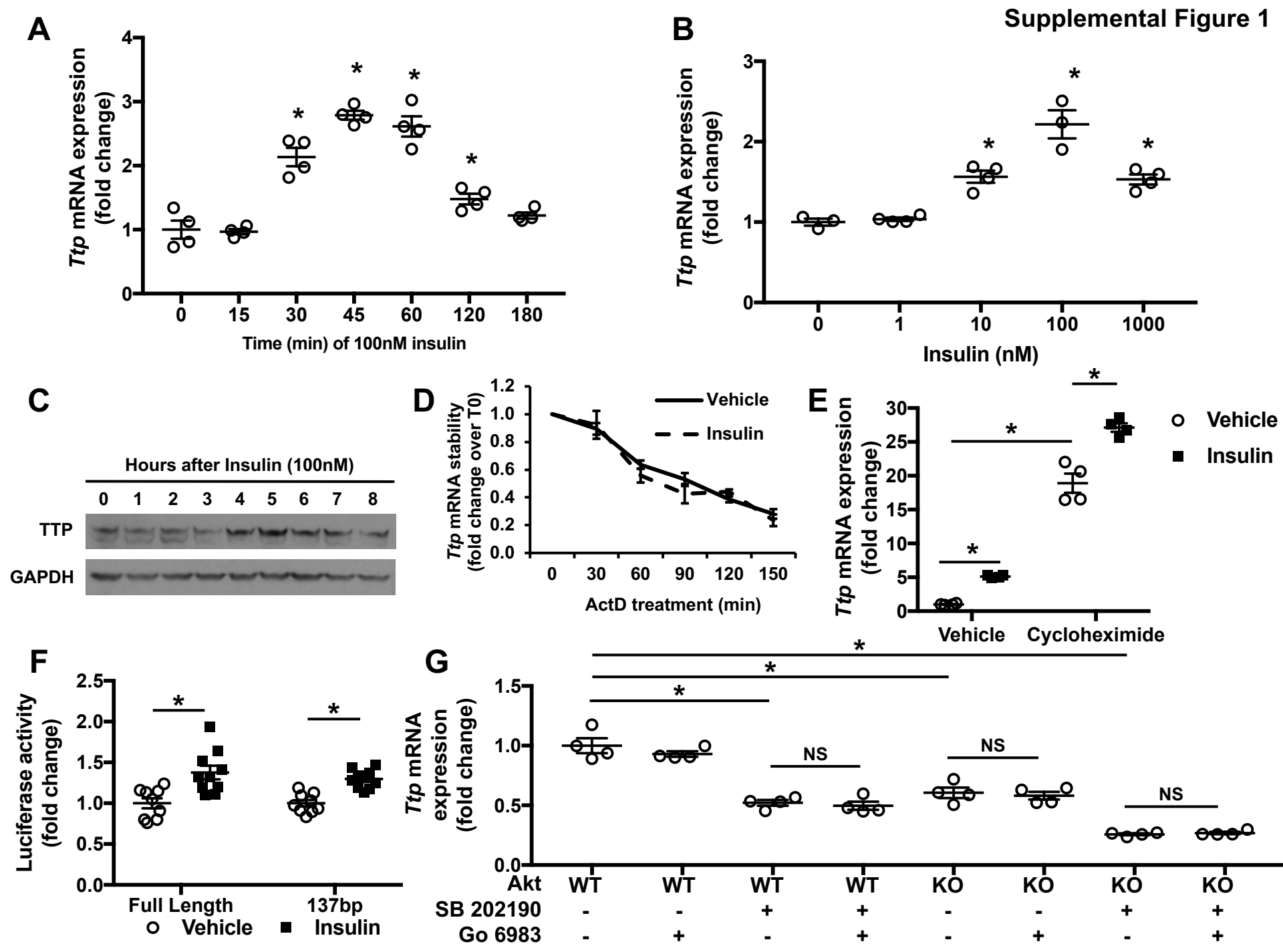
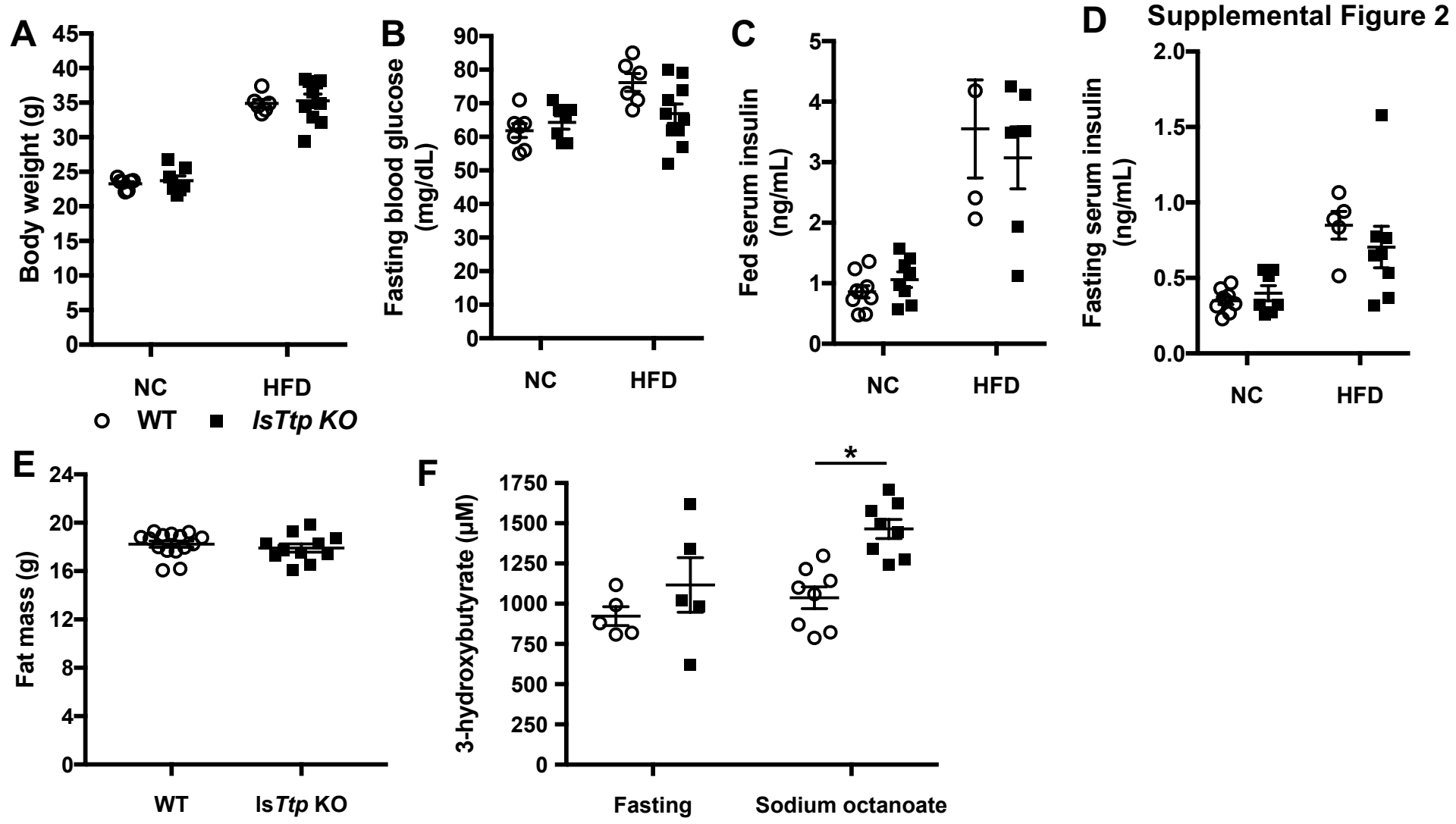


