



Neuroprotective role of ebselen in an experimental glaucoma model

Ebselen as a neuroprotective agent in glaucoma

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Abstract

Aim: To investigate the potential antioxidant and neuroprotective effects of ebselen on the retina in a glaucoma model.

Methods: The rats in the control group were not operated on and received no treatment. In the rats in other groups, an increase in intraocular pressure was induced by limbal vein cauterization. The rats in the sham and ebselen groups were administered, respectively, 1 mL/kg/day dimethyl sulfoxide solution and 400 µmol/kg/day ebselen for 14 days. On the 14th day, the eyes were enucleated. The levels of malondialdehyde (MDA), nitric oxide (NO), and nitric oxide synthase-2 (NOS-2) in anterior chamber fluids were measured. The retina was subjected to immunohistochemical staining for glial fibrillary acidic protein (GFAP), S-100, and vimentin.

Results: The mean levels of MDA, NO, and NOS-2 were higher in the sham group compared to the control group ($P < .05$). The mean levels of MDA, NO, and NOS-2 in the ebselen group did not differ significantly from those in the control group ($P > .05$). The retinal immunostainings in the sham group showed significant increases in the expression of apoptosis, GFAP, S-100, and vimentin compared with the control group ($P < .05$). In the ebselen group, the expression levels of apoptosis, GFAP, S-100, and vimentin were significantly lower than in the sham group ($P < .05$).

Conclusion: Ebselen has neuroprotective effects on the retina in the experimental glaucoma model.

Keywords

experimental glaucoma model, neuroprotection, ebselen, apoptosis, nitric oxide, malondialdehyde, vimentin, TUNEL, immunostaining

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Introduction

Glaucoma, a leading cause of preventable blindness, is a multifactorial optic neuropathy characterized by retinal ganglion cell (RGC) loss, visual field defects, and optic nerve head excavation. Elevated intraocular pressure (IOP) is the primary and only modifiable risk factor for the disease; therefore, IOP reduction remains the cornerstone of management. Surgical treatment is considered when the target IOP cannot be achieved or when glaucomatous damage progresses despite maximal medical therapy. The disease involves thinning of the retinal nerve fiber layer and irreversible loss of RGCs, underscoring the importance of neuroprotective approaches in glaucoma management.^{1,2} Ebselen, a selenium-based antioxidant, possesses multiple pharmacological properties, including neuroprotective, anti-inflammatory, reactive nitrogen species scavenging, and anti-apoptotic effects.³ It has been shown to reduce neuronal death and ischemic injury in experimental models, supporting its potential as a neuroprotective agent.⁴ Based on these findings, we hypothesize that ebselen may provide neuroprotective and antioxidant benefits in the glaucomatous retina. To our knowledge, its retinal effects in glaucoma have not been previously investigated. Therefore, this study evaluates the neuroprotective and antioxidant actions of ebselen in a rat model of glaucoma.

The objective of this study was to investigate whether ebselen exerts neuroprotective and antioxidant effects in an experimental rat model of glaucoma.

Materials and Methods

Ethical Approval and Experimental Design

This study was approved by the institutional ethics committee and conducted in compliance with the Association for Research in Vision and Ophthalmology (ARVO) guidelines and the Guidelines for the Housing of Rats in Scientific Institutions. Twenty-one Sprague–Dawley rats (250 g, 2–3 months old) were housed under controlled conditions (22–26°C, 12-hour light/dark cycle) and fed standard chow. Water was withheld for 12 hours before surgery. All experimental, biochemical, and histopathological procedures were performed as described in the authors' previous study.⁵

Study Groups

The rats were randomly divided into three groups of seven animals each. Group 1 (Control): No surgical procedure or treatment was applied. Group 2 (Sham): Intraocular pressure (IOP) elevation was induced, and rats received intraperitoneal dimethyl sulfoxide (DMSO) at 1 mL/kg/day for 14 days. Since ebselen is insoluble in saline, DMSO (Sigma-Aldrich, St. Louis, MO, USA) was used as its solvent and served as the placebo. Group 3 (Ebselen): After IOP induction, rats were intraperitoneally administered ebselen at 400 µmol/kg/day for 14 days.

