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A Sieve Electrode as a Potential Autonomic Neural Interface for Bionic Medicine

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Abstract — **We examined the applicability of a sieve electrode to the autonomic nervous system as a potential neural interface for bionic medicine. We developed, using a Si-semiconductor process, a sieve electrode having a square diaphragm (1 mm in one side, 12 μm in thickness) with 30-81 penetrating square holes (50-100 μm in one side). In the first protocol, we implanted the sieve electrode to the vagal nerve in rats. One hundred and twenty days after the implantation, cuff electrodes were attached to the vagal nerve proximal and distal to the sieve electrode under halothane anesthesia. The evoked action potential was recorded from the sieve electrode by nerve stimulation via the cuff electrodes. The evoked action potential was also recorded from the cuff electrodes by nerve stimulation via the sieve electrode. In the second protocol, we implanted the sieve electrode to the renal sympathetic nerve in rabbits. Forty days after the implantation, the spontaneous action potential or sympathetic nerve activity was recorded under pentobarbital anesthesia. In conclusion, we were able to record the evoked and spontaneous action potentials using the sieve electrode. The sieve electrode will provide a useful neural interface for recording and stimulating the autonomic nervous system.**

Keywords — **sympathetic nerve, vagus, action potential**

I. Introduction

A sieve electrode, through which a target nerve regenerates, has been proposed as a possible long-term neural interface for sensory and motor nerves [1-3]. However, few studies focused on the application of the sieve electrodes to the autonomic nervous system. Given that the circulatory diseases frequently accompany the autonomic disturbance, the long-term autonomic neural interface will provide information on pathology of such diseases. Further, a successful interface with the autonomic nervous system will enable us controlling artificial organs by native autonomic discharge. The autonomic neural interface will also give us an opportunity to manipulate autonomic tone thereby treating the circulatory diseases. As an example, the survival rate of chronic heart failure following myocardial infarction in rats markedly improved by appropriate vagal nerve stimulation [4]. We termed the new strategy to cope with diseases based on the interface with biological signals as *bionic medicine* [5, 6]. The autonomic neural interface is a key technology for bionic medicine. In the present study, we examined the applicability of the sieve electrode to the autonomic nervous system as a physical neural interface using the vagal nerve in rats and the renal sympathetic nerve in rabbits.

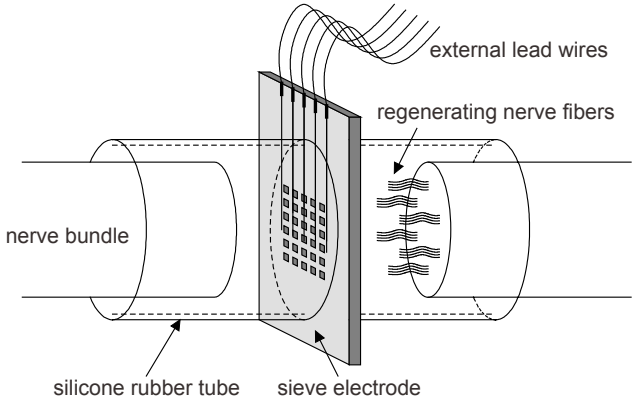

Fig. 1. Schematic diagram of the sieve electrode.

II. Methodology

A. Concept of a Sieve Electrode

Figure 1 schematizes the concept of a sieve electrode. The sieve electrode is placed between the sectioned nerve bundle. The nerve fibers regenerate through the holes of the sieve electrode. The silicone rubber tube serves as a guide along which the nerve regenerates. The action potential of the nerve is detected from electrodes placed around the penetrating holes.

Potential advantages of the sieve electrode are as follows: 1) the attachment of the electrode to the nerve fibers is stable once the nerve regenerated, and 2) the action potential may be recorded from a single fiber or a small group of nerve fibers, so that the regional difference in nerve signals will be utilized.

Possible disadvantage is that the nerve should be cut to place the sieve electrode, and hence the action potential cannot be recorded until the nerve fibers regenerated.

B. Design of a Sieve Electrode

A silicon (Si) wafer (3 × 6 mm in size and 250 μm in thickness) was used as the base of the sieve electrode. A square diaphragm (1 mm in one side, 12 μm in thickness) with 30-81 penetrating square holes (50-100 μm in one side) was fabricated by a Si-semiconductor process. The thickness of the diaphragm was determined by a preliminary experiment so that the diaphragm was strong enough not to be broken by nerve regeneration.

