DPP-4 inhibitor sitagliptin improves reverse cholesterol transport through reduced intestinal cholesterol absorption in obese insulin resistant CETP-apoB100 transgenic mice

François Briand1, Rémy Burcelin2, Thierry Sulpice3
1Physiogenex, Labège, 2Laboratoire de Physiologie-Faculté de médecine Rangueil, Inserm U858, Toulouse, France

INTRODUCTION

Type 2 diabetes is characterized by lower HDL-cholesterol (HDL-c) levels, which would impair macrophage-to-faces reverse cholesterol transport (RCT) and thus increase cardiovascular risk. Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glycemic control in type 2 diabetes, but their benefits on RCT remain to be determined. We therefore evaluated the effects of DPP-4 inhibitor sitagliptin on RCT in obese insulin resistant CETP-apoB100 transgenic mice, which exhibit a human-like lipoprotein profile.

METHODS

- CETP-apoB100 mice were made obese, insulin resistant and dyslipidemic with a 60% high fat diet over 3 months. Mice were then treated over 4 weeks with sitagliptin 500mg/kg/day in drinking water or vehicle (n=7/group). Two other groups of mice were also treated with vehicle or metformin 300mg/kg/day orally as a reference compound.

- Intestinal cholesterol absorption was measured after an oral gavage of C-cholesterol labeled olive oil.

- Blood glucose and plasma insulin levels were measured after an oral glucose load.

RESULTS

1. Effects of metformin and sitagliptin on body weight and biochemical parameters

2. Both metformin and sitagliptin improve glucose tolerance

3. Sitagliptin, but not metformin, increases fecal cholesterol mass excretion

4. Sitagliptin increases macrophage-derived cholesterol mass excretion

5. Sitagliptin decreases intestinal cholesterol absorption

CONCLUSION AND PERSPECTIVES

In obese insulin resistant CETP-apoB100 mice, sitagliptin promotes macrophage-to-faces reverse cholesterol transport through lower intestinal cholesterol absorption. The effects of other DPP-4 inhibitors or GLP-1 analogues remain to be evaluated to discriminate potential sitagliptin off-targets from incretin-mediated effects. The potential benefits of DPP-4 inhibition on cholesterol metabolism should be further investigated in patients with type 2 diabetes.