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REVIEW ARTICLE

The role of electrical stimulation therapy in ophthalmic diseases

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Abstract
Introduction Electrical stimulation therapy (EST) involves the use of a low-intensity electrical current in the treatment of neuromuscular conditions. During the recent two decades, EST has emerged as a potential neuroprotective strategy in certain ophthalmic diseases, aided by a lack of effective management for these conditions.
Purpose The aim of this review is to summarize and discuss current available evidence for the use of EST in ophthalmic diseases in the laboratory setting and in human trials.
Methods The compilation and review of published English-language reports on the use of EST in human ophthalmic disease and animal models of ophthalmic disease.
Results From published reports, research work on the use of EST in ophthalmic diseases began in the last 20 years. Different methods of electrical stimulation have been devised, with varying levels of invasiveness. Results from human trials have favored earlier and repeated treatment after insults to the optic nerve, while EST has shown transient effectiveness in degenerative diseases of photoreceptors. Patients also reported no serious adverse effects from EST in the clinical trials. Results from animal studies have further confirmed survival benefits of EST in retinal cell survival, with the underlying mechanism likely multifactorial, but involving Müller cell modulation.
Conclusions Results from human and animal studies have demonstrated the relevance and potential effectiveness of EST in ophthalmic disease. However, optimal disease and species-specific stimulation settings need to be defined.

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Introduction

Electrical stimulation therapy (EST) is a therapeutic technique that employs a low-intensity electric current and has been used in the treatment of neurodegenerative disease, including those of the musculoskeletal system, peripheral nervous system, central nervous system, and in otorhinolaryngology [1–6]. Within the last two decades, the use of EST in ophthalmic disease has come into prominence due to favorable results in animal models and in human trials. The process involves no generation of perceptible heat. Instead, the nerve endings are directly stimulated for therapeutic effects.

The concept of electrically stimulating an eye through a contact lens electrode first came about from experiments by Potts et al. in 1968 [7]. Electrical stimulation of the retina evokes light sensations known as electrical phosphenes. Rather than study its potential neuroprotective effects, the investigators' aim for the experiments was to describe and quantify electrically evoked responses (EER) from the occipital lobe in healthy human subjects. Potts et al. established that transcorneal electrical stimulation (TcES) was safe without serious adverse effects in both healthy human eyes and in those with underlying disease, and that the electrical stimulus likely acted on structures proximal to the retinal photoreceptors [7, 8]. In the 1990s, work by Miyake et al. on both human subjects and animals showed that EER was normal in those with dysfunctional photoreceptors and further confirmed that the site activated by TcES was the inner retina [9, 10]. Shimazu et al. of the same institution further demonstrated that the measured responses had signatures suggestive of a RGC and bipolar cell origin [11]. As such, the investigators

used TcES as a way to quantify residual inner retinal function in diseased eyes. In 2001, inspired by encouraging results from EST in damaged spinal cord ganglion cells and motor neurons, Morimoto et al. discovered its use also improved the survival of transected RGCs in rats [12]. Since then, further research has been done to study the effects of EST on the retina as well as the underlying mechanisms involved.

In animal research, EST has been shown to prolong retinal cell survival and function in several models of ophthalmic disease (see Table 1), including optic nerve transection (ONT), optic nerve crush injury (ONC), light induced photoreceptor degeneration, ocular ischemia, and retinitis pigmentosa (RP). These studies have provided evidence of neuroprotective effects of EST for both diseases of the inner retinal layer (RGCs) and those of the outer layer (photoreceptors). For human trials, EST was performed on patients with optic nerve ischemia, retinal vascular disease, and RP. Although the study sample sizes were small, patients who underwent the treatment all had some degree of improved visual function (see Table 2).

This review aims to summarize progress in EST for ophthalmic diseases in both in animal models and in humans.

