CHARACTERIZATION OF MYOCARDIAL SODIUM–GLUCOSE COTRANSPORTER 1 EXPRESSION IN HEART FAILURE

PhD thesis

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1. Introduction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors – antihyperglycemic agents that block SGLT2 in the kidney – have become the backbone therapy for heart failure (HF) and reduced ejection fraction (EF) irrespective of type 2 diabetes mellitus (T2DM). The exact mechanism of action is unclear. Interestingly, individuals with partial SGLT2 dysfunction are not protected from the development of HF. SGLT2 is not expressed in the heart, its genetic knockdown in mice does not protect from myocardial or renal ischemic injury. SGLT2 inhibitors non–specifically block SGLT1, which has recently been identified as a major glucose transporter in the heart besides glucose transporter 1 and 4 (GLUT1 and 4). Importantly, persons with partial SGLT1 dysfunction are protected from the development of HF and live longer as compared with controls. Knockdown of SGLT1 in mice prevents the development of HF and protects from myocardial, renal, and cerebral ischemic injury. Therefore, it is relevant to characterize myocardial SGLT1 expression in HF.

2. Objectives

We hypothesized that myocardial SGLT1 expression is increased in HF and correlates with disease severity.

First objective: To characterize myocardial left ventricular (LV) SGLT1 expression in controls and patients with HF and assess its correlation with the echocardiographic severity of HF.

Second objective: To assess LV SGLT1 expression in two distinct small animal models of HF and investigate its association with the extent of nitro–oxidative stress.

3. Methods

3.1. Study in patients with end–stage HF

Overall, 80 LV samples were used from the Transplantation Biobank of the Heart and Vascular Center. Of these, control LV samples (n=9) were obtained from patients undergoing surgical mitral valve replacement due to isolated mitral valve regurgitation with otherwise preserved LV function and no relevant comorbidities. The remaining LV samples were obtained from end–stage HF patients (n=71) during orthotopic heart transplantation. These patients were divided into subgroups based on the etiology of HF (hypertrophic cardiomyopathy, HCM; dilated cardiomyopathy, DCM; ischemic heart disease, IHD with or without T2DM) and whether cardiac resynchronization therapy (CRT) was received.

3.2. Study in rats with severe HF

Overall, 48 male Wistar rats were included in the study. Two distinct rat models of severe HF were used. In the first model, chronic pressure overload was induced via *transverse aortic constriction* (TAC, n=12) with 14–week follow–up. Age and sex–matched sham–operated rats served as controls (Sham-T, n=12). In the second model, chronic volume overload was induced via *aortocaval fistula* (ACF, n=12) with 24–week follow–up. Age and sex–matched sham–operated rats served as controls (Sham-A, n=12). In both models, the development of LV hypertrophy was followed by serial echocardiographic measurements (LVmass), and at the end of follow–up, invasive LV pressure–volume analysis was performed, and LV samples were harvested.

3.3. Molecular and histological measurements

Relative mRNA expression was quantified with quantitative real–time polymerase chain reaction (qRT–PCR). The following targets were assessed in human LV samples: the glucose transporters SGLT1, SGLT2, GLUT1, and GLUT4. The following targets were assessed in rat LV samples: the pathological hypertrophy markers β and α–myosin heavy chain (β/α–MHC ratio). Data were normalized to the expression of the housekeeping glyceraldehyde–3–phosphate dehydrogenase (GAPDH).

Relative protein expression was quantified using Western blotting. The following targets were assessed in human LV samples: the glucose transporter SGLT1; the master regulator extracellular signal–regulated protein kinase 1/2 (ERK1/2, ratio of phosphorylated [P–ERK1/2] and total ERK1/2). The following targets were assessed in rat LV samples: SGLT1; ERK1/2 (ratio of P–ERK1/2 and total ERK1/2); and the pro–oxidative enzyme NADPH oxidase 4 (Nox4). Data were normalized to the expression of the housekeeping GAPDH.

Immunohistochemical analysis was performed in human LV samples to analyze the cell types that express SGLT1 in the heart. Localization of SGLT1 in human cardiomyocytes was assessed using immunofluorescence. In rat LV samples, staining against nitrosative stress marker 3–nitrotyrosin (3–NT) and the oxidative stress marker 4–hydroxy–2–nonenal (4–HNE) was performed to quantify the extent of myocardial nitro–oxidative stress.

