Future Developments in Insulin Delivery Systems

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The future of insulin delivery will be influenced by a current explosion in what might be called glycemic awareness. Self-monitoring of blood glucose, glycohemoglobin, and fructosamine assays, and patient education, have all contributed to an increased awareness of the exact blood glucose levels throughout the day. From this awareness, we now know that even the best diabetic control rarely approaches normoglycemia; what we accept as fair, much less poor, control may average twice the normal mean blood glucose levels. The DCCT has now changed the question of diabetic control from whether to how by definitively proving that improved control reduces the occurrence of long-term complications. This trial also highlighted the major adverse side-effect of our current approaches to euglycemia, severe hypoglycemia.

Meeting the glycemic targets (neither too high nor too low) in this era of increased glycemic awareness is a major challenge that usually goes unmet. The reasons are many, ranging from a lack of available patient education and inadequate access to good health-care professionals to poor patient acceptance of the necessary regimentation. To a significant extent, though, poor glycemic control is the inevitable result of our unphysiological approach to insulin administration.

Even with the most compliant patient, who follows the advice of the most knowledgeable professional, we still do at least three things wrong in replacing normal pancreatic insulin secretion. We produce highly variable patterns of insulin absorption that do not approximate physiological levels, we deliver insulin into the peripheral venous circulation rather than directly to the liver, and we link insulin delivery only very loosely to actual demand.

Insulin absorption is strongly affected by local variables such as site and depth of injection, heat of the skin, vascularity of the tissue, and exercise of the muscle that underlies the site of insulin injection. No practical way has been found to control these variables using standard injection techniques. Furthermore, although insulin disappears from the circulation with a half-life of several minutes, the rate of absorption into the circulation is determined largely by unphysiological chemical modifications. Such alterations include adding protamine to delay absorption (NPH insulin or protamine zinc insulin) or modifying the crystal size by adjusting the zinc concentration (lente insulins). The resulting absorption patterns are broad and gradual; they possess neither the clean, sharp, postprandial peaks needed to cover meals nor the steady basal rate normally found between meals.

When insulin is absorbed from the subcutaneous space, it enters the peripheral venous circulation rather than the hepatic portal system. Because ~50% of insulin is normally cleared in its first pass through the liver, peripheral delivery yields significant peripheral hyperinsulinism, while reducing the exposure of the liver to high insulin concentrations. Early literature discusses the potential results of this unphysiological insulin delivery (1).

Finally, the ability of the β-cell to sense and respond to ambient glucose concentration makes the normal pancreas the ultimate insulin delivery system and makes all open-loop systems intrinsically inferior. Although nonglucose signals—circulating hormonal modulators, neurogenic or paracrine factors—do influence the physiological control of insulin secretion, whether their role is more than a secondary one is not clear. A rapid, sensitive, and accurate glucose sensing system linked to insulin delivery would very likely normalize blood glucose concentrations and, thus, obviate the diagnosis of diabetes, at least as we currently view the disease.

Some of the new approaches to insulin delivery that seek to remedy the weaknesses in conventional injections are described below. Included is a discussion of the background of each technology, its present status, advantages, and disadvantages, and future prospects.

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DCCT, The Diabetes Control and Complications Trial; ADA, American Diabetes Association; NPH, neutral protamine Hagedorn; SPAD, subcutaneous peritoneal access device; CSII, continuous subcutaneous insulin infusion; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; PIMS, programmable implantable medication system; MIP, MiniMed implantable pump.

INSULIN INJECTION DEVICES

Background

In response to the discomfort, inconvenience, and variability of conventional

subcutaneous insulin injections, a variety of improvements in syringe and needle technology have been made over the years. Low-dose (0.5 ml) syringes, syringe attachments that magnify the numbers, and ultrafine needles are among the improvements that, for some years now, have made insulin delivery easier, more accurate, and less painful. Spring-loaded devices also are available and useful for helping the occasional patient who prefers to set off a trigger rather than push a plunger.