Anesthetic Technique

Anesthesia and analgesia were induced with an intramuscular injection of ketamine hydrochloride (50 mg/kg; Ketalar, Eczacıbaşı, Turkey) and xylazine hydrochloride (5 mg/kg; Rompun, Bayer, Turkey). Additionally, 1% proparacaine hydrochloride was applied topically to both eyes before surgical procedures.

Induction of Intraocular Pressure Elevation: Following anesthesia and analgesia, ocular hypertension was induced by cauterizing the episcleral veins, including three branches of the limbal veins, except for the nasal quadrant, using a unipolar ophthalmic cautery.⁶ The eyes were then irrigated with saline, and antibiotic drops were applied.

Intraocular Pressure Measurement: Intraocular pressure was measured with a Tono-Pen tonometer to obtain accurate, repeatable readings. Ten readings with less than 5% error were averaged for each measurement. IOP was recorded before surgery and on postoperative days 5 and 10 after topical instillation of 1% proparacaine hydrochloride.

Histopathologic Preparation: After anesthesia and analgesia, the eyes were enucleated. Aqueous humor samples were aspirated with a 27-gauge needle to measure malondialdehyde (MDA) and nitric oxide (NO) levels. Iris and ciliary body tissues were collected for nitric oxide synthase-2 (NOS-2) analysis. The retina and optic nerve from the remaining posterior segment were dissected for immunohistochemical evaluation of glial fibrillary acidic protein (GFAP), vimentin, and S-100 expression, and apoptosis was assessed using the TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling) method.

Determination of MDA, NO, and NOS-2 Levels

Equal volumes of aqueous humor were collected from each eye. Malondialdehyde (MDA), an indicator of lipid peroxidation, was quantified using a commercial MDA kit (Immuchrom GmbH, Hessen, Germany) via high-performance liquid chromatography (HPLC) with fluorescence detection (excitation: 515 nm; emission: 553 nm). Nitric oxide (NOx) levels were measured using a nitrite/nitrate colorimetric assay kit (Cayman Chemical, Ann Arbor, MI, USA) with an ELISA device. For Western blot analysis of NOS-2, frozen ciliary body samples were homogenized in RIPA lysis buffer containing protease and phosphatase inhibitors and centrifuged at 10,000 × g for 10 minutes. Protein concentrations were determined using a Qubit fluorometer, and 50 µg of protein per sample was loaded onto SDS-PAGE gels, electrophoresed, and transferred to PVDF membranes (An iBlot Dry Blotting System was used to transfer proteins). Membranes were incubated with polyclonal anti-NOS-2 antibody (1:200; Santa Cruz Biotechnology, CA, USA), followed by secondary antibody and chromogenic detection.

TUNEL and Retinal Immunohistochemistry Staining Apoptotic Cell Screening

Five-micrometer sections from paraffin-embedded tissues were mounted on polylysine-coated slides. Apoptotic cells were detected using the ApopTag® Plus Peroxidase In Situ Apoptosis Detection Kit (Chemicon, S7101, USA) following the manufacturer's protocol. After deparaffinization, rehydration, and proteinase K treatment, endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Sections were incubated with TdT, followed by anti-digoxigenin peroxidase, and visualized with diaminobenzidine. Sections were counterstained with Harris hematoxylin. Positive controls used breast tissue, and negative controls omitted TdT. Apoptotic cells were identified by brown-stained nuclei, while blue-stained nuclei indicated normal cells. TUNEL staining intensity was semi-quantitatively scored as 0 (none), 1 (light), 2 (moderate), or 3 (intense).

GFAP, S-100, Vimentin Immunohistochemistry

Four-micrometer sections of the retina and optic nerve were prepared from paraffin-embedded tissue blocks for immunohistochemical analysis. Staining for GFAP, S-100, and vimentin was performed using respective antibody kits (Lifespan BioSciences, Seattle, WA) on an automated Ventana Benchmark XT system. Following staining, sections were sealed and examined under an Olympus light microscope, and representative images were captured at 40× magnification. Nuclear immunoreactivity for GFAP, S-100, and vimentin was evaluated semi-quantitatively and classified as weak (+), moderate (++), or strong (+++).

