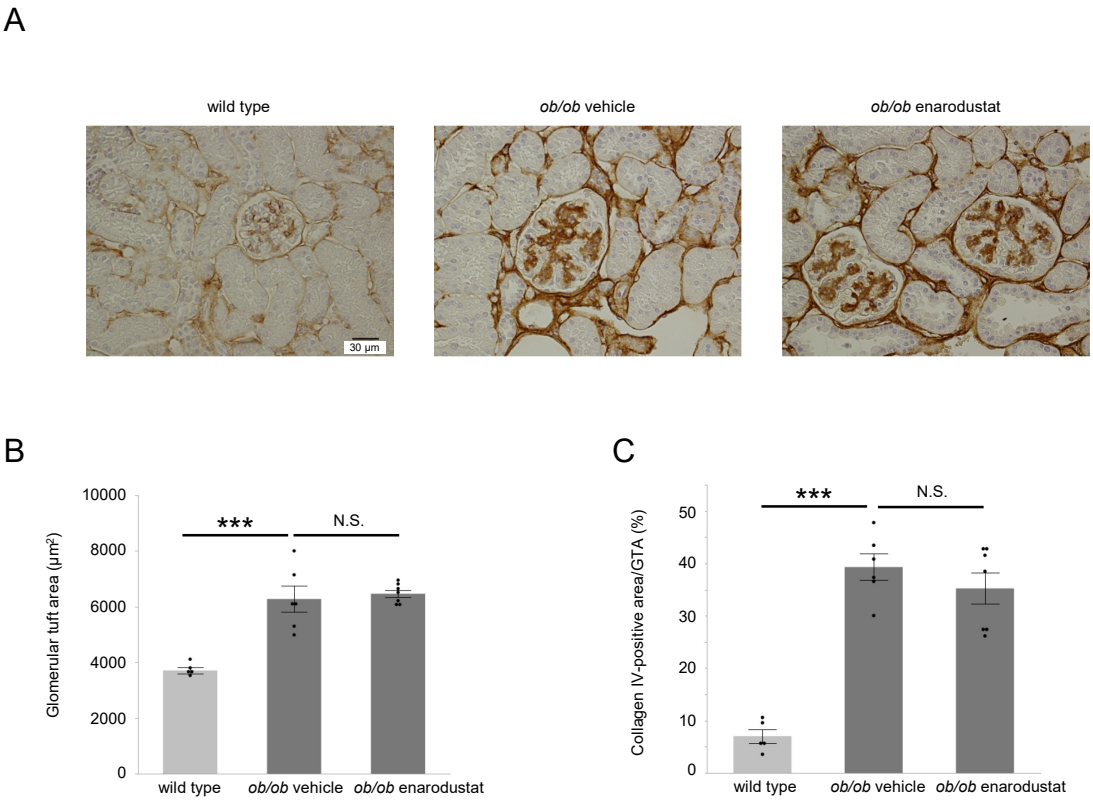
Table of Contents



Supplemental Figure 1. Enarodustat did not reduce glomerular hypertrophy or mesangial expansion. (A) Representative images of collagen IV staining of kidney. (B) Glomerular tuft area (GTA) was measured in 10 glomeruli per mouse. (C) The percentage of collagen IV-positive area within each glomerulus was measured as the index of mesangial expansion. Ten randomly chosen glomeruli were evaluated per mouse. Data are expressed as means ± SEM; wild type, n = 5; *ob/ob* vehicle, n = 6; *ob/ob* enarodustat, n = 7. ***$p < 0.001$, N.S. not significant.

