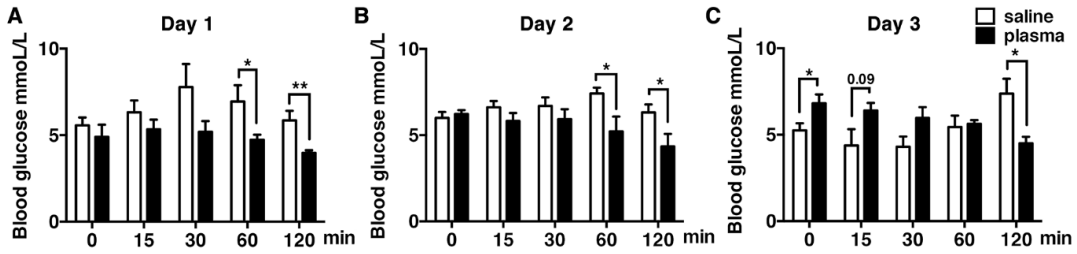
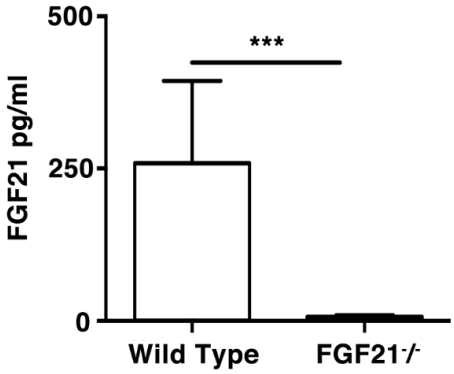


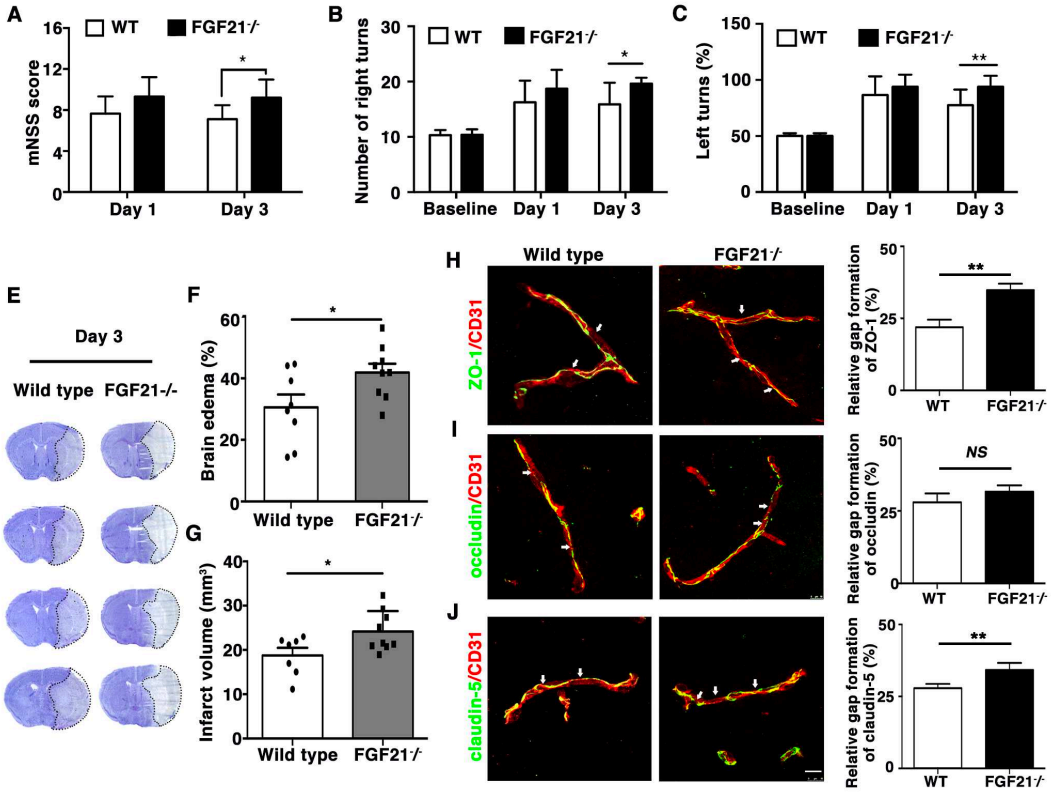
Supplementary Figure 1. The blood glucose changes after plasma or saline injection in tMCAO mice

Bar graph showed the blood glucose level changes at 0, 15, 30, 60, and 120 minutes after tail intervenes injection of saline or plasma to tMCAO mice at 1, 2, and 3 days after occlusion. Data are mean± SD, n=4 per group, *, $p<0.05$, **, $p<0.01$, Wild-Type vs. FGF21/- mice.



