BERBERINE INCREASES LDL-CHOLESTERYL ESTER CATABOLISM AND STIMULATES LDL-DERIVED CHOLESTEROL FECAL EXCRETION IN HYPERLIPIDEMIC HAMSTERS

A-437-0010-00658

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INTRODUCTION

Reduction of low density lipoprotein (LDL) cholesterol levels is a relevant therapeutic strategy to decrease cardiovascular risk. However, whether reducing LDL-cholesterol levels promotes LDL-derived cholesterol fecal excretion remains unknown. To investigate this issue, we evaluated the effects of berberine, a compound known to decrease LDL-cholesterol through up-regulation of hepatic LDL-receptor expression in hyperlipidemic hamsters.

METHODS

- Golden Syrian hamsters were made hyperlipidemic with a 4-week high fat diet, which increased non-HDL-cholesterol levels, CETP activity, liver lipid levels and induced a 35% reduction in LDL-receptor protein expression (all $p<0.05$ vs. chow fed hamsters).
- After 2 weeks of diet, hyperlipidemic hamsters were treated with vehicle or 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 ^{3}H-cholesteryl oleate labeled LDL to measure *in vivo* LDL kinetics. Blood was collected continuously to measure plasma ^{3}H-tracer over 72 hours. Hamsters were then sacrificed and liver was harvested to measure hepatic ^{3}H-tracer recovery. Feces were collected over 72 hours to measure ^{3}H-radioactivity and mass in fecal cholesterol and bile acids fractions.

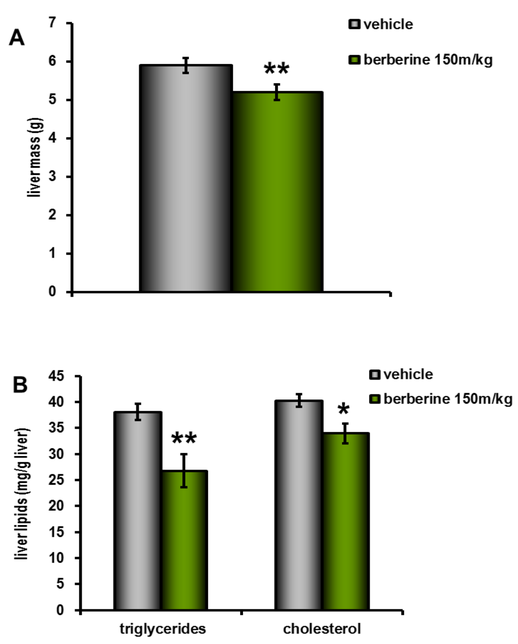
RESULTS

1. Berberine lowers LDL-cholesterol and increases fecal cholesterol excretion

	vehicle	berberine 150 mg/kg
Total cholesterol (g/L)	3.96 ± 0.10	3.04 ± 0.15***
LDL-cholesterol (g/L)	0.93 ± 0.02	0.61 ± 0.06***
HDL-cholesterol (g/L)	2.16 ± 0.15	1.87 ± 0.08
Triglycerides (g/L)	2.95 ± 0.32	1.56 ± 0.23**
CETP activity (pmol/µL/h)	56 ± 3	50 ± 3
Fecal cholesterol (µg/day)	404 ± 24	589 ± 66**
Fecal bile acids (µmol/day)	27 ± 2	23 ± 2

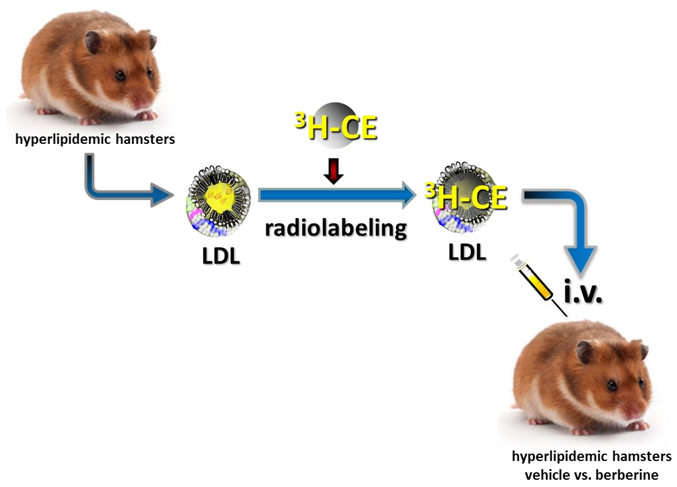
Plasma and fecal parameters in hyperlipidemic hamsters treated with vehicle or berberine 150mg/kg/day (**p<0.01, ***p<0.001 vs. vehicle).

