Electronic Approaches to Restitute Vision in Patients with Neurodegenerative Diseases of the Retina

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Key Words

Neuroprosthetics · Hereditary retinal degenerations · Retinal implants · Artificial vision · Retinitis pigmentosa · Subretinal implant · Epiretinal implant

Abstract

Degenerations of the outer retina are hereditary diseases leading to significant loss of vision. Several concepts of active electrical stimulation of the remaining retinal network resulted in the development of retinal visual implants and prosthetic vision. Subretinal and epiretinal visual implants are currently the leading approaches in restoring functional vision in blind humans with retinitis pigmentosa or other outer retinal degenerations. This review gives a short overview about the principles, advantages, limitations and vision outcome of the up-to-date published artificial vision by electronic visual implants, as well as their known biocompatibility and safety issues.

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Introduction

The research on restitution of vision in neurodegenerative diseases is still in its early stage, although several approaches have reached the phase of clinical trials. Besides gene therapy [1–5], electronic implants have been

shown to restore functional vision in end-stage patients with hereditary photoreceptor degenerations; two of them – the subretinal implant Alpha IMS and the epiretinal implant Argus II – are registered medical devices. Other approaches are still in their preclinical stages: photoreceptor transplantations and stem cells, optogenetics or neuroprotective compounds. Photoreceptor transplantation in murine research uses retinal stem cells, which are transferred into the degenerated retina where they show integration and partial differentiation into functional retinal neurons [6–8]. In humans, however, retinal stem cells are not available postnatally anymore; thus, induced pluripotent stem cells derived from adult somatic cells have been examined [9]. Optogenetic approaches attempt to activate neurons by light stimuli; in eyes with a degenerated outer retina, the remaining cones or cells of the inner retina can be made light sensitive. Proof of principle has been established in animal experiments but light sensitivity is still several orders of magnitude lower than that of cones [10–12]. Neuroprotection in retinal degenerations includes electrostimulation [13], which is believed to release endogenous growth factors (e.g. brain-derived neurotrophic factor, ciliary neurotrophic factor) or encapsulated cell technology, where capsules filled with cells that produce growth factors are inserted into the vitreous of patients with retinitis pigmentosa or geographic atrophy [14, 15]. Also synthetic retinoid administration is used to replace 11-*cis*-retinal, a

key biochemical component of the visual retinoid cycle [16, 17].

In this review we discuss the most important features of the currently known retinal implants, as well as other electronic prosthetic vision, their advantages and disadvantages, functional outcome and limitations. Detailed reviews covering wide ranges of literature on retinal prosthetic vision have been published recently by Weiland et al. [18] and Guenther et al. [19]. However, from the rapidly growing clinical experience in ongoing clinical studies, further new results are known today.

Electronic Retinal Implants

Electronic retinal implants are developed to replace the photoreceptive function of the human eye by light-dependent electrical stimulation of the inner retinal layers and thus to treat blindness in degenerations of the outer retina [18–21]. Given the fact that the high density of photoreceptors in the fovea cannot be achieved by microelectronic devices, they are neither able to restore full visual acuity nor all visual functions, but are intended to transform blindness into low vision. Although there are several types of retinal implants, in general all of them contain an image capture unit (e.g. a microphotodiode array or an external camera) and an array of electrodes for stimulation of the inner retinal neurons to mediate the luminance and spatial information of images. The most commonly used categorization of retinal implants is based on their localization: epiretinal, subretinal or suprachoroidal. In the following review all three types are presented with emphasis on the subretinal Alpha IMS and the epiretinal Argus II.

Subretinal Visual Implants

Subretinal implants are placed in the natural localization of the photoreceptors. They can be divided into passive [22, 23] (driven by the light of the image itself), and active [24–26] (with external power supply). In most of them, the photoreceptive component and the electrode array are combined into one subretinal chip; the number of independently working pixels (photodiode-electrode units) in published reports varies between 200 [26], 512 [2], 1,500 [24, 25], and 5,000 [22]. Because the energy of the incident light necessary for the luminance-current conversion in a single pixel is not sufficient, passive implants turned out not to be able to mediate a meaningful perception, unless they have an additional unit (e.g. near-to-infrared light conversion system [23]). No passive vi-

sual system is in use at present. In active subretinal chips, the incident luminance is converted into a graded electrical current via amplifiers in each pixel, thus creating pixel by pixel an electronic image to be transmitted to the bipolar cells (fig. 1). The image is perceived in shades of gray.