As shown in Figure 2, several holes were rimmed by the gold (Au) rings of 10-μm width, which served as electrodes. The Au rings were anchored by P-SiN (Plasma Chemical Vapor Deposition-Silicon Nitride) membrane to prevent their detachment from the diaphragm. The Au rings were connected to the bonding pads for external lead wires.

C. Preparations

We examined the applicability of the sieve electrode to the vagal nerve in rats and the renal sympathetic nerve in rabbits. Animal care was in strict accordance with *the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences* approved by the Physiological Society of Japan.

In the first protocol, the rats (n = 5) were anesthetized with halothane (1-1.5%) and artificially ventilated. Under sterile conditions, the right vagal nerve of the rat was exposed via the midline cervical incision. The vagal nerve was carefully detached from the common carotid artery. The vagal nerve was sectioned, and its cut ends were introduced into the guide tubes of the sieve electrode and fixed with 9-0 polypropylene suture. The external lead wires were covered with polyethylene tubing and placed under the skin.

In the second protocol, the rabbits (n = 3) were anesthetized with pentobarbital (30 mg/kg) and artificially ventilated. Under sterile conditions, the left renal sympathetic nerve was exposed via the left flank incision. The renal nerve was sectioned and the sieve electrode was placed between the sectioned nerves. The external lead wires were placed under the skin.

After the surgical operation, the experimental animals were recovered from anesthesia and fed with standard chow ad libitum.

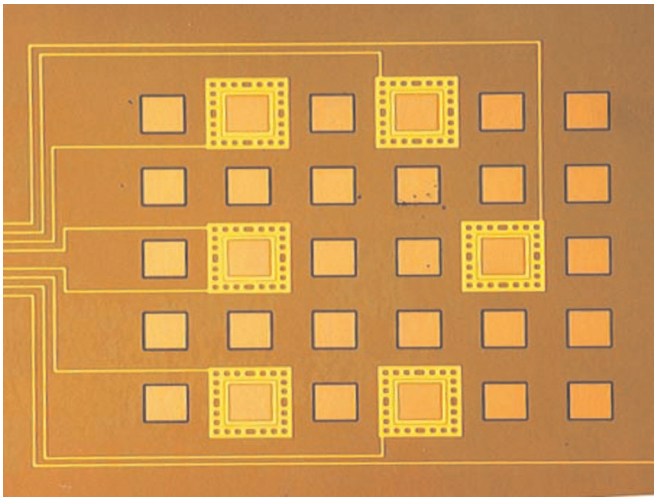

Fig. 2. Design of the diaphragm of the sieve electrode. The photograph shows the diaphragm with 30 penetrating square holes (100 μm in one side). Six of the 30 holes were rimmed with the Au rings.

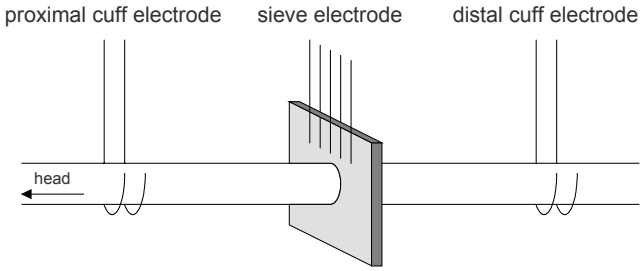

Fig. 3. Configuration of cuff electrodes and sieve electrode to examine evoked action potential.

D. Evoked Action Potential

An evoked action potential was recorded in the rats 120 days after the electrode implantation. The rats were anesthetized with halothane and artificially ventilated. The right vagal nerve was exposed around the implanted sieve electrode and detached from the surrounding tissues. As shown in Figure 3, two pairs of custom-made cuff electrodes were attached to the vagal nerve proximal and distal to the sieve electrode.

First, we stimulated the nerve from the proximal electrode and recorded the evoked action potential from the sieve electrode. Second, we stimulated the nerve from the sieve electrode and recorded the evoked action potential from the proximal and distal cuff electrodes. The pulse duration was 300 μs and the stimulation interval was 500 ms. The magnitude of stimulation was varied from 1 to 7.2 V.

The evoked action potential was amplified and band-pass filtered at 150-1,000 Hz, and then sampled at 5,000 Hz. To increase the signal to noise ratio, 100 recordings of the evoked action potentials were averaged.

