Potent weight loss effects and mechanism of a novel long-acting glucagon analog, HM15136, in animal models

109-LB

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ABSTRACT

Clinical use of glucagon (GCG) has long been limited to the acute treatment of insulin-induced hypoglycemia. However, recent studies demonstrate that GCG also plays a central role in the regulation of lipid metabolism and body weight, suggesting its potential application in managing obesity. Consistent with this new concept, we observed that chronic treatment with the novel long-acting glucagon analog, HM15136, led to body weight loss (BWL) with minimized effects on blood glucose (BG) control. To further explore the therapeutic potential of HM15136 in obesity, the present study compared the BWL effects of HM15136 with various incretin therapeutics targeting obesity, and investigated the potential BWL mechanism *in vivo*

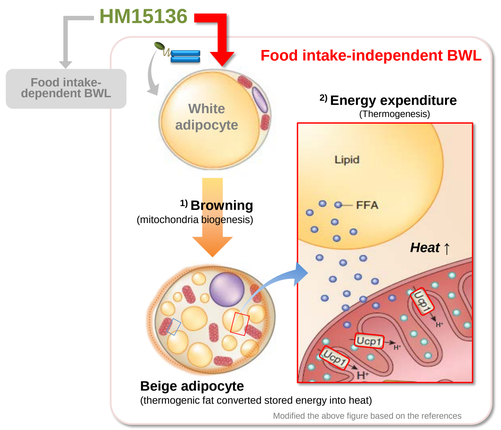
In DIO mice, HM15136 showed greater BWL than GLP-1 agonist such as liraglutide even under pair-feeding conditions indicating appetite-independent BWL by HM15136. As to the postulated mechanism, HM15136 increased the expression of PGC-1α and UCP-1 in white adipose tissue (WAT). Consistent with these results, HM15136 enhanced the energy expenditure in DIO mice. Together with the reduced respiratory exchange ratio (RER), these results suggested that HM15136 may induce WAT browning a mechanism through which energy expenditure can increase. Next, to investigate the potential implication of HM15136 in cardiovascular risk, telemetry system was applied, and HM15136 treatment showed no abnormal increases in heart rate and blood pressure in SD rats

Based on these results, we propose that the novel long-acting glucagon analog, HM15136, could be a potential therapeutic option for the management of obesity. Human studies are needed to confirm these therapeutic benefits and to evaluate the safety of HM15136

BACKGROUND

HM15136 might have therapeutic potential in obesity via food intake inhibition-dependent and -independent mechanism

✓*Expected benefits of HM15136 for obesity treatment*



METHODS

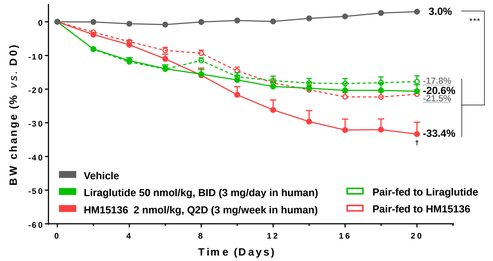
- To compare the BWL efficacy between HM15136 and GLP-1RA, either HM15136 or various GLP-1RAs (liraglutide, dulaglutide or semaglutide) was subcutaneously administered into diet-induced obesity (DIO) mice for 4 weeks. The dose tested were HM15136 2.0 nmol/kg, once every 2 days (Q2D); liraglutide 50 nmol/kg twice-daily (BID); dulaglutide 2.7 nmol/kg Q2D; semaglutide 20.5 nmol/kg Q2D
- To assess the FI inhibition-independent BWL mechanism, BW change in DIO mice was compared with liraglutide under pair-fed controlled condition. At the end of treatment, blood lipid profiles and fat mass were determined. Then, the white adipose tissue (WAT) samples were subjected to immunohistochemistry and H&E staining to examine the thermogenic marker expression (PGC-1α and UCP-1) and adiposity, respectively
- To measure energy expenditure and respiratory exchange ratio (RER), each DIO mouse was subjected to indirect calorimetry, followed by VO_2 and VCO_2 monitoring

RESULTS

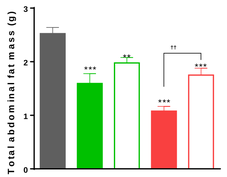
Underlying mode of action for BWL by HM15136

Figure 1. Efficacy comparison of HM15136 and liraglutide in DIO mice with pair feeding controls (n=7)

