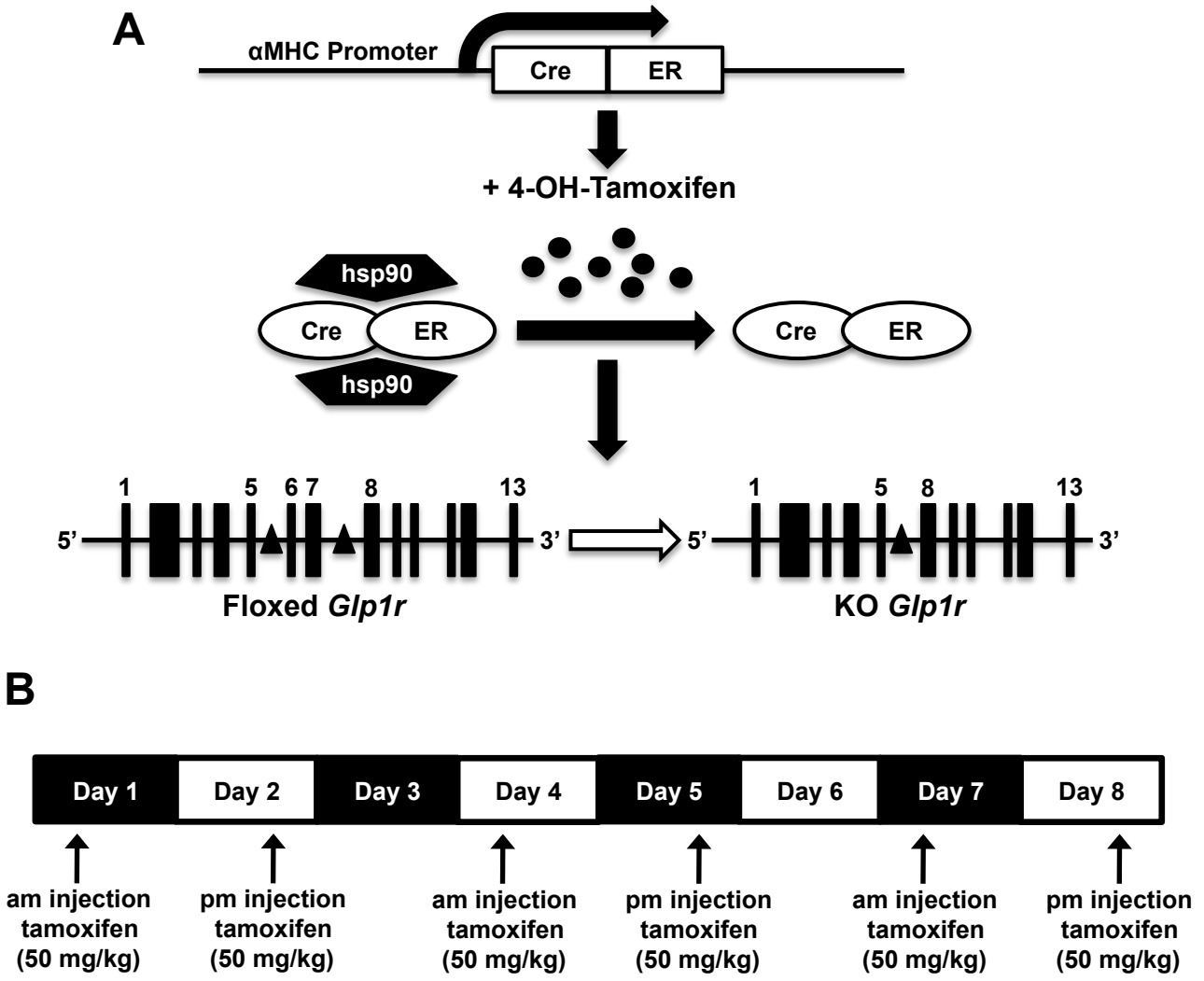
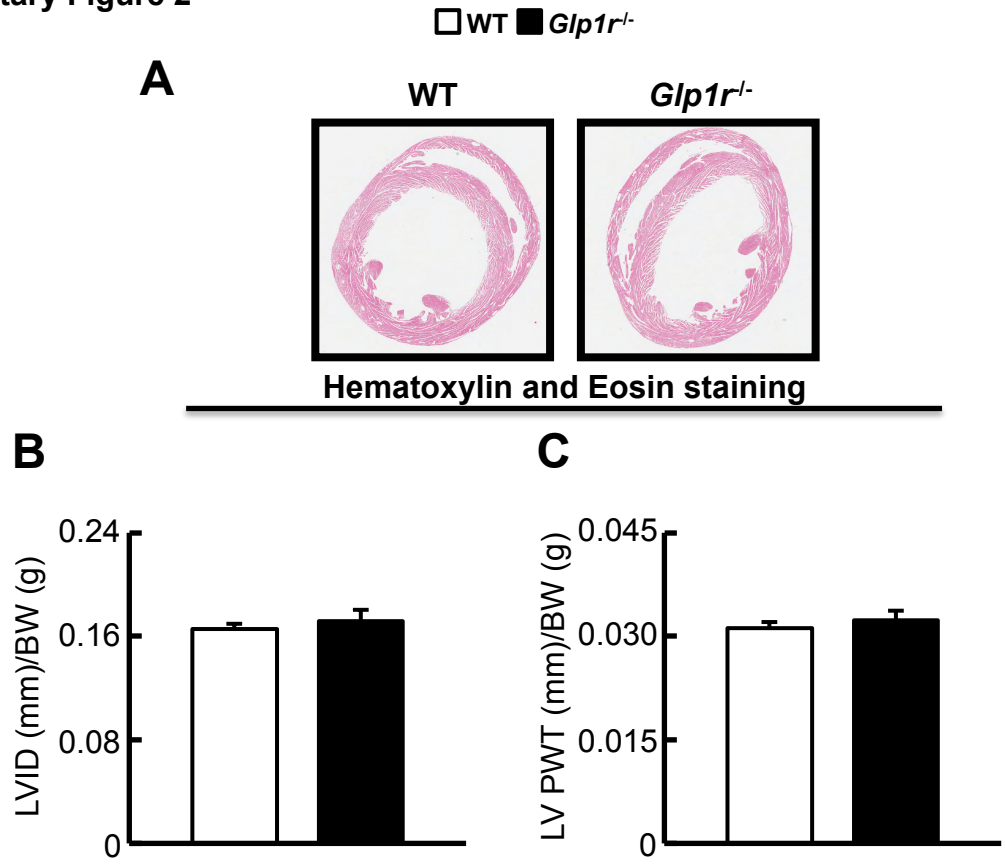
Supplementary Figure 1



