Supplemental Text

Since the recently discovered protein myokine irisin also functions through PPARα we investigated whether BAIBA is increasing PPARα expression through local effects on irisin in white adipose tissue. BAIBA had no effect on irisin expression in primary white adipocytes in *vitro* or in *vivo* in subcutaneous white adipose tissue of mice treated with BAIBA (**Figure S4A and S4B**). We also investigated whether BAIBA may function by activating irisin expression in myocytes. BAIBA had no effect on the expression of irisin and related metabolic genes in myocytes in *vitro* (**Figure S4C**).

Supplemental Figure Legends

Figure S1 BAIBA accumulates dose-dependently in the media of myocytes as a result of forced PGC-α expression. Myocytes were transduced with two doses of an adenoviral vector expressing either PGC-1α (n=2) or GFP (n=2) (Multiplicity of Infection 80 and Multiplicity of Infection 400). After 24 hours of exposure to these cells, media was analyzed using an LC-MS based metabolite profiling method. The concentration of BAIBA increased in the media in response to increased doses of PGC-1α expressing virus. Multiplicity of Infection (MOI). *, $P < 0.05$ Data are represented as Mean ± SEM.

Figure S2 The experimental scheme for differentiation of human pluripotent stem cells into white and brown adipocytes and treatment with BAIBA.

Figure S3 **A)** BAIBA did not significantly alter the expression of the white adipocyte gene adiponectin (ADIPOQ) in hiPSC derived white adpocytes. **B)** Exposure of huES2 human embryonic stem cells to BAIBA during programmed differentiation to mature white adipocytes (using forced expression of PPARG2) increased the expression of the brown-adipocyte specific gene UCP-1. Data are represented as Mean ± SEM. **C)** Exposure of induced human pluripotent stem cells (BJ RiPS) BAIBA during programmed differentiation to mature brown adipocytes (using forced expression of PPARG2 and CEBPB) had no significant effect on the expression of browning program genes. Data are represented as Mean ± SEM.

Figure S4 **A)** Expression of Fndc5 (Irisin) in primary adipocytes differentiated from the stromal vascular fraction isolated from inguinal WAT over 6 days and treated with 5 μM BAIBA. **B)** Expression of Fndc5 (Irisin) in subcutaneous (inguinal) white adipose tissue of control mice and mice treated with 100 mg/kg/day BAIBA for 14 days Data are represented as Mean ± SEM. **C)** Myocytes were treated with 0 μM, 0.3 μM, 1 μM, 3 μM, 5 μM and 10 μM BAIBA for 24hrs (n = 3). Expression of Fndc5 (Irisin), Fndc4, Acadl, Acadm, Cpt2, CytC and Pdk4 were measured using RT qPCR. Data are represented as Mean ± SEM.