Jet injectors deliver insulin transcutaneously by an air-jet mechanism rather than a needle. A very fine stream of insulin penetrates the skin under high pressure. The ADA issued a policy statement in 1988 (2) citing evidence that absorption is faster with jet injectors than with conventional needle delivery (3,4). Because of their expense (≥$1,000), patients are advised to try these devices for a while before purchasing them. However, many people find them no less uncomfortable than standard injections.

Present status

A consumer guide that compares the features and prices of the various devices provides an annual update (5). The ultrafine needles, low-dose syringes, and jet injectors are all currently available options. Many patients now use premixed NPH and regular preparations, usually as 70% NPH/30% regular ratio.

Of the more recently developed devices, pen-injectors have achieved some popularity. The pen-sized syringes house a cartridge containing 1–2 ml of insulin. After setting the dose by a dial, the needle is inserted in the skin, and a plunger delivers the dose. These devices seem to find their best application in patients taking multiple-dose regular insulin before each meal (6,7). They eliminate the inconvenience of carrying insulin and syringes to draw each dose.

A rarely used modification, which bypasses expensive pump technology, is the SPAD (8). As reviewed by Selam and Charles, these devices deliver insulin subcutaneously through an externalized port that remains in place for several days (9,10). At each meal, the patient injects insulin through the access port. Previously, the reservoir tended to become overgrown with tissue. Furthermore, infection resulting from multiple injections and relatively long external exposure is a significant drawback. Although a modification now places the reservoir subcutaneously, with an intraperitoneal delivery site, infection remains a concern. Even though the reservoir is subcutaneous, it is accessed many times a day, and peritonitis could be a serious complication.

Advantages and disadvantages

The goal of delivering subcutaneous insulin more accurately and less painfully is, of course, laudable. New devices have made progress toward that goal. The insulin delivery devices are relatively inexpensive and low tech. Note that all forms of depot insulin will suffer from each of the unphysiological factors listed above and that insulin delivered through the skin inevitably causes discomfort.

Future

Innovative technical advances will undoubtedly be made in these devices. The ability to mix long-acting insulins with regular insulin in the pen devices will be an improvement, as will more reliable jet-injector devices. For years to come, though, conventional injections may remain the accepted method of insulin administration for the vast majority of people with insulin-requiring diabetes. Thus, any measure that can reduce the discomfort and improve the reliability and convenience of insulin delivery is for the better.

CSII

Background

CSII refers to the use of external insulin pumps. When originally tested in the early 1980s, these pumps were relatively large and cumbersome devices. Early studies demonstrated that IDDM could be very well controlled with CSII (11,12) and that such control improved everything from growth in children (13) to lipid status (14–16) to retinopathy (17,18). This approach was used in pregnancy where tight glycemic control is clearly indicated (19,20). Certain centers developed a large experience with CSII (21).

Most of the original studies, however, were performed under metabolic-ward conditions and/or with very small numbers of patients. Inevitably, as use in the field uncovered the limitations of CSII, the enthusiasm was dimmed. Specific complications were documented, such as subcutaneous abscess formation, leaking tubing, and pump malfunction (22). Long-term patient acceptance was not as high as initially forecasted (23); although, according to some reports, the percentage of people that continued to use CSII remained high (24,25). The incidence of diabetic ketoacidosis has increased in people using CSII, because discontinuation of flow (for whatever the reason) results in a very rapid development of insulinopenia that, in turn, leads to a rapid development of ketonemia (26). Serious concern arose after three small studies found that abrupt initiation of tight diabetic control could actually worsen established diabetic retinopathy (see below) (27–29).

Present status

External insulin infusion pumps (CSII) are available as an option for the treatment of insulin-requiring diabetes. The technology has been vastly improved so that the pumps are small, and their use is simple. Therapy is usually initiated during hospitalization so that safe basal rates and prandial boluses can be established. Since the advent of buffered insulins, insulin aggregation is seen much less often now than in the past (30). The question of whether sudden onset of tight control worsens retinopathy was raised by earlier

studies. The DCCT confirms this finding, but also confirms that the worsening (specifically, formation of soft exudates) is transient (29) and that the long-term effect of improved control is positive. Most clinicians recommend that tight control be established over several months rather than several days in instances of significant retinopathy. The occurrence of diabetic ketoacidosis among patients on CSII represents a failure of communication—either the patient was not taught the emergency measures necessary to deal with stopped flow (including the prompt resumption of conventional insulin injections as necessary), or the patient failed to conduct these measures.

