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Ischemic Regulation of BDNF-Mediated Cell Volume Regulation and TrkB Expression in Retinal Glial (Müller) and Bipolar Cells of the Rat Retina

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Purpose

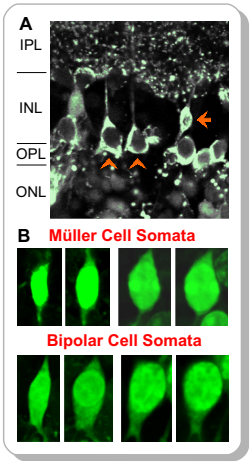
Water accumulations in neurons and glial cells, possibly resulting in osmotic cell swelling, contribute to retinal edema and neurodegeneration. Brain-derived neurotrophic factor (BDNF), a major neuroprotectant in the retina, was shown to inhibit the osmotic swelling of glial (Müller) and bipolar cells in the rat retina; the effect of BDNF on bipolar cell swelling is mediated by inducing a release of neuroprotective cytokines such as bFGF and TGF-ß1 from Müller cells (Berk et al., 2015, Neuroscience, 295:175-186). The aim of the present study was to determine whether the BDNF-mediated cell volume regulation is altered after transient retinal ischemia.

Methods

Retinal ischemia was induced in one eye of adult Long-Evans rats by increasing the intraocular pressure for 60 min; the animals were killed after 3 d. Swelling of Müller and bipolar cell somata was induced by superfusion of freshly isolated retinal slices with a hypoosmotic solution (60% osmolarity) containing barium chloride (1 mM) for 4 min. Freshly isolated Müller and bipolar cells were immunostained for the truncated and full-length isoforms of TrkB.

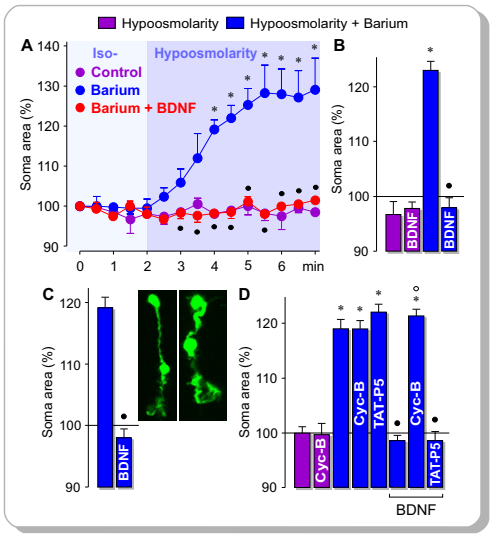
Results

Osmotic Swelling of Müller and Bipolar Cell Somata in Retinal Slices



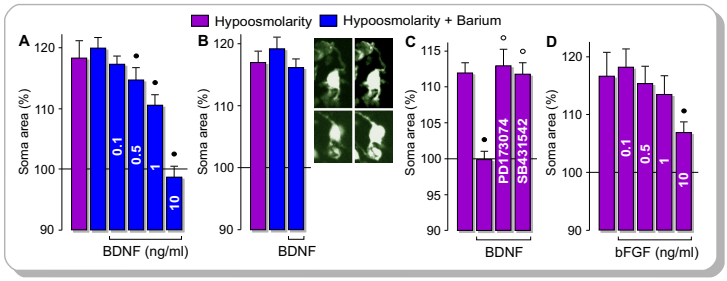
A. Example of a freshly isolated retinal slice loaded with Mitotracker Orange. *Arrow*, Müller cell soma. *Arrowheads*, bipolar cell somata. **B.** Records of cell somata obtained before (*left*) and during (*right*) superfusion of the slices with a barium-containing hypoosmotic solution.

BDNF Inhibits Osmotic Müller Cell Swelling via TrkB Signaling



A. Time-dependent alterations of the cross-sectional area of Müller cell somata during the change from the isoosmotic to the hypoosmotic extracellular solution. BDNF was applied at 1 ng/ml. **B.** Effect of BDNF (1 ng/ml) on the size of Müller cell somata in retinal slices. **C.** Effect of BDNF (1 ng/ml) on the soma size of isolated Müller cells. **D.** The swelling-inhibitory effect of BDNF (1 ng/ml) is prevented by the TrkB inhibitor cyclotraxin-B (Cyc-B; 1 µM) but not by the p75(NTR) inhibitor TAT-conjugated Pep5 (TAT-P5; 1 µM).

