·Review·

The transcorneal electrical stimulation as a novel therapeutic strategy against retinal and optic neuropathy: a review of experimental and clinical trials

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Abstract

• Transcorneal electrical stimulation (TES) is a novel therapeutic approach to activate the retina and related downstream structures. TES has multiple advantages over traditional treatments, such as being minimally invasive and readily applicable in a routine manner. Series of animal experiments have shown that TES protects the retinal neuron from traumatic or genetic induced degeneration. These laboratory evidences support its utilization in ophthalmological therapies against various retinal and optical diseases including retinitis pigmentosa (RP), traumatic optic neuropathy, anterior ischemic optic neuropathy (AION), and retinal artery occlusions (RAOs). Several pioneering explorations sought to clarify the functional mechanism underlying the neuroprotective effects of TES. It seems that the neuroprotective effects should not be attributed to a solitary pathway, on the contrary, multiple mechanisms might contribute collectively to maintain cellular homeostasis and promote cell survival in the retina. More precise evaluations *via* functional and morphological techniques would determine the exact mechanism underlying the remarkable neuroprotective effect of TES. Further studies to determine the optimal parameters and the long-term stability of TES are crucial to justify the clinical significance and to establish TES as a popularized therapeutic modality against retinal and optic neuropathy.

• **KEYWORDS:** transcorneal electrical stimulation; therapeutic strategy; retinal disease; optic neuropathy
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INTRODUCTION

Electrical stimulation is a promising therapeutic tool against various neurological disorders such as the stroke, tinnitus and hyperalgesia. Several laboratory and clinical studies on electrical stimulation have demonstrated significant beneficial effects with optimum safety and tolerability profiles [1-5]. For the eye, transcorneal electrical stimulation (TES) and transorbital electrical stimulation are both noninvasive approaches to activate the retina and downstream structures and thereby exert therapeutic effects on the subjects. Series of animal experiments have shown that they can protect the retinal neurons such as retinal ganglion cells (RGCs) and photoreceptors from traumatic or genetic induced degeneration, and ameliorates the visual function loss [6-9]. These therapeutic evidences support its utilization in ophthalmological therapies against various retinal and optical diseases: TES has been adopted to induce positive effects on patients with retinitis pigmentosa (RP), traumatic optic neuropathy, anterior ischemic optic neuropathy (AION), and retinal artery occlusions (RAOs) with negligible complications[10-13].

Recently, there is an upsurge of researches concentrate on the candidate mechanism of the TES induced benefits[14-16]. It has been proposed that multiple mechanisms would be responsible for the remarkable effects. Moreover, the exact pathway of the TES induced neuroprotective effects seem to vary among different pathology types. These investigations

delineate the precise mechanism underlying the pathophysiological process that would be instrumental to repeat the experimentally attained effects, and enhance clinical efficacy. In the present paper, the implementing measures of TES, beneficial effects on various disease categories, together with related mechanism and cellular principles, are systematically reviewed.

TRANSCORNEAL ELECTRICAL STIMULATION APPLICATION

The TES is readily available and relatively practicable: a bipolar contact lens electrode or a microfiber DTL electrode is placed on the cornea of the subjects after superficially anesthesia, and then the electric current pulses that generated by an electronic pulse generator are delivered through a stimulus isolation unit; another inactive electrode is placed on the skin around the eye to act as the reference electrode.

The existence of an optimal stimulated protocol that generally applies to all subjective species is not realistic. The stimulation parameters such as the pulse duration, current intensity, stimulation frequency, stimulation duration, and repetition times should be adjusted reasonably, and varied according to pathological types and subjective species [8,11]. For example, the suggested current intensity of TES for photoreceptor protection in rats (300 μA, 3ms/phase) is higher than that for RGCs survival (100 μA, 1ms/phase)[7,17]. In human, the threshold intensity should be adjusted necessary to elicit phosphenes in both the peripheral and central visual fields, and generally range between 300-900 μA [18]. A positron emission tomography (PET) study found that TES resulted in retino-topographically matched primary visual cortex activation and led to visual perception in both normal-sighted controls and retinal degenerative patients. However, the threshold current needed to evoke phosphene is significantly higher in the retinal degenerative subjects compared to normal-sighted controls [19]. On the other hand, chronically high intensity stimulus is not proposed for the potential damage to retinas or corneas. Therefore, advisable TES protocols for individual patients should be designed to attain optimum therapeutic benefits and to exclude possible side effects.

