Neurotox Res (2014) 26:440–446
DOI 10.1007/s12640-014-9488-6

ORIGINAL ARTICLE

Effect of the Aβ Aggregation Modulator MRZ-99030 on Retinal Damage in an Animal Model of Glaucoma

T. E. Salt · S. Nizari · M. F. Cordeiro · H. Russ · W. Danysz

Received: 21 May 2014 / Revised: 16 July 2014 / Accepted: 28 July 2014 / Published online: 9 August 2014

Abstract Several lines of evidence suggest that there are similarities in the pathomechanisms of glaucoma and Alzheimer's disease, and that amyloid-beta (Aβ) could be a new, promising target for neuroprotective therapy of glaucoma. In the present study, we evaluated the effect of the Aβ aggregation modulator MRZ-99030 in the Morrison model of glaucoma based on increased intraocular pressure (IOP) in rats. MRZ-99030 provided dose-dependent neuroprotection and at the highest dose (240 mg/kg) reduced the degree of RGC apoptosis to 33 % of that seen after vehicle ($P < 0.05$; one-way ANOVA). No significant effect on IOP was observed. Pharmacokinetic experiments showed that following systemic injection of MRZ-99030, concentrations above affinity for Aβ were reached. Hence the present results are consistent with the notion that Aβ is a promising target for neuroprotective intervention in glaucoma and that MRZ-99030 may be a good drug candidate for further development.

Keywords Amyloid-β · Aggregation modulator · Glaucoma · Retinal ganglion cell · Neuroprotection · MRZ-99030

T. E. Salt · S. Nizari · M. F. Cordeiro
Visual Neuroscience, UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK

H. Russ · W. Danysz (✉)
Merz Pharmaceuticals GmbH, Alfred Wegener Strasse 2, 60438 Frankfurt/Main, Germany
e-mail: wojciech.danysz@merz.de

Introduction

Glaucoma is one of the major causes of irreversible blindness in the world amounting to c.a. 17 million in the industrialized world (eTrack 2013), and given the ageing populations in both the developed and developing world, the prevalence of glaucoma is increasing. Globally, there are approximately 70 million people suspected of suffering with glaucoma. Unfortunately, therapeutic options are limited mainly to lowering intraocular pressure (IOP). Although elevated IOP seems to be a risk factor for glaucoma, there are examples of glaucoma without elevated IOP and elevated IOP not resulting in glaucoma (Hartwick 2001). Recent evidence indicates progressive visual-field loss in patients despite normalization of IOP with pressure-lowering treatment strategies (Oliver et al. 2002). Nevertheless, the final step leading to irreversible loss of vision in glaucoma is retinal ganglion cell (RGC) death and axonal loss by various mechanisms, including apoptosis (Almasieh et al. 2012; Baltmr et al. 2010; Cordeiro et al. 2010; Weinreb and Kaufman 2009).

In view of these findings, alternative treatment options that target the pathomechanism as close to the aetiology as possible have been explored in recent years (Almasieh et al. 2012; Baltmr et al. 2010; Ritch 2000). Amyloid-β (Aβ) is the major constituent of senile plaques in Alzheimer's disease (AD), the formation of which, caused by abnormal processing of amyloid precursor protein (APP), has been implicated in AD neuropathology (Karran et al. 2011; Mattson et al. 1993). However, more recently Aβ has been suggested to play a role in the development of RGC apoptosis in glaucoma (Bayer and Ferrari 2002; Bayer et al. 2002; Guo et al. 2007; Janciauskiene and Krakau 2001, 2003). The evidence includes caspase-3-mediated abnormal amyloid precursor protein (APP) processing and

increased expression of Aβ in RGCs in experimental glaucoma (Goldblum et al. 2007; Guo et al. 2007; McKinnon 2003; McKinnon et al. 2002) and decreased vitreous Aβ levels (consistent with retinal Aβ deposition) in patients with glaucoma (Yoneda et al. 2005). Further evidence has emerged from studies showing that patients with AD have RGC loss associated with typical glaucomatous changes, such as optic neuropathy and visual functional impairment (Blanks et al. 1996a, b; Iseri et al. 2006; Parisi et al. 2001). Thus it is noteworthy that glaucoma and AD are both chronic neurodegenerative diseases with a strong age-related incidence (Johnson et al. 2002; Wostyn et al. 2008) with similar pathological mechanisms involving Aβ and leading to neuronal loss in the retina or brain (Johnson et al. 2002; Loffler et al. 1995; Vickers et al. 2000).

