Cardiorenal Protective Effects of a CRFR2-selective UCN2 analog, HM17321, in Spontaneously Hypertensive Rats (SHR)

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Poster
2538-P

Abstract

Introduction & Objective: A novel UCN2 analog, HM17321, was developed to enhance CRFR2 selectivity and extend therapeutic benefits beyond improvements in weight loss quality (WLQ) to include the cardiovascular and renal systems. Here, we investigated the effects of HM17321 on renal dysfunction and explored the underlying mechanisms.

Methods: Renal and cardiovascular effects of HM17321 were evaluated in SHR. Blood pressure (BP) was continuously monitored by telemetry, and a long-term efficacy study assessed renal and cardiac outcomes, with semaglutide (Sema) as a comparator.

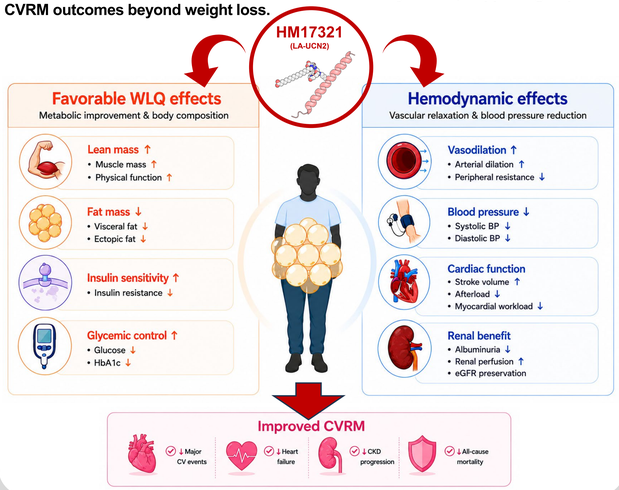
Results: In SHR, HM17321 reduced systemic BP and heart rate, with concomitant increases in blood NO levels, suggesting NO-mediated vasodilation and a strong potential to improve cardiovascular (CV) risk. In a 4-month study, HM17321 consistently improved WLQ, as evidenced by marked fat mass reduction (up to -45.5 percentage points *vs.* SHR) and lean mass gain (up to +9.7 percentage points) with no change in body weight. Notably, HM17321 prevented progressive renal function deterioration observed in vehicle- and Sema-treated SHR. Urinary albumin-to-creatinine ratio and 24-hour urinary albumin excretion were significantly reduced by HM17321 at 300 nmol/kg to 45.5% and 42.2% of vehicle-treated SHR levels, respectively. HM17321 also significantly attenuated cardiac hypertrophy, as evidenced by reduced heart weight. Comprehensive tissue-level analyses of cardiac and renal remodeling are currently underway. Additional mechanistic studies will further delineate the potential direct renal protective effects of HM17321 beyond BP-lowering-mediated benefits.

Conclusion: HM17321 exerted integrated cardiovascular and renal protective effects in preclinical models of hypertension and kidney injury. Beyond its favorable impact on WLQ as a next-generation obesity therapy, HM17321 attenuated the progression of renal dysfunction, supporting its potential applicability as a therapeutic strategy for cardiorenal diseases.

Background

Beyond Weight Loss: Enhancing Cardiovascular, Renal, and Metabolic Health

HM17321 is a novel long-acting CRFR2-selective UCN2 analog with coordinated effects on body composition, metabolism, and hemodynamics, supporting improved CVRM outcomes beyond weight loss.

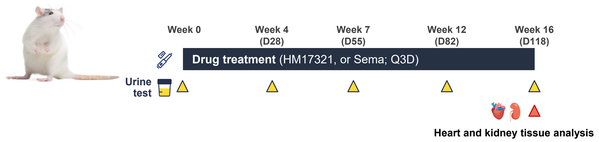


Methods

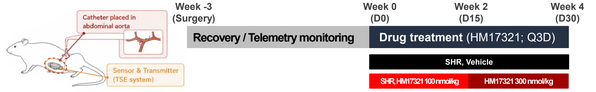
***In vivo* study**

Study 1. SHR*, ♂ 16W (SHR, n=6/group)