Transcorneal Electrical Stimulation Induced Protection Against Photoreceptor Degeneration RP is a hereditary disease characterized by the progressive photoreceptor degeneration and no satisfactory therapy exists thus far[20-21]. TES can alter the electrical activity or electrical charge balance of photoreceptors and exert a neuroprotective effect on the degenerative retinas. It has been demonstrated that TES promoted the survival of photoreceptors and preserved the retinal function of the Royal College of Surgeons (RCS) rat, a hereditary RP animal model [6]. The fundus was examined at the end of the experiments, and neither retinal detachment nor vitreous hemorrhage was observed in these TES treated eyes, indicating that the TES was harmless to the vitreous or retinal tissues in the RP models and providing positive safety profiles for the TES therapy. In another transgenic RP model-the rhodopsin P347L transgenic rabbit, the TES was also proven to be effective, implying that this protection on the degenerative retina was independent of the initiated mutation cause[22]. Intriguingly, different photoreceptors showed different sensitivities to the TES: the ERG examination found that TES preserved the cone components better than rod components of the treated rabbits.

Although the safety and efficacy of TES may be easily verified and more readily acceptable in RP animal models, it remains challenging to prove these virtues in RP patients. The natural course of disease progression in RP patients can be highly variable as the tremendous heterogeneity implied in the initiating mutation: sometimes with years of stagnation at any level followed by sudden worsening, sometimes occurring rapidly within weeks [23-24]. This fact and the decades-long, heterogeneously genetically determined degenerative processes make RP inherently difficult to prove therapeutic efficacy of any treatment. So far, only a prospective, randomized, sham-controlled preliminary clinical trial with a sample size of 24 RP patients could be referred: the positive trends in the vision field (VF) area and scotopic electroretinogram (ERG) were found in these TES treated patients compared with the sham controls [10]. Furthermore, they found that the application of 30min TES weekly of for 6 consecutive times was tolerated well and the investigator suggested the TES induced benefits in RP patients should be transferred to other ocular diseases cautiously, especially to those in which growth factors play an important role, such as diabetic retinopathy or age-related macular degeneration (AMD).

The popularized mechanism suggested to explain the neuroprotective effects is that TES could up-regulate the expression levels of endogenous neurotrophic factors, and simultaneously enhance the neurons' intrinsic sensitivity to these factors. After TES, the mRNA and protein levels of insulin-like growth factor-1 (IGF-1), brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), and vascular endothelial growth factor (VEGF) increased significantly in the Müller cells, which were crucial to activate the intrinsic survival system and maintain the microenvironment homeostasis [6-7,13,15,25]. Moreover, the thinning of the vascular plexus and the obliteration of vessels in the RP retinas would drastically restrict the retinal blood circulation and relate to the nourishment deficiency. In view of this fact, the vasodilatory function of TES may also contribute to the neuroprotective effects in the RP [21]. On the other hand, TES could increase the expression levels of the B-cell lymphoma 2 (Bcl-2), while down-regulate the expression levels of Bax and tumor necrosis factor (TNF)

super family in degenerative retinas [7,26]. These bioactive factors act as key executors of the photoreceptor apoptotic program and indicate that the TES could rectify the abnormities in the apoptotic cascade, thereby preventing themselves from programmed death. Also, a regulation effect of TES on the activator protein 1, an initiator of photoreceptor degeneration, may also be involved [27-28]. Apoptosis is as recognized as the final common death pathway in all RP phenotypes, although tremendous genetic heterogeneity exists in this disorder. The existence of a common cell death mechanism (*e.g.* apoptosis) triggered off by different gene defects may provide a mutation independent therapeutic target which could be generalized to RP patients with different etiologic causes. Therefore, TES may act as a more promising and general strategy for RP treatment in the future.

Chronic inflammation is considered to be another etiologic factor of RP, although, it is still unclear whether it is a central or minor contributor to the RP pathogenesis [29-30]. More recent studies have highlighted the activation of microglia in RP retina preceding photoreceptor death: the highly toxic and inflammatory microglia phenotype, which is designated as the "activated state", can release a variety of highly inflammatory cytokines, reactive oxygen species, nitrogen intermediates and excitotoxins, which are hazardous to photoreceptors [31-33]. Additionally, activated microglia could influence the secondary neurotrophic factor expression in Müller glial and indirectly modulate photoreceptor survival [34]. Thus, restraining the proinflammatory secretion of microglia and "resting" the superactivated microglia are crucial to arrest the photoreceptor degeneration in RP retinas. Recently, an *in vitro* study found that the application of trans-culture well electrical stimulation could ameliorate the light-induced photoreceptor degeneration *via* suppressing the proinflammatory effects of the microglia [14]. These exciting results suggest that the electrical stimulation is anti-inflammatory, and if it is applied *via* the trans-corneal pathway, the chronic inflammatory response of the RP patients might be ameliorated. These possibilities remain to be verified by further clinical investigations.

