Supplementary Material

Prodromal Glutamatergic Modulation with Riluzole Impacts Glucose Homeostasis and Spatial Cognition in Alzheimer's Disease Mice

Supplementary Table 1. RT-PCR primer sequences for liver and hippocampal tissue. Liver and hippocampal targets for RT-PCR analysis and their respective housekeeping genes. Each primer was selected based on previous publication and evaluated with a melt curve prior to experimental use.

| Primer	Forward Sequence	Reverse Sequence
Liver Gene Expression		
B2M	5'- AAG TAT ACT CAC GCC ACC CA -3'	5'- AGG ACC AGT CCT TGC TGA AG -3'
Glucose-6-P	5'- CAC AGT GGA CGA CAT CCG AAA -3'	5'- AGC TAC ATA GGA ATT ACG GGC AA -3'
Glucokinase	5'- TGA GCC GGA TGC AGA AGGA -3'	5'- GCA ACA TCT TTA CAC TGG CCT -3'
GLUT2	5'- TCA GAA GAC AAG ATC ACC GGA -3'	5'- GCT GGT GTG ACT GTA AGT GGG -3'
Hippocampal Gene Expression		
UBE2D2	5'- TGC CTG AGA TTG CTC GGA TCT -3'	5'- TCG CAT ACT TCT GAG TCC ATT CC -3'
NMDARN2A	5'- ACG TGA CAG AAC GCG AAC TT -3'	5'- TCA GTG CGG TTC ATC AAT AAC G -3'
INSR	5'- ACT ATG CCA GCA TCA GCT TCC AGA -3'	5'- AAG ACG TGA GGT CCT GGT TGT GAA -3'
GLUT1	5'- CAG TTC GGC TAT AAC ACT GGT G- 3'	5'- GCC CCC GAC AGA GAA GAT G -3'
GLUT3	5'- ATG GGG ACA ACG AAG GTG AC -3'	5'- GTC TCA GGT GCA TTG ATG ACT C -3'
α7nAChR	5'- CCT GCA AGG CGA GTT CC -3'	5'- CTC AGG GAG AAG TAC ACG GTG A -3'
AdipoR1	5'- TCT TCG GGA TGT TCT TCC TGG -3'	5'- TTT GGA AAA AGT CCG AGA GAC C -3'
CREB1	5'- CCC AAA AAC GAA GGG AAA TCC T -3'	5'- CCT GGT GCA TCA GAA GAT AAG TC -3'

Supplementary Table 2 Overall alterations to each study measure with riluzole treatment. Experimental animals are organized by age, genotype, and sex. Arrows indicate change in measure with riluzole treatment compared to vehicle-treated genotype-, sex-, and age-matched mice. An "X" indicates no change in that measure for the selected group. Experimental measures include insulin tolerance, glucose tolerance, glucose transporter 2 (GLUT2), glucokinase (GK), glucose-6-phosphotase (G6Pase), insulin, adiponectin (Adipo), spatial learning and memory from the Morris water maze (MWM), amyloid beta (Aβ), ionotropic glutamate receptor (NMDARN2A), nicotinic cholinergic receptor (α7), glucose transporter 1 (GLUT1), glucose transporter 3 (GLUT3), insulin receptor (INSR), adiponectin receptor (AdipoR1), and cAMP response element-binding protein 1 (CREB1). All findings p≤ 0.06 reported.

	6 MONTHS OLD						12 MONTHS OLD					
	C57BL/6		AβPP/PS1		APP$^{NL\text{-}F/NL\text{-}F}$		C57BL/6		AβPP/PS1		APP$^{NL\text{-}F/NL\text{-}F}$	
	M	F	M	F	M	F	M	F	M	F	M	F
ITT	X	↑	X	X	X	X	X	X	X	X	X	X
GTT	↑	X	X	X	↑	X	X	X	X	X	X	X
GLUT2	X	X	X	X	X	X	X	X	X	X	↓	↓
GK	↓	X	X	X	X	X	X	X	↑	X	X	X
G6Pase	X	X	↓	X	↑	↓	X	X	↑	X	X	X
Insulin	↓	X	↓	X	X	X	X	X	↓	X	X	X
Adipo	X	X	↓	X	X	X	X	X	X	X	X	X
Learning MWM	X	X	X	↑	X	X	X	X	X	X	X	X
Memory MWM	↑	↑	X	↑	X	↑	↑	↓	↑	↓	↑	↑
Aβ	(gray)	(gray)	X	X	X	X	(gray)	(gray)	X	↑	X	↓
NMDAR N2A	X	X	X	X	X	↓	X	↓	X	X	X	X
α7	↓	↓	X	↑	X	X	↓	X	↓	↓	↑	X
GLUT1	X	X	↓	X	X	X	↓	↑	X	↓	X	X
GLUT3	↑	X	↓	X	X	↑	↓	↑	↓	↓	X	X
INSR	X	X	X	↑	↑	X	↓	↓	↓	X	X	X
AdipoR1	↑	↑	↓	X	X	X	↓	X	X	X	X	X
CREB1	↑	↑	↓	X	↑	X	↓	X	↓	X	↑	↑