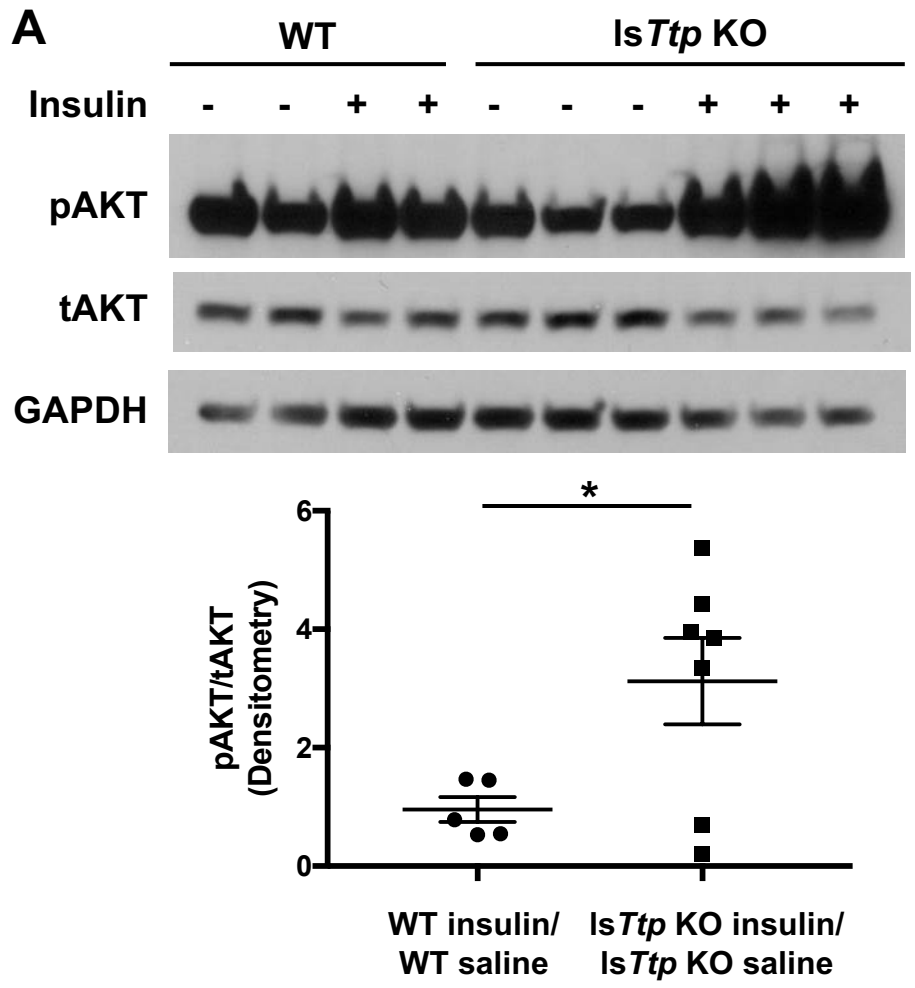
Supplemental Figure 1. Hepatic TTP is induced by insulin, and reduced in diet-induced and genetic murine models of obesity and human diabetics.

