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Fabrication and biocompatibility of polypyrrole implants suitable for neural prosthetics

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Abstract

Finding a conductive substrate that promotes neural interactions is an essential step for advancing neural interfaces. The biocompatibility and conductive properties of polypyrrole (PPy) make it an attractive substrate for neural scaffolds, electrodes, and devices. Stand-alone polymer implants also provide the additional advantages of flexibility and biodegradability. To examine PPy biocompatibility, dissociated primary cerebral cortical cells were cultured on PPy samples that had been doped with polystyrene-sulfonate (PSS) or sodium dodecylbenzenesulfonate (NaDBS). Various conditions were used for electrodeposition to produce different surface properties. Neural networks grew on all of the PPy surfaces. PPy implants, consisting of the same dopants and conditions, were surgically implanted in the cerebral cortex of the rat. The results were compared to stab wounds and Teflon implants of the same size. Quantification of the intensity and extent of gliosis at 3- and 6-week time points demonstrated that all versions of PPy were at least as biocompatible as Teflon and in fact performed better in most cases. In all of the PPy implant cases, neurons and glial cells enveloped the implant. In several cases, neural tissue was present in the lumen of the implants, allowing contact of the brain parenchyma through the implants.

Keywords: Biocompatibility; Micropatterning; Electroactive polymer; Neural prosthesis; In vitro test; In vivo test

1. Introduction

As neurodegenerative diseases become a more pressing concern in society, the need for effective treatment methods increases. Therapeutic possibilities range from electrical interactions with the damaged neuronal circuits to the use of stem cells to replace injured tissue [1–3]. One challenge is finding materials that effectively interact with neural tissue for these applications. The stability and biocompatibility of different polymers have been studied by examining their effect on the surrounding tissue after implantation [4–8]. A unique subset of these materials, conducting polymers, has been investigated for use in biomedical applications [9–11]. Polypyrrole (PPy) has emerged as a promising candidate material that has been effective as a coating in both in vitro and in vivo neural studies [12–14]. PPy also has shown promise as a scaffold material for nerve regeneration [15].

PPy is an electrodeposited polymer that can be doped with various agents to alter its physical, chemical and

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electrical properties [16–19]. The ability to control PPy's surface properties such as wettability and charge density creates the potential for modifying neural interactions with the polymer [20]. Two of the most common dopants that are co-deposited with PPy are polystyrene-sulfonate (PSS) or sodium dodecylbenzenesulfonate (NaDBS). PSS/PPy and NaDBS/PPy polymers have been used in many applications ranging from actuators to neural electrode coatings to neural substrates [12,18,21]. Another strength of PPy is that erodible forms have been developed which increase the scope of biomedical applications including polymeric devices and neural scaffolds [10,12]. The ease of deposition and the ability to control growth in both the horizontal and vertical dimensions [22] enables flexibility in the three-dimensional design of polymer implants.

The following in vitro and in vivo studies show the ability of PPy to interact with neural tissue from the mammalian cerebral cortex. The biocompatibility of the PPy implants is compared to stab wounds (where an implant-sized incision is made with no implant left behind) and Teflon implants with similar size and features, and these results demonstrate the positive surface interactions at the PPy implant-cortical interface.

2. Methods

2.1. Template design

Our research presents a novel method for fabricating stand-alone PPy neural implants. The implants were designed with several apertures to permit potential neural growth through the implant windows. AutoCad software was used to create the designs for the PPy templates used in electrodeposition. These files were converted to DXF format to fabricate chrome-on-glass masks (International Phototool Company). Two designs were produced, one for the dissociated primary cerebral cortical cell studies and one for the in vivo implants. The following steps were the same for both designs. A 3000 Å silicon nitride layer was grown using low-pressure chemical vapor deposition (LPCVD, MRL Industries Model 718 System) on 4-inch (10 cm) silicon wafers (Silicon Quest International) to provide insulation. Standard lift-off was used to pattern the gold template from the mask onto the wafer. In short, photoresist (OCG 825 35 CS G-line photoresist) was patterned on the wafer followed by e-beam deposition of 200 Å of titanium for adhesion and 3000 Å gold. Removal of the photoresist left the patterned gold that was deposited directly on the insulating silicon nitride. The wafers were then diced using a flood-cooled die saw (Disco DAD-2H/6 T) with a layer of photoresist to protect the gold. The wafers were cleaned after dicing using acetone, ethanol, and water.

2.2. Electrodeposition

After the templates were cleaned, various forms of PPy (Aldrich Chemicals) were electrodeposited onto the gold surface using a constant-current power supply (HP 6614C). A current density of 1 mA/cm^2 was applied between the gold template and a platinum wire mesh reference electrode. The electrodeposition chamber was perfused with N_2 5 min prior to the start of deposition as well as throughout the electrodeposition process. By varying dopant composition and electroplating temperature, four types of culture substrates were made for in vitro studies, and five types of implants were made for in vivo studies. Electrodeposition solutions were aqueous solutions of 0.2 M PPy plus 0.2 M PSS (Aldrich), and 0.2 M PPy plus 0.2 M NaDBS (Aldrich). We attempted to control surface textures by varying the temperature during electrodeposition: 4 °C was intended to create a more macroscopic/coarse surface, while 25 °C was intended to create a fine-textured surface. Finally, a fifth formulation, 0.2 M PPy plus 0.2 M PSS in PBS, was electrodeposited at 25 °C to create the fifth type of implant to evaluate solvent conditions on the electrodeposition product (Table 1).

The PPy remained on the silicon die for the in vitro experiments, but for the in vivo work, the implants were released using a variety of methods depending on the PPy dopant. The PSS/PPy implants of both temperatures could be removed from the gold template by a gentle mechanical force. The removal of the NaDBS/PPy implants required chemical etching. The silicon nitride was etched by a 6:100 mixture of fluoroboric acid:phoshoric acid at 105 °C (US patent number 3,859,222) for 12 h. Upon removal of the silicon nitrogen layer (color change from purple of silicon nitride to gray of silicon), the PPy implants and the template die were placed in KOH. After approximately 1 h the PPy implants would float off of the template or could be removed by a gentle mechanical force. After removal from the template, the implants were separated by a razor into individual implants and soaked in 4 separate baths of filtered deionized water for 1 h each.

Table 1
Implants for in vivo experiments

Implant type	3 weeks	6 weeks
Stab	4	4
Teflon	4	4
4 °C PSS/PPy	4	4
24 °C PSS/PPy	4	2
4 °C NaDBS/PPy	4	
24 °C NaDBS/PPy	4	2
24 °C PSS/PPy in PBS		4