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Improving the performance of poly(3,4-ethylenedioxythiophene) for brain–machine interface applications

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ABSTRACT

Conducting polymers, especially poly(3,4-ethylenedioxythiophene) (PEDOT) based materials, are important for developing highly sensitive and microscale neural probes. In the present work, we show that the conductivity and stability of PEDOT can be significantly increased by switching the widely used counter anion poly(styrenesulfonate) (PSS) to the smaller tetrafluoroborate (TFB) anion during the electrodeposition of the polymer. Time-dependent impedance measurements of polymer modified implantable microwires were conducted in physiological buffer solutions under accelerated aging conditions and the relative stability of PEDOT:PSS and PEDOT:TFB modified microwires was compared over time. This study was also extended to carbon nanotube (CNT) incorporated PEDOT:PSS which, according to some reports, is claimed to enhance the stability and electrical performance of the polymer. However, no noticeable difference was observed between PEDOT:PSS and CNT:PEDOT:PSS in our measurements. At the biologically relevant frequency of 1 kHz, PEDOT:TFB modified microwires exhibit approximately one order of magnitude higher conductivity and demonstrate enhanced stability over both PEDOT:PSS and CNT:PEDOT:PSS modified microwires. In addition, PEDOT:TFB is not neurotoxic and we show the proof-of-concept for both *in vitro* and *in vivo* neuronal recordings using PEDOT:TFB modified microelectrode arrays and chronic electrodes, respectively. Our findings suggest that PEDOT:TFB is a promising conductive polymer coating for the recording of neural activities.

1. Introduction

Recording action potentials from neurons through an implantable electrode is among the most fundamental measurements in neuroscience [1–4]. One of the major research objectives in this exciting field is to decrease the size and thereby increase the density of electrodes in order to develop high spatial resolution probes. In addition, smaller electrode sites with a corresponding reduction in the probe size may minimize the inflammatory response, which is believed to be a factor in device failure under chronic recording conditions *in vivo* [5–8]. Unfortunately, as the size of the electrode is decreased, the impedance and thermal noise increase such that recording extracellular action potentials becomes problematic [9–14]. A logical approach to overcome this issue, adopted by several groups, is to make a rough and/or porous metallic electrode surface which increases the effective surface area and provides a low impedance electrochemical interface [15–17]. These fabricated metallic electrodes, however, suffer from unstable electromechanical behavior over time and are not suitable for long term applications [12,17,18]. In this respect, an alternative approach based on coating electrodes with conductive polymers (CPs) has received considerable interest over the last decade [9,10,19]. Because of their highly porous structure, CPs provide a large electrochemically active surface and the modified electrodes have orders of magnitude lower impedance compared to their metallic counterparts of similar geometric dimensions [20,21]. A number of CPs have been tested to date for this purpose, including poly(3,4-ethylenedioxythiophene) (PEDOT) [2,19,22–24], polypyrrole [24] and polycarbazole [25]. Among these, PEDOT (Fig. 1) has received much attention due to its high stability and conductivity compared to other CPs [24,26,27]. Besides, both *in vitro* and *in vivo* studies revealed that PEDOT is biocompatible [25,28,22,29,30] and different

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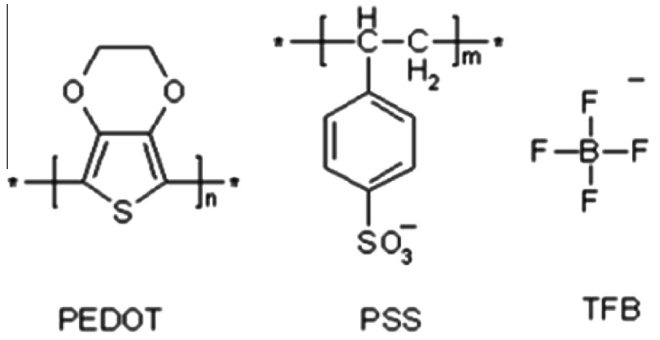

Fig. 1. Chemical structures of PEDOT and the supporting electrolyte anions studied: PSS and TFB.

biomolecules can also be embedded into the polymer matrix to tailor specific cellular functions [23,31].

Further improvement of the conductivity and stability of the PEDOT polymer is an active area of research and critical for developing long-lasting, reliable neural interfaces. Several groups reported the incorporation of carbon nanotubes (CNTs) into the polymer matrix [32–38]. CNTs have high surface area and excellent conductivity [39]. CNT-PEDOT combinations offer unique structural and electrical properties, resulting in an improved neuron–electrode interface without sacrificing the biocompatibility [32–38]. An alternative strategy for improving the performance of PEDOT modified electrodes is related to the fact that the morphology and thus the electromechanical properties of CPs are generally affected by the nature of the counter ion used during the electrodeposition of the polymer [40]. Multivalent poly(styrenesulfonate) (PSS) (Fig. 1) is the most widely used counter ion for preparing PEDOT modified low impedance electrodes [9,19,24,26,27,41]. But recent screening of PEDOT polymerized using different counter ions revealed that the smaller univalent counter ion tetrafluoroborate (TFB) (Fig. 1) can considerably improve the electrical properties of PEDOT electrodes over a wide frequency range and may be more suitable for extensive applications, particularly in neuroscience [21,42]. In the present study, we examined and compared the electrochemical stability of microelectrodes coated with PEDOT:PSS, CNT:PEDOT:PSS and PEDOT:TFB under accelerated aging conditions (at an elevated temperature of 60 °C in the biologically relevant phosphate buffered saline (PBS) for 80 days). We show that by replacing the conventionally used PSS with TFB, both the conductivity and stability of the PEDOT coated electrodes can be enhanced significantly. Finally, we provide proof-of-concept *in vitro* and *in vivo* neuronal recordings using PEDOT:TFB coated electrodes.

