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Review on Prospects of Insulin Delivery: Opportunities and Challenges

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ABSTRACT

Insulin remains indispensable in the management of diabetes mellitus since its discovery in 1921. Relatively, a large percentage of world population is affected by diabetes mellitus. In today's era; insulin delivery by alternative route is an area of current interest in the design of drug delivery system. Most of the global pharmaceutical companies are showing encouraging progress in their attempts to develop alternative insulin delivery technologies. For most patients with type 1 diabetes, the tedious part of the treatment is to tolerate needle after needle, both for glucose measurement and to deliver insulin. The introduction of insulin therapy years ago has saved the lives of millions of patients with diabetes. It is growing increase in the percentage of population having diabetes mellitus due to hereditary and environmental factor. Needle-free insulin delivery appeared to be astonishing approach and its allure rested in being comfortable and safe. The document present here encompass, in brief, the emerging technologies and discoveries that are in pipeline, including insulin inhalers, implantable insulin pumps, insulin spray, smart cells, insulin pill, insulin complement, islet cell transplant, insulin nano pump and the other promising advances in safe and comfortable insulin delivery. Therefore it will be a tripartite task for the researcher, health authorities and community pharmacist to foster the long term safety profile and to provide comfortable insulin delivery.

Keywords: Insulin, Diabetes Future trends, Novel drug delivery system, Implantable insulin pump.

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INTRODUCTION

Diabetes mellitus is a disorder of glucose regulation, characterized by an accumulating glucose concentration in the blood. It is a major public health problem affecting 8% of the United States population. The global prevalence of type 2 diabetes continues to rise[1]. The breakdown of glucose regulation can be attributed to the mobility of the endocrine pancreas to secret insulin or the body in ability of properly use insulin. In case of type 1 diabetes the insulin secreting pancreatic beta cell undergoes an auto immune mediated destruction[2]. Insulin is a proteinaceous hormone require to be taken form external source in case of some patients suffering form diabetes mellitus. Insulin cause most of the body cell to take up glucose form the blood (including liver muscle and fat tissue cell) storing as glycogen in the liver and muscle, and stop use of fat as an energy source. When insulin is absent glucose is not taken up by most body cell and the body being to use fat as an energy source. As its level is a central metabolism control mechanism, its status also used as control signal to other body system (such as amino acid uptake by body cell) when control of insulin level fail, diabetes results it is a produce in the islets of langerhans in the pancreas the name comes from the Latin insulin for "ISLANDS". Insulin structure varies slightly between species of animals sources differs somewhat in "strenght" in human because of those variation porcine (pig) insulin is especially close to the human version.[3]

History about Disease

As reported by the World Health Organization (WHO), 200 million people around the world suffering from diabetes in 2005. Diabetes is a serious condition and its rapidly increasing prevalence on the global scale is a significant cause for concern. By 2030, the WHO estimates that the number of people with diabetes will almost double to 366 million4. About 40% of people with diabetes rely on insulin to maintain control of their blood glucose levels. Patients with Type 1 diabetes are completely dependent on insulin injections. For patients with Type 2 diabetes, which comprises 90% of the world's diagnosed cases of diabetes, about one-third of them rely on insulin as part of their regimen for controlling their blood glucose levels. Normal blood sugar is around 90 to 120 mg/dL5[4].

Future Trends for Delivery System

The goal for delivery exogenous insulin in patient with diabetes is the mimic as closely as possible the normal physiological insulin secretion seen in non- diabetic individuals .in order to achieve optimal glycemic control a more intensive insulin therapy both for patient with TYPE 1 diabetes and TYPE 2 diabetes[5].

Newer inject able insulins

Newer insulins that are promising include long acting basal insulin analogue called insulin degludec and ultra fast acting insulin, human insulin Linjeta™ (formally called VIAject)[6]. VIAject™: VIAject is recombinant human insulin with ultra fast onset of action. Pharmacia-dynamic and pharmaco-kinetic studies have shown the onset of action of VIAject is faster than that of human soluble insulin and insulin lispro. VIAject was reported to have less within- subject variability of plasma insulin compared to human regular insulin, and has a faster absorption/onset of action than insulin lispro. Two pivotal phase Ⅲ clinical studies in both type 1 and type 2 DM are ongoing with VIAject. As the amount of insulin circulating several hours after a meal is low, a possible reduction in hypoglycemia and prevention of weight gain are predicted[7].