Patient selection is crucial for the successful use of CSII. In evaluating potential pump users, promising signs include a demonstrated acceptance of frequent (3–4 times daily) self-monitoring of blood glucose, good understanding of diabetes, stable personality traits, reasonable expectations, and less than end stage complication status (25). The converse of each trait increases the risk that CSII will prove unacceptable. Physician enthusiasm and experience with CSII undoubtedly play a role in patient acceptance. One experience has shown that patients of physicians who have only a few patients using CSII were far more likely to stop the treatment (23). However, there also is a danger in pushing the therapy on unenthusiastic patients.

Advantages and disadvantages

CSII delivers basal/bolus insulin doses with precision and provides a basal rate that does not fade after a peak absorption of subcutaneously delivered insulin. It allows the patient to consider, before each meal, exactly how much insulin is required and to deliver just that amount. It removes most of the variables listed above for conventional injections, such as depth of injection and exercise of the limb, and does not depend on absorption of a large depot of predelivered insulin. In addition, a needle stick is required only every 2 to 3 days, the pump itself can be made unobtrusive, and indwelling polyethylene infusion sets are more comfortable than needles for some patients. For the above reasons, improved diabetic control may be established with CSII. Indeed, such control may even be more likely with CSII than with conventional insulin. However, CSII does not guarantee better control. Studies comparing levels of glycemia (CSII versus conventional injections) find variable results, which depend heavily on patient selection and specific follow-up protocols.

Because CSII remains an externalized system, certain disadvantages are apparent. Occasional subcutaneous abscesses develop that may require incision and drainage and antibiotics. Needles may become dislodged, tubing occasionally leaks, and pumps occasionally have electronic failures. Consequently, patients must remain vigilant with glucose monitoring. The pump is usually removed for bathing or swimming, and careful technique must be used whenever tubing is changed. Finally, it is an expensive therapy; but, in the properly selected patient, CSII has much to recommend it.

Future

Advances in CSII will be marginal—some programming features may be simplified, memory capabilities may be introduced, and, particularly, predictors of patient acceptance should be further defined. The battle between physicians for the pumps and those against should break down so that a larger number of qualified physicians will be in a position to successfully use external pumps in appropriately selected patients.

In the long term, external pumps could possibly be linked to subcutaneously placed glucose sensors similar to those originally developed in Japan (33). Such a device could require only minimal care (i.e., changing a needle every few days) and could deliver the necessary insulin on demand.

IMPLANTABLE INSULIN PUMPS

Background

Research on implantable insulin pumps has progressed gradually over more than two decades. The earliest work was done by Buchwald et al. (34,35) at the University of Minnesota. The original pump was manufactured by Infusaid (Norwood, MA) and had only one delivery rate, which was determined by positive-pressure freon. Although this pump was used successfully in a number of people with type II diabetes (36), its main clinical use was to deliver chemotherapy. Thousands of constant rate pumps were implanted for this purpose.

Variable-rate, implanted insulin pumps were first used in humans in the early 1980s by Irsigler et al. in Austria (37) and Schade et al. in New Mexico (38). However, these pioneering efforts were successful for relatively brief periods.

The first successful variable-rate, implanted insulin pump was the PIMS. This was the product of a large collaborative effort centered at the Johns Hopkins University (39). Robert E. Fischell, in the Johns Hopkins University Applied Physics Laboratory, introduced important advances in design (40). For example, whereas previous devices had a roller-pump mechanism, PIMS used a positive displacement piston that required far less energy and was less traumatic to insulin. The insulin itself was stabilized with a surfactant material to overcome the adherence to the device surfaces and subsequent insulin aggregation (41). Over the course of 2–3 years, with funding from the National Institutes of Health and the National Aeronautics and Space Administration, PIMS prototypes were fabricated and used in dog trials. These preclinical trials alone took 4 yr, but were ultimately successful enough to justify human implantations (42).