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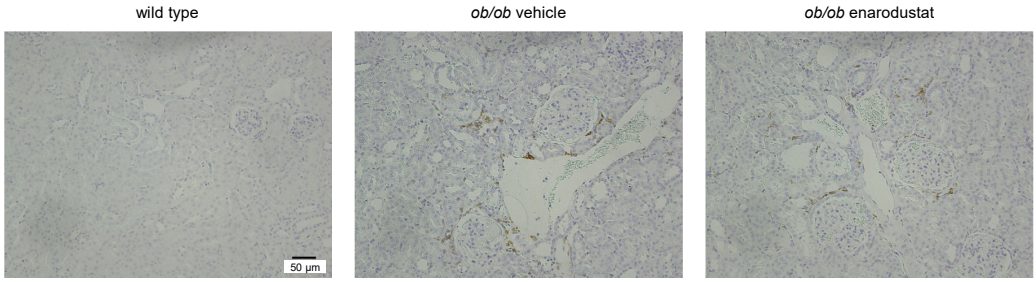
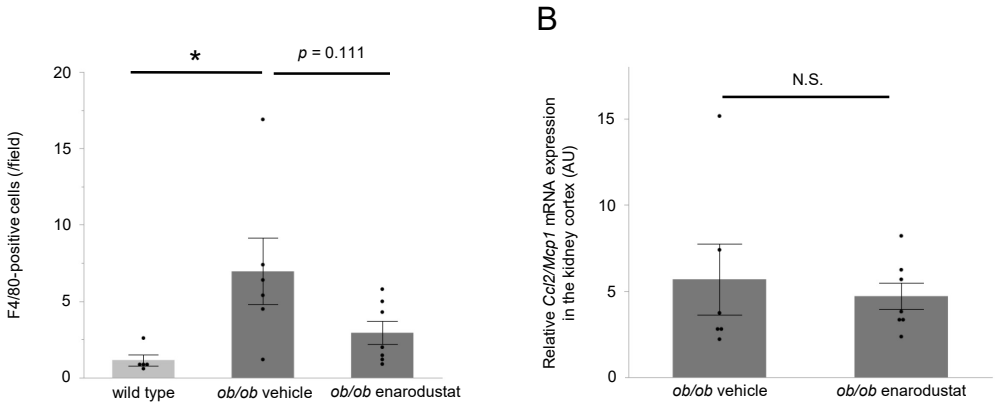
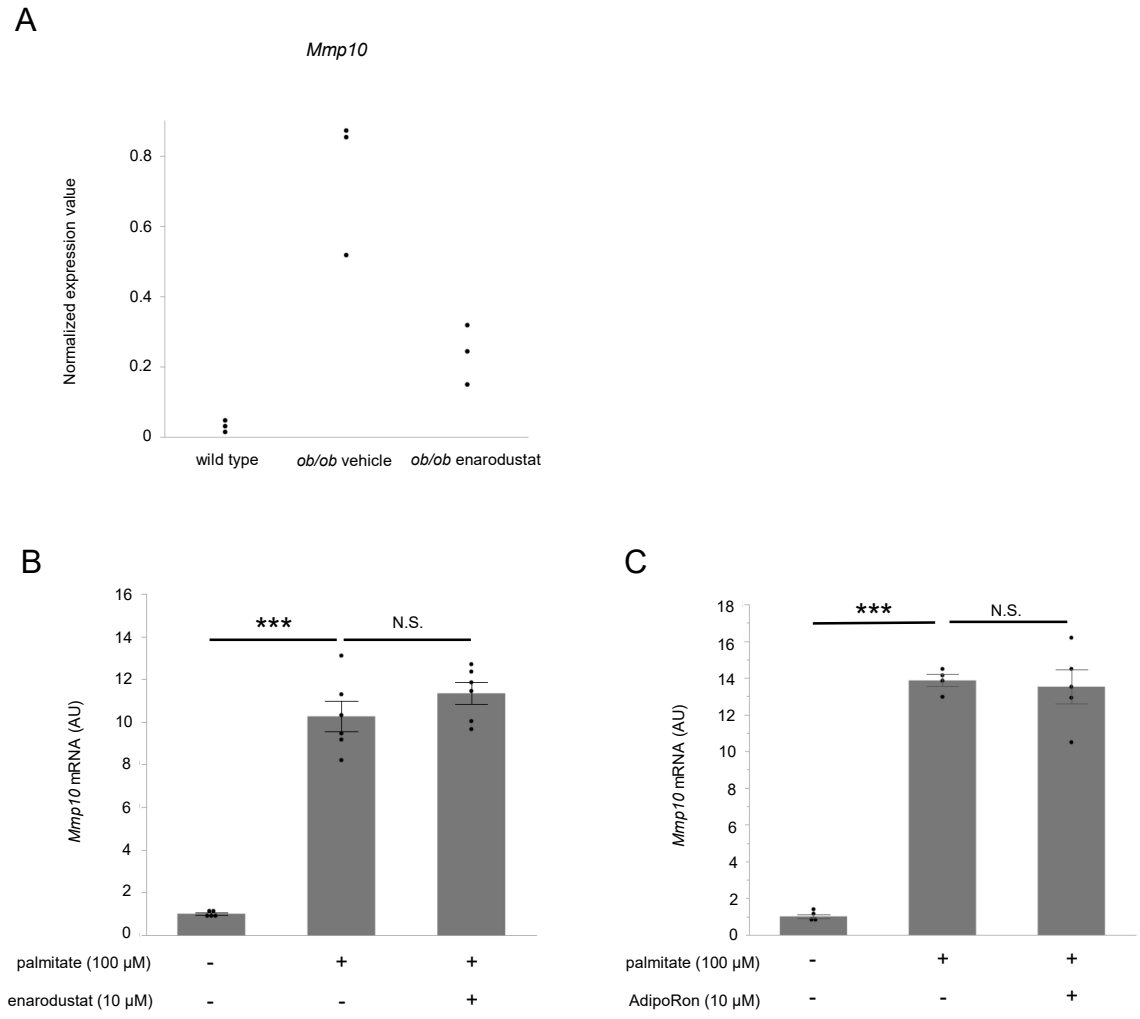
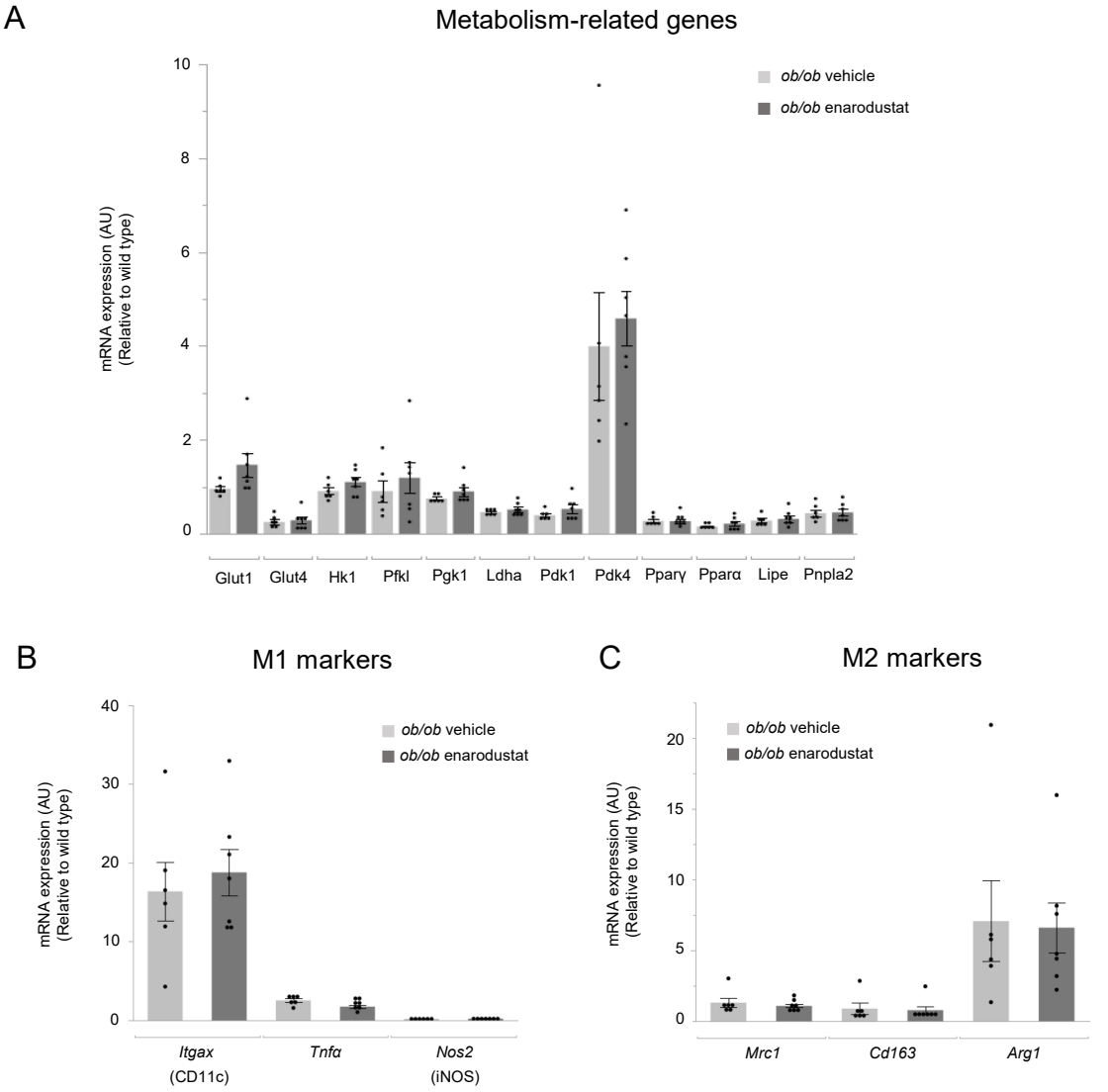




