Serum Glucocorticoid Regulated Kinase 1 (SGK1) Inhibitor Reduced Hypertension in a Salt-Sensitive Hypertension Model of Heart Failure with Preserved Ejection Fraction

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Background

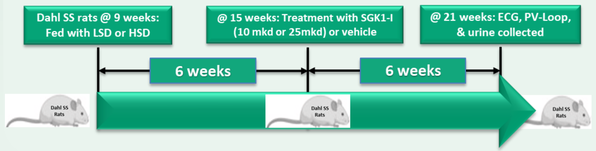
- Heart failure (HF) with preserved ejection fraction (HFpEF) is the subtype of HF with ejection fraction of ≥ 50% and accounts for 50% of HF diagnoses. Despite its high prevalence, treatment options for HFpEF remain limited.
- Hypertension, obesity, and atrial fibrillation are recognized as risk factors for HFpEF. These conditions often share overlapping pathological events, including insulin resistance, systemic inflammation, and cardiac fibrosis.
- **S**erum and **G**lucocorticoid-regulated **K**inase **1** (SGK1) is a PI3-kinase-dependent serine-threonine kinase involved in renal sodium homeostasis, inflammation, and fibrosis.
- Previous studies have suggested a pathological role of SGK1 in cardiac fibrosis and diastolic function of mouse and rabbit model of heart failure.
- Also, SGK1 plays an important role in salt-induced hypertension, insulin resistance, tissue fibrosis, and obesity induced atrial fibrillation.

Objective

- To evaluate the efficacy of a novel and potent SGK1 inhibitor, SGK1-I, in a rat model of HFpEF.

Methods

- Forty-one Dahl salt-sensitive (Dahl SS) rats were fed either a low salt diet (LSD, 0.3% NaCl, N=16) or high salt diet (HSD, 8% NaCl, N=25) for a total of 12 weeks.
- Six weeks after diet initiation, rats were treated with vehicle or SGK1-I (10 or 25 mg/kg QD) via oral gavage for the remaining 6 weeks.
- At 12 weeks, intracardiac hemodynamics and cardiac structure and function were assayed using pressure volume loop (PV-loop) and echocardiography (ECG) respectively.
- Urine was collected from the bladder of some rats at the end of the study to measure albumin levels using the albumin blue fluorescent kit (Active Motif).
- Data is presented as mean ± S.D. Statistical analysis was conducted using a one-way ANOVA with Dunnett's post-hoc test. Statistical significance indicated at p<.05 (*), p<.01 (**), p<.001 (***).



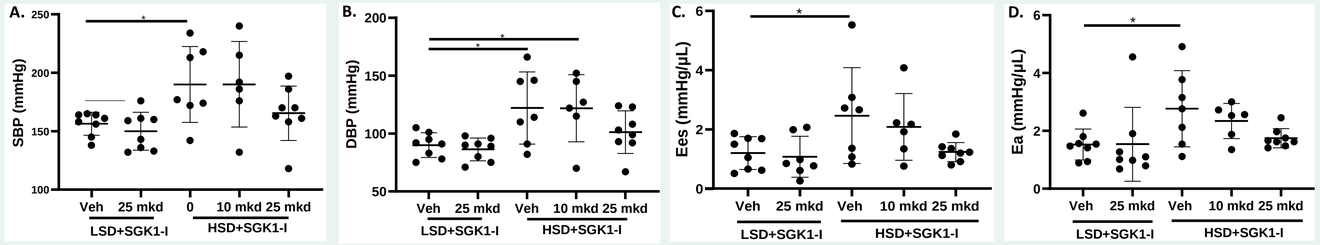
Results

1. No Diastolic Dysfunction was observed in the Dahl SS rats fed with HSD

Diastolic function parameters	LSD+SGK1-I		HSD+SGK1-I		
	Veh	25 mkd	Veh	10 mkd	25 mkd
IVRT (ms)	17.6±2.2	15.0±3.5	21.8±5	20.5±3.4	21.5±2.8
Tau (ms)	5.2±0.4	4.1±0.5*	7.3±1.4*	6.5±0.6*	6.8±0.8*
E/A	1.1±0.29	1.1±0.18	1.27±0.29	1.15±0.01	1.14±0.09
E' (mm/s)	67.3±30.0	76.1±31.8	67.6±15.2	60.2±13.3	75.1±16.4
E/E'	16.4±7.8	15.3±7.4	15.4±2.8	16.7±3.0	14.9±3.8

Diastolic function parameters in Dahl SS rats treated with HSD were similar to the rats treated with LSD.

