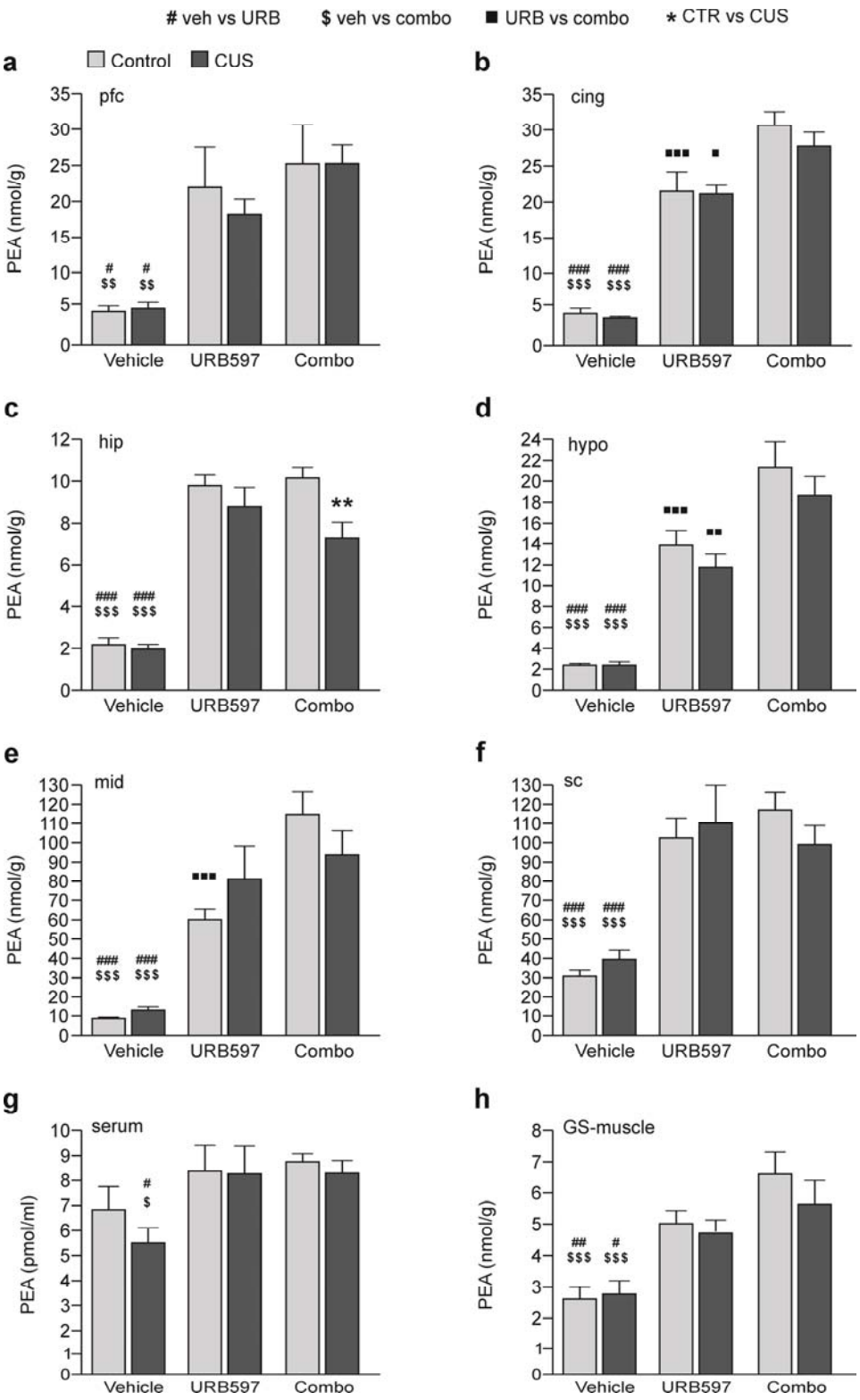
Figure S2


# veh vs URB
$ veh vs combo
■ URB vs combo
* CTR vs CUS
a
Control
CUS
pfc
PEA (nmol/g)
Vehicle
URB597
Combo
b
cing
c
hip
**
d
hypo
e
mid
f
sc
g
serum
PEA (pmol/ml)
h
GS-muscle

Quantification of palmitoylethanolamide (PEA) in brain, muscle and serum by LC-MRM. CUS did not change PEA levels in brain (a-f) and left GS muscle (h) since no difference between vehicle-treated control and CUS mice was found. As for AEA shown in Figure 4, a tendency to a decrease in PEA in CUS mice compared with controls was observed only in serum (g). URB597 treatment induced ~4 to 6-fold increase in PEA level in all brain regions examined (a-f). An increase in PEA level was also measured in the left GS muscle of both animal groups (h). In serum, URB597 induced a significant increase in PEA only in CUS mice (g). Combo treatment induced a statistically significant increase in PEA level compared with vehicle-treated animals in all brain regions (a-f) and GS muscle (h) of both animal groups, whereas serum PEA level was increased only in CUS mice (g). Compared with URB597-treated mice, combo treatment induced a synergistic increase in PEA level in cingulate cortex (b) and midbrain (e) of control mice only; synergism was observed also in hypothalamus (d) of both control and CUS mice. Statistical differences between specific groups are shown on each bar. #, $, ▪,* $p<0.05$; ##, $$, ▪▪, ** $p<0.01$; ###, $$$, ▪▪▪, *** $p<0.001$, Bonferroni's multiple comparison tests after significant two-way ANOVA; n= 8-10 animals per each group. Additional statistical analyses are reported in Table S1. Abbreviations: PEA, palmitoylethanolamide; pfc, prefrontal cortex; cing, cingulate cortex; hip, hippocampus; hypo, hypothalamus; mid, midbrain; sc, spinal cord; GS-muscle, gastrocnemius-soleus muscle.