Insulin degludec

Insulin degludec a novel ultra -long acting basal insulin is almost identical to human. Insulin in structure except for the last amino acid detected from the B chain and addition of a glutamyl link from LYSB29 to a hexadecandioic fatty acid .[12] this insulin forms soluble multihexamers after subcutaneous injection resulting in an ultra long acting profile with half life more then24 hours.[8]

Oral approach

Despite the different approaches being investigated for insulin delivery the development of oral delivery being the elusive goal since the discovery of insulin. Insulin if administered via of oral route will eliminate the pain caused by injection, physiological barrier anxiety and possible infection in additional, oral insulin is advantageous because it is delivery directly to liver, its primary site of action via the portal circulation. A mechanism very similar to endogenous insulin subcutaneous insulin treatment however does not replicate the normal dynamics of endogenous insulin release resulting in a failure to achieve a lasting glycimic control in patient in life of the above distingt benefits pharmacopeial technologists have been trying to desings an oral delivery system for insulin. Such is the interest in oral insulin delivery that some pharmaceutical companies are socially focused on it[9].

IN-105

Oral insulin IN-105 is an insulin analog. It is secondary generation of oral insulin that has an attractive stability profile at ambient condition. It is human recombinant insulin molecules conjugated on position B 29 with polyethylene glycol via an acetyl chain. In IN-105 is said to have improved half life in the digestive tract and improved absorption, lower immunologenicity as compare to insulin. It said to have lower mitogenic potential as compare to insulin but retain a

similar pharmacological activity as insulin and conserves the safety profile and good clearance profile as compare to the insulin. The maximum circulating insulin level after oral administration of 5mg IN-105 were absorbed after 20 min. With maximum drop in glucose at 40 min. However the rapid decline in blood glucose high have include a counter regulatary response that includes an increase in glycimia, Phase 1 and Phase 2 trial were promising in a dose escalating study IN-105 absorption shown to proportional to the does administered. The 2H post pyramidal glucose excursion was also said to have reduce in dose proportional manner[10].

Insulin nano pump

The nano pump is power full device and as many possible application in the medical field, the first application of pump introduce by DEBIOTECH, is insulin delivery, the pump inject insulin to the patient body in a construct rate, balancing the amount of sugar in his or her body (figure 1).[11]

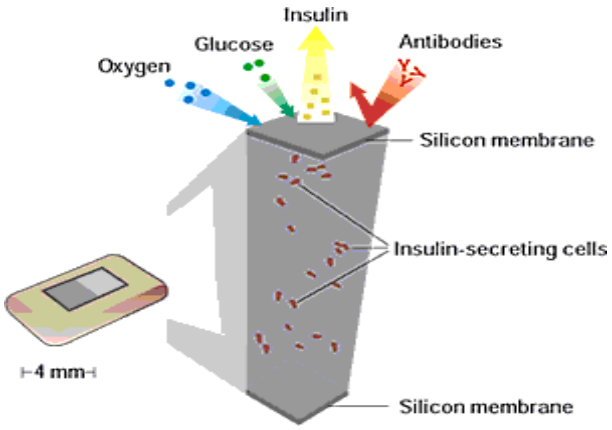

Figure 1: Insulin nano pump

Gene therapy

To recent report describe research into gene therapy for different aspects of dibetes.These reports are the forefront of but will no doubt be on going and exiting research a rising from the decoding of the human genome.

(A) Scientist has identified a gene called SHIP2 that appears to regulate insulin. Such finding make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual insulin regulation.

(B) A protein that blocks the over growth of blood vessel in the eye is being studies as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with protein called pigment epithelium derived factor or PEDF, prevented excessive new blood vessels formation in an animal model of retinopathy. It may also be used to treat muscular degenration.[12]

As scientists identify specific gene whose absence improper functioning are associated with specific condition, more possibilities for gene therapy are offered for diabetes as well as all

diseases.

Enzymatic barrier

The harsh environment of the GIT (gastrointestinal tract) causes insulin to undergoes degradation this is because digestive process are designs to breakdown protein and peptides without any discrimination insulin undergoes enzymatic degradation by pepsin and pancreatic protolytic enzyme such as trypsin and chemotrypsin overall insulin is subjected to acid catalyzed degradation in the stomach animal degradation in the intestine and intramolecular degradation the cytosolic enzyme that degrades insulin in insulin-degrading enzyme (IDE) insulin is however not subjected to protolytic breakdown by brus border enzyme insulin can be preserted for absorption only if the enzyme attract is either reduced or defected.(figure 2)[13].