With subretinal photodiode systems, however, no light adaptation as in natural vision is possible. Instead, e.g. in the subretinal implant Alpha IMS [25], the microelectronics can be controlled externally, allowing a shift of the luminance versus the current output curve along several logarithmic units of luminance. The patient him/herself can therefore manually improve his/her contrast vision under various luminance conditions.

One of the main advantages of subretinal implants is the relatively natural feeling of perception. This is due to the fact that the remaining visual pathway from the bipolar cells onward is used and the information processing in the inner retina can be utilized. Indeed, patients describe that the vision that is perceived is similar to the natural one [25, 27]. Also with the photoreceptive array being inside the eye, natural eye movements are used, which is very important for a natural use of vision and is in contrast to systems with cameras attached to spectacle frames, where head movements are necessary to find the object of interest. Additionally, ocular microsaccades allow for constant refreshing of the retinal images. Furthermore, the number of pixels creating the electronic image in subretinal implants is the highest of all visual implant devices developed so far. This allows for a higher resolution of vision and more potential for the functionality of vision.

To date, only two types of the subretinal visual implants have been applied in human pilot or clinical trials [22, 24, 25]. First, the passive artificial silicone retina (by Optobionics, Ill., USA) was implanted in a series of patients with retinitis pigmentosa, followed by an improvement of the central residual vision such as ETDRS letter recognition, colour recognition, and visual fields [22]. However, these effects were most probably caused by endogenous neurotrophic factors released as a consequence of the chip-mediated retinal electrostimulation in the retinal periphery. Second, the active subretinal implant Alpha IMS (Institute for Microelectronics Stuttgart; produced by Retina Implant AG, Germany) was applied in the authors' group in 11 blind patients in a pilot trial [24, 28] and in 9 blind patients in an ongoing multicenter clinical trial [25, 27]. The chip is able to mediate various visual functions measured by standardized tests [24, 25] (improvement of light thresholds, light source

Fig. 1. Three principal approaches to retinal implants to replace photoreceptor function: epiretinal (bluish; colors in the online version only), subretinal (yellowish) and suprachoroidal (greenish); adapted from Zrenner [21].

detection, repeatable visual acuity with Landolt C rings up to logMAR 1.43, grating acuity up to 3.3 cycles/degree or motion detection up to 35 s/degree), as well as reading of letters [24, 25] and visual experiences in daily life [25, 27]. Most of the patients consider the regained visual functions in their daily lives as subjectively useful, reporting recognition of facial and clothes characteristics, detection and identification of items at their homes or offices, seeing street or car lights at night or localizing objects in unknown environments such as in restaurants [25, 27].

Biocompatibility and safety aspects of subretinal implants have been an issue of earlier publications; animal studies showed a good biocompatibility [29, 30] of the subretinal array. In human postmortem histological preparations, the retina overlying the passive chip artificial silicone retina did not show any differences to the adjacent retina or the other eye [31]. Further, there were no signs of infection, inflammation, rejection, retinal detachment, neovascularization or retinal vascular drop-

outs in the 6 patients during 18 months [22, 31]. The active subretinal implant (Retina Implant AG) causes no significant increase in retinal dropouts, caliber alterations of the capillaries, neovascularization or leakage in a fluorescein angiographic follow-up of up to 4 months [32]. However, a significant increase in microaneurysms is known to occur on the surface of the active chip, possibly as an adaptation mechanism for the regained inner neuronal activity and metabolism or a relative ischemia sign [32]. Safety observations from long-term usage of a subretinal implant have not been published yet.

Mathieson et al. [23] have proposed a new passive device using a photovoltaic subretinal prosthesis, in which several silicon photodiodes in each pixel receive power and data directly through pulsed infrared illumination; their output current directly stimulates neighboring neurons. In this way they overcome the fact that incident light at a given retinal point is 1,000 times too weak to generate a signal in the neuronal chain, via a small single solar cell. Instead each pixel contains 3 photodiodes, arranged cake-

like, that are serially connected in each pixel. This is in principle similar to the natural photoreceptor that stacks thousands of tiny disks filled with light-sensitive rhodopsin molecules to increase light sensitivity. Still the sensitivity of serially connected triple-photodiode pixels is so low that they need a near-infrared laser image projection in a massive goggle-like system that produces pulsed illumination (880–905 nm) of sufficient intensity to drive such photodiode arrays. Despite a convincing proof of concept, the application of their approach in man may still be a number of years away, as biocompatibility with retinal tissue, biostability of the material, and safe surgical procedures have yet to be firmly established. Moreover the proposed goggles that provide high brightness images to the subretinal photovoltaic array need to be developed in such a way that they stimulate the subretinal array spatially correctly through the pupil, despite continuing eye movements; it will be a challenge to get the high energy radiation of the goggles safely to predetermined retinal locations of a moving blind human eye but this may be possible.

