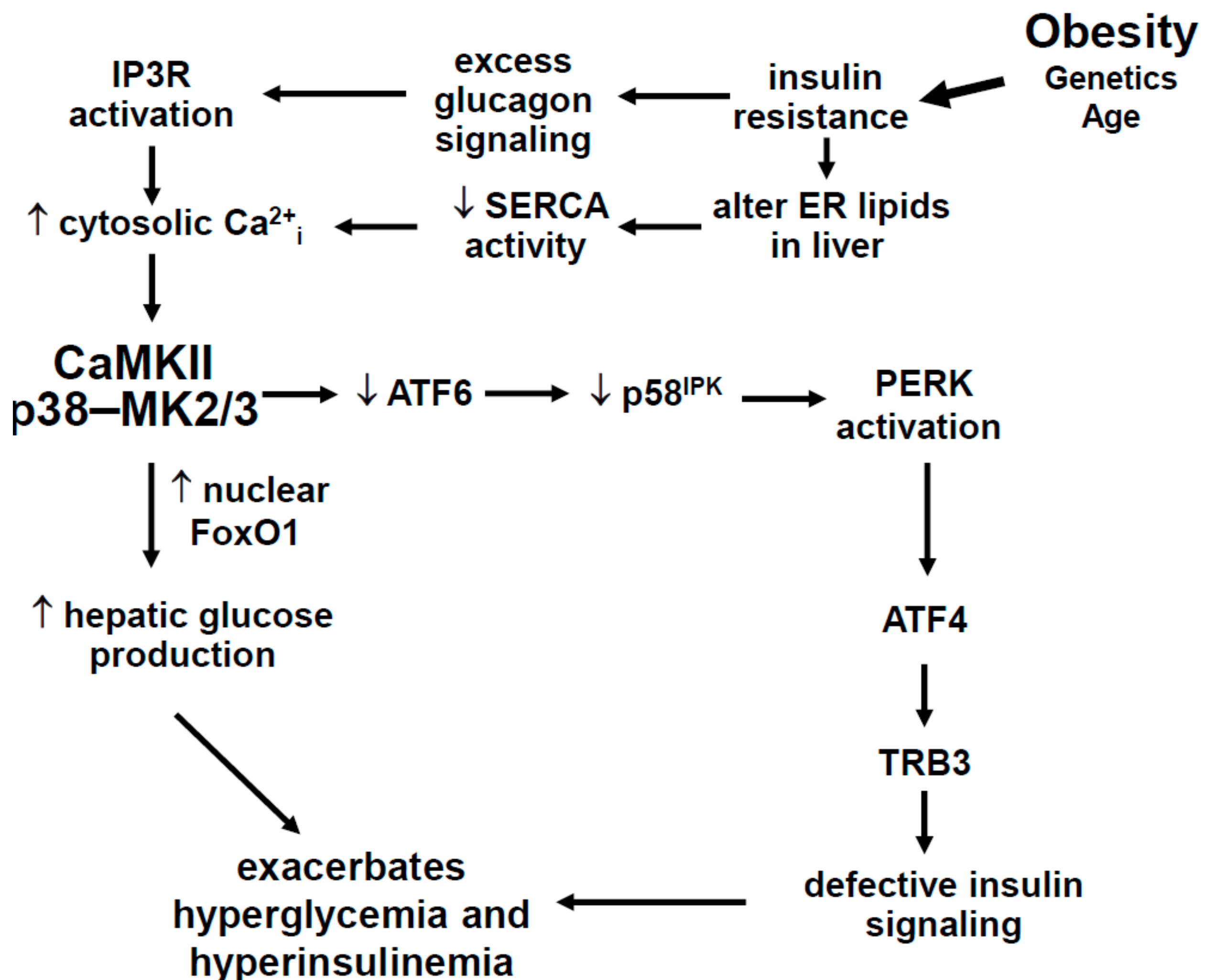
SUPPLEMENTARY DATA

Supplementary Figure S1. Pathway leading to exacerbation of glucose and insulin metabolism in the setting of obesity. Based on the studies in Refs. 13 and 14 and in Wang et al. (2012) Nature 485(7396):128-32; obesity, genetics and age lead to an increase in cytoplasmic calcium in hepatocytes by glucagon-induced activation of the IP3 receptor. Inhibition of the calcium ATPase, SERCA, probably amplifies this effect (Refs. 7 and 8). The increase in cytoplasmic calcium activates CaMKII, which in turn activates p38 and MK2/3. Kinase activation triggers two downstream branches. In the first branch, phosphorylation of nuclear FoxO1 leads to its nuclear translocation and induction of genes that promote hepatic glucose production. In the second branch, the kinase pathway activates PERK by suppressing ATF6 and $p58^{IPK}$. PERK activation, through ATF4 and Trb3, suppresses insulin receptor signaling. The combination of these two pathways exacerbates hyperglycemia and selective insulin resistance.