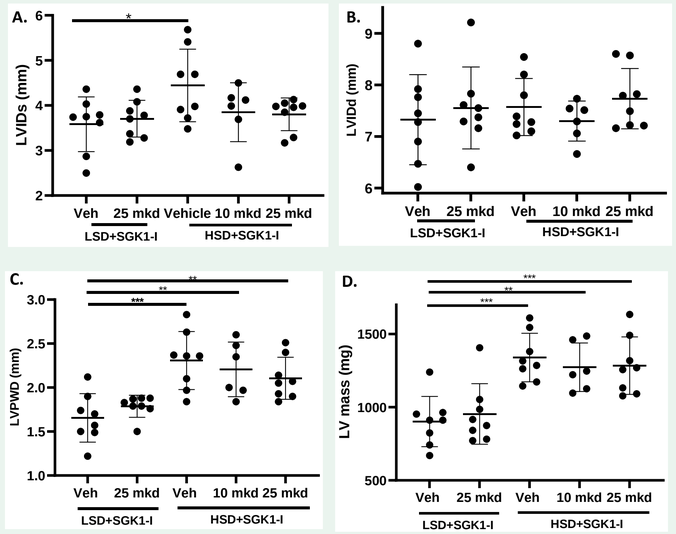
2. SGK1-I decreased HSD-induced hypertension and increased arterial and ventricular stiffness in Dahl SS rats



SGK1-I prevented HSD-induced hypertension (A & B) and dose-dependently reduced the ventricular (C) and arterial stiffness (D).

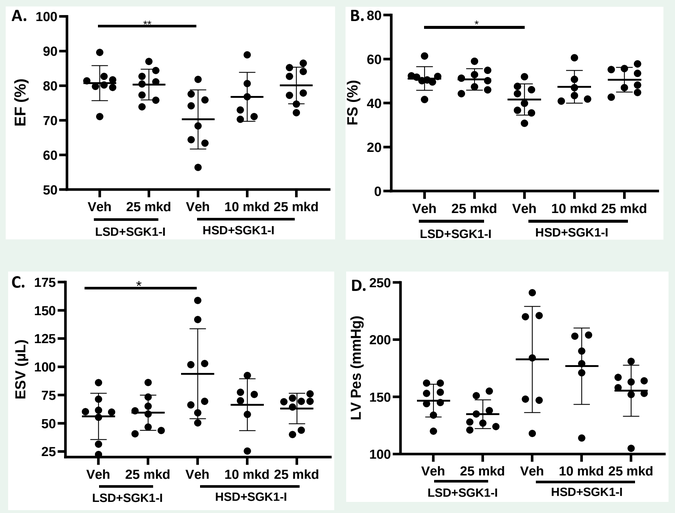
Results

3. SGK1-I slightly reduced the HSD-induced LV thickening



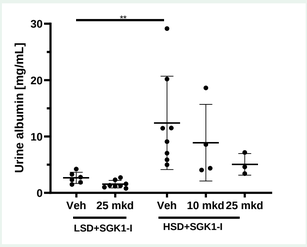
Left ventricle internal diameter during systole (LVIDs) (A), left ventricle posterior wall thickness (LVPWD) (C) and left ventricle mass (D) are significantly increased in Dahl SS rats treated with HSD. SGK1-I lowered the increase in LVIDs, LVPWD which was not statistically different than the vehicle treated rats but did not have any effect in LV mass. HSD did not have any significant effect on left ventricle internal diameter during diastole (LVIDd).

4. SGK1-I prevented progression to systolic dysfunction in Dahl SS fed with HSD



HSD induced systolic dysfunction, measured by ejection fraction (EF, A) and fraction shortening (FS, B), end systolic volume (ESV, C), and left ventricle end systolic pressure (LVP es, E). SGK1-I dose-dependently prevented HSD-induced systolic dysfunction in Dahl SS rats.

5. SGK1-I dose-dependently decreased HSD induced albuminuria in Dahl SS rats



Conclusion

- Therapeutic dosing of SGK1-I protects against development of high salt diet induced HFpEF in the Dahl salt-sensitive model by preventing hypertension and improving cardiac morphology, stiffness and systolic function.
- SGK1-I also protected the kidneys as measured by absence of albuminuria.
- These data support the continued development of SGK1-I as a promising treatment for hypertension-induced HFpEF and other cardiorenal complications.

Disclosures

- This in vivo study is sponsored by Thryv Therapeutics Inc.
- Saumya Das, Philip Sager, Dinesh Srinivasan, Eric Campeau, Shannon Hewgill, and Sabindra Pradhananga have received salary and equity from Thryv Therapeutics.
- Olga Shilova, Melissa Zammit, Peter Senese, and Michael Gralinski are employees of CorDynamics Inc.