Acta Biomaterialia 39 (2016) 25–33

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Multifunctional hydrogel coatings on the surface of neural cuff electrode for improving electrode-nerve tissue interfaces

Dong Nyoung Heo [a,b,1], Su-Jin Song [a,1], Han-Jun Kim [c], Yi Jae Lee [d], Wan-Kyu Ko [a], Sang Jin Lee [e], Donghyun Lee [e], Sung Jin Park [d], Lijie Grace Zhang [b], Ji Yoon Kang [d], Sun Hee Do [c], Soo Hyun Lee [d,*,2], Il Keun Kwon [a,*,2]

[a] Department of Dental Materials, School of Dentistry, Kyung Hee University, Seoul 02447, Republic of Korea
[b] Department of Mechanical and Aerospace Engineering, The George Washington University, DC 20052, USA
[c] Department of Clinical Pathology, College of Veterinary Medicine, Konkuk University, Seoul 05029, Republic of Korea
[d] Center for BioMicroSystems, Korea Institute of Science and Technology, Seoul 02455, Republic of Korea
[e] Department of Dentistry, Graduate School, Kyung Hee University, Seoul 02447, Republic of Korea

ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form 18 March 2016
Accepted 3 May 2016
Available online 6 May 2016

Keywords:
Cuff electrode
Cyclosporine A
Sciatic nerve
Hydrogel coating
Drug delivery
Neural signal recording

ABSTRACT

Recently, implantable neural electrodes have been developed for recording and stimulation of the nervous system. However, when the electrode is implanted onto the nerve trunk, the rigid polyimide has a risk of damaging the nerve and can also cause inflammation due to a mechanical mismatch between the stiff polyimide and the soft biological tissue. These processes can interrupt the transmission of nerve signaling. In this paper, we have developed a nerve electrode coated with PEG hydrogel that contains poly (lactic-co-glycolic) acid (PLGA) microspheres (MS) loaded with anti-inflammatory cyclosporin A (CsA). Micro-wells were introduced onto the electrode in order to increase their surface area. This allows for loading a high-dose of the drug. Additionally, chemically treating the surface with aminopropylmethacrylamide can improve the adhesive interface between the electrode and the hydrogel. The surface of the micro-well cuff electrode (MCE) coated with polyethylene glycol (PEG) hydrogel and drug loaded PLGA microspheres (MS) were characterized by SEM and optical microscopy. Additionally, the conductive polymers, poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT/PSS), were formed on the hydrogel layer for improving the nerve signal quality, and then characterized for their electrochemical properties. The loading efficiencies and release profiles were investigated by High Performance Liquid Chromatography (HPLC). The drug loaded electrode resulted in a sustained release of CsA. Moreover, the surface coated electrode with PEG hydrogel and CsA loaded MP showed a significantly decreased fibrous tissue deposition and increased axonal density in animal tests. We expect that the developed nerve electrode will minimize the tissue damage during regeneration of the nervous system.

Statement of Significance

The nerve electrodes are used for interfacing with the central nervous system (CNS) or with the peripheral nervous system (PNS). The interface electrodes should facilitate a closed interconnection with the nerve tissue and provide for selective stimulation and recording from multiple, independent, neurons of the neural system. In this case, an extraneural electrodes such as cuff and perineural electrodes are widely investigated because they can completely cover the nerve trunk and provide for a wide interface area. In this study, we have designed and prepared a functionalized nerve cuff electrode coated with PEG hydrogel containing Poly lactic-co-glycol acid (PLGA) microspheres (MS) loaded with cyclosporine A (CsA). To our knowledge, our findings suggest that surface coating a soft-hydrogel along with an anti-inflammatory drug loaded MS can be a useful strategy for improving the long-term biocompatibility of electrodes.

* Corresponding authors.
E-mail addresses: shleekist@kist.re.kr (S.H. Lee), kwoni@khu.ac.kr (I.K. Kwon).
[1] D.N. Heo and S.J. Song: both authors contributed equally to this work.
[2] S.H. Lee and I.K. Kwon: both corresponding authors contributed equally to this work.

http://dx.doi.org/10.1016/j.actbio.2016.05.009
1742-7061/

1. Introduction

Implantable neural prosthetics have been developed for use in treating injured nervous systems. These nerve electrodes are used for interfacing with the central nervous system (CNS) or with the peripheral nervous system (PNS). The interface electrodes should facilitate a closed interconnection with the nerve tissue. These should provide for selective stimulation and recording from multiple, independent, neurons of the neural system [1–5]. These nerve electrodes can be divided into two main types based on their location after implantation. There are intraneural types which are located on the inside of a nerve trunk and extraneural types which wrap around a nerve trunk. Amongst these several designs, extraneural electrodes such as cuff and perineural electrodes are widely investigated because they can completely cover the nerve trunk and provide for a wide interface area. Also, these can be easily implanted without nerve damage as compared with the intraneural type, which require additional trauma for their implantation [6,7]. Although the current extraneural electrodes are more stable and biocompatible than intraneural electrodes, they also have some limitations and side effects such as inflammation, fibrosis, and long-term stability [8,9]. When the electrodes are implanted, fibrous tissue layers are formed and chronic inflammatory responses occur due to micro-motion during implantation and a mismatch in the mechanical properties between the nerve tissue and the electrodes. These side effects reduce nerve signal transductions and limit the long-term stability and functionality of nerve electrodes [10,11]. Therefore, there is a need to generate electrodes with enhanced anti-inflammatory effects, reduced apoptosis, and prevention of fibrous tissue deposition in order to reduce the side effects and provide for improved chronic detection of neural signals.