Hypertension-induced CVD/CKD model



Study 2. SHR*, ♂ 30W (telemetry implanted at 27 weeks of age)
(SHR, n=3/group)



Note. *SHR: Spontaneous Hypertensiver Rat

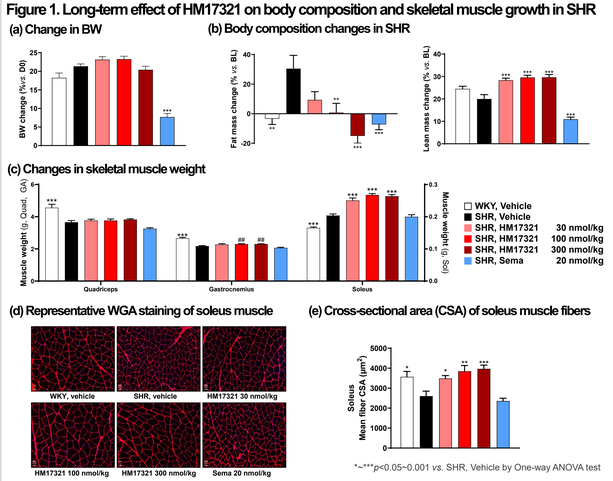
***In vitro* study**

Study 1. Primary Human Cardiac Microvascular Endothelial Cells
obtained from cardiac muscle (ventricle) of a 57-year-old Caucasian female (PromoCell)

- To evaluate the **protective effects** of HM17321 on the heart and kidney, male SHR were treated with HM17321 for up to 16 weeks, followed by periodic urine collection and heart/kidney tissue analyses. To assess the antihypertensive effect, **continuous blood pressure** was monitored using an implanted radiotelemetry system in SHR. Furthermore, to investigate the **direct endothelial mechanisms underlying vasodilatory effects**, primary human cardiac microvascular endothelial cells were used to assess p-eNOS activation and nitric oxide (NO) production following 30 min treatment of HM17321.

Effects of HM17321 on Body Composition and Muscle Growth

Figure 1. Long-term effect of HM17321 on body composition and skeletal muscle growth in SHR

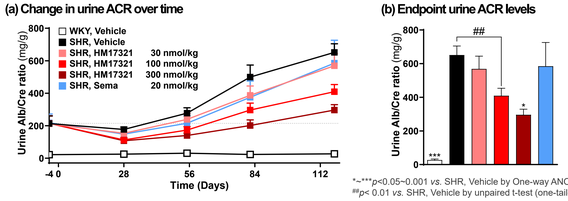


*~***p<0.05~0.001 *vs.* SHR, Vehicle by One-way ANOVA test

➢ Long-term HM17321 treatment improved body composition by reducing fat mass while increasing lean mass, accompanied by increased skeletal muscle weight and muscle fiber hypertrophy in SHR.

Long-term Effects of HM17321 on Renal Function in SHR

Figure 2. Effects of HM17321 on kidney injury progression in SHR



*~***p<0.05~0.001 *vs.* SHR, Vehicle by One-way ANOVA test, #p< 0.01 *vs.* SHR, Vehicle by unpaired t-test (one-tailed)

➢ Long-term HM17321 treatment attenuated progressive increases in uACR in SHR, suggesting reduced albuminuria progression and potential renoprotective effects.

Effects of HM17321 on Cardiac Hypertrophy and Vascular Remodeling

Figure 3. Effects of HM17321 on cardiac hypertrophy in SHR

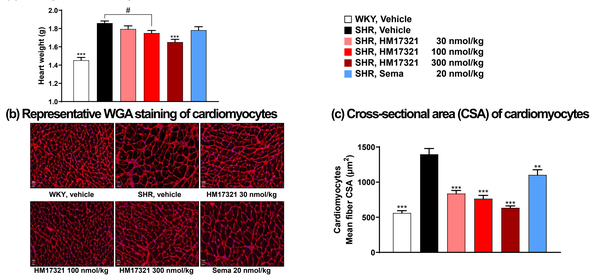
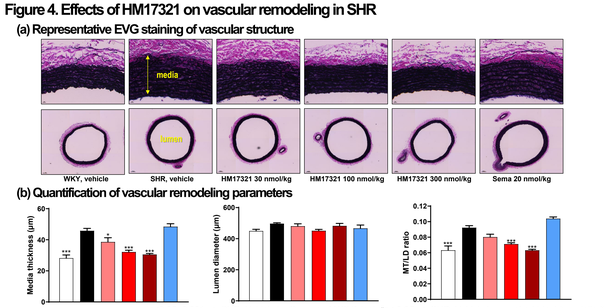


