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Abstract Title: Subretinal Implants for the Restitution of Vision in Blind Patients
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Several concepts have been developed how to restore vision in blind or visually impaired persons by implanting electronic devices into the eye or around the optic nerve or into the visual cortex in order to evoke useful visual sensations. Since 1995, our consortium has worked on subretinal silicon "chips" and has meanwhile developed a so-called "active" retinal microphotodiode array (MPDA), based on in vitro measurements and in various animal models (Schwahn et al.2001).

In vitro experiments with chicken and RCS rat retinæ in a sandwich technique, in which recordings are made by means of multielectrode arrays either from the inner or the outer retina (Zrenner et al, 1999; Stett et al, 2000) revealed:

- (1) charge injections of about 1 nC per electrode are sufficient to excite post-receptoral retinal neurons;
- (2) electrode distances of 50-150 µm in the outer retina can be resolved in ganglion cell recordings;
- (3) retinæ with completely degenerated photoreceptors (RCS rats, 160 days and older) can still be excited by subretinal electrodes in a proper spatially organized manner;
- (4) surface coating of MPDAs as e.g. with laminins can improve cell adhesion and biocompatibility (Guenther et al, 1999).

In vivo experiments revealed:

- 1) inner retinal layers are well preserved in the central retina, as shown by comparative histological studies of human and animal forms of degenerative retinal disorders (see Zrenner et al., 1997);
- 2) Two surgical approaches for safe introduction of the devices have been developed: (a) ab interno: via the classical transvitreal access to the retina, and (b) ab externo: via a scleral flap near the limbus through the subretinal space (like in a tunnel) to the back of the eye (Sachs et al. 2005 and ARVO 1999, Shinoda et al. ARVO 2004);
- 3) inner retinal layers are well preserved after long term implantation of subretinal MPDAs in pigs (up to 28 months);
- 4) MPDAs remain fixated at stable subretinal positions as investigated in both, rabbit and pigs;
- 5) MPDAs initially showed some damage of the silicon oxide surface of the implant. A suited coating had to be developed;
- 6) spatially sensitive electrically evoked cortical potentials recorded with multielectrode and optical recording from the visual cortex of rabbit and pig following acute electrical subretinal stimulation via electrode foil strips reveal a spatial resolution of at least 1 degree (Eckhorn et al. 2006).

From these findings the characteristics of an active subretinal implant were determined that is suited for implantation in the human eye. Presently a clinical study is ongoing, where the wire-bound MPDA is implanted for four weeks into one eye of 8 blind RP patients. The active implant consists of appr. 1500 light-sensitive cells on a surface of 3x3 mm (each cell containing an amplifier and an electrode of 50x50µm, spaced 70µm) as well as a 4x4 array of identical electrodes, spaced 280µm, for direct stimulation (DS), chronically implanted next to the foveal rim in 6 patients. MPDA ("chip") and DS array are positioned on a small subretinal polyimide foil powered via a subretinal transchoroidal, retroauricular transdermal line. Within a layer of 1/10 mm in every of the 1500 cells, there are circuits that adapt the strength of the electrical signal to the nerve cell to the strength of the brightness of the object to be seen and its surroundings. So far, no other chip has been presented that is ready for implantation with this high number of points to be resolved and it is the first active subretinal chip ever implanted in patients (see Zrenner ARVO 2006 and ARVO 2007).

Stimulation parameters for each DS electrode and chip activity and sensitivity can be controlled independently by a comfortable software that allows to transform the orientation of the visual space to the orientation of the electrode field and to set individual stimulation parameters in the stimulation box via a wireless transmitter. Moreover, all stimulation parameters and patient's "yes" or "no"-responses to each parameter are recorded automatically by a particular software. (Sailer, ARVO 2005)

For selection of patients corneal DTL-electrodes and an alternative forced choice method was used to determine electrical excitability of the retina and of optic nerve transmission in normals and patients with degenerative retinal disease; determination of phosphene threshold with corneal electrodes has turned out to provide an important criterion for the suitability of patients for electrical retinal prostheses (Gekeler et al.

2006).