PIMS was first implanted in a human in 1986, at Johns Hopkins. A total of 18 IDDM subjects were implanted

over the next 6 mo, at Hopkins and at the University of California, Irvine, under the direction of Selam and Charles to test the feasibility of long-term implanted insulin pump therapy. Various adverse effects were encountered in these early trials. Most complications, for example, one pump infection of the fibrous tissue pocket that forms around the pump and one electronic failure, are sporadic and not considered systematic. The single clinical adverse event that did (and still does) occur with regularity is fibrous tissue blockage of the catheter in the peritoneal space (see below). Overall, the PIMS experience was considered a success, justifying larger clinical trials (43).

A parallel study was completed contemporaneously, which used a device designed and manufactured by Siemens Company (Frankfurt, Germany) (44). Clinical and device complications occurred at a somewhat greater rate, and this pump was returned to the drawing board before being used in further clinical trials.

PIMS, meanwhile, evolved into a second-generation device, the MIP by MiniMed Technologies (Sylmar, CA), and another variable-rate, implanted insulin pump was designed by Infusaid (Norwood, MA). Although there are differences between these implanted insulin pumps, some of which may be important to the success rate and clinical acceptance by the patient (45), their similarities are greater than their differences.

Present status

Both types of pump in use today (MIP Model 2001 and the Infusaid Model 2000) are surgically implanted subcutaneously, usually on the left side of the abdomen. These pumps are both disk-shaped, 7–9 cm in diameter, 1.9–2.5 cm thick, and weighing 180 to 250 g. The catheter tip, which delivers the insulin, usually is placed in the peritoneal space. The tip can move freely but remains secured proximally as it enters the peritoneum. Intravenous delivery generally has been less successful (46). Both of the pumps deliver a basal infusion of insulin with periodic, timed pulses. This also allows the patient to control prandial bolus insulin doses, using an external telemetry unit.

As of 1993, 2 pumps (in addition to the MIP) are undergoing independent, industry-sponsored trials. One pump is manufactured by Infusaid, and the other by Siemens. Altogether, over 400 IDDM subjects have been implanted in the 3 studies in over 20 centers in the U.S. and Europe. In addition, the U.S. Department of Veterans Affairs has initiated an independent cooperative study in 7 Veterans Affairs medical centers. This trial, which includes randomized allocation of patients to implanted pump or multiple dose therapy, should determine whether implanted pumps offer advantages over multiple dose insulin therapy and whether they can usefully be included in the long-term trials of NIDDM treatment (47).

Thus far, all current trials of implanted insulin pumps have found a low incidence of electronic device failure, pump-pocket infection, and surgical complications. The Infusaid device has reported a problem with pump slow down, which was attributable to insulin precipitation (46).

The most significant complication found thus far with the implanted pumps is, as mentioned, catheter obstruction in the peritoneum. Current experience suggests an incidence of ~0.2 obstructions/patient/yr or possibly somewhat less. The obstructions can be corrected by a laparoscopic surgical approach with minimal morbidity, but they may recur. Whereas earlier experience found relatively large, macroscopic tissue encapsulation of the catheter tip, the newer catheter designs have yielded less macroscopic tissue blockage. Instead, catheter blocks more often have been small fibrin plugs in the tip of the catheter.

From the original cohort of 10 patients who were started on PIMS at Johns Hopkins in 1986–1987, 8 have been successfully managed for 6 to 7 yr continuously, using implanted insulin pump therapy; 2 were explanted for recurrent catheter blocks after 4 to 5 yr. Of the 8 long-term successes, with an average of over 4.75 yr, 4 have never had a complication, 3 have had one laparoscopy, and 1 has been laparoscoped twice.

Advantages and disadvantages

Implantable insulin pumps, like CSII, deliver insulin in a basal/bolus pattern that is controlled by the patient. In most respects, though, the implants are quite different from CSII. Implantation eliminates the need to change the catheter and needle, the need to have a pump attached at all times, the concern that the needle is placed correctly, and infection and inflammation attributable to the external access route.