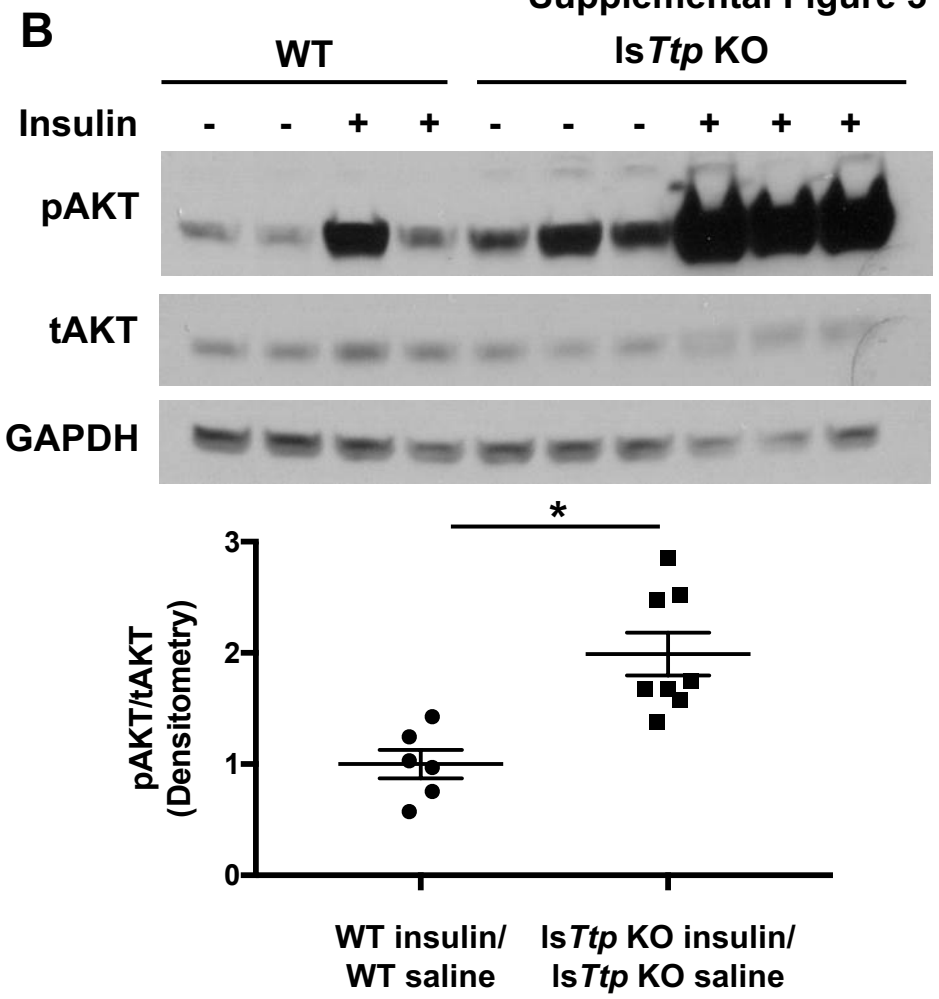
(**A**) *Ttp* mRNA expression is induced by 100nM insulin in a time-dependent fashion in WT primary hepatocytes (n=4). (**B**) *Ttp* mRNA expression is induced by insulin in a dose-dependent manner in WT primary hepatocytes (n=4). (**C**) TTP protein expression is induced by 100nM insulin in a time-dependent manner in WT primary hepatocytes. (**D**) Insulin (100nM) does not alter *Ttp* mRNA stability in WT primary hepatocytes (n=4). (**E**) Inhibition of protein synthesis via 2 hour pre-treatment with 0.1mM cyclohexamide does not inhibit *Ttp* induction after 1 hour treatment of insulin in WT MEFs (n=4). (**F**) Transfection of a luciferase construct containing the proximal 137 base-pairs of the *TTP* promoter is sufficient to induce transcriptional activity compared to the full-length *TTP* promoter (n=9-10 in each group). (**G**) Pre-treatment of *Akt1/2* KO MEFs with a p38 MAPK inhibitor (SB 202190, 10μM) for one hour led to a significant reduction in *Ttp* expression after one-hour of insulin (100nM) stimulation, which was not further reduced with the addition of one-hour PKC inhibitor pre-treatment (Go 6983, 1μM) (n=4). Data are presented as mean ± SEM. *p<0.05 by one-way ANOVA with *post hoc* Fisher's LSD test.