E. Spontaneous Action Potential

A spontaneous action potential was recorded in the rabbits 40 days after the electrode implantation. The rabbits were anesthetized with pentobarbital and artificially ventilated. The external lead wires from the implanted sieve electrode were connected to a preamplifier. The nerve signal was band-pass filtered at 150-1,000 Hz and full-wave rectified and low-pass filtered at 30 Hz to quantify the sympathetic nerve activity. A catheter was introduced into the central ear artery to measure arterial pressure. Another catheter was introduced into the femoral vein for drug infusion. To evoke physiological changes in sympathetic nerve activity, we increased and decreased arterial pressure by bolus injection of intravenous phenylephrine (10-20 μg/kg) and glycerin trinitrate (10 μg/kg), respectively. The increase in arterial pressure was expected to decrease the sympathetic nerve activity via the arterial baroreflex. The decrease in arterial pressure was expected to increase the sympathetic nerve activity.

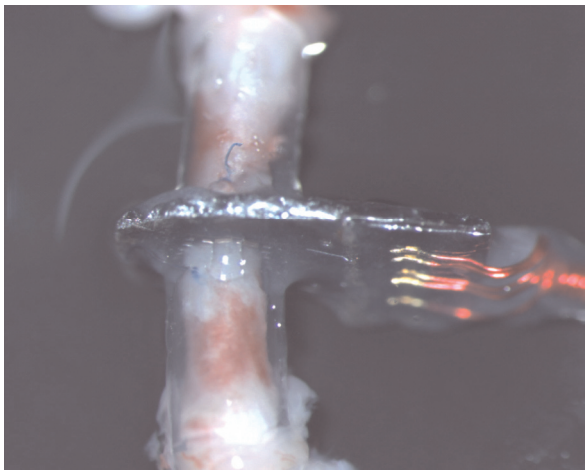

Fig. 4. The rat vagal nerve regenerated through the sieve electrode.

III. Results

A. Evoked Action Potential

Figure 4 illustrates the macroscopic regeneration of the rat vagal nerve 120 days after the implantation. The top and bottom indicate the distal and proximal sides, respectively.

Figure 5 shows the evoked action potential recorded from the sieve electrode implanted into the rat vagal nerve. The nerve stimulation was applied from the proximal cuff electrode. A sharp signal at 0 ms indicates an artifact of electrical stimulation. The stimulation voltage was changed from 1 to 7.2 V. No significant action potential was found at 1V. The compound action potential was observed at the stimulation voltage above 3.2 V. The amplitude of the action potential did not change irrespective of the further increase in stimulation voltage, suggesting that the potential was not an artifact of stimulation. The distance between the proximal electrode and the sieve electrode was 20 mm and the conduction velocity was approximately 1.3 m/s.

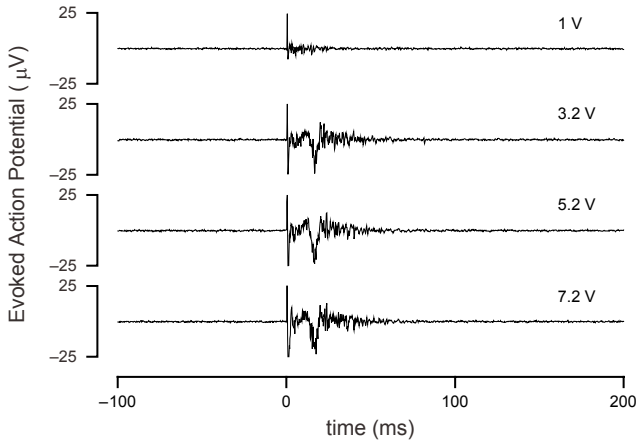

Fig. 5. Evoked action potential recorded from the sieve electrode.

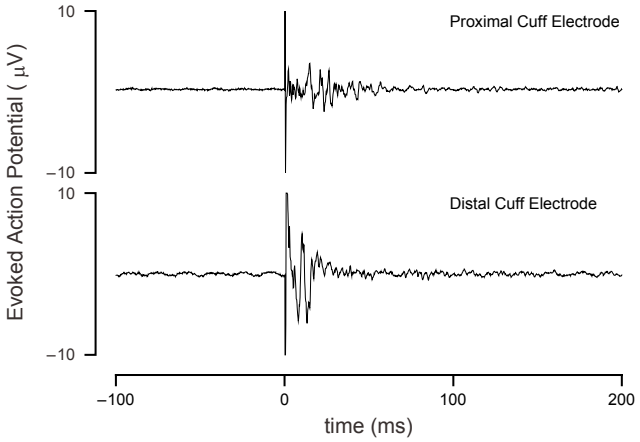

Fig. 6. Evoked action potential recorded from the cuff electrodes.

