LECTURE 13: ARTIFICIAL PANCREAS

13.1 Introduction

The pancreas is an elongated organ in the abdomen with a function in the digestion of food and in the regulation of blood glucose levels. Bicarbonate ions are secreted to neutralize the acidic fluid coming from the stomach. Digestive enzymes are drained directly into the duodenum and convert proteins to amino acids and small peptides (trypsinogen), polysaccharides to mono- and disaccharides and oligosaccharides (amylase), fat to monoglycerides and fatty acids (lipase). Pancreatic failure thus affects predominantly the absorption of large molecules.

The β-cells of the pancreatic Islets of Langerhans secrete insulin, which increases entry of glucose into cells, glycolysis and storage of glucose, and so reduces blood glucose levels. It inhibits breakdown of fat and speeds up its formation and it has an anabolic action on protein metabolism. Also, a protein with an unknown function, amylin, is produced by the β-cells.

The α-cells of the pancreas secrete glucagon. Glucagon raises blood glucose levels by actions opposite to those of insulin. Paradoxically glucagon stimulates insulin secretion by the pancreas, this action tending to lower blood glucose levels.

The pancreatic δ-cells form one of the locations that produce somatostatin, a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation.

Dysfunction of the β-cells is the cause of diabetes, type 1 and 2. It is estimated that currently some 194 million people worldwide have diabetes and that this will increase to 333 million by 2025. So far, development of an ‘artificial pancreas’ is focusing on substitution of the insulin producing function only.

13.2 The Artificial Pancreas

An artificial pancreas is used to substitute endocrine functionality of a healthy pancreas for diabetic and other patients who require it. It can be used to improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia, and it can also ease the burden of therapy for the insulin-dependent. Approaches include using an insulin pump under closed loop control, developing a bio-artificial pancreas consisting of a biocompatible sheet of encapsulated beta cells, or using gene therapy

A (bio-)artificial pancreas would improve the quality of life of insulin dependent patients and would have medical benefits. For over 40 years now, studies have been performed on the development of a closed-loop glucose measurement and insulin delivery system. In the last decennia progress has been made in the development of essential components: glucose monitors and insulin pumps. Both are commercially available, including dose advising algorithms and data management options, and the application possibilities become more sophisticated year after year.

However, fully closed-loop systems are still not reliable and sufficiently accurate to be marketed. This is mainly due to problems with long term glucose measurement and to the complexity of dose controlling algorithms that have to respond to many different physiological circumstances.

Cell-based therapeutic options include the use of stem cells and the construction of a bioartificial pancreas (BAP). Therapies for diabetes based on stem cells have yet not reached maturity and are still in the laboratory phase. BAPs can be intravascular or extravascular. The intravascular devices bear the risk of coagulation and thrombus formation and are currently not the approach of first choice. The extravascular devices do not present these problems and especially microcapsular devices have been studied extensively.

13.3 Medical device-based approach for function recovery

Closed loop systems

Diabetes patients using insulin have to take fingertip blood samples several times a day, followed by the determination of the blood glucose level and the subcutaneous injection of insulin. The goal is to keep the blood glucose concentration within the physiological range (6-7 mmol/l), thus preventing the long-term problems associated with hyperglycemia and the short-term risks of hypoglycemia.

From the medical point of view benefit can be found in the fact that tight glycemic control reduces and delays serious secondary complications. Also, the short time risk of hypoglycemia could be decreased by a continuous controlling system.

Closed-loop feedback systems are systems that use mathematical algorithms to convert measurement results into outputs like administering medication. In medical settings these systems lead to circumvention of the need for patient action/compliance and/or professional interference. In recent years substantial progress has been made in the development of insulin pumps, algorithms, and sensors bringing closed-loop systems for the assistance or replacement of pancreas functions nearer to the market.

13.4 State of development

Glucose sensors

Since 1999 continuous (or frequent intermittent) glucose monitoring systems enabling retrospective data analysis of blood glucose profiles are commercially available for short time diagnostic use and treatment optimization. Most systems can also be used as an alarm for blood glucose levels exceeding the physiological range.

These systems are minimally or non-invasive and measure glucose concentration in the interstitial fluid of subcutaneous tissue. Main approaches for sampling are:

- subcutaneous insertion of an electrochemical sensor,

- subcutaneous insertion of a microanalysis catheter which is perfused with dialysate in which the glucose concentration is measured electrochemically outside the body,
- transdermal extraction of interstitial fluid in which the glucose concentration is measured electrochemically.

