ABSTRACT

Long-chain fatty acids (LCFA) are the primary energy source in the myocardium and an imbalance in the LCFA and glucose utilization could cause cardiovascular diseases. More than 50% of LCFA uptake by the heart is mediated by the fatty acid translocase CD36 and disruption of its function has been shown to impair cardiovascular functions. The spontaneously hypertensive rat (SHR) harbors a deletion variant of the Cd36 gene that results in reduced LCFA transport into myocytes. Therefore, the main aim of this thesis was to investigate the importance of a functional CD36 to sustain normal physiological functions of the heart. We used SHR and two genetic modified SHR strains, the congenic SHR-4 and the transgenic SHR-Cd36, with fully functional CD36. They differ in the CD36 expression and in the manner how they were derived from the SHR.

CD36 has been proven to play a role in the pathogenesis of insulin resistance. Therefore we analyzed the effect of a functional CD36 on insulin resistance and protein kinase C (PKC) expression, which is known to be involved in the mechanism of insulin resistance, in the heart of SHR-4 and SHR. We showed that the SHR-4 had lower serum free fatty acids (FFA) and triacylglycerols (TAG) concentrations, indicating improved insulin sensitivity. Furthermore, SHR-4 had increased PKC ε expression when compared to the SHR. High sucrose diet (HSD), applied for 14 days, caused the accumulation of heart TAG in the SHR, while increased PKC δ and decreased PKC ε expression was found in the SHR-4. These findings suggest that CD36 in the SHR-4 is associated with reduced insulin resistance, in which PKC δ and ε may play a role.

Fatty acids (FA) are known to be arrhythmogenic. Using the SHR-Cd36, with a wild-type Cd36, we proved that the insertion of Cd36 onto the SHR genome increases the severity and duration of arrhythmias but lowers the myocardial infarct size after coronary occlusion. In addition, we also showed that the higher arrythmogenesis in the SHR-Cd36 is independent of FA uptake but it is rather caused by to increased sensitivity of the β-adrenoceptors (β-AR) signaling pathway documented by higher β-AR density, increased expression of adenylyl cyclase and protein kinase A. Taken together, we proved that the wild-type Cd36 affects the ischemia/reperfusion tolerance in the SHR in β-AR signaling pathway dependent manner.

It can be concluded that the CD36 function plays an important role in various pathophysiological conditions of the heart, including insulin resistance and arrhythmias, which are dependent on PKC isoforms and the β-AR signaling pathway, respectively.