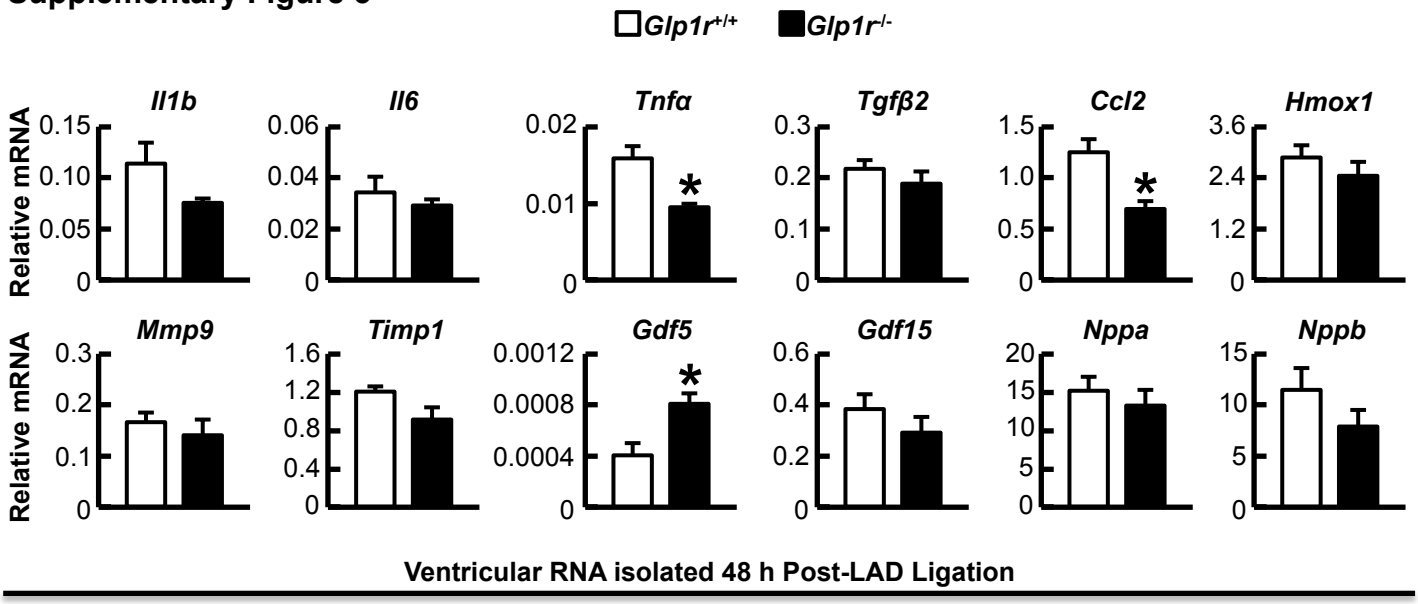
Supplementary Figure 1. *Use of a tamoxifen inducible α-myosin heavy chain (αMHC) Cre expressing promoter to reduce Glp1r expression in cardiomyocytes via cre-lox technology.*
A: Cells expressing the *αMHC* promoter express *Cre* flanked by mutated estrogen receptor ligand-binding domains bound to heat shock protein 90 (hsp90) in the cytoplasm that are sensitive to activation with the selective estrogen receptor antagonist, tamoxifen. Upon binding of tamoxifen, hsp90 dissociates from Cre, allowing Cre to translocate from the cytoplasm to the nucleus, enabling Cre-mediated excision of loxP flanked sequences (loxP sites indicated via black triangles) to generate gene knockdown. B: We knocked down the *Glp1r* specifically in *αMHC-Cre* expressing cells via 6 i.p. injections of tamoxifen (50 mg/kg) spread across 8 days. On day 1 mice were injected in the morning, while the injection took place in the afternoon on day 2. No injection took place on day 3, whereas mice were injected again in the morning on day 4 and in the afternoon on day 5, followed by no injection on day 6, with the final injections taking place during the morning on day 7 and the afternoon of day 8.