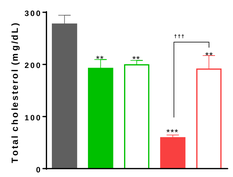
(a) BW change



(b) Fat mass



(c) Blood CHO



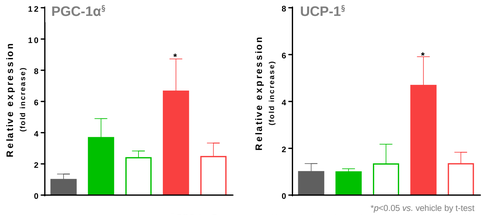
** ~ ***p<0.01 ~ 0.001 *vs.* DIO mice, vehicle by One-way ANOVA, † ~ †††p<0.05 ~ 0.001 *vs.* each pair-fed group by t-test

➢In contrast to liraglutide, HM15136 showed greater BWL, fat mass reduction, and blood CHO reduction than pair-fed group, suggesting additional satiety-independent BWL

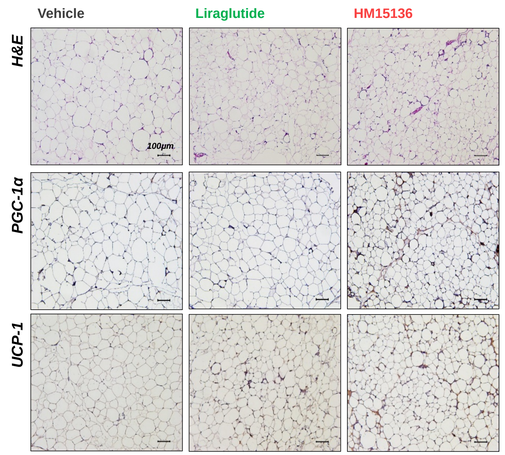
Promotion of WAT browning and energy expenditure

Figure 2. Effect of HM15136 on WAT phenotype change in DIO mice (n=7)

(a) PGC-1α and UCP-1 mRNA level in white adipose tissue (WAT)



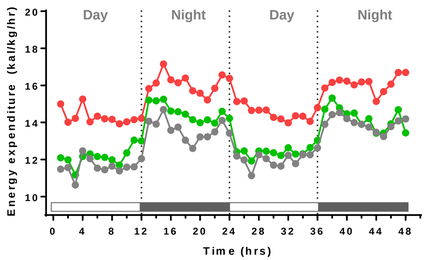
(b) H&E staining and immunohistochemistry in WAT



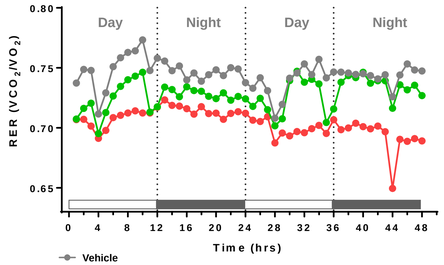
➢HM15136 increased PGC-1α & UCP-1 expression in WAT of DIO mice, suggesting WAT browning

Figure 3. Effect of HM15136 on energy expenditure and RER in DIO mice (n=9~11)

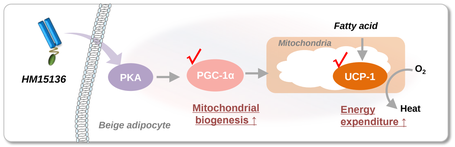
(a) Energy expenditure



(b) Respiratory exchange ratio (RER)



(c) Suggested mechanism for WAT browning and enhanced energy expenditure by HM15136

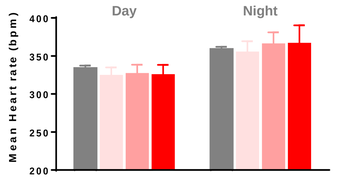


➢Unlike liraglutide, HM15136 increased energy expenditure in DIO mice. Reduced RER suggests more fat burning by HM15136

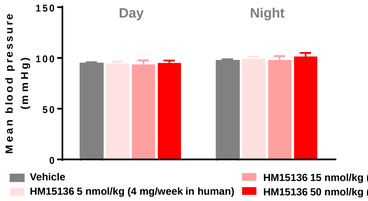
Safety assessment: cardiovascular (CV) risk

Figure . CV risk assessment in SD rats (n=3)

(a) Mean heart rate



(b) Mean blood pressure



➢In SD rats, HM15136 dose escalation up to 50 nmol/kg did not show any increases in HR and BP, suggesting negligible CV risk of HM15136

CONCLUSIONS

- **HM15136 is a novel long-acting glucagon analog developed for the treatment of obesity**
- **Unlike liraglutide, HM15136 shows greater BWL than pair-fed group in DIO mice**
- **HM15136 increases the expression of PGC-1α and UCP-1 in WAT, leading to WAT browning**
- **Consistently, HM15136 increases energy expenditure via enhanced fat burning in DIO mice**
- **No CV-related effects are observed in SD rats**
- **Therefore, HM15136 might be a novel therapeutic option for obesity by providing favorable metabolic phenotype changes not observed in current anti-obesity drugs such as GLP-1RA**

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