To patients who use implanted insulin pumps, the perceived advantage is the ability to deliver insulin without the bother and the discomfort of insulin injections or an external insulin infusion pump. Scientifically, the major advantage may be the precision of the insulin dosage and, at least potentially, the absorption of insulin into the hepatic portal system (1). Much remains to be learned about whether intraperitoneal insulin has advantages over subcutaneous delivery, but the avoidance of peripheral hyperinsulinism may be a significant benefit, particularly in NIDDM patients. Preliminary studies have achieved excellent diabetic control without excess hypoglycemia, although proof of this awaits the results of the Veterans Affairs trial.

With the benefits of a subcutaneous pump, however, comes the need to develop a device that is extremely reliable and safe. Problems cannot be solved simply by removing the pump and returning it to the manufacturer, nor can design modifications be easily implemented. Earlier models implanted in humans had unacceptable mechanical failure rates. Detailed and sometimes

tedious preclinical trials have proven necessary prior to human implantations.

Other disadvantages of implanted insulin pumps include the need for surgical implantation (performed either under local or, more frequently, general anesthesia); the chance of intraperitoneal catheter block; the need (as with CSII) for frequent blood glucose monitoring, both to choose a proper dose of insulin and to quickly recognize a failure to deliver insulin; and the fact that implanted pumps are, at present, research devices, which are only available as part of approved protocols. The cost of the system also is a disadvantage; although, given the overall costs of treating diabetes and its complications, this expense may not be a major factor.

Future

Upcoming advances in implanted insulin pumps could include premarket approval by the U.S. Food and Drug Administration allowing the devices to be available in general medical practice. With proper oversight, this increased availability could allow more careful definition of the clinical indications and contraindications and the detection of long-term complications. Minimizing the rate of catheter block will be important with further modifications of the catheter design. There also is room for improved communicator design and refinement of the catheter correction procedures. From a corporate view, implanted insulin pumps have had an extremely long gestational period without sales-generated income. However, it is reasonable to assume that market approval will stimulate companies to invest in further improvements.

GLUCOSE SENSING AND THE CLOSED-LOOP SYSTEM

Background

The ultimate dream for people working with implanted insulin pumps is to develop a closed-loop system; that is, a system with continuous glucose monitoring that automatically translates changes in blood glucose concentration into appropriate changes in insulin delivery rate. Such a system would have an input (glucose sensing) arm and an output (insulin delivery) arm with a delivery system much more developed than that discussed above. The problems with such a system, which have been reviewed many times, are found in the biotechnology of glucose sensing (48,49). Fixing glucose oxidase on a disposable reagent strip for use in the self-monitoring of blood glucose was itself a major physical chemical accomplishment. Fixing an enzyme to a probe, keeping it active and exposed to the fluid being sensed while implanted in the human body for months or years at a time is far more difficult. Although the sensing itself can be readily accomplished on a laboratory bench, implanted insulin sensing in vivo is much more difficult. Major obstacles to this include the longevity of the system, calibration requirements, and, in particular, the body's ability to wall-off sensor tips (50,51).

Present status

Using the Gough sensor, Armour et al. (52) reported significant results in dogs over a period of 1–15 wk. This potentiostatic oxygen sensor, based on immobilized glucose oxidase, was implanted within a blood vessel and changes in blood glucose concentration were closely tracked. Nevertheless, the problem with glucose oxidase sensors is to keep the enzyme active with adequate oxygen supply and adequately sensitive measurement of the rate of reaction.

Other innovative approaches that use glucose oxidase include one that uses the by-products of the glucose oxidase reaction to modify the permeability of gels to insulin. This allows insulin to be released at a greater rate when the glucose oxidase–catalyzed reaction is occurring.

Sensor work also is underway that would not use the glucose oxidase reaction at all; instead, it would measure absorbance spectra using light spectroscopy in the near infrared range (53–55). The advantage is that this system does not rely on a fragile enzyme, but it has the disadvantage of myriad interfering substances found in the blood or tissue. This sensor system is being developed particularly for noninvasive monitoring (replacing methods that require a finger prick); however, it also is potentially applicable, through a miniaturizing of the spectroscopic technology, to implanted devices.