2. Materials and methods

2.1. Materials

3,4-Ethylenedioxylthiophene (EDOT), sodium polystyrene sulfonate (PSS), acetonitrile, gold(III) chloride hydrate, tetrabutylammonium tetrafluoroborate, poly-D-lysine (PDL), ascorbic acid and laminin were obtained from Sigma–Aldrich (St Louis, MO). CNT dispersion was from CheapTubes.com (Brattleboro, VT). Pt/Ir microwires (PI20030.1A5), gold coated 64-electrode planar microelectrode arrays (MMEP-3) and chronic probes (A1 × 16-5 mm-100-177-CM16) were received from MicroProbes for Life Sciences (Gaithersburg, MD), Center for Network Neuroscience (University of North Texas, Denton, TX) and NeuroNexus Technologies (Ann Arbor, MI), respectively. PBS was obtained from Mediatech Inc. (Manassas, VA). L15, Dulbecco's modified eagle medium (DMEM), B27 and fetal bovine serum (FBS) were purchased from Life Technologies (Grand Island, NY). DNase and papain were obtained from Worthington Biochemical Corp. (Lakewood, NJ) and horse serum was obtained from Atlanta Biologicals (Lawrenceville, GA).

2.2. Preparation of polymer modified microwires, microelectrode arrays (MEAs) and chronic probes

The Pt/Ir wires were first electroplated with a thin layer of gold to improve the adhesion between the electrode and the polymers [43]. The electroplating process involved cycling the wires between 0 and −1.5 V three times in an aqueous solution (degassed with N_2) of $HAuCl_4$ (5 mM) and $NaClO_4$ as the supporting electrolyte (100 mM). The polymers were then deposited using Gamry potentiostat/galvanostat/ZRA (Reference 600, Gamry Instruments, Warminster, PA) or a CHI 660D potentiostat (CH Instruments, Inc., Austin, TX). PEDOT:TFB deposition was performed from a solution of 0.01 M EDOT in 0.1 M tetrabutylammonium tetrafluoroborate in acetonitrile at 1.3 V for 60 s (vs. Ag/AgCl reference electrode). These conditions are similar to those used in Ref. [21] and the film thickness is 1.5 μm [21]. PEDOT:PSS was deposited from an aqueous solution of similar monomer concentration (0.01 M EDOT) with 0.1 M sodium polystyrene sulfonate (NaPSS). For CNT:PEDOT:PSS polymer deposition, 1 mg ml^{-1} CNT dispersion was used to make an aqueous solution containing 0.01 M EDOT and 0.1 M NaPSS with a CNT content of 20%. After the polymer deposition, electrodes were cycled between 0 and 0.5 V (50 cycles, cyclic voltammetry) in 1× PBS. Acetonitrile was kept dry using 3 Å molecular sieves until the day of use and the monomer solution was bubbled with N_2 prior to the electrochemical deposition. All aqueous solutions were prepared using deionized (DI) water (18.3 MΩ, Millipore purification system, EMD Millipore, Billerica, MA). The adapted protocol for polymer deposition was used to modify every other electrode of gold coated 64-electrode planar MEAs for *in vitro* neuronal recordings. Chronic probes for *in vivo* studies were modified using the adapted gold and polymer deposition protocols.

2.3. Accelerated aging study using electrochemical impedance spectroscopy (EIS)

The polymer modified Pt/Ir microwires ($n = 4$ for PEDOT:PSS, CNT:PEDOT:PSS and PEDOT:TFB each) were placed in a vial containing PBS at 60 °C and the impedance was monitored over time using a potentiostat (CHI 660D, CH Instruments, Inc., Austin, TX) equipped with a multiplexer (CHI 684, CH Instruments, Inc., Austin, TX). The impedance was measured at the open circuit potential from 0.1 Hz to 1 MHz, with a peak-to-peak amplitude of the sinusoidal voltage of 20 mV. Note that the temperature used here is in compliance with methods based on the ASTM F1980-07 "Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices" [43]. The half-life ($t_{1/2}$) of the microwires at 60 °C was obtained by exponentially fitting the admittance data of the electrodes over time using OriginPro (OriginLab Corporation, Northampton, MA). EIS data were fit with ZsimpWin (Princeton Applied Research, Oak Ridge, TN).

2.4. Scanning electron microscope (SEM) studies

The morphology of the polymer modified samples was investigated using an SEM (Zeiss SUPRA55-VP). The microwires were cut and placed on conductive carbon tapes attached to sample stubs. An acceleration voltage of 8 kV was employed and the samples were imaged under ultrahigh vacuum.