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Out-of-plane microtube arrays for drug delivery—liquid flow properties and an application to the nerve block test

Kuniharu Takei · Takahiro Kawashima · Takeshi Kawano · Hidekazu Kaneko · Kazuaki Sawada · Makoto Ishida

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Abstract We have proposed fabricating very fine out-of-plane silicon-dioxide microtube arrays using a selective vapor–liquid–solid (VLS) growth technique and microfabrication processes. In this study, we elucidated the liquid-flow properties of microtubes with different inner diameters. Our fabricated microtubes were 0.5 μm in wall thickness; 20 μm in height; and either 2.5 μm, 4.1 μm, 4.6 μm, or 6.4 μm in inner diameter. We determined the relationship between the flow pressure and the liquid flow rate through the microtube. We also conducted a nerve block test, in which a microtube with 4.6 μm inner diameter was used to administer lidocaine solution (Na channel blocker) to the rat sciatic nerve. This successful test represents the first reported use of a microtube for drug delivery to the peripheral nerve of a rat. We conclude that the proposed microtube array and its fabrication process might contribute to developing pharmacological devices.

Keywords Microtube · Microneedle · Drug delivery · Vapor–liquid–solid (VLS)

K. Takei (✉) · T. Kawano · K. Sawada · M. Ishida
Department of Electrical and Electronic Engineering,
Toyohashi University of Technology,
1-1 Hibarigaoka, Tempaku-cho,
Toyohashi, Aichi 441-8580, Japan
e-mail: takei@dev.eee.tut.ac.jp

T. Kawashima
Department of Production Systems Engineering,
Toyohashi University of Technology,
Toyohashi, Aichi, Japan

H. Kaneko
National Institute of Advanced Industrial Science
and Technology (AIST),
Tsukuba, Ibaraki, Japan

T. Kawano · K. Sawada · M. Ishida
Japan Science and Technology Agency—CREST,
Kawaguchi, Saitama, Japan

K. Takei
Japan Society for the Promotion of Science,
Tokyo, Japan

1 Introduction

The responses of neurons and neural networks to biochemicals have been investigated by using local drug delivery systems. Freedman et al. proposed a method of automated microiontophoresis to deliver pulses of agonists from glass micropipettes, and used this method to investigate pharmacological antagonism in the central nervous system (Freedman et al. 1975). Legault et al. used dual-probe microdialysis to study the elevation of dopamine in the nucleus accumbens before, during, and after drug injections into the ventral subiculum and the ventral tegmental area (Legault et al. 2000). By suppressing cortical activities pharmacologically with a unilaterally implanted cannula connected to a minipump, Li et al. (2005) demonstrated that the effects of a unilateral cortical lesion are due to the diminution or elimination of interhemispheric activity. The devices used in these studies are very useful for the investigation of the responses of both neurons and neural networks to biochemicals. However, fabrication of such devices requires a great deal of skill, and thus is not easy to densely arrange the channels of drugs.

Microfabrication techniques have the capability to construct high-density microchannel array of drugs and to deliver drugs into relatively small areas (McAllister et al.

2000; Prausnitz 2004). Choi et al. (2007) proposed a perfusion device that would be constructed by arranging microtubes with 20-μm diameter in an array at 250-μm intervals for *in vitro* thick tissue culturing. Lin and Pisano (1999) reported microhypodermic needles with 30 μm square fluid ports, for use in localized drug delivery and very precise sampling of small volumes of fluids.

Microfabrication techniques provide further advantage, in that they allow integrate with microelectrodes for recording neuronal signals while injecting drugs. This gives neurophysiologists an opportunity to investigate the responses of individual neurons to specific biochemicals. Several types of needle device in which each microtube surrounded by a few microelectrodes have been fabricated using etching or deposition techniques (Chen et al. 1997; Takeuchi et al. 2005; Ziegler et al. 2006; Rajaraman et al. 2007). The aperture sizes of these microtubes are more than 50 μm in diameter, and the intervals between microtubes and microelectrodes are more than 500 μm. Even using microfabrication techniques, the sizes of previously proposed microtubes are still large for biochemical stimulation of single neurons, and the densities of the adjacent microelectrodes are still low for individually recording the activities of single neurons. This is because the cell body of a neuron is on the order of a few tens of microns, and they are often densely packed within a small area.

