Biohybrid Visual Prosthesis for Restoring Blindness

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ABSTRACT

A visual prosthesis is an artificial organ to restore vision in blind patients by applying electrical stimulation to the visual nervous system. For years, our research group has been studying "biohybrid" visual prosthesis, which combine the characteristics of regenerative medicine and visual prostheses. Since the mid-90's, our group has conducted basic research and system design and integration on a biohybrid visual prosthesis, that combines microelectromechanical system (MEMS) technology and regenerative medicine. In this implant, the axons of neurons cultured on the MEMS are guided toward the central nervous system (CNS) by a peripheral nerve graft. Because cultured neurons form functional connections between the MEMS and the CNS, electrical stimulation causes the cultured neurons in the biohybrid visual prosthesis to send visual information to the CNS. Our recent research has included the development of various micro/nanoelectrode arrays using MEMS technology including a conductive polymer micro/nanoelectrode array, in vitro nerve cell culture and axon guidance experiments on the fabricated micro/nanoelectrode array, in vivo electrical stimulation experiments, and various computer simulations including the psychophysical evaluation of reading ability with a visual prosthesis simulator. Our first prototype consists of an external and an internal device. In operation, visual information is captured by a video camera in the external device. After encoding, this information is then sent to the internal device through an infrared (IR) communication unit. After the internal device receives the IR data, it generates appropriate electric pulses for stimulating the cultured neurons.

Keywords: Visual Prosthesis; Biohybrid; Regenerative Medicine; MEMS; Blindness

1. INTRODUCTION

The sense of sight is important not only to see objects but also for perceiving light and darkness so that our internal biological clock works normally. Therefore, loss of sight can lead to autonomic imbalance. The development of effective treatments for blindness is urgently needed; however, the prospects for such treatments have not yet been established.

This situation leads to the research and development of visual prostheses. For more than thirty years, it has been known that electrical stimulation evokes light perception, called phosphene [1]. A visual prosthesis is developed based on this principle. While there are slight differences between research groups, a visual prosthesis should essentially restore the lost sense of sight by applying electrical stimulation to the visual nervous system [2][3]. It stimulates the primary visual cortex or nerves in the pathway from the retina to the primary visual cortex, through an electrode array of the MEMS implanted in the body. Groups in the US, Germany and Belgium have already successfully undertaken clinical experiments on volunteer blind patients to temporarily restore phosphene perception and simple-shape recognition function. Hence, the electrical stimulation of visual nervous systems is effective in restoring visual sensation.

2. BIOHYBRID VISUAL PROSTHESIS

Visual prostheses can be broadly classified into three categories, according to the Visual prostheses can be broadly classified into three categories, according to the implantation site of the MEMS; "cortical implants," "optic nerve implants," and "retinal implants." Furthermore, our research group has proposed a fourth category, "biohybrid implants," which combine the characteristics of regenerative medicine and artificial visual prostheses [4][5]. The biohybrid implants require the implantation of not only the MEMS, but also the transplantation of nerve cells (Fig. 1). Recently, it has been shown that when nerve cells and Schwann cells are together, irrespective of their origin, the visual cortex or periphery, the lengthening of nerve fibers is promoted by factors produced by Schwann cells, and myelin sheath formation occurs [6]. Hence, the biohybrid implants require the ocular implantation of the MEMS with nerve cells for transplantation attached to the surface of an electrode array. Using an artificial optic nerve prepared from Schwann cells (a semipermeable membrane tube filled with cultured Schwann cells, extracellular matrix, and neurotrophic factors), the axons of these nerve cells are guided to the higher visual cortex, connecting the MEMS with the visual cortex. That is the nerve cells are used as a "living electrical

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cable." Once the connection is complete, it is considered that nerve cells transmit signals to the visual cortex in response to electrical pulses provided by the electrode array. Because nerve cells are transplanted as part of the process of fitting this visual prosthesis, a biohybrid implant is appropriate for blind patients whose optic nerves and/or retinal ganglion cells are NOT intact such as glaucoma and diabetic retinopathy patients.

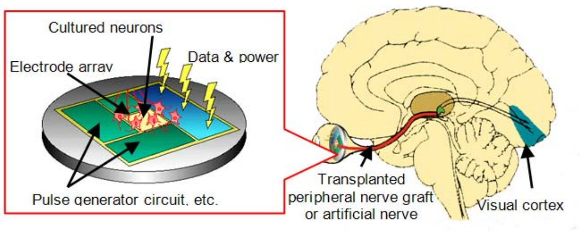

Fig.1: *Biohybrid visual prosthesis.*

Although biohybrid implants have advantages, there are many challenges related to nerve cell transplantation. Even if the axons of nerve cells can be guided to the visual cortex, unless a connection is formed between the neurons of the visual cortex and synapses, and a functional connection achieved via neurotransmitters, the signals cannot be communicated. That is the fundamental challenge for this prosthesis is the reliable reconstruction of signal transmission function between an artificial device and transplanted nerve cells, and between transplanted nerve cells and the visual cortex. For years, our research group has conducted basic research and system design/integration. The following are a brief summary of our recent achievements.

