Combining HM17321 and Incretins Augments Fat Loss and Preserves Lean Mass in Mouse Model of Obesity

Poster-329

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ABSTRACT

Background: Incretin-based drugs have demonstrated remarkable efficacy in body weight reduction and improving metabolic parameters. However, there may be challenges associated with lean mass loss when used as long-term therapy. Urocortin-2 (UCN2) is a selective CRFR2 agonist and has been shown to reduce fat mass while simultaneously promoting muscle hypertrophy. This suggests a potential for UCN2 both as a monotherapy and in combination with incretin-based drugs for healthy weight loss. In current study, we explore the combination efficacy of HM17321, a novel CRFR2 selective and biased UCN2 analog, and incretin-based drugs in improving body composition in mouse model of diet-induced obesity (DIO).

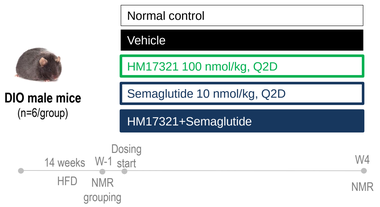
Method: C57BL/6 mice fed a HFD were subcutaneously injected with HM17321 alone or in combination with incretin-based drugs including semaglutide and HM15275 (a GLP-1/GIP/GCG triple agonist) for 4 weeks. Body composition was assessed based on TD-NMR (minispec, LF90II) at baseline and after treatment. Histological analysis of skeletal muscle was performed after treatment.

Results: In DIO mice, HM17321 significantly reduced fat mass, similar to the reduction observed with semaglutide alone. HM17321 alone resulted in a significant increase in lean mass despite similar body weight loss with semaglutide alone. Co-treatment of HM17321 and HM15275 led to a greater reduction in body weight and fat mass in DIO mice. Notably, HM17321/HM15275 combination preserved lean and skeletal muscle mass.

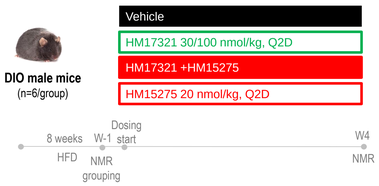
Conclusion: Combining HM17321 with incretin-based drug led to additional fat reduction while preserving lean mass compared to incretin alone, suggesting improved body composition during weight loss. Thus, HM17321 could be a therapeutic option along with incretin-based drugs for healthy weight loss.

METHODS

Study scheme 1. Combination with semaglutide



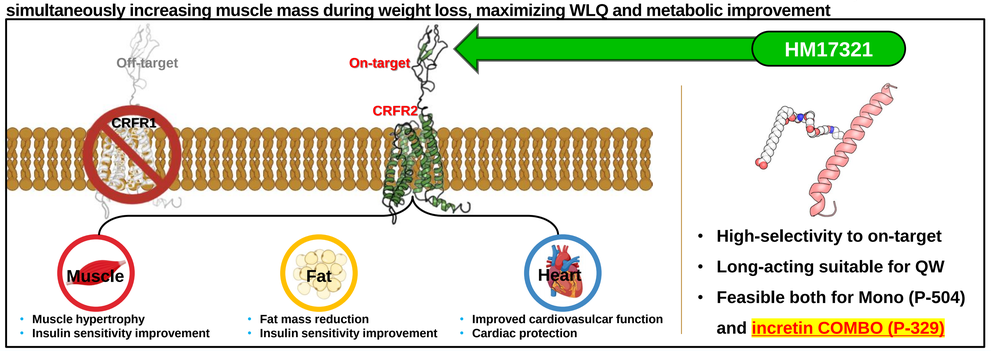
Study scheme 2. Combination with HM15275



BACKGROUND

The next generation obesity drugs : Is it possible to burn fat while gaining muscle?

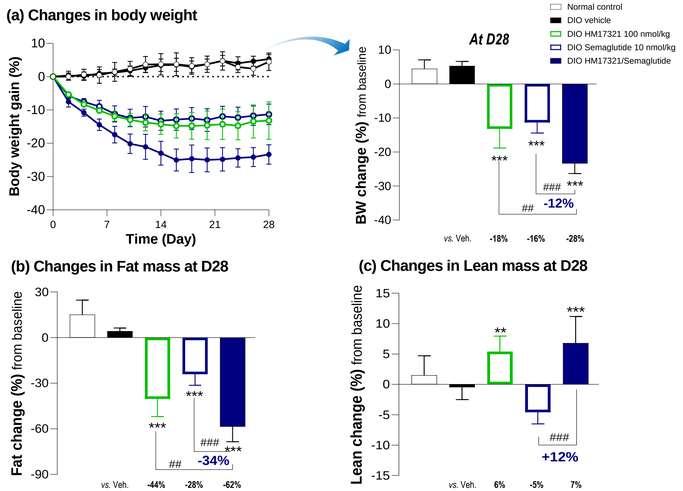
HM17321, a novel long-acting CRFR2 selective and biased UCN2 analog, is optimally designed to selectively reduce fat while simultaneously increasing muscle mass during weight loss, maximizing WLQ and metabolic improvement