Supplementary Figure 2



Supplementary Figure 2. *Normal cardiac structure in 2-month-old Glp1r$^{-/-}$ mice in the C57BL/6J background.*
A: Representative H&E heart cross sections depicting normal LV structure in 2-month-old *Glp1r$^{-/-}$* mice (n = 3). B: LV internal diameter (LVID) and C: LV posterior wall thickness (LV PWT). Values represent mean ± SE.

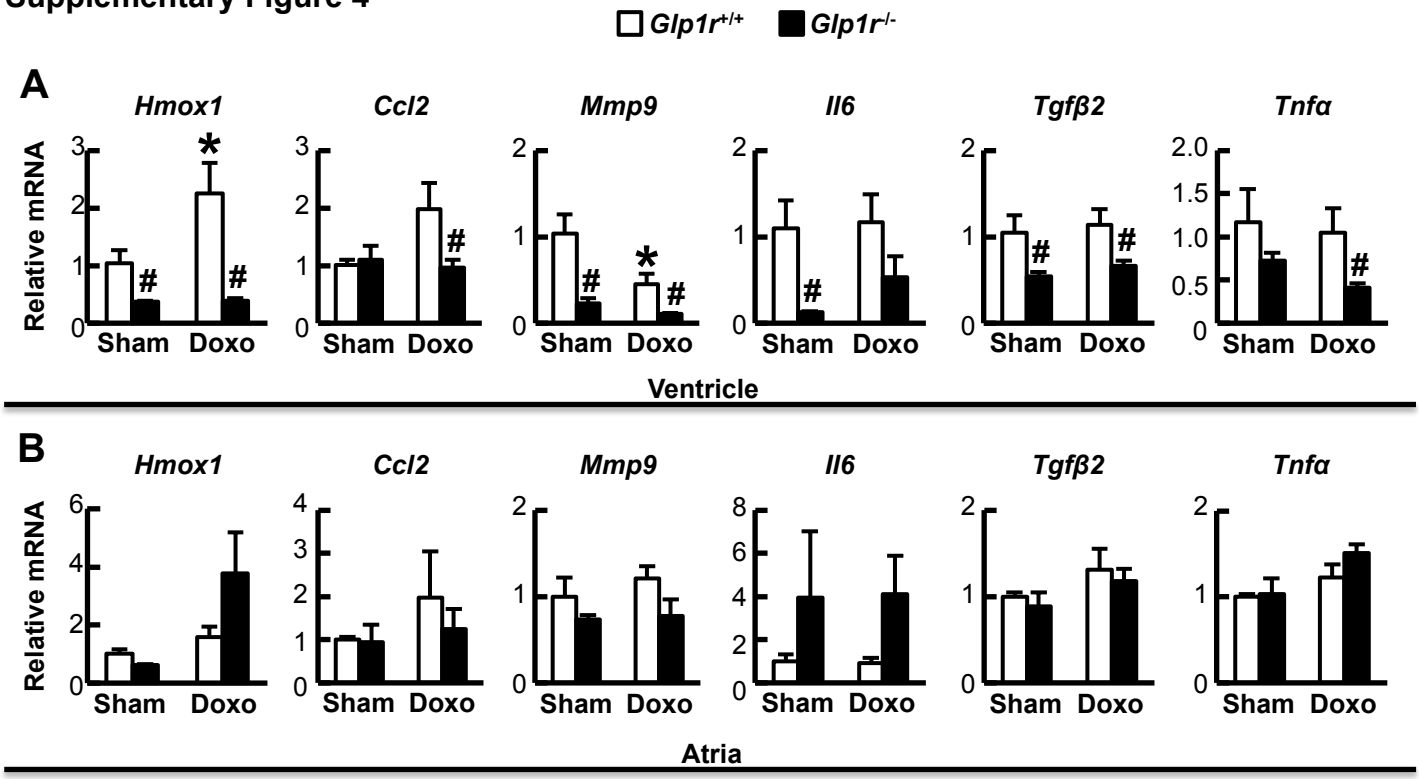
Supplementary Figure 3



Supplementary Figure 3. *Ventricular mRNA expression profiling from Glp1r$^{-/-}$ mice and wild-type littermates following myocardial infarction.*

Ventricular RNA was isolated to determine mRNA expression of *Il1b, Il6, Tnfα, Tgfβ2, Ccl2, Hmox1, Mmp9, Timp1, Gdf5, Gdf15, Nppa,* and *Nppb* from *Glp1r*$^{-/-}$ mice and their wild-type littermates at 48 h post-LAD coronary artery occlusion (n = 5). Values represent mean ± SE. The significance of differences was determined by an unpaired, 2-tailed Student's *t*-test .*Significantly different from wild-type (WT) littermate.