Advantages and disadvantages

The advantages of delivering insulin based on continuous glucose monitoring are obvious. It is doubtful that open-loop delivery will ever normalize glycemia on a reliable basis. With a closed-loop pump, diabetes could be made essentially forgettable with no concern about diet, exercise, self-monitoring of blood glucose, fewer injections, and with relatively little medical upkeep. However, no glucose sensor has reached the stage of development that would make it applicable to extended preclinical or clinical trials. It is not clear, in fact, which overall approach to glucose sensing will be practical for human implantation, either glucose oxidase or spectroscopy.

If the sensor technology itself is solved, then the question will become what body fluid to test (blood, tears, saliva, peritoneal fluid, or cerebrospinal fluid) and how to keep the sensor in contact with that fluid on a permanent basis. These biological factors could be more difficult to overcome than expected; but, at present, they seem less of an obstacle than the sensor technology itself.

Future

Connecting a glucose sensing system to a computer algorithm, which would determine an appropriate amount of insulin to release, should also be less of a problem. And, as discussed above, the insulin de-

livery system itself is relatively far along in development. However, no way has been found to predict just when the ultimate implanted insulin pump will be available, complete with reliable sensor, closed-loop feedback control of insulin delivery, and proven longevity in the body.

LECTIN- AND POLYMER-BOUND INSULIN DELIVERY SYSTEMS

Background

An ingenious idea surfaced in the late 1970s (56) proposing that insulin bound to a lectin (concanavalin A) could be competitively displaced by glucose. This produced a closed-loop system: as glucose concentration rose, more insulin was released. The idea was pursued to the point of in vitro demonstration that, in fact, insulin could be displaced by saccharides (57).

Cathodal iontophoresis (the controlled release of a highly ionized and monomeric form of insulin under the influence of an electrical current) has lowered blood glucose in diabetic rabbits (58). In another approach, an implant that consists of a compressed mixture of 15% insulin in palmitic acid delivers a basal flow of insulin (59). Polyalkylcyanoacrylate nanocapsules containing insulin have apparently been effective, even when administered orally (60).

Present status

To my knowledge, these approaches have not been pursued to the point of practical in vivo applicability.

Advantages and disadvantages

The ligand-bound insulin system appears to rely on a molar equivalence of increasing glucose with released insulin, which may be problematic. The pellet or capsulized insulin release mechanisms would, at least in their simpler forms, deliver a constant rate of insulin rather than provide prandial peaks. This might be of some use in treating NIDDM, but of little use in treating IDDM.

NASAL INSULIN DELIVERY

Background

In the search for other body surfaces through which insulin might be absorbed, none has received more attention in recent years than the nasal mucosa. Attempts at nasal delivery of insulin can be traced at least to 1935 (61), and the clinical success of vasopressin by nasal route was a stimulus to continue studies with insulin. In the 1980s, a breakthrough occurred when it was observed that insulin complexed to surfactant materials, such as the bile acid glycocholate, could traverse the nasal mucosa more effectively (62). This general approach was used in trials that delivered insulin for up to 3 mo as supplements to conventional depot insulin administration (63). A variety of complexing agents has been tried. However, it has become clear that nasally delivered insulin is absorbed at a rate even faster than subcutaneously delivered regular insulin and that the fraction absorbed is relatively low, in the range of 10 to 20%.

Present status

Clinical trials continue with nasal administration of insulin. A pharmaceutical company is interested in improving absorption and testing long-term tolerance. At present, though, it remains unclear whether changes in nasal absorption will occur over time or under differing conditions (for example during an upper respiratory illness or low versus high humidity, warm versus cold temperature).

Advantages and disadvantages

Nasal insulin delivery, like most of the approaches discussed herein, could deliver insulin without injection. The peak absorption is rapid and success has been demonstrated over periods of at least several months, without adverse sequelae in the nose. Thus, nasal insulin could possibly be used as regular insulin supplements to long-acting, depot injections.

The fact that only a relatively small portion of insulin is absorbed is a disadvantage because small changes in absorption may have considerable clinical effects. To be reliable, the fraction of insulin absorbed would have to remain close to constant. Another disadvantage is the fact that longer-acting insulins have not been available for nasal delivery.

Future

The future of intranasal insulin is unclear. It may become a viable adjunct to subcutaneous insulin injections, but the variability of absorption and patient acceptance in the long term must be tested further.