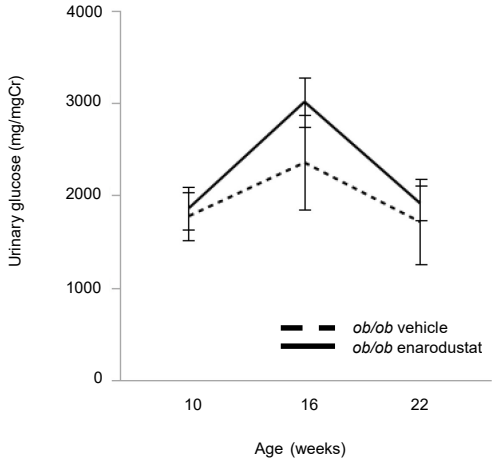
Supplemental Figure 2. Enarodustat tended to decrease macrophage infiltration in the tubulointerstitium, but *Ccl2/Mcp1* mRNA expression in the kidney cortex was unchanged. (A) Representative images of F4/80 staining of kidney. The numbers of F4/80-positive cells were evaluated in 10 randomly chosen fields per mouse. (B) The mRNA expression levels of *Ccl2/Mcp1* in the kidney cortex, shown as means relative to wild type after normalization to *Actb* (β-actin). *Ccl2*, C-C motif chemokine ligand 2; *Mcp1*, monocyte chemoattractant protein-1. Data are expressed as means ± SEM; wild type, n = 5; *ob/ob* vehicle, n = 6; ob/ob enarodustat, n = 7. **p* < 0.05, N.S. not significant.



