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Porous, Dexamethasone-loaded polyurethane coatings extend performance window of implantable glucose sensors *in vivo*

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ABSTRACT

Continuous glucose sensors offer the promise of tight glycemic control for insulin dependent diabetics; however, utilization of such systems has been hindered by issues of tissue compatibility. Here we report on the *in vivo* performance of implanted glucose sensors coated with Dexamethasone-loaded (Dex-loaded) porous coatings employed to mediate the tissue-sensor interface. Two animal studies were conducted to (1) characterize the tissue modifying effects of the porous Dex-loaded coatings deployed on sensor surrogate implants and (2) investigate the effects of the same coatings on the *in vivo* performance of Medtronic MiniMed SOF-SENSOR™ glucose sensors. The tissue response to implants was evaluated by quantifying macrophage infiltration, blood vessel formation, and collagen density around implants. Sensor function was assessed by measuring changes in sensor sensitivity and time lag, calculating the Mean Absolute Relative Difference (MARD) for each sensor treatment, and performing functional glucose challenge test at relevant time points. Implants treated with porous Dex-loaded coatings diminished inflammation and enhanced vascularization of the tissue surrounding the implants. Functional sensors with Dex-loaded porous coatings showed enhanced sensor sensitivity over a 21-day period when compared to controls. Enhanced sensor sensitivity was accompanied with an increase in sensor signal lag and MARD score. These results indicate that Dex-loaded porous coatings were able to elicit an attenuated tissue response, and that such tissue microenvironment could be conducive towards extending the performance window of glucose sensors *in vivo*.

Statement of Significance

In the present article, a coating to extend the functionality of implantable glucose sensors *in vivo* was developed. Our study showed that the delivery of an anti-inflammatory agent with the presentation of micro-sized topographical cues from coatings may lead to improved long-term glucose sensor function *in vivo*. We believe that improved function of sensors treated with the novel coatings was a result of the observed decreases in inflammatory cell density and increases in vessel density of the tissue adjacent to the devices. Furthermore, extending the *in vivo* functionality of implantable glucose sensors may lead to greater adoption of these devices by diabetic patients.

1. Introduction

It is well-established that tight regulation of blood glucose levels is the single most important factor in preventing complications from diabetes [1]. Researchers have been developing closed-loop artificial pancreas (AP) systems where real-time changes in glucose are used to trigger an insulin pump to deliver the appropriate dosages. In recent years, AP development has been stalled due to the unreliability and untimely failure of implantable glucose sensors [2].

Classical continuous glucose sensors are amperometric and percutaneous systems that rely on glucose oxidase [3–5]. Due to the short *in vivo* life of these sensors, new fully subcutaneous systems that rely on novel biomaterial platforms, unconventional enzymes, and novel optical technologies for glucose detection are in various stages of development [6–8]. However, the complexities of development and regulatory approval of these novel platforms makes their availability uncertain. Therefore, in addition to developing new approaches to sensing, it is imperative to also improve upon

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classical glucose sensing systems for technological advances to reach the public in acceptable timeframes.

Upon implantation, a glucose sensor is presented with a dynamic microenvironment that results from the foreign body response (FBR) [9,10]. Within seconds of implantation, proteins biofoul the sensor surface followed soon by the arrival of immune cells that attempt to degrade and consume the sensor. Since the sensor cannot be eliminated by the host, this response often culminates in the formation of an avascular fibrous capsule that surrounds the implanted sensor. As a result, blood glucose measurements from the sensor may be delayed, erratic, attenuated, and/or unreliable [6,9–11].

Initial biomaterial strategies to extend glucose sensor functionality have focused on preventing protein adsorption through the incorporation of hydrogel coatings. Although anti-biofouling strategies proved to be well suited for acute sensor applications, they appear to be insufficient to achieve reliable long-term glucose sensor performance [12–14]. Most recently, modeling and experimental studies have shown that inflammation and tissue encapsulation are critical stages affecting sensor function *in vivo* [15,16].

As summarized in Table 1 *in vivo* strategies for modulating the tissue response to implanted sensors have employed either the release of "tissue response modifiers", topographical cues, or biomimicry. Strategies for the attenuation of inflammation and the promotion of tissue vascularization have employed the release of growth factors (VEGF, PDGF), nitric oxide [17,18], or anti-inflammatory glucocorticoids [19–21]. Topographical approaches have exploited the application of porous polymer coatings, whereas biomimicry approaches have used tissue-like overlayers of collagen and/or cells [11,22–24]. To date, combined strategies to improve sensor biocompatibility have involved either dual agent release or antifouling gels merged with localized drug delivery.

