Involvement of Proteasome- and Macrophage M2-mediated Response in the Protection Afforded by Telmisartan Against the Acute Myocardial Infarction in ZDF Rats with Metabolic Syndrome

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This study investigated the involvement of proteasome and macrophage-mediated response in the protection afforded by telmisartan against the acute myocardial infarction (AMI) in Zucker Diabetic Fatty (ZDF) rats with metabolic syndrome.
ZDF rats were treated for three weeks with telmisartan at doses of 2, 7 and 12 mg/kg/day. After treatment, rats were subjected to a 25 min occlusion of the left descending coronary artery followed by 2 h reperfusion (I/R) (Rinaldi B et al., 2012) . At the end of the I/R period biochemical and histological evaluations were done.
Telmisartan reduced the extension of the infarct size in a dose-dependent fashion. A 28% and 45% decrease in IS/AR ratios were observed in ZDF rats treated with 7 and 12 mg/Kg/day telmisartan, respectively. Interestingly, following telmisartan treatment there was a change in the profiling of the cytokinome and chemokinome within the cardiac tissue. Indeed, IL1-β, IL-6, IL-13, IL-17, MIP-1α and MIP-1β decreased as evidenced by specific Cytokine Array. This change in the cytokines profile was paralleled by a reduction of the expression of proteasome subunits 20S and 26S within the cardiac specimen. Particularly, these subunits were found reduced by sub-maximal dose of telmisartan (7 mg/Kg/day telmisartan for 3 weeks) of 75 % and 50% respectively, as evidenced from semi-quantitative western blot. In conjunction with the reduction of the damage from I/R we observed an increased M2 macrophage phenotype in the infarcted tissue.
In conclusion, treatment of ZDF rats for three weeks with telmisartan, a dual angiotensin II receptor antagonist and partial PPAR-γ receptor agonist, resulted in a significant reduction of myocardial damage induced by I/R possibly due to a reduced activity of the Proteasome system which in turn reduces the expression of the main pro-inflammatory cytokines and chemokines related to the elevated presence of macrophage M2 within the cardiac tissue with respect to the non-treated control.

Rinaldi B et al. (2012). Diabetes Obes Metab.14, 320-8