Previous experiments using intravitreal application provided first hints that Aß-based approaches might be beneficial to prevent Aß-associated cell death in the retina (Guo et al. 2007). However, the compounds applied so far were not suitable for therapeutic use in patients. The challenge here was to identify a small molecule with a sufficient anti-Aß effect and suitable toxicological and pharmacokinetic properties for human use. The ideal compound should be also bioavailable after topical administration via eye drops. MRZ-99030 discovered by Gazit (2005) might fulfill all these requirements. Therefore, the present study was devoted to evaluate the neuroprotective potential of the new Aβ aggregation modulator MRZ-99030 (Gazit 2005; Rammes et al. 2011), after systemic administration in a glaucoma model based on increased IOP as a first step. The present work shows the first promising in vivo data warranting further development of the compound as a unique topical neuroprotectant for progressing glaucoma patients.

Materials and Methods

Pharmacokinetics (PK) Experiments and Analysis of MRZ-99030 in Plasma and Eyes

Animals

Male Dark Agouti rats (~250 g, Harlan Winkelmann, Germany) used in the PK study were housed in a temperature-controlled room (20–24 °C) and maintained in a 12-h light/12-h dark cycle. Food and water were available ad libitum.

Treatment

MRZ-99030 was administered at 3 doses (35 and 70 mg/kg; s.c.; 2 ml/kg), and vehicle was used to serve as blank sample for analysis ($n = 3$ for each timepoint).

Blood and Tissue Sampling

Plasma samples were collected by heart puncture under isoflurane anaesthesia at 5, 15, 30 min and 1, 2, 4, 8 and 24 h after subcutaneous application. Blood was collected in heparinised tubes stored on ice and subsequently centrifuged at 645×*g* for 10 min at 4 °C. The harvested plasma was kept at −80 °C until assayed. After the last blood sampling, the animals were sacrificed by CO_2 inhalation and eyes were removed. Excessive tissue containing fat and blood vessels was removed. The eyes were then stored at −80 °C until they were assayed.

Analysis (Liquid chromatography–mass spectrometry, LC–MS)

The HPLC system consisted of a MS Plus pump (Surveyor) and an AS Plus auto sampler (Surveyor). MS was performed on a TSQ Quantum Discovery Max triple quadrupole MS equipped with a heated electrospray (H-ESI) interface (Thermo Fisher Scientific, USA) connected to a PC running the standard software Xcalibur 2.0.7. The most intensive product ion(s) was used to quantify the test item in the selected reaction monitoring mode (SRM). The HPLC pump flow rate was set to 300 µl/min, and the compounds were separated on a Gemini C6-Phenyl, 3 µm, 50 × 2.0 mm (Phenomenex, Germany) analytical column with a precolumn (Gemini C6-Phenyl, 3 µm, 4 × 2.0 mm). Gradient elution with 10 mM ammonium acetate/0.1 % formic acid as aqueous phase (A) and acetonitrile/0.1 % formic acid as organic phase (B) was used: % B (t, min), 0(0–0.2)–97(1.2–4.0)–0(4.2–6.0).

Plasma

To 50 µl of rat plasma and calibration standard (rat plasma), 100 µl acetonitrile containing the internal standard (Griseofulvin, 150 ng/ml) was added. Samples were vigorously shaken and centrifuged for 10 min at 6,000×*g* and room temperature. The supernatant was diluted 1:1 with water, and a portion of the mixture was transferred to 200-µl sampler vials and subsequently subjected to LC–MS/MS. The starting solution of MRZ99030 (1 mg/ml FBE in water) was diluted with acetonitrile/water (1:1) to a final concentration of 200 µg/ml (stock solution). Calibration standards were prepared by spiking 50 µl of blank rat plasma with 6 µl working solution.

Eyes

Both eyes of each rat were weighed, and 100 µl PBS buffer was added and homogenized in a 1.5-ml Eppendorf cup using a polypropylene homogenizer. Afterwards, 500 µl of

acetonitrile containing the internal standard (Griseofulvin, 240 ng/ml) was added and homogenized. The sample was vortexed vigorously for 30 s, then sonicated for 30 s and finally shaken for 10 min. The debris was spun down using a centrifugation step at 6,000×*g* for 10 min at room temperature. An aliquot (100 µl) of the supernatant was diluted with two volumes (200 µl) of water and transferred to a 200-µl sampler vial and subsequently subjected to LC–MS/MS.

