Supplementary figure legends

Supplementary Fig. 1. Effect of low dose insulin on cerebral insulin receptor signaling pathway. Mice were injected with insulin at 2 U/kg. The protein levels of p-Akt (Thr308), Akt, p-p70S6K (Thr389), and P70S6K were analyzed by Western blotting in the whole brain lysates 20 min after insulin injection. **(A)** Representative Western blots of p-Akt (Thr308), Akt, p-p70S6K (Thr389), and P70S6K. (**B)** Quantification of the p-Akt (Thr308). **(C)** Quantification of the p-p70S6K (Thr389). Values were normalized to β-actin and were shown by the relative density (p-Akt/Akt and p-p70S6K/p70S6K). Values are means ± SD, n = 4. $^{*}p< 0.05$ vs. control animals.

Supplementary Fig. 2. Effect of low dose insulin on HIF-1α expression, BBB permeability, and brain infarction in diabetic mice. Diabetic mice were treated with a low dose of insulin (2 U/kg) at the onset of reperfusion. The protein levels of HIF-1α were analyzed by Western blotting in cerebral microvessels lysates from contralateral and ipsilateral hemispheres of mice. **(A)** Representative Western blots of HIF-1α. (**B)** Quantification of the HIF-1α protein level in contralateral hemispheres (white bars) and ipsilateral hemispheres (dark bars) (n=5 (diabetic), 3 (low dose insulin)). Values were normalized to β-actin and contralateral hemispheres of diabetic animals. $^{*}p< 0.05$ vs. contralateral brains of diabetic animals. **(C)** Quantification of EB leakage in contralateral and ipsilateral hemispheres (n=5 (diabetic), 3 (low dose insulin)). White bars, contralateral hemisphere; dark bars, ipsilateral hemisphere. (**D)** Quantification of infarct volume estimated by TTC stained sections (n=8 (diabetic), 3 (low dose insulin)). Values are means ± SD.

Supplementary Fig. 3. Effect of glucose administration at reperfusion on HIF-1α expression and BBB permeability. Mice were rendered hyperglycemia by receiving an initial 25% glucose injection (5 ml/kg, i.p.) at the onset of reperfusion. A booster dose of glucose (2 ml/kg, i.p.) was injected every 90 min after the first injection. At 6 h post-ischemia, the protein levels of HIF-1α were analyzed by Western blotting in cerebral microvessel lysates. **(A)** Representative Western blots of HIF-1α. HG: high glucose treated mice. (**B)** Quantification of the HIF-1α protein level in contralateral hemispheres (white bars) and ipsilateral hemispheres (dark bars) (n=3). Values were normalized to β-actin and contralateral hemispheres of control animals. $^{*}p< 0.05$ vs. contralateral brains of control animals. $^{\#}p< 0.05$ vs. ipsilateral brains of control animals. **(C)** Quantification of EB leakage in contralateral and

ipsilateral hemispheres at 6 h of reperfusion (n=3). White bars, contralateral hemisphere; dark bars, ipsilateral hemisphere. $^{*}p< 0.05$ vs. control animals. Values are means ± SD.

Supplementary Fig. 4. Effect of high glucose on intracellular succinate level in hCMEC/D3 cells (a human cerebral microvascular endothelial cell line). Cells were incubated in normal glucose medium (5.5 mM) or high glucose medium (25 mM) for 3 days. **(A)** ^{1}H NMR spectra of cell lysates. The arrow indicates the succinate peak. **(B)** Quantification of succinate concentration. Values were normalized to cell protein concentration. Values are means ± SD, n = 3. $^{*}p< 0.05$ vs. control.