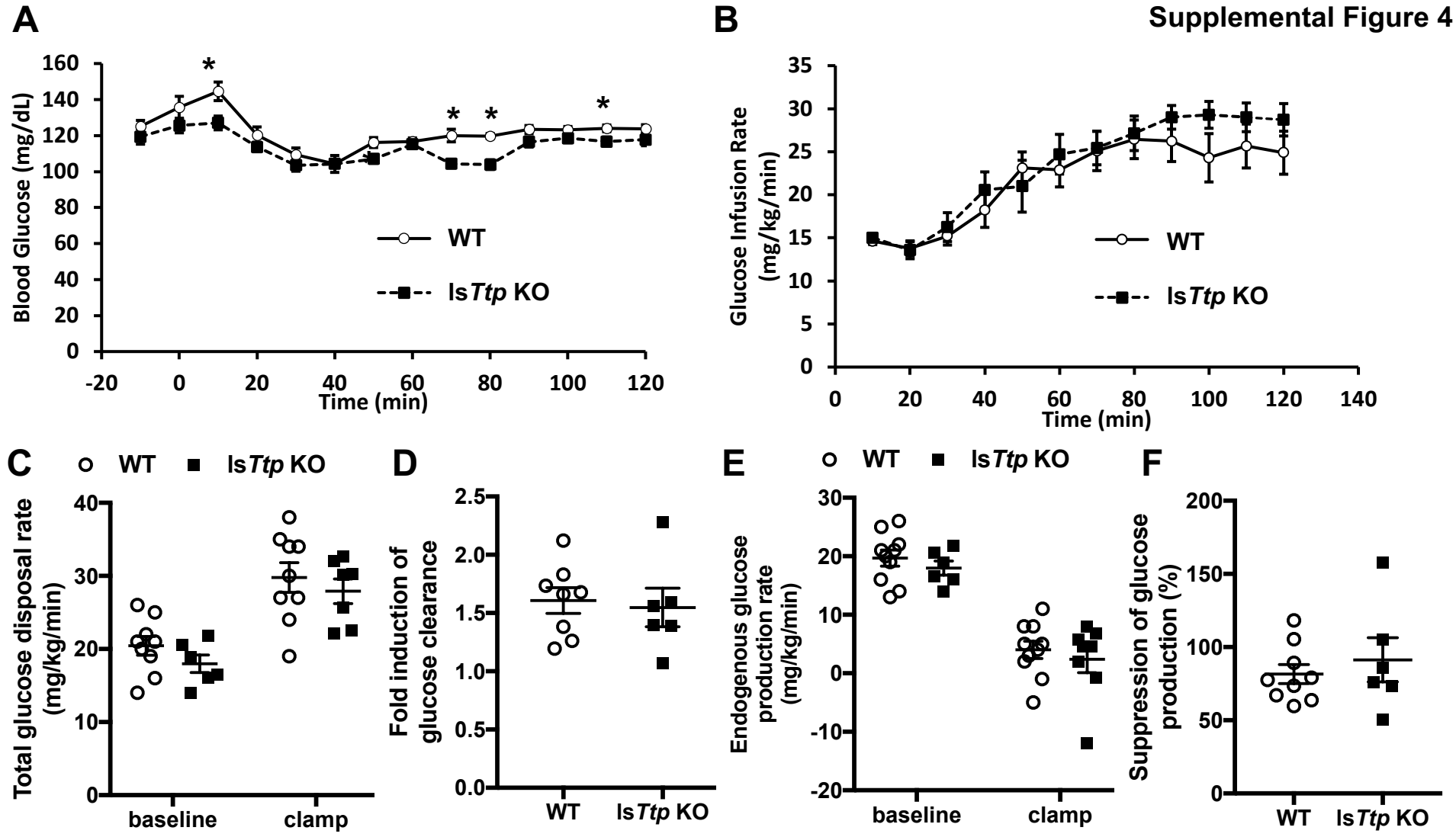
Supplemental Figure 2. Liver-specific *Ttp* KO mice have improved glucose tolerance and insulin sensitivity after high-fat diet despite normal circulating systemic lipid parameters.

(**A-D**) Body weight (**A**, n=5-10), fasting blood glucose levels (**B**, n=6-10), and fed (**C**, n=3-9) or fasting (**D**, n=5-9) serum insulin levels are similar between WT and ls*Ttp* KO mice after 12 weeks of normal chow or high-fat diet. (**E**) Total fat mass in WT and ls*Ttp* KO mice fed HFD (n=8-11). (**F**) ls*Ttp* KO mice fed high-fat diet for 11 weeks have increased ketogenic potential 2 hours after injection of sodium octanoate compared to control mice (n=5-9). Data are presented as mean ± SEM. *p<0.05 by 2-sided unpaired Student's t-test.