Two thousand-milligram blank eye material was homogenized using a plastic potter and supplemented with 1,000 µl of PBS buffer. The starting solution of MRZ99030 (1 mg/ml FBE in water) was diluted in acetonitrile/water (1:1, v/v) to final concentrations of 300 µg/ml (stock solution). The working solutions for spiking the homogenized tissue were prepared by dilution of the stock solution in acetonitrile/water (1:1, v/v). The lowest calibration quality control level (LLQC) as well as the quality controls QC1, QC2 and QC3 were prepared in quintuplicate.

Neuroprotection in the Morrison Model of Glaucoma

Test Item

MRZ-99030 (base, Merz Pharmaceuticals, Frankfurt, Germany) was dissolved in PBS on the day of the experiment and injected in a total volume of 4 ml/kg i.e. 2 ml/kg s.c. on each side of the rat immediately before glaucoma induction. Control animals were injected with the vehicle. Experiments were carried out with three doses of MRZ-99030 (60, 120 and 240 mg/kg) and one vehicle control group.

Animals

Experiments were carried out in adult Dark Agouti (150–200 g weight) male rats (Harlan, UK). The animals were allowed to acclimatise for at least 7 days before the study was started. There was automatic control of light cycle, temperature and humidity. Light was on at 07:00 (coming on at 25 % and rising through to 75 % by 08:00); lights start to dim at 19:00 and were completely off by 20:00. Temperature and humidity remained within the target ranges of 21 ± 5 °C and 55 ± 10 %, respectively. The animals were housed two per cage in Techniplast polycarbonate cages (60 × 38 × 200 cm, with mesh tops). Cage bases were changed every week and the entire rack, cage and lid every month. Water was offered ad-lib twice a week, and SDS RM1 (rat and mouse maintenance Diet1) was offered ad-lib. The environment is enriched by the use of Lillico Forage mix offered weekly and Maxi fun tunnels.

Surgery

All animals were anaesthetised by intraperitoneal injections of ketamine (37.5 %), Dormitor (25 %; Pfizer Animal Health, Exton, PA) solution (0.75 ml ketamine, 0.5 ml Dormitor, and 0.75 ml sterile water) at 0.1 ml/100 g. Intraocular pressure (IOP) was elevated in the left eye of each animal by injection of 50 µl of hypertonic saline solution (1.80 M) into the episcleral vein using a syringe pump (60 µl/min; UMP2, World Precision Instruments, Sarasota, FL), the contralateral eye acting as a control (Guo et al. 2007; Morrison et al. 1997). Four groups of six animals were prepared which were housed in pairs and followed for 6 weeks.

Intraocular Pressure Measurement

The IOP of both eyes in each rat was measured at regular intervals under inhalational anaesthesia of a mixture of oxygen and isoflurane (Merial; Animal Health Ltd., UK), with a handheld tonometer (Tonopen XL) at the same time of the day on all test days. IOP measurements were taken before surgery and at regular weekly intervals after surgery. After a drop of topical anaesthetic (proxymetacaine 0.5 %, Chauvin Pharmaceuticals Ltd, Essex, UK), 10 IOP readings were taken and averaged.

In vivo Retinal Imaging Using Detection of Apoptosing Retinal Ganglion Cells (DARC)

All animals were imaged in vivo with fluorescent-labelled annexin V with our recently established DARC imaging technique at 3 and 6 weeks after OHT induction (Guo et al. 2007, 2006). For imaging, animals were held in a stereotaxic frame and their pupils dilated. For each eye, a retinal montage was constructed from images captured at the same time point. All animals had baseline images recorded before receiving intravitreal injections of Alexa Fluor 488-labelled annexin V for visualization of annexin V positivity (Guo et al. 2007, 2006).