We have proposed using a penetrating array of silicon dioxide (SiO_2) microtubes, with diameters of a few microns, for drug delivery into the tissues (Takei et al. 2008a, b). The microtube array was fabricated by using selective vapor–liquid–solid (VLS) growth and microfabrication processes. This fabrication process has an advantage, in that it is possible to integrate microtubes, microprobe electrodes, and microelectronics into one chip (Kawano et al. 2004; Takei et al. 2008a, b).

However, some issues of the proposed microtubes still remain to be clarified before these devices can be used for drug delivery. In this paper, we detail flow properties of the microtube, as functions of flow pressure and tube inner diameter, in order to precisely control the dose of drug. Controlling the dose of drug is essential for the investigation of biochemical reactions of neurons and/or neural networks (Takoh et al. 2005), because the effects of biochemical stimulation/suppression of neuronal activities often shows dose-dependent responses. Here we verify whether the flow properties of the microtube follows the Hagen–Poiseuille equation, which defines the relation between liquid flow rate and pressure through a tube (Richter et al. 1997). Furthermore, to address some issues concerning *in vivo* drug delivery, we also report a nerve block test in which the fabricated microtubes were used for the first time.

2 Methods

2.1 Preparation of out-of-plane SiO_2 microtube array

Figure 1 illustrates the process sequence of the microtube array (Takei et al. 2008a, b). Silicon (Si) (111) substrates are used for VLS growth, because Si microprobes are grown with <111> directions perpendicular to Si (111) substrate. First, the substrates were oxidized to form SiO_2 and etched by a deep reactive ion etching (DRIE) from the reverse side of the wafer to form liquid flow channels (Fig. 1(a)). On the top surface, Au was evaporated and patterned by a lift-off process (Fig. 1(b)). In this work, Au dots with different diameters of 7 μm, 13.7 μm, 15.4 μm, and 23 μm were formed in order to generate the microtubes with various diameters of 2.5 μm, 4.1 μm, 4.6 μm, and 6.4 μm, respectively. Next, Si microprobes were fabricated by selective VLS growth, using Si_2H_6-based gas source molecular beam epitaxy (GS-MBE) (Fig. 1(c)). SiO_2 was deposited over the substrate by plasma-enhanced chemical vapor deposition (PECVD) to form the tube wall after Au-Si alloys were removed by *aqua regia* (Fig. 1(d)). The SiO_2 film at the tip of the probe was selectively etched by buffered hydrofluoric acid (BHF), while protecting SiO_2 film on the side of the probe by thick photoresist. Next, the

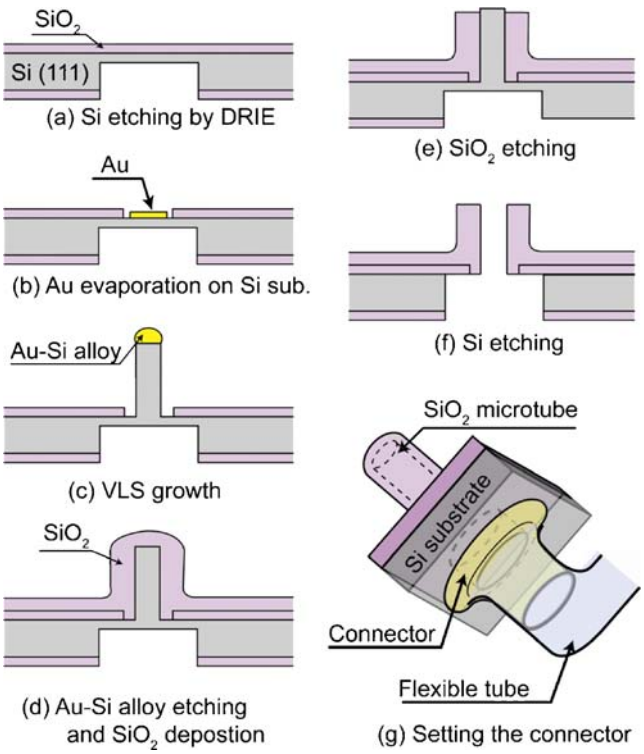

Fig. 1 Fabrication sequence of a SiO_2 microtube

photoresist was removed (Fig. 1(e)). Si probe was then etched by XeF_2 gas until it connected to the flow channel on the reverse side, in order to complete the tube structure (Fig. 1(f)). Finally, a connector between the microtube and a flexible tube for a plastic syringe was mounted on the reverse side of the wafer using a resin (Fig. 1(g)).