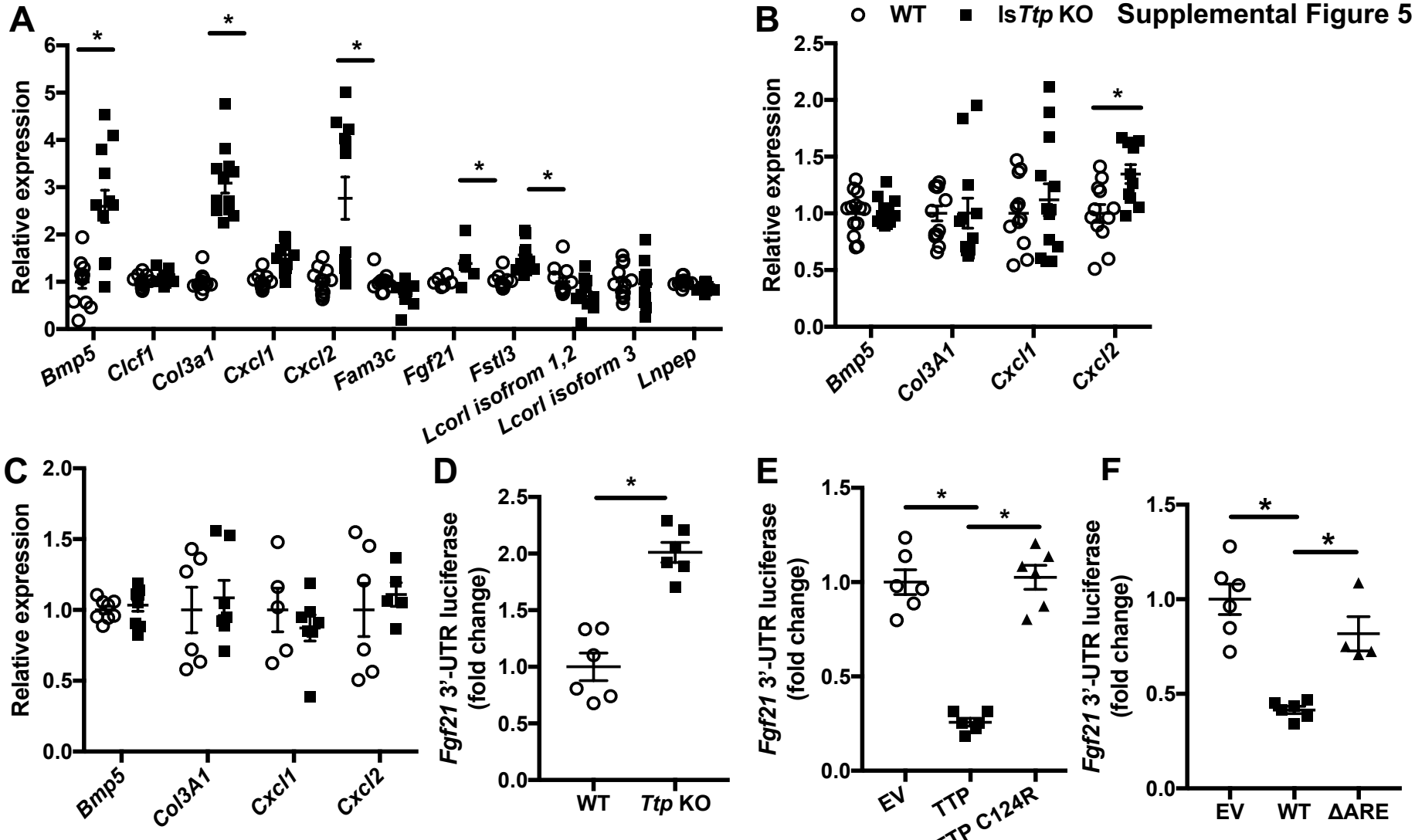


Supplemental Figure 3. Liver-specific *Ttp* KO mice have increased peripheral tissue insulin sensitivity after high-fat diet. (**A-B**) ls*Ttp* KO mice have improved insulin sensitivity in the heart (**A**) and liver (**B**) after 12 weeks of HFD compared to WT mice, as assessed by phosphorylated AKT S473 (pAKT) to total AKT (tAKT) ratio in insulin-treated mice relative to that in saline treated-mice of the same genotype (n=6-9 in each group). Representative western blotting results are shown, and densitometry analysis is provided in the same panel. Data are presented as mean ± SEM. *p<0.05 by one-way ANOVA with *post hoc* Fisher's LSD test.