Supplemental Figure 3. Glomerular expression of MMP-10 was suppressed in enarodustat-treated BTBR *ob/ob* mice, but its expression in cultured mesangial cells were not affected by enarodustat or AdipoRon (a small molecule adiponectin receptor agonist). (A) Normalized expression values of *Mmp10* in the glomeruli of BTBR wild type and BTBR *ob/ob* mice treated with either vehicle-only or enarodsutat. The expression levels were obtained from the transcriptome analysis (n = 3 for each group). (B) Quantitative real-time PCR was performed to assess mRNA expression levels of *Mmp10* in murine mesangial cells after 12-hour stimulation by palmitate, with or without enarodustat (n = 5-6 for each group). (C) The mRNA expression levels of *Mmp10* in murine mesangial cells after 12-hour stimulation by palmitate, with or without AdipoRon (n = 4-5 for each group). The mRNA expression levels are shown as means relative to the control after normalization to *Actb* (β-actin). ***$p < 0.001$, N.S. not significant.



Supplemental Figure 4. Enarodustat did not change the expression levels of metabolism-related genes or M1/M2 macrophage markers in white adipose tissue. Quantitative real-time PCR was performed to analyze mRNA levels of metabolism-related genes (A), M1 macrophage markers (B), and M2 macrophage markers (C) in WAT. *Glut1*, glucose transporter type 1; *Glut4*, glucose transporter type 4; *Hk1*, hexokinase-1; *Pfkl*, phosphofructokinase; *Pgk1*, phosphoglycerate kinase-1; *Ldha*, lactate dehydrogenase; *Pdk1*, pyruvate dehydrogenase kinase 1; *Pdk4*, pyruvate dehydrogenase kinase 4; *Pparγ* and *Pparα*, peroxisome proliferator-activated receptors γ and α; *Lipe*, hormone-sensitive lipase; *Pnpla2*, patatin-like phospholipase domain-containing protein 2; *Itgax*, integrin alpha X; *Tnfα*, tissue necrosis factor-α; *Nos2*, nitric oxide synthase 2; *Mrc2*, mannose receptor c-type 1; *Arg1*, Arginase 1. The mRNA expression levels are shown as means relative to wild type mice after normalization to *Actb* (β-actin) ± SEM; wild type, n = 5; *ob/ob* vehicle, n = 6; *ob/ob* enarodustat, n = 7.



Supplemental Figure 5. The urinary glucose levels did not differ significantly between vehicle-only and enarodustat-treated groups. Urinary glucose of BTBR *ob/ob* mice treated with either vehicle-only or enarodustat at 10, 16, and 22 weeks of age. Data are expressed as means ± SEM; *ob/ob* vehicle, n = 6; *ob/ob* enarodustat, n = 7.