Epiretinal Visual Implants

The surgical placement of the epiretinal implants is intraocular on top of the ganglion cell layer, the electrode array is usually fixed to the retina with retinal tacks. Here the ganglion cells are stimulated directly, whereas the image information comes from an external camera mounted on glasses and is mediated wirelessly via an inductive coil to the intraocular electrode array. Bypassing the bipolar cells requires transformation electronics for signal generation for direct ganglion cell stimulation. All epiretinal visual implants are provided with an external battery system for power supply [33–36].

Technically, the external camera capturing the image allows for magnification and zoom. This enables an optimization of the functional artificial vision despite a relatively low number of pixels in the electrode array (ranging from 16 to 60 [33, 35–37]). The external camera also eliminates natural eye movements from the vision process, which may result in perception fading due to missing microsaccades refreshing the retinal image. A big advantage of the epiretinal system is its stability. In recently reported interim results from a multicenter clinical trial using Argus II (Second Sight Medical Products Inc., Calif., USA), the follow-up period of implanted patients reached up to 2.7 years and 94.4% of the electrodes remained functional throughout the study [33]. Also, the implantation in the epiretinal space is less extensive than in the subretinal case, the median implant surgery time is about 4 h [33].

To date, human clinical trials with only two types of epiretinal implants have been published [33, 35–37]. Both systems can elicit phosphenes, but functional vision has been reported only for the Argus I and Argus II prostheses (Second Sight Medical Products) [33, 37]. With the implant, light source localization improved (for 96% patients), as well as motion perception (for 57% patients), grating acuity was measurable up to 1.8 logMAR, but so far no standard visual acuity tests with optotypes were possible [33]. Tasks of mobility and orientation are performed significantly better with the system switched on and use of the implant in daily living was possible.

The safety of epiretinal implants has been published from two human application trials with follow-ups of 4 weeks to over 2 years [33, 35, 36, 38] and an animal study observation with implantation time of 3–8 weeks [34]. Clinically, there were some retinal detachments needing surgical interventions, isolated cystoid macular edema or epiretinal membranes, as well as proliferations around the retinal tacks [33, 35, 36, 38]. In the case of epiretinal implants no signs of vascular ischemia in fluorescein angiography were described, albeit during only 4 weeks after implantation [38].

Suprachoroidal Implants

In suprachoroidal transretinal stimulation the electrode array is placed on the other side of the choroidea [39]. This enables a less extensive implant surgery. Substantial basic research is being performed in vitro and in rabbits [40–42]. Bionic Vision in Australia has reported about their first clinical trial in 3 patients with a cable-bound suprachoroidal array [43].

Cortical Prosthesis

Following the early work of G. Brindley in the late 1960s [44], several groups attempted to stimulate the primary visual cortex, using fine wire electrodes that were inserted into the area V1 for the purpose of restoring vision in blind patients [45, 46]. A major limitation of this work is the development of an image-processing system to convert an electronic image captured by a camera into a real-time data stream for stimulation of the implanted electrodes in a way that can be ‘understood’ by the cortical neurons. Flexible arrays with penetrating electrodes have been developed (Utah Electrode Array [47]) that have been tested in various animals including monkeys. It is, however, not yet clear to which extent such approaches can provide useful vision.

Other Electronic Implants

Cuffs around the optic nerve with electrodes stimulating optic nerve fibers have been implanted in 2 patients [48, 49]. Reliable phosphene perception, recorded visual evoked potentials and grasping for objects with little training were reported [48–50]. However, this approach has not been pursued further, probably due to the rather extensive surgery and the low spatial resolution. Also optic nerve stimulation by implanting microelectrodes onto the head of the optic nerve [51] and extraocular electrical stimulation [52] were tested. At the University of Wisconsin a device has been developed that delivers spatially structured input to the tongue via a matrix of electrodes worn inside the mouth [53]. Using a camera, a computer and the input device, individuals who have been blind for their whole life are able to use this relatively simple and

noninvasive device to recognize basic patterns (Brain-Port-Technology by WIBCAB).

Presently there are only 2 clinical studies with visual implants worldwide going on, the Argus II and the Alpha IMS studies, both registered medical devices. So far it can be predicted that electronic retinal implants will finally be available for the blind for restitution of visual abilities that are truly useful in daily life. However, the competing approaches will have to undergo the test of time.

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