Prostaglandin E receptor subtype 4 regulates bile acid synthesis and its activation protects against hypercholesterolemia

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The liver plays a central role in maintaining cholesterol homeostasis by regulating de novo cholesterol biosynthesis, reverse cholesterol transport and bile acid synthesis. Prostaglandin E receptor subtype 4 (EP4) knockout mice develops spontaneous hypercholesterolemia but the detailed mechanisms by which EP4 affects cholesterol homeostasis remains unexplored. To determine the cause of hypercholesterolemia in EP4 knockout mice, we focused on the role of EP4 in regulating the synthesis and elimination of cholesterol. The absence of EP4 significantly decreased hepatic bile acid synthesis and their subsequent excretion in stool, as supported by a 26.2% loss in total bile acids in liver and a 27.6% loss in fecal bile acid content. Deletion of EP4 negatively regulated bile acid synthesis through repression of phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2)-mediated cholesterol 7 α -hydroxylase (CYP7A1) expression and that the hypercholesterolemia in EP4 knockout mice was due to a defect in cholesterol conversion into bile acids. Deletion of EP4 also increased de novo cholesterol biosynthesis and altered cholesterol fluxes in and out of the liver. To investigate whether or not activation of EP4, by increasing bile acid excretion, might serve as a potential novel therapeutic approach for lowering plasma cholesterol, mice were treated with CAY10580 (a pharmacological EP4 agonist, 200 ug/kg body weight/day i.p) for three weeks. CAY10580 treatment markedly alleviated hypercholesterolemia (by 28.5%) and slowed the body weight gain (by 25.3%) in high fat diet (HFD) challenged mice through enhancing endogenous bile acid synthesis and their fecal excretion. In summary, these findings demonstrated that EP4 plays a critical role in maintaining cholesterol homeostasis by regulation the synthesis and elimination of bile acids. Activation of EP4 appears to be an effective novel strategy to promote disposal in the forms of bile acids in order to lower plasma cholesterol levels and slow weight gain.