Ex vivo Retinal Analysis

After the 6-week imaging timepoint, animals were sacrificed for ex vivo histological analysis. The ex vivo analysis following in vivo injection of annexin V has been previously described by ourselves (Guo et al. 2007, 2006). The eyes were enucleated and fixed in 4 % fresh paraformaldehyde overnight. The retinae were dissected and whole retinae were flat-mounted. Fluorescent retinae were assessed with a confocal laser-scanning microscope (CLSM 510 META; Zeiss, Goettingen, Germany) with LSM software. Using 16× magnification, we assessed 81 adjacent microscopic fields (each measuring 0.329 mm^2) radiating outward from

the optic nerve head in the rat and accounting for 40 % of the whole retina. A retinal montage was then made for each whole retina. The number of apoptotic RGCs (labelled with annexin V) was counted manually with image-analysis software (MetaMorph; Universal Imaging Corp., West Chester, PA). Data collection and analysis was carried out with the operator unaware of the experimental group.

Statistical Analysis

All data are expressed as mean ± SEM and were analysed using one-way ANOVA which if significant was followed by post hoc Holm-Sidak test using Sigma Plot software (Systat, Chicago, Illinois, USA).

Results

Plasma and Whole Eye Concentrations of MRZ-99030

In these experiments, two doses of 35 and 70 mg/kg (s.c.) were used. There was a dose-dependent increase of MRZ-99030 concentration in the eye (Fig. 1a and in plasma (Fig. 1b). There was a rapid, time-dependent decrease in MRZ-99030 concentration in both compartments (50 % decrease at c.a. 1 h) but at the 8-h time point, drug levels were still detectable. The affinity of MRZ-99030 to Aβ is ca 30 nM and at 70 mg/kg, plasma levels of ca. 50 nM were obtained. Therefore, for the present efficacy study, the doses of 60, 120 and 240 mg/kg were selected as the middle dose that would be predicted to produce plasma levels close to the above-stated affinity.

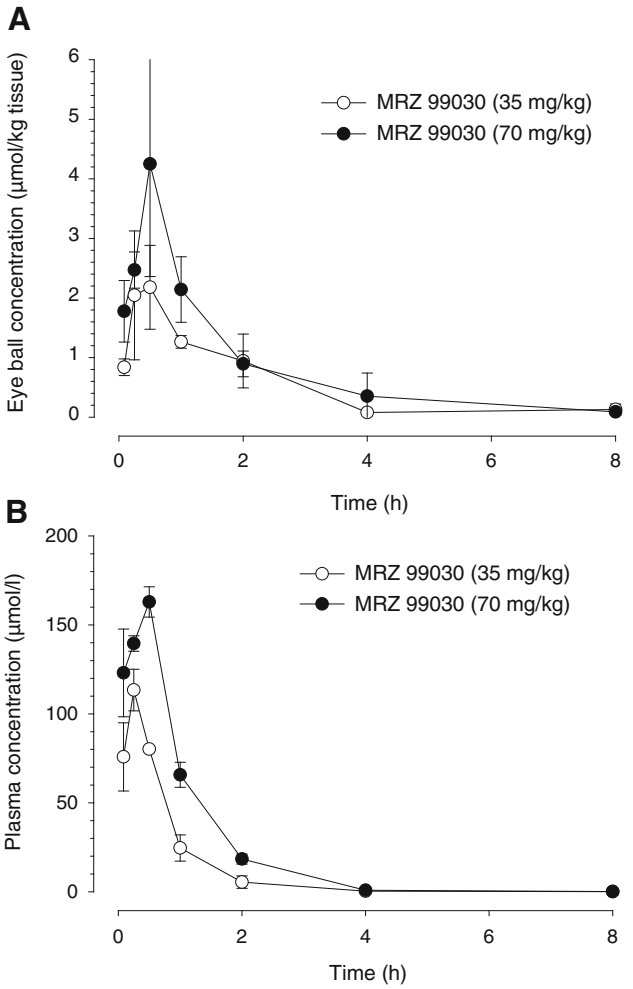

Fig. 1 Concentration of MRZ-99030 in the eye (**a**) and in plasma (**b**) after systemic administration. Results are expressed as mean ± SEM. $N = 3$

General Observations

Systemic injection of MRZ-99030 did not appear to cause any immediate adverse effects. There were cases of animal mortality within all groups at the 3-week time point and the later ones which occurred mainly during or after recovery from the anaesthesia were used for in vivo imaging. This was not related to MRZ-99030 treatment.

