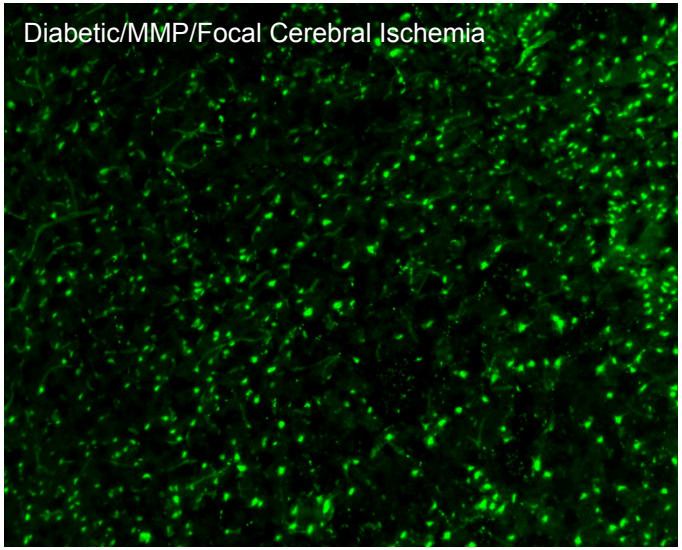
SUPPLEMENTARY METHODS:

**Streptozotocin rat model of diabetes.**

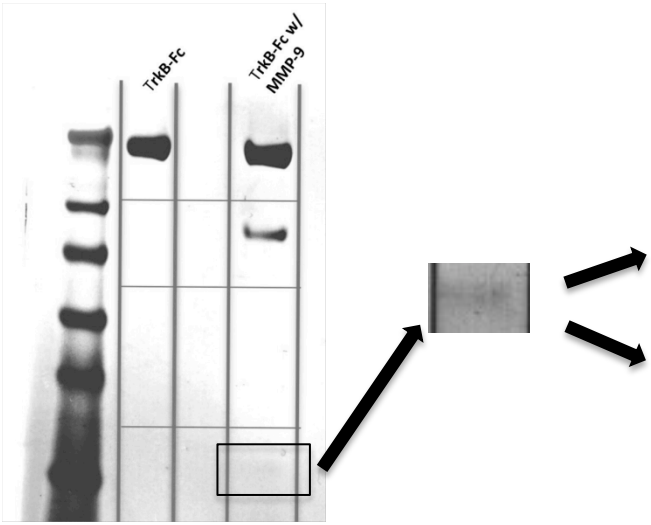
Diabetes was induced with streptozotocin (STZ) (57.5 mg/kg body wt) dissolved in citrate buffer, pH 4.5, through a tail-vein injection. Induction of diabetes was verified after 3 days, and rats with blood glucose concentrations greater than 250 mg/dL were included in these studies. Blood glucose was monitored once a week, rats that did not have elevated blood glucose levels (greater than 250 mg/dL) were not included in the study.

Body weight was measured three times per week, and 3–4 units of neutral protamine Hagedorn insulin (0.5 IU) was administered subcutaneously to only rats that lost more than 10g bodyweight in a week. In this study, only one rat received a single dose of insulin to prevent rapid weight loss and prevent severe ketoacidosis. We also confirmed through histologic assessments that no overt liver damage was present in our model at 48 hours after streptozotocin injection **(Supplementary Fig. S9)**. The diabetic rats were euthanized and brains were collected after perfusion along with age-matched controls. Cerebral cortex was dissected from whole brains for microvessel-enriched fractions and was stored at -80$^0$C prior to fraction preparation. At the time of death, blood was obtained by cardiac puncture for estimation of GHb (Glyco-Tek Affinity Kit, Helena Laboratories, Beaumont, TX). Values of blood glucose and glycated hemoglobin matched expected levels from the literature **(Supplementary Fig. S8)**. All experiments were performed following an institutionally approved protocol in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