Previously, we reported on the characterization of porous polyurethane coatings with a controllable microstructure, tunable drug loading and bioactive release of Dexamethasone (Dex) [25]. However, questions regarding the effects of coatings on the FBR and subsequent effects on glucose sensor function still remained. The current article presents two animal studies that assessed the effects of porous Dex-loaded coatings on Medtronic MiniMed SOF-SENSOR™ glucose sensors implanted in rat dorsal subcutis for up to 21 days. The first study examined whether Dex-loaded porous coatings deployed on fully subcutaneously-implanted Tygon® tubes both diminished inflammation and promoted vascularity of the tissue surrounding the implants. The second study examined whether Dex-loaded porous coatings deployed on functional percutaneous sensors resulted in improved sensor performance *in vivo*. Results of both studies indicate that Dex-loaded porous coatings are capable of (1) eliciting an attenuated tissue response and (2) extending the performance window of implanted functional glucose sensors.

2. Methods

2.1. Porous coatings

2.1.1. Coating preparation

As detailed elsewhere [25], porous coatings were fabricated by gas-foaming/salt-leaching technique. Briefly, a polyurethane solution of 6.5% w/w was prepared by dissolving Tecoflex® 93A pellets (Lubrizol, Technologies) in a solution of 75:25 chloroform to ethanol ratio. Forty-five milligrams of pharmaceutical grade Dexamethasone (Sigma, D9184) were added to the polymer solution to obtain a desired weight ratio of Dexamethasone/polyurethane solution of 0.8% v/v. The solution was then stirred until clear. One and a half grams of sieved ammonium bicarbonate salt particulates (50–75 μm) were added and homogenously mixed. Concentration of salt particles was varied in ratios to obtain scaffolds of desired porosities. Copper wire mandrels (Belden, 20 AWG) were used in place of glucose sensors to protect glucose oxidase bioactivity. Mandrels were allowed to dry overnight under vacuum. Finally, coatings were cut to a length of 1.5 cm to match Medtronic MiniMed SOF-SENSOR™ tip dimensions.

2.1.2. Coating sterilization

Dex-free and Dex-loaded porous coatings were slid onto Medical Grade Tygon® tubing mandrels (formulation S-54-HL Saint-Gobain, Courbevoie, France) to prevent deformation during sterilization and handling. Coatings were ethylene oxide sterilized and allowed to out-gas for at least seven days prior to implantation.

2.2. Tygon® tubing implantation study

2.2.1. Specimen preparation

Tygon® tubing was selected for testing of the foreign body response. Tygon® implants were of similar dimensions (1.5 cm long and 0.8 cm outer diameter) and mechanical properties to the tips of Medtronic MiniMed SOF-SENSOR™. As shown in Fig. 1a, Bare, Dex-free porous and Dex-loaded porous coated Tygon® implants were prepared for implantation. The coatings fitted snugly over the Tygon® tubing and did not need further affixing. Bare and coated implants were ethylene oxide sterilized as described above. Bare Tygon® tubing was used as a positive control

Table 1
Recent strategies used to regulate tissue response to implanted glucose sensors.

Strategy	Material and platform	Active agent (delivery window)	Test subject/implant site/ implant type	Length of study	Refs.
Attenuate inflammation	Rapid release of small molecule donors	Nitric oxide (1–3 days)	Rat/percutaneous/ microdialysis probes	2 weeks	[18]
Anti-fouling, attenuate inflammation	PVA hydrogel and drug loaded PLGA microspheres	Dex (1–3 months)	Rat/subcutaneous/stainless steel needle	4 weeks	[21]
Attenuate inflammation, promote vascularization	pHema-PEG hydrogel and PLGA microspheres	Dex and VEGF (3 days for Dex, 2 months for VEGF)	Rat/percutaneous/ microdialysis probes	6 weeks	[19,25]
Tissue biomimicry	Adipose derived stem cells (ASCs) coatings	N/A	Rat, percutaneous, microdialysis probes	8 weeks	[24]
Tissue biomimicry	Porous collagen coatings	N/A	Rat/percutaneous/glucose sensors	4 weeks	[23]
Promote tissue integration, vessel growth	Porous pHEMA and silicone scaffolds	N/A	Mouse/ percutaneous/cylindrical scaffolds	6 months	[26]
Promote tissue integration, vessel growth	Porous ePTFE coatings	N/A	Dog/percutaneous/glucose sensors	3–6 months	[27]
Promote tissue integration, vessel growth	Porous PLLA coatings	N/A	Rat/sub- and percutaneous/ glucose sensors	3 weeks	[11]

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