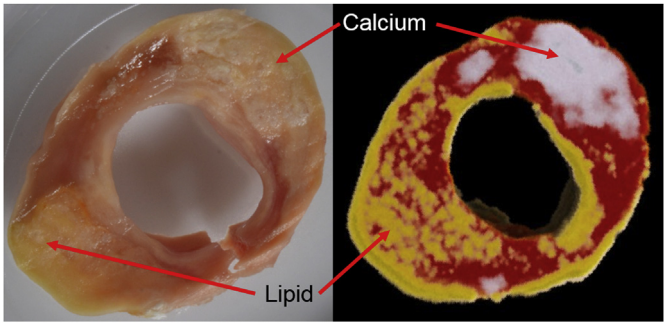

C1-13.05

THE ANTI-ATHEROGENIC POTENTIAL OF LIPOSOME-MEDIATED DELIVERY OF LXR AGONISTS TO MACROPHAGES: A PRECLINICAL VALIDATION STUDY

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Objective: Ligands for the nuclear receptor LXR increase the efflux of cholesterol from macrophages and lower the susceptibility for atherosclerosis. To overcome the hepatic steatosis development associated with systemic LXR agonism and facilitate clinical application of LXR agonists, macrophage-specific LXR activation has to be achieved. Here we performed a proof-of-principle study to show the anti-atherogenic potential of liposome-mediated delivery of LXR agonists to macrophages.
Methods: The synthetic LXR agonist T0901317 was encapsulated into cationic liposomes for use in vitro and in vivo studies.
Results: The ability of T0901317 to stimulate cholesterol efflux genes ABCA1 and ABCG1 in vitro was maintained after encapsulation into liposomes. Peritoneal injection of T0901317-loaded liposomes (5 mg/kg/day) into hyperlipidemic apoE knockout mice for 4 days increased hepatic expression levels of the macrophage-specific LXR target ABCG1 to an equal extent as observed after standard oral dosing with 10 mg/kg/day of the free compound (2.8-fold versus 3.0-fold). In contrast, fatty acid synthase expression was only 2.9-fold higher in T0901317 liposome-treated mice versus 15-fold after oral treatment ($P<0.001$). Treatment of apoE knockout mice with T0901317 liposomes for 8 weeks increased peritoneal cell ABCA1 (2-fold; $P<0.01$) and ABCG1 (10-fold; $P<0.001$) expression levels. Chronic T0901317 liposome treatment did – however – not alter the susceptibility to atherosclerosis as judged from the similar aortic root lesion size and aortic arch gene expression levels of the macrophage marker CD68. Notably, peritoneal cell expression of the PXR target gene CD36 was also >2-fold increased ($P<0.001$) in T0901317 liposome-treated mice. It thus appears that the atheroprotective T0901317-induced increase in macrophage cholesterol efflux may be nullified by the unwanted increase in cholesterol influx associated with T0901317's PXR agonistic action.
Conclusions: In conclusion, our study is the first to show the improved clinical application potential of liposome-mediated delivery of LXR agonists to macrophages over oral/systemic administration of these compounds as the macrophage cholesterol efflux increasing effect is retained in the context of an elimination of the unwanted hepatocyte LXR-mediated metabolic effects.