A Novel CRFR2-Selective UCN2 Analog, HM17321, Improves Glycemic Control across Multiple Preclinical Models

Seon Myeong Lee, Eunseon Kim, Jung Kuk Kim, Wonki Kim, Eunjin Park, Jeong A Kim, Sung Hee Hong, Sung Min Bae, Sang Hyun Lee and In Young Choi
Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea

Hanmi

Poster
842-P

Abstract

Introduction and Objective: Obesity is a major cause of various metabolic diseases, particularly type 2 diabetes (T2D), and most of the T2D patients are overweight or obese. Thus, glycemic control efficacy becomes to be recognized as one of the essential features of anti-obesity medication. HM17321, a novel CRFR2-selective UCN2 was developed for high quality weight management, and its proof of concept was demonstrated in animal models of obesity. Here, the potential benefits of HM17321 on glucose homeostasis and related mode of action was further investigated.

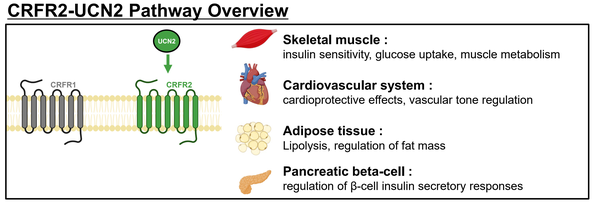
Methods: ipGTT was performed in normal mice after single drug administration. In DIO mice, HOMA-IR was determined after 8 weeks treatment of HM17321. To evaluate overall glycemic control effect, db/db mice were administered with HM17321 for 4 weeks, followed by HbA1c measurement and ipGTT. Semaglutide (Sema) was included as a comparative control.

Results: In normal mice, single administration of HM17321 significantly reduced BG during ipGTT, indicating its rapid glucose tolerance improvement effects. Similarly, chronic treatment of HM17321 significantly reduced HOMA-IR in DIO mice (8.8 ~ 11.8 vs. 65.7 for DIO vehicle; 11.2 for normal vehicle), indicating its improvement effect on insulin resistance. In line with these findings, 4 weeks treatment of HM17321 in diabetic db/db mice significantly decreased HbA1c and ipGTT AUC_{BG} compared to vehicle. Notably, overall glycemic control effect in db/db mice was comparable to even higher than Sema.

Conclusion: Series of nonclinical evaluations clearly demonstrate improvement effects of HM17321 on glucose tolerance and insulin resistance, which eventually leads to HbA1c lowering effect. These results suggest additional benefits of HM17321 in glycemic control in addition to high quality weight management. Further studies will elucidate the mechanisms by which HM17321 contributes to improved glucose homeostasis, including direct improvement of insulin signaling.

Background

CRFR2-UCN2 Pathway Overview



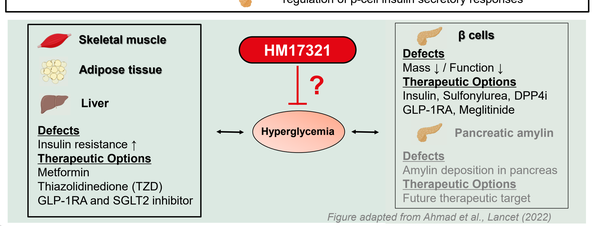
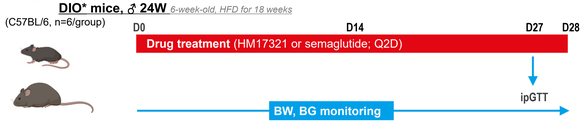


Figure adapted from Ahmad et al., Lancet (2022)

Methods

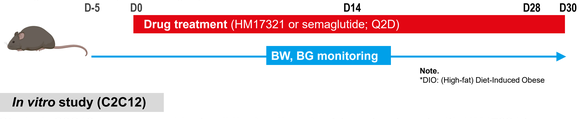
***In vivo* study**

Study 1. Normal ♂ 7W, DIO* mice, ♂ 24W *6-week-old, HFD for 18 weeks*
(C57BL/6, n=6/group)



Study 2. DIO mice, ♂ 24W *6-week-old, HFD for 18 weeks*
(C57BL/6, n=6/group)

Study 3. *db/db* mice, ♂ 16-17W *8-week-old*
(BKS.Cg-Dock7 m +/+ Lepr db /J, n=6/group)



***In vitro* study (C2C12)**

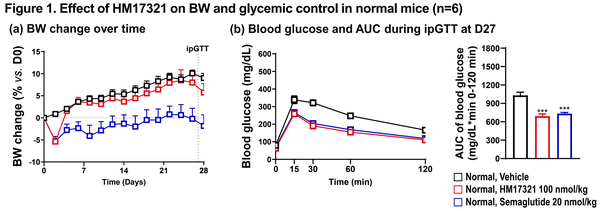
Study 1. C2C12 (mouse myoblast cell line) cells : **short-term treatment with HM17321 to assess glucose uptake.**

Study 2. **long-term with HM17321 to evaluate glucose uptake potentially driven by muscle hypertrophy.**

Study 3. C2C12 cells with **TNF-α–induced insulin resistance** were treated with HM17321 and assessed for glucose uptake.

