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Supplemental Information

Uncoupling Hepatic Oxidative Phosphorylation Reduces Tumor Growth in Two Murine Models of Colon Cancer

Yongliang Wang, Ali R. Nasiri, William E. Damsky, Curtis J. Perry, Xian-Man Zhang, Aviva Rabin-Court, Michael N. Pollak, Gerald I. Shulman, and Rachel J. Perry

Figure S1

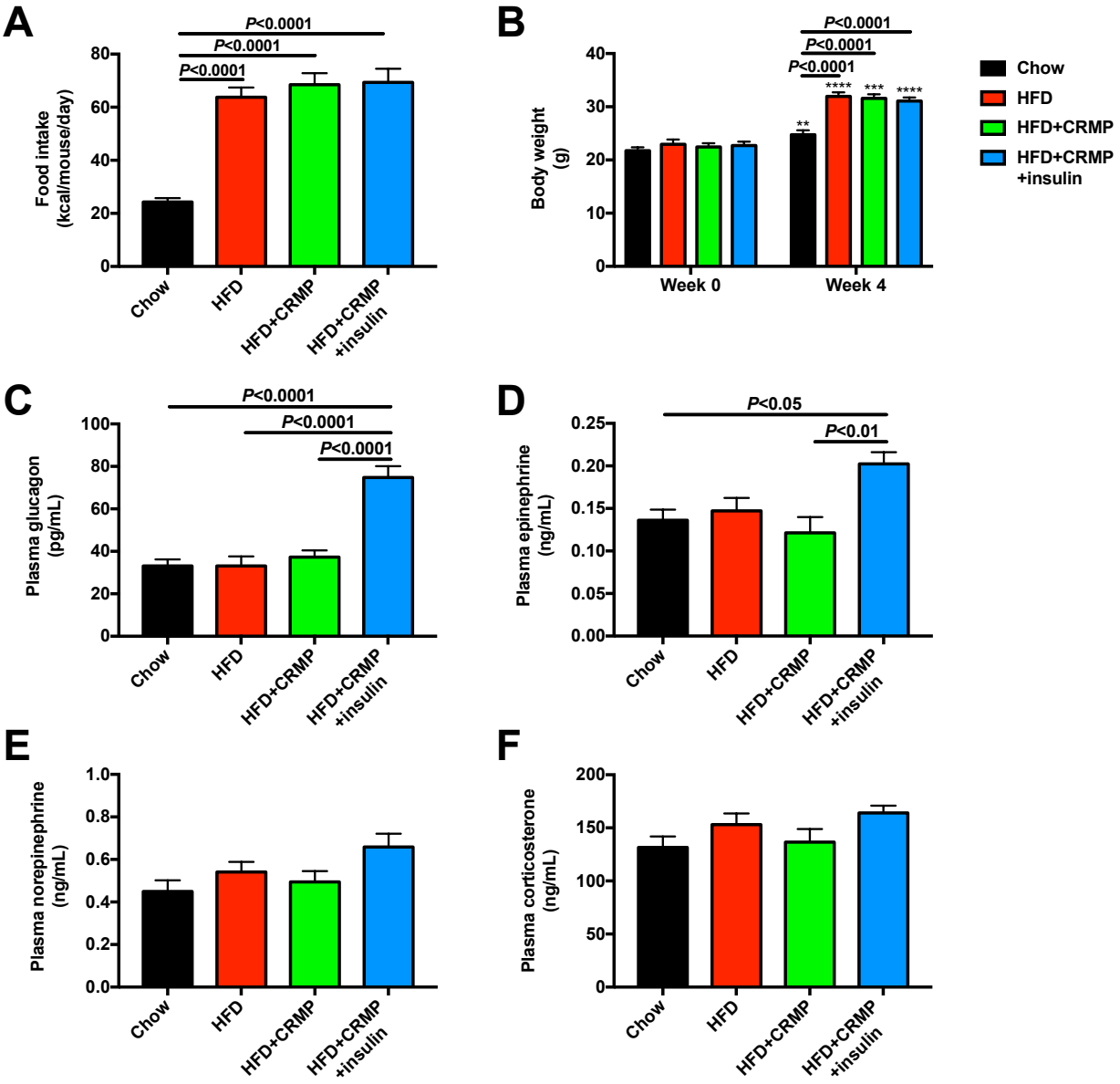

Figure S1, related to Figure 1. Controlled release mitochondrial protonophore slows tumor growth and limits tumor glucose uptake and oxidation due to reversal of hyperinsulinemia, independent of body weight. (A) Daily food intake during week 3 of treatment. (B) Body weight (n=7-8 per group). ***P*<0.01, ****P*<0.001, *****P*<0.0001 by the 2-tailed paired Student's t-test as compared to the same mice at week 0. (C)-(F) Plasma glucagon, epinephrine, norepinephrine, and corticosterone concentrations. In all panels, unless otherwise specified, data are the mean±S.E.M. and groups were compared by ANOVA with Bonferroni's multiple comparisons test.

