Cardiovascular Actions and Therapeutic Potential of Novel Anti-Diabetic Agents: A Focus on the Endothelium.

The current epidemic of overweight/obesity has led to a marked increase in insulin resistance/hyperinsulinemia, the cardiometabolic syndrome and Type II diabetes. Over 34% of adults and children in the US are overweight while rates of obesity (BMI > 30 kg/m^2) and severe obesity (BMI > 35) are predicted to reach 50% and 25% by 2030, respectively. Consequently, rates of cardiovascular disease will likely also continue to increase. Encouraging findings from a number of recent studies have shown that some anti-diabetes drugs exert cardioprotective benefits that are not fully explained by improved glucose control. These observations have raised interest in whether such agents exert their cardioprotective effects via systemic actions (including decreased blood pressure and weight; anti-inflammatory) or more direct actions on the vasculature.

Interest has been focused on the vascular endothelium. The endothelium lines the inner surface of blood vessels contributing to the regulation of the diameter of arteries, blood flow and permeability, while providing an anti-thrombotic and anti-inflammatory surface. It further releases a variety of paracrine acting factors which regulate the contractile activity of the underlying smooth cells while maintaining the muscle cells in a relatively quiescent, non-proliferative state.

Excessive stiffening of the vasculature and endothelial cell dysfunction have both been shown to be predictive of future vascular disease. Stiffening of the vasculature being typically measured by pulse wave velocity and endothelial cell (EC) function by assessing vasodilation to infused agents or transient occlusion (reactive hyperemia). Indeed, these pathological changes are closely related, with endothelial dysfunction contributing to vascular remodeling and stiffening through several mechanisms including reduced bioavailability of nitric oxide (NO), increased active vascular tone and alterations to the extracellular matrix.

A number of clinical studies have assessed indices of EC function in human subjects treated with sodium-glucose transport protein 2 (SGLT2) inhibitors. While several of these studies have reported the inhibitors to improve EC function some have not; notably a recent multi-center randomized double blind trial reported that 24 weeks of empagliflozin did not improve EC function in subjects with T2D. This latter study assessed EC function by non-invasive peripheral tonometry while several of the positive studies examined brachial artery FMD. Although both methods assess EC function in response to a hyperemic challenge, they reflect contributions from differing vascular compartments and neither can be considered a pure endothelial cell response. Data from experimental animal models (diabetes and diet-induced obesity) more consistently suggest the SGLT2 inhibitors improve EC function through enhanced NO bioavailability and amelioration of oxidative stress, inflammation and indicators of fibrosis. Both clinical and experimental studies have also provided evidence for SGLT2 inhibitors being effective in preventing stiffening of the walls of large arteries.

In experimental models of cardiometabolic syndrome alterations to the mechanical properties of endothelial cells, such as stiffening of the cortical cytoskeleton and loss of the glycocalyx, contribute to the development of remodeling and overt stiffening of the vascular wall. At the mechanistic level, increased activity of the endothelial cell form of the amiloride sensitive epithelial Na^+ channel (EnNaC) occurs in response to mineralocorticoid receptor activation and hyperinsulinemia in part through serum and glucocorticoid regulated kinase (SGK1). Increased EnNaC activity leads to enhanced Na^+ influx, cortical actin polymerization and impaired function of endothelial nitric oxide synthase (eNOS) resulting in decreased NO bioavailability. Interestingly, experimental animals fed an obesogenic Western Diet and treated with SGLT2 inhibitors show improved EC function and NO bioavailability, reduced inflammation in association with decreased levels of EnNaC and SGK1.

Collectively, the available data support beneficial actions of SGLT2 inhibitors on improving EC function and decreasing pathological vascular stiffening. Questions remain as to their exact mechanisms of action, particularly at the level of vascular cells.