2.2 Liquid flow properties

We set up a measurement system for the liquid flow properties through the microtube in order to measure the flow rate and flow pressure. The system consists of a syringe pump (Model 11 PicoPlus, Harvard, USA), a precise flow meter (SLG1430, Sensirion, Switzerland), a pressure sensor (MM series, Honeywell, USA), and the fabricated microtube, all in series. The flow meter and the flow pressure can be recorded simultaneously. Experimental measurements were performed with deionized (DI) water. The flow of DI water was controlled by the syringe pump with desired flow rates ranging from 100 nl min^{-1} to 1,500 nl min^{-1}.

2.3 Animal experiments

A male Sprague–Dawley (SD) rat (CREA, Japan) weighting 370 g was used for demonstrating the use of the microtube for drug delivery. We tested whether the peripheral nerve can be blocked by local application of pH-adjusted lidocaine solution (2% xylocaine; AstraZeneca, Osaka, Japan) through the microtube, as illustrated in Fig. 2(a). All experimental procedures were based on the guidelines from the National Institutes of Health of the United States (1996) and the Japan Neuroscience Society. The institutional committee for animal experiments at AIST Tsukuba Central 6 approved the experimental protocols for this study.

The rat was anesthetized with an intraperitoneal injection of a mixture of ketamine hydrochloride (75 mg/kg; Sankyo Yell Yakuhin Co., Tokyo, Japan) and xylazine (7.5 mg/kg; Bayer Medical Ltd., Tokyo, Japan), and maintained with supplementary intramuscular injections (40 mg/kg ketamine and 4 mg/kg xylazine every 30 to 50 min). The rat was fixed in a stereotaxic frame. The rat's body temperature was

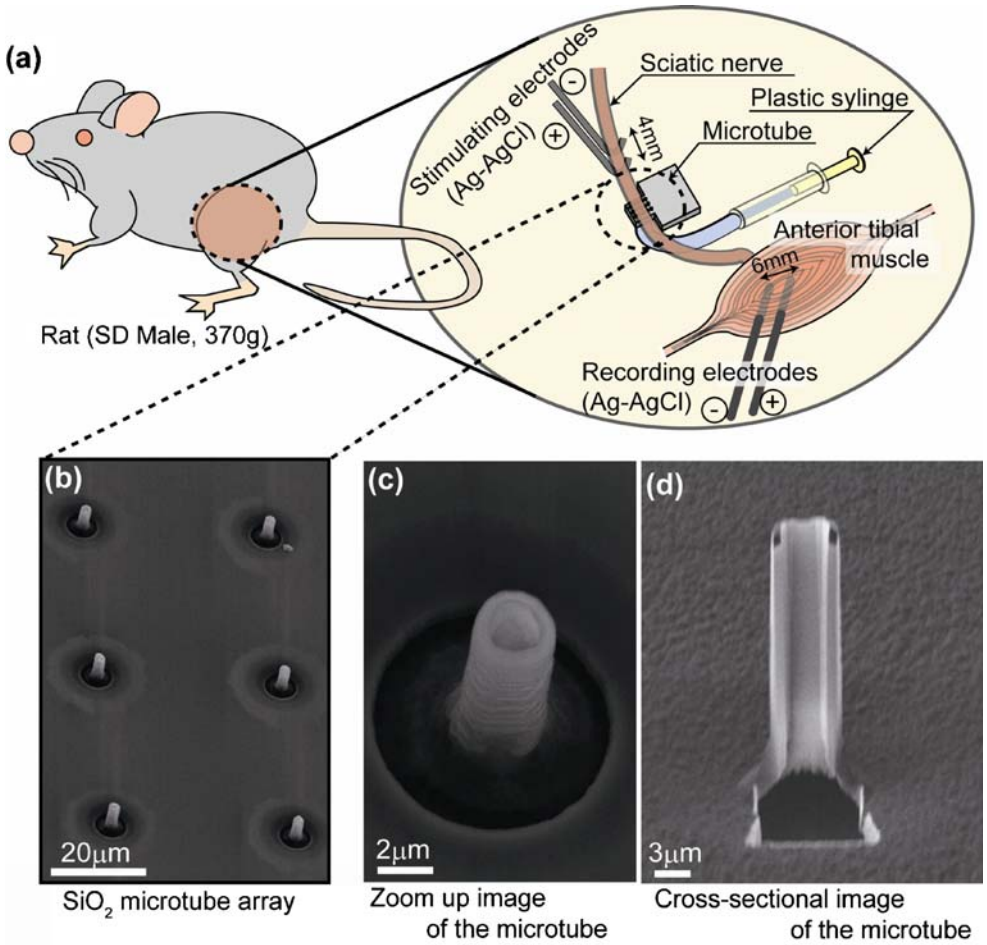

Fig. 2 (**a**) Schematic image of drug delivery experiments using a rat. Ag–AgCl electrodes are used for stimulation of the nerve as well as recording of myoelectric potential. Between the stimulation and the recording electrodes, the microtube device was set up, and lidocaine was delivered to the sciatic nerve. (**b**) SEM image of typical microtube array, (**c**) close-up image of a microtube, and (**d**) cross-sectional image of the microtube formed by a focused ion beam system