3.4. Statistical analysis

Values are expressed as mean ± standard error of the mean (SEM) for continuous variables. Student *t*–test with Welch's correction or Mann–Whitney *U* test was performed to assess the significance of difference between two groups. One–way analysis of variance (ANOVA) with Welch's correction (with Dunnett T3 post hoc test) was performed if more than two groups were analyzed. Analysis of covariance (ANCOVA) was employed to quantify the observed differences in the human study after adjusting for age, sex, and body mass index (BMI). To analyze the temporal development of LV hypertrophy (LV mass) in the rat models, mixed–effects ANOVA was conducted. In all cases, Spearman's *rho* (r_s) was computed for all correlation analyses. The two–tailed $P<0.05$ was considered as the threshold for significance in all cases.

4. Results

4.1. Study in patients with end–stage HF

As expected, patients with end-stage HF had substantially reduced EFs compared with healthy controls.

As compared with controls, patients with DCM, IHD, and IHD–T2DM had significantly higher LV SGLT1 mRNA expression (Figure 1). In case of patients with HCM, there was no significant difference. According to ANCOVA, these differences in LV SGLT1 expression persisted even after adjusting for age, sex, and BMI ($P=0.024$). While GLUT1 mRNA expression showed a similar upregulation in the above HF groups, these differences disappeared after correcting for age, sex, and BMI. GLUT4 expression showed no differences in the studied groups.

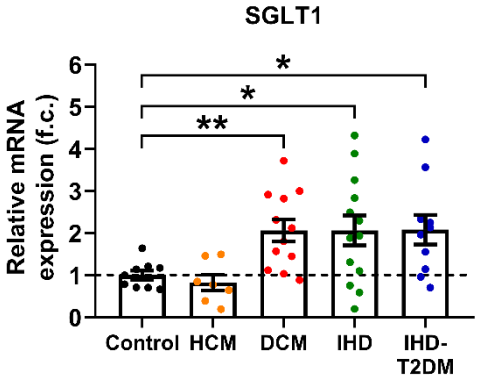

Figure 1. Myocardial LV SGLT1 mRNA expression.

Unlike those of GLUT1 and GLUT4, LV SGLT1 mRNA expression positively correlated with the severity of LV dilation (LV end–diastolic diameter, LVEDD) and systolic dysfunction (EF) (Figure 2).

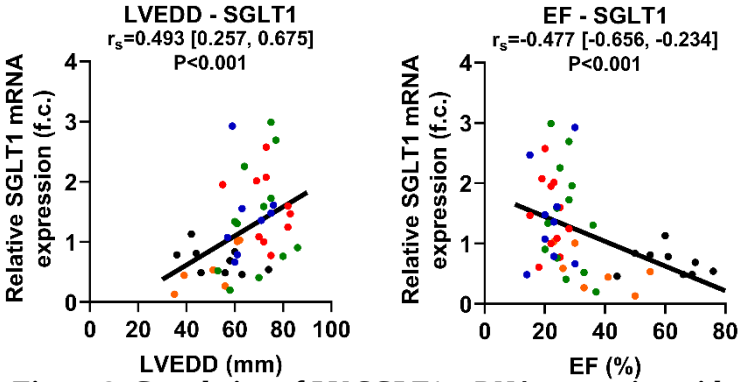

Figure 2. Correlation of LV SGLT1 mRNA expression with LV dilation (LVEDD) and LV systolic function (EF).

These correlations remained significant even after adjusting for age, sex, and BMI.

On the protein level, LV SGLT1 expression was significantly higher in patients with DCM, IHD, and IHD–T2DM (Figure 3.) The activity of the survival kinase ERK1/2 was lower in the same patient groups.

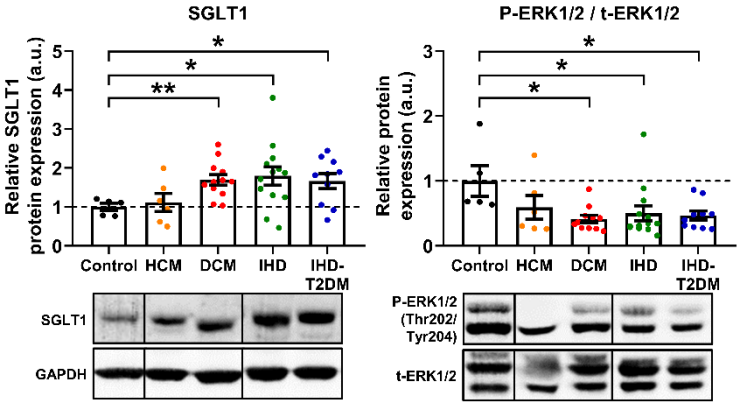

Figure 3. Relative protein expression of LV SGLT1 and the activating phosphorylation of the master regulator ERK1/2.

