Physiogenex
THE METABOLIC DISEASES EXPERTS

HDL / LDL cholesterol turnover

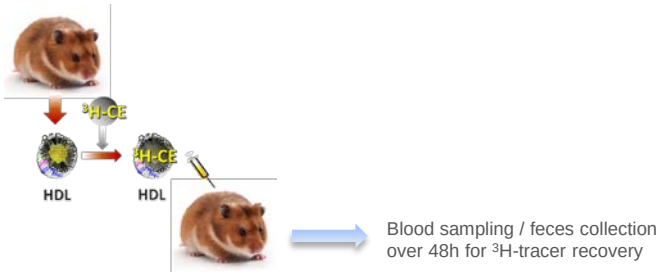
State-of-the-art technique to investigate and quantify the effects of your compound on HDL-c metabolism as well as HDL-derived cholesterol fecal excretion.
HDL-CE kinetics using radioactive labeled tracers is a direct approach to evaluate drugs affecting HDL metabolism and reverse cholesterol transport

Key benefits :

- ✓ Directly detect a beneficial effects of your compound on HDL-c metabolism and HDL-derived cholesterol fecal excretion
- ✓ Direct mechanisms targeted by your compound: how your compound modulates HDL-c levels
- ✓ Essential and robust data to demonstrate that your compound promotes HDL-derived cholesterol fecal excretion and has therefore the potential to prevent atherosclerosis

DESCRIPTION AND PARAMETERS EVALUATED

- Species: mouse, hamster

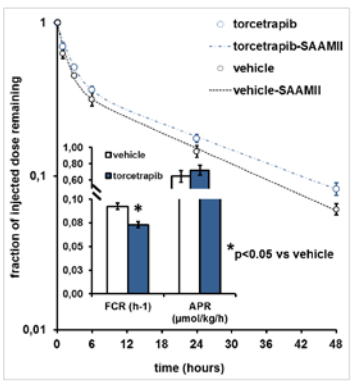


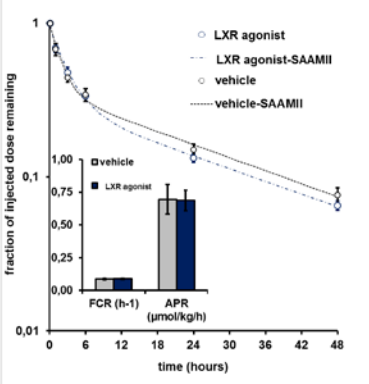
- Plasma total cholesterol, HDL-c and HDL-c/TC ratio
- HDL-CE kinetic parameters: catabolism (fractional catabolic rate (FCR)) and production (absolute production rate (APR))
- HDL-derived cholesterol fecal excretion: ^{3}H-tracer recovered in fecal free sterols and bile acids

SCIENTIFIC AND PHARMACEUTICAL RELEVANCE

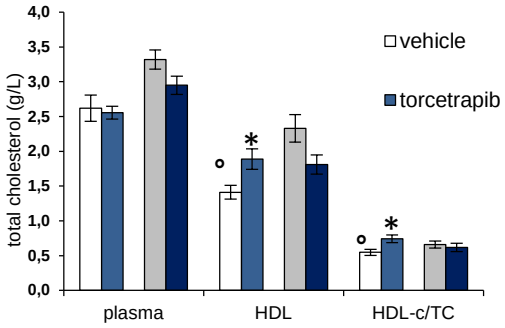
Method: 10-day treatment with torcetrapib 3mg/kg/day or LXR agonist GW3965 30mg/kg twice daily.

- Torcetrapib increases HDL-c and HDL-c/TC ratio through a lower HDL-CE catabolism
- Torcetrapib does not compromise HDL-derived cholesterol fecal excretion
- Despite no effect on HDL-CE catabolism, LXR activation increases HDL-derived cholesterol fecal excretion (as free sterols)

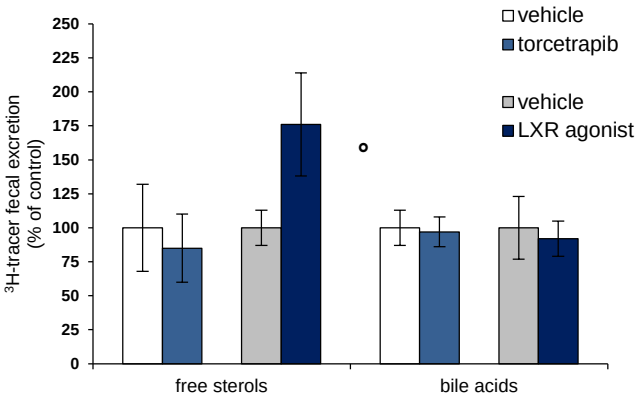




Plasma total cholesterol
HDL-c & HDL-c to total cholesterol ratio (HDL-c/TC)



^{3}H-tracer recovery in fecal free sterols and bile acids 48h after ^{3}H-cholesteryl oleate labeled HDL injection



*p<0.05 torcetrapid *vs.* vehicle ; °p<0.05 LXR agonist *vs.* vehicle

ADD-ON STUDIES

- Macrophage-to-feces reverse cholesterol transport
- Biochemical analysis: plasma lipids, HDL-c, lipoprotein profiles, transfer protein activity assays (CETP, PLTP), etc.

REFERENCES

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Prologue Biotech – 516, rue Pierre et Marie Curie
31670 Labège - FRANCE
Phone : +33 561 287 040
Fax : +33 561 287 043
www.physiogenex.com
business@physiogenex.com

Member of cardio metabolic