Sustained glucagon effect on cardiovascular renal and metabolic disorders mediated by a long-acting glucagon analog, HM15136, in animal disease models

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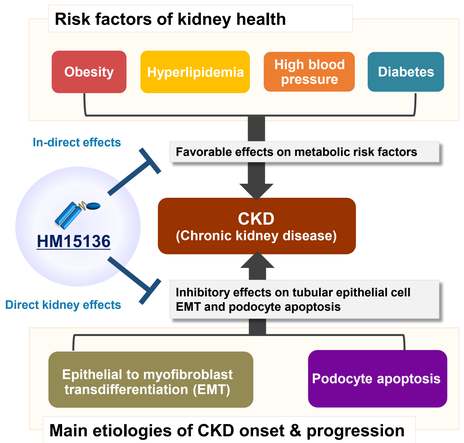
ABSTRACT

Obesity is an increasing health problem worldwide, implicated with various metabolic disorders such as cardiovascular disease and chronic kidney disease (CKD). Previously, we showed that chronic treatment of HM15136, a long-acting GCG analog, led to robust body weight loss (BWL) in rodent obese models. Moreover, recent studies unveiled a novel role of GCG in vasodilation and inflammation. So, we hypothesized that HM15136 improve chronic metabolic disorders via direct action in addition to secondary effect to BWL. Here, we investigated potential therapeutic effect of HM15136 in animal models of cardiovascular renal and metabolic diseases.

In DIO mice, BW, liver triglyceride (TG), and blood cholesterol (CHO) were measured, and all measurements were significantly reduced by HM15136 treatment (-37.5, -72.7, -78.4% *vs.* vehicle for BW, liver TG, blood CHO at day 17). Next, to explore therapeutic effect of HM15136 on cardiovascular renal diseases, spontaneously hypertensive rats (SHRs), known model for hypertensive CKD, were used. Interestingly, abnormal elevation in blood pressure and renal function markers such as urine albumin/creatinine ratio (-23.6% *vs.* SHR vehicle at day 46) was meaningfully reduced by HM15136 treatment. In unilateral ureteral obstruction (UUO) mice, known as acute kidney injury model, similar results were observed (-17.6%, -48.2% *vs.* vehicle for serum creatinine, kidney pro-collagen1α1 at day 12). Consistently, decrease of EMT markers in HK-2 cell and inhibition of human primary podocyte apoptosis were confirmed, explaining underlying mechanism for these beneficial effects.

Therefore, HM15136 could mitigate obesity and related complications especially hypertension and CKD. Hence, mechanistic study results highlight the essential role of direct GCG engagement in improvement of cardiovascular renal and metabolic diseases. Further studies are needed to assess a clinical relevance of these findings.

BACKGROUND



METHODS

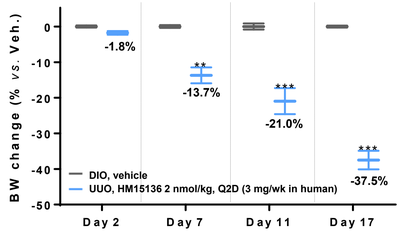
- To investigate beneficial effects of HM15136 on risk factors of CKD, HM15136 was subcutaneously administered into diet-induced obesity (DIO) mice for 17 days. The tested doses of HM15136 were 2.0 nmol/kg, once every 2 days (Q2D, 3 mg/week in human). Pharmacologic action of HM15136 such as BW, blood and liver lipid contents was determined at D2, D7, D11, and D17.
- To evaluate therapeutic effect of HM15136 on CKD, HM15136 was subcutaneously administered into both SHR for 6 weeks and UUO mice for 2 weeks. The tested doses of HM15136 were 3.0 nmol/kg (Q3D, 6 mg/week in human) and 4.0 nmol/kg (Q2D, 6 mg/week in human), respectively. CKD related markers including urine albumin and kidney pathologic scores were analyzed.
- To investigate the direct treatment effect of HM15136 on CKD, EMT marker expression in HK-2 cell (proximal tubular epithelial cell) and apoptosis in human primary podocyte were evaluated after HM15136 treatment.

RESULTS

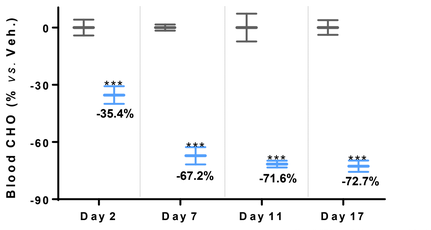
Time-course changes of risk factors associated to CKD by HM15136

Figure 1. Effect of HM15136 on BW reduction, liver TG and blood CHO in DIO mice (n=7)

(a) BW change



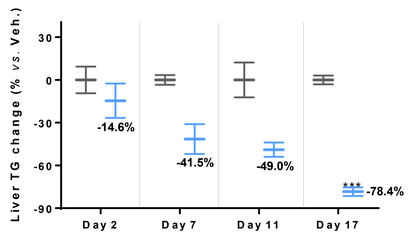
(c) Blood CHO



***p<0.001 *vs.* DIO, vehicle by t-test

➢ At D7, D11 and D17, HM15136 3 mg treatment continuously decreased the risk factors of CKD such as BW, liver TG and blood cholesterol in DIO mice