S1



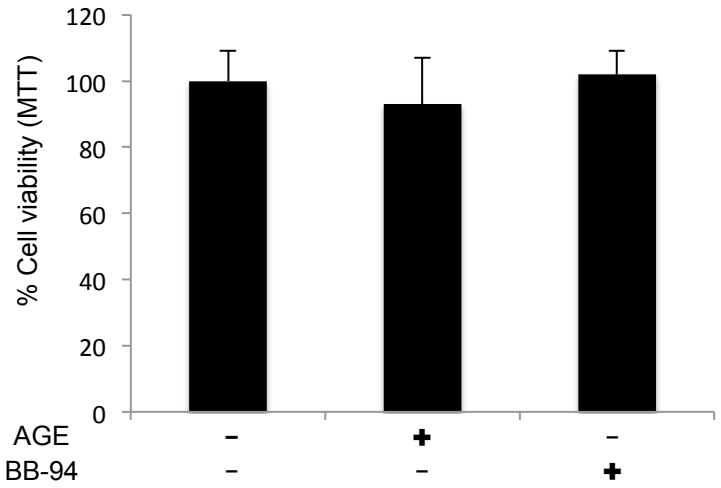
S2




| | |
|---|---|
| TrkB Sequence (111-120) | FLK-**NSNLQHI NFTRNK**- LTSL |
| Fragment Alignment | **NSNLQHINFTRNK** |

| Proten ID name | Confidence % | Sequence | Prec MW | Theoretical MW |
|---|---|---|---|---|
| BDNF Receptor | 99 | NSNLQHI NFTRNK | 1585.754 | 1585.796 |

S3



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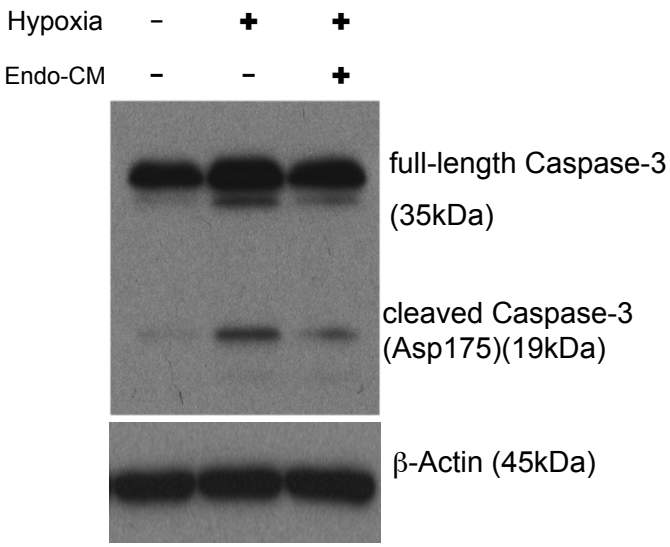
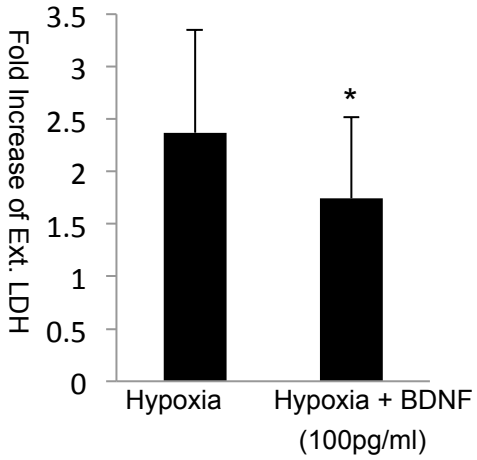
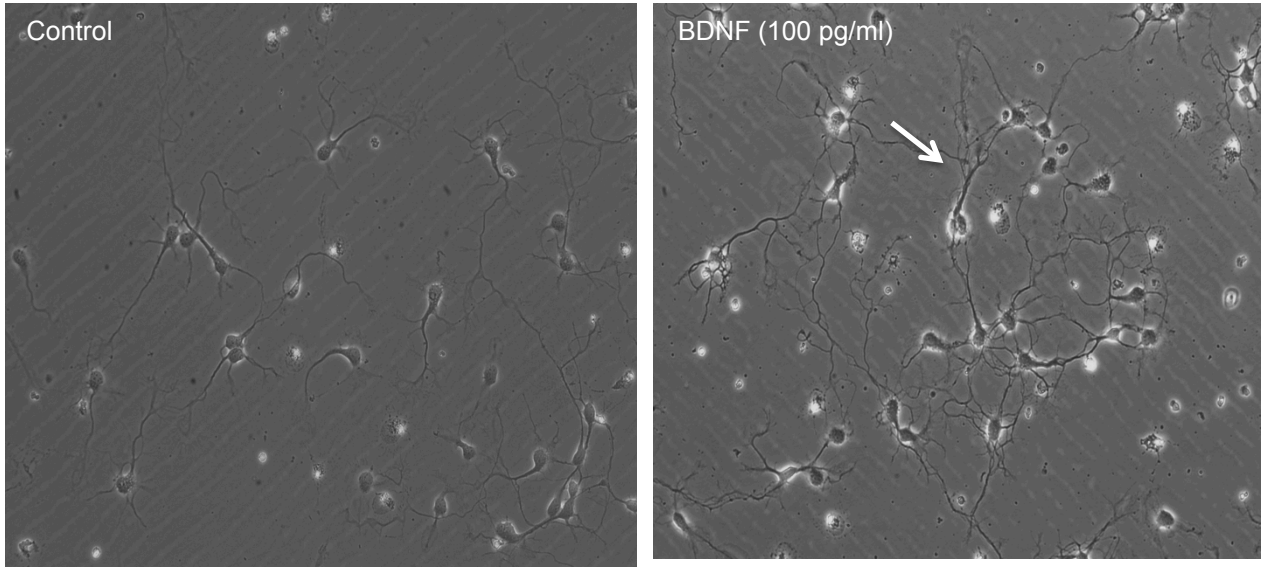

