An Implantable Closed-Loop Insulin Delivery Device for Glucose Control in Type I Diabetes

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Introduction: Achieving and maintaining normal blood-glucose levels is critical for long-term care of insulin-dependent diabetic patients and avoidance of many diabetes complications. Numerous clinical trials have demonstrated that tight control of blood glucose levels can mitigate the progression of negative consequences associated with diabetes mellitus. Unfortunately, this is not being achieved with current open-loop insulin therapies available. Even with basal-bolus therapy, a combination of continuous insulin infusion with bolus doses of insulin at meals, constant peaks of hyper and hypoglycemia persists in most patients. The development of an implantable closed-loop device able to release insulin automatically in response to blood glucose concentrations has long been a long-term goal to obtain improved insulin therapy.

Objectives: The main objective of this research is the development and the *in vitro* and *in vivo* evaluation of a nanotechnology-enabled, implantable closed-loop insulin delivery device prototype for tight control of glycemia in Type-1 diabetes in a rat model.

Hypothesis: We hypothesize that through the implantation of the device it will be possible to obtain sustained normoglycemia in Type 1 diabetic rats and avoidance of hypoglycemia. The developed prototype device was expected to release insulin automatically in response to glucose levels and to provide basal and hyperglycemic insulin to control both fasting and mealtime glucose levels without the requirement of insulin injections.

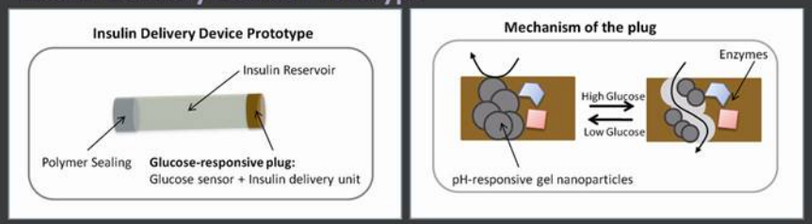
Methods

Preparation of devices: Devices were prepared by integrating a glucose-responsive plug with a biocompatible insulin reservoir as described by Gordijo et al. Devices were filled with buffered insulin solution.

***In vitro* tests:** *In vitro* insulin release was determined by placing devices in buffered glucose solutions (100, 200 and 400 mg/dL). Insulin release was monitored manually overtime using a UV-VIS system set at 276 nm for insulin detection.

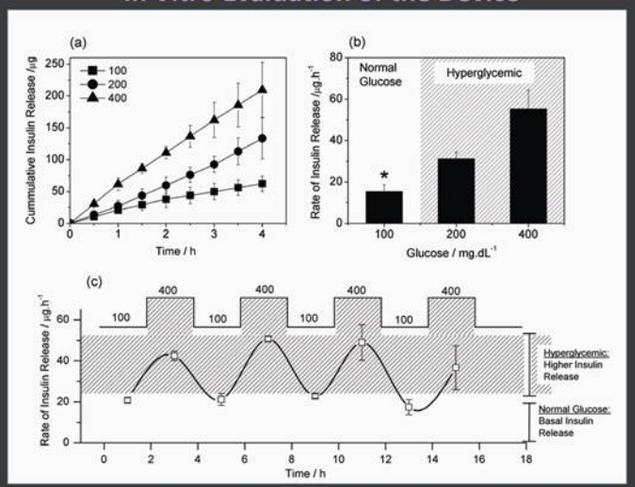
***In vivo* tests:** Streptozotocin (STZ)-induced diabetic male Sprague Dawley rats were intraperitoneally implanted with devices, and blood glucose levels and plasma insulin were monitored daily. For glucose challenge test, implanted rats received intravenous glucose injection (1g.kg^{-1}) and glucose and plasma insulin levels were monitored for 1h following injection.

