

# Phenylbutyrate inhibits Diet induced Obesity through inhibition of pyruvate dehydrogenase kinase

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## INTRODUCTION and OBJECTIVES

Obesity caused by excess energy intake has been emerging as a major health concern in the world, with increased risk leading to diabetes, hypertension, nephropathy, and cardiovascular disease. A better understanding of the molecular mechanism on how obesity develops is of critically clinical importance. Accumulating data suggest that ER-stress is strongly related with development of obesity, implying that ER stress can be a therapeutically target of obesity. 4-Phenylbutyrate (PBA) which is known as a chemical chaperon has known to decrease ER-stress. However, the detailed molecular mechanism by which PBA decreases ER-stress remains elusive. In this study, we examine the effect of PBA on diet-induced obesity.

## METHODS

Animal study :

Diet induced obesity (DIO) model. Ob/Ob model

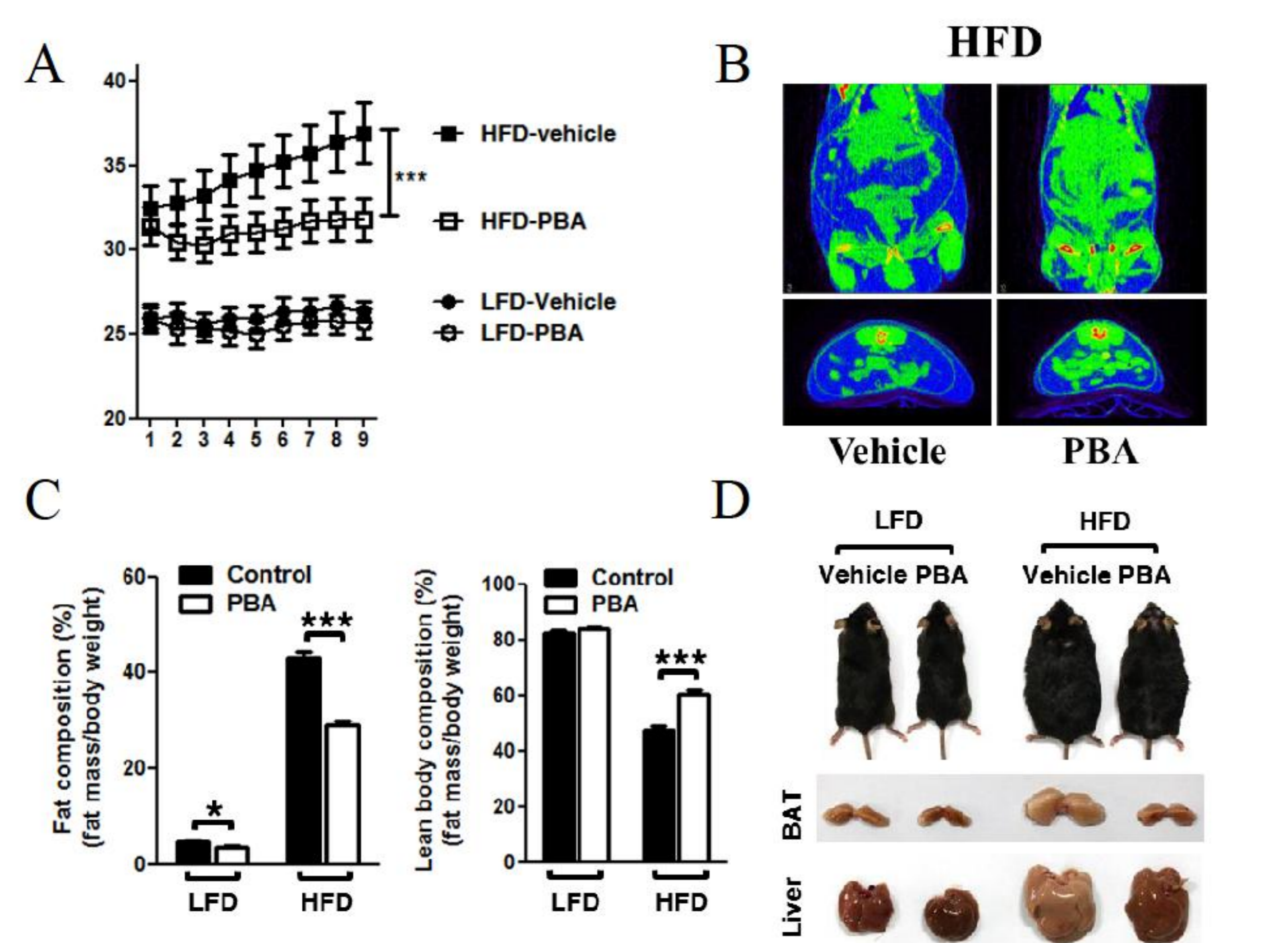
For DIO model, C57/BL6 mice were fed High fat diet (60% fat) for 8 weeks and were treated with PBA (1g/kg) and vehicle control (PBS) for 8 weeks.