Figure S1 Related to Figure 1

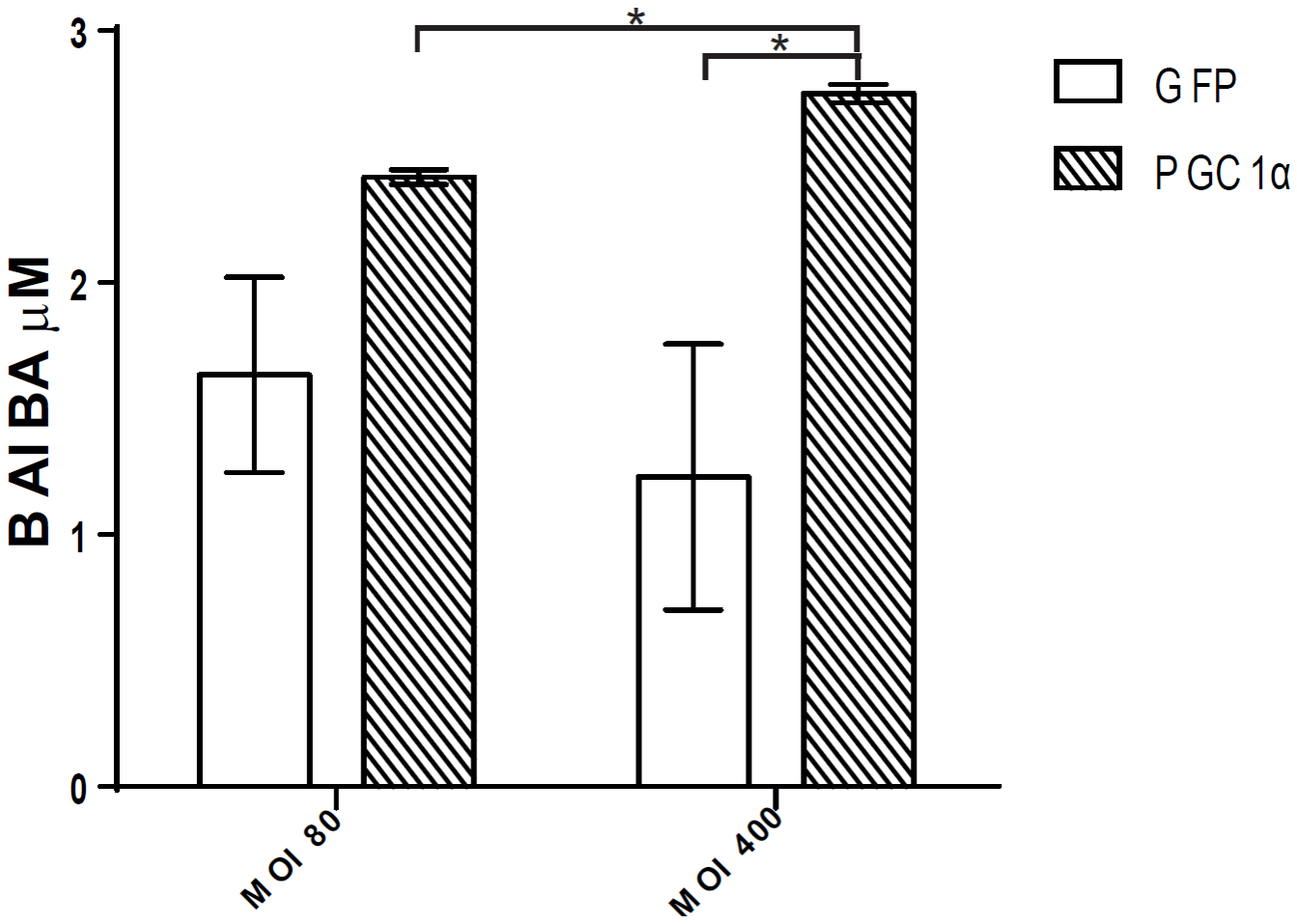


Figure S2 Related to Figure 2

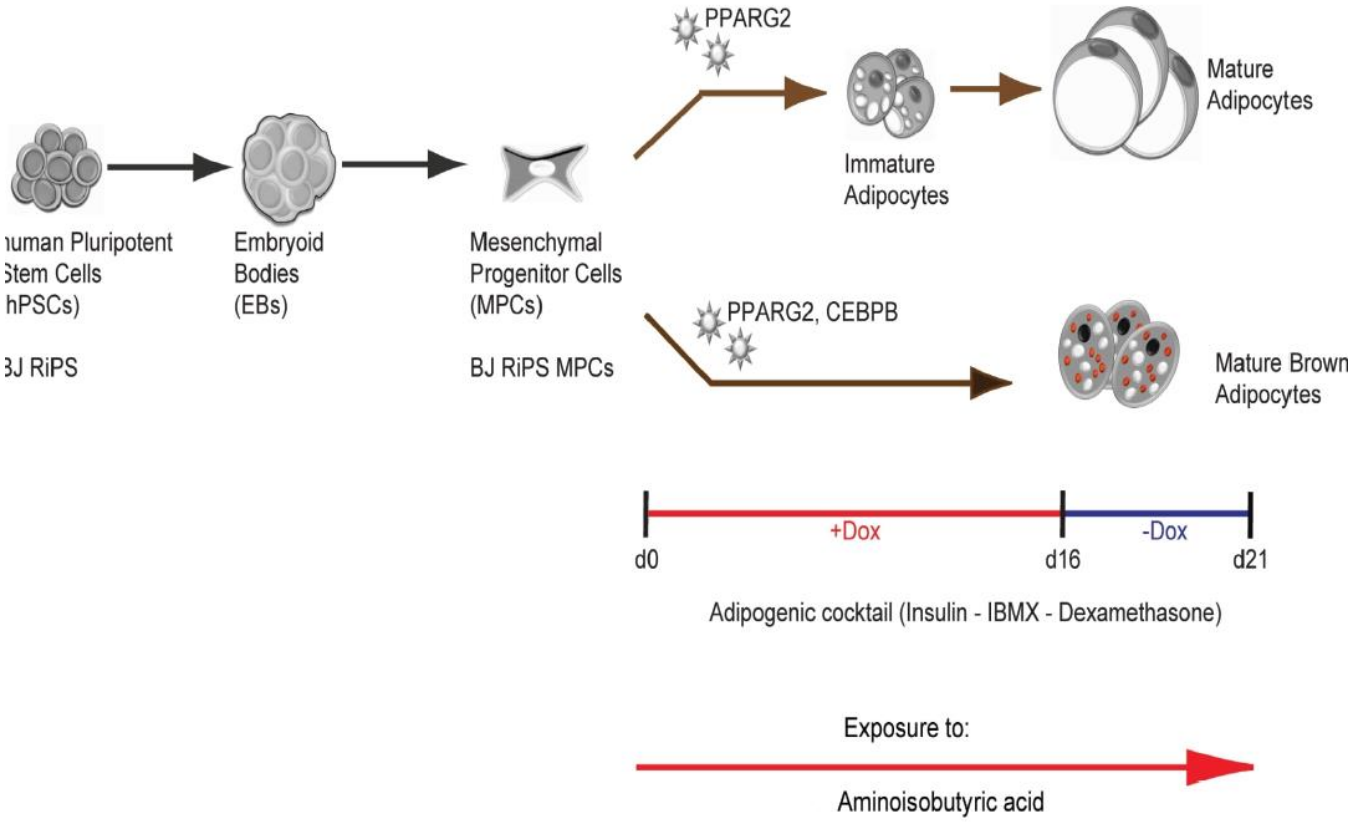


Figure S3 Related to Figure 2

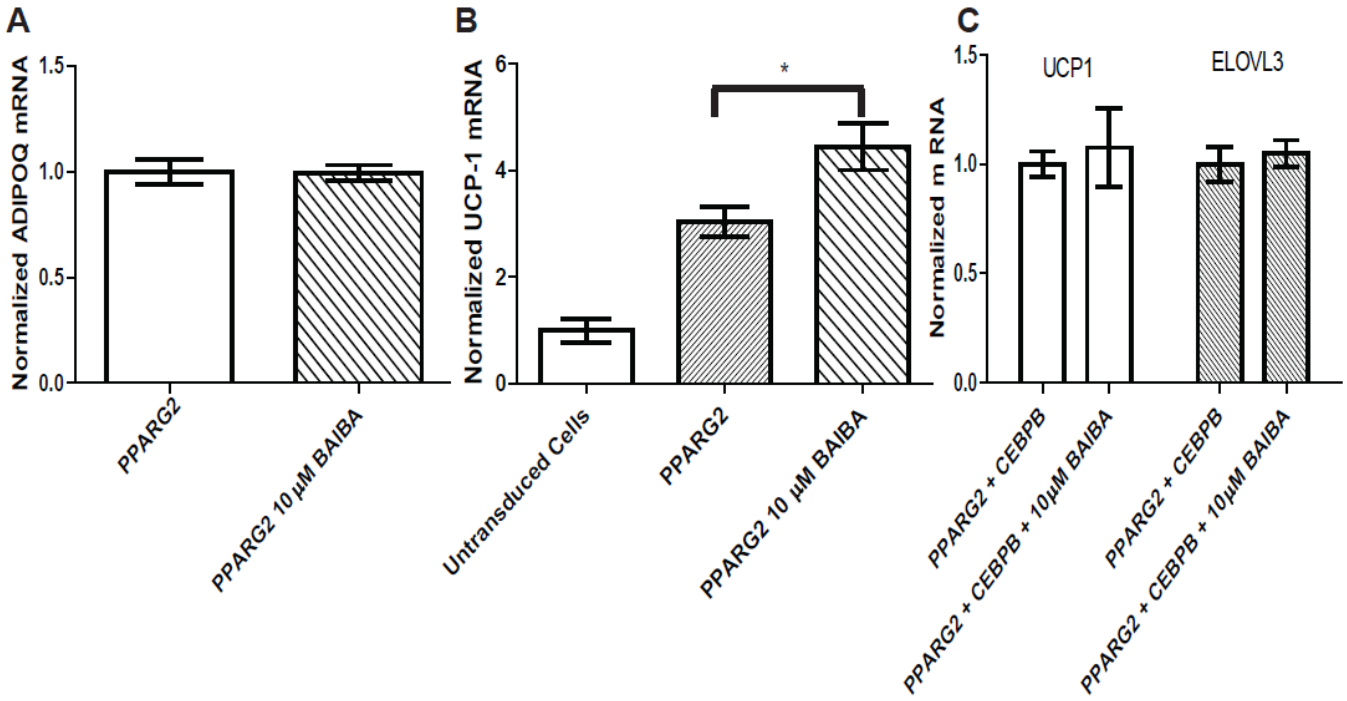
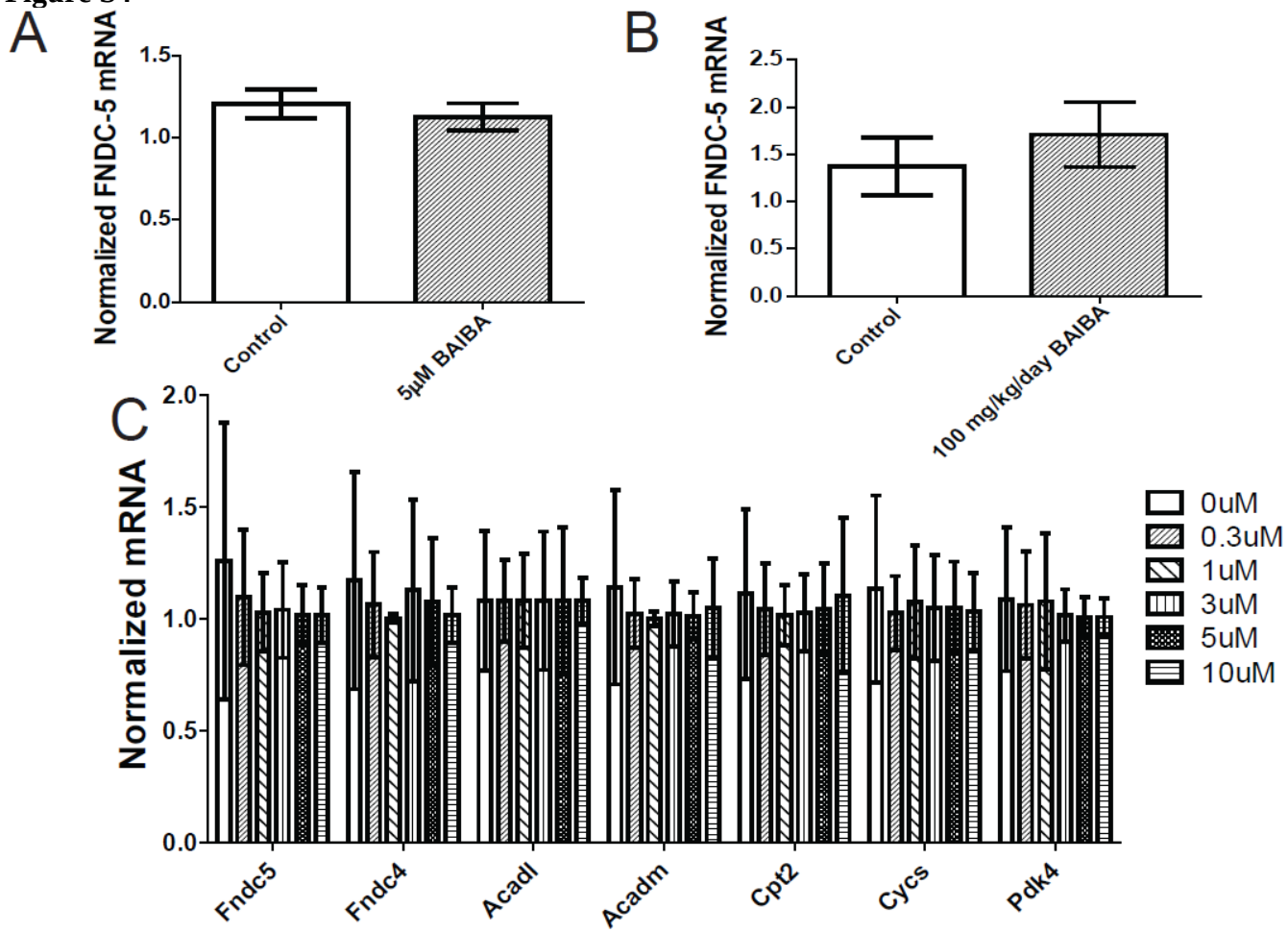


Figure S4


A
Normalized FNDC-5 mRNA
1.5
1.0
0.5
0.0
Control
5μM BAIBA
B
Normalized FNDC-5 mRNA
2.5
2.0
1.5
1.0
0.5
0.0
Control
100 mg/kg/day BAIBA
C
Normalized mRNA
2.0
1.5
1.0
0.5
0.0
Fndc5
Fndc4
Acadl
Acadm
Cpt2
Cycs
Pdk4
0uM
0.3uM
1uM
3uM
5uM
10uM

Supplemental Tables

Table S1. Heritage exercise study demographics

SEX (% Male)	AGE (years)	BMI	Baseline VO_2 MAX	Post Exercise VO2 MAX	Δ VO2 MAX
50	34.1 ± 14	26 ± 5.4	2577.3 ± 717.2	3007.4 ± 849.6	430 ± 390.3

BMI, body mass index. Data presented as mean ± SD. $V0_2$ max is reported in mL 0_2/min.