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Novel Routes of Insulin for Diabetes Treatment

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Abstract:

Diabetes complications include both microvascular and macrovascular disease, both of which are affected by optimal diabetes control Novel routes of insulin administration are an area of interest in the diabetes field, given that insulin injection therapy is burdensome for many patients. This review will discuss pulmonary delivery of insulin via inhalation. Subcutaneous insulin has been used to treat diabetes since the 1920 however, despite a number of different formulations, intensive insulin therapy with multiple daily injections has not gained widespread clinical acceptance. However, a growing body of evidence suggests that inhaled insulin is an effective, well-tolerated, noninvasive alternative to subcutaneous regular insulin. Critically, inhaled insulin shows a more physiological insulin profile than that seen with conventional insulin. Further studies are needed to confirm long-term efficacy and pulmonary safety, to compare the different approaches, and to characterize better their relative places in practice. As a result of the recognition of the importance of tighter control of glycaemia and the growing number of patients with type 2 diabetes who receive insulin, inhaled insulin could become an increasingly integral part of managing diabetes.

Keyword : Type 1 diabetes mellitus, drug formulations, drug administration routes, insulin, portal system, nanoparticles, biodegradable polymers

Introductions :

Assessing insulin secretion in vivo is quite more complex: 1) insulin is secreted in high-frequency pulses (recurring every 5–15 minutes) superimposed on slower, ultradian oscillations (every 80–120 minutes). Glucose administration mainly amplifies secretory burst amplitude/mass; 2) insulin pulses are secreted in the portal vein and undergo ~40%–80% first-pass hepatic extraction with consequent waveform damping in the systemic circulation. The amplitude of insulin pulses is the principal determinant of hepatic insulin clearance; 3) plasma insulin levels in the peripheral circulation reflect hormone secretion, distribution, and degradation; 4) C-peptide is secreted in equimolar amounts with insulin but is more slowly catabolized than insulin. Unlike insulin, C-peptide is not extracted by the liver, thus C-peptide secretion rate can be estimated from plasma C-peptide levels; 5) proinsulin and insulin are not released equimolarly, and proinsulin clearance is lower than that of insulin. Circulating proinsulin accounts for ~10%–20% of normal fasting insulin, but it may be disproportionately increased in type 2 diabetes; however, highly specific immunoassay methods are required to differentiate between intact proinsulin and the specific and unspecific proinsulin derivatives.Insulin inhibits directly hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis; indirect effects include inhibition of glucagon secretion, lipolysis in fat, and proteolysis in muscle. During a pancreatic clamp in the overnight-fasted, conscious dog, insulin infusion was switched from the hepatic portal vein to a peripheral vein; as a result, Edgerton et al obtained a doubliug of the arterial insulin level and a 50% decrease in the insulin level within the hepatic sinusoids. The arterial plasma free fatty acids level and net hepatic free fatty acid uptake decreased by 40%–50%; hepatic glucose output increased more than twofold and remained elevated.B- and T-cell responses to subcutaneous (SC) insulin are well understood, and there are abundant examples of interactions of the insulin molecule with the immune system. The immune response can include induction of diabetes, insulin allergy, insulin resistance, prolonged insulin action, and prevention of diabetes.

Induction of T cell-mediated insulitis and diabetes was first shown in the 1960 with administration of bovine insulin in Freund's adjuvant. An IgE response to insulin can cause either local or systemic immediate reactions or delayed responses. Generalized insulin allergy is a rare but potentially life-threatening systemic manifestation of the IgE-mediated response.

B-cell responses can also include production of insulin antibodies that delay and decrease insulin action. This response was seen more frequently with animal-species insulin preparations used > 10-20 years ago. With these preparations, insulin antibodies also led to lipoatrophy (beginning 3-6 months after initiation of insulin treatment) and were associated with abnormal deposition of IgM, IgG, and IgA. Insulin antibodies can increase the apparent distribution

space of free insulin, and can lead to delayed insulin rise and to prolonged hypoglycemia with subsequent release.Immunologic insulin resistance (defined as the need for > 200 units/day with exclusion of other causes of severe insulin resistance) is rare, usually has a duration of < 1 year, and may require a period of corticosteroid treatment, which usually eliminates the syndrome after a short course of therapy.

