IMPLANTABLE MICROFLUIDIC INTERFACE DEVICES WITH DRUG PERFUSION FUNCTION THROUGH HYDROGEL MEMBRANE

Hiroaki Takehara[1,2], Akira Nagaoka[2,3], Jun Noguchi[3], Takanori Akagi[1], Haruo Kasai[3] and Takanori Ichiki[1]

[1]School of Engineering, The University of Tokyo, Japan
[2]Research Fellow of the Japan Society for the Promotion of Science, Japan
[3]Center for Disease Biology and Integrative Medicine, The University of Tokyo, Japan

ABSTRACT

An implantable microfluidic device with a function of drug perfusion through a hydrogel membrane has been newly developed for the in vivo analysis of neural cells. The device has a hybrid structure of PDMS microchannels and a perfusion membrane made of Tetra-PEG gel, which is a high-strength biocompatible hydrogel. We also established a device manufacturing procedure fully compatible with the sterilization process. Consequently, we could observe neural cells in a living mouse brain in good physiological condition by two-photon laser scanning microscopy (TPLSM). Furthermore, we demonstrated the local delivery of model chemicals into brain tissues using microchannels in the device.

KEYWORDS

Implantable device, neural cell, two-photon laser scanning microscopy, brain, tetra-PEG hydrogel

INTRODUCTION

The observation of neural cells in the intact brain of a living animal using TPLSM is one of the most significant challenges in neuroscience[1]. We reported an implantable microfluidic device for the in vivo analysis of neural cell[2], but there is still room for improvement in the controllability of the dose amount and delivered space in brain tissues. To address these problems, we have developed an implantable microfluidic device with a drug perfusion function using a PDMS/Tetra-PEG hydrogel hybrid microchannel.

DEVICE PRINCIPLE

The device, which was designed to be implantable into a certain part of the skull to close a drilled hole, is 2.7 mm in diameter and 500 μm in thickness (Figure 1). The bottom of the microchannels (100 μm width and 200 μm height) is sealed with the newly designed high-strength biocompatible hydrogel called Tetra-PEG gel[3] to transport chemicals from the microchannels into brain tissues. The fabrication procedure of the device is shown in Figure 2. Tetra-PEG gel was sterilized by filtration and PDMS with microchannel structures was sterilized by autoclave treatment. The microchannels were sealed with Tetra-PEG gel by the binding of Tetra-PEG gel to PDMS via chemical bonds.

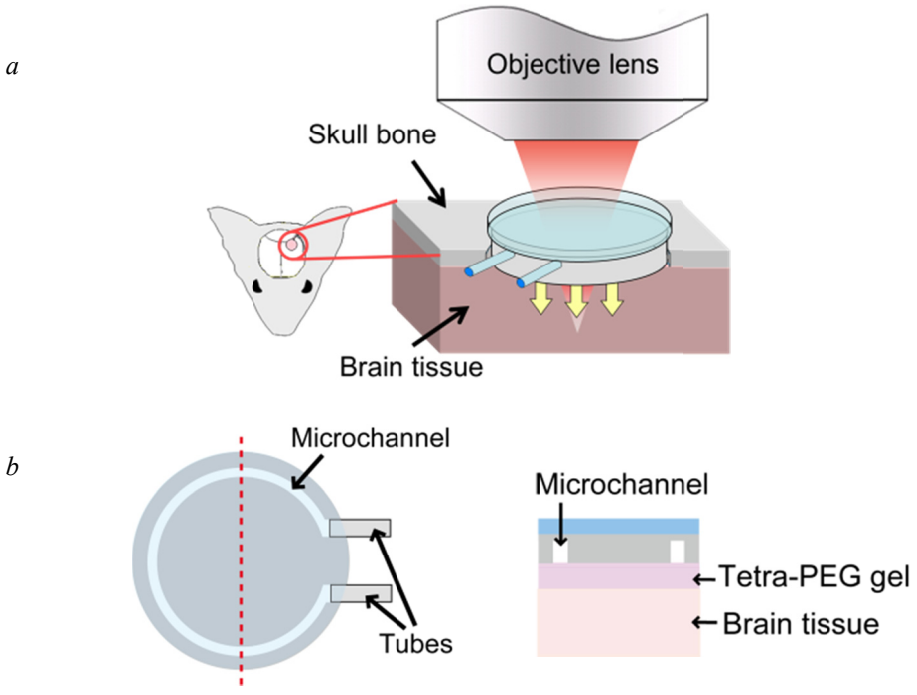

Figure 1. Brain interface device with a permeable hydrogel membrane. (a) Schematic of the microfluidic interface device mounted on a mouse skull. (b) Schematic of a microchannel in the device.

