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

François Briand, Quentin Thieblemont, Elodie Muzotte, Thierry Sulpice
Physiogenex, Labège, France

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 3H-cholesterol oleate labeled LDL to measure in vivo LDL kinetics. 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 cholesterol and bile acids fractions.

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

<table>
<thead>
<tr>
<th></th>
<th>vehicle</th>
<th>berberine 150 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>3.86±0.10</td>
<td>3.04±0.10**</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>0.83±0.02</td>
<td>0.81±0.01**</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>2.18±0.15</td>
<td>1.87±0.08**</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>2.95±0.12</td>
<td>1.99±0.22**</td>
</tr>
<tr>
<td>CETP activity (pmol/L)</td>
<td>56±3</td>
<td>58±2</td>
</tr>
<tr>
<td>Fecal cholesterol (mg/day)</td>
<td>40±6</td>
<td>50±0.09**</td>
</tr>
<tr>
<td>Fecal bile acids (mg/day)</td>
<td>27±2</td>
<td>22±2</td>
</tr>
</tbody>
</table>

Plasma and fecal parameters in hyperlipidemic hamsters treated with vehicle or berberine 150 mg/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

4. In vivo LDL kinetics

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

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

CONCLUSION AND PERSPECTIVES
• Berberine reduces LDL-cholesterol through higher LDL-cholesterol 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.