Intraocular Pressure Measurement

Induction of OHT produced an elevated intraocular pressure (IOP) comparable to that seen in our previous studies in the same strain of rats. Administration of MRZ 99030 did not produce any effects on IOP (data not shown).

In vivo Retinal Imaging (DARC)

DARC imaging was carried out at 3 and 6 weeks after OHT induction. Overall, in vehicle- and MRZ-99030-treated subjects, it was possible to perform good quality imaging as there was a clear vitreous and cornea in most subjects. In vehicle-treated animals, clear evidence of apoptosis was seen at the early and late time points. Less evidence of apoptosis was seen in MRZ-99030-treated animals, particularly in the case of the 240 mg/kg dose group. This was evidenced by a significant effect at this dose and a strong trend already at 120 mg/kg (Fig. 2).

Ex vivo Retinal Analysis

Ex vivo histological assessment at the 6-week time point revealed apoptosis in vehicle-control subjects which was less evident in animals treated with MRZ-99030 as visualised in histological pictures. When expressed quantitatively, MRZ-99030 dose dependently reduced the degree of RGC apoptosis (Fig. 3) to 33 % at the highest dose (240 mg/kg) of that seen after vehicle. This effect was

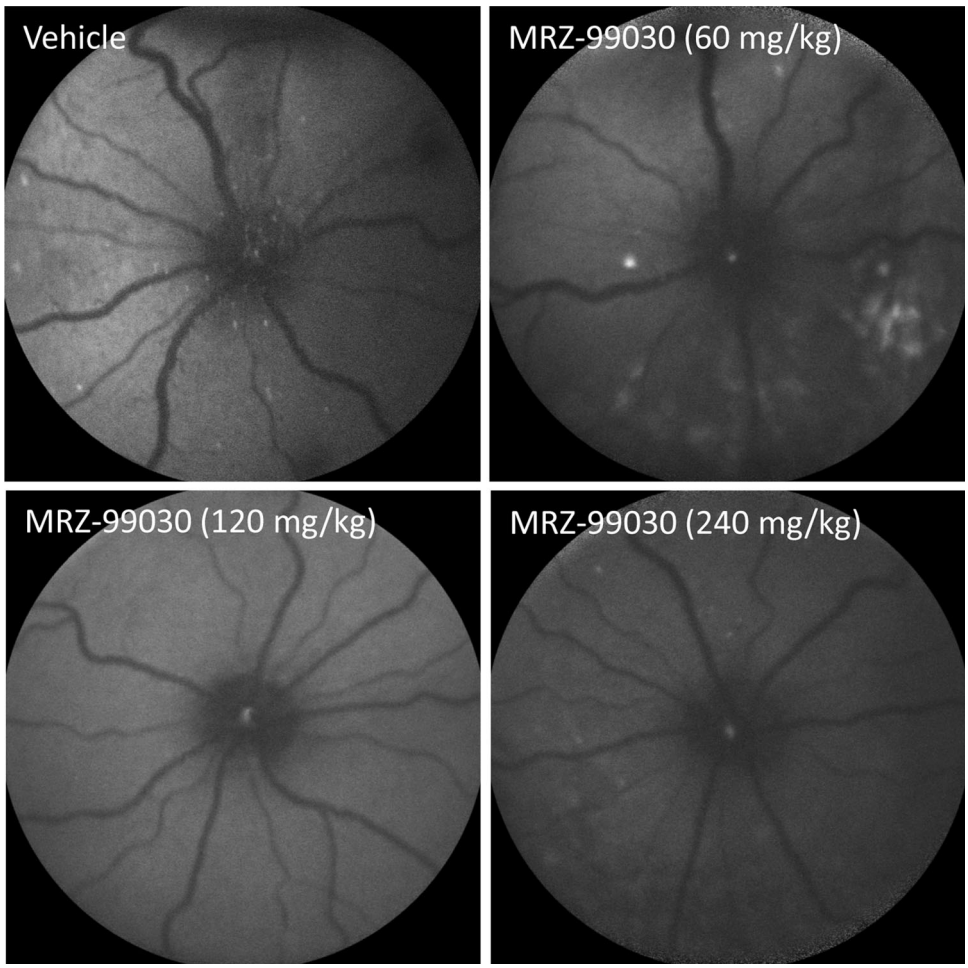

Fig. 2 Effect of vehicle or MRZ-99030 given systemically on RGC apoptosis as assessed in vivo at 6 weeks. *Pictures* show representative results obtained in each experimental group. The out- of-focus fluorescent spots in the 60 mg/kg image are due to corneal damage in the eye

statistically significant as revealed by one-way ANOVA, $F(3,15) = 5.33$ ($P = 0.015$) and post hoc (Holm-Sidak) also showed significant effect of highest dose vs. vehicle ($P < 0.05$).

