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Atheroprotective Mechanisms of High Density Lipoproteins

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11

HDL-induced cardioprotection is independent of the HDL receptor, scavenger receptor B1

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Purpose: High-density lipoproteins (HDL) are atheroprotective. New evidence shows that HDL has widespread actions, including protection against cardiac ischemia reperfusion injury (IRI). This cardioprotective role has been attributed to several constituents of the HDL particle, including apolipoprotein A1 (apoA1) the major protein constituent and sphingosine-1-phosphate (S1P). However, the exact mechanisms of HDL-induced cardioprotection are still unknown and are under intensive investigation. A particular unresolved question remains the specific role of the HDL receptor, Scavenger Receptor BI (SR-BI), in the heart. The latter mediates many of the intracellular effects of HDL.
The aim of this study was to evaluate the specific role of SR-BI in the protective impact of HDL on the heart.

Methods and Results: The effects of HDL on the heart was evaluated in vitro using rat cultured neonatal cardiomyocytes and ex vivo in mice using the isolated heart Langendorff model of IRI (global no flow ischemia 35min, reperfusion 60min). In this model, HDL (400μg/mL) was injected during the first 7min of reperfusion and infarct size was assessed by triphenyltetrazolium chloride (TTC) staining. The specific role of SR-BI was investigated in vitro using specific siRNA facilitated knockdown and ex vivo using SR-BI knockout (SR-BI KO) mice.
We confirmed that SR-BI is expressed in the cardiomyocytes and that HDL binds specifically to these cells. Treatment of cardiomyocytes with HDL induced the activation of several prosurvival signalling proteins, including Akt, STAT3 and ERK1/2 and protected the cells against oxidative stress induced by doxorubicin. Although specific binding of HDL was significantly reduced in SR-BI knockdown cardiomyocytes, activation of the prosurvival pathways was not affected. Similarly, SR-BI knockdown did not reduce the in vitro protective influence of HDL against oxidative stress induced by doxorubicin.
Ex vivo, IRI induced an infarct size of 17.3 $\pm$ 0.6% in isolated hearts of wildtype mice. HDL treatment during the first phase of reperfusion significantly reduced the infarct size by approximately 35% ($p<0.05$). This protective effect induced by HDL is maintained in SR-BI KO mice (40% of infarct size reduction ($p<0.05$) compared to non-treated SR-BI-KO mice).

Conclusion: This is the first time that the specific role of SR-BI in the impact of HDL on the heart is investigated. Our results do not support a role for the HDL receptor SR-BI in the protective influence of HDL. Further investigations will be required to elucidate the exact mechanisms of HDL-induced cardioprotection.