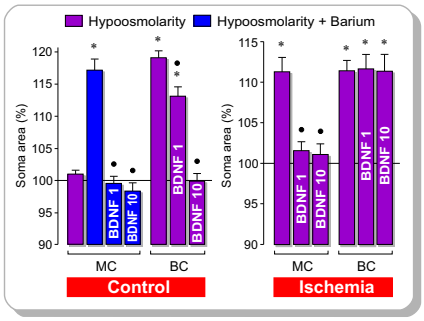
BDNF Inhibits Bipolar Cell Swelling in Retinal Slices, but not the Swelling of Isolated Bipolar Cells, via FGF and TGF-ß1 Receptor Signaling



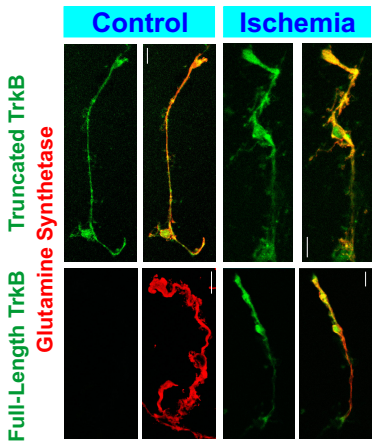
A. Dose-dependent inhibition of the osmotic bipolar cell swelling in retinal slices by BDNF. **B.** BDNF (10 ng/ml) does not inhibit the osmotic soma swelling of isolated bipolar cells. **C.** The effect of BDNF (10 ng/ml) in retinal slices is prevented by the FGF receptor kinase inhibitor PD173074 (500 nM) and the inhibitor of TGF-ß1 receptors, SB431542 (10 µM), respectively. **D.** bFGF inhibits dose-dependently the osmotic swelling of bipolar cells.

BDNF Inhibits Bipolar Cell Swelling in the Control Retina, but not in the Ischemic Retina

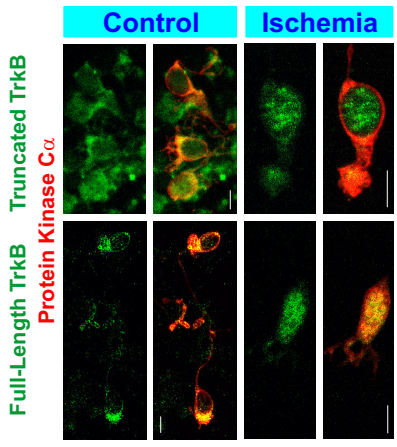
Effects of BDNF on the osmotic swelling of Müller (MC) and bipolar cells (BC) in slices of control and 3-days postischemic retinas. BDNF was applied at 1 and 10 ng/ml, respectively.



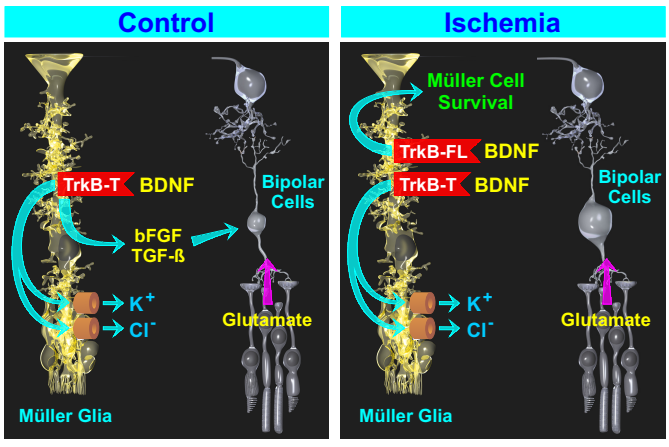
Expression of Truncated and Full-length TrkB in Müller Cells



Expression of Truncated and Full-length TrkB in Bipolar Cells



Conclusions



- The ischemic abrogation of the swelling-inhibitory effect of BDNF in bipolar cells may be related to the altered TrkB expression in Müller cells.
- The ischemic upregulation of the full-length TrkB may have two consequences: full-length TrkB signaling may increase Müller cell survival, but may inhibit the release of neuroprotective cytokines from the cells.

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Potenzielle Interessenkonflikte:
1. Nein 2. PW 3. PW (Bayer, Novartis) 4. Nein 5. Nein