Discussion

The degree of RGC neuroprotection seen with MRZ-99030 in the current study is similar to that seen in our previous studies with administration of an Aβ antibody (Guo et al. 2007) or combined administration of an N-methyl-D-aspartate (NMDA) receptor antagonist ((+)-MK-801, dizocylpine, (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate) and metabotropic glutamate group II agonist (LY354740, (1S, 2S, 5R, 6S)-2-aminobicyclo[3.1.0] hexane-2,6-dicarboxylic acid) in the OHT glaucoma model in the Dark Agouti rat (Guo et al. 2006). However, it should be stressed that in contrast to the above agents that were given intravitreally, MRZ-99030 was administered systemically. This effect of MRZ-99030 was not related to changes in IOP. Present data indicate that MRZ-99030 has good efficacy as a retinal neuroprotective agent in glaucoma, and this further supports the concept that Aβ plays a role in the development of RGC apoptosis in glaucoma (Bayer and Ferrari 2002; Bayer et al. 2002; Guo et al. 2007; Janciauskiene and Krakau 2001, 2003). From a mechanistic point of view, our finding with MRZ-99030 is of interest as this compound affects Aβ aggregation, and this suggests that treatments which prevent this process would be effective in preventing RGC apoptosis in glaucoma.

The present study showed efficacy when MRZ-99030 was given shortly before the insult initiation. It should be stressed that from a translational point of view, it might appear that treatment post insult with longer intervals would be desirable. However, it should be borne in mind that the dynamics of retinal damage in the Morrison model may be different from the situation in glaucoma patients. In patients, retinal damage develops over several years, presumably due to a mild continuous insult, which is not the case for the Morrison model of glaucoma.

It should be stressed, that the translational value of experimental glaucoma models in relation to

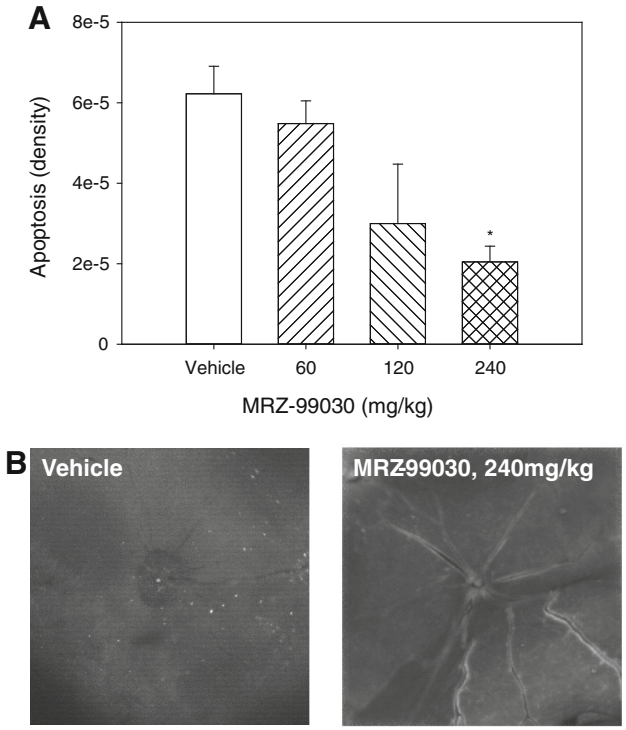

Fig. 3 Effect of MRZ-99030 given systemically on RGC apoptosis as assessed ex vivo. Results (**a**) are expressed as mean ± SEM. $P < 0.05$ versus vehicle as assessed using one-way ANOVA followed by Holm–Sidak test. $N = 5, 2, 4, 5$ for shown groups, respectively. For insight, the representative image picture is provided (**b**) for control and 240 mg/kg group

