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EDITORIAL

Electrical stimulation — a therapeutic strategy for retinal and optic nerve disease?

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Introduction

Since Galvani's experiments with frog legs in 1791, we know that neural tissue can be readily excited by electrical currents. Doctors have utilized the therapeutic potential of electricity ever since, with such lasting achievements as cardioversion and defibrillation. In ophthalmology, one of the earliest scientific mentions of electrical currents is from Henri Dor in 1873 [1]. He used complicated machines for the treatment of "amblyopia and amauroses", "retino-choroiditis with pigment infiltration", "glaucoma", and "white optic atrophy" — following a tendency of a technology minded era when electrical currents were praised for all kinds of ailments. His experiments and studies, however, fell into oblivion in the following decades at the beginning of the twentieth century, with giant progress of scientific medical practice in many other areas. Electrical stimulation of the visual system was re-discovered in the 1970s for elicitation of visual percepts, or phosphenes, by supra-threshold stimulation [2]. These experiments constituted the basis for retinal implants which today allow patients to recognize letters and shapes in laboratory and natural settings [3, 4]. During the course of these trials, the therapeutic potential of sub-threshold electrical stimulation was detected in 2004 by Chow [5] in patients carrying an inactive subretinal prosthesis which produced only sub-threshold currents. His patients experienced amelioration of their residual vision even in retinal areas far from the implant. This effect was attributed to the release of neurotrophic factors, and various groups worldwide started to explore the therapeutic potential in animal experiments and in human trials. For practical reasons — such as ease of use and availability — application of currents through corneal electrodes has been widely adopted since then, coining the term transcorneal electrical stimulation (TES). Various types of contact lens-electrodes or DTL-electrodes deliver currents to counter-electrodes, usually integrated in the corneal electrode or on the periorbital skin, to ensure good transretinal currents. More than 20 peer-reviewed publications in PubMed in the last 5 years are evidence for this renewed interest in electrical stimulation of ocular tissue.

Animal experiments

Around the world, research groups have found support for the beneficial effects of electrical stimulation on the retina and optic nerve in animal models. They produced strong support in vivo and in vitro that degenerative processes in Royal College of Surgeons (RCS) rats [commonly used as a model for retinitis pigmentosa (RP)] can be markedly slowed by electrical stimulation [6–8]. They have also collected evidence for enhanced survival of ganglion cells after optic nerve injury [9–13] (crush or axotomy), for increased survival of different retinal cell populations after light-induced retinal damage [14, 15], and for increased cell survival in ischemic rat retinas [16]. Likely mechanisms, elucidated in these experiments, include advantageous regulation of neurotrophins such as endogenous insulin-like growth factor (IGF)-1 [10, 14, 17] and Fgf2 [18], involvement of B-cell lymphoma 2 (Bcl-2)

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protein and co-factors of the BAX family [19], members of the tumor necrosis factor family [19], ciliary neurotrophic factor (CNTF), and brain-derived neurotrophic factor (BDNF) [14].

Clinical studies

In humans, Kurimoto has shown that TES increases choroidal blood flow [20], a mechanism that may further underlie the effects of TES. Fujikado reported on efficacy of a single stimulation session in eight patients with nonarteritic ischemic and traumatic optic neuropathy [21]. Inomata treated three patients with longstanding retinal artery occlusion, and found benefits in visual acuity and visual field area [22], and Oono has detected amelioration of multifocal ERG parameters and visual field parameters in his series of eight patients with fresh or longstanding branch retinal artery occlusion (RAO) [23]. Controlled, randomized and partially blinded short-term studies are available for RAO [24] and Stargardt's disease [25]: 12 patients in each study were divided into three subgroups according to stimulation strength in relation to the individual phosphene threshold (0%, 66%, or 150%). After a 6-week period of weekly stimulation, a small but statistically not significant positive trend was seen in the 150% group. In a similar design with 24 patients with RP, Schatz et al. found statistically significant improvements in visual field area and the b-wave of the scotopic electroretinogram in the 150% group [26]; other parameters in this study mostly improved, but two parameters also worsened non significantly. In age-related macular degeneration, no scientific data in peer-reviewed journals are available.

Current status and perspective

While data from laboratory animals with different disease models show a clear beneficial effect of electrical stimulation on the retina and optic nerve, data from human trials appear less strong with mostly anecdotal character, lacking randomization and/or sham control. For RP, data are available from a study conducted according to good medical practice, but this study only lasted 6 weeks, and included only eight patients in the group for which efficacy has been shown. Nevertheless, several companies advertise stimulation devices and electrodes for use in RP and AMD. However, as prescribing doctors we should not get confused but offer our patients only well-proven and safe therapies. Required are well-designed studies with clear endpoints, reproducible stimulation paradigms, long enough duration and high statistical power. Some of these studies are already under way, and their rigorous scientific analysis will hopefully decide in the near future if electrical stimulation will have a place in the therapy for retinal and optic nerve disease in our era of evidence-based medicine.

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