Figure 6 shows the evoked action potentials recorded simultaneously from the proximal (*the top panel*) and distal (*the bottom panel*) cuff electrodes. The nerve stimulation was applied from the sieve electrode. A sharp signal at 0 ms indicates an artifact of electrical stimulation. The stimulation voltage was 6 V. The compound action potential recorded from the proximal cuff electrode showed longer duration than that recorded from the distal cuff electrode.

B. Spontaneous Action Potential

Figure 7 shows the spontaneous action potential or sympathetic nerve activity recorded from the sieve electrode implanted into the renal sympathetic nerve. The top panel illustrates changes in arterial pressure, and the middle panel illustrates changes in the rectified and low-pass filtered renal sympathetic nerve activity. Both signals were resampled at 1 Hz to clarify the relationship between the two signals: a decrease in arterial pressure increased sympathetic nerve activity, and an increase in arterial pressure decreased sympathetic nerve activity.

The bottom panels in Figure 7 indicate the raw signals of spontaneous action potential recorded from the sieve electrode. Labels A, B, and C correspond to the time points A, B, and C in the middle panel.

IV. Discussion

We have demonstrated, for the first time to our best knowledge, that the sieve electrode can serve as a physical neural interface for recording and stimulating the autonomic nervous system.

Although there are many studies on the sieve electrode, most works have been focused on the sensory and motor nerves [1-3]. The autonomic nervous system including the sympathetic and vagal nerves is essential for controlling cardiovascular system. Once the autonomic neural interface is realized, it will provide a new paradigm of controlling ar-

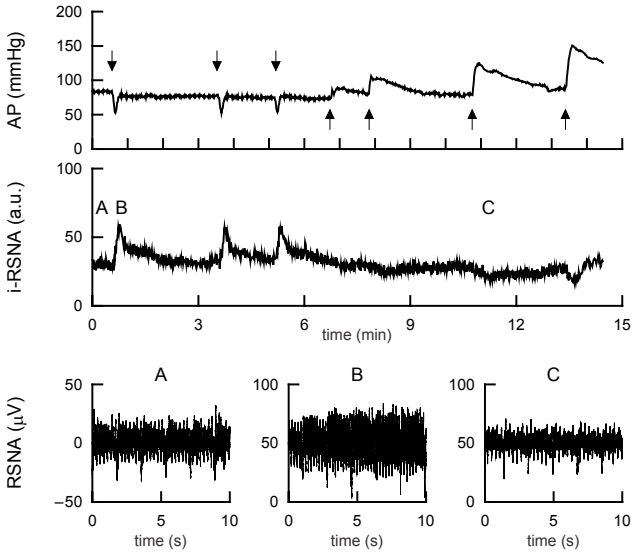

Fig. 7. Spontaneous action potential or renal sympathetic nerve activity recorded from the sieve electrode. Downward and upward arrows in the top panel indicate the bolus injections of glycerin trinitrate and phenylephrine, respectively.

tificial organs by native biological signals as if the organs were native ones. Further, bidirectional nature (i.e., recording and stimulation) of the electrode will contribute to the development of bionic medicine where the circulatory diseases etc. are treated via logical and physical interface with the autonomic nervous system [4-6].

The nerve recording and nerve stimulation using the sieve electrode were achieved in the rat vagal nerve. The fact that the evoked action potential from the proximal cuff electrode showed longer duration than that from the distal cuff electrode suggests that the nerve fibers distal to the sieve electrode contained fewer components. Whether the regeneration differs between nerve fiber types awaits future clarification.

Because spontaneous nerve activity could not be recorded in the vagal nerve even with the ordinary cuff electrode under anesthetic conditions, we examined the nerve activity recording from the sympathetic nerve. Because the renal sympathetic nerve in rats was too thin for the present sieve electrode, we applied the sieve electrode to the renal sympathetic nerve in rabbits. As can be seen in Figure 7, the sympathetic nerve activity responding to changes in arterial pressure was clearly recorded. Because stimulation-synchronized averaging was not required for the sympathetic nerve activity recording, the signal to noise ratio was sufficiently large for the potential autonomic neural interface for bionic medicine.

In the present study, we could not record the spontaneous action potential in conscious animals. In addition, the minimum time period necessary for nerve regeneration was not determined. The maximum time period for successful nerve activity recording was unanswered. Future studies should overcome these limitations.

V. Conclusion

The sieve electrode will provide a useful neural interface for recording and stimulating the autonomic nervous system. Although further studies are required to examine the stability and durability, the sieve electrode will provide a useful autonomic neural interface for bionic medicine.

Acknowledgment

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