PULMONARY ADMINISTRATION OF AEROSOLIZED INSULIN

Background

A new approach to the delivery of aerosolized insulin is to administer it with an inhaler. This approach has received far less attention than nasal delivery, but there are some inherent advantages, particularly the larger absorptive surface represented by the lungs and the lesser susceptibility to major changes in mucous secretion. A regular insulin (U-500) currently is delivered with an inhaler during inspiration.

Present status

Preliminary studies have been presented and are promising (64). In trials on several people, aerosolized insulin was distributed evenly in the lungs, and if given in 0.2 U/kg dose, insulin was absorbed in amounts sufficient to the lower blood glucose of normal people or people with NIDDM.

ORAL INSULIN

Background

Ever since insulin's discovery, investigators have attempted to develop a preparation that could be administered orally. Each attempt eventually encounters the proficiency of the gastrointestinal tract in its breakdown of proteins. A number of attempts have been made, including packaging insulin in small liposomes (lipid spheres with an aqueous core) (65,66). The fraction of administered insulin that actually is absorbed, however, is consistently disappointing. In addition, the technology involved in preparing liposomes is expensive to the point of being impractical (67). It is not yet clear if oral administration of insulin has a future in the treatment of diabetes. Some fascinating preliminary results suggest, however, that oral insulin can actually modify the immune response responsible for damaging pancreatic islets in pre-IDDM. These results are being extended in larger trials. However, distinguishing the use of oral insulin for the purpose of immunomodulation from its less promising use to treat hyperglycemia is important.

ENCAPSULATION OF ISLET CELLS

Background

Transplantation of unprotected islet cells, like that of whole pancreas, is fraught with problems of immune rejection. Pending a major breakthrough in transplant biology, patients receiving islet tissue will need immunosuppression and cross-species transplantation (xenografts) will be difficult or impossible. Pancreas transplantation is discussed extensively elsewhere. Novel approaches are being attempted, however, to protect transplanted islets against immune rejection by isolating them from the immune response. One way is to encapsulate the cells in tubing made of a biocompatible material that will protect the cells from the immune system while allowing them to react to ambient glucose. In 1976, islets were inserted into a small copolymer tubing with pores that allow nominal access to molecules, up to 50,000 molecular weight (68). The device improved blood glucose concentration in diabetic rats for a matter of hours. Since then, refinements in materials and technical aspects of such devices have improved the longevity of islets. Colton, Galletti and Chick have collaborated over the past decade to develop such biomaterials (69). Groups in Paris (70), Ontario (71), and Toronto (72) have all contributed significantly.

Present status

In one laboratory, fragments of human insulinomas are being placed in polyvinal chloride acrylic copolymer tubing (1 mm inner diameter and 30 mm long) and implanted in diabetic rats. The results demonstrate some degree of function for 4–6 mo, although secretion was noted to be variable and response also varied to changes in blood glucose (73). A second report demonstrated function for up to 144 days (59).

Lacy et al. (74) have recently published a report on islets suspended in a gel and then inserted into small-lumen tubing that was implanted into mice. Their work demonstrated function for 60 days.

Advantages and disadvantages

The idea that islets could be kept in a special environment, in which they could be protected from immune destruction while able to react to glucose concentrations with closed-loop insulin secretion, is both ingenious and potentially practical. Nonhuman islet cells might be used, obviating the enormous problem of donor availability that clouds all transplantation work. Protected islets may not be susceptible to the autoimmune destruction that caused IDDM in the first place. Implantation with a minor surgical procedure would not be an obstacle.

The only disadvantage to this approach is that it has not yet been developed to the point of reliability. The technical blocks are formidable: enough islets have to be encapsulated to deliver the requisite amount of insulin, they must be viable to the point of lasting for long periods of time, and they must be kept in contact with a body fluid. Thus far, to my knowledge, no trials in humans or primates have been conducted.

Future

The future of islet cell encapsulation depends on solving the developmental problems mentioned.