Effect of electrical stimulation therapy in human ophthalmic diseases

There are six published studies on the use of EST in human ophthalmic disease. However, only one of the six is a randomized sham-controlled clinical trial [25]. Treated conditions involved those with currently no definitive management option, including ischemic optic neuropathy, retinal artery occlusive diseases, as well as photoreceptor and macula dystrophies.

In 2006, Fujikado et al. reported results from EST on three eyes with nonarteritic anterior ischemic optic neuropathy (NAION) and five eyes with traumatic optic neuropathy (TON) [23]. Two out of three eyes with NAION and four of five with TON had significant improvements in best-corrected visual acuity (≥0.3 logMAR) after a 3-month course of EST. In the following year, two eyes with central retinal artery occlusion (CRAO) and one with branch retinal vein occlusion (BRAO) underwent EST. There was an increase in best-corrected visual acuity (BCVA) by more than 0.2 logMAR in two of the three eyes, while visual field by perimetry and retinal function by multifocal electroretinography improved in all eyes [23]. In 2011 Oono et al. found that in eyes with retinal artery occlusion, EST was more helpful in improving visual function in long-standing, established cases. In this study, eyes with recent onset branch retinal artery occlusion (<16 weeks) did not show significant improvements in visual function parameters after EST, while long-standing cases (>16 weeks) had improvements [26]. It is, however, important to note that the study had a small sample size with only two long-standing cases and three cases of recent onset for comparison. In the only randomized sham-controlled trial of EST in human patients to date, Schatz et al. randomly assigned 24 patients with RP to either of three groups: weekly TcES for six consecutive weeks at 66 % of electrical phosphene threshold (EPT), weekly TcES treatment for 6 weeks at 150 % EPT, or sham treatment. The investigators noted that patients treated at 150 % EPT had significant improvements in visual field on perimetry as well as scotopic b-wave amplitude on flash electroretinography. There were no significant differences in visual parameters between the 66 % EPT treated group and the sham controls. The study was an exploratory investigation [25]. A follow-up study with larger sample sizes and longer study duration is in progress. Most recently, there was a case report of EST treatment in a patient with Best Vitelliform Macular Dystrophy (BVMD). There was noted improvement in best-corrected visual acuity at 6 months (20/200 to 20/25) after undergoing two treatments 1-month apart. More significantly, the authors found that when visual acuity deteriorated again, repeat treatment with the same frequency and parameters resulted in improvements in BCVA [27].

Table 1 List of studies on electrical stimulation therapy in animal models of ophthalmic disease

Year	Animal	Disease model	Target neuronal cells
2001	Wistar rat [12]	optic nerve transection	retinal ganglion cell
2005	Wistar rat [13]	optic nerve transection	retinal ganglion cell
2007	Long-Evans rat [14]	optic nerve crush	retinal ganglion cell
2007	Royal College of Surgeons rat [15]	retinal dystrophy	photoreceptor
2009	Sprague–Dawley rat [16]	photoreceptor degeneration	photoreceptor
2009	Wistar rat [17]	optic nerve crush	retinal ganglion cell
2009	Wistar rat [18]	optic nerve transection	retinal ganglion cell
2011	Sprague–Dawley rat [19]	ocular ischemia	retinal ganglion cell
2012	rhodopsin P347L transgenic rabbit [20]	retinitis pigmentosa	photoreceptor
2013	Charles River Rat [21]	optic nerve crush	retinal ganglion cell
2013	Sprague–Dawley rat [22]	NAION*	retinal ganglion cell

* NAION, nonarteritic ischemic optic neuropathy

Table 2 List of studies on electrical stimulation therapy in human ophthalmic disease

Year	Disease	Evaluation parameters	Sample Size
2006	nonarteritic ischemic optic neuropathy [23]	BCVA* VF#	3
2006	traumatic optic neuropathy [23]	BCVA, VF	5
2007	retinal artery occlusion [24]	BCVA	3
2011	retinitis pigmentosa [25]	BCVA, VF, mfERG^	24
2011	branch retinal artery occlusion [26]	BCVA, VF, mfERG	5
2013	best vitelliform macular dystrophy [27]	BCVA, VF, mfERG	1