Moreover, the TES was also shown to be beneficial in the best vitelliform macular dystrophy (BVMD), an atrophy of the retinal pigment epithelium which then affects the photoreceptors and leads to an impairment of central visual function [35]. The case report showed that the best-corrected visual acuity (BCVA) significantly improved for 2mo after only two TES treatments. Consequently, both the clinical case reports and laboratory evidences strongly indicate that TES is a safe, effective, and readily available approach to protect against photoreceptor degeneration. Further large case series studies with longer durations are be necessary to establish TES as a popularized therapeutic modality for retinal and optical nerve disorders.

Protective Effects of Transcorneal Electrical Stimulation Against Ischemic Retinal Diseases RAOs usually lead to permanent retinal damages and functional impairments, and in which the central retinal artery occlusion (CRAO) act as especially terrible impediments due to the blockage of retinal blood flow to the macula. Clinically studies have found that TES improves visual functions in both the CRAO and the branch retinal artery occlusion (BRAO) cases[13,18]. Examined with the Humphrey field analyzer, it was found that even these longstanding cases had at least 3 dB augments in the mean deviation of the visual fields after TES treatment. More importantly, multifocal electroretinograms (mfERGs) examination showed that the amplitudes and implicit time of all component waves were improved after the TES treatment, indicating that TES had beneficial effects on both the inner and outer retinal neurons of these RAO patients.

The ability to attenuate the glutamate-mediated excitotoxicity in retinas could act as one of the potential mechanisms that contribute to the TES induced neuroprotective effects. Excessive exposure to glutamate is an essential element to trigger a self-reinforcing destructive cascade involving calcium influx and oxidative stress in the retinas[36-37]. A novel investigation indicated that TES can protect RGCs against ischemic insults in an ocular hypertension-induced retinal ischemia model, and the markedly functional and morphological restorations are closely related to the increasing levels of glutamine synthetase (GS) localized in the Müller cells [8]. Induction of GS expression protects against neuronal degeneration while inhibiting GS activity causes neurons more susceptible to injuries [38-39]. These experimetal evidences verified that TES can affect the glutamate metabolic process by enhancing the expression of GS, and thereby alleviated the ischemic retina from glutamate-mediated excitotoxicity[8].

Another underlying mechanism responsible for the TES induced protection against ischemic retinal diseases would be the vasodilation effects. TES could increase the retinal blood flow and improve the visual impairment induced by ischemic insults [12]. A sham controlled study based on the healthy human subjects suggested that a single application of TES increased the retinal blood flow within 30min and persisted for at least for 40h while minimal effect was found on the systemic blood circulation and the intraocular pressure (IOP). This vasodilation effect is sustainable and the investigator hypothesized that TES might stimulate the synthesis of some molecules to mediate the dilation of retinal vessels.

Neuroprotective Effects of Transcorneal Electrical Stimulation Against the Optic Neuropathy Electric stimulation is known to trigger off axonal regeneration, axon sprouting and promote RGCs survival [40-41]. *In vivo* studies

based on the optic nerve crush (ONC) rat model displayed that TES significantly delayed the post-traumatic RGCs death and the optic nerve benefited in long-term from TES treatment [42]. TES could reduce ONC-associated neuronal swelling and shrinkage especially in RGCs which survived in long-term. TES would not only delay degeneration dynamics, but also change the pathophysiology of early post-traumatic processes as indicated by the less affected soma size of RGCs. Morimoto *et al* [9] reported that TES could rescue the axotomized RGCs and promote the axonal regeneration of injured RGCs in rat retinas. They defined in more detail the stimulation parameters which lead to the most effective neuroprotection against optic nerve cut. Miyake *et al* [43] reported that a single TES given immediately after partial optic nerve injury can induce a rapid functional recovery of visual evoked potentials (VEPs) within hours and protect RGCs axons from the ensuing degeneration with slower time course.

In a clinical setting, such a delay of posttraumatic cascades and an induced stability of the neuronal morphology would be advantageous to provide additional time-window for early post-lesion therapeutic intervention. A recent clinical study already verified that TES could improve the visual function of the patients with traumatic optic lesions (TON) or nonarteritic ischemic optic neuropathy (NION) [11]. An improvement in visual acuity was defined as a change of > or =0.3 log minimum angle of resolution (logMAR) units and it was found in two patients with NAION and in four patients with TON. This visual function recovery was relatively modest, and could be partially due to the duration of TES application from the onset was late.

