Cardiac sodium/hydrogen exchanger (NHE11) as a novel potential target for SGLT2i in heart failure

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Background: Despite the cardiac benefits of sodium/glucose cotransporter 2 inhibitors (SGLT2i), their basic of action remains unclear. Sodium/hydrogen exchanger (NHE) has been proposed as mechanism of action of SGLT2i, but there are controversies related to its function and expression in heart failure (HF).

Purpose: We hypothesized that sodium transported-related molecules could be altered in human HF and they could be modulated through SGLT2i.

Methods: Transcriptome-level differences in genes involved in sodium transport between HF and control (CNT) were investigated in 36 heart samples with RNA-sequencing technology (HF, n=26; CNT, n=10). In addition, NHE11 and NHE1 protein levels were determined in 80 heart samples (HF, n=70; CNT, n=10) by ELISA assay. Furthermore, the effect of empagliflozin on NHE11 mRNA levels in rat left ventricular tissue (n=22) was studied through RT-qPCR.

Results: We observed alterations in several genes involved in sodium transport. Among them the overexpression in SLC9C2 (p=0.005) and SCL9A1 (p=0.020) genes, which encode the NHE11 and NHE1 proteins, respectively. In addition, cardiac protein levels of these molecules were determined. We found a significant increase in the concentration of NHE11 (p=0.042) and NHE1 (p=0.018) in HF. Moreover, NHE11 levels were correlated with left ventricular diameters. Due to the relevance of NHE11 changes observed, we studied the effect of SGLT1 on its expression. NHE11 mRNA levels were reduced in rats treated with empagliflozin (p=0.010).

Conclusions: Our findings show alterations in several sodium transport, reinforce the importance of these channels in HF progression. We described upregulation in NHE11 and NHE1 in HF patients, but only NHE11 correlated with cardiac dysfunction. In addition, the most relevant finding is the change observed in the expression of the unknown NHE11 after treatment with empagliflozin. These results propose NHE11 as a potential target of SGLT2i in cardiac tissue.