* BCVA, best-corrected visual acuity, # VF, visual field, ^ mfERG, multifocal electroretinography

In total, 41 patients with different ophthalmic diseases underwent EST, including three patients with NAION, five with TON, eight with retinal artery occlusion, 24 with RP, and one with BVMD. None of the patients experienced serious adverse events from the treatment. Although the studies were limited in impact by their small sample sizes, the presence of visual improvements in diseases that are otherwise untreatable is encouraging. Furthermore, the lack of serious adverse effects in any of the reported patients as well as the possibility of repeat treatment in the case of relapse means that EST is a promising modality that deserves further exploration. Optimal disease- and species-specific stimulation settings also need to be defined. Thus, further randomized controlled trials with adequately powered sample sizes are essential for progress to clinical practice.

Effect of electrical stimulation study on animal models of ophthalmic diseases

In order to test the effect of EST in a controlled environment and to uncover the molecular mechanisms involved, investigators have turned to animal models of ophthalmic diseases. Morimoto et al. led the way by first testing EST in a model of ONT using Wistar rats [12]. Electrical stimulation, using a pair of silver ball electrodes attached to the nerve stump, was given immediately after the optic nerve was transected. After 7 days, it was noted that the groups using a current intensity of 30 μA or more had significantly better RGC survival. However, the reported method of electrical stimulation is invasive and technically demanding. A major breakthrough was the development of a less invasive technique of EST using the electroretinography jet-electrode attached to a contact lens. This method is now known as TcES and is the most popular method of EST to date [13].

As of now, there are 11 published papers on EST in animal models with the majority coming from Morimoto's group. The animal models used in the studies can be divided into two types: those with RGC loss and those with photoreceptor cell loss. To induce RGC loss, the most common methods were ONC and ONT. Raised intraocular pressure was also shown to specifically damage RGCs, but if pressures reached above 50 mmHg, bipolar cells and photoreceptors were also damaged [28]. To induce photoreceptor cell loss, Royal College of Surgeons (RCS) rats and rhodopsin P347L transgenic rabbits were used. Both animals have genetic defects causing premature photoreceptor degeneration. One other paper reported the use of light-induced photoreceptor degeneration as an acquired method of photoreceptor cell loss [16].

Among the published results, authors have demonstrated varying degrees of improvement with EST using different parameters of visual function. The first few studies focused on improving RGC survival. In the landmark trial using the ONT model, Morimoto reported that 7 days after transection immediately followed by electrical stimulation, the mean RGC density was 70 %, 85 %, and 83 % of the normal control for EST treatment using 0.5, 1, and 3 ms/phase pulse duration, respectively, whereas it was only 53 % in the sham treatment group [13]. When comparing EST to steroid treatment in an ischemic optic neuropathy model, the EST-treated group showed significantly improved RGC survival compared to the steroid-treated group up to 4 weeks after treatment [22]. An additional question, derived from human studies, was whether EST treatment was effective only when given early after retinal insult or if delayed treatment was effective. Henrich-Noack et al. looked into this, and their study reported that EST was only able to improve RGC survival in damaged optic nerves if given no more than 3 days after ONC injury [21].

For models of photoreceptor cell loss, the survival of the photoreceptors was determined indirectly through measurement of outer nuclear layer thickness (ONL) and flash electroretinography. The RCS rat is an animal model of RP. A mutation in the receptor tyrosine kinase of retinal pigment epithelial cells in RCS rats causes them to lose their phagocytic activity [29]. Morimoto et al. conducted weekly TcES on RCS rats starting at 3 weeks of age, for up to 6 weeks. The team found that the ONL in EST-treated eyes was significantly thicker throughout the entire treatment duration (6 weeks). However, retinal function was only preserved in EST-treated eyes for up to 4 weeks while on RP used in Morimoto's experiments. Similarly, EST was shown to increase photoreceptor survival for up to 6 weeks while on weekly therapy [19]. In the light-induced photoreceptor degeneration model using Sprague–