The correlation between LV SGLT1 expression and the severity of LV dilation (LVEDD) and systolic dysfunction (EF) was evident on the protein level, as well (Figure 4).

Immunohistochemical analysis showed that the primary sources of SGLT1 expression in the heart were cardiomyocytes, whereas fibrotic and adipose tissues showed no relevant SGLT1 positivity. Immunofluorescent staining revealed that SGLT1 resides in the sarcolemma of cardiomyocytes, as it co–localized with the membrane marker Na–K–ATPase (Figure 5).

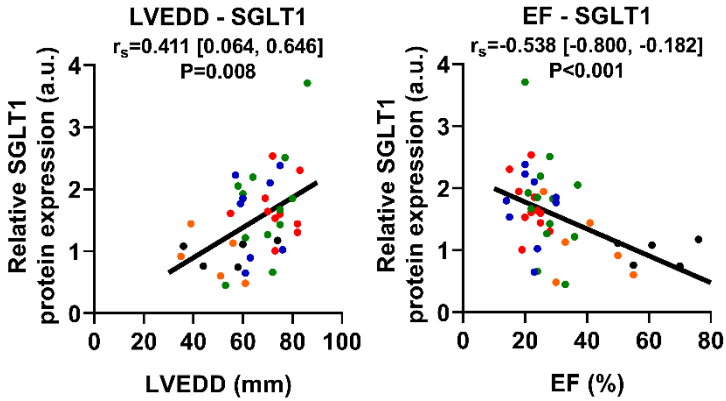

Figure 4. Correlation of LV SGLT1 protein expression with LV dilation (LVEDD) and LV systolic function (EF).

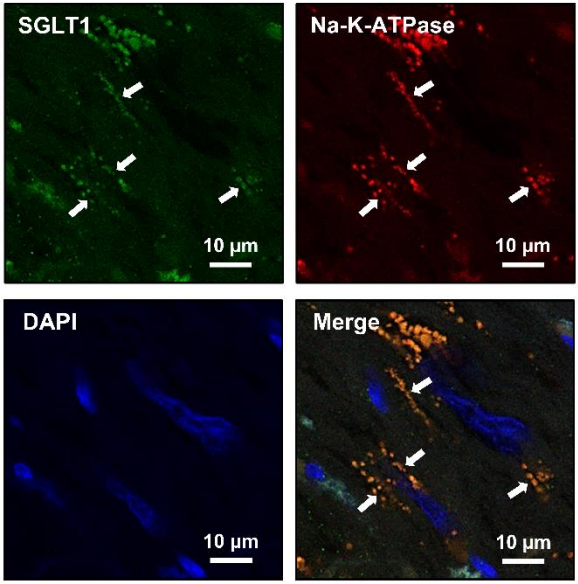

Figure 5. Immunofluorescent staining against SGLT1 and the membrane marker Na–K–ATPase, visualization of nuclei (DAPI), and the merge of these images in.

Interestingly, DCM patients who were on CRT had significantly reduced LV SGLT1 protein expression compared with those who were not on CRT (Figure 6.). Again, the activating phosphorylation of ERK1/2 changed to the opposite direction, being significantly higher in patients with DCM on CRT (Figure 6.). SGLT1 expression in other HF was similar regardless of CRT.

