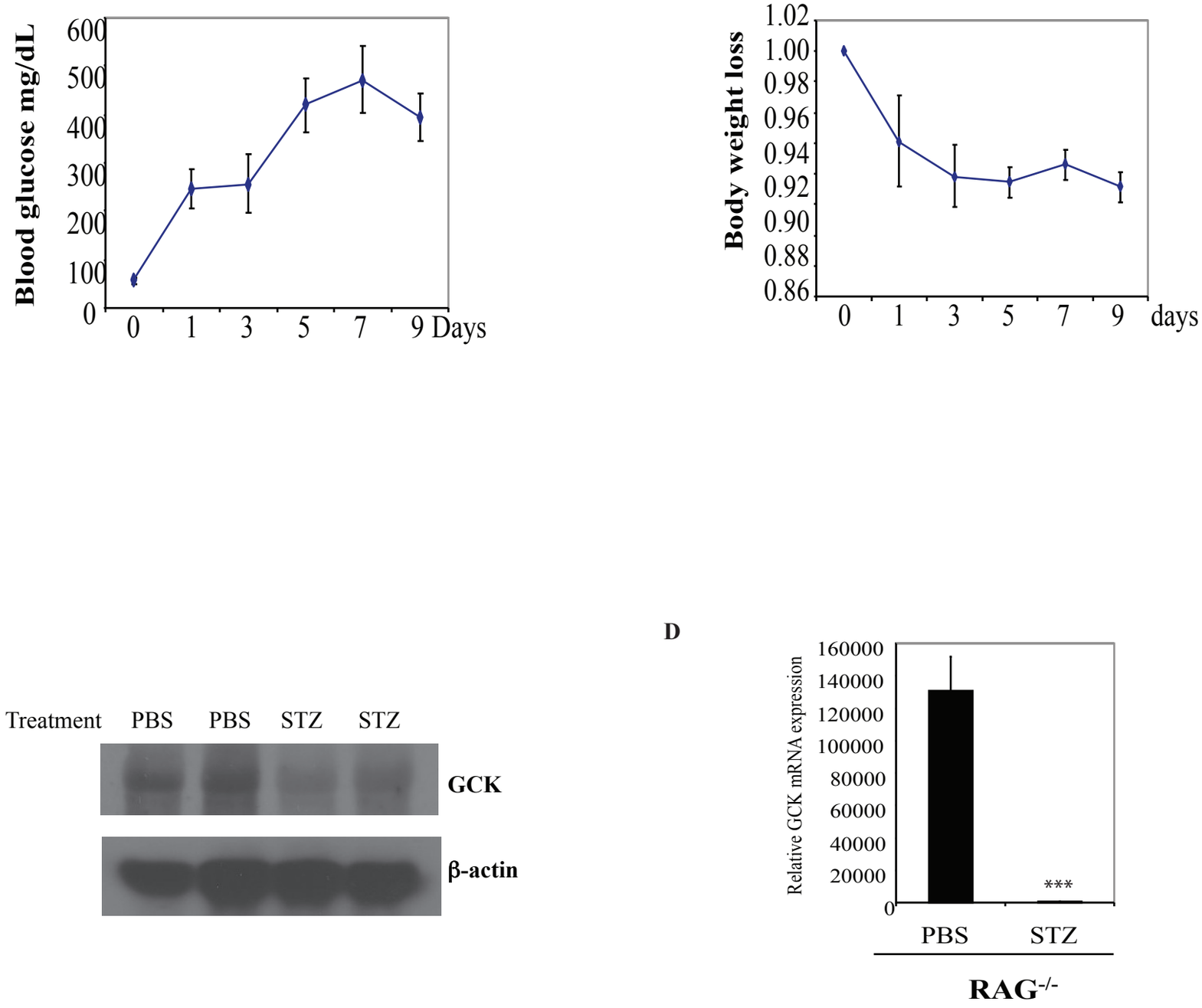Supplymentary Figure 4