Measurements are mostly based on the generation of hydrogen peroxide from glucose via the enzyme glucose oxidase, which is specific for glucose. The electric current generated is measured. Regular calibration using finger sticks and common glucose meters is however still necessary. Most subcutaneous sensors are disposable and last for three to four days. The sensor is connected to a non-disposable monitor. Data on glucose levels, insulin dosing, errors and alarms are stored and can be downloaded afterwards.

For glucose monitors precision, accuracy, sensitivity and stability are important, as well as calibration requirements, availability of results, longevity and robustness.

Readings are transmitted wirelessly to a hand-held receiver. The system is currently under clinical investigation. Other devices based on various technologies have not yet reached the market: the use of ultrasound (to increase permeability and transdermal transport), fluorescence, near or middle infrared light (to measure glucose on the base of absorption, reflection or optical rotation), or ‘smart’ glucose sensitive gels (that show reversible viscosity change under influence of glucose leading to controlled release of insulin.

For the European market, blood glucose monitors must meet the European standard EN-ISO-15197: 2003 In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus.

13.4.1 Mimicking the ß-cell response shows some complications:

- it is complicated to imitate the insulin-secretion profile for meal (BSL increasing) and exercise (BSL decreasing);

- depending on the type of sensor and its location, different delays and noise in the transmitted signals will be present;
- glucose monitoring is accompanied by a delay due to glucose diffusion and measurement (sensing delay). Thus, glucose measurements are not completely 'realtime'.

This is a problem in case of large disturbances such as following daily meals. Similarly, depending on the type of pump and its location (subcutaneous or intraperitoneal), the insulin dynamics will be different. They give a delay in the peak of the glucose lowering effect due to the time necessary for absorption of insulin from the subcutaneous or intraperitoneal environment (insulin delay) and for insulin action.

The delays must be dealt with by algorithms. Noise can be reduced by the use of filters in the algorithm.

There are some other factors to be dealt with using algorithms for closed-loop systems:

- the insulin sensitivity of an individual may vary substantially, e.g. due to changes in fitness or health, time of day or mental stress levels;
- insulin absorption characteristics and sensor dynamics can vary due to a new placement of the delivery catheter or sensor [Bequette, 2005];
- the performance of algorithms can be affected by factors like dietary fat (delays gastric emptying and induces postprandial insulin resistance), alcohol (suppresses hepatic glucose production), and caffeine (induces insulin resistance).

13.4.2 Smart insulin pumps

External pumps can be used for Continuous Subcutaneous Insulin Infusion (CSII). The first commercially available insulin pumps for subcutaneous administration and ambulatory use appeared on the market around 1980 [Steil et al., 2004a]. Short acting insulin analogs are administered at a low rate. The insulin reservoir has to be filled by the

patient every two or three days. Currently, pumps with memory allow for data downloading. An external pump delivering a rapid analog of insulin is considered 'the gold standard of insulin delivery'.

Some of the newer external insulin pumps on the market are listed in Textbox 6.3. An example of a combination of a continuous glucose monitoring system communicating with an insulin pump is shown in Figure 1.

Figure 1. A combination of a continuous glucose monitoring system communicating with an insulin pump.

13.4.3 Closed-loop systems for insulin administration

Based on the abovementioned components prototypes of closed-loop systems have been developed. The two main approaches are:

- Extracorporeal: subcutaneous glucose monitoring and subcutaneous insulin administration (s.c.-s.c.). This system is a minimal invasive solution that can benefit from

the experience of more than 200,000 external insulin pump users. Therefore, it seems to be the best possibility for widespread application.

- Implantable: intravenous glucose monitoring and intraperitoneal insulin delivery (i.v.-i.p.). Intravenous sensors implanted in the circulatory system, e.g. vena cava, are mainly for short time use in a hospital environment. There is less experience with implantable pumps delivering insulin intraperitoneally.

Due to longer delays particularly users of s.c.-s.c. systems will have to enter information on meals or physical exertion, and due to this the loop system is not fully closed anymore. There are different ways to handle mealtime insulin delivery:

- 'fully closed-loop': insulin is administered by evaluating the rise in postprandial glucose.
- 'semi-closed loop' or 'closed-loop with meal announcement': patient gives information about time and size of the meal in advance and the controller advises on an insulin bolus.
- 'closed-loop with qualitative meal announcement': patient gives information about time of the meal and the controller switches to a more aggressive mode of insulin delivery. Meal announcement or "feedforward control" improved results.