Hypoxia
-
+
+
Endo-CM
-
-
+
full-length Caspase-3
(35kDa)
cleaved Caspase-3
(Asp175)(19kDa)
β-Actin (45kDa)

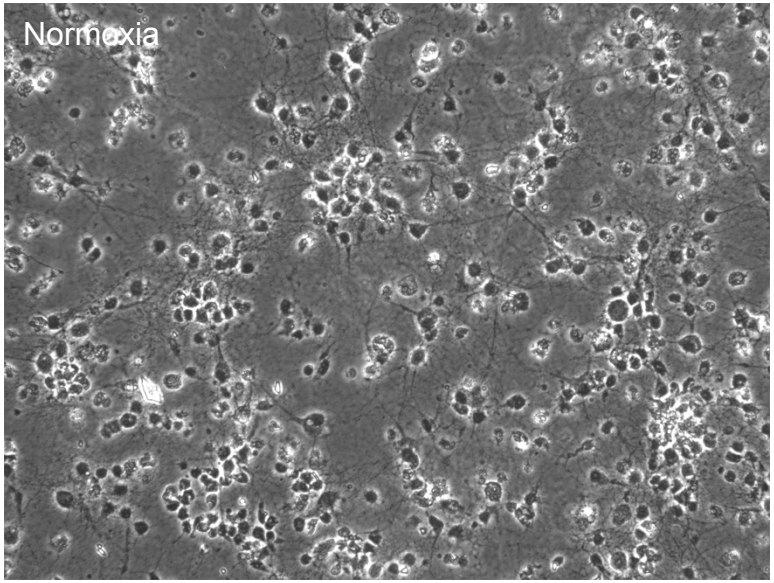
S5

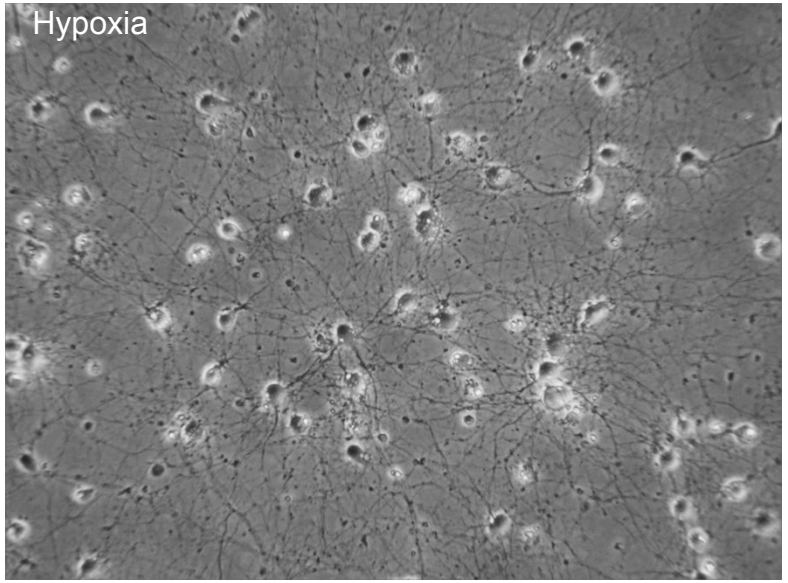

Fold Increase of Ext. LDH
3.5
3
2.5
2
1.5
1
0.5
0
*
Hypoxia
Hypoxia + BDNF
(100pg/ml)