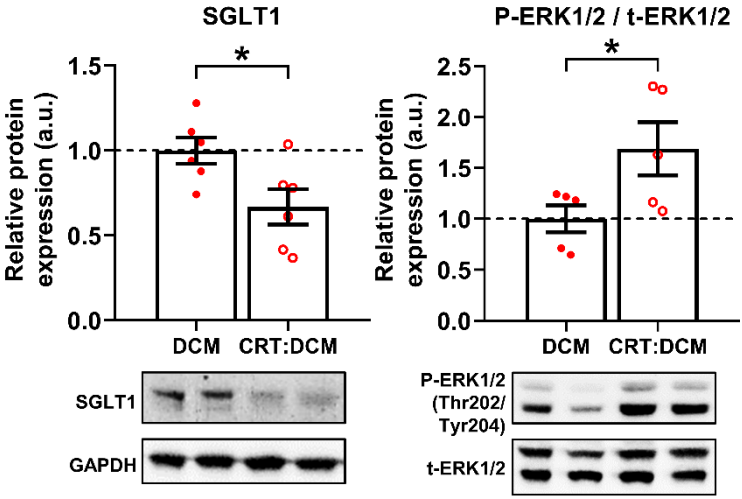

Figure 6. Effect of CRT on LV SGLT1 protein expression and on the activating phosphorylation of the survival kinase ERK1/2 in patients with DCM.

4.2. Study in rats with severe HF

Rats with chronic pressure (TAC) and volume (ACF) overload developed significant LV hypertrophy (LVmass), and ultimately HF in contrast with age and sex–matched sham–operated controls. Myocardial β/α–MHC ratio was significantly upregulated in both types of HF.

In the failing hearts of TAC and ACF rat models, LV SGLT1 protein expression was significantly upregulated compared with controls. Furthermore, the pro–oxidative enzyme Nox4 showed a comparable upregulation. In rats with TAC, ERK1/2 phosphorylation was preserved (which corresponds to a reducing tendency after an initial upregulation), but it was significantly reduced in ACF rat hearts (Figures 7. and 8.).

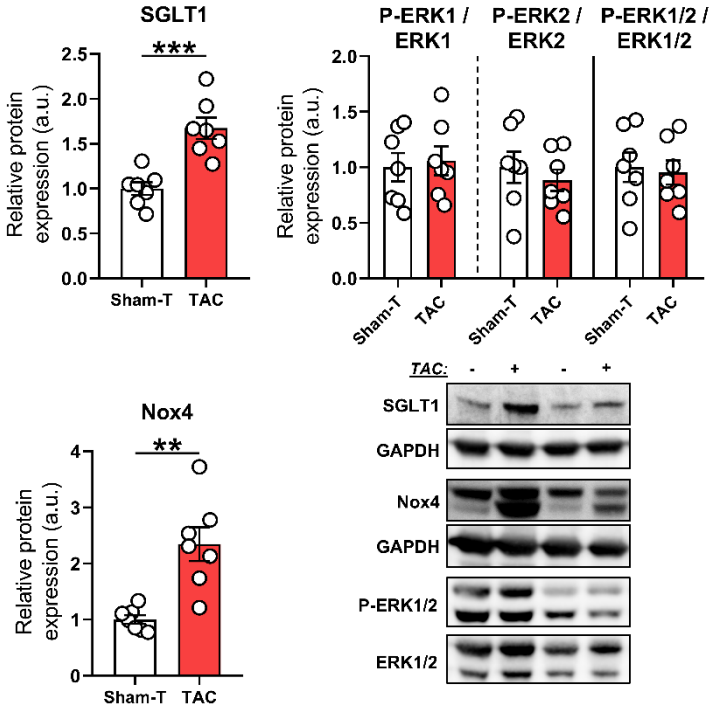

Figure 7. Myocardial LV SGLT1 and Nox4 expression, and the activating phosphorylation of ERK1/2 in rats with pressure–overload (TAC) induced HF and controls.