Insulin immunogenicity in pregnancy is another potential issue, with IgG antibodies crossing the placenta and having the potential to cause abnormal glucose homeostasis in the fetus and neonate.

The immune response to insulin may also produce beneficial effects. In the nonobese diabetic mouse model of type 1 diabetes, daily administration of insulin at high doses or administration of an analog of insulin not causing hypoglycemia gave 61% and 57% protection against diabetes.All the approaches deliver insulin to the lungs, leading to rapid absorption of insulin similar to that seen with insulin lispro but with somewhat longer duration of action. The bioefficacy of inhaled insulin is approximately 10% with the Exubera and AERx systems. Technosphere insulin particles appear to be the most rapidly absorbed, with 30% to 45% bioactivity. The intrasubject coefficient of variation is approximately 15%, which is similar to that seen with SC insulin.

With all systems, cigarette smoking leads to more rapid and greater degrees of absorption. There is little change in bioavailability with respiratory infection (although some patients cannot tolerate inhaled insulin during a respiratory infection) and some decrease in absorption with asthma.

The most-studied inhaled insulin is Exubera, which has been the subject of phase 3 clinical trials carried out thus far in 1256 persons with type 1 and type 2 diabetes. These studies have shown no loss of glycemic control and somewhat variable changes in hypoglycemia frequency, suggesting that insulin can be delivered through the lungs in a fashion similar to that of rapid-acting SC insulin in both type 1 and type 2 diabetes.

Long-term safety of inhaled insulin still needs to be established. Cough has been shown in a number of studies to be a side effect of inhaled insulin treatment. As a caution, an audience member at the symposium noted that there was a report of a 4-fold increase in pulmonary fibrosis with pulmonary insulin, and Dr. Skyler stated that he was aware of 2 patients found to have pulmonary fibrosis on CT scanning in the Exubera studies.

Type1 diabete :

Type 1 diabetes develops when the cells of the pancreas stop producing insulin. Without insulin, glucose cannot enter the cells of the muscles for energy. Instead the glucose rises in the blood causing a person to become extremely unwell. Type 1 diabetes is life threatening if insulin is not replaced. People with type 1 diabetes need to inject insulin for the rest of their lives.

Type 1 diabetes often occurs in children and people under 30 years of age, but it can occur at any age. This condition is not caused by lifestyle factors. Its exact cause is not known but research shows that something in the environment can trigger it in a person that has a genetic risk.

Type 2 diabete:

Type 2 diabetes develops when the pancreas does not make enough insulin and the insulin that is made does not work as well as it should (also known as insulin resistance). As a result, the glucose begins to rise above normal levels in the blood. Half the people with type 2 diabetes do not know they have the condition because they have no symptoms.

Type 2 diabetes (once known as adult-onset diabetes) affects 85 to 90 per cent of all people with diabetes. People who develop type 2 diabetes are very likely to also have someone in their family with the condition. It is considered a lifestyle condition because being overweight and not doing enough physical activity increases the risk of developing type 2 diabetes.

People from certain ethnic backgrounds, such as Aboriginal or Torres Strait Islander, Polynesian, Asian or Indian are more likely to develop type 2 diabetes. When first diagnosed, many people with type 2 diabetes can manage their condition with healthy diet and increased physical activity.

Types of insulin:

Rapid- and short-acting insulin helps reduce blood glucose levels at mealtimes and intermediate or long-acting insulin helps with managing the body's general needs. Both help manage blood glucose levels.

Insulin is grouped according to how long it works in the body. The five different types of insulin range from rapid- to long-acting. Some types of insulin look clear, while others are cloudy. Check with your pharmacist whether the insulin you are taking should be clear or cloudy.

Before injecting a cloudy insulin, the pen or vial needs to be gently rolled between your hands to make sure the insulin is evenly mixed (until it looks milky). Don't use clear insulin if it appears cloudy.