A safe transchoroidal subretinal access is mandatory for a successful chronic implantation of a cable bound visual prosthesis. In order to establish the prerequisites for human implantation, results of long-term implantations in adequate animal models were performed. Domestic pigs had received subretinal cable bound stimulation devices for 6 month (Sachs et al. 2005 and ARVO 2006). The same transchoroidal procedure was applied in 6 patients without adverse events such as retinal detachment, bleeding, infection etc. (Sachs et al. ARVO 2007); radiodiathermy and a specially designed implantation instrument were used to penetrate the choroid without bleeding; silicone oil was used as a tamponade. There were no problems with transdermal cables either. OCT examinations turned out to be very valuable assessing the subretinal alignment of the device and the stability of its position in relation to the retina. OCT scans demonstrated small intraretinal densifications that corresponded in funduscopy to well demarcated changes at the edges of the chip (Kuttenkeuler et al, ARVO 2006). After explantation, which took place according to the four week study plan, the retina showed only minor changes at the implantation site. In fluorescence angiography (FA) in all patients the capillary bed was nicely visible over the implant region due to blockade of background fluorescence. In 5 patients some drop-out of the retinal capillaries was observed. Some degree of retinal microaneurysm formation and various degrees of vessel rarefactions at the region overlying the MPDA and DS were seen (Gekeler et al. ARVO 2007). One patient decided to keep the implant for a period of more than one year. FA findings remained stable, only microaneurysm formation increased in the last three months. One eye developed mild macular edema. The retina of one patient after >30 yrs of blindness did not respond to electrical stimulation within the safety limit. Four subjects had pattern recognition via direct electrical stimulation and two patients reported visual perceptions through the MPDA. The changes of retinal vascularization during the observation period were not correlated to functional outcome and even eyes with marked findings reacted to electrical pattern stimulation.

A battery of computerized, standardized tests for patients with visual prostheses was developed to quantify the functional outcome (Zrenner et al. ARVO 2004). Visual perception of brightness elicited by applying biphasic voltage impulses from 1 to 2,5V ($t = 3$ ms) was assessed using a scale from 5 (very strong) to 0 (none); additionally double impulses with differences up to 0.8V between two stimuli (10 s interval) were applied. Electrical stimulation of rows, columns and blocks of 4 electrodes allowed some patients to clearly distinguish horizontal from vertical lines and positions, respectively. Under optimal conditions, dot alignment and direction of dot movement was properly recognized, if three neighbouring electrodes were switched on simultaneously or sequentially at 1 s intervals (Zrenner et al. ARVO 2007). Brightness perception of spots varied from scale 0 to 5 in a linear manner if voltages between 1.5 and 2.5 were applied (randomly 6 times) to a square of 4 electrodes. This corresponds to a charge increase of approximately 0.23 mC/cm² for each of the 5 steps. A difference in brightness between two consecutive pulses was discerned, if a difference in charge of at least 16 μ C/cm² was applied. If equal charges were applied to both conditions, the second flash always was perceived slightly dimmer irrespective of the stimulation level. Subjective brightness amplification phenomena were observed at medium stimulation levels and at certain frequencies. The subjective size of spot perception upon stimulation of a square of 4 electrodes increased from 1 to 5 mm at arms length, if the voltage was increased from 1,5 to 2,5 V. In SLO microperimetry of the chip, single light spots down to 100 to 400 μ m in diameter were detected, allowing the patient to localize a white plate on a black table cloth correctly (Zrenner et al. ARVO 2007). Apparently subretinal electrical multielectrode stimulation can in principle provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters.

The brief symptom inventory (BSI) by Derogatis, a validated 53-item questionnaire was used for the assessment of variations in psychological stress of the patients before and during the four week study. The sum score total Global Severity Index (tGSI) was used for evaluation (Peters et al ARVO 2007). In the first six blind patients participating in the pilot trial, the BSI showed that study participation was tolerated well. At screening all subjects (mean 50.33, SD 12.17) were in the normal range of the tGSI. The difference at close out visit compared to screening (t-test: mean diff 6.17, SD 8.95; $p=0.08$) showed a tendency to lower values in a sense of better emotional balance at the end of trial participation.

In summary: Subretinal electrical multielectrode stimulation can provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters. However, it is still not clear what type of image a patient will be able to see after prolonged use of such devices. It is expected, that like in cochlear implants for hearing, the brain can learn to interpret images from their features, like in learning to interpret art sketches in normal vision.

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