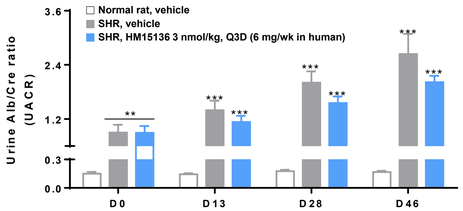
(d) Liver TG



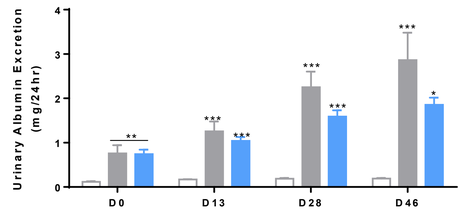
Kidney function improvement in SHR

Figure 2. Time-dependent effect of HM15136 on UACR and urinary albumin excretion in SHR (n=7)

(a) Urine albumin/creatinine ratio



(b) Urinary albumin excretion

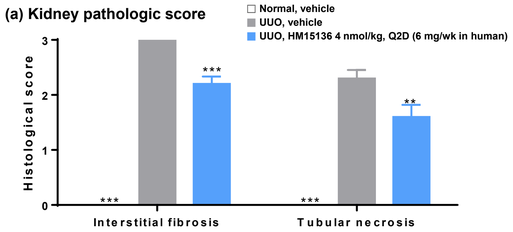


➢ In SHR, HM15136 treatment continuously improved kidney function as indicated by UACR and urinary albumin excretion level, suggesting therapeutic potential of HM15136 on CKD

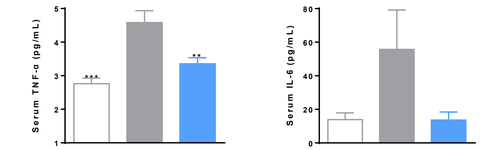
CKD improvement in UUO mice

Figure 3. Effect of HM15136 on fibrosis, inflammation and kidney function in UUO mice (n=10)

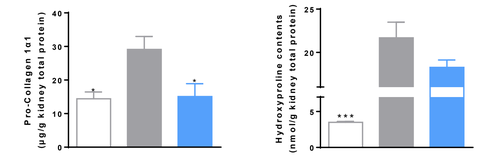
(a) Kidney pathologic score



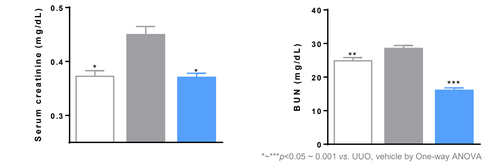
(b) Blood inflammation markers



(c) Kidney fibrosis markers



(d) Kidney function markers



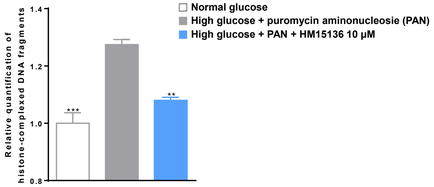
*~***p<0.05 ~ 0.001 *vs.* UUO, vehicle by One-way ANOVA

➢ In UUO mice, HM15136 effectively improved histological score, blood inflammation markers, markers for kidney fibrosis and function, further demonstrating therapeutic potential of HM15136 on CKD

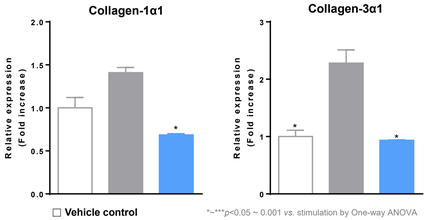
Evaluation of direct beneficial MoAs on CKD

Figure 4. Effect of HM15136 on human podocyte apoptosis and EMT marker expression in HK2 cell

(a) Apoptosis of primary human podocyte



(b) EMT marker expression in HK-2 cell



*~***p<0.05 ~ 0.001 *vs.* stimulation by One-way ANOVA

➢ HM15136 prevented from not only stress-induced human podocyte apoptosis, but also TGF-β induced EMT marker expression in HK-2 cell, elucidating underlying MoAs how HM15136 improves renal inflammation and fibrosis

CONCLUSIONS

- **HM15136 is a novel long-acting glucagon analog**
- **Chronic treatment of HM15136 shows time dependent BWL, which correlates with improvement of obesity related CKD risk factors**
- **HM15136 improves kidney function markers in SHR. Also, CKD related pathologic markers were effectively improved by HM15136 treatment in UUO mice**
- **HM15136 treatment directly reduces human podocyte apoptosis and EMT marker expression in HK-2 cell, explaining the underlying mechanisms for renal protective effects of HM15136 *in vivo***
- **Therefore, sustained glucagon engagement by HM15136 could confer beneficial effects on CKD improvement as well as obesity management. Additional investigation is required for the clinical relevance of these findings**