Figure 4. Effects of HM17321 on vascular remodeling in SHR

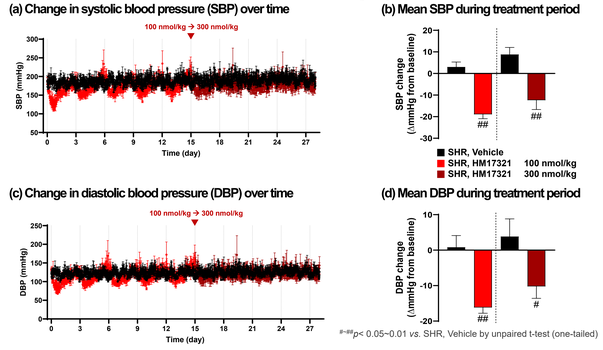


*~***p<0.05~0.001 *vs.* SHR, Vehicle by One-way ANOVA test, #p< 0.05 *vs.* SHR, Vehicle by unpaired t-test (one-tailed)

➢ HM17321 attenuated cardiac and vascular remodeling in SHR, accompanied by reduced hypertrophy, fibrosis, and arterial wall thickening, supporting potential cardiovascular protective effects.

Effects of HM17321 on Blood Pressure in SHR

Figure 5. Effect of HM17321 on blood pressure assessed by implantable radiotelemetry in SHR

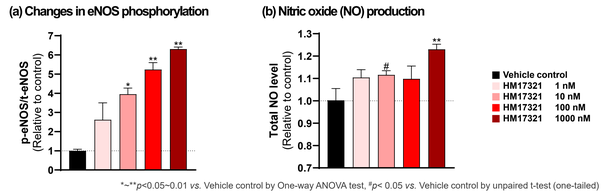


#~##p< 0.05~0.01 *vs.* SHR, Vehicle by unpaired t-test (one-tailed)

➢ HM17321 lowered systolic and diastolic blood pressure in SHR, supporting potential antihypertensive and cardiovascular protective effects.

Effects of HM17321 on Vasodilation-Related Signaling in HCMVECs

Figure 6. Effects of HM17321 on endothelial vasodilation signaling in HCMVECs



*~**p<0.05~0.01 *vs.* Vehicle control by One-way ANOVA test, #p< 0.05 *vs.* Vehicle control by unpaired t-test (one-tailed)

➢ HM17321 enhanced endothelial vasodilation signaling in HCMVECs by increasing eNOS phosphorylation and NO production, supporting potential vasodilatory effects.

Concluding Remarks

- HM17321 improved body composition and promoted skeletal muscle growth in SHR.
- HM17321 reduced blood pressure and attenuated albuminuria progression, supporting potential cardiorenal protective effects.
- HM17321 alleviated cardiac hypertrophy and vascular remodeling, indicating broad cardiovascular protective benefits.
- HM17321 enhanced eNOS activation and NO production, suggesting a potential mechanism underlying vasodilatory effects.
- Collectively, HM17321 demonstrated integrated benefits across muscle, renal, vascular, and cardiovascular systems beyond conventional metabolic effects.
- HM17321 is currently in a **Phase 1 clinical trial in the U.S.**
- Please also note additional presentations from our pipeline

  : Therapeutic potential of HM17321 in Sarcopenia (1783-P), Osteoarthritis & Osteoporosis (1803-P), Muscle Proteomics (2579-P), Heart Failure (2872-LB), and Incretin/Amylin Combination Therapy (3078-LB)

  : Discovery of HM500197, peptide-based MSTN inhibitor (3073-LB)

American Diabetes Association (ADA), June 5-8, 2026

Hanmi Pharm. Co., Ltd.