Supplemental Table 1. Hematocrit and intake of BTBR *ob/ob* mice treated with different doses of enarodustat.

	Hematocrit (%)	Intake (g/day)
vehicle	46.8 ± 0.9	10.9 ± 0.2
0.015 mg/g	45.4 ± 0.4	-
0.05 mg/g	49.5 ± 0.7*	10.6 ± 0.1
0.15 mg/g	65.3 ± 1.4***	8.2 ± 0.1***

Data are expressed as means ± SEM. Hematocrit was measured at 22 weeks of age. Intake was measured at 20 weeks of age. *$p < 0.05$, ***$p < 0.001$ compared to the vehicle-only group.

Supplemental Table 2. List of primers used in this study.

Gene	F/R	Sequence (5'→3')
Actb	Forward	AAGATCAAGATCATTGCTCCTCCT
	Reverse	AAACGCAGCTCAGTAACAGTCC
Arg1	Forward	TTTTTCCAGCAGACCAGCTT
	Reverse	GGAACCCAGAGAGAGCATGA
Ccl2/Mcp1	Forward	CAGCTCTCTCTTCCTCCACCAC
	Reverse	GCGTTAACTGCATCTGGCTGAG
Cd163	Forward	TCTCCTGGTTGTAAAAGGTTTGT
	Reverse	TCATTCATGCTCCAGCCGTT
Glut1	Forward	GTGACGATCTGAGCTACGGG
	Reverse	ACTCCTCAATAACCTTCTGGGG
Glut4	Forward	CTTATTGCAGCGCCTGAGTC
	Reverse	GGGGGTTCCCCATCGTCAG
Hk1	Forward	CTGCTCACCAGGGCTACTG
	Reverse	CCCTTTTCTGAGCCGTCCG
Hif-1α	Forward	GTTTACTAAAGGACAAGTCACC
	Reverse	TTCTGTTTGTTGAAGGGAG
Hif-2α	Forward	GTCACCAGAACTTGTGC
	Reverse	CAAAGATGCTGTTCATGG
Il1β	Forward	ACTGTGAAATGCCACCTTTTG
	Reverse	TGTTGATGTGCTGCTGTGAG
Il10	Forward	GGCGCTGTCATCGATTTCTC
	Reverse	ATGGCCTTGTAGACACCTTGG
Il6	Forward	ACAAAGCCAGAGTCCTTCAGAGAG
	Reverse	TTGGATGGTCTTGGTCCTTAGCCA
Itgax	Forward	GCTGTTGGCTTGTGGTCCTA
	Reverse	AACTGCATCAGGGAGAACCG
Lipe	Forward	CAGAAGGCACTAGGCGTGATG
	Reverse	GGGCTTGCGTCCACTTAGTTC
Ldha	Forward	GGATGAGCTTGCCCTTGTTGA
	Reverse	GACCAGCTTGGAGTTCGCAGTTA
Mmp10	Forward	ACTGGAGATTTGATGAGACAAGAC
	Reverse	GTCCTGGCATTGGGGTCAAA
Mrc1	Forward	TGGATGGATGGGAGCAAAGT
	Reverse	AATGCCAACCTTCCTTGCAG
Nos2	Forward	CACCTTGGAGTTCACCCAGT
	Reverse	ACCACTCGTACTTGGGATGC
Pdk1	Forward	GCTACGGGACAGATGCGGTTA
	Reverse	CAGGCGGCTTTATTGTACACAGG
Pdk4	Forward	AGCTGCTGGACTTTGGTTCA
	Reverse	TGCCTTGAGCCATTGTAGGG
Pfkl	Forward	CAAACCGGGTACACAGGCAG
	Reverse	AGCATTCATACCTTGCGCATC
Pgk1	Forward	GGAGCGGGTCGTGATGA
	Reverse	GCCTTGATCCTTTGGTTGTTTG
Pnpla2	Forward	CAACGCCACTCACATCTACGG
	Reverse	GGACACCTCAATAATGTTGGCAC
Pparα	Forward	CTGCAGAGCAACCATCCAGAT
	Reverse	GCCGAAGGTCCACCATTTT
Pparγ	Forward	GCCCACCAACTTCGGAATC
	Reverse	TGCGAGTGGTCTTCCATCAC
Tgfβ	Forward	GGACTCTCCACCTGCAAGAC
	Reverse	CATAGATGGCGTTGTTGCGG
Tnfα	Forward	ACGTCGTAGCAAACCACCAA
	Reverse	ACAAGGTACAACCCATCGGC