3. DEVELOPMENT OF EXTERNAL AND INTERNAL DEVICE

We have developed various types of stimulation electrode array so far. They are i) platinum electrodes on a polyimide base film, ii) platinum wire electrodes coated with epoxy, and iii) gold electrodes on a silicon wafer. It is easy to fabricate this type of electrode array by conventional batch-fabricated processes [7]. Fabrication begins using a silicon wafer of standard thickness. The wafer is first oxidized to a thickness of 1 micrometer. Over the oxidized silicon, aluminum conductors are next deposited to a thickness of 0.3 micrometers by physical vapor deposition (PVD), and then patterned by etching. Next, the entire wafer surface is covered with 1.0-micrometer-thick layer of silicon nitride for insulation, by plasma chemical vapor deposition (plasma-CVD). To open stimulating sites and bonding areas, reactive ion etching (RIE) is carried out to remove silicon nitride from those areas. Liftoff is performed to cover the exposed areas with Au/Ni. Finally, bonding areas are solder-bonded with a flexible cable. This electrode technology has been incorporated into the following first prototype.

Fig.2: *Prototype of external device (left) and internal device (right). (Courtesy: NEDO)*

Fig. 2 shows the system being developed in our project. It consists of an external device and an internal device. The external device is composed of a visor, an image processor, a data transmitter, and a primary coil for electricity transmission. The internal device consists of an IC (integrated circuit) for data reception and stimulation output, an electrode array, and a secondary coil for electricity reception. The video camera attached to the visor captures an image. After the captured image is processed to generate stimulus data, the stimulus data is transmitted to the internal device by infrared light. The IC in the implanted device receives the stimulus data, and an electrical pulse is generated based on the data. This electrical pulse is applied to the cultured neurons, and those cells would send signals to the brain and the user can recognize visual information.

4. NEURON CULTURE AND AXON GUIDANCE

In a biohybrid implant, it is the most prominent feature that the axons of transplanted neurons are used as living electric cables to form functional connections between neurons on the array and the CNS. We have confirmed that the transplanted peripheral nerve graft with some neurotrophic factors can accelerate neurite outgrowth (Fig. 3) [8]. To determine which neurotrophic factor is the most effective for outgrowth, we have performed an in vitro experiment [9]. In that experiment, a piece of a gelatin sponge containing a neurotrophic factor was placed on one side of the dish. Once the concentration gradient of a molecule could be formed, neurons might extend their neurites toward the gelatin sponge. In the experiment, several types of molecule were tested such as, 7S-NGF, p-NGF, CNTF, BDNF, NT-3, and NT-4.

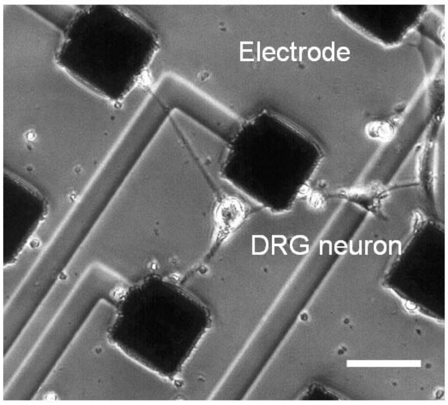

Fig.3: *Axon guidance on a stimulation electrode.*

5. ELECTRICAL STIMULATION OF NERVOUS SYSTEMS

It is important to evaluate the relationship between the specification of an electrode array and its electric charge density distribution. We have performed both an in vivo electrical stimulation experiment [10] and a computer simulation of charge density distribution around electrodes [11].

In the in vivo experiment, an electrode array was implanted into the LGN to stimulate neurons extracellularly. Then, neural responses were recorded from the visual cortex, changing several parameters of the array and simulation pulse. In the experiment, selecting a pair of different electrodes, the center distance between an anode and a cathode varied from 100 to 300 micrometers. As a stimulation electric pulse, a monophasic single current pulse was used. The parameters of pulse were "pulse duration" and "pulse amplitude." Various combinations of these parameters and anode/cathode distances were tested in the experiment.

When an electric current pulse was applied to the LGN, a biphasic potential could be recorded. For quantitative analysis, the magnitude of neural responses was defined as the difference between the maximum and the minimum of the secondary potential. Figure 4 shows the magnitude of neural responses corresponding to pulse parameters, that is, pulse amplitude and pulse duration, in three different anode/cathode distances. The gray scale of the figure indicates the magnitude of neural responses. (The brighter area shows a large response.) As shown in these figures, the magnitude of neural responses increased proportionally to pulse amplitude and pulse duration. In particular, the increase rate with respect to pulse amplitude was larger and more significant than that with respect to pulse duration. For example, a neural response depended on pulse amplitude only when the pulse duration was 0.2-1.0 milliseconds in the case of d=100 micrometers. Consequently, the response mainly depends on pulse amplitude than on pulse duration. In addition, the comparison of the three graphs shows that the neural response was not always proportional to the anode/cathode distance. Although the minimum response was recorded in the case of 100 micrometers, the maximum was observed in the case of not 300 but 200 micrometers. These findings suggest that there might be an optimum anode/cathode distance.

