Inhibition of the endocannabinoid system alleviates dyslipidemia and attenuates atherosclerosis development

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Background

The cannabinoid type 1 receptor (CB1R) inverse agonist rimonabant was identified and sold as an anti-obesity drug, but withdrawn from the market due to psychiatric side effects. Mechanistically, we have shown that rimonabant potentiates the sympathetic activation of brown adipose tissue (BAT; see figure below). We hypothesized that lowering endogenous endocannabinoid synthesis provides a safe alternative for rimonabant, that can be used in the treatment of both metabolic and cardiovascular disorders.

The aim of the current project is to provide proof that CB1R inverse agonism by rimonabant attenuates dyslipidemia and atherosclerosis in APOE*3-Leiden.CETP transgenic mice, a well-established mouse model for human-like lipoprotein metabolism.

Conclusions

CB1R inverse agonism by rimonabant strongly lowers atherosclerosis development in APOE*3-Leiden.CETP mice. CB1R inverse agonism furthermore stimulates BAT, lowers plasma non-HDL-C and triglyceride levels and potently increases plasma HDL-C levels. Together, these data suggest that increased reverse cholesterol transport as a consequence of BAT activation may be responsible for the lowering in atherosclerosis development (Bartelt & Berbee, Nat Commun 2017).

CB1R inverse agonism increases energy metabolism by activating BAT in diet-induced obese male mice

CB1R inverse agonism decreases body weight and lowers respiratory quotient in lean Western-type diet-fed female mice

CB1R inverse agonism alleviates dyslipidemia in lean Western-type diet-fed female mice

CB1R inverse agonism attenuates atherosclerosis development in lean Western-type diet-fed female mice