Often, people need both rapid- and longer-acting insulin. Everyone is different and needs different combinations.

The five types of insulin are:

1.rapid-acting insulin
2.short-acting insulin
3.intermediate-acting insulin
4.mixed insulin

5.long-acting insulin.

1. rapid-acting insulin: Rapid-acting insulin starts working somewhere between 2.5 to 20 minutes after injection. Its action is at its greatest between one and three hours after injection and can last up to five hours. This type of insulin acts more quickly after a meal, similar to the body's natural insulin, reducing the risk of a low blood glucose (blood glucose below 4 mmol/L). When you use this type of insulin, you must eat immediately after you inject.
2.short acting insulin: Regular insulin (Novolin R) is also known as short-acting insulin. It is also used to cover your insulin needs at mealtime, but it can be injected a little bit longer before the meal than rapid-acting insulin.
3. Intermediate acting: Insulin NPH (Humulin N, Novolin N) is an intermediate-acting insulin that is a suspension of crystalline zinc insulin combined with the positively charged polypeptide protamine. Unlike the shorter-acting insulins, NPH has a longer duration of action, yet not as long as the newer long-acting insulins
4. Long acting insulin: Tresiba (insulin degludec) is the longest acting insulin available, and there don't appear to be any coming down the pipeline that give this duration of effect. What makes Tresiba a hero is its long duration of action (more than 40 hours) with minimal fluctuations in blood levels of the drug. It's given once a day.
Basal–bolus insulin:
therapy best mimics the natural insulin secretion of the body. Basal insulins such as glargine have a longer duration of action representing the ongoing low levels of insulin secretion needed to maintain normal glucose levels regardless of food intake. Bolus insulins such as aspart, glulisine, or lispro are shorter-acting agents given to manage glucose increase in response to food intake. Bolus insulin is often administered three times daily with meals. Different types and formulations of insulin can be used to accomplish basal–bolus insulin dosing. Further details on these individual insulin types are described below.

Premixed insulin:

Preparations combine short/rapid and intermediate/long-acting insulin in a fixed ratio. Although this provides convenience for some and may be appealing to those who refuse more than two injections a day, it does not allow for flexibility in mealtime or changes in ratio of short- to long-acting insulin doses. Combining protamine with aspart or lispro allows for slow, continuous release and serves as the basal component of the combination with the lower percent of aspart or lispro serving as the bolus or mealtime component. The numbers expressed in the ratio after the insulin name refer to the percentage of the insulin in the premixed solution.

Safety :

Given the numerous products and concentrations currently available, medication safety with regard to insulin dosing, administration, and monitoring is exceedingly important. There are several look-alike/sound-alike (LASA) products that are easily confused especially when brand or trade names are prescribed. For example, Novolin® is often confused with NovoLog® and Humulin® confused with Humalog®. Various concentrations of insulin further amplify the potential for LASA errors. It is most important that every practitioner be certain that the correct type and specific concentration of insulin is administered without error. If one were to inadvertently administer U-500 regular insulin in place of U-100 regular insulin at the volume indicated for U-100, the patient would receive a fivefold insulin overdose. Strategies such as auxiliary colorful labels highlighting insulin type and concentration may be used to safeguard against potential errors. Also, storing a basal insulin (e.g., in the bedroom area if dosed at bed time) separate from the bolus or mealtime insulin may help to diminish the potential for error. Using unsafe abbreviations such as using “u” rather than spelling out the word “units,” has contributed to significant insulin-related medication errors. The hand written “u” can be read as a zero causing 10u to appear and be given as 100, resulting in a 10-fold dose increase of insulin dose.

Objective :

The current review aims to analyze the pathophysiology of insulin secretion, discuss current therapies for the management of diabetes, provides an updates on the recent advancements of IIT, and proposes its mechanism of action.