Dawley rats, Ni et al. compared the efficacy of pre-exposure EST treatment and post-exposure EST treatment. While the authors noted that both pre- and post-exposure treatment prolonged photoreceptor survival, post-exposure treatment provided better and longer neuroprotection. However, in both cases, the protective effect was transient and did not last for the entire 2-week treatment duration [16]. Therefore, the neuroprotective effect of EST on damaged RGCs and photoreceptors may be dependent on the severity and type of the initial insult, the timing and mode of electrical stimulation, the stimulation parameters, and also the species of animal treated.

Modalities of electrical stimulation

Electrical stimulation can be performed on the eye through different types of electrodes. The main consideration in deciding the type of electrode used is to minimize the invasiveness and technical expertise of the approach as much as possible. Therefore, trans-corneal electrical stimulation, via a contact lens-connected electrode, is by far the most popular choice in humans and rodents. In human patients, there are two types of electrodes that attach to the cornea: the Dawson-Trick-Litzkow (DTL)-plus electrode, which is composed of a fine conductive thread gently attached to the inferior limbus of the eye, and the ERG-jet electrode, which is a contact lens mounted with a golden foil either in its inner surface (monopolar) or its outer surface (bipolar) [30]. It has been reported that the two electrodes differ slightly in terms of the preferential areas of retina stimulated. When using ERG-jet electrodes, researchers have found that the activated primary visual cortex region corresponded better with the stimulated retinal area [31]. The ERG-jet electrode is also able to elicit brighter phosphene perception than the DTL-plus electrode. Side effects were uncommon and mild for both electrodes, with some patients experiencing foreign body sensation with the DTL-plus electrode [25] and some patients having mild corneal punctate keratopathy on slit lamp exam after using the ERG-jet electrode [23]. In animal models, besides the mentioned two types of corneal electrodes, the golden ring electrode, without the contact lens, can also be used in contact with the cornea [16]. The DTL-plus, ERG-jet, and golden ring electrode are all forms of TcES [15]. For a more invasive procedure, a silver ball electrode can be directly attached to the stump of an optic nerve, as discussed in the ONT model experiments [12]. For in vitro experiments, retinal cell cultures can be placed on a microelectrode array in order to accept current from an electrical stimulator [32].

Among the mentioned electrodes, the DTL-plus and ERG-jet electrodes are both equally popular in human experiments, while in animal experiments, the ERG-jet electrode is more popular because of the ease at which the apparatus can be fixated on sedated animals.

Parameters for electrical stimulation therapy

EST is still a relatively new treatment modality for ophthalmic diseases. Much of the current evidence is based on studies, each with small sample sizes, treating a wide range of ocular conditions. Hence, there is difficulty in formulating a standard guideline on optimal treatment settings. In human studies, the most frequently used setting includes biphasic pulses, a duration of 5 to 10 ms, and frequency of 20 Hz. Current intensity is titrated according to the measured electrical phosphene threshold for each patient [23–27]. For example, Morimoto et al. tested a range of current intensities in healthy human subjects and compared this with those who had forms of hereditary retinal degeneration. In the experiment, the current intensity was gradually increased stepwise from 50 μA to 2 mA to reach certain electrical phosphene thresholds. In normal eyes the maximum response in the experiment (pupil constriction) was achieved with an average intensity of 128±13 μA. In patients with hereditary retinal degeneration, the required current intensity to achieve a comparable response was more variable and at least 7–8 times higher than in normal subjects [33]. In animals, investigators are unable to measure electrical phosphene thresholds; therefore, choosing an optimal current