neuroprotective activity is not clear. For example, in spite of positive results in rodent and primate models of glaucoma (Hare et al., 2004a, b; Woldemussie et al. 2002), the NMDA antagonist memantine (1-amino-3,5-dimethyl-adamantane, HCl), (Parsons et al. 1999) failed to show significant efficacy in a large clinical trial in glaucoma patients; this may be partially due to methodological issues (Osborne 2009). One major difference is the fact that patients recruited in the negative study already had advanced glaucoma and it could be that at this disease stage, no halting or significant delay of progression is possible. One possibility is that with systemic administration, the increased doses needed to achieve a sufficient target effect were not possible due to side-effects, and this is likely to be a particular issue with NMDA antagonists. Taken in this context, it is interesting that the current study shows promising efficacy of the Aβ aggregation inhibitor MRZ-99030 after systemic administration in the Morrison model of glaucoma. This substance is under development for this indication and further studies were designed to address efficacy after topical application, as this is a desired route of administration. Furthermore, topical application has potential advantages over systemic treatment since fewer side-effects may be expected.

In conclusion, the present data support the claims that Aβ is a promising target for neuroprotective therapy in glaucoma and also indicate that MRZ-99030 may be a good drug candidate for further development.

Acknowledgments We wish to thank Prof. Ehud Gazit from Tel Aviv University for first bringing our attention to this dipeptide ((R)-(2-[2-Amino-3-(1H-indol-3-yl)-propionylamino]-2-methyl-propionic acid) that was first synthesized/characterized in his laboratories and for his continuous intellectual support in our preclinical studies.

References

Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A (2012) The molecular basis of retinal ganglion cell death in glaucoma. Prog Retin Eye Res 31:152–181

Baltmr A, Duggan J, Nizari S, Salt TE, Cordeiro MF (2010) Neuroprotection in glaucoma: is there a future role? Exp Eye Res 91:554–566

Bayer AU, Ferrari F (2002) Severe progression of glaucomatous optic neuropathy in patients with Alzheimer's disease. Eye (Lond) 16:209–212

Bayer AU, Ferrari F, Erb C (2002) High occurrence rate of glaucoma among patients with Alzheimer's disease. Eur Neurol 47:165–168

Blanks JC, Schmidt SY, Torigoe Y, Porrello KV, Hinton DR, Blanks RH (1996a) Retinal pathology in Alzheimer's disease. II. Regional neuron loss and glial changes in GCL. Neurobiol Aging 17:385–395

Blanks JC, Torigoe Y, Hinton DR, Blanks RH (1996b) Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiol Aging 17:377–384

Cordeiro MF, Guo L, Coxon KM, Duggan J, Nizari S, Normando EM, Sensi SL, Sillito AM, Fitzke FW, Salt TE, Moss SE (2010) Imaging multiple phases of neurodegeneration: a novel approach to assessing cell death in vivo. Cell Death Dis 1:3

E-Track (2013) http://www.pharmaetrack.com/. Accessed 10 July 2013

Gazit E (2005) Mechanisms of amyloid fibril self-assembly and inhibition. Model short peptides as a key research tool. FEBS J 272:5971–5978

Goldblum D, Kipfer-Kauer A, Sarra GM, Wolf S, Frueh BE (2007) Distribution of amyloid precursor protein and amyloid-beta immunoreactivity in DBA/2J glaucomatous mouse retinas. Invest Ophthalmol Vis Sci 48:5085–5090

Guo L, Salt TE, Maass A, Luong V, Moss SE, Fitzke FW, Cordeiro MF (2006) Assessment of neuroprotective effects of glutamate modulation on glaucoma-related retinal ganglion cell apoptosis in vivo. Invest Ophthalmol Vis Sci 47:626–633

Guo L, Salt TE, Luong V, Wood N, Cheung W, Maass A, Ferrari G, Russo-Marie F, Sillito AM, Cheetham ME, Moss SE, Fitzke FW, Cordeiro MF (2007) Targeting amyloid-beta in glaucoma treatment. Proc Natl Acad Sci USA 104:13444–13449

Hare WA, Woldemussie E, Lai RK, Ton H, Ruiz G, Chun T, Wheeler L (2004a) Efficacy and safety of memantine treatment for reduction of changes associated with experimental glaucoma in monkey, I: functional measures. Invest Ophthalmol Vis Sci 45:2625–2639

