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Long-term usability and bio-integration of polyimide-based intra-neural stimulating electrodes

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ABSTRACT

Stimulation of peripheral nerves has transiently restored lost sensation and has the potential to alleviate motor deficits. However, incomplete characterization of the long-term usability and bio-integration of intra-neural implants has restricted their use for clinical applications. Here, we conducted a longitudinal assessment of the selectivity, stability, functionality, and biocompatibility of polyimide-based intra-neural implants that were inserted in the sciatic nerve of twenty-three healthy adult rats for up to six months. We found that the stimulation threshold and impedance of the electrodes increased moderately during the first four weeks after implantation, and then remained stable over the following five months. The time course of these adaptations correlated with the progressive development of a fibrotic capsule around the implants. The selectivity of the electrodes enabled the preferential recruitment of extensor and flexor muscles of the ankle. Despite the foreign body reaction, this selectivity remained stable over time. These functional properties supported the development of control algorithms that modulated the forces produced by ankle extensor and flexor muscles with high precision. The comprehensive characterization of the implant encapsulation revealed hyper-cellularity, increased microvascular density, Wallerian degeneration, and infiltration of macrophages within the endoneurial space early after implantation. Over time, the amount of macrophages markedly decreased, and a layer of multinucleated giant cells surrounded by a capsule of fibrotic tissue developed around the implant, causing an enlargement of the diameter of the nerve. However, the density of nerve fibers above and below the inserted implant remained unaffected. Upon removal of the implant, we did not detect alteration of skilled leg movements and only observed mild tissue reaction. Our study characterized the interplay between the development of foreign body responses and changes in the electrical properties of actively used intra-neural electrodes, highlighting functional stability of polyimide-based implants over more than six months. These results are essential for refining and validating these implants and open a realistic pathway for long-term clinical applications in humans.

1. Introduction

The ability to communicate bi-directionally with the peripheral nervous system has opened promising perspectives to control

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neuroprostheses, restore lost sensation, and alleviate motor deficits resulting from neurological disorders [1,2]. For example, peripheral nerve stimulation has been successfully used in humans to alleviate foot drop after neuromotor disorders [3–7], to treat bladder dysfunction [8,9], and to reanimate paralysed muscles after spinal cord injury [10–13].

In all these applications, the stimulation was applied using an epi-neural cuff electrode [14]. While this type of interface is suitable when a simple and non-selective control of the stimulation is required, more advanced neuroprostheses rely on the ability to target specific fiber bundles within the nerve in order to modulate their recruitment in real-time using application-specific control strategies. In general, for a desired outcome, the type of neural interface is chosen based on the trade-off between invasiveness, selectivity, and reliability [1,15]. To this respect, intra-neural electrodes are the most appropriate implants since they provide superior selectivity of recording and stimulation, increased signal-to-noise ratio of recordings, and lower threshold of activation than extra-neural implants [16,17]. For instance, intra-neural stimulation of the median and ulnar nerves re-established graded sensory feedback that improved the control of a hand prosthesis after amputation in humans [18,19]. Despite this success, clinical studies using intra-neural implants have remained investigational and restricted to short-term implantation periods.

Several limiting factors have prevented the deployment of intra-neural implants for extended durations in human patients. First, these implants are markedly more invasive compared to epi-neural cuffs [20–23]. Second, the anatomical and functional consequences of the immediate penetration into and long term implantation within the host tissue have been solely characterized on passive implants without cabled connections [24,25]. Third, little is known about the stability and selectivity of intra-neural implants to enable functional applications over extended time.

To remedy these limitations, we evaluated the selectivity, stability, functionality, and biocompatibility of a polyimide-based intra-neural implant over a period of 6 months. Polyimide is a common material used in thin film technology for in vivo applications that allows versatile microfabrication of electrode implants with varying shape and geometry [25–27]. Polyimide-based intra-neural implants have emerged as a viable alternative to rigid silicon-based penetrating microelectrode arrays [19,28–32] for clinical applications.