Insulin Delivery Device Prototype



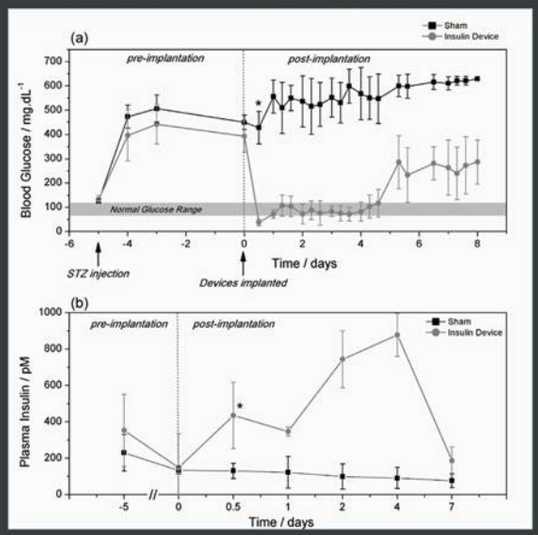
The device: A biocompatible insulin reservoir sealed with a specially designed glucose-responsive plug. The plug functions both as a glucose sensor and controlled delivery unit releasing insulin from the reservoir in response to hyperglycemic blood glucose levels and decreasing insulin release from the reservoir upon sensing normal or hypoglycemic blood glucose concentrations.

In Vitro Evaluation of the Device



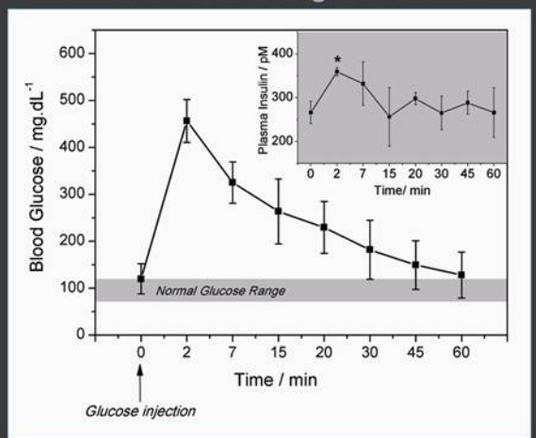
In vitro experiments showed that the device is able to respond quickly to alterations of glucose levels relevant to a diabetic scenario and release insulin on-demand in real time. A 3-fold increase in insulin permeation was observed when the glucose concentration was increased from normal to hyperglycemic levels, which returned to the baseline level when the glucose concentration was reduced to a normal level.

In Vivo Evaluation of the Device



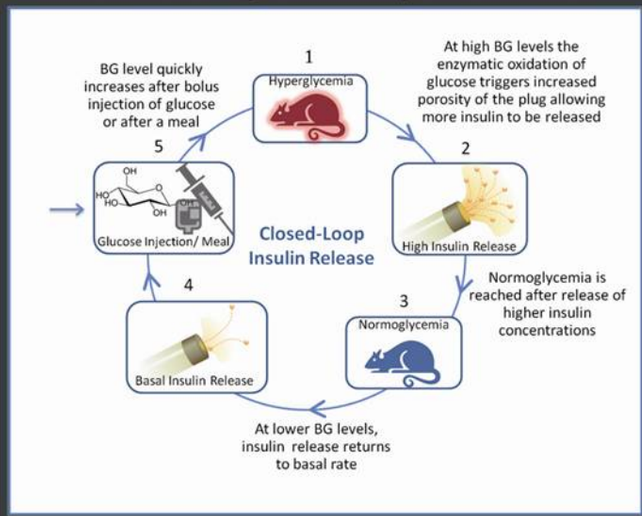
The device was demonstrated to be safe and effective in STZ-diabetic rats. The blood glucose of the implanted group was maintained in the normal level (~90 mg/dL) for up to 6 days without peaks of hyper or hypoglycemic states.

Glucose Challenge Test



In a glucose challenge test the device exhibited rapid insulin release and restoration of normoglycemia *in vivo* when implanted diabetic rats were challenged with glucose injection.

Glucose-Regulated Mechanism of the Device for the Control of Glycemia in Implanted STZ-Rats



The automatic feed-back mechanism of the glucose-responsive plug produces closed-loop insulin release. Unlike the insulin pumps, which require external inputs to regulate the rate of insulin release, the prototype device can sense the glucose levels in real time and release insulin automatically according to the glucose levels. In addition to the closed-loop profile, the device also presents the advantage of continuous release of a low basal rate of insulin that is required to manage normal glucose fluctuations and maintain normoglycemia.

Conclusions: We have applied nanotechnology to design and fabricate a polymeric, implantable, closed-loop insulin delivery device prototype which combines both continuous glucose sensing and controlled insulin delivery in a single platform. The device showed great success both *in vitro* and *in vivo* for glucose-controlled release of insulin. In initial testing with STZ-diabetic rats the device demonstrated safe control of blood glucose levels for one week with fast, reversible response to glucose challenges *in vivo*.

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