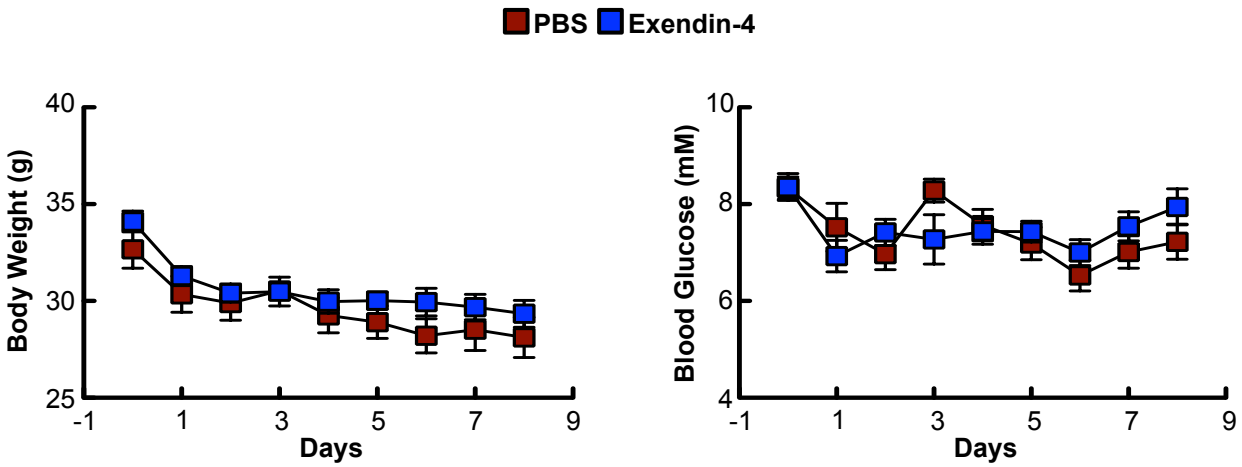
Supplementary Figure 4



Supplementary Figure 4. *Ventricular and atrial mRNA expression profiling from Glp1r$^{-/-}$ mice and their wild-type littermates following experimental cardiomyopathy.*

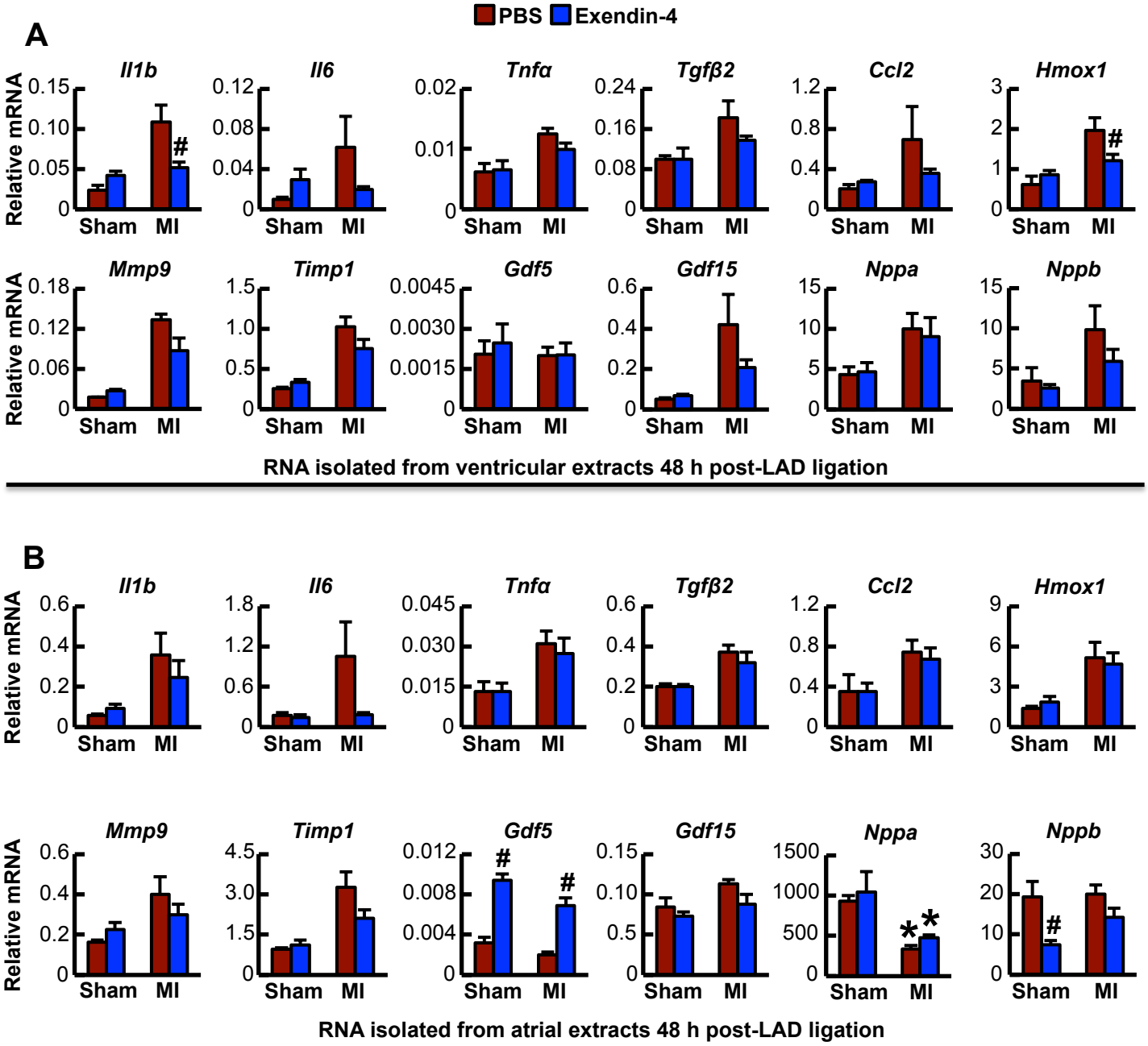
A: Ventricular and B: atrial RNA was used to determine mRNA expression of *Hmox1, Ccl2, Mmp9, Il6, Tgfβ2,* and *Tnfα* from *Glp1r$^{-/-}$* mice and their wild-type littermates at 10 days post-doxorubicin injection (n = 3-5). Values represent mean ± SE. The significance of differences was determined by a two-way ANOVA followed by a Bonferroni post-hoc analysis.*Significantly different from sham counterpart. #Significantly different from corresponding wild-type (*Glp1r$^{+/+}$*) littermates.

