Glut4 expression in pro-atherogenic monocytes is associated with estrogen induced ROS formation

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Background: Glucose transporter (GLUT) 4 was shown to be expressed on monocytes with dynamic alterations. Moreover, increased formation of monocyte related reactive oxygen species (ROS) is an important marker for atherosclerosis and estrogen is known to increase ROS. However, the impact of estrogen on human monocytes have not been investigated. This is of great importance as a high number of aging women receive hormone replacement therapy (HRT) due to meno-pause symptoms. This was shown to be associated with high risk for ischemic events. In this study, we investigated the impact of estrogen on human monocytes about membrane expression of GLUT4 and ROS formation.

Methods: In this pilot study, we investigated human leukocytes from 88 healthy volunteers (54 female and 34 male) and 114 patients (56 female and 58 male) treated in the department of Cardiology, Pneumology and Vascular medicine, University Hospital Düsseldorf. Buffy coat was extracted out of whole blood by centrifugation and analysed by flow-cytometry. Amount of CD14+ and CD16+ monocytes was measured in % of all leukocytes in all participants. ROS and GLUT4 expression were assessed for monocyte type in dependence from increasing estrogen concentrations in a sub cohort by in-vitro incubation representing physiological peak and HRT concentrations (0, 500 and 2000 pM).

Results: Mean age of healthy volunteers was 31.2 years. Mean age of patients was 75.9 years. In patients, 51% were male, 58% had arterial hypertension, 33% diabetes mellitus type II, 16% were smokers and 19% were obese. Antiatherogenic monocytes (CD16+) were stable in males but decreased with age in females (female: r=-0.3130 p=0.0010; male: r=-0.1011 p=0.3946). In contrast, pro-atherogenic monocytes (CD14+) increased with age in females (female: r=0.4013 p=<0.0001; male: r=0.09135 p=0.4389). Increasing estrogen concentrations induced ROS formation in all monocytes in a dose dependent manner (0 – 947±124, 500 - 1312±258, 2000 - 1248±629 geometric mean, p=0.0327 [one-way ANOVA]). Separation in CD14+ and CD16+ monocytes revealed that this effect was only driven by increase in CD14+ monocytes (0 - 1021±325, 500- 1160±239, 2000 – 513 geometric mean, p=0.0179), whereby CD16+ monocytes did not show relevant increase. GLUT4 membrane expression was inversely related to increasing estrogen levels with decrease in CD14+ (0 - 578±81, 500- 498±55, 2000- 507±41 geometric mean, p=0.0131) and numerical reduction in CD16+ monocytes by high estrogen levels (0- 592±77, 500 - 544±80, 2000- 537±72 geometric mean, p=0.0784)

Conclusion: In this study, we could show that high estrogen levels induce decrease of GLUT4 membrane expression in human monocytes. This might be associated with increased ROS formation in pro-atherogenic CD14+ monocytes which are already increased with age in women. This might reflect a relevant mechanism for the increased rate of ischemic events by HRT.