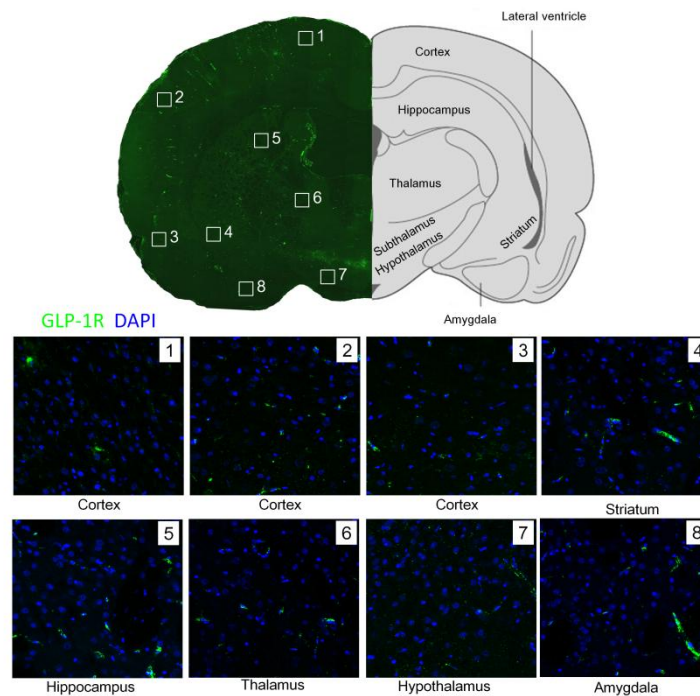
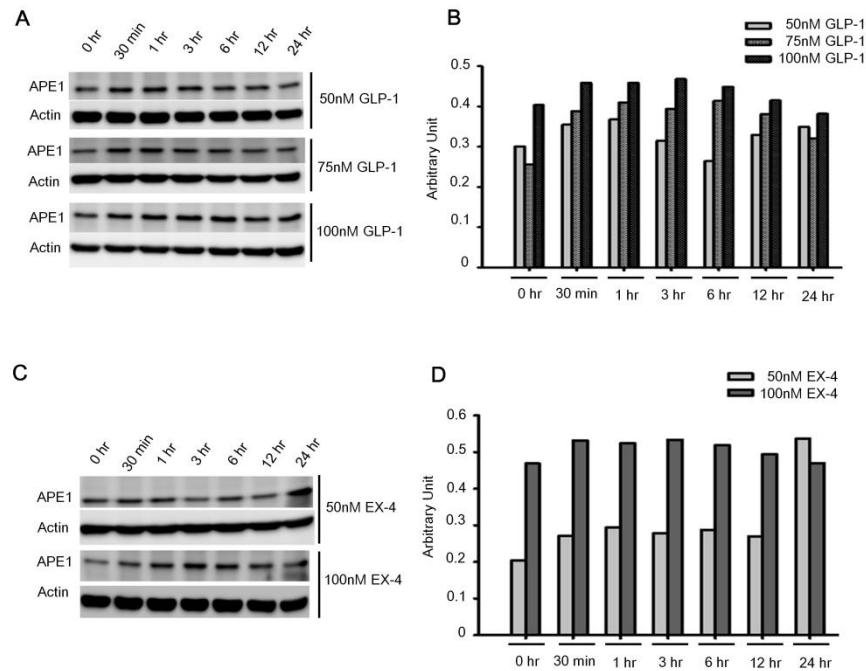