Ethical Approval

This study was approved by the Ethics Committee of Firat University (Date: 22.11.2011, Decision No: 126).

Statistical Analysis

Data were analyzed using SPSS 16.0 and are presented as mean ± standard deviation (SD). A P value < 0.05 was considered statistically significant. Parametric data were analyzed by one-way ANOVA followed by Tukey's post hoc test. In contrast, nonparametric data were evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U test. The Wilcoxon test was applied to related variables.

Reporting Guidelines

This study was reported in accordance with the ARRIVE guidelines for animal research.

Results

Intraocular Pressure

Mean intraocular pressure (IOP) significantly increased in both the sham and ebselen groups after episcleral vein cauterization (P < .05), whereas the control group showed no significant change (P > .05) (Table 1). The sham group exhibited significantly higher IOP than controls at postoperative days 5 and 10 (P < .05).

Table 1. Mean IOP Value Changes According to Days

	IOP 0 Day	IOP 5 Day	IOP 10 Day
Control	13.79 ± 2.05	13.98 ± 1.98	14.16 ± 1.78
SHAM	14.14 ± 2.04	^a 31.23 ± 3.97	^b 33.57 ± 3.44
Ebselen	14.08 ± 1.25	^a 25.46 ± 1.81	^b 25.77 ± 1.37

Iop, Intraocular pressure;

^aCompared to the control group there is a significant difference in IOP on day 5 (P < .05).

^bCompared to the control group there is a significant difference in IOP on day 10 (P < .05).

MDA Levels

Aqueous humor MDA levels were significantly elevated in the sham group compared to controls (P < .01). Ebselen treatment markedly reduced MDA levels compared with the sham group (P < .01), and no significant difference was observed between the ebselen and control groups (P > .05) (Table 2).

Table 2. MDA, NOx and NOS-2 Levels by Group

	CONTROL	SHAM	EBSELEN
MDA, µmol/L	1.68 ± 0.22	3.51 ± 0.45	1.91 ± 0.43
NOx, µM	5.19 ± 1.0	9.9 ± 3.18	5.33±1.91
NOS-2, m	17.0 ± 2.16	31.7 ± 8.01	13.42±5.74

MDA, Malondialdehyde; NOx, Nitric oxide; NOS-2, Nitric oxide synthase 2

NO Levels

Nitric oxide (NOx) levels were significantly higher in the sham group versus controls (p≤0.01). Ebselen significantly decreased NOx levels compared to the sham group (P < .05), with no significant difference from controls (P > .05) (Table 2).

NOS-2 levels: Ciliary body NOS-2 levels were significantly elevated in the sham group compared to controls (P < .05). Ebselen treatment markedly decreased NOS-2 levels relative to both the sham and control groups (P < .01) (Table 2).

Retinal Immunohistochemistry and TUNEL staining. Apoptosis: Retinal apoptosis, assessed by TUNEL staining, showed weak positivity in the control group (Supplementary Figure 1A). In the sham group, TUNEL positivity was markedly increased, particularly in the OPL and INL, indicating significant apoptosis (P < .05) (Supplementary Figure 1 B). Ebselen treatment significantly reduced apoptosis compared with the sham group, with staining similar to the control group (Supplementary Figure 1C). When examined in retinal sections, the TUNEL+ RGC layer was observed in the IPL and INL. Compared with the control group, the prevalence of TUNEL staining increased in the sham group and was statistically significant (P < .05). In the ebselen group, TUNEL+ cells were significantly decreased (P < .05).

Hematoxylin and Eosin (H&E) Staining

H&E-stained retinal sections demonstrated thinning of the INL in the sham group (Supplementary Figure 2 B), reflecting pressure-induced retinal damage. The control group exhibited normal retinal thickness (Supplementary Figure 2 A), while the ebselen group showed preserved INL thickness similar to controls (Supplementary Figure 2 C).

