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SELF-REGULATED INSULIN DELIVERY—ARTIFICIAL PANCREAS

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ABSTRACT

A chemical mediated artificial pancreas has been designed that will deliver glycosylated insulin (G-Ins) in response to glucose concentrations. This system is based on the competitive binding between G-Ins and glucose to a saccharide binding substrate, Concanavalin A (Con-A). Con-A has was evaluated as a soluble monomeric protein, enclosed within microcapsules, formed into microspheres, and synthesized as a soluble high molecular weight oligomer. These forms were designed to maintain the binding characteristics of Con-A and G-Ins and to prevent leakage or permeation of Con-A across the device membrane.

INTRODUCTION

Diabetes is one of the three prevalent causes of death in the United States following cardiovascular disease and cancer (1). Diabetic complications is also the leading cause of blindness, kidney disease, neurological disorders, cardiovascular disease and amputation of limbs (2). Insulin has been used for Type I diabetic patients for 80 years. Although insulin injection saves millions of patients lives, effective control of blood glucose is difficult due to failure of insulin concentration responses to the glucose concentrations. For these reasons, the development of an artificial pancreas, or a device which will release insulin in response to blood glucose levels is under intense investigation (3,4).

We have been working on an insulin delivery system which consists of glycosylated insulin (G-insulin) bound to concanavalin A (Con-A) (5). The system is contained within a membrane pouch and will release G-Ins in response to the amount of glucose influx, as shown in Figure 1.

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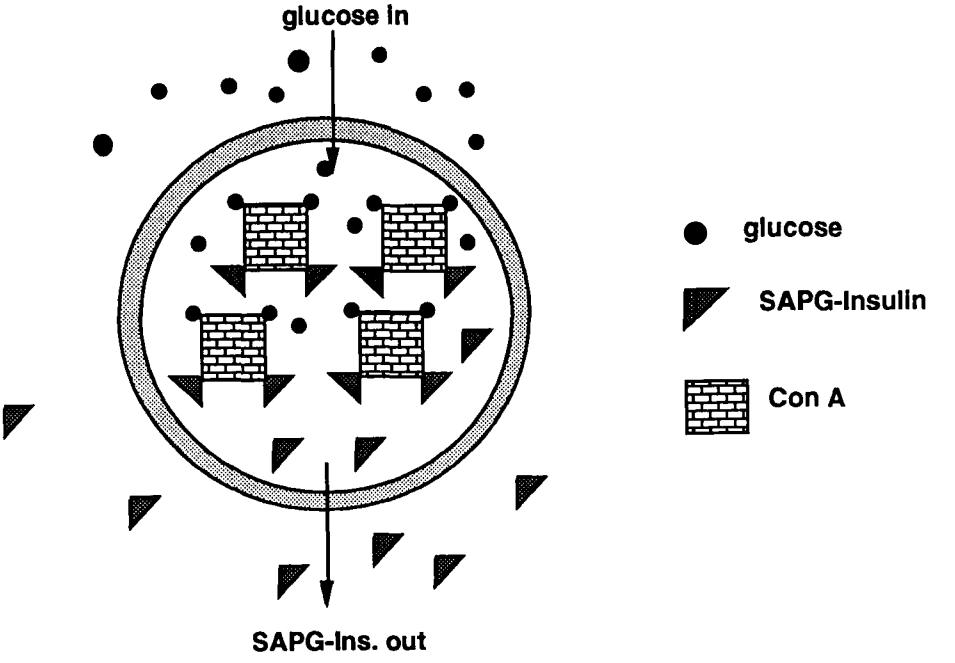

Figure 1

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EXPERIMENTAL

To date, we have successfully synthesized succinyl-amido-phenylglucopyranosyl (SAPG)-insulin, and a variety of other saccharide derivatives, such as maltosyl, galactosyl, and fucosyl insulins (6-9). SAPG-insulin was evaluated extensively and determined to be bioactive, non-immunogenic, and presented a pharmacodynamic profile in man similar to unmodified native insulin. In addition, G-Ins was found to be more stable with a reduced tendency to aggregate than native insulin (6). The substrate, Con-A has been modified into such forms, such as: soluble solution (7,8), intermolecular coupling to form high molecular weight oligomers (12), and synthesized into microspheres (10) and beads (9), all in an attempt to optimize its potential for self-regulated insulin delivery, as described in Tables I and II.

Experimentally, we have designed and evaluated the fabricated device under various conditions. For optimization of the system, SAPG-Ins release was evaluated by varying specific parameters, such as device surface area, membrane permeability, and loading amount and loading ratio (SAPG-Ins to ConA). The *in vitro* results should be compared with the predictions of mathematical models and optimal conditions should be decided for further *in vivo* application, as shown in the flow-chart in Figure 2.

