

## IN VIVO STIMULATION OF LXR INCREASES THE EFFLUX POTENTIAL OF SERA AND PROMOTES THE REVERSE CHOLESTEROL TRANSPORT

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The Liver-X-Receptors (LXR) play a key role in lipid metabolism by acting as regulators of the expression of several genes. In the present study we investigated the in vivo effect of a short term administration of the synthetic LXR agonist T0901317 on reverse cholesterol transport (RCT). The RCT in vivo was quantified by injecting [<sup>3</sup>H]-cholesterol-loaded J774 macrophages into the peritoneum of mice pretreated with T0901317 100mg/kg/day or vehicle for 6 days; 48h later the animals were sacrificed and the radioactive cholesterol content in feces, plasma and liver was measured. To evaluate whether the pharmacological treatment resulted in the modification of serum efflux potential, sera from control and T0901317-treated mice were used as cholesterol acceptors in efflux experiments utilizing cultures of J774 mouse macrophages as model for passive diffusion and ABCA1-mediated efflux, and Fu5AH rat hepatoma cells as model for SR-BI-mediated efflux.

The in vivo stimulation of LXR produced a 2,7 fold increase in the hepatic expression of *AbcA1* and resulted in higher amount of cholesterol in plasma (20310±9260 vs 31397±9672, p<0,05; n=5), in the liver (146247±7763 vs 297034±96853, p<0,05; n=5) and in the feces (30687±4801 vs 50458±8548, p<0,01; n=5) compared to control mice.

Sera from mice administered with T0901317 100mg/kg/day showed an improved ability to promote the release of cholesterol via SR-BI compared to control (13,5±1,5 vs 10,1±1,7; p<0,05). Similarly, cholesterol efflux that occurs by passive diffusion was more efficiently promoted by sera from T0901317-treated mice (15,3±2,1 vs 11,5±1,4; p<0,05). When ABCA1 was upregulated in J774 by cpt-cAMP 0,3mM, sera from the two groups did not significantly differ (14,0±4,9 vs 13,1±1,5). Consistent with these data, the evaluation of profile by FPLC evidenced a slight increase of HDL in plasma derived from mice treated with T0901317, while the analysis of HDL subpopulations revealed that the pharmacological treatment caused the formation of larger particles.

Taken together these results suggest that the in vivo stimulation of LXR caused the increase of cholesterol mobilization from macrophages to the feces, thus improving the RCT process. This effect is at least in part related to the increase of serum efflux potential and to a rearrangement of those fractions of HDL able to promote lipid efflux by passive diffusion and SR-BI-mediated mechanisms.