maintained at 37°C with a thermostatically regulated heating pad. The skin of the left leg was cut and opened under local anesthesia (application of 2% xylocaine gel on the skin; AstraZeneca K.K., Osaka, Japan). The left biceps femoris muscle was removed and the left sciatic nerve was dissected from the surrounding connective tissue. The branches of the sciatic nerve were cut except for the tibial nerve branch. Then the nerve blockade test described below was performed by electrically stimulating the sciatic nerve while lidocaine solution was administered through the microtube.

Figure 2 shows the experimental setup for a nerve block test and the fabricated SiO_2 microtubes observed by a scanning electron microscope (SEM). For the stimulation of the sciatic nerve, an Ag–AgCl bipolar electrode (distance between electrode sites: 4 mm, anode: distal site, cathode: proximal site) was located proximally to the fabricated microtube (4.6 μm in inner diameter, 5.6 μm in outer diameter, and 20 μm in height). Every two seconds, the sciatic nerve was stimulated by a series of three pulses; pulses were of 100 μs duration and were separated by 20 ms intervals. The evoked potentials of the left anterior tibial muscle were derived using an Ag–AgCl bipolar electrode (distance between electrode sites: 6 mm). The signals were amplified with a gain of 1,000, band-pass filtered from 15 Hz to 3 kHz, and digitized at 20 kHz.

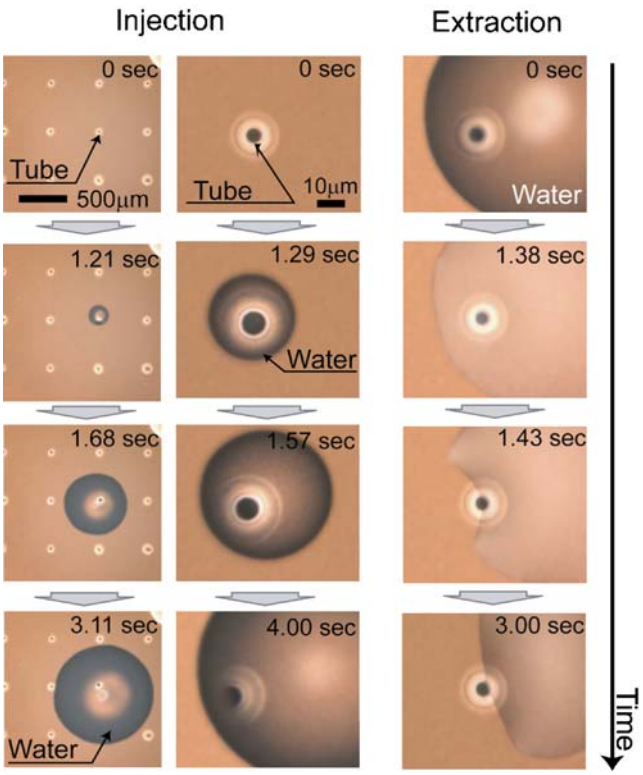

Fig. 3 Optical microscopic observations of the injection and extraction of DI water through a microtube. *Left side images* are observed injections of DI water, confirming that water was released from one microtube in the array within 3 s. Center images are close-up images of injections (~4 s). *Right side images* are extractions of water to the microtube (~3 s)

3 Results

3.1 Liquid flow properties

We measured the liquid-flow properties of the microtubes to control the dose of drugs for precise drug delivery. Figure 3 shows microscopic top-view observations of 4.6 μm-inner diameter microtubes during the injection and extraction of DI water through the microtube. The pressure of the liquid injection was ~40 kPa, and the extraction with negative pressure was ~10 kPa. Figure 4 shows schematic images of the microtube structures used, and the resulting flow properties. Figure 4(c) shows the relationship between flow rates and flow pressures in the microtubes. These results indicate linear characteristics between flow rates and pressures for each microtube.

