Potent body weight loss and efficacy in a NASH animal model by a novel long-acting GLP-1/Glucagon/GIP triple-agonist (HM15211)

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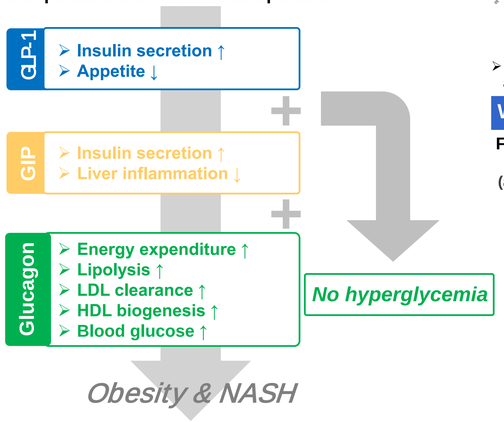
ABSTRACT

Obesity and related complications are an increasing threat to public health with . existing therapy having only limited effectiveness. Recent clinical and pre-clinical advances indicate that simultaneous targeting of more than one signaling pathway could lead to superior metabolic efficacy with fewer adverse events. Thus, we have developed a long-acting GLP-1/glucagon/GIP triple-agonist, HM15211. HM15211 is a modified glucagon analog which binds to and activates all three receptors. This triple-agonist is conjugated to the human aglycosylated Fc fragment via a short PEG linker to enhance duration of action. Potent glucagon activity of HM15211 allows potent body weight loss (BWL) and improves lipid profiles. In addition, GLP-1 and GIP receptor agonism by HM15211 could balance glucagon induced glucose production by stimulating glucose dependent insulin release. GLP-1 may also contribute to BWL by regulating food intake. Here, we evaluated therapeutic efficacy of HM15211 for obesity and nonalcoholic steatohepatitis (NASH) in rodent models.

After 4 weeks of treatment, HM15211 showed significantly improved BWL (~3.0 fold in DIO mice, relative to liraglutide dose equivalent to 3 mg/day in humans) under similar food intake conditions. As to proposed MoA, HM15211 could induce increased energy expenditure compared to liraglutide. In addition, HM15211 had no hyperglycemic risk owing to its balanced GLP-1/GIP action. We also investigated therapeutic roles of HM15211 in NASH by using methionine choline-deficient (MCD) mice, a well-established NASH model. Compared to liraglutide, HM15211 treatment showed greater reduction of hepatic triglycerides, and oxidative stress, as indicated by hepatic TBARS. Furthermore, the NAFLD activity score was significantly reduced after HM15211 treatment. Similar results were also observed when the therapeutic efficacy of HM15211 was investigated in high sucrose diet (HSD) rats. Our results suggest that GLP-1/glucagon/GIP triple agonism of HM15211 may have therapeutic potential in the treatment of obesity and related complications including NASH.

BACKGROUND

Rationally designed Triple-agonist could have therapeutic potential in metabolic syndromes by independent MoA of each component.



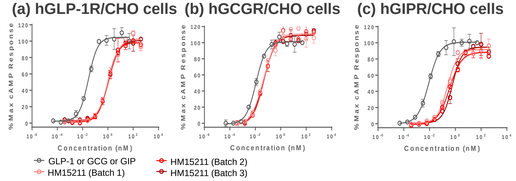
METHODS

- To measure intracellular cAMP levels, CHO cells stably expressing either hGLP-1R, hGCGR, or hGIPR were treated with HM15211 for 15 minutes. Native GLP-1, Glucagon, or GIP was used as reference control. Accumulated intracellular cAMP was measured using the LANCE™ cAMP assay Kit (Perkinelmer)
- Potent body weight loss efficacy of HM15211 was evaluated in DIO mice. After 4 weeks of drug treatment, changes (*vs.* vehicle) in body weight, food intake, and blood cholesterol were measured.
- Energy expenditure in DIO mice was investigated by using a combined indirect calorimetry system. O_2 consumption and CO_2 production were continuously monitored during indirect calorimetry occupation to determine the respiratory quotient and energy expenditure of individual mouse. To rule out body-composition effect on energy expenditure, the results were adjusted by ANCOVA.
- Therapeutic potential of HM15211 in NASH was evaluated in MCD mice and HSD rats. After 4 weeks of drug treatment, liver tissue was prepared to measure hepatic TG, oxidative stress (TBARS analysis, only for MCD mice), and NAS (NAFLD activity score).
- The effect of HM15211 on blood glucose was investigated by intraperitoneal glucose tolerance test (*ip*GTT) after administration of a single dose of HM15211 10 nmol/kg in normal C57BL/6 mice. To investigate the role of GLP-1 and/or GIP portion of HM15211 in blood glucose control GLP-1 antagonist (600 nmol/kg EXD(9-39)) and/or GIP antagonist (50 nmol/kg GIP (3-42)).

RESULTS

In vitro activity of HM15211

Figure 1. cAMP accumulation by GLP-1, GCG, and GIP receptor

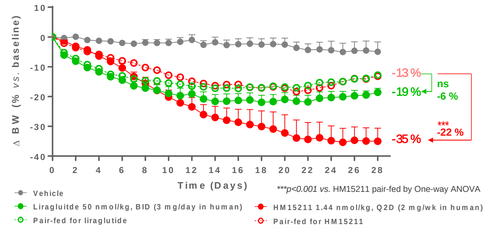


➢HM15211 possesses relatively high GCG activity and balanced GLP-1/GIP activity, which is well-reproduced in different batches

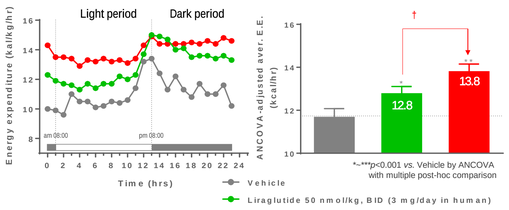
Weight loss efficacy in obesity animal model