Supplementary Figure 5



Supplementary Figure 5. *Systemic GLP-1R activation with exendin-4 does not affect body weight and random fed glycemia.*
A: Body weight change in PBS (phosphate buffered saline) and exendin-4 (5 nmol/kg BW i.p., twice daily)-treated C57BL/6J mice over 9 days following permanent LAD coronary artery occlusion (n = 5-8). B: Random fed glycemia in PBS- and exendin-4-treated C57BL/6J mice over 9 days following permanent LAD coronary artery occlusion (n = 5-8). Values represent mean ± SE.

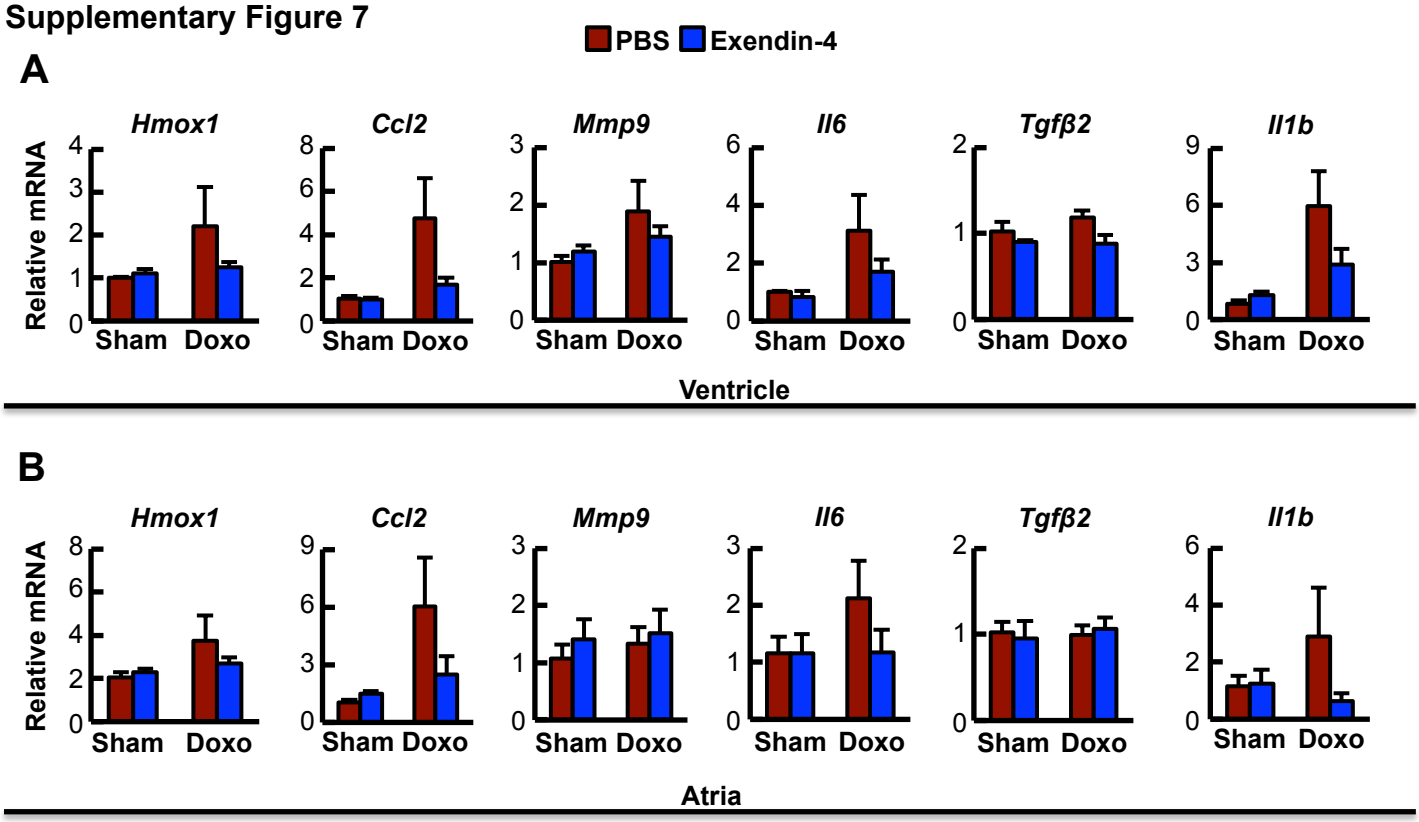
Supplementary Figure 6



Supplementary Figure 6. *Ventricular and atrial mRNA expression profiling from exendin-4 vs PBS-treated C57BL/6J mice subjected to permanent LAD-ligation induced MI.*