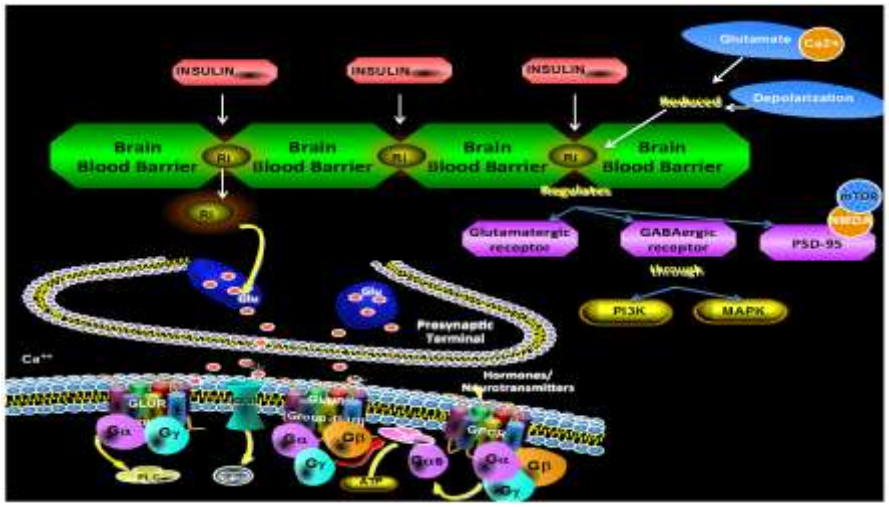

Figure 2: Enzymatic barrier for Insulin

Chemical modification

Modifying the chemical structure and thus increasing its stability is another approach to enhance bioavaibility of insulin an example of chemical modification is that of hexayl-insulin monoconjugate 2 (HIM2) where in a short chain polyethylene glycol (PEG) linked to an alkyl group is in there linked to (LYS-29) of the beta chain of insulin alternation of the physiochemical characteristics leads to enhanced stability and resistance to intestinal degradation of oral insulin.[14]

Formulation approaches

A third strategy to circumvent the carrier system is the formation approaches here the peptides or protein drug is haused with in a delivery system that is designed not only to protect the drug from contact with luminal protease but also to release the drug only an reaching an area favorable for its absorption[15]. The oral bioavability of insulin can be exhausted by the base of novel carrier system which delivers insulin to the target site of absorption liposome's microspheres and nano particles

have been developed for use a carrier system for insulin.[16]

Challenges to oral insulin delivery

Generally peptides and proteins such as insulin cannot be administered via the oral rout due to rapid enzyme degradation in the stomach inactivation and digestion by proteolytic enzyme in the instine lumer and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity the oral bioavability of most peptides and protein therefore is the less than 1% challenges here is to improve the bioavability to anywhere between 30to 50%.[17]

Afrezza®

(Mankind Corporation, Valencia, CA, USA) is recombinant human insulin, using the Technosphere® concept and administered using a next-generation inhaler called Dream- boat®. Technosphere® is a drug delivery system created by micro particles (2-3 µm) that form microspheres, which are then lyophilized into a dry powder for inhalation.

Islet cell transplant

In contrast to conventional insulin treatment, islet transplantation is far superior for achieving a constant normoglycaemic state and avoiding hypoglycemic episodes. Insulin-producing beta cells are taken from a donor's pancreas and transferred into a person with diabetes. Once transplanted, the donor islets begin to make and release insulin, actively regulating the level of glucose in the blood.[18] Successful transplantation can provide the following benefits: (1) it can eliminate the need for frequent blood glucose measurements and the need for daily insulin injections. Although only a few are free of insulin injections a year after transplantation. (2) It can provide more flexibility with meal planning. (3) It can help protect against the serious long-term complications of diabetes, including heart disease, kidney disease, stroke and nerve and eye damage.[19]

Other Up Coming Methods

It is implanted just under and insulin is delivered into the peritoneal cavity net into the subcutaneous tissue the primary advantage of an insulin pump is person able to achieve normal or near-normal blood sugar level (tight control) which can help prevent long term diabetes complication Transdermal patch: the althea therapeutics pass port system was the first product in development shown in US FAD clinical trials to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the suin the pass port system enables fast controlled drug delivery without the pain of the injection or the possible complication associated with inhaled medication. It is also avoids the first pass gastro intestinal and liver metabolism that occurs often after oral administration. Intra-nasal approach: An insulin inhaler is used to take powdered insulin. This device offers a quick easy way to short acting insulin. Advantages to inhaled insulin include

the convenience of carrying the compact inhalers and its past acting nature. Inhaled insulin can be taken minutes before to control blood sugar increase[20].

Table 1: Methods of insulin and their mechanism of action

Methods	Mechanism
Artificial pancreas	Insulin pump controlled by algorithm with glucose monitor
Bucal insulin	Insulin through an aerosol spray
Oral insulin	Various nanopartical encasinga bounds to insulin
Inhalable insulin	insulin absorbed through alveolar membranes
Transdermal insulin	insulin absorbed through pores in skin opened with ultra sound energy
Intranasal insulin	absorbed through nasal mucosa

CONCLUSION

Recent developments in insulin therapy have potential for reducing some of the negative aspects of current method. Long acting insulin, such as insulin degludec, may require less frequent injections. fast acting insulin , such as via ject, have been shown to improve postprandial glycimic control and reduce hypoglycemia the globle market of insulin that there is high demand of insulin consumption, so it become a widal role of researcher to develop more convenient, compliance and a safe delivery of insulin to target the more population all around the globe.

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