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Restoring neuroretinal function: new potentials

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Several concepts of how to restore vision in blind or visually impaired persons have been developed based on 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 sub-retinal silicon "chips" and has meanwhile developed a so-called "active" retinal microphotodiode array (MPDA), based on in vitro measurements and using various animal models (Schwahn et al. 2001). This lecture will present the multitude of steps that have been necessary to apply this technique in a clinical study of seven patients showing the feasibility of this approach and thereby opening the door to new therapeutic possibilities for patients, blind from outer retina diseases.

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

- (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 sub-retinal electrodes in a proper, spatially-organized manner.
- (4) Surface coating of MPDAs (e.g. with laminins) can improve cell adhesion and biocompatibility (Guenther et al. 1999).

In vivo experiments have revealed that:

- (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 trans-vitreous access to the retina, and (b) ab externo via a scleral flap near the limbus through the sub-retinal space (like in a tunnel) to the back of the eye (Sachs et al. 2005; 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 multi-electrode and optical recording from the visual cortex of rabbit and pig following acute electrical sub-retinal stimulation via electrode foil strips reveal a spatial resolution of at least 1° (Eckhorn et al. 2006).

From these findings the characteristics of an active sub-retinal implant were determined that is suited for *implantation in the human eye*. A clinical study has been completed, where the wire-bound MPDA is implanted for 4 weeks into one eye of seven blind retinitis pigmentosa patients. The active implant consists of approximately 1500 light-sensitive cells on a surface of 3×3 mm (each cell containing an amplifier and an electrode of $50 \times 50 \mu\text{m}$, spaced at $70 \mu\text{m}$) as well as a 4×4 array of identical electrodes, spaced at $280 \mu\text{m}$, 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 sub-retinal, trans-choroidal, retro-auricular, trans-dermal line. Within a 0.1 mm layer, each of the 1500 cells has 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 with a similar high resolution that is ready for implantation and this is the first active sub-retinal chip ever implanted in patients (see Zrenner ARVO 2006; ARVO 2007).

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

For patient selection, corneal DTL-electrodes and an alternative forced choice method was used to deter-

mine electrical excitability of the retina and of optic nerve transmission in normals and patients with degenerative retinal disease; this 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 trans-choroidal sub-retinal 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 sub-retinal cable bound stimulation devices for 6 months (Sachs et al. 2005; ARVO 2006). The same *trans-choroidal procedure* was applied in the 7 patients without adverse events such as retinal detachment, bleeding, infection etc. (Sachs et al., ARVO 2007); radio-diathermy 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. OCT examinations turned out to be very valuable assessing the sub-retinal alignment of the device and the stability of its position in relation to the retina. OCT scans demonstrated small intra-retinal densifications that corresponded in funduscopy to well demarcated changes at the edges of the chip (Kuttenkeuler et al., ARVO 2006). After explanation, which took place according to the 4-week study plan, the retina showed only minor changes at the implantation site. Fluorescence angiography (FA) in all patients showed that 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 in 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 1 year. FA findings remained stable, only microaneurysm formation increased in the last 3 months. One eye developed mild macular oedema. The retina of one patient after >30 years 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 2.5 V ($t = 3$ ms) was assessed using a scale from 5 (very strong) to 0 (none); additionally double impulses with differences up to 0.8 V between two stimuli (10 s interval) were applied. Electrical stimulation of rows, columns and blocks of four 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 six times) to a square of four electrodes. This corresponds to a charge increase of approximately 0.23 mC/cm^2 for each of the five steps. A difference in brightness between two consecutive pulses was discerned, if a difference in charge of at least $16 \text{ l } \mu\text{C/cm}^2$ was applied. If equal charges were applied to both conditions, the second flash always was perceived as 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 four 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 μm in diameter were detected, allowing the patient to localize a white plate on a black tablecloth correctly (Zrenner et al., ARVO 2007). Apparently sub-retinal electrical multi-electrode 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. A small b-wave-like electrically evoked retinal potential was recorded with amplitudes up to 10 mV and peak latencies near 40 ms after stimulation with short signals (0.5–4 ms) of 2.5 V.

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 4-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 ± 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 ± 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: Sub-retinal, electrical, multi-electrode stimulation can provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters and does produce a new kind of electrical retinal potentials. 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, as in cochlear implants for hearing, the brain can learn to interpret images from their features, like learning to interpret art sketches in normal vision. Nevertheless, the clinical study has shown the potential of this approach to help blind patients in object localization; active, power-driven, sub-retinal, electronic, multi-photodiode arrays thereby can improve mobility and visual communication.

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