13.4.4 Possible risks

The possible risks of (semi-) closed-loop systems can be clustered around several aspects of these systems.

Sensor reliability: Inaccurate glucose values or inappropriate alarms could result in inappropriate administration of insulin.

Invasiveness: Implantation of sensors or pumps requires surgery and brings the risk of infections. Intravenous monitoring may cause thrombosis or embolization. Implanted pumps require surgical removal after their functional lifetime.

Algorithms: Blood glucose is complicated by several variables like food intake, physical activity, stress, illness and sleep. Rapid changes in blood glucose are difficult to be dealt with by algorithms without patient input of information. Failure of algorithms may cause substantial risk because people may put a lot of faith in advised or recommended doses.

Wireless information transfer: Radio frequency (RF) transmission of data may give interference with cell phones or other radio traffic and can give problems inside planes.
User interface: The user interface must be straightforward and programming and calibration must be easy. The patient must be capable to deal with the information provided by the system and must be well trained.

Data storage: Battery removal or static electricity may cause loss of stored settings and historical data. At the moment there are no really-closed-loop systems for diabetics that are ready for marketing.

13.5 Cell/tissue-based approach for function recovery

13.5.1 State of development

Patients suffering from glycaemia lability despite optimized medication are the candidates for pancreas transplantation. Islet transplantation, where islet cells are harvested from brain-dead donors, processed according to a standardized protocol and infused in the recipient's liver has also been clinically investigated, but the results are inferior to pancreas transplantation. Furthermore, islet transplantation is an inefficient use of donated islet cells (for a single recipient, 2 to 4 donors are needed), so currently whole-pancreas transplantation is a better option. Because of the organ shortage, there is a stimulus for research into the possibility to use other cell or tissue sources. Basically, two approaches are being explored.

The first is the use of stem cells and the second is the construction of a bio-artificial pancreas (BAP), where islet cells from different sources are contained in a device.

13.5.2 Human stem cells

Transplantation of islet cells can provide reestablishment of normal blood glucose levels in insulin dependent diabetic patients [Shapiro, 2006]. However, the availability of suitable numbers of donor islet cells is very low compared to the demand, therefore alternative sources of these cells have been searched for. Theoretically, human stem cells can also provide islet cells and this notion has indeed been proven in laboratory circumstances. It has been shown that a substantial fraction of an initial number of human embryonic stem cells (hES) can be guided to differentiate into pancreatic islet-like cells, that produce high amounts of insulin.

Other sources for stem cells that are being studied are derived from bone marrow, the lining of the pancreatic duct, liver, bile duct epithelium. Still, full and consistent control of the development of these cells into functional, insulin secreting cells has not been achieved.

13.5.3 Bio-artificial pancreas (BAP)

The bio-artificial pancreas (BAP), also referred to as encapsulated cell therapy, generally contains a number of islet cells, encapsulated by a semi-permeable membrane of which the geometry and characteristics may vary. In order to be successful it is required that the BAP has the following characteristics:

- biocompatible (e.g. no encapsulation with fibrous tissue by the body);
- good diffusional properties (e.g. for cell nutrition, to allow physiological feedback in response to glucose and to dispose of waste products);
- guarding the islet cells from allogenic or xenogenic sources against damage from host immune responses (thereby eliminating the need for immunosuppressive drugs);
- maintenance of cell viability over long periods of time;

- easy retrievability.

Alternatively, a transplantation space can be created prior to filling this space with islet cells. To this end a stainless-steel meshed rod holding a PTFE tubular membrane is implanted subcutaneously in the anterior abdominal wall. After allowing the formation of small blood vessels around this rod for two months, the PTFE tubular membrane is removed through a small incision and islet cells are introduced into the rod.

The application of these technical and theoretical concepts in animal models (rats, mice, dogs and monkeys) and in man learns that a number of problems has to be solved. The results from animal studies show that although encapsulated islet cells performed better than nonencapsulated cells, the duration of euglycemia was limited (from several to 6 months). The intravascular devices bear the risk of coagulation and thrombus formation.