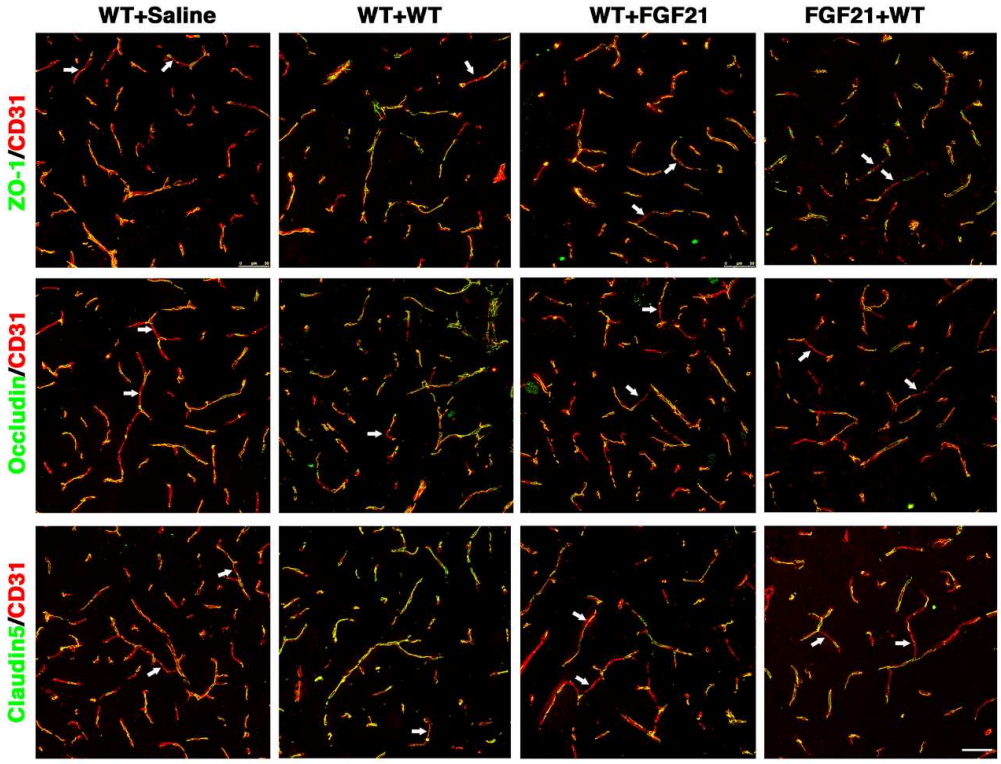
Supplementary Figure 2. Plasma concentration of FGF21 protein in wild-type and FGF21-/- transgenic mice

Bar graphs showed the FGF21 protein concentration in wild type and FGF21/ mice blood plasma. Data are mean± SD, n=3 per group. ***, $p<0.001$, FGF21/ mice vs. Wild-type mice.



Supplementary Figure 3. The neurobehavioral and ischemic injury outcomes in wild-type and FGF21/ transgenic mice at 3 days after tMCAO

Bar graphs showed that the results of modified neurological severity score **(A)**, EBST **(B),** and corner test **(C)** in wild type and FGF21/ mice at 1and 3days after tMCAO. Representative images of cresyl violet-stained brain sections of wild type and FGF21/ mice at 3 days **(D)** after tMCAO. Bar graph showed quantification of brain edema and infarct volume in wild type and FGF21/ mice at 3 days **(E-F)** after tMCAO. Data are mean± SD, n=7-9 per group. *, $p<0.05$, **, $p<0.01$, Wild-Type vs. FGF21/ mice. Photomicrographs showed that the endothelial cell marker CD31 (red) with BBB tight junction proteins (green), ZO-1**(G)**, occludin **(H)**, and claudin-5 **(I)** in the peri-infarct area of the striatum in wild-type and FGF21/ mice. Arrows indicate that the gaps in BBB tight junctions. Scale bar=10 μm. Bar graphs showed that quantification of BBB tight junction proteins ZO-1, occludin, and claudin-5 in wild type and FGF21/ mice at 3 days of tMCAO. Data are mean± SD, n=3 per group. *, $p<0.05$, **, $p<0.01$, Wild-Type vs. FGF21/ mice.



Supplementary Figure 4. Depletion of FGF21 in plasma diminished the beneficial effects of plasma-induced BBB protection after 3 days after tMCAO Co-immunostaining of endothelial cell marker CD31(red) with BBB (green) Zo-1**(A)**, occludin **(C)**, and claudin-5 **(E)** in the peri-infarct area of the striatum in wild type mice that treated with saline (WT+ saline), wild type mice that treated with wild mouse plasma (WT+WT), wild type mice that treated with plasma from FGF21$^{-/-}$ mice (WT+ FGF21$^{-/-}$ plasma), and FGF21$^{-/-}$ KO mice that treated with wild type plasma (FGF21$^{-/-}$+ WT plasma) at 3 days of tMCAO. Arrows indicate the gaps in BBB tight junction proteins, scale bar=50 μm.