GFAP Immunohistochemistry

Retinal GFAP staining indicated weak positivity (+1) in the control group (Supplementary Figure 3 A). Sham eyes exhibited strong GFAP immunoreactivity (+++) throughout Müller cells and their processes, particularly in the IPL, INL, OPL, and ONL, extending even to the photoreceptor layers (Supplementary Figure 3B, P < .05). Ebselen treatment reduced GFAP expression (++), resembling the control pattern, without extending to the photoreceptor layer (Supplementary Figure 3 C, P < .05 vs. sham).

S-100 Immunohistochemistry

Müller cell S-100 expression was limited to INL and sparsely in RGCs in controls (+1, Supplementary Figure 3 D). Sham eyes showed significantly increased S-100 immunoreactivity (+++) across IPL, INL, and ONL (P < .05, Supplementary Figure 3 E). Ebselen treatment reduced S-100 expression (++), notably decreasing staining in the IPL and ONL compared to sham (P < .05, Supplementary Figure 3F).

Vimentin Immunohistochemistry

Control retinas displayed vimentin expression (+1) in RGC, IPL, OPL, and MC processes in INL (Supplementary Figure 3 G). Sham group retinas showed significantly increased vimentin immunoreactivity (+++) across all retinal layers, including the ONL (P < .05, Supplementary Figure 3H). Ebselen treatment restored vimentin expression to near-control levels (+1) in RGC, IPL, INL, and OPL (P < .05 vs. sham, Supplementary Figure 3 I).

Discussion

Glaucoma is a major cause of irreversible vision loss worldwide, primarily due to RGC apoptosis and axonal degeneration.⁷ Although elevated IOP is a key risk factor, neuronal damage may persist even with controlled IOP, underscoring the importance of neuroprotective strategies. Oxidative stress and lipid peroxidation are thought to contribute significantly to glaucomatous neurodegeneration.⁸ Malondialdehyde (MDA), a marker of lipid peroxidation, indicates oxidative stress-related RGC damage and has been reported to increase in glaucoma patients and in experimental models.⁹ In our study, MDA levels increased in the sham group but decreased after ebselen treatment, indicating reduced oxidative-nitrative stress and supporting ebselen's neuroprotective potential in glaucoma. Oxidative and nitrosative stress play a critical role in glaucomatous optic nerve damage. Experimental studies

