Conclusions: Retinal edn2 and ednrA are necessary for stress-induced neuroprotection using the light damage model. Retinal edn2 knockout mice have defective upregulation of GFAP in Müller cells. It may be that edn2 is involved in regulating the Müller glial response to stress. As such, future questions are centered on whether other Müller cell functions are regulated by edn2.
Commercial Relationships: Marcus Hooper, None; **John Ash**, None
Support: NIH R01EY016459-10

Program Number: 4391 **Poster Board Number:** A0262
Presentation Time: 8:30 AM–10:15 AM
Mesencephalic astrocyte-derived neurotrophic factor (MANF) up-regulates CHOP and ATF6 in the rat retina
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Purpose: We have shown previously that recombinant human MANF protects photoreceptors in a retinal degeneration rat model carrying the S334ter rhodopsin mutation. In the present work, we examined the effects of MANF on the expression of 5 ER-stress markers, including BiP, IRE1α, PERK, ATF6, and CHOP, in rat retina.
Methods: Recombinant human MANF was expressed in E. coli and purified. MANF (10 μg in 3 μl) was intravitreally injected to the left eyes, and the right eyes were injected with 3 μl PBS (phosphate buffered saline) as controls. The levels of ER stress markers BiP, IRE1α, PERK, ATF6, and CHOP, were assessed by Western blot analysis.
Results: We first examined the expression levels of BiP, IRE1α, PERK, ATF6, and CHOP in the retinas of the S334ter (line 3) rats during rapid photoreceptor degeneration from postnatal day (PD) 6 to PD 20. Among the 6 markers, only the level of PERK showed a decrease from PD 6 to PD12. Surprisingly, MANF treatment induced a dramatic increase in ATF6 by 6 hr post injection (injected at PD9). The increase in ATF6 then rapidly declined to control level by 12 hr post injection. In addition, a significant increase in CHOP was detected at 6 hr, peaked at 12 hr, and lasted to 48 hr post injection. No significant changes were seen in the other 4 proteins. Similar increases in ATF6 and CHOP were observed in wild-type Sprague Dawley rats after MANF injection.
Conclusions: No significant changes in ER stress marker were found during the rapid photoreceptor degeneration in the S334ter-3 rats, suggesting that ER stress does not play a major role in photoreceptor degenerations in this model. Intravitreal injection of MANF significantly induces the levels of ATF6 and CHOP.
Commercial Relationships: Zhenya Gao, None; **Yanming Huang**, None; **Yuan Kang**, None; **Yiwen Li**, None; **Rong Wen**, None
Support: Supported by NIH grants R01EY023666, P30-EY014801, Adrienne Arsht Hope for Vision fund, an unrestricted grant from Research to Prevent Blindness, Inc. and National Natural Science Foundation of China (81170872)

Program Number: 4392 **Poster Board Number:** A0263
Presentation Time: 8:30 AM–10:15 AM
Visual decline in aged mice is delayed by proinsulin
Enrique J. De La Rosa[1], Alberto M. Hernandez-Pinto[1], Javier Vicente-Tejedor[2], Laura Ramírez[2], Eduard Ayuso[3], Patricia Boya[1], Catalina Hernandez- Sanchez[1], Fátima Bosch[3], Pedro de la Villa[2]. [1]CIB-CSIC, Madrid, Spain; [2]Universidad de Alcalá, Alcalá de Henares, Spain; [3]CBATEG-UAB, Bellaterra, Spain.
Purpose: Visual decline is normally associated to the aging process. We search for cellular and molecular processes associated to normal aging. In addition, we have previously shown that human proinsulin (hPi) delays vision loss, as determined by electroretinography (ERG), and retinal degeneration, as determined by photoreceptor counting, in the *rd10* mouse and the *P23H* rat models of Retinitis Pigmentosa. Our aim is to reveal additional potential benefits of a hPi-based treatment in the aged retina.
Methods: Wild type mice (C57BL/6) were studied at 3- to 22-months of age. Retinal structure was determined in cryo-sections. Pro-inflammatory gene expression was characterized by RT-qPCR. Insulin resistance was established in organotypic retinal cultures, measuring AKT phosphorylation by western blot. In addition, mice were treated by intramuscular injection of adeno-associated viral vector, either empty (AAV-Ø) or encoding hPi (AAV-hPi) at six month of age. Visual function was evaluated by ERG in 9- to 18-month old animals.
Results: In comparison with young adult animals, visual function decline was evident at 12 months of age, with a 30-40% reduction in the amplitude of several ERG waves. In parallel, TNF-α gene expression increased 2-4 fold, and cultured retinas did not longer show AKT phosphorylation in response to insulin. AAV-mediated expression of hPi delayed 3 to 6 month the onset of visual decline at mid-age.
Conclusions: Retinal aging involves processes found in normal and precocious brain aging, namely low level of chronic inflammation, insulin resistance and functional decline. Neuroprotection with hPi provides a potential treatment to maintain visual quality under different physiopathological conditions, including aging.
Commercial Relationships: Enrique J. De La Rosa, ProRetina Therapeutics (P), ProRetina Therapeutics (I); **Alberto M. Hernandez-Pinto**, None; **Javier Vicente-Tejedor**, None; **Laura Ramírez**, None; **Eduard Ayuso**, ProRetina Therapeutics (I); **Patricia Boya**, ProRetina Therapeutics (P), ProRetina Therapeutics (I); **Catalina Hernandez- Sanchez**, ProRetina Therapeutics (I); **Fátima Bosch**, ProRetina Therapeutics (P), ProRetina Therapeutics (I); **Pedro de la Villa**, ProRetina Therapeutics (P), ProRetina Therapeutics (I)
Support: CONSOLIDER CSD2010-00045 Spain

Program Number: 4393 **Poster Board Number:** A0264
Presentation Time: 8:30 AM–10:15 AM
***In vivo* protection of degenerating cones in the *cpfl1* mouse by HDAC inhibition**
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Purpose: Recent evidence indicates that photoreceptor cell death in inherited retinal degeneration is governed by non-apoptotic mechanisms (Arango-Gonzalez et al., Plos One., 9(11):e112142, 2014). These mechanisms involve an over-activation of histone deacetylase (HDAC) and are also driving primary cone death in the cone-photoreceptor-function-loss (*cpfl1*) mouse. In the present study, we investigated whether HDAC inhibition could prevent *cpfl1* cone loss *in vivo*.
Methods: *Cpfl1* and wt animals (n=11 and n=6, respectively) were injected intravitreally, in one eye, at the onset of cone degeneration (PN14) with 1nM or 10nM Trichostatin A (TSA), an inhibitor of