For Ob/Ob mice, 8 weeks old mice were treated with PBA (1g/kg) and vehicle control (PBS) for 5 weeks

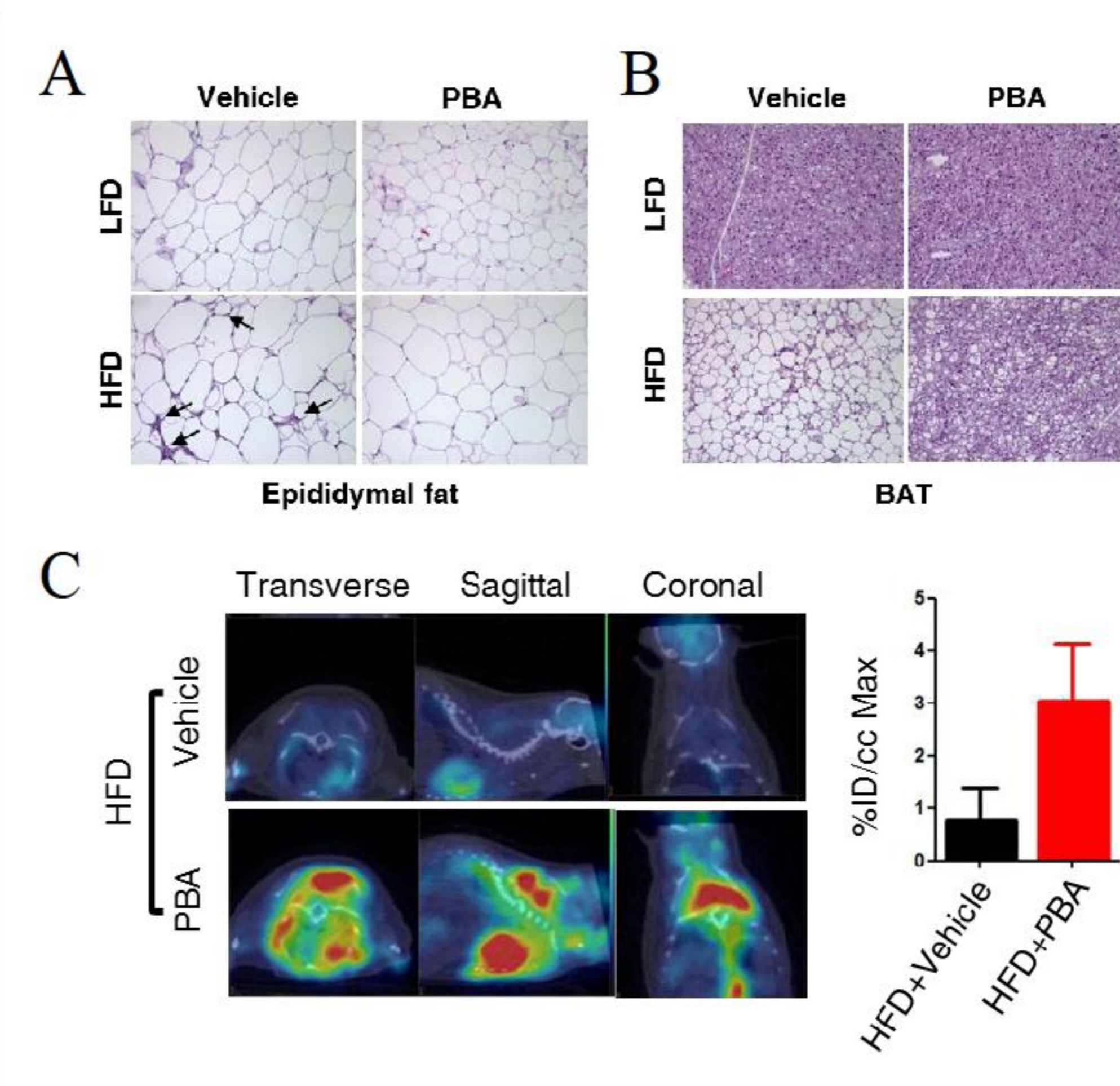
18-FDG uptake

C57BL6/J (8 weeks) were fed HFD (60% fat) for 8 weeks then administered with or without PBA (1g/L) for 1 weeks. Glucose uptake was measured by PET/CT.