Supplementary Figure 1. Weight change immediately following treatment cessation and at 6 months post-treatment. All mice were weighed on a weekly basis, corresponding with water changes (vehicle or riluzole). Baseline weights were taken a week before the start of treatment. Graphs depict percent change compared to baseline weight taken at 7 weeks old. Within-genotype age-matched unpaired t-test (n=10-21), *$p<0.05$. An age-, genotype-, and treatment-matched one-way ANOVA, Sidak, was conducted for sex comparisons (not pictured).
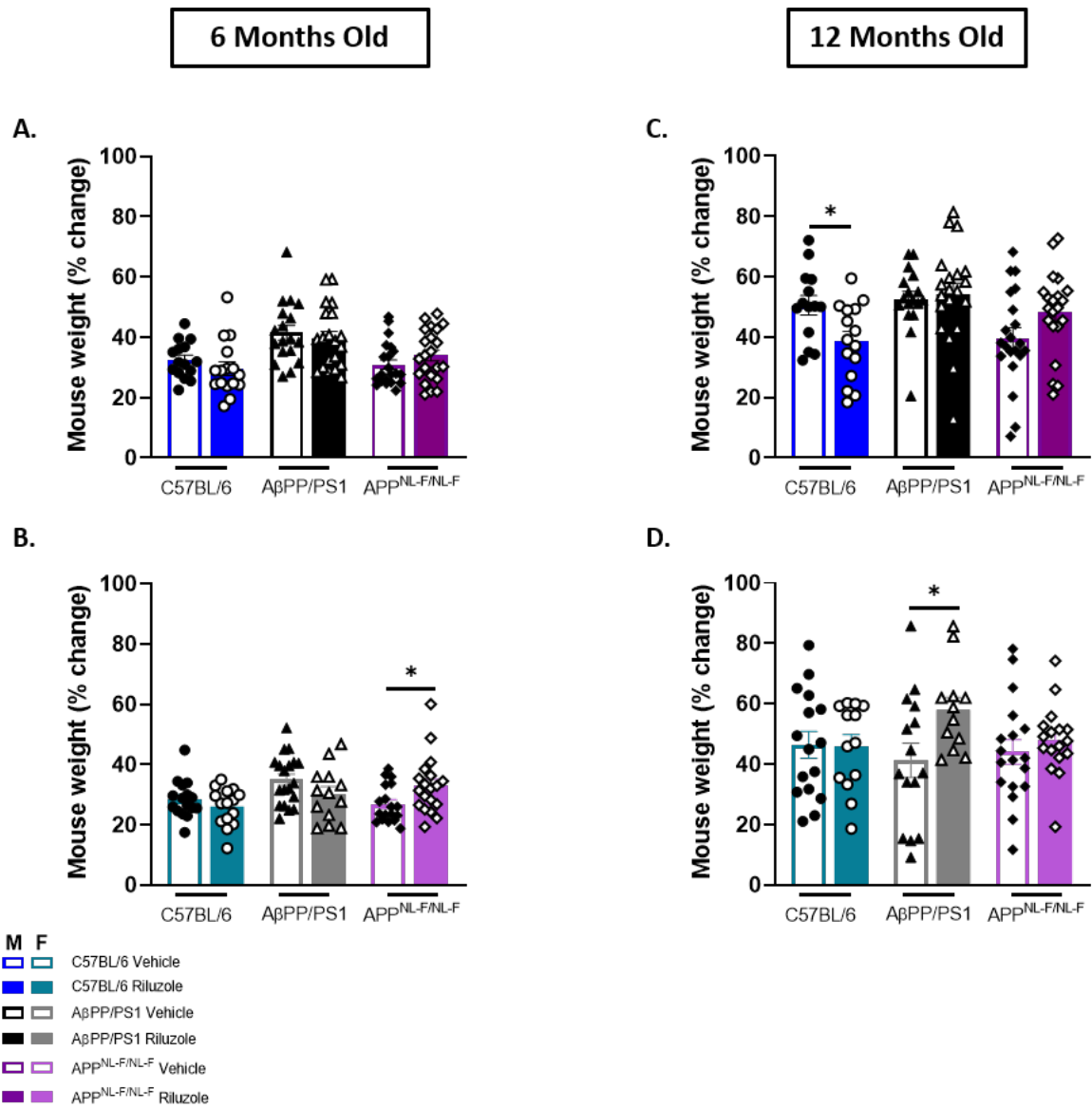
Supplementary Figure 2. No significant treatment differences in liver glycogen content on- or off-treatment across all genotypes. Analysis of liver glycogen content in male (A,C) and female (B,D) mice for each genotype and treatment group immediately following cessation of treatment at 6 months old and at 6 months post-treatment. Within-genotype age-matched unpaired t-test (n=5-6).