3.2 Animal experiments

Under repetitive electrical stimulation of the sciatic nerve, evoked potentials of a tibial muscle were recorded before and after lidocaine administration through a microtube. We confirmed that before releasing the drug, the tibial muscle of the rat's left leg contracted synchronously with the stimulation. Because the threshold of the stimulation current was 3.0 μA, we set the stimulation current to 3.5 μA for the nerve-block test. Lidocaine was injected manually into the sciatic nerve through the fabricated microtube. The volume of lidocaine solution injected through the microtube was less than 5 μl (injection time: 1.5 min). After the disappearance of muscle contractions (10.5 min after the release of lidocaine), the tube device was removed from the nerve (Fig. 5(b)). Thereafter saline was poured over the nerve to prevent drying. Finally, the evoked muscle potentials recovered ~140 min after the lidocaine injection, as shown in Fig. 5(a) and (c).

We also measured threshold currents for inducing muscle evoked potentials. Although the threshold current was 3.0 μA before the lidocaine injection, it increased after the injection, as shown in Fig. 6. Next, the threshold current decreased drastically from 50 μA to 9 μA between 55 min and 73 min after the injection. The phenomena of alteration in threshold current indicate recovery from channel block after the administration of lidocaine.

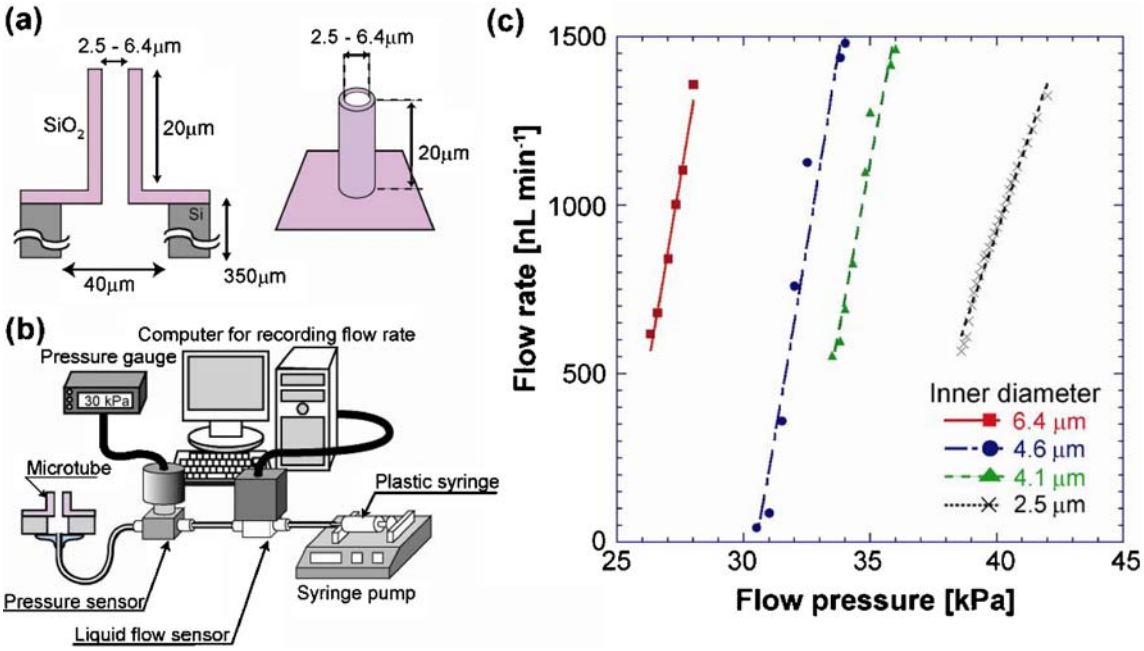

Fig. 4 Properties of liquid flow through the microtube: (**a**) microtube design, (**b**) schematic image of the measurement system for liquid flow properties, (**c**) liquid flow rate-flow pressure characteristics as a function of inner diameter of microtube

4 Discussion

We have proposed the SiO_2 microtube arrays as a means of generating a localized drug delivery system (Takei et al. 2008a, b). In this paper, we describe the liquid flow properties of SiO_2 microtubes with inner diameters of a few microns. Furthermore, to address some issues concerning drug delivery *in vivo*, we conducted a nerve block test, representing the first demonstration of drug delivery using a fabricated microtube.

