KUPFFER CELL DEPLETION IMPROVES HEPATIC INSULIN SENSITIVITY

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Objectives: We hypothesize that inflammatory cells in the liver participate to metabolic disturbances and hepatic insulin resistance (IR). In a model of high fat diet (HFD)-induced steatosis and IR, we therefore analysed the activation of macrophages and studied the effect of Kupffer cells (KC) depletion on hepatic lipid storage and insulin sensitivity.
Methods: Male mice were fed a standard or a HFD (60% calories from lipids) for 3 days preceded by injection of liposome-encapsulated PBS (controls) or clodronate to deplete KC. Liver macrophage populations (F4/80, CD11b, CD11c and CD68) were evaluated by flow cytometry and immunohistochemistry (IHC). The insulin signalling pathway upon insulin stimulus was analysed by western blot. RT-qPCR was used to examine mRNA expression of macrophage activation, lipid metabolism and inflammatory markers.
Results: Upon HFD, hepatic lipids increased 4-fold and IHC of liver sections revealed enlarged $F4/80^+$ KC in close proximity to fat-laden hepatocytes. FACS analysis demonstrated an increased proportion of activated $F4/80^+CD68^+$ KC. In response to insulin, phosphorylation of insulin receptor and intermediates of the insulin signalling cascade was significantly lower in HFD than in control livers. Liposome-encapsulated clodronate depleted (by 70%) $F4/80^+CD68^+$ KC and restored phosphorylation levels of insulin signalling in HFD-fed animals close to those seen in controls, without affecting hepatic lipid content. PCR analyses showed that increased gene expression of F4/80, CD68, TLR4 seen in HFD-fed animals was blunted by clodronate.
Conclusions: High fat feeding induces steatosis, hepatic IR and an early KC activation. KC depletion by clodronate restores hepatic insulin sensitivity, suggesting that targeting their activation may represent an attractive tool to relieve HFD-induced hepatic IR.