Figure 2. Weight loss and energy expenditure in DIO mice (QW mimic)

(a) Body weight change in DIO mice (n=6)

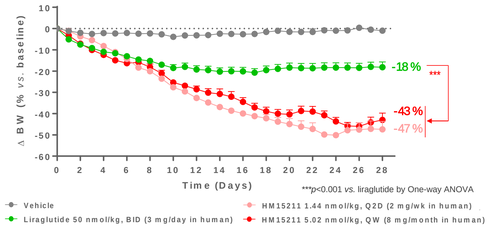


(b) Energy expenditure (n=10)



➢Weekly mimic HM15211 shows more potent body weight loss than daily GLP-1RA despite similar food intake inhibition *via* more enhanced energy expenditure.

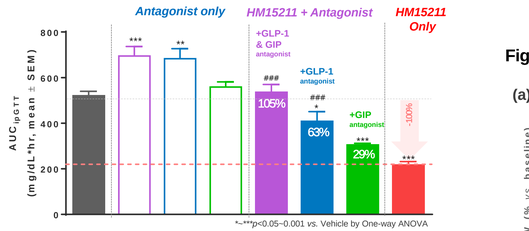
Figure 3. Weight loss in DIO mice (n=7, QM mimic)



➢Both administration cycles (weekly and monthly mimic) show similar body weight loss efficacy, which is superior than daily GLP-1RA

Hyperglycemic risk assessment

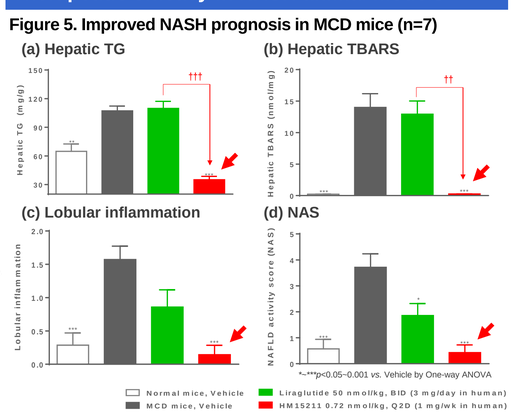
Figure 4. *ip*GTT in normal mice in the presence or absence of GLP-1 and/or GIP receptor antagonist



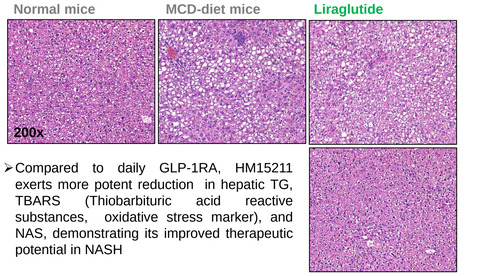
➢ Balanced GLP-1/GIP of HM15211 could effectively neutralize potential hyperglycemic risk induced by its potent GCG action

Therapeutic efficacy in NASH animal models

Figure 5. Improved NASH prognosis in MCD mice (n=7)



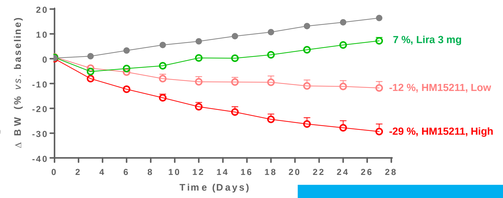
(e) H&E staining of liver section



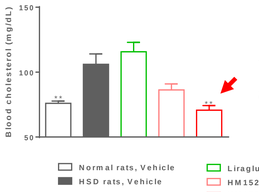
➢Compared to daily GLP-1RA, HM15211 exerts more potent reduction in hepatic TG, TBARS (Thiobarbituric acid reactive substances, oxidative stress marker), and NAS, demonstrating its improved therapeutic potential in NASH

Figure 6. Therapeutic benefits of HM15211 in HSD (high sucrose diet) rats (n=6)

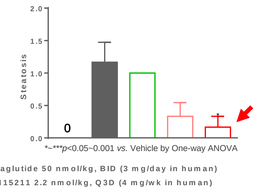
(a) Body weight change



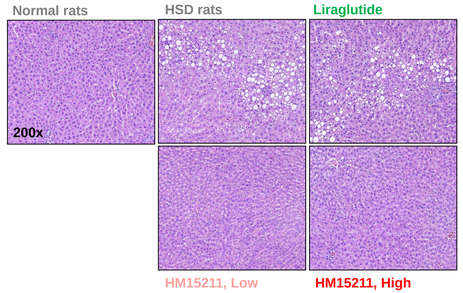
(b) Blood cholesterol



(c) Steatosis



(d) H&E staining of liver section



➢HM15211 shows potent body weight loss, followed by reduction in blood cholesterol, and hepatic steatosis in HSD rats, further emphasizing its therapeutic benefits in NASH

CONCLUSIONS

- **HM15211 is a novel long-acting triple-agonist with high GCG & balanced GLP-1/GIP action, optimal for next generation AOM (anti obesity medication) by providing more potent BWL efficacy than conventional AOMs including GLP-1RA**
- **Both weekly and monthly mimic HM15211 could exert superior BWL efficacy than daily GLP-1RA in DIO mice, which results from more potent energy expenditure induction**
- **Balanced GLP-1/GIP could effectively neutralize high GCG-induced hyperglycemic risk**
- **HM15211 reduces hepatic TG, oxidative stress, and NAS in MCD mice more than GLP-1RA, indicating therapeutic benefits in NASH**
- **Therapeutic benefits in NASH was further confirmed in HSD rats**

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