Sustained glucagon effect on blood glucose and improvements of insulin resistance mediated by a novel long-acting glucagon analogue, HM15136, in animal models

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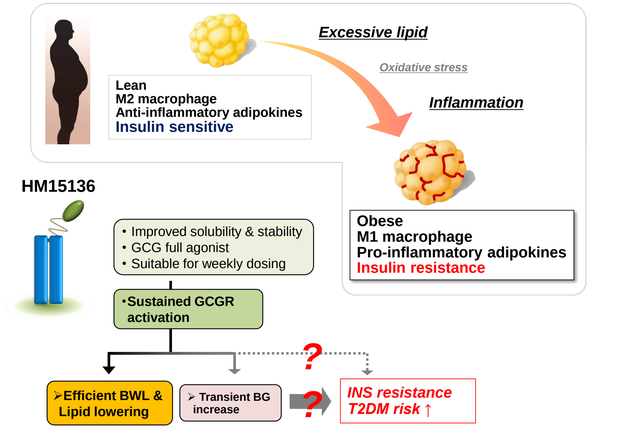
BACKGROUND

In obese condition, excessive lipid influx increases adiposity and subsequent inflammation, leading to insulin resistance and T2DM

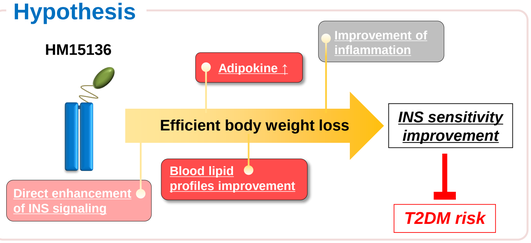


Despite efficient body weight loss (BWL), potential effects of HM15136 on glucose homeostasis were not closely investigated

AIMS

- **In the present study, the potential effects of HM15136 on blood glucose (BG), and the mechanism leading to IR improvement by HM15136 were investigated**

Hypothesis



METHODS

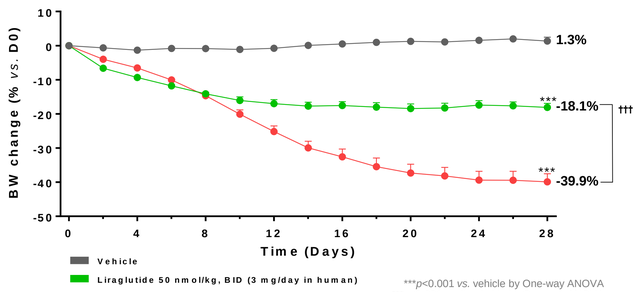
- To evaluate the therapeutic potential of HM15136 in obesity, DIO mice were chronically administered with HM15136, and BW and BG were monitored. At the end of treatment, blood lipid profiles, HOMA-IR, and HbA1c were determined.
- For in vitro mechanism studies, insulin resistant 3T3-L1 adipocytes induced by FFA incubation and rat primary hepatocytes were utilized. After HM15136 treatment, expression and secretion of adipokines (FGF21 and adiponectin) were determined by qPCR and ELISA, respectively. To monitor insulin-mediated signaling, Akt phosphorylation was measured.

RESULTS

In vivo efficacy in obesity animal models

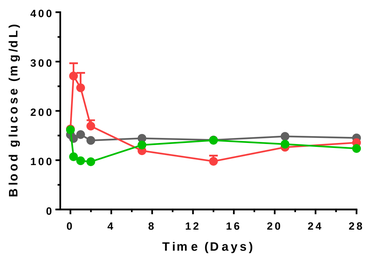
Figure 1. HM15136 effect on BW, BG and HbA1c in DIO mice (n=7)

(a) Body weight change

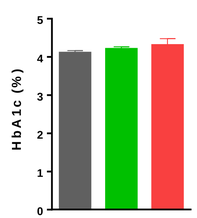


***p<0.001 vs. vehicle by One-way ANOVA
†††p<0.001 vs. liraglutide by One-way ANOVA

(b) Blood glucose profile



(c) HbA1c

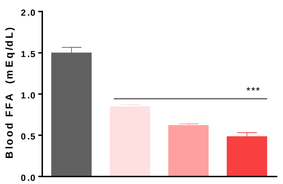


➢ In DIO mice, HM15136 showed more BWL than liraglutide. Transient BG elevation is rapidly normalized. No increased HbA1c is observed

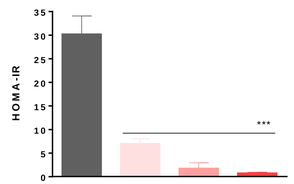
Improved lipotoxicity and insulin resistance (IR)

Figure 2. Effect of HM15136 on blood free-fatty acid (FFA) and HOMA-IR in DIO mice (n=7)