6. COMPUTER SIMULATION OF PROSTHETIC VISION

In developing a visual prosthesis, it is essential for us to determine its specifications that meet the minimal needs in the daily lives of patients. For this purpose, we have proposed a prosthetic vision simulator that enables us to experience prosthetic vision in the virtual space.

The vision restored by present visual prostheses will be very different from normal vision. It might be similar to an "electric scoreboard," in which visual information is represented by the blinking of many light spots, for the following reasons. By applying electricity to one electrode in the array, a large electric potential is formed around the electrode. If the potential surpasses the threshold potential of a neuron such as a retinal ganglion cell or a bipolar cell, a large number of neurons around the electrode will be excited simultaneously. Hence, an electrical stimulus through one electrode is equivalent to one uniform light in a visual field. (This single-light perception is equivalent to phosphene.) On the other hand, there are neurons that will not be stimulated because the electric pulse does not reach their location. This means that there are dark areas in the visual field of patients where no light perception can be evoked. This presumption has been supported in clinical experiments. It has been reported that an electric stimulation of the human visual nervous system, that is, the retina, the optic nerve, or the visual cortex, evokes a sensation such as the perception of "twinkling stars in the dark sky." Therefore, prosthetic vision will be a phosphene-based vision as shown in Figure 5.

Using the system, we have quantitatively evaluated the reading ability of subjects, and estimated the appropriate range for electrical stimulation [12]. Experimental results suggest that electric current amplitude in stimulation has small effects on reading ability. In the next phase, we will evaluate other abilities such as "object manipulation" or "walking."

7. CONCLUSION

Although the first prototype of the MEMS has been completed [13], there are many remaining issues that need to be resolved. The most critical problem is the interface between electrodes and neural tissues. Conventionally, rare metals, such as gold, platinum, iridium, and titanium nitride, are often used as a

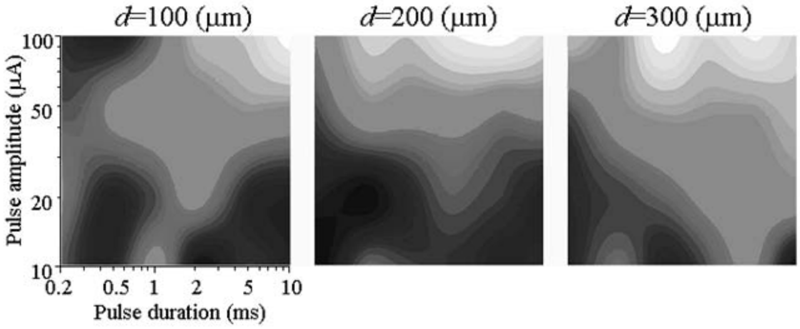

Fig.4: *Electrical evoked potential at various pulse amplitudes and pulse durations.*

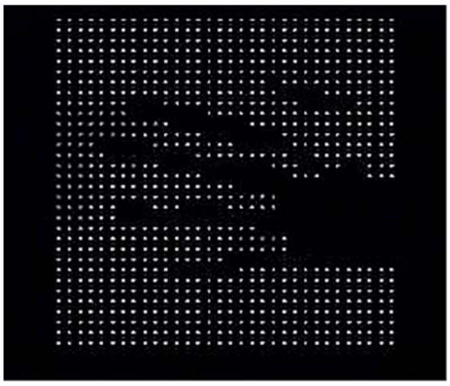

Fig.5: *Computer simulation of prosthetic vision in the case of 32×32 (=1024) electrodes.*

stimulation electrode material. The long-term use of metallic electrodes, however, induces connective tissues covering metal parts, and causes glioma aggregation and/or scar formation. Moreover, the extracellular stimulation increases the already high threshold of neural tissues, and connective tissues worsen the problem. To develop an electrode for a visual prosthesis, we have focused on conductive polymers, which are expected to improve electrical functionality and biocompatibility. Because conductive polymers are easily modified using various molecules, it may be possible to develop a conductive polymer electrode that has a high affinity to biological tissues. This electrode may be bound to neural tissues at the molecular level so that a neuron will be stimulated intracellularly or quasi-intracellularly to decrease the threshold current significantly, and the functionality and biocompatibility of electrodes will be improved. For that purpose, we have been developing the technique of micro/nanofabrication of conductive polymers, which is a photolithography technique using the photochemical reaction of oxidative polymerization agents [13]. Although the conductivity of the present electrode must be improved in further studies, we have obtained promising data in our pilot studies. In the next phase, we will perform a biocompatibility test and evaluate its functionality in electrophysiology testing.

8. ACKNOWLEDGMENT

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