Supplemental Material

Data S1.

Inclusion and Exclusion Criteria

The first study was prospectively performed in the Third Xiangya Hospital, Changsha, China, from January 2017 to November 2018.The inclusion criteria were as follows: 1）age over 18 years old; 2) diagnosed essential hypertension; Those who had no history of diabetes, cancer, severe hepatic or renal dysfunction, acute coronary syndrome (ACS), myocardial infarction (MI), or recent surgery were excluded.

The second study included 26 children with congenital heart disease (mean age= 5.44±3.82) who underwent cardiac thoracic surgery or cardiovascular interventional treatment at the Xiangya Third Hospital from January 2016 to November 2016. Those without completed general information and biological samples were excluded.

The third study included male patients > 18 years old with essential hypertension and depression who visited the Second Xiangya Hospital from January 2017 to March 2019. The exclusion criteria were consistent with the first study.

Table S1. Primer sequences of identification in ADRB1 KO rats.

Primer	Sequence	Length
Rat-Adrb1-Tal1-check-F1	GAACCCTGCAACCTGTCGT	708bp
Rat-Adrb1-Tal1-check-R1	CACCCGGAGGTACACGAA	

Table S2. PCR primers.

Gene	Forward Primer	Reverse Primer
BNP Rat	AGTCTCCAGAACAATCCACGATGC	CCGGAAGGCGCTGTCTTGAG
Collagen I Rat	TGTTGGTCCTGCTGGCAAGAATG	GTCACCTTGTTCGCCTGTCTCAC
Ctgf Rat	CACCGCACAGAACCACCACCAC	GGCAGGCACAGGTCTTGATGAAC
MHC Rat	GGTTCATCGCTGTCGGCTACG	TGGCGATCTGTGTCTCCTCCTC
GAPDH Rat	GACATGCCGCCTGGAGAAA	CAGCCCAGGATGCCCTTTAGT

Table S3. Baseline characteristics of all participants.

Parameters	normotensive (n=24)	patients with pre-HBP (n=24)	patients with HBP (n=24)	P value
age (years)	40.42±10.78	34.58±6.02	43.00±11.29	0.24
BMI (kg/m2)	23.64±2.52	25.11±3.24	26.22±2.76	0.68
SBP (mmHg)	118.88±5.59	133.08±3.00	147.20±5.17	<0.01
DBP (mmHg)	74.06±6.22	82.92±4.52	87.20±14.55	<0.01
HR (min-1)	81.55±12.75	80.00±6.47	90.60±12.03	0.21
HDL-C (mg/dL)	1.33±0.20	1.28±0.18	1.32±0.11	0.73
LDL-C (mg/dL)	2.88±0.84	2.47±0.46	2.45±0.79	0.21
TG (mg/dL)	1.66±0.88	1.97±1.38	2.35±1.43	0.35
FPG (mmol/L)	5.50±1.35	5.47±0.33	6.05±1.32	0.61
HGB (g/L)	154.39±17.18	157.92±5.90	157.00±9.95	0.76
ALT (U/L)	26.88±14.70	35.50±13.29	30.40±14.82	0.41
AST (U/L)	20.33±4.82	23.43±5.50	20.25±6.18	0.30
TB (umol/L)	12.40±4.26	8.84±2.15	11.36±2.22	0.04
BUN (mmol/L)	4.99±1.28	4.55±1.30	5.30±1.10	0.47
Cre (umol/L)	81.03±12.58	81.17±9.14	87.00±10.15	0.52

The data represent mean ± standard deviation，P value is shown compared to the normal population by chi-square test. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglyceride; FPG, fasting plasma glucose; HGB, hemoglobin; ALT, glutamic-pyruvic transaminase; AST, glutamic oxaloacetic transaminase; TB, total bilirubin; BUN, blood urea nitrogen; Cre, creatinine.

Table S4. The primers and illustration for the plasmid and vectors.

	Primer name	Sequence 5'---3'
pmCherry-N1-flag-ADRB1	flag-ADRB1-f1	ATGGGCGCGGGGGTGCTCGT
	flag-ADRB1-f2	ATGGACTACAAGGATGACGACGACAAGGGA
	flag-ADRB1-r	CACCTTGGATTCCGAGGCGAA
pHBLV-CMV-MCS-3flag-EF1-ZsGreen	h-GRK2-E/B-F	AGGATCTATTTCCGGTGAATTCGCCACCATGGCGGACCTGGAGGCGGT
	h-GRK2-E/B-R	AGTCACTTAAGCTTGGTACCGAGGATCCGAGGCCGTTGGCACTGCCGC

Table S5. Nucleotide sequence of tags.

