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Supplementary	Table S1:	: Metabolic profile	e of NRs treated with	metformin
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Outcome	Hfib	Chow	Chow+met	
Body weight (g)	71.5±1.9	77.0±2.6	78.8±2.3	
BMI (kg/m <sup>2</sup> )	4.6±0.1	$4.8 \pm 0.1$	4.8±0.1	
Weight gain (%)	46±8	44±5	$44\pm 5$	
Fasting state				
FBG (mmol/L)	2.9±0.3	3.2±0.7	2.5±0.3	
Insulin (ng/mL)	0.6±0.5	4.9±1.7*	5.0±1.7*	
ISI	$1.7{\pm}0.2$	1.0±0.2*	$1.0{\pm}0.2$	
HOMA-IR	2.0±1.5	23.0±11.0*	16.7±6.3	
HOMA-B	$0.9{\pm}0.7$	7.6±2.7*	9.1±3.0*	
Glucagon (pg/mL)	47.8±36.3	325.7±74.2*	480.6±162.2*	
Glucagon/Insulin	$0.7{\pm}0.5$	$0.4{\pm}0.2$	$0.7{\pm}0.4$	
Fed state				
Glucose (mmol/L)	3.2±0.2	3.3±0.2	3.6±0.2	
Insulin (ng/mL)	$2.8{\pm}0.4$	$7.0{\pm}1.41$	11.3±2.3*	
Glucagon (pg/mL)	102.1±30.2	89.0±33.7	55.9±23.9	
Glucagon/Insulin	$0.04{\pm}0.01$	$0.01 {\pm} 0.004$	$0.02{\pm}0.01$	
GLP-1 (pmol/L)	1.2±0.2	$0.7{\pm}0.4$	$0.4{\pm}0.1$	

2 BMI: body mass index; ISI: insulin sensitivity index; HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-B:

homeostatic model assessment of β-cell function. Data were represented as mean  $\pm$  SEM and analyzed using the Kruskal-Wallis

4 test. \*p<0.05 vs age-matched Hfib.

## 5 Supplementary Table S2: Antibodies and dilutions used in western blot and immunofluorescent microscopy

Antibody	Source	Dilution
Rabbit Anti-AMPKα	2532, Cell Signaling Technology, Danvers, MA, USA	1:1000
Rabbit Anti-phospho-	2525 Call Signaling Technology Danyorg MA USA	1.1000
Thr172-AMPKα	2353, Cen Signating Technology, Danvers, MA, USA	1.1000
Rabbit Anti- PEP		
	10004943, Cayman Chemical, Ann Arbor, MI, USA	1:200
СК		
Rabbit Anti-G6Pase	Sc-25840, Santa Cruz Biotechnology, Dallas, Texas, USA	1:1000

Mouse Anti-Glut2	Sc-518022, Santa Cruz Biotechnology, Dallas, Texas, USA	1:200
Rabbit Anti-IR	3025, Cell Signaling Technology, Danvers, MA, USA	1:500
Rabbit Anti-PGC1α	Ab54481, Abcam, Cambridge, UK	1:1000
Rabbit Anti-PKA C	4782, Cell Signaling Technology, Danvers, MA, USA	1:1000
Rabbit Anti-phospho- Thr197-PKA	4781, Cell Signaling Technology, Danvers, MA, USA	1:1000
Rabbit Anti-Bip	3177, Cell Signaling Technology, Danvers, MA, USA	1:1000
Rabbit Anti-Grp94	2104, Cell Signaling Technology, Danvers, MA, USA	1:1000
Mouse Anti-CHOP	2895, Cell Signaling Technology, Danvers, MA, USA	1:500
Rabbit Anti-caspase3	9665, Cell Signaling Technology, Danvers, MA, USA	1:500
Mouse Anti-CHOP	2895, Cell Signaling Technology, Danvers, MA, USA	1:500
Rabbit Anti-phospho- Ser79-ACC	3661, Cell Signaling Technology, Danvers, MA, USA	1:1000
Guinea Pig Anti-Insulin	A0564, Dako, Burlington, ON, Canada	1:200
Mouse Anti-Glucagon	ab10842, Abcam, Cambridge, UK	1:200
Rabbit Anti-PDI	3501, Cell Signaling Technology, Danvers, MA, USA	1:200
Rabbit Anti-ERp44	3798, Cell Signaling Technology, Danvers, MA, USA	1:200
Rabbit Anti-Ki67	Ab15580, Abcam, Cambridge, UK	1:200