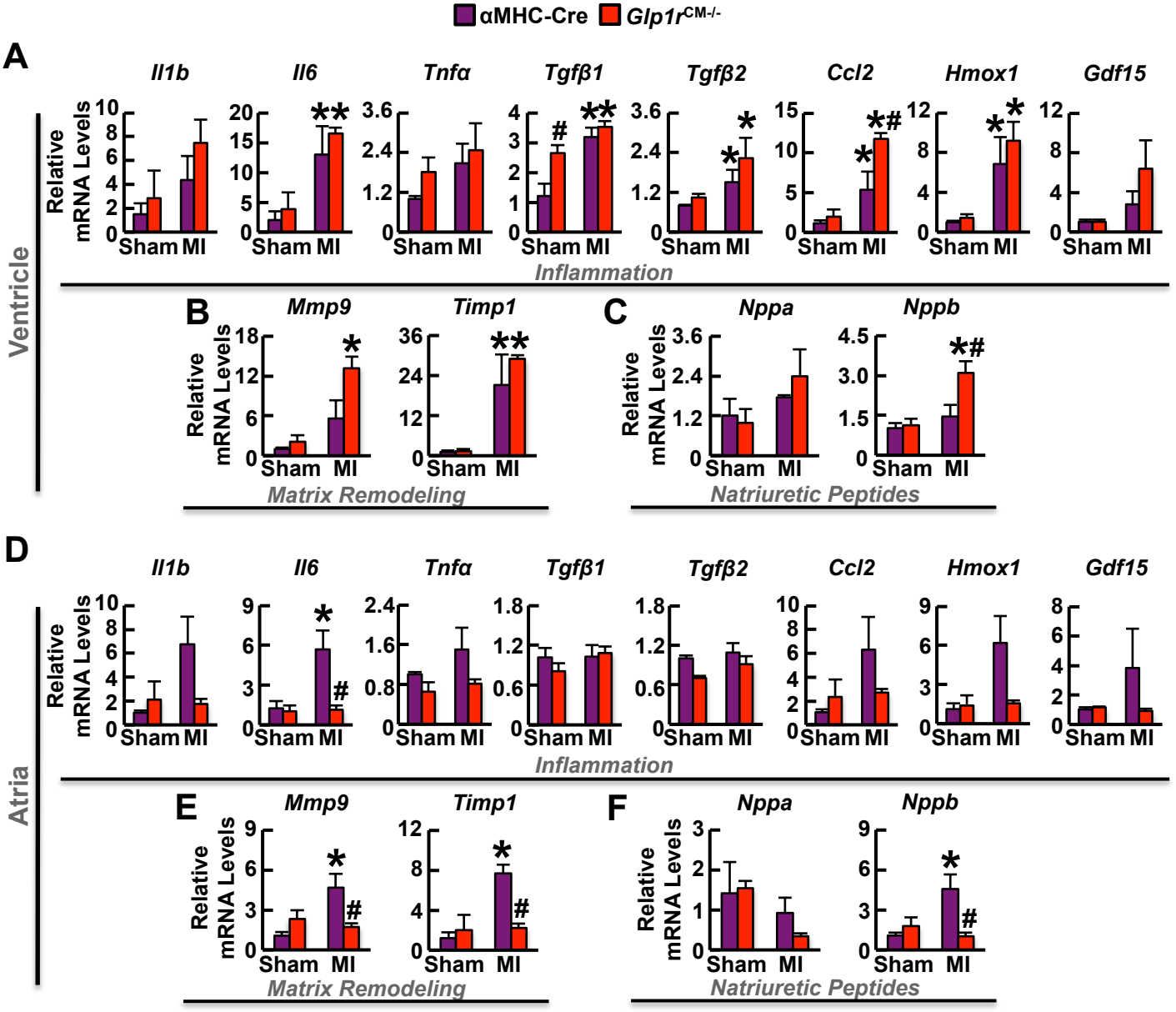
A: Ventricular and B: Atrial RNA was used to determine expression of *Il1b, Il6, Tnfα, Tgfβ2, Ccl2, Hmox1, Mmp9, Timp1, Gdf5, Gdf15, Nppa,* and *Nppb* from PBS and exendin-4 (5 nmol/kg BW i.p., twice daily)-treated C57BL/6J mice at 48 h post-LAD coronary artery occlusion (n = 5-6). Values represent mean ± SE. The significance of differences was determined by a two-way ANOVA followed by a Bonferroni post-hoc analysis.*Significantly different, Sham vs. MI; #Significantly different from corresponding PBS-treated counterpart.