Figure S2

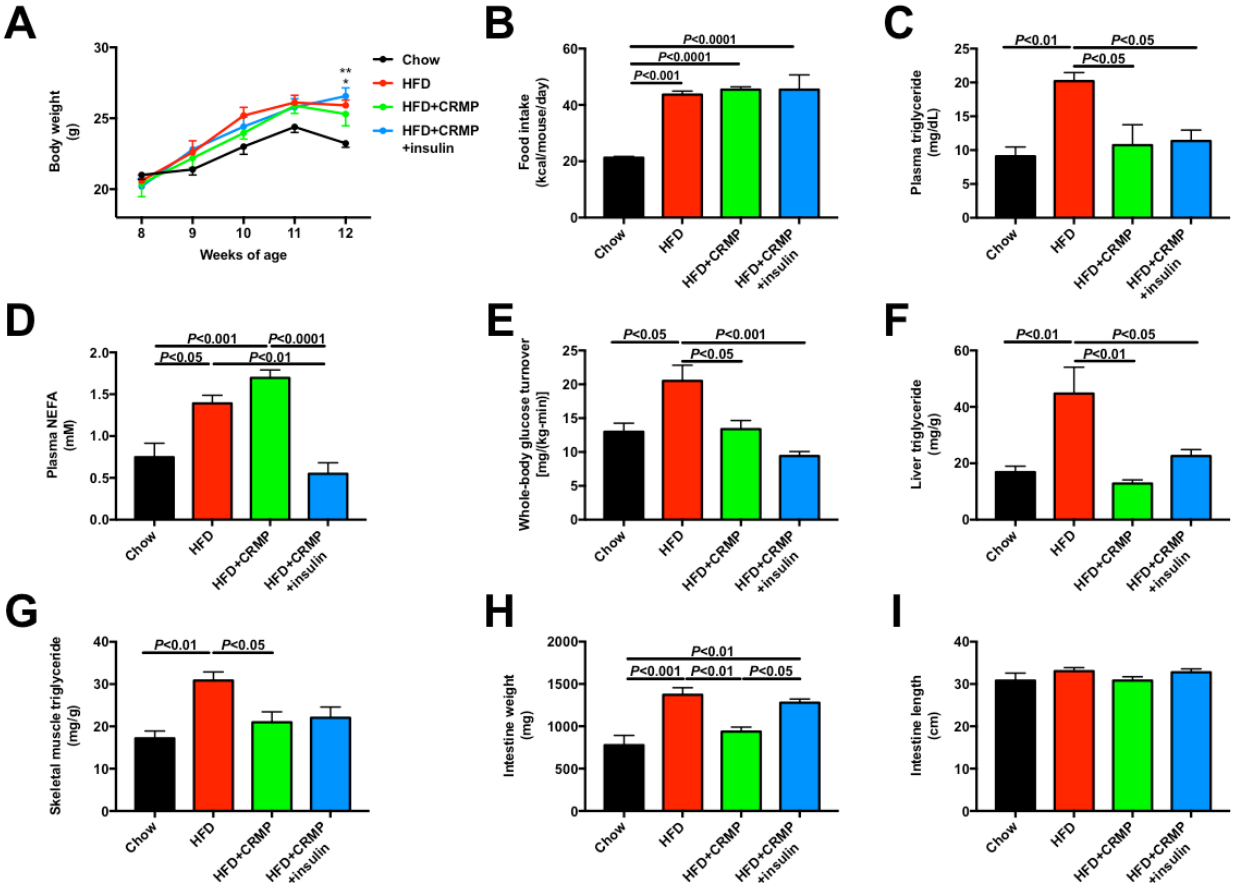

Figure S2, related to Figure 3. CRMP slows tumor growth in high fat fed $Apc^{Min+/-}$ mice, a murine model of familial adenomatous polyposis, by reversing hyperinsulinemia. (A) Body weight. Treatments were begun at 8 weeks of age and continued for four weeks. **P*<0.05 (chow vs. HFD), ***P*<0.01 (chow vs. HFD+CRMP+insulin). (B) Food intake measured during the third week of treatment. (C)-(D) Plasma triglyceride and NEFA concentrations. (E) Whole-body glucose turnover (n=4-5 per group). (F)-(G) Liver and skeletal muscle triglyceride content. (H)-(I) Length and weight of the small and large intestine. Unless otherwise specified, data are the mean±S.E.M. of n=5 per group, with comparisons by ANOVA with Bonferroni's multiple comparisons test.