# 6 Supplementary Table S3: qPCR primers and annealing temperatures

Gene		Primer	Tm (°C)
Ins	Forward	5'-AAGTGGCACAACTGGAGCTG-3'	58

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	Reverse	5'-GATGCTGGTGCAGCACTGA-3'		
IR	Forward	5'-AGACCCGAAGATTTCCGAGAC-3'	58	
	Reverse	5'-GAGCCTCGGATGACTGTGAG-3'	58	
	Forward	5'- GTCAGAAGACAAGATCACCGGAAC -3'	58	
Glut2	Reverse	5'- CCTCTTGAGGTGCATTGATCACAC -3'		
Gck	Forward	5'-GAGCTGGTACGACTTGTGCT -3'	58	
	Reverse	5'-AACCGCTCCTTGAAGCTCG -3'		
Pdx1	Forward	5'-GCTGGAGCTGGAGAAGGAATTC-3'	50	
	Reverse	5'-CTTCATGCGACGGTTTTGGAACC-3'	58	
	Forward	5'-AGTTCGAGGTGAAGAAGGAGCC-3'		
MafaA	Reverse	5'-CGCTCATCCAGTACAGATCCTCC-3'	58	
Pgc1a	Forward	5'-CCAGCCTCTTTGCCCAGAT-3'		
	Reverse	5'-AGGGCAATCCGTCTTCATCC-3'	58	
	Forward	5'-AACATGACCGAGATGAGCTTCCTG-3'		
Atf4	Reverse	5'-AAGTGCTTGGCCACCTCCA-3'	56	
Atf6	Forward	5'-TGCTCTGGAACAGGGCTC-3'		
	Reverse	5'-ATGGACACCAGGATCCTCCA-3'	56	
	Forward	5'-CTGAGTCCGCAGCAGGT-3'	56	
spliced Xbp1	Reverse	5'-GGTCCAACTTGTCCAGAATGCC-3'		
	Forward	5'-AGTCCGCAGCACTCAGACTA-3'		
Xbp1	Reverse	5'-GGTCCAACTTGTCCAGAATGCC-3'	56	
Chop	Forward	5'-GGAGCTGGAAGCCTGGTATGAG-3'		
	Reverse	5'-TGGTCAGGCGCTCGATTTCC-3'	56	
Bax	Forward	5'-CAGGGTTTCATCCAGGATCGAGC-3'		
	Reverse	5'-GCAATCATCCTCTGCAGCTCC -3'	56	
	Forward	5'-GGATGACTGAGTACCTGAACCGG-3'	56	
Bcl-2	Reverse	5'-GTCTTCAGAGACAGCCAGGAG -3'		

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## 8 Supplementary Figure S1



### 9

Supplementary Figure S1 Protein abundance of GLUT2 (A) and IR (B) in isolated islets. Data are presented as means + SEM.
n=3-5. \*indicates p<0.05 vs Hfib, # p<0.05 vs Chow using the Kruskal-Wallis test followed by Dunn's multiple comparison test.</li>

#### 12 Supplementary Figure S2





14 Supplementary Figure S2 Analysis of hepatic AMPK pathway in the fasting condition. A-D quantification of phospho-AMPK to

15 AMPK (A), phospho-PKA to PKA (B), PEPCK (C) and G6Pase (D) relative to GAPDH. Data are presented as means + SEM. n=5-

16 11. \*indicates p<0.05 vs Hfib, # p<0.05 vs Chow using the Kruskal-Wallis test followed by Dunn's multiple comparison test.