Tag	Sequence 5'---3'
V5-tag	GGTAAGCCTATCCCTAACCCTCTCCTCGGTCTCGATTCTACG
Flag-Tag	GATTACAAGGATGACGACGATAAG

Table S6. The siRNA and shRNA sequence.

siRNA	Sequence 5'---3'
Control	TTCTCCGAACGTGTCACGTAA
SiGRK2	TGCCCATTCATTGTCTGCATGTCAT

shRNA	Top strand	Bottom strand
Control	GATCCGTTCTCCGAACGTGTCACGTAATTCAAGAGATTACGTGACACGTTCGGAGAATTTTTTC	AATTGAAAAAATTCTCCGAACGTGTCACGTAATCTCTTGAATTACGTGACACGTTCGGAGAACG
ShGRK2	GATCCGTGCCCATTCATTGTCTGCATGTCATTTCAAGAGAATGACATGCAGACAATGAATGGGCATTTTTTG	AATTCAAAAAATGCCCATTCATTGTCTGCATGTCATTCTCTTGAAATGACATGCAGACAATGAATGGGCACG

Table S7. Baseline characteristics of patients with congenital heart disease(n=19).

Parameters	n=19
age (years)	5.44±3.82
Male (n (%))	13(68.4%)
BMI (kg/m2)	16.33±2.94
SBP (mmHg)	105.65±15.54
DBP (mmHg)	68.72±9.93
HR (min-1)	97.03±18.35
HDL-C (mg/dL)	1.02±0.05
LDL-C (mg/dL)	2.42±0.26
TG (mg/dL)	1.53±0.25
FPG (mmol/L)	4.95±0.33
HGB (g/L)	134.04±13.72
ALT (U/L)	14.56±4.24
AST (U/L)	5.44±3.82
TB (umol/L)	13.71±4.54
BUN (mmol/L)	4,34±1.34
Cre(umol/L)	35.24±15.28

Statistics represent mean ± standard deviation

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglyceride; FPG, fasting plasma glucose; HGB,hemoglobin;ALT,glutamic-pyruvic transaminase;AST,glutamic oxaloacetic transaminase;TB, total bilirubin; BUN, blood urea nitrogen;Cre,creatinine;UA, uric acid;PRO,urinary protein.

Table S8. Changes of SBP and HR in WKY rats with different treatments.

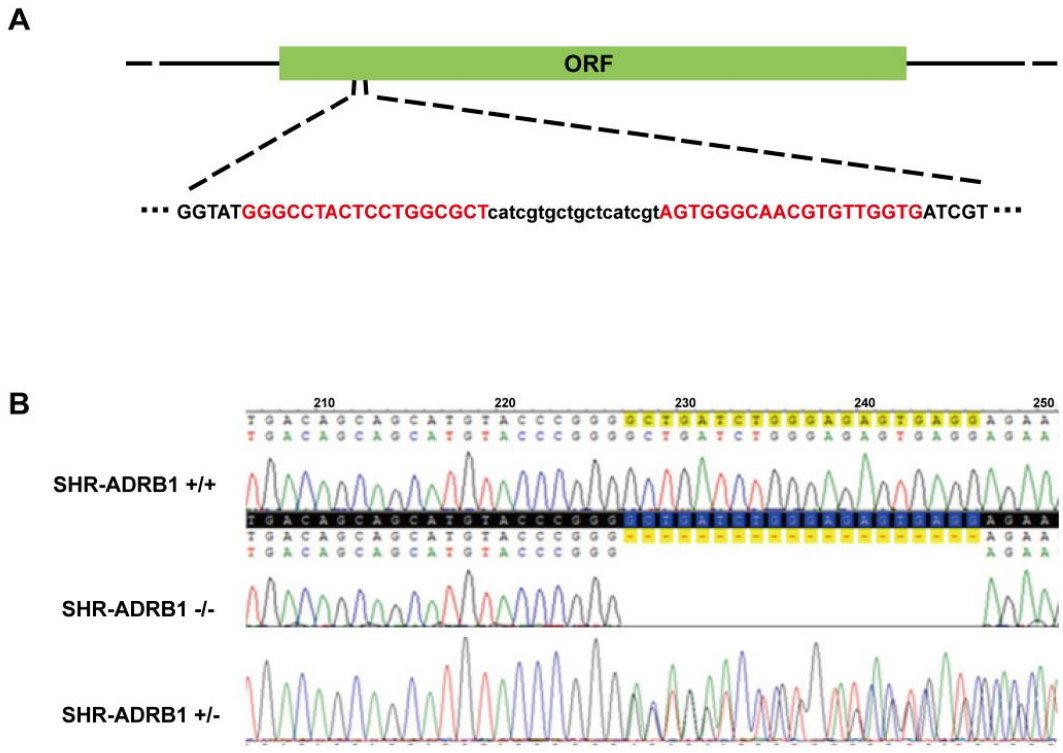
A.SBP in WKY rats with different treatments(mmHg)

