of SGLT2 Inhibitor Protects the Cardiovascular System

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Abstract: SGLT2 inhibitor, a kind of hypoglycemic drug, whose mechanism is to suppress glucose reabsorption in proximal renal tubules in the kidney to promote the excretion of glucose, has been demonstrated to have a positive effect on our cardiovascular system and reduce the risk of suffering from cardiovascular events. In this review, we will focus on four aspects to elaborate on its mechanism. First: diuresis and electrolytes, second: blood pressure, hormone, and nerve, third: regulating lipid metabolism, and the last: the direct effect on cardiomyocytes. This paper presents some puzzles of different mechanisms, aiming for waiting to be answered in later research.

Keywords: Sglt2 Inhibitor; Cardiovascular Event; Heart Failure; Metabolization

Introduction

SGLT2 inhibitor is a new kind of oral antihyperglycemic drug. It has been confirmed that making some differences to the cardiovascular system, whether accompanied by type 2 diabetes. There have been many clinical trials that discovered the drug can improve the outcomes of heart failure patients, reducing the risk of hospitalization. There are many possible mechanisms existing, such as reversing myocardial remodeling, improving water-sodium retention, inhibiting inflammatory response, regulating lipid metabolism, and so on. In this paper, we want to explain the different functions and potential benefits of SGLT2 inhibitors to people suffering from cardiovascular disease, making guidance for future clinical usage.

1. Natriuretic diuresis and electrolyte regulation

The diuresis effect of the SGLT2 inhibitor is still in debate. We think its diuretic effect may be mainly caused by the natriuretic effect. It can only increase urine output for a short period. It can prompt the excretion of glucose for a long time, which is the primary pharmacological action. Its effect on sodium excretion is complex. Though it suppresses the function of sodium-dependent glucose transporters 2, its natriuretic effect is not as significant as we thought.[1] Scientists speculate that the ability of other parts of renal tubules and collecting ducts to reabsorb sodium and water increases compensatory over time. [1] This may lead to changes in other electrolytes in the urine and blood. Sodium-potassium transporter or sodium hydrogen transporter or other transporters may be activated secondarily and bring some unpredictable changes in ion distribution in the body. So far, it has not been found that it will bring severe fluctuations of electrolytes in the human body after taking the drugs for a long period.[2] But there have been studies showing that taking these drugs can affect the blood concentration of magnesium, chloride, and sulfate,[3] also SGLT2 inhibitors will increase serum phosphorus and PTH without affecting serum calcium.[4] Both of them can be explained by the activation of other channels in the kidney partly. In future clinical use, we need to be more careful when giving drugs to patients with electrolyte disorders, for it may have unexpected harm.

2. Improve volume load and pressure in neurohumoral aspects

This mechanism has a strong connection with diuresis. The renin-angiotensin- aldosterone system will be activated due to the sodium excretion effect in the early stage of medication, which will bring a short fluctuation of blood pressure. With the long-term use of the drug, the patient's blood pressure was observed to decrease notably. [5] For now, some idea has been presented. First, SGLT2 inhibitors can improve hematocrit, meaning that blood is concentrated and less body fluid.[6] Second, there is evidence showing that it can inhibit sympathetic activity and increase parasympathetic activity, which will bring slower heart rate and smaller contractions.[7] Now these two points are widely accepted.

The drug will also bring some changes to pulmonary circulation. Experiments have shown that the long-term application of dapagliflozin can effectively improve lung fluid volumes.[8] Empagliflozin can produce rapid reductions in pulmonary artery (PA) pressures that were amplified over time. The symptoms of heart failure have improved a lot. [9] However, these views are contradictory to the diuretic ability mentioned above, for its diuretic effect can't last for a long-time. Will changes in electrolyte concentration or blood glucose lead to the redistribution of body fluids within or outside cells or do SGLT2 inhibitors have the effect of dilating blood vessels related to the releasing of vasodilator? The specific mechanism is still waiting to be explored. In clinical application, this will effectively alleviate the symptoms of heart failure, especially left heart failure accompanied by pulmonary congestion.

3. Regulating lipid metabolism

With the further study of SGLT2 inhibitor, researchers found that it can regulate blood lipid profile. The evidence-based medicine has already confirmed that TC, HDL-L, and LDL-L increase significantly after taking that drug, and TG decreases. If we only focus on lipid profile, it is difficult to find its relationship with coronary atherosclerosis, because its control of different risk factors is contradictory.

The regulatory capacity of this lipoprotein is generally considered to be promoted the lipid efflux of macrophages by ameliorating insulin resistance, reducing the absorption of lipids, and accelerating their metabolism. [10] This can improve the fat metabolism of the liver, promote the degradation of VLDL and chylomicrons, and promote their conversion to HDL.

Its influence on LDL is still in huge debate. Some experiments still can't find a significant difference in the level of LDL after taking that drug. It brings more subtle changes, sdLDL-c decreases, and IbLDL-C increases, [11] which has little to do with AS. The mechanism of affecting LDL-C is not clear now. We can hypothesize that it may be caused by the ketogenic effect caused by the massive excretion of glucose. The liver transports cholesterol to various organs of the body using LDL to meet energy needs. But this can't explain the change of subspecies of LDL-C, which is a fascinating but puzzling alteration that needs further research. We predict that though the total amount of LDL increases, the risk of suffering from AS still decreases.

SGLT2 inhibitor will bring no reversion to the atherosclerotic or fat accumulation that has already occurred, however, the preventive effect brought by lipid regulation should be paid attention to, which may become a valuable role in clinical application.

4. Changes in myocardial metabolism

The function that regulating lipid metabolism will also bring some subsequent metabolic changes, especially in the myocardium. Due to the obvious ketogenic effect, we speculate that the ability of the myocardium to use the ketone body (KB) to provide energy will increase. Noteworthy, the high level of KB is a protection factor for our hearts. When suffering from acute myocardial infarction, KB will inhibit the inflammatory reaction, reduce necrotic area and effectively maintain mitochondrial function. [12] This is also equivalent to providing another layer of protection for our heart. The second

biomarker is uric acid. Experts think that a higher level of uric acid means a worse state of cardiac function. [13] Fortunately, experiments have confirmed that this medicine can reduce the concertation of uric acid which shows a better condition of the myocardium. [14] Except for KB and uric acid, SGLT2 inhibitor will also decrease myocardial blood flow (MBF). [15] The load on the heart is improved and may also have an impact on oxygen consumption. Both of these alterations may be the potential to safeguard our hearts. The harm of acute ischemia and hypoxia will be less because cells are more adaptive to that environment.

Conclusion

SGLT2 inhibitor was regarded as an oral hypoglycemic drug. The most amazing thing is that SGLT2 inhibitors can benefit all patients, whether accompanied by type 2 diabetes. It brings changes in the energy metabolism of the whole body. With more and more cardiovascular benefits being demonstrated, some scholars have recommended adding these drugs to the guidelines for the treatment of heart failure, although the specific mechanism is still waiting for us to explore. What surprises will SGLT2 inhibitor bring to us in the future? We look forward to it with complete confidence.

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