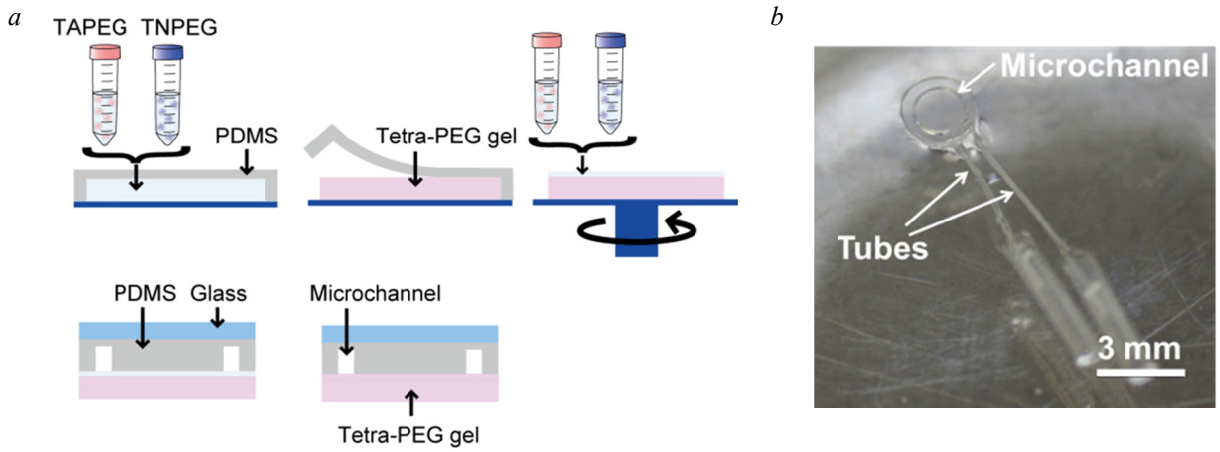

Figure 2. (a) Fabrication process of the device. PDMS with microchannels was sealed with Tetra-PEG gel. (b) Photograph of the microfluidic interface device. The device is 2.7 mm in diameter and 500 μm in thickness.

EXPERIMENT

Prior to the implantation experiments, transient diffusion experiments were performed. We also conducted a numerical simulation of the flow and diffusion in the device using the CFD-ACE+ software. The experimental and simulation results showed excellent agreement, as shown in Figure 3. Thus, the device developed was proved to be applicable to the well-controlled delivery of chemicals or drugs into the mouse brain.

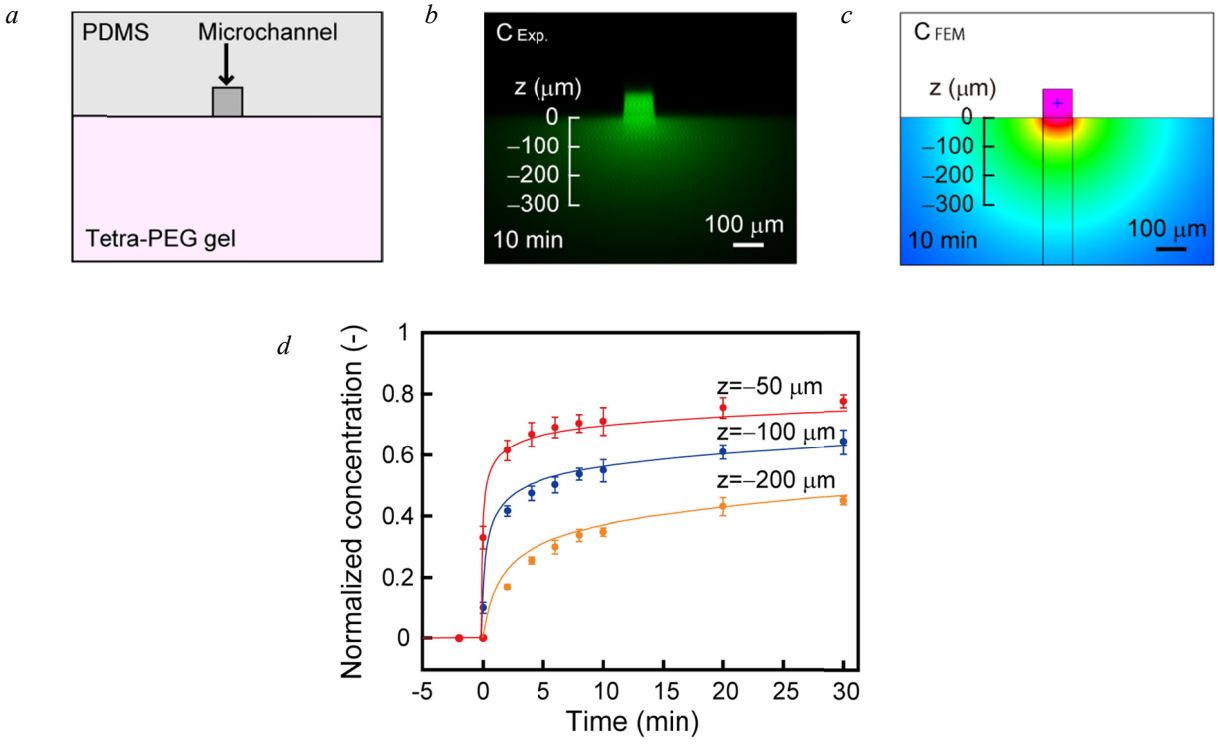

Figure 3. (a) Schematic illustration of Tetra-PEG gel/PDMS hybrid microchannels. (b) Fluorescence images of a cross section of the microchannel after the delivery of 5 μM fluorescein for 10 min. (c) Concentration distribution of fluorescein after the delivery of 5 μM fluorescein for 10 min calculated by the finite-element method (FEM). (d) Experimentally measured fluorescence intensity ($I_{Exp.}$; symbols) and computationally calculated fluorescein concentration (C_{FEM}; solid lines) at various depths (50 μm, 100 μm, 200 μm). Error bars show the standard deviations.