have demonstrated NOS-2 expression in the retina and optic nerve head, implicating NO in glaucoma pathogenesis.¹⁰ Under inflammatory conditions, excessive NO production by inducible NOS-2 contributes to cytotoxicity and apoptosis via the formation of reactive nitrogen species.¹¹ Elevated IOP upregulates NOS-2 expression and protein nitration, while NOS-2 inhibition protects RGCs from degeneration.¹² In the present study, apoptosis observed in the RGC, inner nuclear, and inner plexiform layers supports the involvement of NOS-2–mediated nitrative stress in glaucomatous neurodegeneration. Ebselen, a seleno-organic compound with antioxidant and anti-inflammatory properties, inhibits NOS activity and NO production. Consistent with previous reports, NOS-2 and NO levels were significantly lower in the ebselen-treated group, suggesting that ebselen mitigates glaucomatous injury by reducing oxidative and nitrative stress.^{3,13} Multiple hypotheses exist regarding RGC apoptosis in glaucoma, including axoplasmic flow blockage, neurotrophin withdrawal, elevated vitreous glutamate, and vasospasm.¹⁴ Experimental studies using TUNEL assays have demonstrated that apoptosis occurs mainly in the RGC layer.¹⁵ Glaucomatous neurodegeneration is further associated with axonal loss, microglial activation, and activation of inflammatory cytokines and the complement pathway.¹⁶ In the present study, TUNEL staining revealed significantly higher apoptosis in the sham group and reduced apoptosis in the ebselen-treated group, supporting the neuroprotective effect of ebselen on RGCs. Astrocytes, Müller cells (MCs), and microglia play dual roles in retinal homeostasis, contributing to both neuroprotection and neurodegeneration.¹⁷ Experimental models have shown that elevated IOP triggers glial activation, which is associated with neuronal degeneration and debris clearance.¹⁸ Glial fibrillary acidic protein (GFAP), primarily expressed in MCs, is a sensitive marker of retinal stress and is markedly upregulated following IOP elevation.¹⁹ In our study, GFAP expression was increased in the sham group but reduced with ebselen treatment, indicating that ebselen suppresses glial activation and protects against retinal injury. Vimentin, an intermediate filament protein, maintains cytoskeletal integrity in MCs and astrocytes.²⁰ Experimental glaucoma models have shown increased vimentin expression in the retinal nerve fiber layer, reflecting MC activation and altered glutamate metabolism.²¹ In our study, vimentin expression was elevated in the sham group but decreased with ebselen treatment, suggesting that ebselen reduces glial activation and cytoskeletal stress in the glaucomatous retina. S-100 protein, a Ca²⁺-binding guanylate cyclase activator, is a specific marker of retinal MCs in adult mammals.²² Its upregulation in experimental glaucoma indicates MC activation and injury.¹⁸ In our study, S-100 expression was markedly increased in the sham group, particularly in MCs within the inner nuclear layer, but decreased after ebselen treatment, suggesting that ebselen protects against MC damage. Ebselen, an organoselenium compound, exhibits antioxidant, anti-inflammatory, and neuroprotective properties.²³ Acting as a glutathione peroxidase mimetic, it scavenges reactive oxygen and nitrogen species, thereby reducing lipid peroxidation and oxidative stress. Owing to its lipid solubility, ebselen readily penetrates cells and protects neural tissues from ischemia- or reperfusion-induced injury.²⁴ Animal studies have demonstrated that ebselen reduces oxidative stress and lipid peroxidation, resulting in significant neuroprotection in various tissues.⁴ Oxidative stress is a major contributor to apoptosis, and ebselen limits injury-induced cell death primarily through its antioxidant effects. Although ocular studies are limited, available evidence indicates that systemic ebselen can penetrate ocular barriers, normalize retinal MDA and

GSH levels, preserve glutathione peroxidase activity, and reduce oxidative damage in experimental models of retinal injury and cataract formation.^{18,19,25} In our study, ebselen reduced MDA, NO, and NOS-2 levels in aqueous humor and decreased retinal apoptosis, GFAP, S-100, and vimentin expressions in TUNEL and immunohistochemical analyses.

Limitations

The small sample size may limit the generalizability of the findings. Future studies with larger sample sizes and extended follow-up periods are needed to confirm the neuroprotective and antioxidant effects of ebselen in experimental glaucoma.

Conclusion

Ebselen demonstrates significant neuroprotective effects in experimental glaucoma by reducing oxidative and nitrative stress, inhibiting RGC apoptosis, and attenuating glial activation. The treatment lowered MDA, NO, and NOS-2 levels and decreased the expression of GFAP, vimentin, and S-100 in retinal tissues. These findings suggest that ebselen may serve as a promising therapeutic agent to complement intraocular pressure–lowering strategies and protect retinal neurons from glaucomatous damage.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed Consent

Not applicable.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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None.

Author Contributions (CRediT Taxonomy)

Conceptualization: N.D., B.T.
Methodology: N.D., N.C., B.T.
Data Curation: N.D., N.C.
Formal Analysis: N.İ., İ.H.Ö., T.K.
Investigation: N.D., N.C., T.D.
Writing – Original Draft Preparation: N.D.
Writing – Review & Editing: B.T., S.F.F.
Supervision: B.T.

AI Usage Disclosure

The authors declare that no AI-assisted technologies were used.

Abbreviations

ARVO: Association for research in vision and ophthalmology
DMSO: Dimethyl sulfoxide
GFAP: Glial fibrillary acidic protein
INL: Inner nuclear layer
IOP: Intraocular pressure
IPL: Inner plexiform layer
MC: Müller cell
MDA: Malondialdehyde
NO: Nitric oxide
NOS-2: Nitric oxide synthase-2
ONL: Outer nuclear layer
OPL: Outer plexiform layer

RGC: Retinal ganglion cell

TUNEL: Terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling

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