4.1 Liquid flow properties of microtubes

Although the liquid flow properties of microtubes with inner diameters of tens of microns have been reported to obey the Hagen–Poiseuille law (Richter et al. 1997), the properties of thinner microtubes have not been reported. To the best of our knowledge, this is the first report of the liquid flow properties of out-of-plane microtubes with inner diameters of a few microns. Microtubes with 2.5–6.4 μm inner diameters allow us to control the flow rate level of 10^{-7} l min^{-1} at a flow pressure on the order of 10^5 Pa. The results indicate the linear relationship between flow pressure and flow rate, similar to the Hagen–Poiseuille law, even though the sizes of the microtubes are only a few micrometers (Fig. 4(c)). However, the observed values of liquid flow rates through our microtubes are not consistent with the theoretical values estimated by the Hagen–Poiseuille law. This discrepancy is probably due to eddy flow occurred at the connection between the bottom of microtube and the top of the silicon channel (all channels are 40 μm in diameter and 350 μm in length). We also found that microtubes with smaller inner diameter (e.g., 2.5 μm) have different slopes than others. The slope is

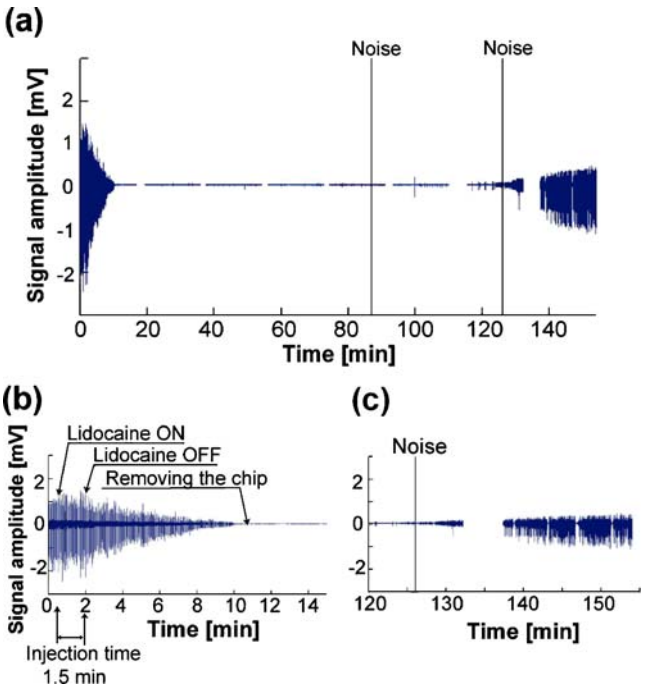

Fig. 5 Myoelectric potentials of the rat left tibial muscle during the nerve block test: (**a**) the whole recording periods, (**b**) initial 12-min period, and (**c**) 115 min after the lidocaine injection. Two spikes in (**a**) were artifacts resulting from pouring saline onto the nerve, to prevent drying

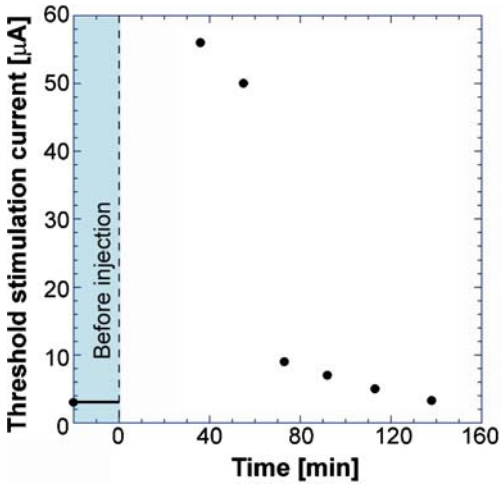

Fig. 6 The time course of the threshold current for stimulating the nerve innervating the rat left tibial muscle. Before lidocaine injection, the threshold current was 3.0 μA. The increased threshold after the lidocaine injection gradually recovered to baseline

probably decreased because the roughness of the inner surface of the microtube influences flow behavior prominently. This slope difference will need to be carefully considered in the preparation and characterization of smaller-diameter-microtube samples (e.g., inner diameters 2, 1.5, 1, 0.5 μm). The details of flow properties of microtubes with inner diameters of a few microns or smaller, based on theoretical predictions, will be investigated in the near future. In any case, since the observed flow rate correlates strongly with the flow pressure, as shown in Fig. 4(c), understanding of these flow properties will be useful in efforts to precisely control the dose of drug and to design drug delivery systems.

