S1P content as a characteristic of the cardioprotective properties of HDL in coronary heart disease and diabetes mellitus

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Background: Many basic science studies have demonstrated the cardioprotective effect of high-density lipoprotein (HDL). At the same time, several clinical studies in which plasma levels of HDL were pharmacologically increased showed no benefit in cardiovascular risk patients. Accordingly, HDL quantity seems to be less important than HDL quality. Many beneficial effects of HDL are attributed to the bioactive sphingolipid S1P in HDL (HDL-S1P).

Purpose: In this study, we are now investigating a) the cardioprotective properties of HDL of different patient groups and b) the possibility of loading S1P to restore cardioprotection that may be lacking.

Methods: HDL was extracted from plasma of diabetic (dmHDL), as well as CHD patients (CHD-HDL) and healthy subjects (healthy HDL) of the same age by ultracentrifugation and injected i.v. into the mouse five minutes before 30 minutes of ischemia (43 mg/KG). This was followed by 24 hours of reperfusion. Systolic cardiac function was determined by ultrasound, infarct size by TTC (2,3,5-triphenyltetrazolium chloride) staining, and S1P levels by mass spectrometry. The level of apolipoprotein M in HDL was determined by ELISA.

Results: Mice treated with healthy HDL showed smaller infarct size and improved ejection fraction (EF) after I/R than control mice (IS: control 42.95±7.40% [n=26] vs. healthy HDL 33.15±4.68% [n=16], p=0.0001; EF: control 33.68±4.49% vs. healthy HDL 40.00±5.74%, p=0.0016). Treatment with CHD-HDL or dmHDL showed no cardioprotective effects compared to control mice (IS: CHD-HDL 42.22±6.53% [n=16], p=0.9863; dmHDL 43.67±7.81% [n=12], p=0.9899). In both cases, the lack of cardioprotection is associated with lowered HDL-S1P levels (total HDL 210.6±32.6 pmol/mg; CHD-HDL 157.6±49.0 pmol/mg, p=0.0073; dmHDL 171.1±64.7 pmol/mg, p=0.0176). Loading the "sick" HDL with S1P restores cardioprotection only in CHD-HDL (IS: CHD-HDL 42.22±6.53% [n=16] vs. CHD-HDL loaded 32.03±6.45% [n=10], p=0.0023), but not in dmHDL (IS: dmHDL 43.67±7.81% [n=12] vs. dmHDL loaded 38.44±5.98% [n=7], p=0.5110). The very low level of apolipoprotein M (ApoM), responsible for S1P binding, could be a reason for this (total HDL 23.45±6.23 µg/mg [n=15] vs. dmHDL 13.79±4.72 µg/mg [n=14], p=0.0007).

Conclusion: We highlighted worsened cardioprotection as another characteristic of HDL dysfunction in CHD and in diabetes. This characteristic was based on a lower HDL-S1P content and could be therapeutically corrected by loading S1P in the case of CHD-HDL. A low content of ApoM in dmHDL may prevent successful restoration of cardioprotection by S1P loading.