Many researchers have focused on surface modifications and coatings of electrodes with polymers, drugs, or anti-inflammatory biomolecules. Many different methods have been developed and tested to improve electrode biocompatibility and prevent loss of signal quality over time. These include (1) surfaces coated with poly(ethylene glycol) (PEG)-based polymer brushes for preventing non-specific protein adsorption and cell adhesion by steric repulsion [12–14], (2) coating of the neural electrodes with anti-inflammatory drugs to prevent inflammation [15–17], and (3) coating the electrode with a conductive polymer to improve the communication between the neural tissue and electrode and to obtain a high quality nerve signal [18–20]. Particularly, conductive polymer-hydrogel composites have been widely used for compensating electrical properties loss. For example, Abidian et al. reported the use of PEDOT nanotubes with PLGA and anti-inflammatories (dexamethasone) for controlled release by electrical stimulation [21]. Hassarati et al. developed a conductive polymer/hydrogel hybrid (PEDOT/pTS with PVA) as a cochlear implant in order to improve the electrical performance of the neural interface [22]. For the neural probe, Kim et al. reported the use of polypyrrole/PSS electrochemically and vertically grown through alginate hydrogel scaffolds for promoting signal transport [23]. In order to increase conductivity, Ouyang et al. investigated conductivity of PEDOT:PSS with various additives such as ethylene glycol, dimethyl sulfoxide and sorbitol [24]. However, in spite of these efforts, improvements in long-term functionality are still necessary.

In view of the importance of the above studies, we have designed and prepared a functionalized nerve cuff electrode coated with PEG hydrogel containing Poly lactic-co-glycol acid (PLGA) microspheres (MS) loaded with cyclosporine A (CsA). Before surface coating, the electrode substrates were altered to possess micro-wells and chemically treated in order to improve hydrogel adhesion and increase the total CsA load. Additionally, the conductive polymers, poly(3,4-ethylenedioxythiophene)-poly (styrenesulfonate) (PEDOT/PSS), were formed on the hydrogel layer for improving the nerve signal quality. The overall schematic illustration is shown in Fig. 1. The surface chemical characterization and distribution of CsA-loaded MS on the electrode surface were determined by X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM), and optical microscopy. Electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) of functionalized nerve cuff electrodes were evaluated to determine the electrochemical effectiveness. Additionally, the effectiveness of the functionalized nerve cuff electrode for improvement of biocompatibility and reduction of inflammatory responses and formation of fibrous tissue was evaluated under *in vivo* conditions.

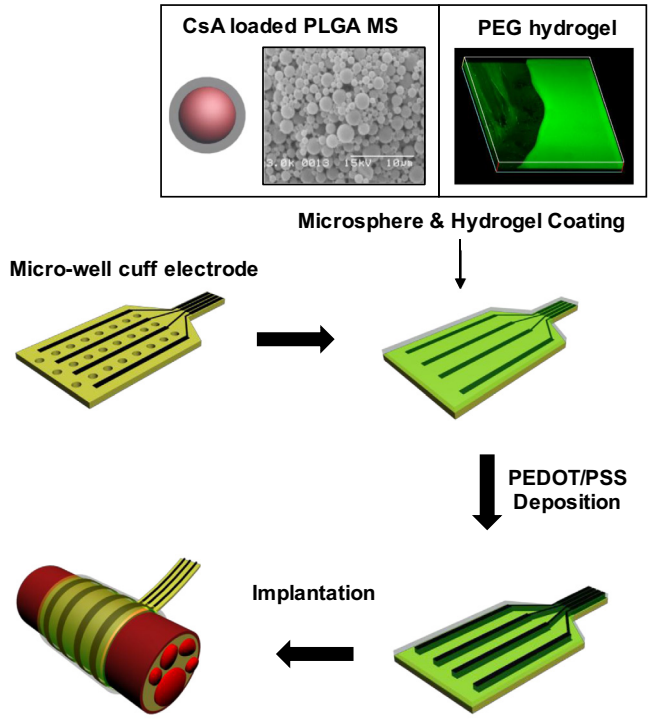

Fig. 1. Schematic diagram of the fabrication process for the functionalized nerve cuff electrode. Microwell-type cuff electrode is coated with CsA-loaded PLGA, MS, and PEG hydrogel mixture. After PEDOT deposition inside of hydrogel layer, the surface-coated electrode is implanted into the rat sciatic nerve.

2. Materials and methods

2.1. Materials

Polyimide (PI, VTEC PI-1338) was purchased from Richard Blaine International, Inc. (Pennsylvania, USA). Poly lactic-co-glycolic acid (PLGA, Resomer RG 757S) was purchased from Evonik (Essen, Germany). Cyclosporin A (CsA), N-(3-Aminopropyl) methacrylamide hydrochloride (APMA), tributylamine, and poly (vinyl alcohol) (PVA) were purchased from Sigma-Aldrich (St. Louis, MO). Poly(ethylene glycol) diacrylate (PEGDA, average Mw: 1000 g/mol) was purchased from Polyscience, Inc. (Philadelphia, PA, USA). The photoinitiator, 1-[4-(2-hydroxyethoxy)-phenyl]-2-hydroxy-2-methyl-1-propanone (Irgacure 2959) was purchased from Ciba Specialty Chemicals (Basel, Switzerland). All chemical solvents were used as received without further purification.