Age	WKY Control	WKY+ Paroxetine	WKY+ Metoprolol	WKY+ Met+Par	WKY+ Amlodipine
10wks	126.27±4.38	125.28±4.46	126.37±2.46	126.14±3.67	127.12±4.26
12wks	126.67±5.13	126.47±4.48	126.38±1.13	126.39±3.19	126.27±5.11
14wks	126.62±4.48	127.17±3.53	126.87±2.01	126.22±4.12	126.78±4.27
16wks	126.74±4.63	127.05±3.13	127.34±4.23	125.18±4.34	127.67±6.54
18wks	127.69±5.04	126.93±4.34	126.37±5.52	127.67±2.13	127.35±4.37
20wks	126.94±3.83	127.62±5.64	126.88±1.25	128.45±4.87	128.67±3.83
22wks	127.64±4.33	127.87±4.26	127.65±2.13	128.67±5.23	128.67±5.33

B.HR in WKY rats with different treatments(bmp)

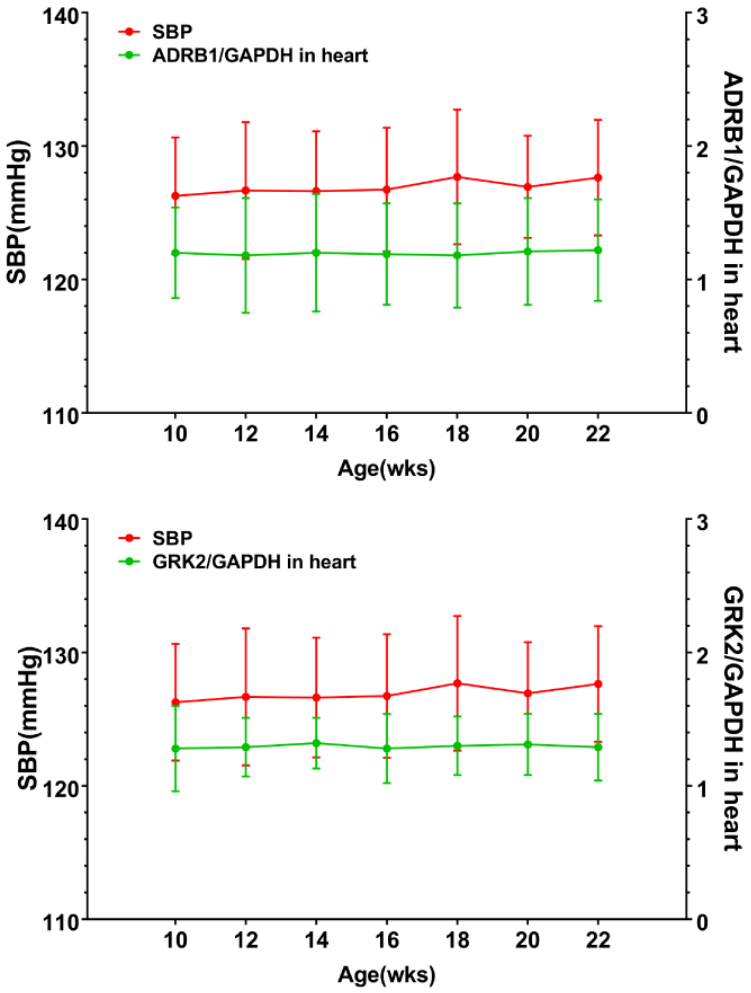
Age	WKY Control	WKY+ Paroxetine	WKY+ Metoprolol	WKY+ Met+Par	WKY+ Amlodipine
10wks	321.42±14.31	326.34±13.43	328.35±12.36	325.14±14.67	323.12±13.35
12wks	322.26±9.43	326.34±11.49	326.13±11.15	329.39±11.47	326.63±11.36
14wks	319.32±11.78	332.17±10.23	326.87±12.35	326.55±12.12	325.64±12.44
16wks	310.24±14.24	325.26±12.56	328.34±9.79	325.57±13.54	327.35±13.24
18wks	324.49±12.02	326.93±14.36	330.37±10.52	332.67±12.24	330.35±9.32
20wks	329.34±11.83	331.62±9.64	326.73±10.35	329.59±11.46	332.43±15.03
22wks	330.35±13.23	326.87±8.23	327.65±9.96	328.67±9.78	330.67±10.33

Figure S1. ADRB1 KO rats.