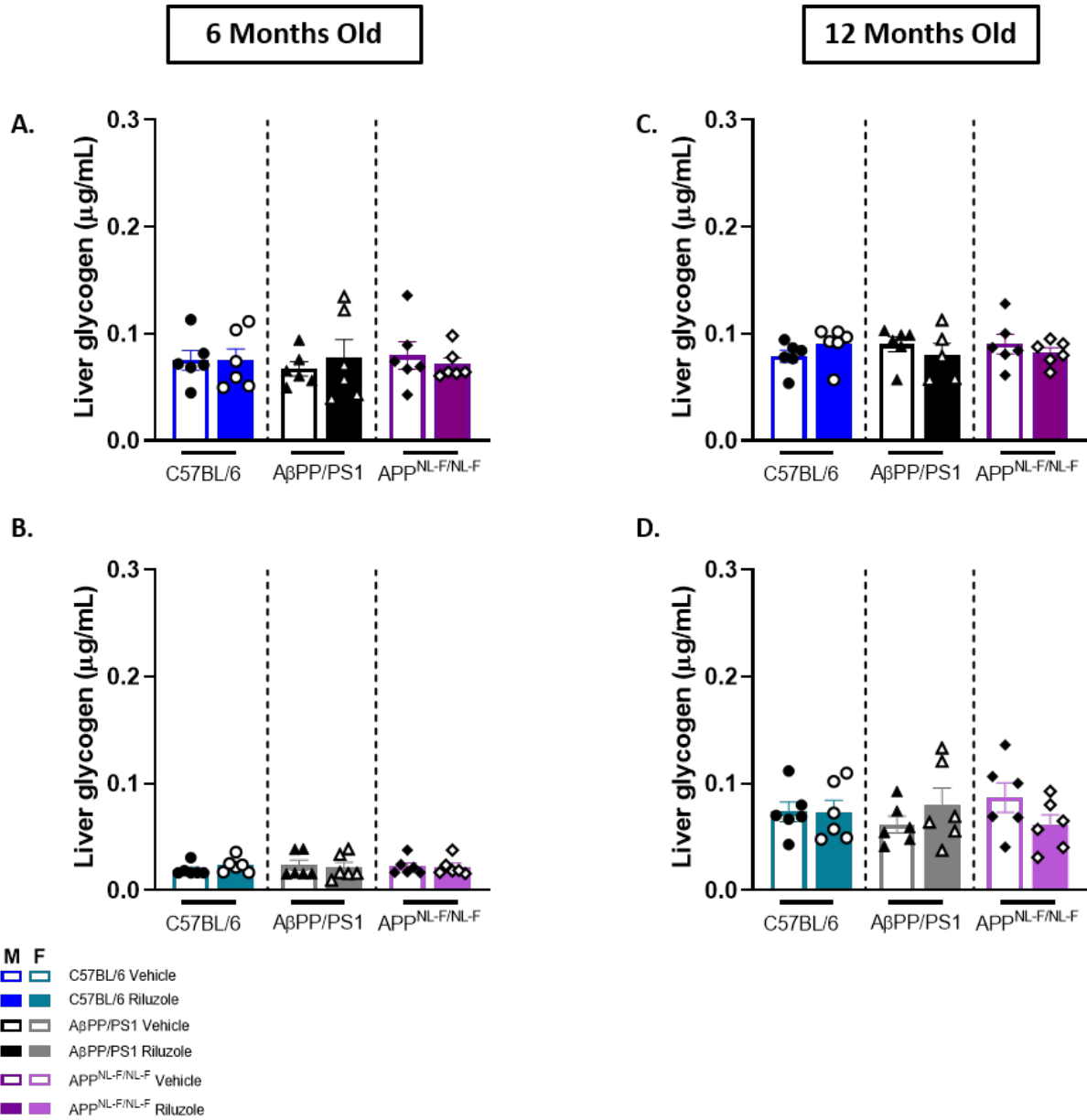
Supplementary Figure 3. No long-term changes in peripheral glucose metabolism with riluzole treatment. A, K) Blood glucose levels acquired from the tail vein after a 4-hour fast. B-D, L-N) Insulin tolerance by percent change from baseline (T=0). E, O) Percent change AUC for each genotype and treatment group. F, P) Blood glucose levels obtained from the tail vein after a 15-hour fast. G-I, Q-S) Mice received an intraperitoneal injection of glucose following the baseline blood glucose reading at T=0. Blood glucose levels were again measured on the same time course as previously described. J, T) AUC for each genotype and treatment group. ITT/GTT time course, within-genotype repeated measures two-way ANOVA, Fisher's LSD; AUC (n=13-22) unpaired t-test.