Neuroprotective Effects of Transcorneal Electrical Stimulation on the Light Induced Retinal Injury Excessive exposure to light induces irreversible visual dysfunction and photoreceptor degeneration partly resembles that of RP and AMD patients. Moreover, the light induced photoreceptor degeneration proceeds relatively faster and in a more synchronized way than that of the hereditary mode. Therefore, this reproducible model is now universally utilized in the explorations of photoreceptor degeneration[44-45]. A sham-controlled study showed that TES can protect photoreceptor against mild light-induced degeneration in the Sprague Dawley rats [46]. Recently, Ni *et al* [7] reported the TES induced anti photo-toxicity effect might stem from the modulation of an imbalance between the intrinsic survival system and the apoptotic cascade signaling. Neutralizing this subtle imbalance could block crucial steps in the programmed cell death to maintain cellular homeostasis, which had been suggested as a key element for the TES induced neuroprotection. Furthermore, TES resulted in the down-regulation of proinflammatory cytokines which also constituted a nurturing environment suitable for the survival for the light damaged photoreceptor cells[14]. In greater detail, it was found that TES provided better preservation in the central retina than the peripheral retina, and this regional difference may be caused by the asymmetrical distribution of the relative low-density current as it preferred to go through the vitreous *via* a low-impedance path such as the optic nerve, which is located in the central retina [7]. Another assumption is a better intraretinal circulation and higher expression of neuroprotective factors in the central retina after TES. It is especially noteworthy that BDNF might act as the most important molecules than other Müller cells derived factors to facilitate the survival of photoreceptor cells in light damaged retinal[7].

An *in vitro* study on the light-induced photoreceptor degeneration suggested that electrical stimulation had a prominent inhibitive effect on the microglia secretion of interleukin (IL)-1β and TNF-α [14]. Furthermore, electrical stimulation significantly restrained the light-damage induced microglia activation and promoted the trophic Müller cell reaction, as verified by the decreased the numbers of ameboid shape microglia cells and the increased numbers of reactive Müller cells. These findings indicate the potential anti-inflammatory mechanism is involved in the neuroprotective effects of electrical stimulation, and it would be rational to create a nourishing microenvironment that characterized by the diminished microglia activation and the fortified Müller cells reactive gliosis[47-48].

The Primary Principle of the Transcorneal Electrical Stimulation Induced Cellular Activation Several physiological investigations sought to clarify the primary principle by which the electrical stimulation activates retina neurons and exerts beneficial effects on retinal neurons. The most plausible theory is that electrical stimulation could change the functional status of retinal neurons by adjusting the activity voltage-gated ion channels. The retinal neuron membrane is rich of the voltage-gated ion channels, which are reactive to extracellular electric changes and leading a central role in the visual signal transmission [49-52]. For example, it has been verified that the electrical stimulation enhances the Ca^{2+} influx through the L-type voltage-gated channels and triggers off neurotrophin exocytosis [25]. Moreover, the Ca^{2+} influx can activate an anti apoptotic cellular pathway [53]. Therefore, it seems feasible that TES induces calcium influx in the retinal cells by activating the voltage-gated Ca^{2+} channels, and thereby initiate the Ca^{2+} mediated neuroprotection. Additional pharmacological experiments using various channel blockers are needed to explore whether the functional mechanism of the TES conform to this rule.

Recently, an electrophysiological study was established on the base of optic imagining technique. It was found that the TES induced reflectance changes in the retinal neurons

represented the secondary hemodynamic responses to neural activity [54-55]. Therefore, it can be deduced that TES does not activate the retinal neurons or vessel independently. On the contrary, it might extensively act on the "neurovascular coupling", which stands for the fundamental relationship between the neural activity, blood flow, and cellar metabolism.

DISCUSSION

There is an upsurge of interests concentrate on the mechanism of the TES induced protective effects against the retinal and optic pathology [13-14,26,48]. Generally, five theories are prevailing: 1) vasodilatory mechanism; 2) neurotrophic mechanism; 3) anti-apoptotic mechanism; 4) anti-glutamate mechanism; 5) anti-inflammatory mechanism. However, the exact pathway responsible for the TES induced neuroprotection has not been determined definitively. On one hand, the exact mechanism underlying the TES induced neuroprotection seems to be varied according to the specific pathology type. On the other hand, multiple mechanisms might collectively contribute to maintain cellular homeostasis and promote cell survival. For example, at least three potential protective mechanisms should be responsible for the anti phototoxicity effects of TES: TES simultaneously regulates the expression of both apoptosis-associated genes and retinal neurotrophic factors to neutralize the intrinsic survival microenvironment of light damaged retinas. Meanwhile, the TES-induced anti inflammatory effects are also involved in the whole amelioration process. These experimental and clinical studies might have considerable impacts on the potential use of TES to protect the retina and optic nerve from trauma or diseases.

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