SGLT2 expression in the left ventricle of cardiac patients is correlated with low-grade inflammation involving the pro-oxidant AT1R/NADPH oxidases/SGLT2 crosstalk: potential role in heart failure

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Introduction: Clinical studies showed that sodium-glucose co-transporter2 inhibitors (SGLT2i) have beneficial effects in heart failure patients regardless of ejection fraction and diabetes. Such cardiac diseases are often characterized by low-grade inflammation and impaired endothelial coronary microcirculation function. Recently, angiotensin II and TNF-α were shown to induce SGLT2 expression in endothelial cells (ECs) to sustain oxidative stress leading to endothelial dysfunction. However, the role and function of SGLT2 in the human left ventricle (LV) remain unclear. Therefore, this study evaluated the expression of SGLT2 in the LV of patients with cardiac diseases and, if so, determined the cellular localization, the underlying mechanism and the functional role.

Methods: Human LV biopsies were collected from 20 patients subjected to valve surgery at the Nouvel Hôpital Civil, Strasbourg, France. Expression levels of targets were determined by RT-qPCR and Western blot analysis, the in situ tissue localization by immunofluorescence (IF) staining and oxidative stress by dihydroethidium staining.

Results: RT-qPCR analysis of LV revealed variable SGLT1 and SGLT2 mRNA levels with no significant correlation. However, SGLT2 mRNA expression showed a positive correlation with those of pro-inflammatory markers (IL-1β, IL-6, TNF-α, MCP-1 and CD68), AT1R, and VCAM-1. Western blot analysis confirmed the heterogenous SGLT2 protein expression level in LV with a difference up to 3.5-fold among the specimens. SGLT2 protein levels showed a positive correlation with markers of oxidative stress (phospho-p65 NF-κB, AT1R, nitrotyrosine) and markers of ECs activation (VCAM-1, ICAM-1), and a negative correlation with levels of eNOS. Further, immunofluorescence analysis of LV cryosections showed SGLT2 staining in the endothelium of the coronary microcirculation, as indicated by its co-localization with the endothelial cell marker CD31, and throughout the heart tissue. SGLT2 signals were also observed in areas showing IF signals for TNF-α, phospho-p65 NF-κB, CD68 and VCAM-1 suggesting that SGLT2 expression is localized to sites of inflammation. LV specimens with high SGLT2 protein levels showed elevated levels of oxidative stress, which were inhibited by N-acetylcysteine, VAS-2870, perindoprilat, losartan, empag列cin, and infliximab.

Conclusions: The findings indicate that endothelial and cardiac SGLT2 expression in the LV of cardiac patients is associated with low-grade inflammation and oxidative stress. They further indicate that the pro-inflammatory cytokines/AT1R/NADPH oxidases/SGLT2 crosstalk contributes to sustain a pro-oxidant state. Thus, SGLT2 inhibitors might ameliorate HF by mitigating the low-grade inflammatory-related pro-oxidant state and, hence, preserve the crucial endothelial control of the cardiomyocyte function in the LV.