Supplementary Figure 7



Supplementary Figure 7. *Ventricular and atrial mRNA expression profiling from PBS vs. exendin-4 treated C57BL/6J mice following doxorubicin (doxo)-induced cardiomyopathy.*
A: Ventricular and B: Atrial RNA was used to determine expression of *Hmox1, Ccl2, Mmp9, Il6, Tgfβ2*, and *Il1b* from PBS- and exendin-4 (5 nmol/kg BW i.p., twice daily)-treated C57BL/6J mice at 10 days post-doxorubicin injection (n = 4-5). Values represent mean ± SE.

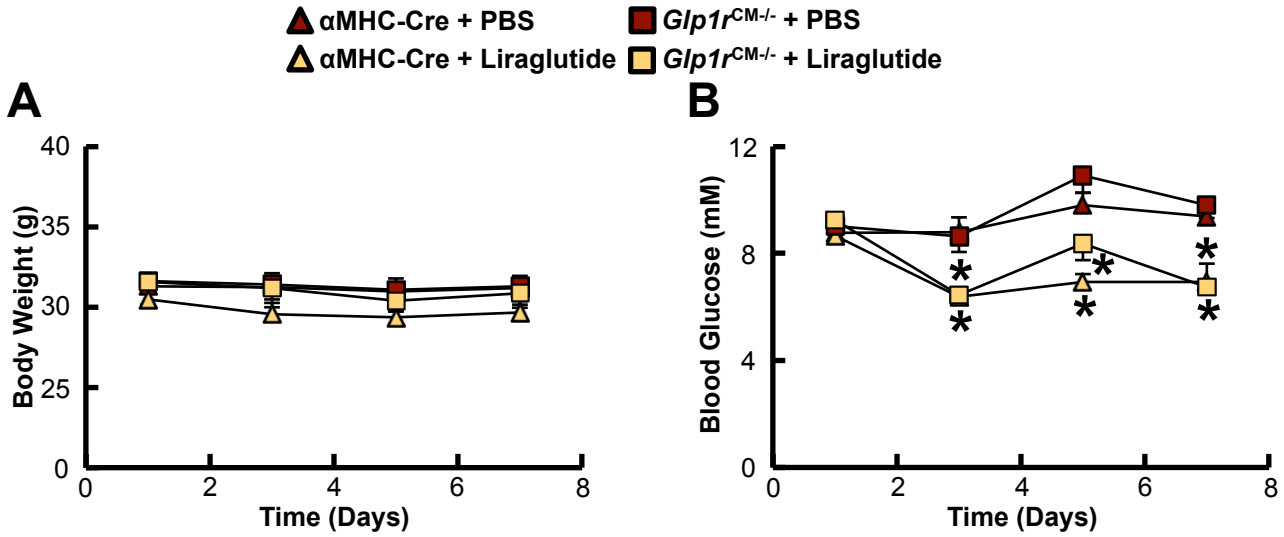
Supplementary Figure 8



Supplementary Figure 8. *Ventricular and atrial mRNA expression profiling from Glp1r$^{CM-/-}$ mice and their αMHC-Cre littermates subjected to permanent LAD-ligation induced MI.*

A: Ventricular RNA was used to determine expression of the inflammatory markers *Il1b, Il6, Tnfα, Tgfβ1, Tgfβ2, Ccl2, Hmox1,* and *Gdf15* in *Glp1r*$^{CM-/-}$ mice and their αMHC-Cre littermates at 48 h post-LAD coronary artery occlusion (n = 3-4). B: mRNA transcripts for matrix remodeling factors *Mmp9* and *Timp1,* and C: the natriuretic peptides *Nppa* and *Nppb* were also determined from ventricular RNA extracts from *Glp1r*$^{CM-/-}$ mice and their αMHC-Cre littermates at 48 h post-LAD coronary artery occlusion (n = 3-4). D: Atrial RNA was similarly analyzed for expression of the inflammatory markers *Il1b, Il6, Tnfα, Tgfβ1, Tgfβ2, Ccl2, Hmox1,* and *Gdf15* in *Glp1r*$^{CM-/-}$ mice and their αMHC-Cre littermates at 48 h post-LAD coronary artery occlusion (n = 3-4). E: mRNA transcripts for the matrix remodeling factors *Mmp9* and *Timp1,* and F: the natriuretic peptides *Nppa* and *Nppb* were also determined from atrial RNA from *Glp1r*$^{CM-/-}$ mice and their αMHC-Cre littermates at 48 h post-LAD coronary artery occlusion (n = 3-4). Values represent mean ± SE. The significance of differences was determined by a two-way ANOVA followed by a Bonferroni post-hoc analysis.*Significantly different from sham counterpart. #Significantly different from corresponding αMHC-Cre littermate.