The microtubes can be driven with existent micropumps. The initial flow pressure for starting liquid flow through a microtube can be estimated from its flow properties (Fig. 4(c)). According to the obtained flow properties, and assuming that flow rates from 0 to 1.5 μl min^{-1} change linearly with flow pressure, initial flow pressure through the microtube with an inner diameter of 2.5 μm is estimated to be approximately 36 kPa. Even though the pressure is not increased linearly, we confirmed that the measured pressure was not over the flow pressure of 39 kPa. The values of initial flow pressure are sufficiently low (less than 40 kPa). C. Chen et al. and L. Chen et al. have developed an electroosmotic micropump, which generates a flow pressure of tens of kPa and flow rates ranging between nl and μl per minute (Chen et al. 2002, 2003). Since the performance of these micropumps satisfy the required specifications for our microtubes, it will be possible to produce a fully integrated microtube-based drug delivery system.

4.2 Nerve block test for the first trial of drug delivery

The nerve block test using fabricated microtubes demonstrated that it is possible to use microtubes in pharmacological devices and/or systems. As a model agent for drug delivery, we used lidocaine, which is a local anesthetic agent and often used for pain control (Edmonds-Seal et al. 1980; Wolff et al. 2004; Paavola et al. 1995). Because nerve action potentials are conducted sodium (Na) channels on the axon membrane in the nodes of Ranvier, the administration of lidocaine (a reversible Na-channel blocker) temporarily disrupts the conduction of the nerve action potentials. As shown in Fig. 5(a) and (c), the amplitude of myoelectric potentials from the rat anterior tibial muscle gradually decreased with time after the administration of lidocaine solution through the microtube. The amplitude then recovered to levels similar to those before the lidocaine administration. The threshold current for inducing the evoked muscle potentials also increased, and then decreased, as shown in Fig. 6. Furthermore, the time of recovery from the nerve blockade (~140 min) was comparable to what has been reported in the literature (Todd Sitzman et al. 2001; Chan et al. 1999; Rodriguez et al. 2001). These data indicate that the lidocaine solution was properly applied to the nerve between the stimulation point and the neuromuscular junctions, and the nerve block test was successfully conducted by using the fabricated microtube.

The nerve block test clarified some issues concerning the application of the fabricated microtubes to drug delivery. In our experiments, the device was removed from the nerve to stop the diffusion of the lidocaine through the tube (Roxhed et al. 2008; Papageorgiou et al. 2006). Furthermore, to wash out lidocaine and to prevent drying of the nerve, sometimes saline was poured over the nerve. However, the removal of the device is not as easy as implantation, and such a requirement restricts the application of the device. Thus, it will be necessary to minimize leakage of the administered agent, and other channels should be positioned to wash out the administered agent and to withdraw administered solutions. For reducing leakage of the administered agent, a few techniques have been proposed. Papageorgiou et al. (2006) proposed a “cantilever beam” type microshutter at each flow port of the microtubes, which can be opened by the injection pressure, thereby pushing the biochemical out of the channel. Furthermore, although we applied only the fabricated microtube with 20-μm height in the nerve block test, microtubes with several-hundred-micron height will be required in order to perform the same test in the brain tissue. Since microtubes are constructed based on microprobes whose height increases with VLS growth time (Takei et al. 2008a, b; Wagner et al. 1964), it is possible to fabricate microtube arrays with a

height in excess of 500 μm. The above issues should be addressed in future study, before fabricated microtubes can be used in general applications.

5 Conclusion

This paper demonstrated the liquid flow properties through out-of-plane microtubes with diameters of a few microns, and demonstrated *in vivo* drug delivery to the peripheral nerve of a rat through a microtube. Since the flow properties depend on the flow pressure and the tube inner diameter, the flow rate can be controlled, and this enables us to estimate the dose of delivered drug and to precisely control it. As a demonstration of the applicability of our microtube to drug delivery, a nerve block test was successfully conducted. We conclude that the proposed microtube and its fabrication process could contribute to developing pharmacological devices and systems.

In future, a microtube array should be fully integrated with a microprobe electrode array and on-chip circuits, and the integrated device might be applicable to the investigation of single neurons' responses to specific biochemicals.

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References

V.W.S. Chan, S. Nazarnia, Z. Kaszas, A. Perlas, Anesth. Analg. **89**, 1006 (1999). doi:10.1097/00000539-199910000-00034

C. Chen, J.G. Santiago, J. Microelectromech. Syst. **11**, 672 (2002). doi:10.1109/JMEMS.2002.805055

J. Chen, K.D. Wise, J.F. Hetke, S.C. Bledsoe, IEEE Trans. Biomed. Eng. **44**, 760 (1997). doi:10.1109/10.605435

L. Chen, J. Ma, F. Tan, Y. Guan, Sens. Actuators B Chem. **88**, 260 (2003). doi:10.1016/S0925-4005(02)00348-9

Y. Choi, M.A. McClain, M.C. LaPlaca, A. Bruno Frazier, M.G. Allen, Biomed. Microdevices **9**, 7 (2007). doi:10.1007/s10544-006-9004-8

