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Insulin Releasing Polymers for Treatment of Diabetes

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INTRODUCTION

Although the discovery of insulin by Banting and Best in 1922 has lead to treatment regimens for diabetics, daily insulin injections do not maintain glucose homeostasis. It is this inadequacy of current insulin therapy which results in the eventual serious long term complications of diabetes such as glaucoma, kidney and heart disease. Thus, there is a need for new methods which will constantly maintain euglucemia.

The difficulty in designing insulin delivery systems is that two types of insulin release are required. The first is the release of a baseline level of insulin to maintain normal fasting blood sugar levels. Secondly, a higher rate of insulin must be delivered to lower the increased blood glucose levels present immediately after meals. Thus, insulin delivery systems must have the ability to release a low baseline level of insulin and also periodically release insulin at an increased rate.

The research efforts in development of new insulin delivery devices using polymeric membranes can be divided into three categories. The first one includes systems which have a low baseline release of insulin and have mechanisms which can be activated by external stimuli, thereby increasing insulin release. Second, are the systems which regulate the rate of insulin release by the amount of glucose present. Thus, after meals when glucose levels are high, insulin release is amplified. Finally, there are hybrid devices which are both living pancreatic cells and polymeric membranes.

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EXTERNALLY STIMULATED INSULIN RELEASING SYSTEMS

The concept is utilized in several systems currently under development. The external stimuli can be magnetic, sonic, electrical, or thermal. Langer et al[1] have developed a hemispheric EVA insulin releasing system imbedded with a magnetic ring. They have shown the ability of the device when implanted in rats to increase insulin release when an external oscillating magnetic field is applied. This group is also studying the effect of ultrasound on insulin release rates. Another application of this concept is being developed by Sefton et al[2]. Their sytems employs an insulin reservoir which is situated in a micropump. Baseline insulin release is a diffusion controlled process though a hydrophilic membrane. Augmented release is effected by the application of current to a built-in solenoid and subsequent compression of the piston like device causing the "squeezing" ofinsulin through a compressible hydrophilic polyurethane foam. Finally, tempe-

rature sensitive polymers have been developed our group[3]. These acryl amide derivative copolymers have an increased degree of swelling at lower temperatures. At 37 C, these polymers could release insulin at a fixed rate. After meals, it is possible insulin release by decreasing the temperature of the polymer.

GLUCOSE REGULATING INSULIN RELEASE SYSTEMS

There are also devices designed to release insulin in direct response to the amount of glucose present. In this group are several systems which utilize the enzyme glucose oxidase to effect changes in a polymer membrane and thereby increase the rate of release of insulin. Ishihara and Shinohara[4] have developed a DEA-HMPA copolymer membrane with immobilized glucose oxidase. Glucose reacts with the immobilized enzyme forming gluconic acid and hydrogen peroxide. Hydrogen peroxide can cause a redox reaction on a polymer having a nicotinamide moiety, causing the increase of polarity of the polymer and the subsequent increase in insulin permeability.

Horbett and Ratner[5] are developing a glucose oxidase containing hydrogel. The formation of gluconic acid by the reaction of glucose oxidase and glucose increases the swelling of the hydrogel and insulin permeability is increased. The main advantage of this system over Ihsihara's membrane is the reversibility of the effects. No mechanism for reversing the oxidation to cause a return of the membrane to its reduced glucose sensitive state is apparent. In this case however, the membrane swelling has been demonstrated to be fully reversible.

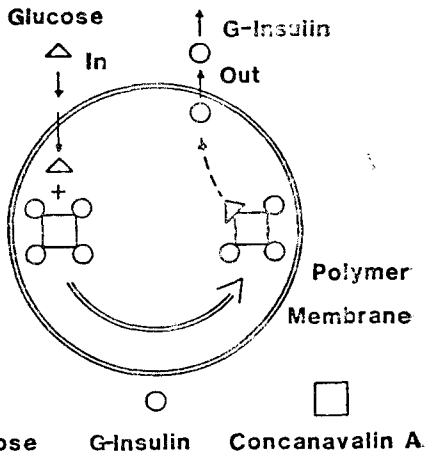

Fig. 1. Schematic of Self Regulating Insulin Delivery Systems

Heller et al. are also developing a glucose oxidase containing polymer[6]. This is a biodegradable system using a poly orthoester dispersed with glucose oxidase and insulin. The reaction between glucose and glucose oxidase is hypothesized to occur in the outer layers of the device and the gluconic acid thus generated will catalyze the surface erosion of the polymer. Thus, this system should undergo a surface erosion process at rates directly proportional to the surrounding glucose concentration.

Another application of the glucose controlled insulin delivery system is being developed by our group[7~9]. This design as shown in figure 1, is based on a combination of biological modulation and controlled release. The design of this delivery system utilizes the concept of the competitive and complementary binding behavior of a plant lectin, Concanavalin A(Con A) with glucose and glycosylated insulin. The derivatized insulin is bound to Con A which is also complemetary to glucose. This complex is enclosed in a polymer membrane. Glucose diffuses thro-

ugh the polymer membrane and into the device and displaces glycosylated insulin in proportion to the amount of sugar present. The derivatized insulin then diffuses out of the device. The feasibility of this system has been demonstrated both *in vitro* and *in vivo*. In the *in vitro* experimentation the device was exposed to a step function glucose challenge and the efflux of glycosylated insulin from the device was monitored. It was found that the device was sensitive to changes in glucose concentration[8].

In vivo experiments utilizing this design in dogs have also been conducted. It was found that a cellulose acetate pouch filled with a Con A-glycosylated insulin conjugate implanted intraperitoneally was capable of decreasing glucose levels in diabetic dogs for up to a week[9]. Longer term implantation is currently being investigated.

HYBRID INSULIN RELEASING SYSTEMS

Hybrid systems under development involve the use of pancreatic islet cells. Sun and O' Shea[10] have encapsulated rat islet cells in a biocompatible alginate-polylysine-alginate membrane. These capsules injected intraperitoneally in diabetic rats maintained normal blood glucose for almost two years. Another design utilizing islet cells has been studied by Ohgawara and Sakurai[11]. They developed a system with a monolayer of islet cells covered by a polycarbonate membrane. Using this design they were able to obtain variable insulin rclease in response to changing glueose concentrations with lag times of less than 15 minutes.

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