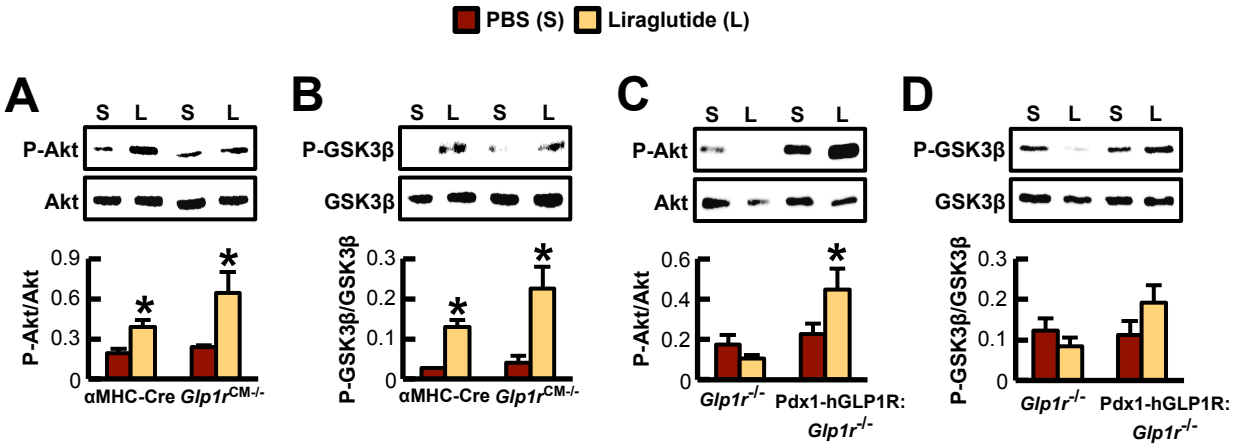
Supplementary Figure 9



Supplementary Figure 9. *Systemic GLP-1R activation with liraglutide treatment does not significantly affect body weight.*

A: Body weight change in PBS and liraglutide (30 µg/kg BW i.p. twice daily) treated *Glp1r*$^{CM-/-}$ mice and their αMHC-Cre littermates over 7 days (n = 10-16). B: Random fed glycemia in PBS and liraglutide (30 µg/kg BW i.p. twice daily) treated *Glp1r*$^{CM-/-}$ mice and their αMHC-Cre littermates over 7 days (n = 10-16). Values represent mean ± SE. The significance of differences was determined by a two-way ANOVA followed by a Bonferroni post-hoc analysis.*Significantly different from corresponding PBS treated counterpart.

Supplementary Figure 10



Supplementary Figure 10. *Systemic GLP-1R activation with liraglutide increases ventricular Akt/GSK3β signaling.* A: Akt phosphorylation, and B: GSK3β phosphorylation in *Glp1r*$^{CM-/-}$ mice and their *αMHC-Cre* littermates following a 1 week treatment with liraglutide (200 µg/kg BW i.p. twice daily)(n = 3-4). C: Akt phosphorylation, and D: GSK3β phosphorylation in *Glp1r*$^{-/-}$ and Pdx1-hGLP1R:*Glp1r*$^{-/-}$ mice following a 1 week treatment with liraglutide (200 µg/kg BW i.p. twice daily)(n = 4). Pdx1-hGLP1R:*Glp1r*$^{-/-}$ mice exhibit selective restoration of functional GLP-1R expression in islet beta cells of *Glp1r*$^{-/-}$ mice, thereby enabling examining the contribution of GLP-1R-dependent insulin secretion in mice that otherwise have no functional *Glp1r* expression outside beta cells (Lamont et al J Clin Invest. 2012 Jan 3;122(1): 388-402). Due to the enhanced insulin levels and activation of cardiomyocyte insulin signaling pathways seen with this higher 200 µg/kg dose of liraglutide, we used a much lower dose, 30 µg/kg for all other experiments. Values represent mean ± SE. The significance of differences was determined by a two-way ANOVA followed by a Bonferroni post-hoc analysis.*Significantly different from corresponding PBS treated counterpart.

Supplementary Table 1. List of Real-Time Primers

Primer Set	ABI Catalog #	Amplicon Length
Ccl2	Mm00441242_m1	74
Gdf5	Mm00433564_m1	74
Gdf15	Mm00493434_m1	134
Glp1r	Mm01351007_m1	93
Hmox1	Mm00516005_m1	69
Il1b	Mm01336189_m1	63
Il6	Mm00446190_m1	78
Mmp9	Mm00442991_m1	76
Nppa	Mm01255748_g1	67
Nppb	Mm01255770_g1	68
Ppia	Mm02342430_g1	148
Timp1	Mm00441818_m1	90
Tnf	Mm00443258_m1	81
Tgfb1	Mm01178820_m1	59
Tgfb2	Mm00436955_m1	82

Supplementary Table 2 Antibodies used for Western blot analyses

Anti-Akt (Cell Signaling Technologies)
Anti-phosphoSerine-473 Akt (Cell Signaling Technologies)
Anti-GSK3β (Cell Signaling Technologies)
Anti-phosphoSerine-9 GSK3β (Cell Signaling Technologies)
Anti-AMPK (Cell Signaling Technologies)
Anti-phosphoThreonine-172 AMPK (R&D Systems)
Anti-nuclear respiratory factor 2 (Nrf2, Santa Cruz)
Anti-peroxisome proliferator activated receptor β/δ (PPARβ/δ, Santa Cruz)
Anti-heme-oxygenase-1 (HO-1, Stressgen)
Anti-heat shock protein 90 (hsp90, BD Biosciences)