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REVIEW

Insulin sources and types: a review of insulin in terms of its mode on diabetes mellitus

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Abstract

Insulin is involved in regulation of glucose utilization in the body. Inability of the body to synthesize insulin or human cells resistance to insulin leads to a condition called Diabetes mellitus which is characterized by chronic hyperglycaemia. There are two types of diabetes; type 1 and type 2. Exogenous supply of insulin is needed consistently for type 1 diabetes treatment and type 2 diabetes also needs to be cured by the exogenous supply of insulin in advance stages of the disease. These sources have been proved very useful to meet the needs of the patients. However, these insulin types are expensive for the large population of patients in the developing countries. Furthermore, the incidence of diabetes is advancing at an alarming rate. Hence production systems with even higher capabilities of production are desired. Therefore, currently plants are being investigated as alternative production systems. Based on the mode of action of insulin various formulations of insulin have been developed that have different onset of action, peak effect and duration of action according to the needs of the patients.

Key words: Insulin; Diabetes mellitus; Insulin analogs

INTRODUCTION

Insulin is an important polypeptide hormone that regulates carbohydrate metabolism. Insulin is derived from the Latin word insula meaning "island" because the hormone is produced in the islets of langerhans. It was discovered by Banting and Best in 1921-1922 at the University of Toronto. It helps transport blood glucose into the body cells where the glucose is metabolized to produce energy. It maintains glucose concentration in the blood. When glucose concentration in the blood is increased, insulin lowers it by increasing glucose uptake by muscle, liver and fat cells. Excess glucose is converted to glycogen by these tissues. When glucose concentration is reduced in the blood, glycogen is converted back to glucose and released in the blood. It is involved in regulating amino acid uptake by increasing DNA replication and protein synthesis. Insulin facilitates fatty acid synthesis through the uptake of lipid from blood by fat cells. It also decreases proteinolysis, lipolysis and gluconeogenesis.

Insulin is synthesized by β-cells of the pancreas in the form of a single chain of three peptides B, C and A in the order: B chain-C peptide-A chain.[1,2] This proinsulin is converted to mature insulin after the removal of the central C-peptide by the action of proteolytic enzymes known as prohormone convertases PCl/PC3 and PC2.[3] The mature insulin consists of B-chain (30 amino acids) and A- chain (21 amino acids) linked by two inter-chain and one intra-chain disulphide bridge. Its structure has been highly conserved among vertebrates.[4-7]

When the body is unable to produce insulin or the body develops resistance against insulin, a metabolic disorder called diabetes mellitus arises which leads to

abnormal carbohydrate metabolism. Diabetes mellitus is treated by the exogenous supply of insulin. For this purpose, various types of insulin have been developed with different action times according to the needs of patients. In this review, insulin sources and types were summarized in terms of its action mode.

Treatment of diabetes mellitus

The condition refers to a metabolic disorder characterized by chronic hyperglycaemia in which the patient experiences disturbances in metabolism of carbohydrate, fat and protein as a result of deficiency in insulin secretion, insulin action or both.[8] Diabetes is the fifth-leading causes of mortality in most developed countries and there are thoughts to be about 246 million people suffering from diabetes.[9] It has been estimated that by 2025 there will be nearly 380 million people suffering from diabetes if not controlled.[9]

There are two types of diabetes mellitus i.e. type 1 and type 2 diabetes mellitus. Type 1 diabetes is caused by the destruction of β-cells of pancreas that are involved in insulin synthesis. The destruction is caused by an auto-immune reaction where these cells are destroyed by the body's own defence system. As a result, very little or no insulin is produced and hence carbohydrate, especially glucose, metabolism is disturbed leading to the characteristic symptoms. Type 1 diabetes is also known as insulin dependent, juvenile or immune- mediated diabetes. The causes of type 1 diabetes are still largely unknown; however, both genetic and environmental factors have been implicated. Children of parents with type 1 diabetes have an increased risk of developing the disease. Important environmental factors include obesity, diet, physical inactivity and viral infection. Type 1 diabetes mostly affects children and young adults. Patients suffering from type 1 diabetes consistently require insulin treatment (*via* injection or oral administration) for their continued survival.

Type 2 diabetes occurs as a result of insulin resistance and relative insulin deficiency. Insulin resistance refers to the condition where the insulin is not very effective in reducing the blood glucose levels. Type 2 diabetes can appear at any stage of life; however, it is mostly diagnosed in adults at the age of 40 or above. Symptoms of type 2 diabetes involve frequent urination, constant thirst, increased hunger, weight loss and tiredness. Like type 1 diabetes both genetic and environmental factors contribute to the development of type 2 diabetes. Genetic factors leading to type 2 diabetes are not well understood, while potential environmental factors include physical inactivity, obesity, diet and aging. Patients with type 2 diabetes generally do not need to be administered exogenous insulin; however, in extreme cases of hyperglycemia administration of exogenous insulin might be required. Treatment generally involves controlling blood glucose, blood pressure, lipids, changing lifestyle through exercise and medication.

Treatment of diabetes involves regular monitoring of glucose levels in the blood so as to provide insulin when required to prevent hyperglycaemia. Necessary changes in lifestyle and diet are also required to keep diabetes in control. Insulin is primarily given in the form of injections; however, recent advances in drug delivery have included pulmonary, oral and nasal administration routes which have been developed to overcome the inconveniences associated with regular insulin injections.[10,11]

INSULIN SOURCES: PLANTS AS ALTERNATIVE FOR MASS SCALE PRODUCTION

Since the 1920s, insulin has been used for treatment of diabetes. The initial sources of insulin were from bovine, porcine, and equine. Methods to convert porcine insulin into the human insulin equivalent were developed in the 1970s and early 1980s.[12,13] With the development of genetic engineering and modern biotechnology, efforts were shifted towards the production of insulin through recombinant DNA technology. Human insulin was one of the first pharmaceutical proteins that were manufactured through recombinant DNA technology in the late 1970s, which has been marketed since 1982.

Since 1980s, recombinant insulin from bacteria[14] and yeast.[15] has been the main source of commercial insulin. These systems have been helping to meet the demand of this important pharmaceutical since this time. However, the incidence of diabetes is increasing and this demand for insulin cannot be provided by these sources in the near future due to the scale and costs involved. It has been estimated that the demand for insulin will double in the next 10 years.[16] Developing countries are facing further challenges as patients in these countries are not able to afford the cost of this expensive drug. Furthermore, alternate delivery systems such as oral, inhalable and buccal forms which aim to provide relief to patients from the painful insulin injections require a higher amount of insulin to be effective as a treatment as these methods are not very efficient.[16]

In view of the increasing demand for insulin, currently plants are being investigated as factories for the production of insulin which have the potential for a high yielding and cost effective method of production for this important pharmaceutical.[17-19] In an attempt to achieve this goal, Arakawa *et al* [17] produced a cholera toxin B subunit-insulin fusion protein in transgenic potato tubers as an autoantigen against insulin-dependent diabetes mellitus. The fusion protein accumulated to 0.1% of total soluble protein. The transgenic tobacco tuber tissues were fed to diabetic mice which helped in the reduction of insulitis and delayed the onset of diabetes. Nykiforuk *et al* [18] expressed the desB30 form of human insulin (lacking threonine at position B30) as an oleosin-insulin fusion protein in Arabidopsis thali-