New mechanisms for steroid pro-atherogenic action: up regulation of macrophage LDL receptors, down regulation of cholesterol efflux transporters and increase in intracellular cholesterol stores

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Glucocorticoids are widely used for the therapy of autoimmune and inflammatory disorders, but long term treatment is associated with increased cardiovascular risk. It is commonly believed that the increased prevalence of cardiovascular events in this context is secondary to hyperlipidaemia, diabetes and salt/water retention induced by glucocorticoids.
The aim of the study is to investigate the effect of corticosteroids on macrophages cholesterol metabolism.
THP-1 derived macrophages, normal and low density lipoprotein receptor (LDLr)-lacking fibroblasts and hepatocytes FU5AH were incubated with hydrocortisone (100 mg/ml), as representative agent of the steroid class. Cell cholesterol content and cholesterol efflux were measured through fluorimetric and radioisotopic techniques respectively; LDL uptake was directly observed by confocal microscopy technique; the expression of LDLr receptor, cholesterol transporters ATP binding cassette A1 (ABCA1) and G1 (ABCG1), Scavenger Receptor Type B Class I (SR-BI) and LXR/RXR receptor was evaluated by western blotting. Macrophage cholesterol esterification was measured with radioisotopic technique and thin layer chromatography.
First, we observed that hydrocortisone increases the velocity and degree of LDL internalization in macrophages. Our further results indicate that hydrocortisone-induced increase in macrophage cholesterol uptake is largely mediated by LDLr (cell cholesterol content increase is significantly lower in LDLr-lacking versus normal fibroblasts), which is overexpressed in macrophages and fibroblasts upon hydrocortisone treatment, but not in hepatocytes. Second, we observed that hydrocortisone reduces cholesterol efflux by reducing the activity and expression of ABCA1, ABCG1 and SR-BI cholesterol transporters for cell cholesterol efflux and their regulator LXR/RXR nuclear receptor. Finally, we observed that hydrocortisone increases cholesterol esterification, further opposing to cholesterol discharge from macrophages.
Our results showed that steroids are pro-atherogenic not only because of systemic metabolic effects, but also through the direct dysregulation of cholesterol metabolism in human macrophages, leading to foam cells formation, the principal cells type involved in atheroma development. In particular, hydrocortisone promotes macrophage cholesterol accumulation through multiple molecular mechanisms involved in cholesterol uptake, efflux and storage. Our observations could pave the way to new strategies to counteract steroid pro-atherogenic activity.