Figure S3

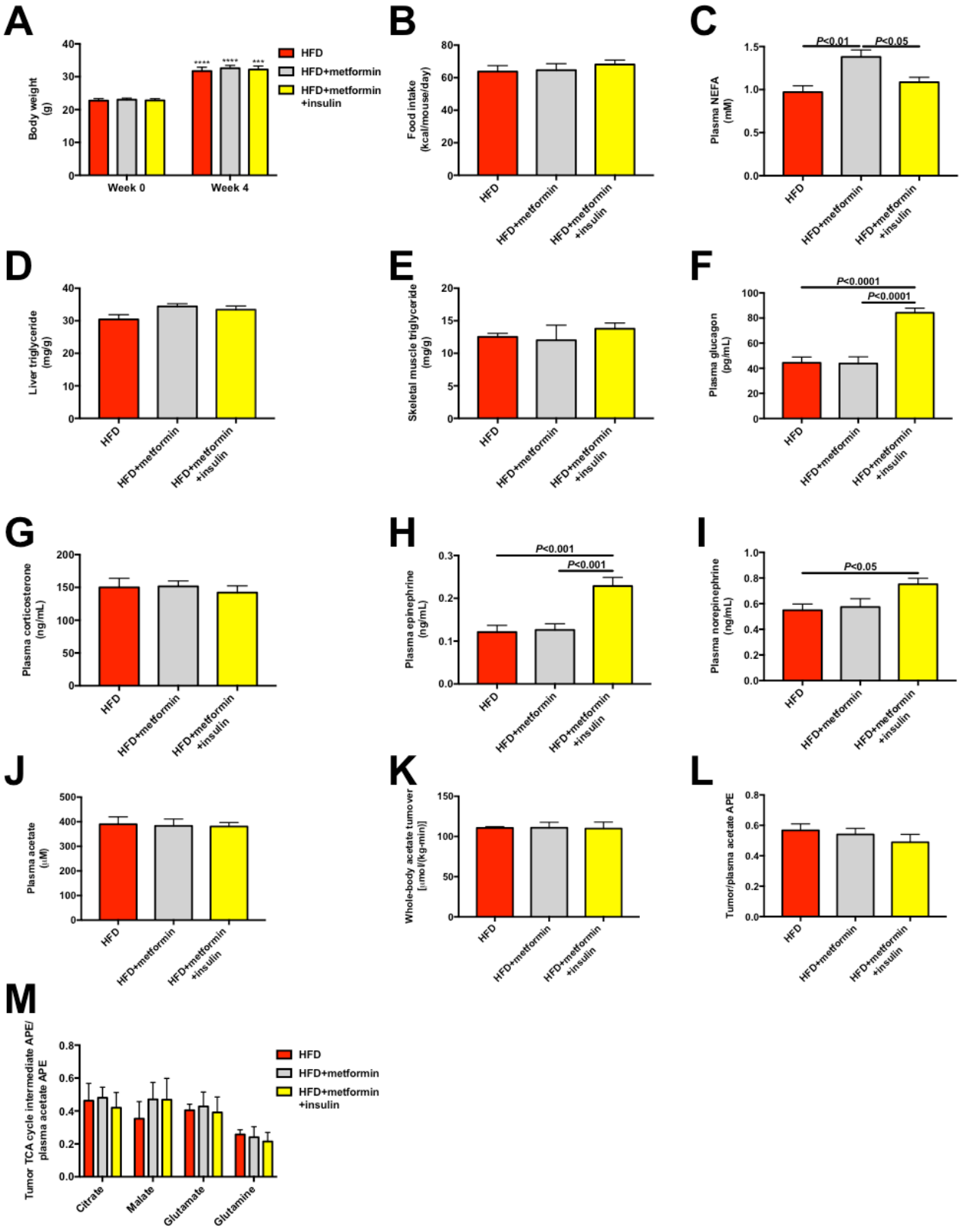
A
Body weight (g)
HFD
HFD+metformin
HFD+metformin +insulin
Week 0
Week 4
B
Food intake (kcal/mouse/day)
C
Plasma NEFA (mM)
P<0.01
P<0.05
D
Liver triglyceride (mg/g)
E
Skeletal muscle triglyceride (mg/g)
F
Plasma glucagon (pg/mL)
P<0.0001
P<0.0001
G
Plasma corticosterone (ng/mL)
H
Plasma epinephrine (ng/mL)
P<0.001
P<0.001
I
Plasma norepinephrine (ng/mL)
P<0.05
J
Plasma acetate (μM)
K
Whole-body acetate turnover [μmol/(kg·min)]
L
Tumor/plasma acetate APE
M
Tumor TCA cycle intermediate APE/ plasma acetate APE
Citrate
Malate
Glutamate
Glutamine

Figure S3, related to Figure 4. Metformin slows tumor growth and limits tumor glucose uptake and oxidation secondary to reversal of hyperinsulinemia in HFD mice. (A) Body weight. (B) Food intake in week 3 of treatment (n=6 per group). ***P<0.001, ****P<0.0001 vs. week 0 by the 2-tailed paired Student's t-test. (C) Plasma NEFA concentrations. (D)-(E) Liver and quadriceps triglyceride content. (F)-(I) Plasma glucagon, corticosterone, epinephrine, and norepinephrine concentrations. (J)-(K) Plasma acetate concentrations and whole-body acetate turnover. (L) Ratio of tumor to plasma acetate enrichment in mice infused with [1-^{13}C] acetate. (M) Ratio of tumor TCA cycle intermediate enrichment to plasma acetate enrichment in mice infused with [1-^{13}C] acetate. Unless otherwise specified, data are the mean±S.E.M. of n=8 per group, with comparisons between groups by ANOVA with Bonferroni's multiple comparisons test.