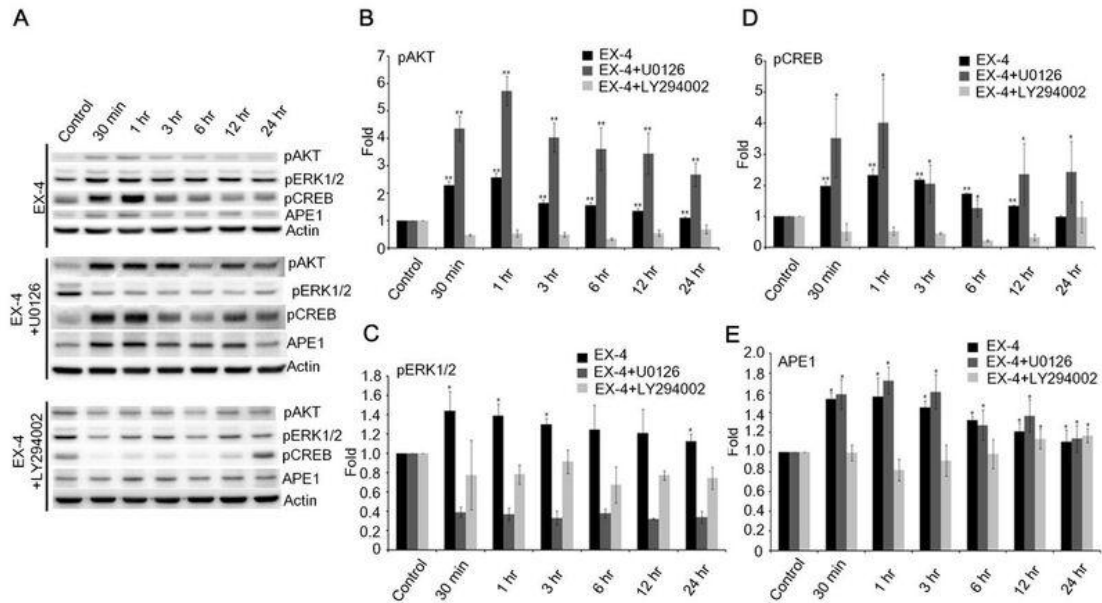
Supplementary Figures



Supplementary Figure S1. Expressions of GLP-1 receptor (GLP-1R) are ubiquitously expressed in the rat brain. The brain from a 8-week old SD rat was fixed and dissected for GLP-1R immunofluorescent staining. The image of whole brain scan (10X) has shown that GLP-1Rs are distributing all over the rat brain (green staining). Higher magnification of images (20X) were taken from various brain regions, including cortex, hippocampus, amygdale, thalamus, hypothalamus, and striatum, all imagines clearly demonstrated that GLP-1Rs express in the brain regions. (Green: GLP-1R; Blue: Nucleus).



Supplementary Figure S2. Upregulation of APE1 expression via activation of GLP-1R is agonist dose-dependent. The 8-day *in vitro* cultured primary cortical neurons were treated with various doses of the GLP-1R agonists, GLP-1 and EX-4, to determine the correlation between APE1 expression and concentration of GLP-1R agonists. Western blotting detections of APE1 demonstrated that APE1 expression was upregulated in various concentration of GLP-1 (panel A and B) or EX-4 (panel C and D) treated cortical neurons. 100 nM of both GLP-1 and EX-4 have shown the highest induction of APE1 expression within the tested concentrations. Taking together of results, which suggested that active GLP-1R triggered APE1 expression is agonist dose-dependent. (n=2).



Supplementary Figure S3. The downstream PI3K-Akt signaling axis of GLP-1 receptors (GLP-1Rs) is the major pathway that regulates expression of APE-1.

(A) Western blot analyses of pAKT, pERK1/2, pCREB, APE1, and actin levels in neuronal cultures treated with 100 nM of EX-4, EX-4 plus MEK inhibitors U0126, or EX-4 plus PI3K inhibitor LY294002. (B) LY294002 specifically inhibited GLP-1-induced AKT phosphorylation. (C) U0126 specifically inhibited GLP-1-induced pERK1/2 phosphorylation. (D) pCREB levels and (E) APE1 were specifically inhibited by LY294002 but not U0126. The results suggested that PI3K-AKT-CREB is the predominant downstream signaling pathway of GLP-1R elevating APE1 expression. ($M \pm SE$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; compared to the value of control group, $n=4$).