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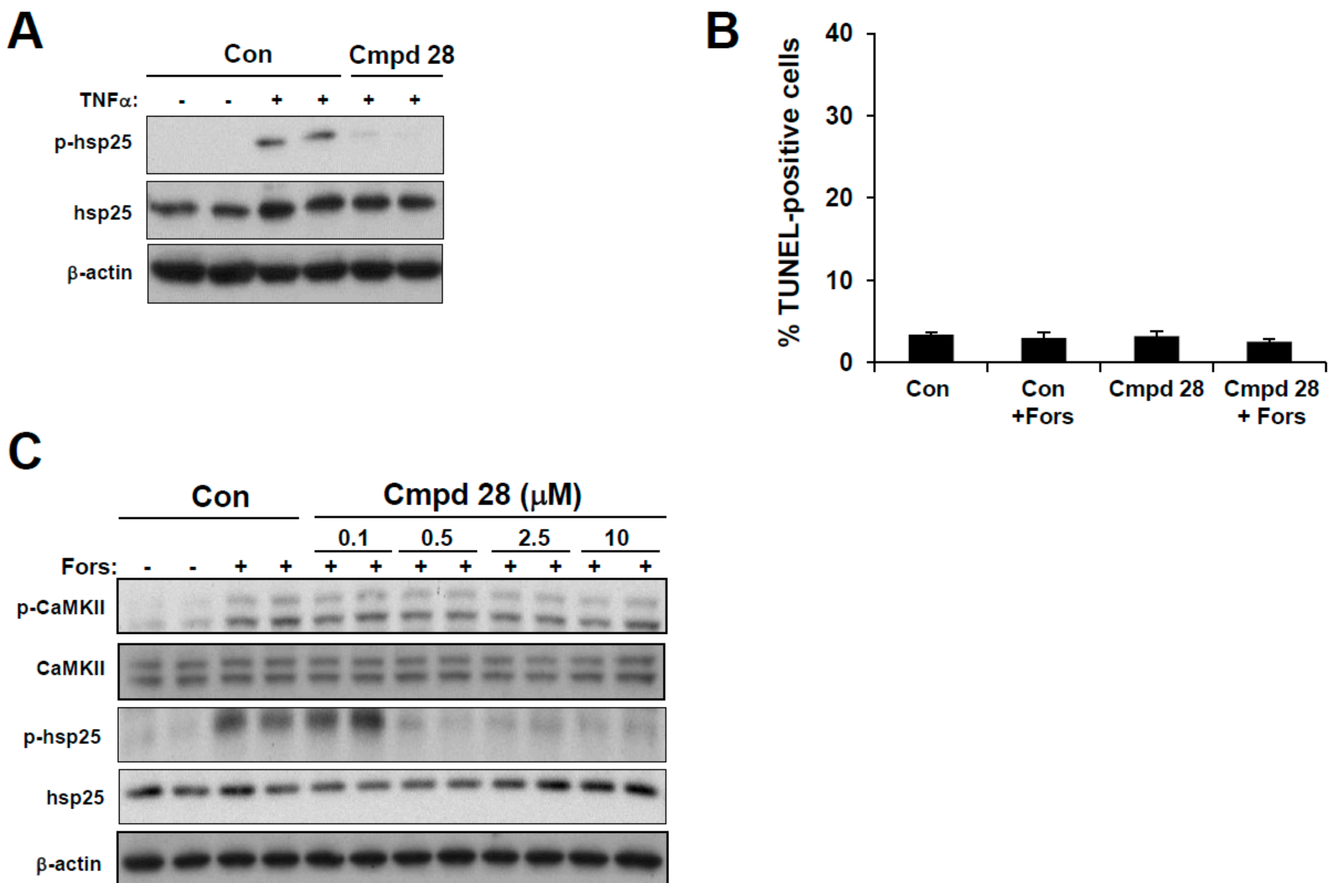
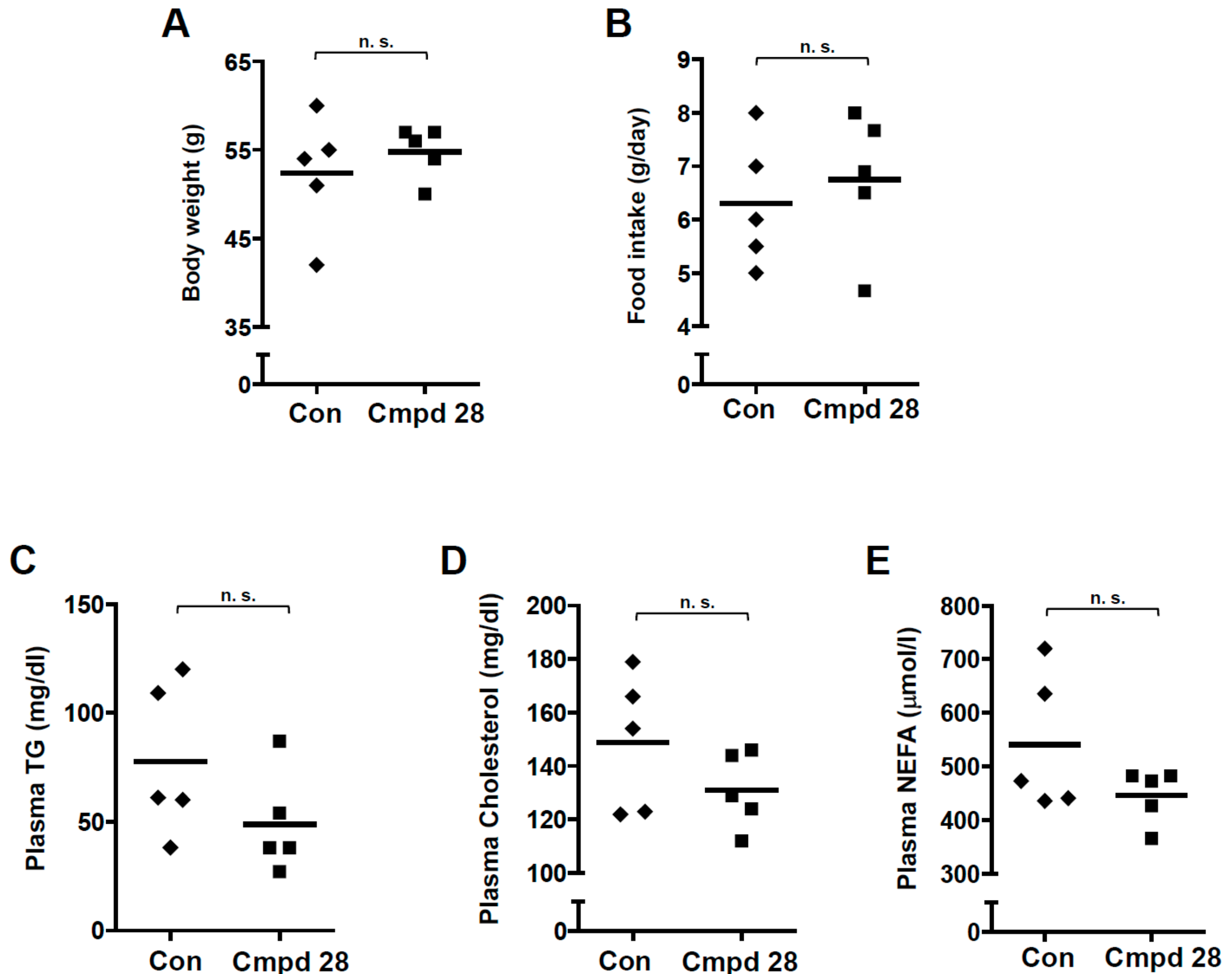
Supplementary Figure S2. Cmpd 28 inhibits TNFα- and forskolin-induced hsp-25 phosphorylation without an effect on cell viability. (**A**) Primary HCs from WT mice were pretreated with either vehicle (Con) or 500 nm of cmpd 28 (Cmpd 28) for 1 h and then treated with 5 ng/ml of tumor necrosis factor α (TNFα) for 20 mins. Lysates were assayed for p-hsp25, hsp25, and β-actin by immunoblot. p, phospho. (**B**) Primary HCs from WT mice were pretreated with either vehicle (Con) or 500 nm cmpd 28 (Cmpd 28) for 1 h, followed by co-treatment with cmpd 28 ± forskolin for 5 h. The cells were stained for TUNEL, counterstained with DAPI (nuclei), and quantified as percent TUNEL-positive cells from 3 fields for each condition. None of the groups were statistically different from the control group. (**C**) Primary HCs from WT mice were pretreated with either vehicle (Con) or the indicated concentrations of cmpd 28 (Cmpd 28) for 1 h, followed by co-treatment with cmpd 28 ± forskolin for 1 h. Lysates were probed for p-CaMKII, CaMKII, p-hsp25, hsp25, and β-actin by immunoblot. p, phospho.