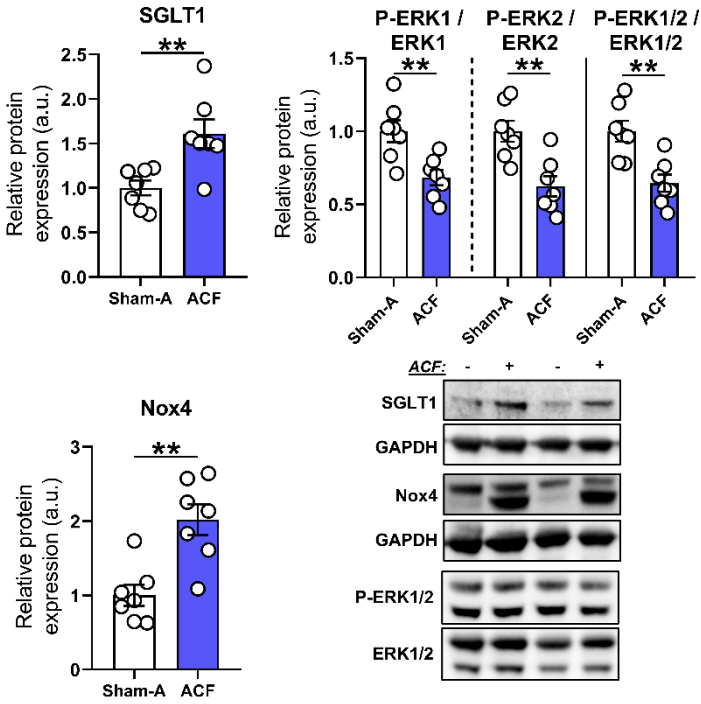

Figure 8. Myocardial LV SGLT1 and Nox4 expression, and the activating phosphorylation of ERK1/2 in rats with volume–overload (ACF) induced HF and controls.

The protein expressions of LV SGLT1 and the pro–oxidative enzyme Nox 4 showed a significant positive correlation in the respective groups (Figure 9.). Immunohistochemical staining against the nitrosative stress marker 3–NT and the oxidative stress marker 4–HNE, respectively, returned a more intense signal in TAC and ACF failing hearts as compared with controls, suggesting increased nitro–oxidative stress.

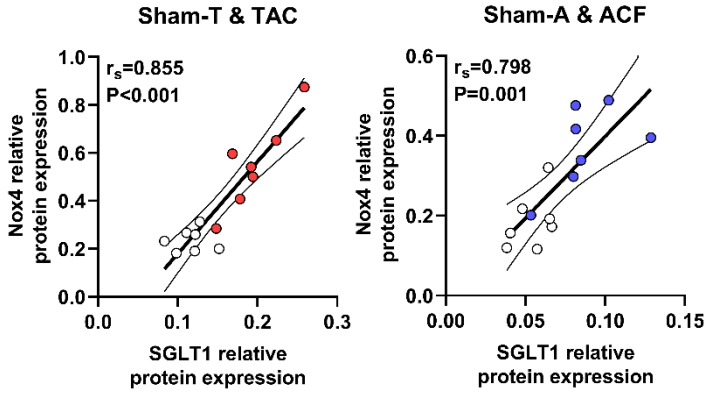

Figure 9. Correlation between the protein expressions of LV SGLT1 and the pro–oxidative enzyme Nox4 in the two experimental study groups.

Accordingly, in failing rat hearts, higher LV SGLT1 protein expression correlated robustly with increased nitro–oxidative stress (Figure 10.)

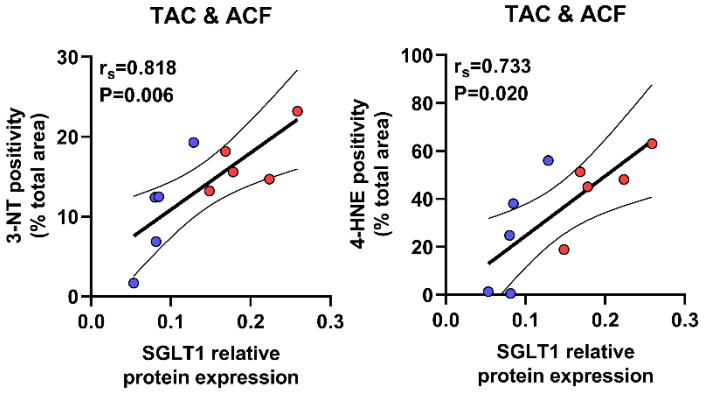

Figure 10. Correlation between LV SGLT1 protein expression and the extent of myocardial nitro–oxidative stress in failing rat hearts.

5. Conclusions

The LV expression of SGLT1 is upregulated in patients with HF (except in HCM) and correlates with LV dilation and systolic dysfunction. Hence, LV SGLT1 expression might be a tissue marker of HF. Such increase in LV SGLT1 expression can be evoked irrespective of the nature of hemodynamic overload and corresponds to more severe myocardial nitro–oxidative stress. Since SGLT2 inhibitors non–specifically block SGLT1, its increased myocardial expression in HF should be accounted for when interpreting the salutary effects of SGLT2 inhibitors in HF.

6. Bibliography of the candidate's publications

6.1. Publications directly related to the present thesis (Σ IF=23.834)

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