A New Structural Design of a Closed-Loop Insulin Delivery Implant Extends the Duration of Insulin Efficacy in a Type 1 Diabetic Rat Model by Impeding Immune Cell Infiltration

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ABSTRACT SUMMARY

A fully-implantable chemically-driven closed-loop insulin delivery device was developed for the long-term treatment of Type 1 diabetes in a rat model. To prolong insulin efficacy, the device structure and surface characteristics were carefully designed to impede immune cell infiltration to the glucose-responsive enzyme-containing implant surface while simultaneously preserving efficient transport of glucose and insulin between the device and the host tissue. As a result the host inflammatory response to the implant was drastically reduced and a greater than 3-fold increase in the insulin efficacy of the implant was achieved.

INTRODUCTION

Implantable closed-loop insulin delivery systems could offer diabetic patients improved glycemic control, compliance and quality of life. However long-term efficacy has yet to be achieved due to poor device biocompatibility resulting in fibrous encapsulation and/or cell-mediated degradation of the implant.

These systems must interact unimpeded with the host tissue for proper function and therefore cannot be masked using inert biocompatible materials. Thus active strategies for modulating the inflammatory response, including the sustained administration of anti-inflammatory agents such as dexamethasone and nitric oxide, have been proposed. However such strategies are often accompanied with side-effects and are difficult to implement.

The processes of fibrous encapsulation and cell-mediated degradation are preceded first by cell migration and attachment to an immunogenic implant surface, and subsequently by cell activation and release of pro-inflammatory factors. Hence we hypothesize that the host inflammatory response may be minimized by impeding cell infiltration to the potentially immunogenic implant surface.

Previously we have developed a self-regulated, chemically driven closed-loop insulin delivery membrane-reservoir system in which pH-sensitive poly(N-isopropyl acrylamide-co-methacrylic acid) (poly(NIPAM-co-MAA)) hydrogel nanoparticles serve to regulate insulin delivery in response to local glucose levels.¹⁻³ Here we demonstrate prolonged functional lifetime of the closed-loop insulin delivery implant by impeding cell infiltration to the implant surface using a microfabricated polymeric microporous membrane.

EXPERIMENTAL METHODS

A glucose-responsive plug was prepared by embedding pH-responsive poly(NIPAM-co-MAA) nanoparticles, nano-powdered MnO₂ particles, glucose oxidase and catalase within an albumin matrix (Fig. 1a).¹

A membrane-reservoir insulin delivery implant was formed by sealing the insulin reservoir opening with the glucose-sensitive variable porosity plug. Topographically smooth PDMS membranes featuring uniform and well-defined micron-sized pores (60 µm) were constructed using soft-lithography and affixed overtop of a chemically-driven closed-loop insulin delivery system (Fig. 1b).

Devices with and without the microporous membrane were implanted subcutaneously in healthy Sprague-Dawley rats for up to 30 days. Implants and their surrounding tissue was excised and prepared for histology. Tissue sections were stained using H&E and Mason’s...
trichrome. Inflammation was graded by a board certified veterinary pathologist. Cell migration to the glucose-responsive plug and subsequent cell-mediated degradation was assessed using environmental scanning electron microscopy.

Device efficacy was assessed in a STZ-induced Type 1 diabetic rat model. Blood insulin, glucose, and c-peptide levels were measured for 30 days.

RESULTS AND DISCUSSION

Microporous membranes minimized the accumulation of cells at the glucose-responsive plug surface and cell-mediated degradation compared to ‘no-membrane’ devices.

The microporous membranes further resulted in resolution of the inflammatory process to the implant as evidenced by minimal residual perivascular lymphocytic and histocytic inflammation, absence of neutrophils at the implant site, and a thinner fibrous capsule by day 30 following implantation as compared to those without the membrane coverage (Fig. 2).

As a result, use of the microporous membrane and space between the glucose-responsive plug and the membrane successfully prolonged the in vivo efficacy duration by up to 3-fold (28 days) compared to unprotected ‘bare’ devices (Fig. 3).

REFERENCES


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