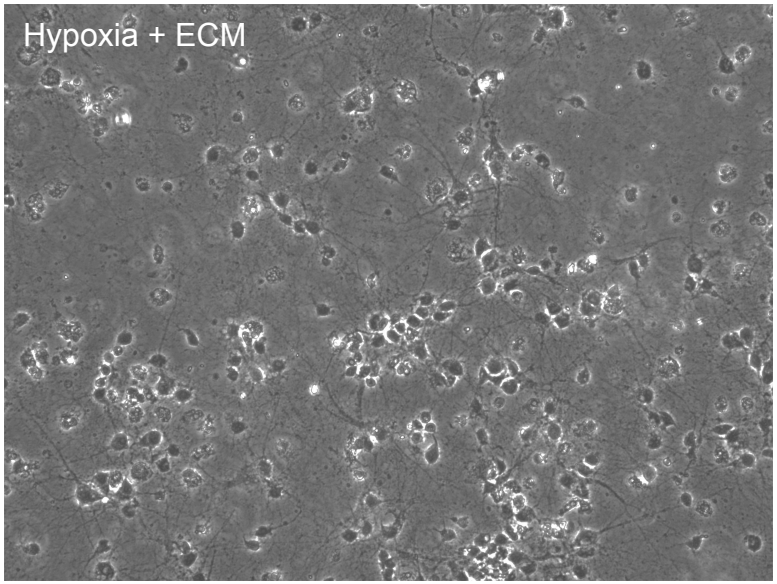
S6

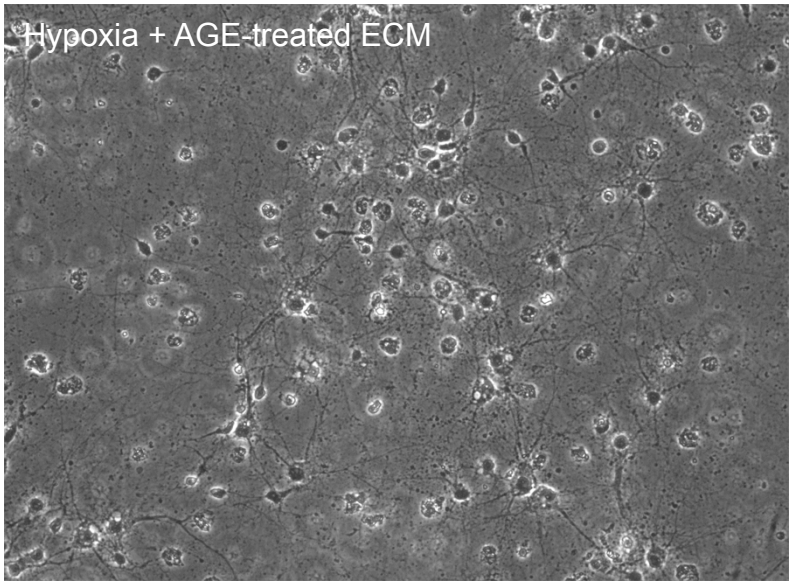


S7



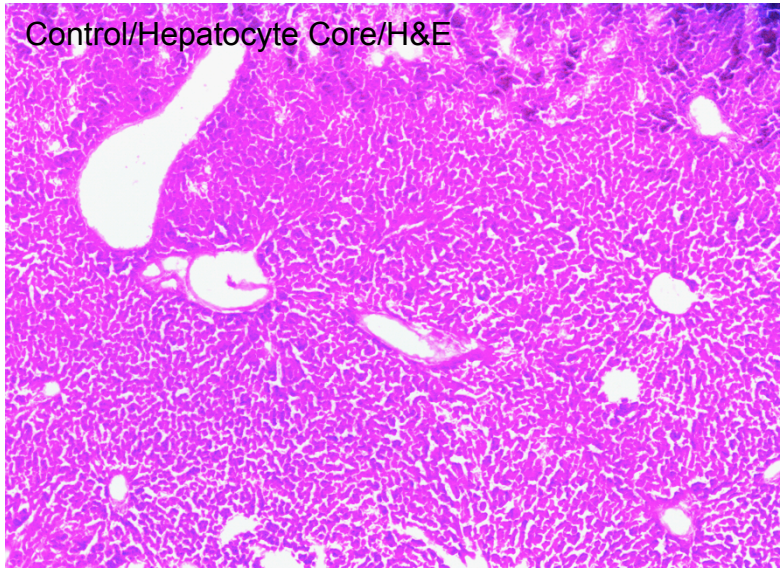



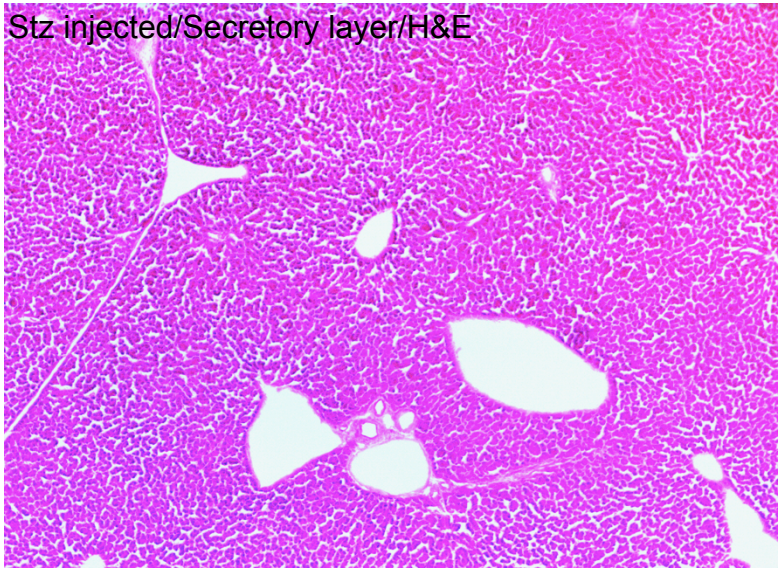



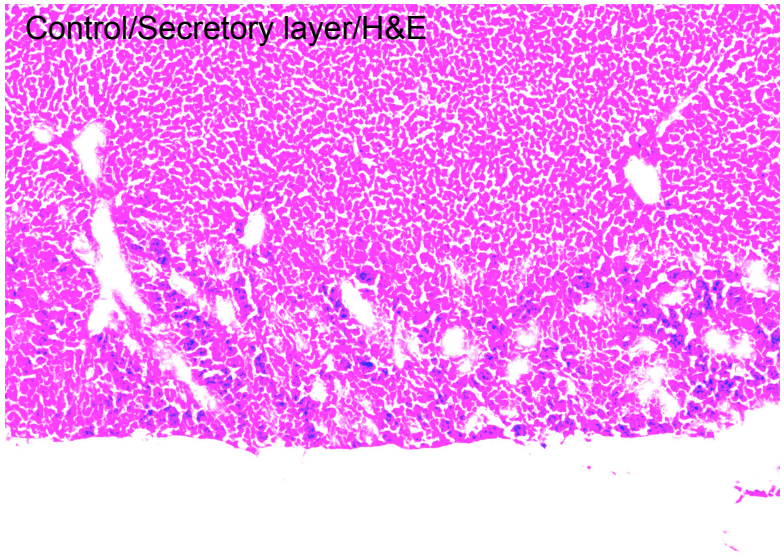



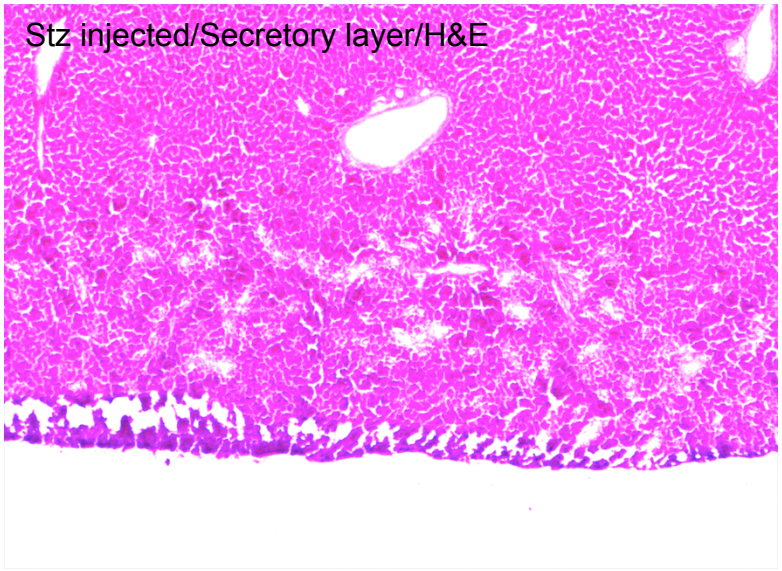
| Type | N | Blood glucose average (mg/DL) | Glyated Hemoglobin (HbA1c) |
|---|---|---|---|
| Age-matched rat | 5 | 115 | 4.2 +/- 0.2 |
| 6-week Diabetic rat | 5 | 375 | 10.3 +/- 0.8 |

S9


Control/Hepatocyte Core/H&E


Stz injected/Secretory layer/H&E


Control/Secretory layer/H&E


Stz injected/Secretory layer/H&E