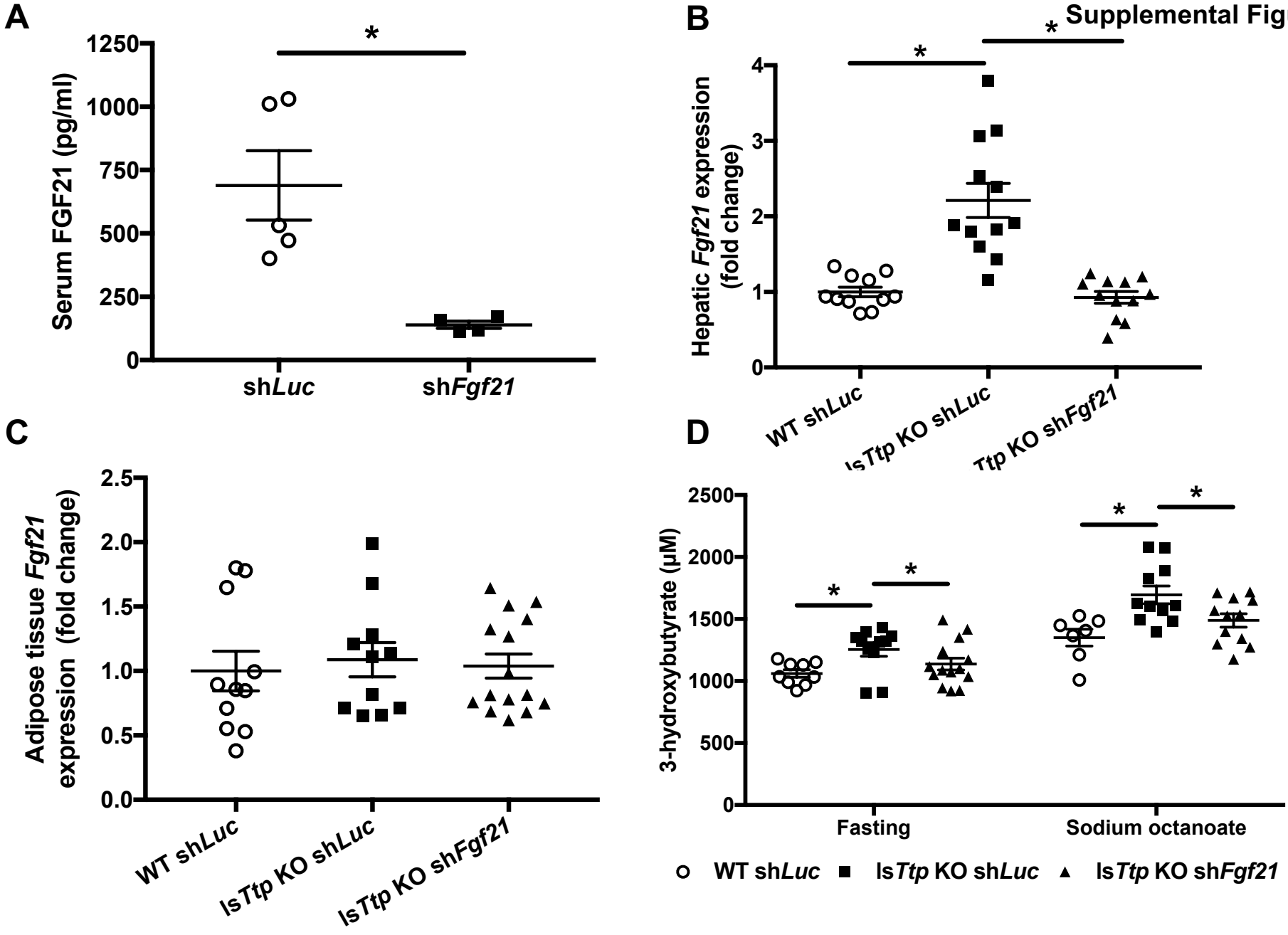
Supplemental Figure 4. Liver-specific *Ttp* KO mice have similar peripheral glucose disposal and endogenous glucose production rate after HFD compared to WT mice.