H. Cui, Z. Silber-Li, S. Zhu, Phys. Fluids **16**, 1803 (2004). doi:10.1063/1.1691457

J. Edmonds-Seal, G.M.C. Paterson, A.B. Loach, J. R. Soc. Med. **73**, 111 (1980)

R. Freedman, B.J. Hoffer, D.J. Woodward, Br. J. Pharmacol. **54**, 529 (1975)

T. Kawano, Y. Kato, R. Tani, H. Takao, K. Sawada, M. Ishida, IEEE Trans. Elctron Devices **51**, 415 (2004). doi:10.1109/TED.2003.822473

M. Legault, P.P. Rompre, R.A. Wise, J. Neurosci. **15**, 1635 (2000)

L. Li, V. Rema, F.F. Ebner, J. Neurophysiol. **94**, 3342 (2005). doi:10.1152/jn.00357.2005

L. Lin, A.P. Pisano, J. Microelectromech. Syst. **8**, 78 (1999). doi:10.1109/84.749406

D.V. McAllister, M.G. Allen, M.R. Prausnitz, Annu. Rev. Biomed. Eng. **02**, 289 (2000). doi:10.1146/annurev.bioeng.2.1.289

A. Paavola, J. Yliruusi, Y. Kajimoto, E. Kalso, T. Wahlstrom, P. Rosenberg, Pharm. Res. **12**, 1997 (1995). doi:10.1023/A:1016264527738

D.P. Papageorgiou, S.E. Shore, S.C. Bledsoe Jr., K.D. Wise, J. Microelectromech. Syst. **15**, 1025 (2006). doi:10.1109/JMEMS.2005.863733

M.R. Prausnitz, Adv. Drug Deliv. Rev. **56**, 581 (2004). doi:10.1016/j.addr.2003.10.023

S. Rajaraman, S. Choi, R.H. Shafer, J.D. Ross, J. Vukasinovic, Y. Choi, S.P. DeWeerth, A. Glezer, M.G. Allen, J. Micromech. Microeng. **17**, 163 (2007). doi:10.1088/0960-1317/17/1/021

M. Richter, P. Woias, D. Weib, Sens. Actuators A Phys. **62**, 480 (1997). doi:10.1016/S0924-4247(97)01486-6

J. Rodriguez, V. Rodriguez, A. Naveira, O. Quintela, M. Barcena, E. Gallardo, F. Gude, J. Alvarez, Acta Anaesthesiol. Scand. **45**, 893 (2001). doi:10.1034/j.1399-6576.2001.045007893.x

N. Roxhed, P. Griss, G. Stemme, Biomed. Microdevices **10**, 271 (2008). doi:10.1007/s10544-007-9133-8

K. Takei, T. Kawashima, K. Sawada, M. Ishida, IEEE Sens. J. **8**, 470 (2008a). doi:10.1109/JSEN.2008.918262

K. Takei, T. Kawashima, T. Kawano, H. Takao, K. Sawada, M. Ishida, J Micromechanics Microengineering, **18**, 035033 (2008b). doi:10.1088/0960-1317/18/3/035033

S. Takeuchi, D. Ziegler, Y. Yoshida, K. Mabuchi, T. Suzuki, Lab Chip **5**, 519 (2005). doi:10.1039/b417497f

K. Takoh, T. Ishibashi, T. Matsue, M. Nishizawa, Sens. Actuators B Chem. **108**, 683 (2005). doi:10.1016/j.snb.2004.12.090

B. Todd Sitzman, C.A. DiFazio, P.A. Playfair, R.A. Stevens, C.F. Hanes, T.B. Herman, H. Kendall Yates, G.S. Leisure, Reg. Anesth. Pain Med. **26**, 246 (2001). doi:10.1053/rapm.2001.22587

R.S. Wagner, W.C. Ellis, Appl. Phys. Lett. **4**, 89 (1964). doi:10.1063/1.1753975

A.P. Wolff, O.H.G. Wilder Smith, B.J.P. Crul, M.P. van de Heijden, J. Groen, Anesth. Analg. **99**, 496 (2004). doi:10.1213/01.ANE.0000122268.70154.A9

C. Ziegler, T. Suzuki, S. Takeuchi, J. Microelectromech. Syst. **15**, 1477 (2006). doi:10.1109/JMEMS.2006.879681