Previous studies in acute animal preparations showed that polyimide-based intra-neural implants enable the preferential activation of specific groups of muscles that are innervated by different branches of the same stimulated nerve [17,25,26,33]. However, the long-term stability of this selectivity has not been investigated. Independently, the foreign body response to polyimide-based intra-neural implants has been evaluated using passive, untethered implants over periods of up to 3 months [24,25,34,35]. Taken together, these studies described the formation of a mild fibrotic encapsulation around the implant that developed in parallel to inflammatory responses, but had no sustained impact on the density of nerve fibers, axonal conduction velocity, or locomotor capacities of the implanted animals.

While these studies have provided critical information that supported preliminary clinical applications, the results have all been obtained in different groups of animals, focusing on specific modalities, and at discrete time-points. Therefore, the interactions and inter-dependencies between foreign body reactions and electrical properties over time have not been studied systematically and conjointly in longitudinal studies. To date, no chronic and realistic studies on intra-neural thin-film electrodes have been carried out that would allow to understand the impact of cabled implants and regular stimulation on electrode function and implant bio-integration.

Here, we studied the selectivity, stability, functionality, and biocompatibility of the SELINE polyimide-based intra-neural implant [25,27] that was inserted into the sciatic nerve of 28 healthy rats for durations of up to 6 months. After a period of adaptation that approximatively lasted one-month, the electrodes exhibited stable and selective responses to charge delivery that persisted over the remaining duration of the experiments. This selectivity supported the development of real-time stimulation paradigms that precisely controlled the forces produced at the ankle. In the same rats, we characterized the development of foreign body reaction over time, and showed that they tightly correlated with concomitant changes in the electrical properties of the electrodes. The removal of the implant did not cause detectable motor impairments and did not further harm the tissue. These results uncover relationships between actively used implants and neural tissue responses in rats and demonstrate the stability of intra-neural electrodes for reliable long-term interfacing with the peripheral nervous system. Our study assessed for the first time intra-neural thin-film electrode performance and in vivo biocompatibility in a chronic rat model. These unprecedented findings obtained in ecological settings provide a framework for the safe and long-term implantations of polyimide-based intra-neural electrodes in clinical applications.

2. Material and methods

2.1. Animals

All animal procedures and experiments were approved by the Veterinarian Offices of the Cantons of Vaud and Geneva, Switzerland. A total of 28 adult female Lewis rats (LEW-ORlj, Charles River Laboratories, France) with initial weight of ~200 g were implanted with a SELINE electrode [25] into their left sciatic nerve (Fig. 1A), with different indwelling times up to 6 months (Fig. 1B and Table 1). Animals were housed three by three on a 12-h light-dark cycle with food and water ad libitum and were given social time three times a week.

2.2. Chronic experimental model

The experimental model is graphically summarized in Fig. 1A. All surgical interventions were performed under aseptic conditions and full anaesthesia with isoflurane in oxygen enriched air (1–2%). Animals were placed on a heating pad to prevent hypothermia during surgery. Analgesic medication (Buprenorphine (Temgesic), ESSEX Chemie AG, 0.01–0.05 mg per kg, subcutaneous) and antibiotics (Amoxicillin (Clamoxyl), Pfizer AG, 0.5 ml/kg, subcutaneous) were administered during 5 days post-surgery.

2.2.1. Intra-neural electrode implantation with connector on backstage

The detailed implantation procedure for the SELINE electrode has been described previously [25]. Briefly, two longitudinal skin incisions of about 2 cm were made over the lower lumbar spine for the fixation of the backstage and at the level of the mid-thigh for access to the sciatic nerve. The sciatic nerve was carefully exposed and freed from surrounding tissues. Then, the 3D printed pedestal was sutured via its five suture-holes to the fascia of the back-muscles (multifidus muscle and gluteus superficialis) through a 2 × 2 cm piece of surgical mesh (Mersilene mesh, Ethicon Inc., NJ) to favour the stabilization by fibrotic healing. The wires (CZ1187, Cooner Wire Corp. CA), leading from the nano-strip connector (NPD-18-DD-GS, Omnetics Connector Corp, MN) incorporated in the pedestal to the printed circuit board (PBC), were passed