(**A-B**) Blood glucose (**A**) and glucose infusion rate (**B**) during hyperinsulinemic-euglycemic clamp studies. * P<0.05 by 2-tailed unpaired Student's t-test. (**C**) After HFD, ls*Ttp* KO mice have similar total glucose disposal rate at baseline and during hyperinsulinemic-euglycemic clamp studies compared to WT mice. (**D**) Fold induction of glucose clearance during hyerinsulinemic-euglycemic clamp studies. (**E**) Endogenous glucose production at baseline and during hyperinsulinemic-euglycemic clamp studies in WT and ls*Ttp* KO mice after HFD. (**F**) Insulin-mediated suppression of glucose production in WT and ls*Ttp* KO mice during hyperinsulinemic-euglycemic clamp studies. Data are presented as mean ± SEM. N=6-10 for each group.



Supplemental Figure 5. TTP regulates the expression of *Fgf21*.

(**A**) mRNA levels of predicted TTP-targeted hepatic secretory proteins in WT and ls*Ttp* KO primary hepatocytes. N=6 for each group. (**B**) Expression of hepatic secretory proteins that are putative TTP targets in liver from WT and ls*Ttp* KO mice fed regular diet. N=10-12 for each group. (**C**) Expression of putative TTP-targeted hepatic secretory proteins in WT and ls*Ttp* KO mice after 15 weeks of HFD. (**D**) Transfection of a mouse *Fgf21* 3'-UTR-luciferase construct into *Ttp* KO MEFs increases luminescence signal compared to WT MEFs (n=6). (**E**) Overexpression of WT TTP but not C124R mutant TTP reduces luciferase activity in HEK293 cells transfected with mouse *Fgf21* 3'-UTR-luciferase construct (n=6). (**F**) TTP overexpression in *Ttp* KO MEFs reduces the activity of mouse *Fgf21* 3'-UTR-luciferase construct (WT) but not mouse *Fgf21* 3'-UTR-luciferase construct with deletions of the ARE sites (ΔARE). n=5-6. Data presented as the relative luciferase activity in the presence of TTP overexpression for each construct. EV= empty pMIR-Report vector. Data are presented as mean ± SEM. *p<0.05 by one-way ANOVA with *post hoc* Fisher's LSD test.



Supplemental Figure 6. Increased liver-derived circulating Fgf21 is responsible for improved systemic diabetic parameters after high fat diet in the setting of hepatic *Ttp* deletion.

(**A**) Circulating fasting levels of FGF21 are effectively reduced using AAV8 sh*Fgf2*1 in WT mice on normal chow (n=4-5). (**B-C**) AAV8 sh*Fgf21* specifically reduces hepatic (**B**), but not adipose tissue (**C**), *Fgf21* mRNA expression in ls*Ttp* KO mice (n=11-14). (**D**) ls*Ttp* KO mice injected with AAV8 sh*Fgf21* virus have reversal of ketogenic potential after HFD compared to WT mice (n=7-12). Data are presented as mean ± SEM. *p<0.05 by one-way ANOVA with *post hoc* Fisher's LSD test.