Supplementary Figure S3. Cmpd 28 treatment does not alter body weight, food intake, or plasma lipids. 10 week-old *ob/ob* mice were injected i.p. with 0.2 mg/kg body weight of cmpd 28 (Cmpd 28) or vehicle (Con) each day for 3 weeks (n=5 mice per group). The mice were then assayed for (**A**) body weight; (**B**) food intake; (**C**) plasma triglyceride (TG); (**D**) plasma cholesterol; and (**E**) plasma non-esterified free fatty acids (NEFA). n.s., non-significant.



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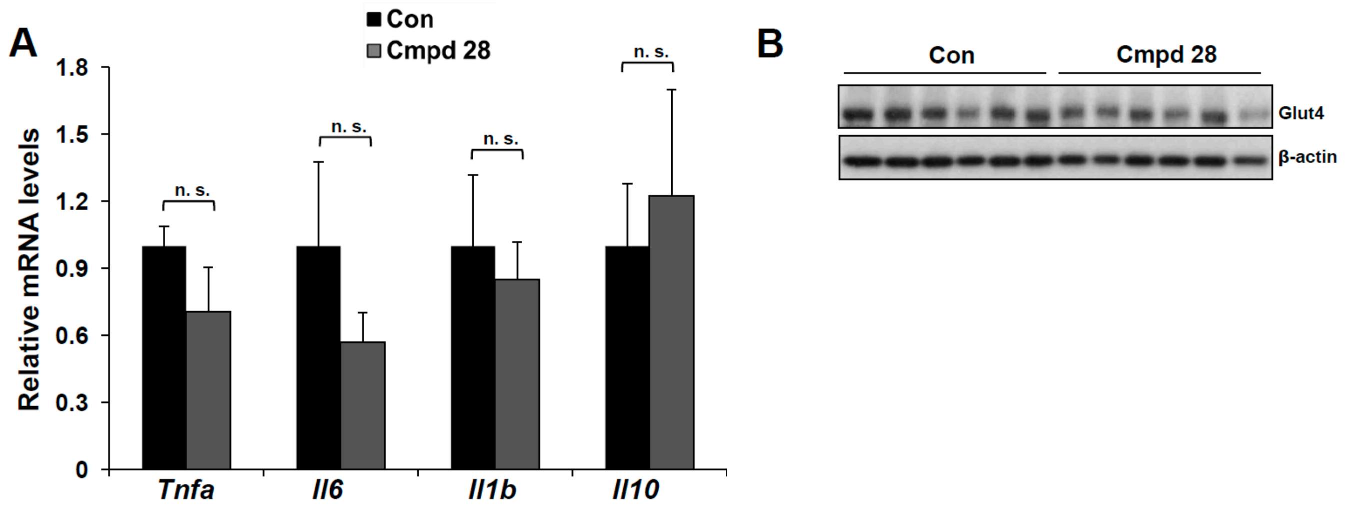
Supplementary Figure S4. Cmpd 28 treatment does not change visceral adipose tissue inflammatory markers or GLUT4 levels. 17-week-old DIO mice were injected i.p. with 0.2 mg/kg body weight of cmpd 28 (Cmpd 28) or vehicle (Con) each day for 3 weeks (n=6 mice per group). (**A**) RNA was extracted from visceral adipose tissue and assayed by RT-qPCR for *Tnfa*, *Il6*, *Il1b* and *Il10* mRNA. n.s., non-significant. (**B**) Protein lysates were assayed for Glut4 and β-actin by immunoblot. The Glut4:β-actin densitometric ratio was statistically similar between the 2 cohorts of mice.



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