Effect of a novel long-acting GLP-1/GIP/glucagon triple agonist (HM15211) in a dyslipidemia animal models

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BACKGROUND
Known targets of current dyslipidemia drugs, and suggested effects of HM15211 on lipid metabolism

RESULTS
Lipoprotein metabolism and cholesterol lowering activity of HM15211

AIMS
• Previously, we showed that a long-acting GLP-1/GIP/Glucagon triple agonist, HM15211, not only provided efficient weight loss, but also improved lipid profiles in DIO mice. With its triple agonism, HM15211 could affect multiple pathways in lipid metabolism, suggesting HM15211 as a novel therapeutic option for dyslipidemia.
• In the present study, we investigated the therapeutic effect of HM15211 on dyslipidemia in disease animal model and its mode of action (MoA).

METHODS
• To evaluate the therapeutic efficacy in dyslipidemia, high-fat and high-fructose diet hamsters were administered with HM15211, and blood lipids were monitored. Commercially available dyslipidemia drugs such as evolocumab and rosuvastatin were used as comparative control. At the end of study, liver tissues were prepared, and protein level of LDLR and HMGCR was evaluated.
• To evaluate the inhibitory effect of HM15211 on lipid absorption, oral lipid tolerance test was performed. Briefly, overnight fasted normal mice were fed with olive oil, followed by blood TG monitoring.
• For in vitro MOA studies, cell lysates of HepG2 cells treated with HM15211 were subjected to western blot analysis (LDLR, and HMGCR) and qPCR (lipid metabolism-related genes).
• Additionally, LDL uptake and enzymatic activity of HMGCR in HepG2 cells were also determined after HM15211 treatment by using commercially available kits.

CONCLUSIONS
• In dyslipidemia hamsters, HM15211 provides greater CHOlowering than commercial dyslipidemia drugs such as evolocumab and statin.
• In the series of mechanistic studies, responsible MoAs for this potent CHOlowering by HM15211 are elucidated as follows: (1) inhibition of lipid absorption, (2) enhanced LDL clearance, (3) inhibition of CHOlowering synthesis, and (4) improved FFA metabolism.
• In conclusion, our results suggest that HM15211 might be a good therapeutic option for dyslipidemia patients.

REFERENCES
• Khalturin et al. Mol Metab. 3, 221–229 (2013)