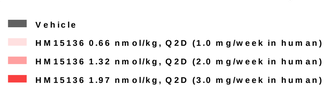
(a) Blood FFA



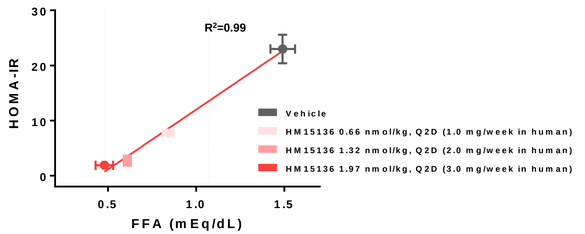
(b) HOMA-IR



***p<0.001 vs. vehicle by One-way ANOVA



(c) Relationship between FFA and HOMA-IR

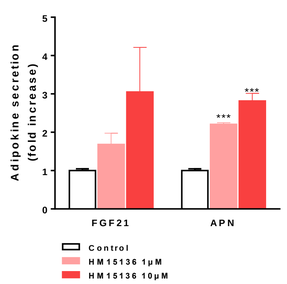


➢HM15136 reduced blood lipids and HOMA-IR in DIO mice, suggesting the reversal of of insulin resistance by lipotoxicity improvement

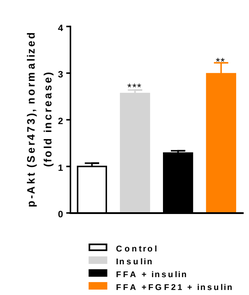
Induction of insulin sensitizing adipokines

Figure 3. Effect of HM15136 on FGF21 and adiponectin (APN), and its impact on INS signaling in 3T3-L1 adipocytes

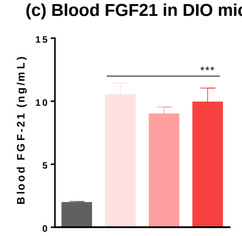
(a) FGF21 and APN secretion

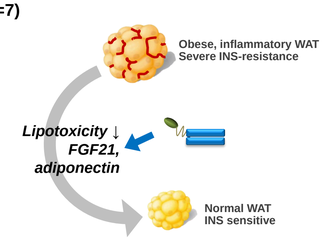


(b) Akt phosphorylation by INS



(c) Blood FGF21 in DIO mice (n=7)





* ~ ***p<0.05 ~ 0.001 vs. vehicle or control by One-way ANOVA

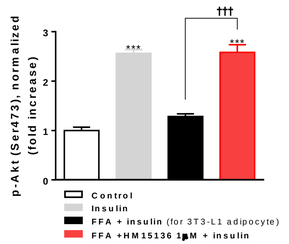
➢HM15136 increased the secretion of FGF21 and APN, and FGF21 reversed FFA-induced insulin resistance in 3T3-L1 adipocytes. Blood FGF21 was also increased by HM15136 treatment in DIO mice

Direct involvement of HM15136 in insulin signaling

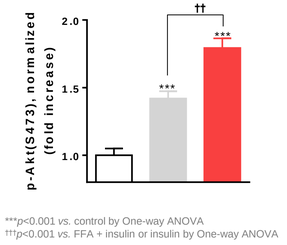
Figure 4. Direct HM15136 effect on INS signaling

(a) Akt phosphorylation

In 3T3-L1 adipocyte

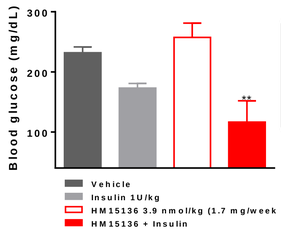


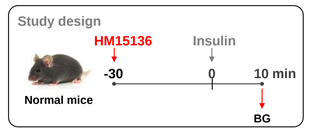
In rat primary hepatocytes



***p<0.001 vs. control by One-way ANOVA
†††p<0.001 vs. FFA + insulin or insulin by One-way ANOVA

(b) BG level after insulin challenge in normal mice (n=5)





**p<0.01 vs. vehicle by One-way ANOVA

➢HM15136 reversed insulin resistance and enhanced insulin signaling in 3T3-L1 adipocytes and rat primary hepatocytes, respectively. Accordingly, pretreatment of HM15136 further enhanced BG lowering

CONCLUSIONS

- **HM15136, a novel long-acting glucagon analog, provides greater BWL than liraglutide. Transient BG elevation is rapidly normalized, and no HbA1 increase is observed in DIO mice**
- **HM15136 reduces blood lipids and HOMA-IR, indicating the improvement of lipotoxicity and insulin resistance**
- **HM15136 increases FGF21 and APN secretion, which, in turn, enhances insulin-mediated Akt phosphorylation**
- **Unexpectedly, HM15136 also directly improves insulin action**
- **Therefore, sustained GCG action by HM15136 could lead to insulin resistance improvement by which BG could be maintained normal, further supporting a therapeutic potential of HM15136 in obesity**

REFERENCES

- Campbell JE and Drucker DJ., *Nat Rev Endocrinol.* **11**, 329-38 (2015)
- Muller TD *et al.*, *Physiol Rev.* **97**, 721-66 (2017)

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