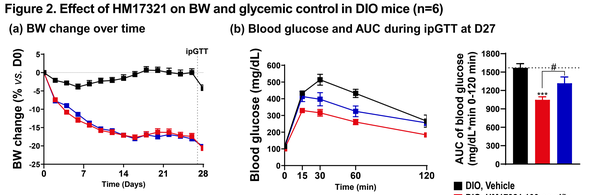
Enhanced Glucose Disposal in Mice (Repeated Dose)

Figure 1. Effect of HM17321 on BW and glycemic control in normal mice (n=6)



***p< 0.001 *vs.* Normal vehicle control by one-way ANOVA test

Figure 2. Effect of HM17321 on BW and glycemic control in DIO mice (n=6)

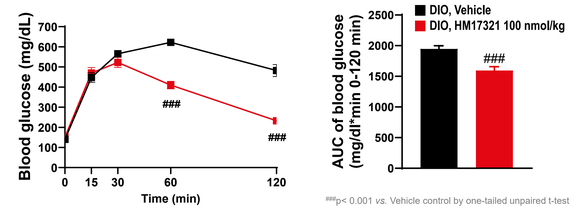


***p< 0.001 *vs.* DIO vehicle control by one-way ANOVA test, #p< 0.05 *vs.* by one-tailed unpaired t-test

➢ To eliminate the confounding effects of appetite suppression, ipGTT was conducted after overnight fasting following the final dosing on Day 26. In normal mice, HM17321 showed glucose-lowering efficacy comparable to Sema, while in DIO mice, HM17321 demonstrated significantly greater glucose reduction than Sema.

Enhanced Glucose Disposal in DIO Mice (Single Dose)

Figure 3. Acute glucose-lowering effect of HM17321 in DIO mice (n=6)

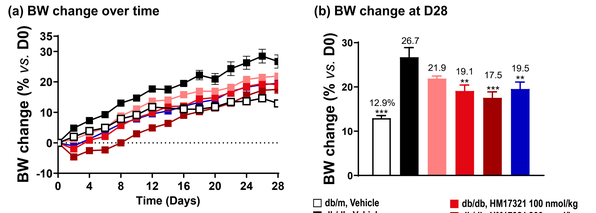


###p< 0.001 *vs.* Vehicle control by one-tailed unpaired t-test

➢ To exclude the effects of appetite suppression, ipGTT was conducted after overnight fasting following a single dose of HM17321. In DIO mice, HM17321 significantly reduced BG levels from 60 to 120 min post-administration compared to vehicle.

Improved Glycemic Control and Metabolic Profile in *db/db* Mice

Figure 4. Effect of HM17321 on BW and glycemic control in *db/db* mice (n=6)

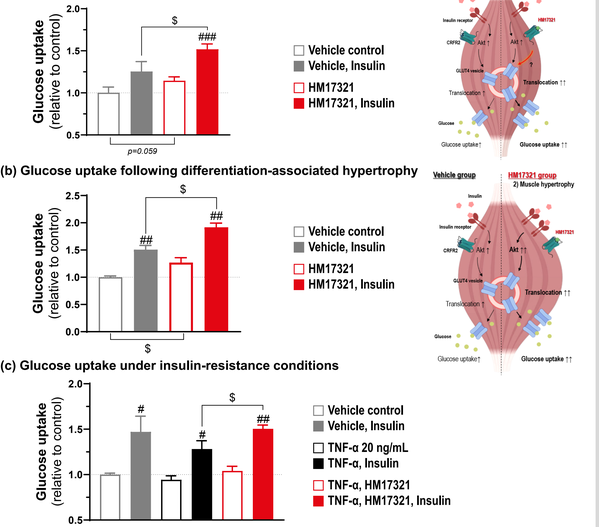


*,**,***p< 0.05~0.001 *vs.* db/db vehicle control by one-way ANOVA test, #-###p< 0.01~0.001 *vs.* by one-tailed unpaired t-test

➢ In *db/db* mice, 28-day treatment with HM17321 resulted in significant suppression of body weight gain at 100 and 300 nmol/kg doses. Notably, at these doses, HbA1c levels were maintained without further deterioration, which were significantly lower than those observed with Sema. In addition, increased adiponectin levels were observed, suggesting a potential mechanistic marker for the improved glycemic control.

Enhanced Glucose Utilization Under Diverse Metabolic States

Figure 5. Effect of HM17321 on glucose uptake in C2C12 cells



#-### p < 0.05–0.001 *vs.* corresponding control groups, determined by one-tailed unpaired t-test.
$ p < 0.05 for comparisons between indicated groups; statistical significance denoted by connecting lines.

➢ HM17321 increased glucose uptake under both basal and insulin-stimulated conditions, consistent with its *in vivo* glucose-lowering effect independent of body recomposition. In long-term treated myoblasts with enhanced differentiation, basal uptake was further increased, suggesting greater glucose disposal capacity. Additionally, HM17321 reversed TNF-α–induced insulin resistance, supporting its direct action on glucose regulation.

Concluding Remarks

In vivo findings

- HM17321 consistently **improved glycemic control** in normal, DIO, and *db/db* mice, independent of appetite suppression.
- In *db/db* mice, it suppressed body weight gain, progressive HbA1c elevation, and elevated adiponectin levels.
- In both DIO mice and *db/db* mice, repeated HM17321 treatment resulted in **superior glucose lowering compared to Sema.**

In vitro findings

- HM17321 **enhanced glucose uptake in muscle cells** under both basal and insulin-stimulated conditions.
- Long-term treatment increased basal uptake in differentiated myoblasts, suggesting improved glucose disposal via hypertrophic activity. It also reversed TNF-α–induced insulin resistance, supporting **a direct insulin-sensitizing mechanism**.

*** Please note additional posters presenting Hanmi's incretin pipeline, a GLP-1/GIP/Glucagon triple agonist, HM15275 (755-P, 774-P: Preclinical; 1980-LB: Phase 1 clinical) and its COMBO w/ HM17321 (Poster, 886-P).**

References

1. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. *Lancet.* **2022**;400(10365):1803-1820