RESULTS

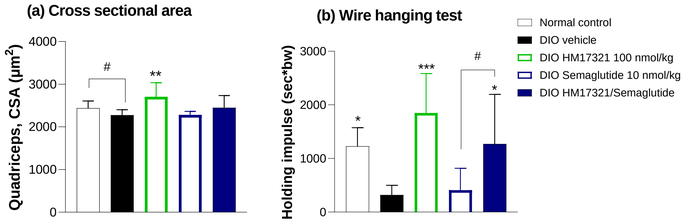
Efficacy of HM17321 as a mono- and combination therapy with Semaglutide

Figure 1. HM17321 enhances fat mass reduction and increases lean mass during semaglutide-induced weight loss in DIO mice



➢ In DIO mice, HM17321/semaglutide combination resulted in an additional body weight and fat loss, while increasing lean mass compared to semaglutide alone.

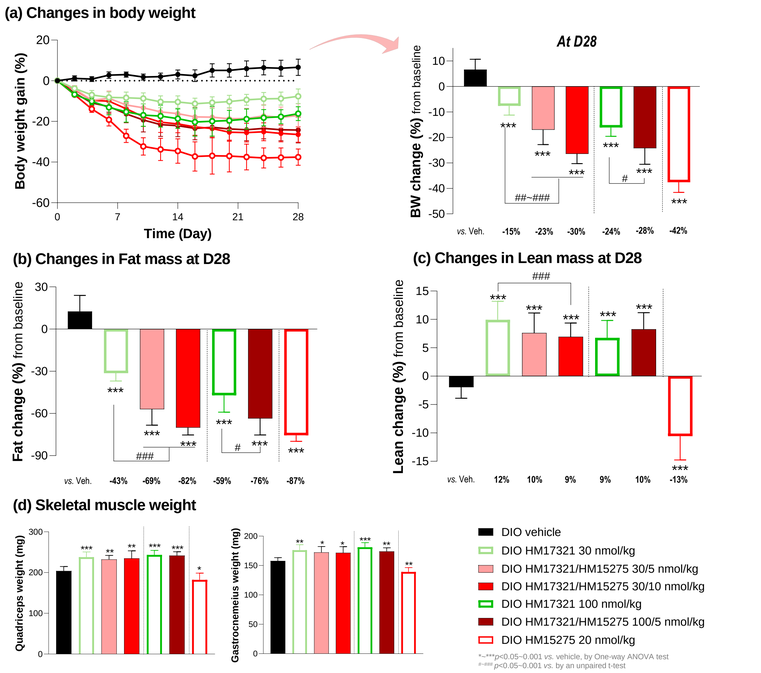
Figure 2. HM17321 promotes skeletal muscle hypertrophy and improves muscle endurance in DIO mice



➢ HM17321/semaglutide combination restored myofiber size and muscle endurance to levels of normal control.

Combination efficacy of HM17321 with HM15275 (a GLP-1/GIP/GCG triple agonist)

Figure 3. Combined HM17321 and HM15275 treatment augments fat mass reduction and prevents loss of lean and skeletal muscle mass in DIO mice



*~***p<0.05~0.001 vs. vehicle, by One-way ANOVA test
†~***p<0.05~0.001 vs. by an unpaired t-test

➢ HM17321/HM15275 combination showed greater reduction in body weight and fat mass without loss of lean and muscle mass compared to HM15275 alone.

CONCLUSIONS

- **HM17321, a novel long-acting CRFR2 selective and biased UCN2 analog, significantly improved the efficacy of semaglutide as evidenced by greater weight and fat mass loss simultaneously increasing lean mass, suggesting HM17321 as an ideal combination partner for GLP-1 therapy.**
- **Combination of HM17321 with the potent GLP-1/GIP/GCG triple agonist HM15275 resulted in superior fat mass reduction (-56~70%) with increasing lean (5~10%) and muscle mass. This indicates that even combination with high efficacy of incretin drugs, HM17321 synergistically improved body composition and therefore could be a promising therapeutic for obesity.**

***Please note additional posters presenting Hanmi's obesity pipeline, HM15275 (Poster-335)**