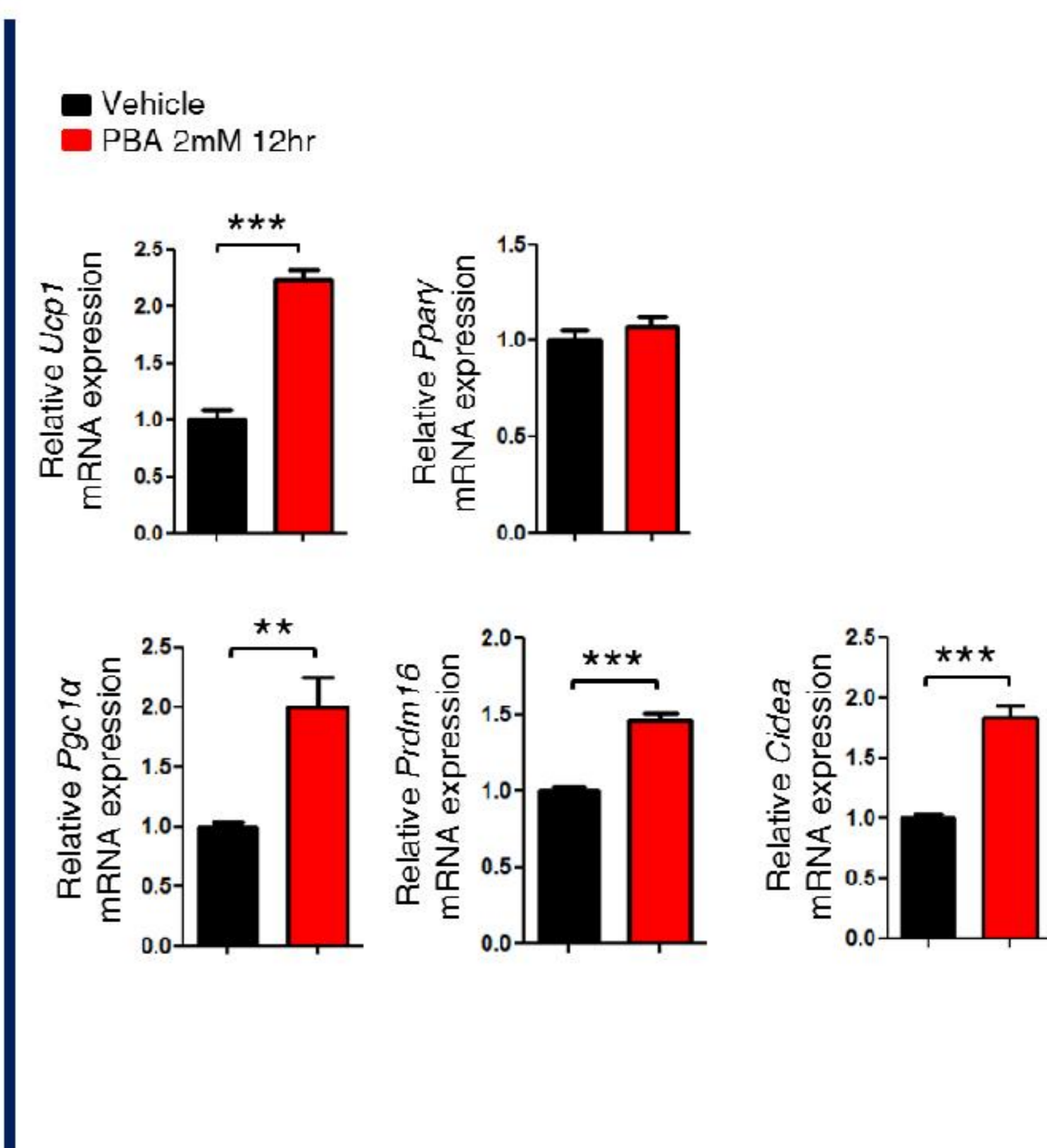
## RESULTS



**Figure 1. PBA ameliorate HFD induced obesity**  
 (A) PBA decrease Body weight gain by HFD (n=10)  
 (B) CT scan identify PBA decrease Fat accumulation  
 Blue color indicates Fat  
 (C) Tissue composition analysis showed that PBA decreased Fat mass  
 (D) Fatty Liver and BAT by HFD is recovered to normal phenotype by PBA