**SUPPLEMENTARY DATA**

**S1.** *In situ* zymogram showing very large elevations in MMP activity after focal cerebral ischemia in rats. In comparison, MMP signals are much lower in diabetic rat brains and was predominantly localized in cerebrovasculature. Furthermore, MMP signals after cerebral ischemia are detected in endothelium as well as neurons.

**S2.** Mass spectrometry shows that the MMP-9-cleaved 25 kDa fragment contains TrkB sequences.

**S3.** MTT viability assays show that AGE-BSA and BB-94 had no direct effects on neuronal survival.

**S4.** Western blots show that endothelial-conditioned media suppresses caspase-3 in primary neurons after hypoxic injury.

**S5.** MTT assays show that 100 pg/mL BDNF modestly protected primary neurons against 24 hours hypoxia.

**S6.** Incubation of primary neurons with 100 pg/mL BDNF over 24 hours increased neurite formation.

**S7.** Photomicrographs show improved neuronal viability of conditioned media from normal endothelial cells, and loss of protection with conditioned media from AGE-stressed endothelial cells.

**S8.** Blood glucose and glycated hemoglobin levels in 6-week diabetic rats.

**S9.** Representative hematoxylin-eosin stained histology of liver sections from normal and streptozotocin-treated rats. No overt damage was observed.