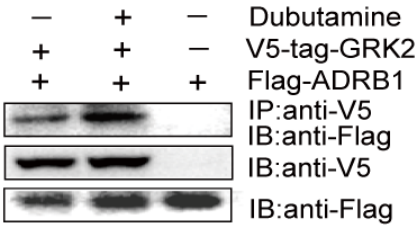
A. The red font is underlined to indicate the target sequence of TALEN, the lowercase font is the speacer sequence, the system generates a DNA double-strand break at the speacer, and then the cell uses its own non-homologous recombination repair mechanism without providing a repair template When repairing, nucleotide insertions or deletions may be introduced during the repair process, which may cause frameshift mutations in the gene and eventually lead to inactivation of the target gene. **B.** Comparative map of PCR results of three genotypes, including ADRB1+/+, ADRB1-/-, and ADRB1+/- in SHR rats. There is no bimodal or chaotic peak phenomenon, and it is completely continuous with the target sequence in SHR-ADRB1+/+ rats. There is a gene deletion, which is homozygote knockout rat (SHR-ADRB1-/-) while there are bimodal phenomena near the recognition sequence in SHR-ADRB1+/- rats.

Figure S2. Expressions of ADRB1 and GRK2 in WKY.



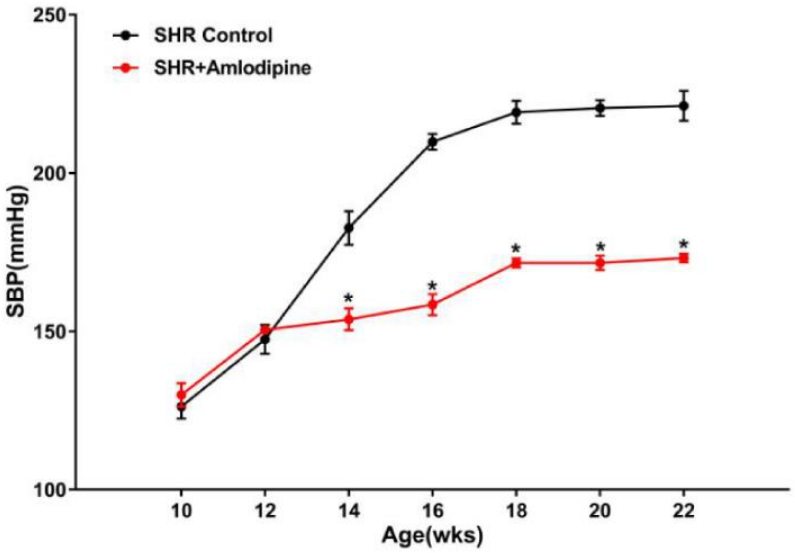
The relative mRNA expressions of ADRB1 and GRK2 in the myocardium (n=6) and dynamic change in SBP (n=6) from 10-week to 22-week of age in WKY. Data are presented as the means ± SD.

Figure S3. Dobutamine enhances the interaction between GRK2 and ADRB1.