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TABLE I

	Binding Substrate	G-Insulin	Membrane	Comments
System I	Soluble ConA tetramer	SAPG-Ins SAPM-Ins	p-HEMA Cellulose acetate	ConA Leakage. Decreased permeability of glucose and G-Insulin. Long Lag times.
System II	ConA immobilized onto Sepharose® beads	SAPG-Ins SAPM-Ins	Cellulose acetate (porous) Nucleopore membranes	ConA Beads settled out of device. Fabrication. Poor G-Ins response to glucose.
System III	ConA hydrogel	SAPG-Ins	Durapore® membrane fabricated into a 'pouch'	No ConA leakage. Short lag times for glucose/G-Ins. Heat sealable membrane for fabrication.
System IV	ConA microcapsules	SAPG-Ins	Durapore® membrane fabricated into a 'pouch'	Microcapsules (30-250 μm) contain ConA/SAPG-Ins. No microcapsule leakage from device. Short lag times and good permeabilities for glucose and G-Insulin.

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The *in vivo* performance of the current designed devices (Table II) containing modified Con-A and SAPG-Ins were evaluated in a diabetic canine model. The device was implanted into the peritoneal cavity of a pancreatectomized dog and the blood glucose level monitored to evaluate the function of the implanted device by refilling or recharging with fresh Con-A/SAPG-Ins solutions. As shown in Figure 3, the device successfully controlled blood glucose levels in response to feeding challenges for up to

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TABLE II

	Binding Substrate	G-Insulin	Membrane	Comments
System V	ConA Microspheres	SAPG-Ins	Durapore® membrane fabricated into a 'pouch'	Microspheres fabricated from ConA, bound with SAPG-Ins. No microcapsule leakage from device, however, tended to settle in the device. Short lag times and good permeabilities for glucose and G-Insulin.
System VI	Soluble ConA oligomer	SAPG-Ins	Hollow fiber recirculation system	ConA oligomer not permeable to hollow fiber membrane, yet good permeability to glucose and SAPG-Ins. Short lag time and good permeability to glucose and SAPG-Ins. Refillable system

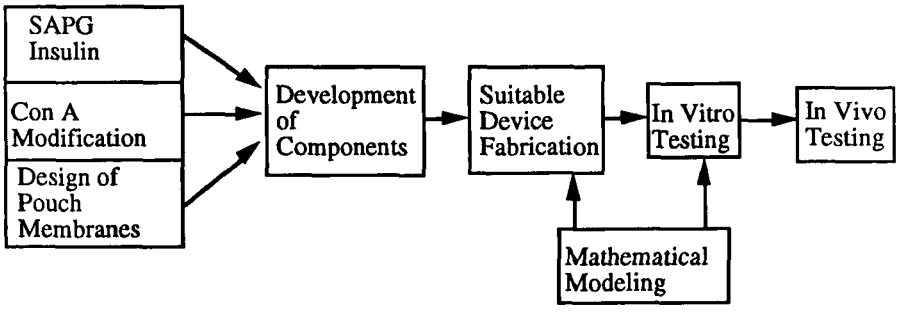

FIGURE 2

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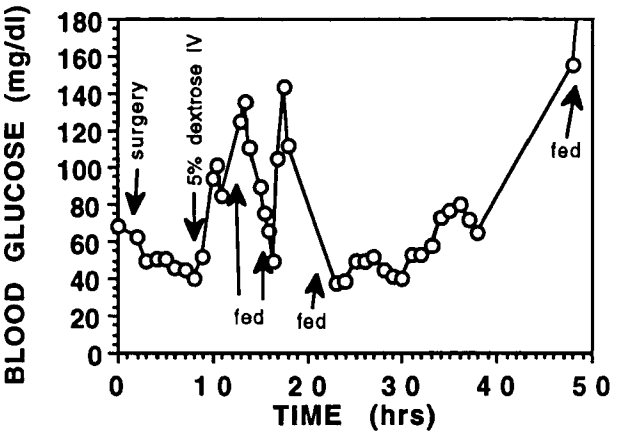

Figure 3

48 hours. After that time, the device failed, even with recharging. Postmortem, the devices were infiltrated with proteins and covered with fibrous tissue, restricting the transport of G-Ins and interfering with glucose and G-Ins binding to Con-A.

Our current research is aimed at developing a protein selective membrane (13) with which to house the Con-A/SAPG-Ins device. This new material will allow free diffusion of glucose into the device to displace G-Ins bound to Con-A. Preliminary results demonstrate the membrane to present a low molecular weight cut-off (70,000), which will prevent permeation of most plasma proteins and immunoglobulins, hopefully, extending the usefulness of the implantable artificial pancreas.

ACKNOWLEDGMENT

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