MICROENCAPSULATION OF ISLETS

Background

Microencapsulation of islets is based on the same principle: keep β-cells in contact with biological fluids and allow them to secrete insulin while protecting them from immune attack. In the case of microencapsulation, though, rather than being placed in fine tubing, islets are prepared in small numbers and encapsulated in tiny beads that are then injected into a vein or freely into the abdomen. Reach et al. (75) have used an alginate-polylysine procedure to microencapsulate ~10 islets at a time in beads of sizes varying from 350 to 650 μm). They found that larger capsules were less responsive.

Present status

Progress has been made on techniques to mix islets into small beads, particularly by the groups in Paris, France, and in Providence, Rhode Island. Whether they can implant sufficient numbers of islets and have them survive sufficiently long to be of practical use remains to be seen.

Advantages and disadvantages

A significant advantage of the microencapsulation approach is that the micro-

beads could be injected into the portal vein, allowing direct delivery of the insulin to the liver. The implantation of the microencapsulated islets by whatever route should be technically simple.

The disadvantage of developing the technique for application is the need to encapsulate so many islets and to handle them gently enough to allow viability.

BIOHYBRID ARTIFICIAL PANCREAS

Background

The term biohybrid artificial pancreases can be used for any of the encapsulation techniques because they all combine artificial membranes or capsules with live islet cells. However, in this discussion, this term is reserved for the approaches in which sequestered islets are placed into a device that is then implanted itself. The principle of the biohybrid artificial pancreas, then, is to contain the whole system in a single acrylic casing, 9 cm in diameter and 2 cm thick (76). Semipermeable tubing (30–35 cm) is coiled within the chamber, with the proximal and distal ends of this tubing attached to blood vessels at an inlet and outlet port of the chamber. This allows blood flow into, through, and out of the chamber. Islet cells are planted inside the chamber but outside the tubing. As the blood flows through the lumen of the tubing, glucose diffuses out and makes contact with the extralumenal β-cells. As the β-cells respond to glucose, their secreted insulin diffuses back into the tubing and out of the casing, into the systemic circulation.

Present status

The above device delivered insulin from canine islet allografts into 10 pancreatectomized dogs. Using 2 devices in each of the 6 dogs resulted in freedom from insulin requirement for as long as 5 mo (63).

Advantages and disadvantages

The enormously attractive feature of all these islet-implantation approaches is that islets can respond to ambient glucose concentration, delivering insulin in a closed-loop fashion. Yet they remain protected against immune rejection without the need for immunosuppression. The macro- or micrencapsulation techniques, and the biohybrid artificial pancreas, could accommodate xenografts. Islets could be isolated from some readily available source, such as pigs, and inserted into humans. This would solve the other major drawback of pancreas transplantation, donor availability. The size of the device should not be a problem. If successful, the approach will be remarkably useful.

Disadvantages of peripheral insulin delivery have been mentioned, and this approach does rely on continued patency of vascular access. The most significant technical obstacles, though, includes the problem of islet cell viability. Large numbers of islets will have to be of sufficient consistency to allow routine implantation, and they will have to remain viable for reasonable periods of time.

Future

The most recent report on the hybrid artificial pancreas suggested the sort of inconsistency that would be expected in early trials (63). Techniques for islet separation, for implantation into such a device, and for maintenance within the device undoubtedly will be developed in the quest for a sturdy, robust system that could deliver insulin on a physiologically closed-loop basis.

CONCLUSIONS — Whether one or any of these approaches will ultimately be the answer to the treatment of insulin-requiring diabetes is unclear, and how quickly each will be developed also remains unclear. Some, such as external insulin pumps, are currently available (although not widely used); others, such as implanted pumps and nasal insulin, could soon be available; and still others, such as the hybrid artificial pancreases and closed loop implanted pumps, are in the more distant future.

It is also uncertain whether just one approach will be the answer. Various new approaches will likely find a niche, with their own set of clinical indications and contraindications. Pancreas transplantation now, for example, is done primarily in patients in need of coexisting kidney transplantation, whereas implanted pumps may be used much earlier in the course of the diabetes.

Despite the many unknowns, however, there are several certainties. We have come a long way since the original injection of regular canine insulin in 1922, and we have come even further since the introduction of human insulin. Life is easier (if not yet easy) for people with diabetes; and, given adequate biomedical research funding, progress on insulin delivery will continue well into the future.

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