2. Berberine improves liver steatosis



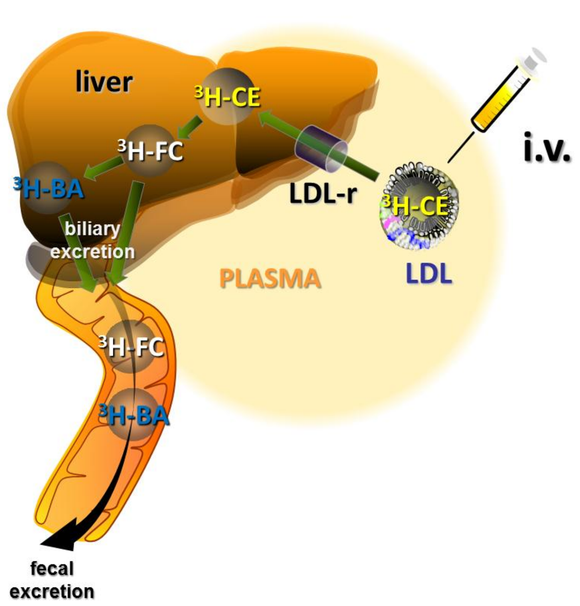
Liver mass (A) and hepatic triglycerides and cholesterol levels (B) in hyperlipidemic hamsters treated with vehicle or berberine 150 mg/kg over 14 days (*p<0.05, **p<0.01 vs. vehicle).

3. LDL radiolabeling procedure



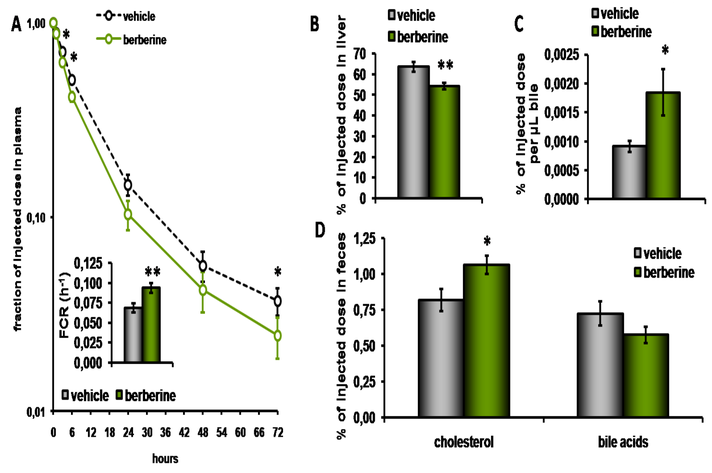
LDL radiolabeling procedure (^{3}H-CE, ^{3}H-cholesteryl oleate)

4. *In vivo* LDL kinetics



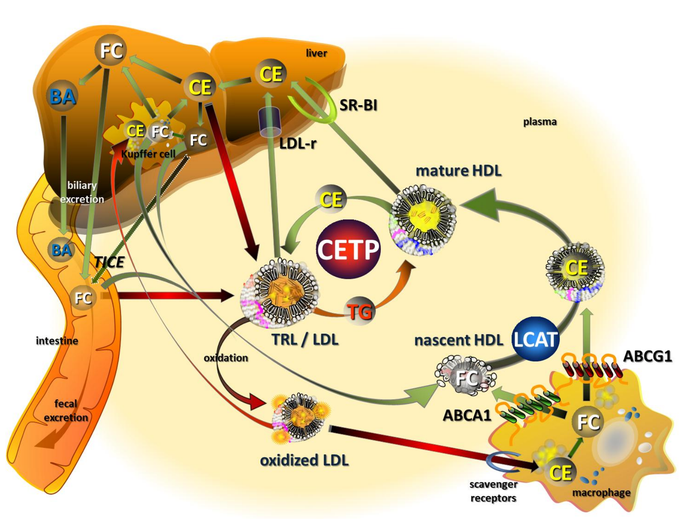
In vivo LDL kinetics (BA, bile acids; CE, cholesteryl esters; FC, free cholesterol; LDL-r, LDL-receptor),

5. Berberine increases LDL-CE catabolism and LDL-derived cholesterol fecal excretion



Plasma ^{3}H-tracer decay curve (A) and ^{3}H-tracer recoveries in liver (B), bile (C) and feces (D) after ^{3}H-cholesteryl oleate-labeled LDL injection in hyperlipidemic hamsters treated with vehicle or berberine 150mg/kg/day (*p<0.05, **p<0.01 vs. vehicle).

6. LDL-cholesterol trafficking in macrophage-to-feces reverse cholesterol transport



Cholesterol trafficking in macrophage-to-feces reverse cholesterol transport (ABCA1, ATP-binding cassette A1; ABCG1, ATP-binding cassette G1; BA, bile acids; CE, cholesteryl esters; CETP, cholesteryl ester transfer protein; FC, free cholesterol; LCAT, lecithin:cholesterol acyl transferase; LDL-r, LDL-receptor; TG, triglycerides; TICE, trans intestinal cholesterol excretion; TRL, triglyceride-rich lipoprotein; SR-BI, scavenger receptor class B type I).

CONCLUSION AND PERSPECTIVES

- Berberine reduces LDL-cholesterol through higher LDL-cholesteryl esters catabolism and stimulates LDL-derived cholesterol fecal excretion in hyperlipidemic hamsters.
- The concomitant reduction of liver steatosis by berberine (e.g. reduction in hepatic cholesterol levels) might be beneficial for LDL-derived cholesterol trafficking towards biliary and fecal excretion.
- Whether other LDL-lowering drugs have similar effects should be investigated.

80th European Atherosclerosis Society Congress , May 25-28, 2012, Milan, Italy .

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This work has been funded by OSEO.