Therapeutic potential of novel combination of a long-acting glucagon analog (HM15136) and anti-diabetic drugs for the treatment of obesity

1011-P

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ABSTRACT

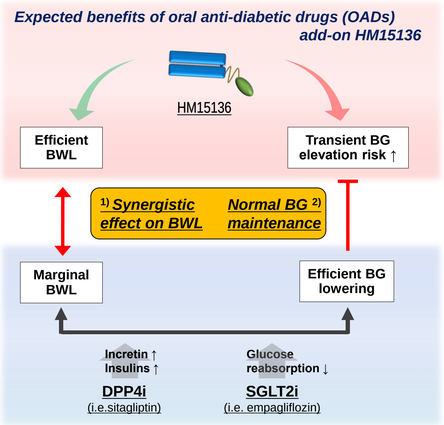
The obesity epidemic represents a major challenge for public health. However, existing anti-obesity drugs have limited efficacy because they only suppress appetite, emphasizing the development of next generation therapeutic option. Recently, we showed that prolonged glucagon receptor (GCGR) activation with HM15136, a long-acting GCG analog, could provide potent body weight loss (BWL) in obese animal models. Considering the stimulatory effect of GCG on glucose production, tight regulation of blood glucose (BG) might be important when utilizing HM15136 as a novel anti-obesity drug. Anti-diabetic drugs such as DPP-4 inhibitor and SGLT2 inhibitor have been widely used for T2DM patients. Considering their safety profile and treatment adherence in addition to BG lowering nature, we hypothesized that combination of anti-diabetic drugs might minimize the transient BG elevation by HM15136 and confer additional benefits in obesity management. To investigate this hypothesis, the present study evaluated the combination effects of HM15136 and anti-diabetic medication on BG and BW *in vivo*

Firstly, chronic treatment of HM15136 provided potent BWL efficacy in DIO mice. As to the effect on BG, transient BG elevation during initial treatment was rapidly normalized, and maintained normal thereafter. Interestingly, when combined with anti-diabetic drugs such as sitagliptin and empagliflozin, HM15136-induced transient BG increase was effectively neutralized. In addition, oral anti-diabetic drugs (OADs) add-on HM15136 could provide additional benefits in obesity management as indicated by BWL and fat mass reduction profiles, rationalizing this novel therapeutic option

In conclusion, our results demonstrate that simultaneous treatment of OADs strengthen the position of HM15136 as a novel anti-obesity medication

BACKGROUND

Treatment of the long-acting glucagon analog, HM15136, along with OADs may offer a new therapeutic option to successfully treat obesity



METHODS

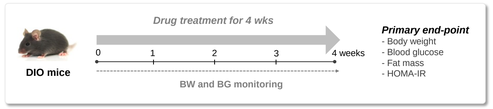
- HM15136 and/or sitagliptin (Sita, DPP-4 inhibitor), empagliflozin (Empa, SGLT-2 inhibitor) were administered to diet-induced obesity (DIO) mice for 4 weeks. The doses tested were as followed: HM15136 (2.0 nmol/kg, once every 2 days, subcutaneous injection), sitagliptin (49.2 mg/kg, once daily, oral gavage), empagliflozin (12.3 mg/kg, once daily, oral gavage). BW and BG were monitored.
- At the end of the treatment, fat mass and HOMA-IR were determined and compared between the HM15136 mono group and the COMBO groups.

RESULTS

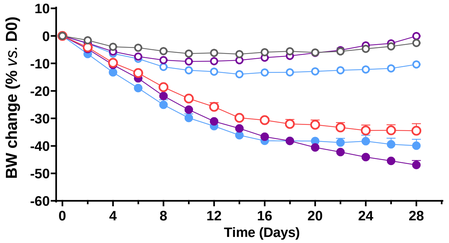
BWL efficacy of OADs add-on in DIO mice

Figure 1. Effect of HM15136 and/or OADs on BW change in DIO mice (n=7)

(a) Experimental design for animal study



(b) Body weight change



(c) Body weight change at day 28

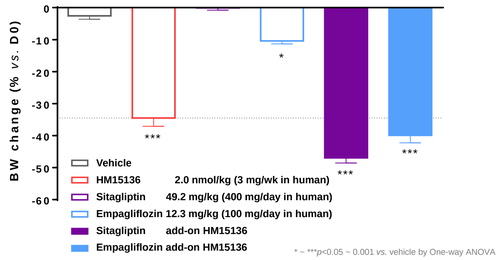
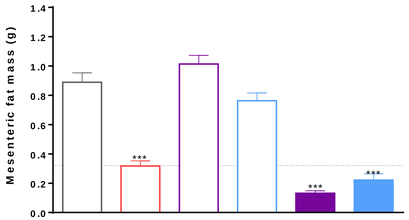


Figure 2. Effect of HM15136 and/or OADs on mesenteric fat and epididymal fat mass in DIO mice (n=7)