Insulin therapy :

Bovine insulin was first extracted and used as a subcutaneous treatment for patients with type 1 diabetes by Banting and Best in 1922. Since its discovery, subcutaneous insulin administration still remains an essential therapy to achieve tight glycemic control. As indicated in the Diabetes Control and Complications Trial, intensive insulin injection regimens are associated with significant weight gain and an increase in severe hypoglycemic events.1 Rapid- and long-acting insulin analogues as well as insulin-infusion pumps have been developed in an attempt to attain and maintain near-euglycemia. Studies have suggested that continuous insulin delivery using insulin pumps could be beneficial in patients with diabetes with frequent, unpredictable hypoglycemia or dawn phenomenon. Intrapulmonary insulin administration through inhalation offer a more convenient method for insulin delivery and has been demonstrated

have a longer duration with a comparable absorption rate to rapid-acting insulin. Its short-term efficacy and safety have been studied in both patients with type 1 and type 2 diabetes, showing either similar or improvement in glycemic control in comparison to conventional insulin injections after 3 months with no marked change in pulmonary function. The benefits of inhaled insulin are mainly due to a reduction in the need of multiple insulin injections, leading to a reduction in the significant weight gain phenomenon and improved adherence, especially in patients who are unwilling to comply with insulin injections. Although inhaled insulin therapy is an appealing option, its cost is significantly higher than subcutaneous insulin. Studies to establish clear dosage guidelines, particularly in patients with compromised lung function, and the clinical consequence of increased production of anti-insulin antibody are still lacking. In addition, limited large-scale studies on the long-term potency and safety of inhaled insulin prevent its widespread clinical use. Despite significant developments, current insulin therapy has limited success in replicating the pulsatile pattern of natural insulin secretion or effectively maintains long-term glycemic control, leading to the development of microvascular and macrovascular complications.

Methods :

A literature search on PubMed, MEDLINE, Embase, and CrossRef databases was performed on multiple key words regarding the history and current variations of pulsatile and IIT for diabetes treatment. Articles reporting the physiology of insulin secretion, advantages of pulsatile insulin delivery in patients with diabetes patients, efficacy and adverse effects of current conventional insulin therapies for the management of diabetes, benefits and shortcomings of pancreas and islet transplantation, or clinical trials on patients with diabetes treated with pulsed insulin therapy or advanced IIT were included for a qualitative analysis and categorized into the following topics: mechanism of insulin secretion in normal subjects and patients with diabetes and current therapies for the management of diabetes, including oral hypoglycemic agents, insulin therapy, pancreas and islet transplantation, pulsed insulin therapy, and advances in IIT.

Results :

Our review of the literature shows that IIT improves the resolution of diabetic ulcers, neuropathy, and nephropathy, and reduces emergency room visits. The likely mechanism responsible for this improvement is increased insulin sensitivity from adipocytes, as well as increased insulin receptor expression.

Conclusion:

The insulin system consists of insulin originating from the pancreas and ubiquitously expressed insulin receptors throughout the body. Insulin is transported via the plasma throughout the body including the brain. Peripherally, insulin provides a conduit for glucose sequestration into cells. Insulin therapy is often combined with oral agents in patients with uncontrolled type 2 diabetes. For practical purposes, the type of insulin regimen is chosen according to blood glucose profiles.high-fiber foods, including beans and lentils. some whole grains, such as oats, quinoa, and barley. protein-rich foods, including lean meats, fish, soy, legumes, and nuts. fish with a high omega-3 fatty acid content, such as salmon, sardines, and herring.It is an exciting time in diabetes care given the expanding options available for both oral antidiabetic agents and insulin. But with the multitude of products now available, it is extremely important that practitioners understand the differences in products. Insulin is an essential drug in the treatment of diabetes but it is also a high-risk medication. Errors in its use can have devastating consequences. Understanding the differences in insulin preparations and their use reduces errors. The use of insulin in the home care setting is a common occurrence. Both patients and caregivers are frequently asked to manage diabetes care and maintain a safe glucose range at home. Clinicians with a clear understanding of insulin therapy can assist in this effort by ensuring safe insulin use and careful glucose monitoring. Understanding the onset, peak, and duration of various insulin preparations assists in troubleshooting glucose excursions. Close attention must be paid to each and every insulin dose administered. Supporting patients on optimal insulin use, monitoring, and safe practices will promote glycemic control and overall positive outcomes.

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