UP-REGULATING REVERSE CHOLESTEROL TRANSPORT WITH CETP INHIBITION REQUIRES REDUCTION OF APOLIPROTEIN-E RICH HDL LEVELS IN HYPERLIPIDEMIC HAMSTERS

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INTRODUCTION

Cholesteryl ester transfer protein (CETP) inhibition increases the levels of elevated/apoE-rich HDL particles (apoE-HDL). Whether these particles are functional to promote reverse cholesterol transport (RCT) remains unclear. Here we investigated this issue in hyperlipidemic hamsters.

METHODS

• Golden Syrian hamsters were fed a chow or a hyperlipidemic diet (27% fat, 0.5% cholesterol, 0.25% deoxycholate and 10% fructose in drinking water) over 4 weeks. Biochemical parameters were then measured to evaluate the effects of the hyperlipidemic diet.

• Another set of hyperlipidemic hamsters were treated with vehicle, CETP inhibitor torcetrapib 30mg/kg/day alone, berberine 150mg/kg/day alone or the combination of torcetrapib 30mg/kg/day and berberine 150mg/kg/day over 14 days. Biochemical parameters were measured after 10 days of treatment.

• After 11 days of treatment, hamsters were injected i.v. with [3H]-cholesteryl oleate labeled/oxidized LDL (3H-oLDL) to measure in vivo reverse cholesterol transport or with [3H]-cholesteryl oleate labeled/unaltered LDL (3H-LDL) to measure in vivo LDL kinetics.

• In both radioactivity studies, blood was collected continuously to measure plasma 3H-tracer over 72 hours. Hamsters were then sacrificed and liver was harvested to measure hepatic 3H-tracer recovery. Feces were collected over 72 hours to measure 3H-radioactivity and mass in fecal cholesteryl and bile acids fractions.

CONCLUSION AND PERSPECTIVES

• CETP inhibition with torcetrapib significantly increases HDL-C and apoE-HDL levels but does not promote reverse cholesterol transport in hyperlipidemic hamsters.

• Combination of torcetrapib with berberine, a compound known to up-regulate LDL-receptor expression, reduces apoE-HDL levels and promotes reverse cholesterol transport in hyperlipidemic hamsters.

• Stimulating reverse cholesterol transport under CETP inhibition requires reduction of apoE-HDL levels. These findings should be investigated in humans to evaluate the benefits of CETP inhibitors.

RESULTS

1. Effects of the hyperlipidemic diet on biochemical parameters

2. Effects of the hyperlipidic diet on liver parameters

3. Measurement of in vivo reverse cholesterol transport

4. Torcetrapib does not promote reverse cholesterol transport in hyperlipidemic hamsters

5. Berberine increases LDL-CE catabolism and LDL-derived cholesteral favoring in hyperlipidemic hamsters

6. Effects of torcetrapib and torcetrapib+berberine on biochemical parameters

7. Torcetrapib + berberine combination promotes reverse cholesterol transport in hyperlipidemic hamsters

Authors disclosure: F. Briand, Q. Thieblemont, E. Muzotte and T. Sulpice are employees of Physiogenex.