Table 3 Possible neuroprotective mechanisms of ES in previous studies

Disease model	Possible protective mechanism
optic nerve transection [12]	increased expression of neurotrophic factor by activation of RGC soma
optic nerve transection [13]	enhanced production of IGF-1 by Muller cells
optic nerve crush [14]	activation of synaptic NMDA receptors, voltage-dependent Ca2+ channels
retinal dystrophy [15]	influence the electrical activity and charge of photoreceptors
retinal dystrophy [32]	hyperneurotrophic response after injury
light-induced photoreceptor degeneration [16]	upregulation of Bcl-2 and CNTF in Muller cells
ocular ischemia [19]	increased level of glutamine synthetase
retinitis pigmentosa [20]	increased expression of neurotrophic factors, chorioretinal blood circulation, and suppressed TNF and Bax

intensity is a much more difficult process. The optimal settings must thus strike a balance between providing maximal neuroprotection and minimizing complications, which, while rare, include retinal detachment, retinal degeneration, transient superficial keratopathy, and scleral penetration when current amplitude was increased [12, 16]. Inomata et al. used intrinsic signal imaging to determine optimal stimulus current intensity in Macaque monkeys undergoing EST. The investigators demonstrated that signal strength correlated well with stimulation intensity, with the maximum signal responses recorded above 600 μA [34]. In order to provide a better reference for TcES, Morimoto et al. tested different combinations of parameter settings using the rat ONT model. The optimal settings from the study was as follows: pulse duration of 1 and 3 ms, current intensity of 100 and 200 μA, stimulation duration of at least 30 min, stimulation frequencies of 1, 5, and 20 Hz, and finally symmetrical pulse waves without inter-pulse intervals [18]. Morimoto et al. also discovered that repeated stimulation was superior to single treatment. At the moment, this remains the only published study on optimal EST settings in the treatment of ophthalmic disease.

Possible neuroprotective mechanisms of electrical stimulation therapy

After an initial insult such as ONT, there is rapid loss of directly injured RGCs. There is also a delayed, but significant secondary loss of RGCs whose axons are not damaged [35]. While there is no evidence that loss of the directly injured cells can be stopped, it is likely that the neuroprotective effect of strategies such as EST lie in their ability to prevent secondary apoptosis of the undamaged RGCs.

There are several proposed mechanisms of electrical stimulation-related neuroprotection revealed from studies on animal models (see Table 3). It is now thought that Müller cell activation is central to the therapeutic process, as it has been shown to mediate several effects. Firstly, the upregulation of neurotrophic factors may play a key role in this process. Ni et al., as well as other investigators, demonstrated that higher levels of insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), and ciliary neurorophic factor (CNTF) were released from Müller cells after EST in the RCS rat model of photoreceptor degeneration. The teams further showed that inhibition of these neurotrophic factors prevented EST from prolonging photoreceptor and RGC survival and function [13, 16, 17]. A second possible mechanism is elevated secretion of glutamine synthetase from Müller cells, which may ameliorate glutamate-mediated neuro-excitotoxicity. This hypothesis was proposed by Wang et al., based on their work on Sprague Dawley rats using a model of retinal ischemia [19]. Other possible mechanisms of EST include an intracellular calcium (Ca^{2+}) influx, which causes neuronal cell depolarization and thus increases intracellular cyclic adenosine monophosphate (cAMP). This may further contribute to survival of the nerve cells [12].

Conclusion

Evidence from human and animal studies support the hypothesis that EST prolongs retinal survival and preserves visual function in ophthalmic diseases with otherwise no other available form of effective treatment. EST has been shown to be safe in rodents and in humans with no serious adverse effects recorded in the latter group. A better understanding of the underlying mechanism of action and the investigation into optimal parameter settings are essential for the continued development of EST. For future directions, the use of EST in glaucomatous optic neuropathy will be an important next step, as glaucoma is currently the leading cause of irreversible blindness worldwide and only treatable, albeit incompletely, by intraocular pressure-lowering therapy. Our research team is currently conducting experiments on the neuroprotective effect of TcES in animal glaucoma models with promising results.

Declaration All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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