Hare WA, Woldemussie E, Weinreb RN, Ton H, Ruiz G, Wijono M, Feldmann B, Zangwill L, Wheeler L (2004b) Efficacy and safety of memantine treatment for reduction of changes associated with experimental glaucoma in monkey, II: structural measures. Invest Ophthalmol Vis Sci 45:2640–2651

Hartwick AT (2001) Beyond intraocular pressure: neuroprotective strategies for future glaucoma therapy. Optom Vis Sci 78:85–94

Iseri PK, Altinas O, Tokay T, Yuksel N (2006) Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. J Neuroophthalmol 26:18–24

Janciauskiene S, Krakau T (2001) Alzheimer's peptide: a possible link between glaucoma, exfoliation syndrome and Alzheimer's disease. Acta Ophthalmol Scand 79:328–329

Janciauskiene S, Krakau T (2003) Alzheimer's peptide and serine proteinase inhibitors in glaucoma and exfoliation syndrome. Doc Ophthalmol 106:215–223

Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH (2002) The Alzheimer's A beta -peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. Proc Natl Acad Sci USA 99:11830–11835

Karran E, Mercken M, De Strooper B (2011) The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov 10:698–712

Loffler KU, Edward DP, Tso MO (1995) Immunoreactivity against tau, amyloid precursor protein, and beta-amyloid in the human retina. Invest Ophthalmol Vis Sci 36:24–31

Mattson MP, Barger SW, Cheng B, Lieberburg I, Smithswintosky VL, Rydel RE (1993) ß-amyloid precursor protein metabolites and loss of neuronal ca2+ homeostasis in Alzheimer's disease. Trends Neurosci 16:409–414

McKinnon SJ (2003) Glaucoma: ocular Alzheimer's disease? Front Biosci 8:s1140–s1156

McKinnon SJ, Lehman DM, Kerrigan-Baumrind LA, Merges CA, Pease ME, Kerrigan DF, Ransom NL, Tahzib NG, Reitsamer HA, Levkovitch-Verbin H, Quigley HA, Zack DJ (2002) Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. Invest Ophthalmol Vis Sci 43:1077–1087

Morrison JC, Moore CG, Deppmeier LM, Gold BG, Meshul CK, Johnson EC (1997) A rat model of chronic pressure-induced optic nerve damage. Exp Eye Res 64:85–96

Oliver JE, Hattenhauer MG, Herman D, Hodge DO, Kennedy R, Fang-Yen M, Johnson DH (2002) Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. Am J Ophthalmol 133:764–772

Osborne NN (2009) Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. Acta Ophthalmol 87:450–454

Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci MG, Pierelli F (2001) Morphological and functional retinal impairment in Alzheimer's disease patients. Clin Neurophysiol 112:1860–1867

Parsons CG, Danysz W, Quack G (1999) Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist: a review of preclinical data. Neuropharmacology 38:735–767

Rammes G, Hasenjäger A, Sroka K, Parsons CG (2011) Aggregation inhibitors reverse ß-amyloid (Aβ)-induced inhibition of long term potentiation (LTP) in murine hippocampal slices., Soc Neurosci Abstr. 41th Society for Neuroscience Annual Meeting, Washington, USA, p. #47.15

Ritch R (2000) Neuroprotection: is it already applicable to glaucoma therapy? Curr Opin Ophthalmol 11:78–84

Vickers JC, Dickson TC, Adlard PA, Saunders HL, King CE, McCormack G (2000) The cause of neuronal degeneration in Alzheimer's disease. Prog Neurobiol 60:139–165

Weinreb RN, Kaufman PL (2009) The glaucoma research community and FDA look to the future: a report from the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium. Invest Ophthalmol Vis Sci 50:1497–1505

Woldemussie E, Yoles E, Schwartz M, Ruiz G, Wheeler LA (2002) Neuroprotective effect of memantine in different retinal injury models in rats. J Glaucoma 11:474–480

Wostyn P, Audenaert K, De deyn PP (2008) Alzheimer's disease-related changes in diseases characterized by elevation of intracranial or intraocular pressure. Clin Neurol Neurosurg 110:101–109

Yoneda S, Hara H, Hirata A, Fukushima M, Inomata Y, Tanihara H (2005) Vitreous fluid levels of beta-amyloid((1-42)) and tau in patients with retinal diseases. Jpn J Ophthalmol 49:106–108