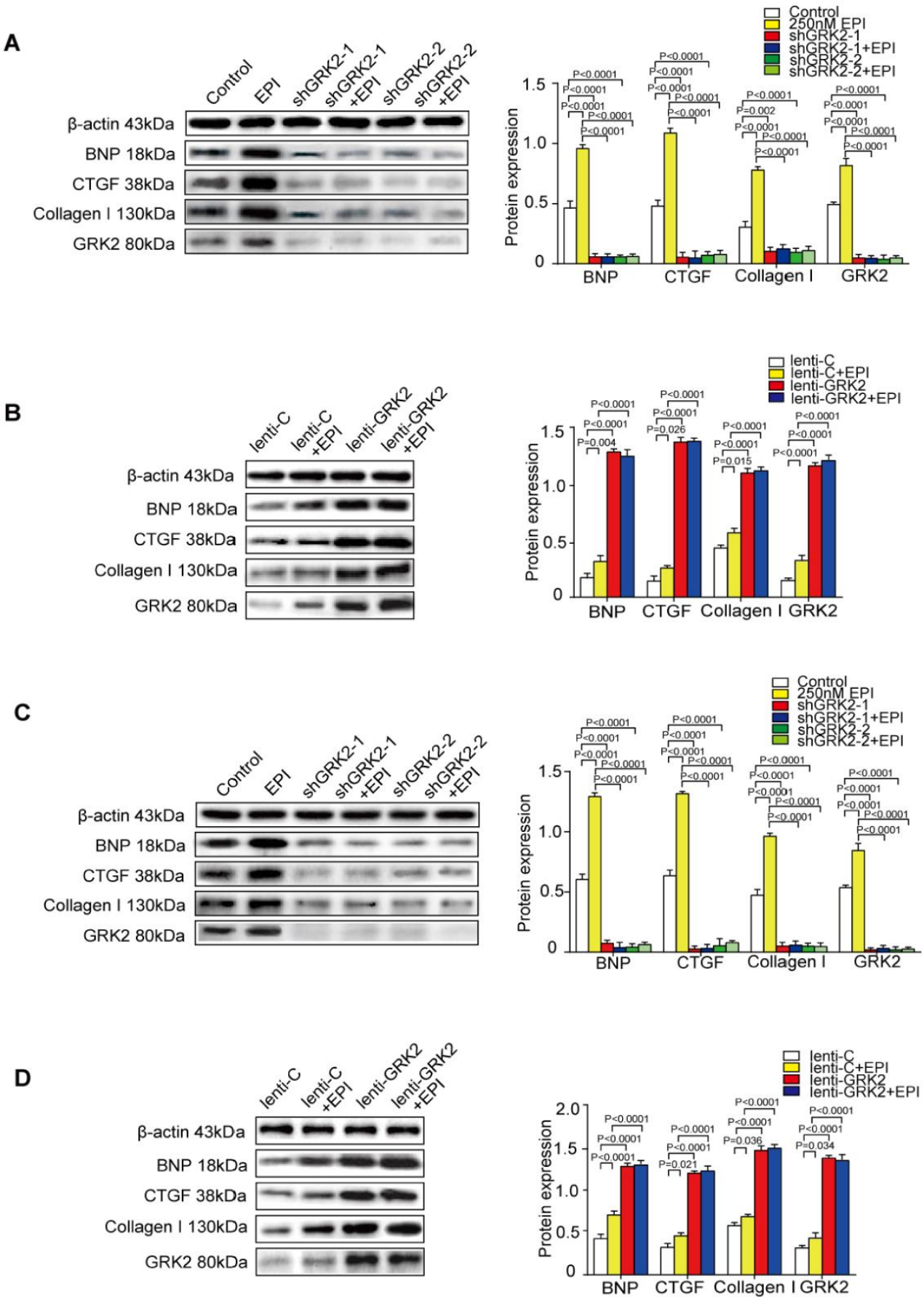
Representative immunoblots confirming dobutamine enhance the interaction between V5-tag-GRK2 and Flag-ADRB1.

Figure S4. Changes of SBP in SHR rats with amlodipine.



The dynamic change in systolic blood pressure of SHR and SHR treated with amlodipine at the age from 10 to 22 weeks. Data are presented as the means ± SD. *P<0.05 compared with the controls.

Figure S5. GRK2 promotes epinephrine induced cardiomyocyte hypertrophy in rat cardiomyocytes.



A.Immunoblots (left) and quantification (right) of expression levels of β-actin, BNP, CTGF, collagen I and GRK2 in cultured H9C2 cells infected with the indicated recombinant adenovirus with or without stimulation by epinephrine (n=4 samples per group). **B.** Representative western blots and the bar graphs presenting the quantitative data for β-actin, BNP, CTGF, collagen I and GRK2 in the indicated groups of H9C2 cells (n=4 samples per group). **C.** Immunoblots (left) and quantification (right) of expression levels of β-actin, BNP, CTGF, collagen I and GRK2 in cultured primary rat cardiomyocytes infected with the indicated recombinant adenovirus with or without stimulation by epinephrine (n=4 samples per group). **D.** Representative western blots and the bar graphs presenting the quantitative data for β-actin, BNP, CTGF, collagen I and GRK2 in the indicated groups of primary rat cardiomyocytes (n=4 samples per group). Data shown are mean ± SD (A-D). Data were first analyzed and passed normality test (Shapiro-Wilk test in A-D). P values were shown and assessed by one-way ANOVA with Tukey’ s test (A-D). EPI: epinephrine. All data are shown as the mean ± SD.