Then, in vivo experiments were demonstrated as follows. The brain of a living mouse implanted with the device was observed by TPLSM, and high-resolution (<1 μm) microscopy images of neural cells were obtained because the device was sufficiently sterilized and the pulsatile motion was successfully suppressed (Figure 4). Fluorescent solutions were injected into the microchannels of the device, and the diffusive transfer of the delivered fluorescent substance in brain tissues was measured by TPLSM (Figure 5).

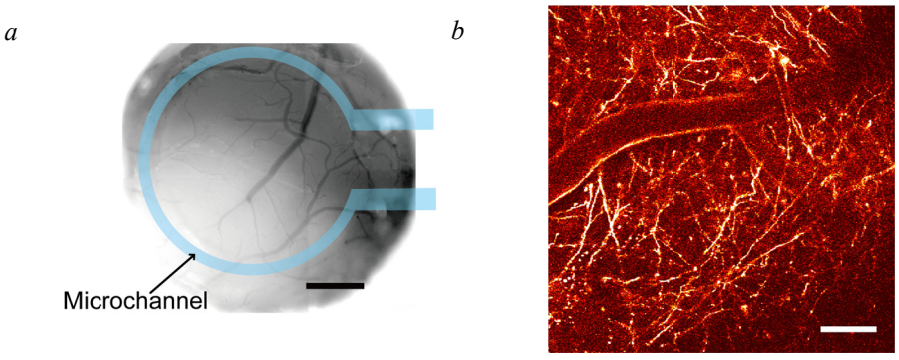

Figure 4. (a) Bright image of the brain surface under the device. (b) Two-photon image of neural cells. Scale bars: (a) 500 μm and (b) 100 μm.

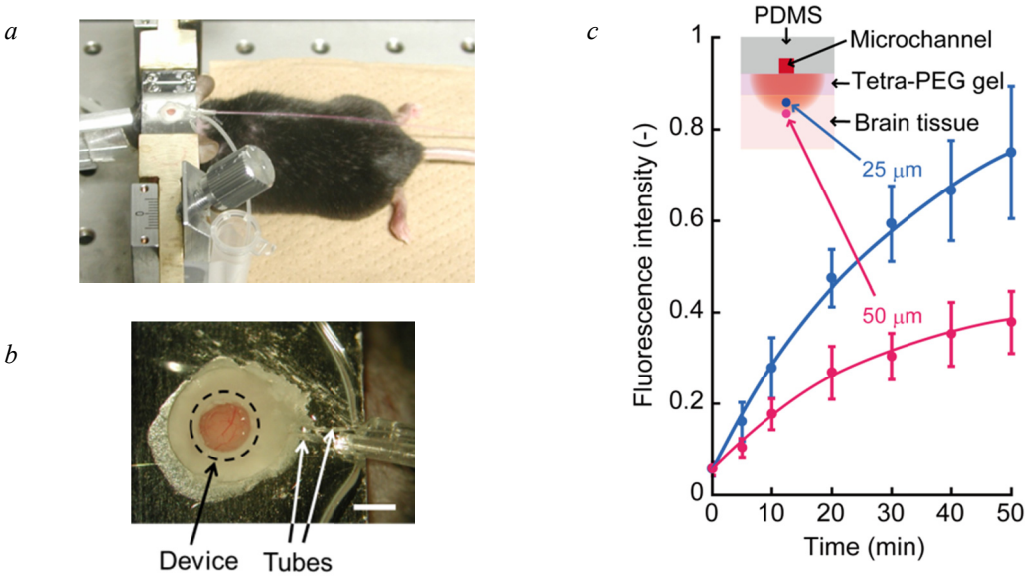

Figure 5. (a) A living mouse immobilized with the headgear. Teflon tubes were connected to the device tubes to inject solutions into the microchannels. (b) Device in the headgear. Scale bar: 2 mm. (c) Diffusive transfer of fluorescent substance in brain tissues at depths of 25 μm and 50 μm. Error bars show the standard deviations.

CONCLUSION

We have presented the usefulness of an implantable microfluidic device with a permeable hydrogel membrane for delivering chemicals in a controlled manner and for observing fine structures of cells in tissues of living animals. Implantable microfluidic device technology is expected to be a powerful tool for *in vivo* analysis in the field of neuroscience and for the discovery of drugs for treating brain diseases.

ACKNOWLEDGEMENTS

This research was supported by Grant-in-Aid for JSPS Fellows (22-8063).

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CONTACT

Hiroaki Takehara, tel: +81-3-5841-1180; h-takehara@bionano.t.u-tokyo.ac.jp