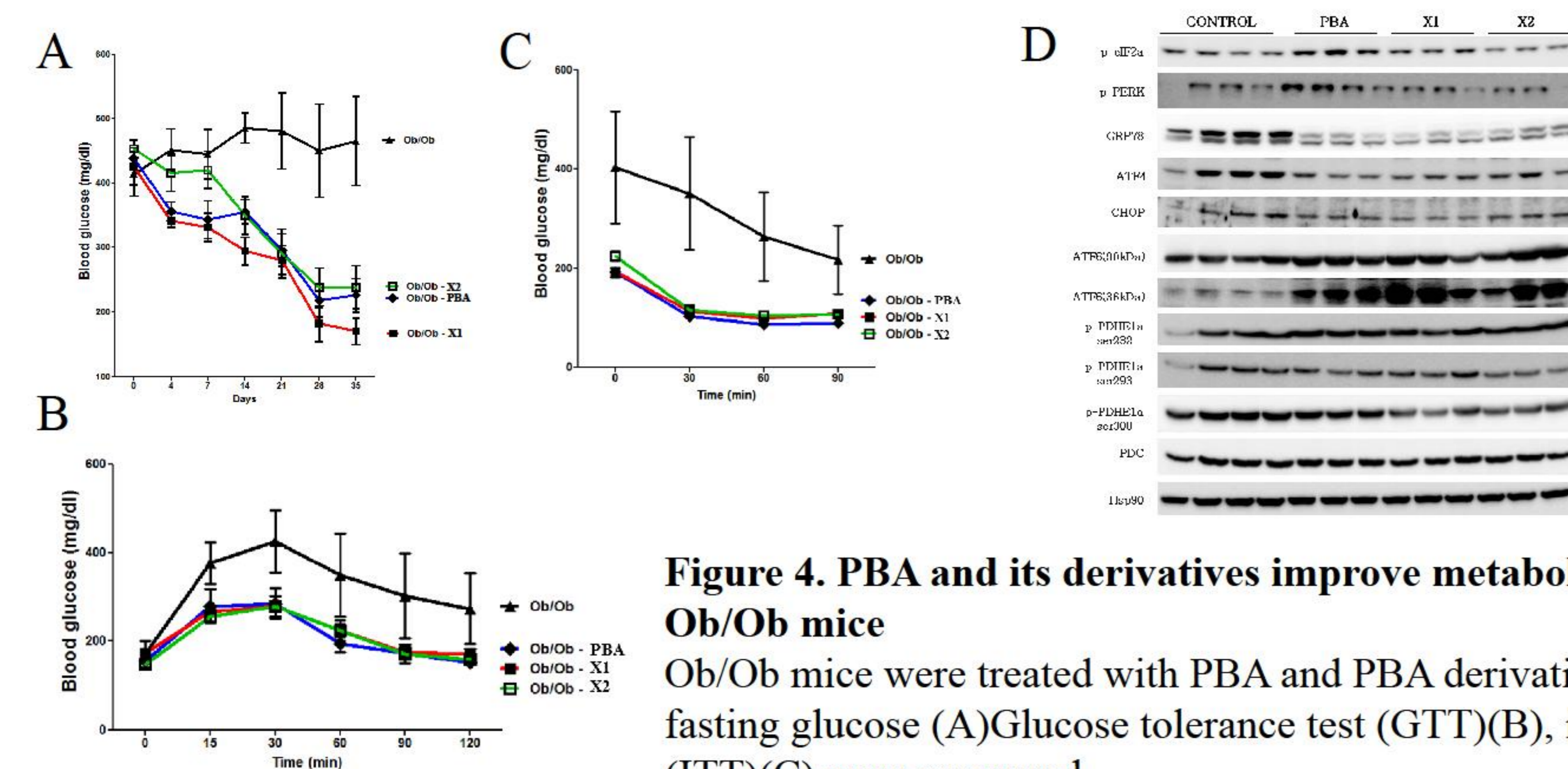


**Figure 2. PBA improve Fat activities**  
 (A) PBA decrease macrophage infiltration by HFD in White adipose tissue (WAT)  
 (B) PBA decreased fat accumulation in Brown adipose tissue (BAT)  
 (C) 18-FDG uptake identified that PBA increase glucose uptake in BAT



**Figure 3. PBA increase genes expression related with BAT activities**  
 mRNA expression level of UCP1, Pparg, Pgc1a, Prdm16, Cidea was significantly increased by PBA Treatment in primary cultured BAT cells

## RESULT



**Figure 4. PBA and its derivatives improve metabolic phenotype in Ob/Ob mice**  
 Ob/Ob mice were treated with PBA and PBA derivatives (1g/kg) and fasting glucose (A)Glucose tolerance test (GTT)(B), insulin tolerance test (ITT)(C) were measured.  
 (D) Liver tissue treated with PBA and its derivatives was subjected to western analysis

## CONCLUSION and REFERENCE

1. PBA ameliorate obesity in DIO and Ob/Ob mice model
2. PBA Increase BAT activities and Improved fatty liver and decrease macrophage infiltration in WAT.
3. In liver tissue, PBA ameliorate ER stress, accompanied with decreased PDK activities
4. PDK may be therapeutic target to control ER stress induced in obese patients

### REFERENCE

1. Science. 2006 Aug 25;313(5790):1137-40.
2. Sci Transl Med. 2013 Mar 6;5(175):175ra31.