(a) Mesenteric fat mass



(b) Epididymal fat mass

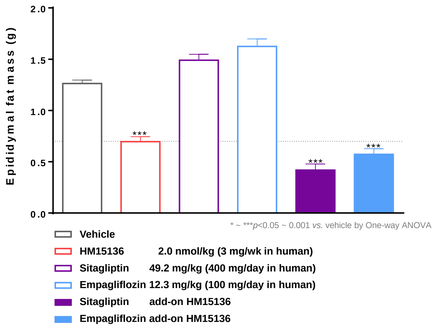


Table 1. Summary : BW change and fat mass in DIO mice

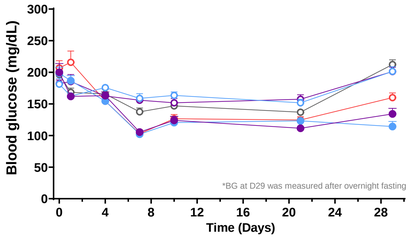
Group	BW change (% *vs.* D0, at D28)	Mesenteric fat (g, at D29)	Epididymal fat (g, at D29)
Vehicle	-2.56 ± 1.06	0.89 ± 0.06	1.26 ± 0.03
HM15136	-34.48 ± 2.58	0.32 ± 0.04	0.70 ± 0.05
Sitagliptin	-0.06 ± 0.70	1.01 ± 0.06	1.49 ± 0.06
Empagliflozin	-10.37 ± 0.97	0.76 ± 0.05	1.62 ± 0.07
Sita add-on HM15136	-46.93 ± 1.61	0.13 ± 0.02	0.42 ± 0.06
Empa add-on HM15136	-39.91 ± 2.35	0.22 ± 0.04	0.57 ± 0.06

➢In DIO mice, HM15136 mono treatment showed potent BWL and fat mass reduction. In addition, sitagliptin or empagliflozin add-on HM15136 provided additional benefits in BWL and fat mass reduction

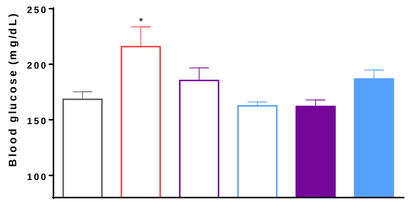
Glycemic control efficacy of OADs add-on

Figure 3. Effect of HM15136 and/or OADs on Blood glucose profile in DIO mice (n=7)

(a) Blood glucose profile



(b) Blood glucose level at day 1



(c) AUC_{BG} (D0-D29)

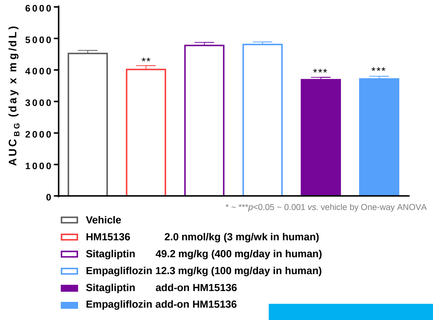


Figure 4. HOMA-IR in DIO mice (n=7)

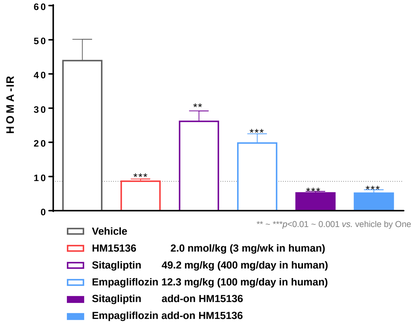


Table 2. Summary : BG profile and HOMA-IR in DIO mice

Test material	BG at day 1 (mg/dL)	$AUC_{BG\ (D0\text{-}D29)}$ (day x mg/dL)	HOMA-IR (at D29)
Vehicle	168 ± 7	4523 ± 100	43.9 ± 6.2
HM15136	216 ± 18	4017 ± 122	8.6 ± 0.7
Sitagliptin	185 ± 11	4779 ± 97	26.2 ± 3.0
Empagliflozin	163 ± 3	4811 ± 78	19.8 ± 2.7
Sita add-on HM15136	162 ± 6	3693 ± 72	5.2 ± 0.5
Empa add-on HM15136	187 ± 8	3713 ± 90	5.1 ± 1.0

➢Sitagliptin or empagliflozin add-on HM15136 mitigated transient BG elevation observed at day 1 in HM15136 mono group. HM15136 treatment reduced HOMA-IR, which tended to be further reduced by OADs add-on

CONCLUSIONS

- **HM15136, a novel long-acting glucagon analog, shows potent BWL in DIO mice. Transient BG elevation during initial treatment is rapidly normalized, and maintains normal**
- **When OADs add-on HM15136, transient BG elevation is effectively neutralized, and additional benefits in BWL, fat mass reduction and Insulin sensitivity improvement are observed**
- **Our results demonstrate that OADs add-on HM15136 treatment as well as HM15136 mono therapy could be a novel therapeutic option for obesity treatment**

REFERENCES

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- Farghali H *et al.*, *Physiol. Res.* **57**, 569-575 (2008)
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