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INSULIN DRUGS AND THEIR ASSOCIATION WITH ALZHEIMER'S DISEASE

Anu Bhatia, Ankush Kumar,Sara Sharma, Anjana Devi*
School of Pharmacy Career Point University, Bhoranj (Tikker - kharwarian), Hamirpur, Himachal Pradesh, India 176041

ABSTRACT

The insulin formerly derived from animal sources such as bovine, porcine and bovine-porcine has been replaced by human insulin and its equivalents. Structurally modified synthetic versions of these are created. These come from a variety of sources, mainly human insulin analogs. The only difference between human insulin and similar substances is the duration of action. For example, in the US only similar insulin is used and commercially available bovine and porcine insulin is not. Absorption, potency, and duration of action will change as a result of these changes. Similar to the first phase of insulin release, these forms are observed to achieve rapid pharmacodynamics and pharmacokinetics (ADME). These analogs work by mimicking the typical physiology of insulin. These are also believed to aid in postprandial glycemic management. Physiological and anatomical impairments are the early diagnostic features of Alzheimer's disease. These are now understood to be a crucial part of the pathogenesis of Alzheimer's disease. The sensitizer offers comfort and support for ideas that have been established in animal models of amyloidosis, such as B. An abnormal production can lead to insulin resistance, which contributes to a variety of cognitive disorders. Brain injury stimulates the production of A and causes insulin resistance, which is then alleviated by the sensitizer. The focus of this review is on insulin medicine, molecular mechanisms, and all aspects of memory related to Alzheimer's disease.

Keywords: Insulin Analogues, Human Insulin, Insulin administration, and Hyperkalaemia.

INTRODUCTION

Insulin drug is a pharmaceutical preparation of the naturally occurring hormone insulin. Insulin is mainly used to treat diabetes mellitus or we can speak of elevated blood sugar levels. Insulin can also be used in conjunction with glucose to treat hyperkalemia. It is generally injected under the skin, but some of its forms can also be injected into muscles or veins. Different types of insulin are available for different periods. It is part of the World Health Organization's List of Essential Medicines. In the US, regular insulin was the 298th most commonly prescribed drug in 2019, with more than 1 million prescriptions. Insulin is derived from the pancreas of pigs (pigs) or cows (beef). Human versions of insulin are made by modifying porcine versions or using recombinant technology. There are three main insulins: regular insulin (short-acting), neutral protamine (intermediate-acting), and insulin glargine (long-acting insulin), according to the University of Toronto.

Fig: Insulin Drugs

HISTORY OF INSULIN DISCOVERY

Insulin was discovered in 1921 with the ideas of Frederick G. Banting, an orthopedic surgeon from Canada, and made possible with his assistant Charles Best and John MacLeod's chemical skills at the University of Toronto in Canada. Dr. Frederick G. Banting was the first person to isolate islet cell secretions in 1921, and then they were considered a possible diabetes treatment. He noted that the other scientists couldn't find any insulin because insulin had been destroyed by the digestive enzyme before it was extracted. Until the enzyme-producing cells degenerated, Banting tied up the lab dog's pancreatic duct, left strong islet cells alive, and then extracted the debris. Unaware of the development of blood glucose testing to accurately check for diabetes, he tested urine, but it was less accurate. But it was no idea that other scientists had also made pancreas extract, which was used to lower blood sugar and wasn't particularly useful since Banting could only extract the hormone in small amounts. In addition, toxic properties appeared in this extract and severe side effects such as pain and fever appeared in animals.

MODIFIED INSULIN FOR PHARMACEUTICAL USES

Originally, insulin extracted from the pancreas was used as a drug for type 1 diabetes mellitus for 60 years. Protamine insulin was first developed by Hagedorn and Jensen in 1936 when protamine was mixed into insulin. The recombinant insulin Humulin was first discovered by Eli Lilly in 1982. Research has now focused on

developing forms and analogs of insulin that are either long-acting or fast-acting so that they mimic insulin secretion in healthy people. Fast-acting insulin is used prandially, while long-acting insulin is used primarily to confirm basal coverage during fasting. Generally, a needle mounted in a pen is used to deliver the insulin into subcutaneous tissues. During storage at pH 4.0, the residue is steamed in Gly to avoid acid-labile AsnA deamination. This time the drug was successfully formulated at pH 4.0 and injected subcutaneously, and then it meets the physiological subcutaneous pH, the micro precipitates are formed analogously, which slowly withdraw the insulin monomers and dimers into the subject's bloodstream. Lantus insulin has become a prodrug and the Arg-Arg sequence is shared in the body. Half of life was prolonged and this was achieved through insulin modification with fatty acids or fatty acids facilitated by human serum albumin (HSA).

HUMAN INSULIN AND INSULIN ANALOGUES AND THEIR SOURCES

In type 1 diabetes, insulin medicine is one of the most commonly prescribed medications. Insulin plays a major role in various metabolic mechanisms such as nucleotides, glucose, potassium, and amino acids. Insulin promotes several complex organic syntheses such as glycogen, triglycerides, and proteins. These are obtained from various sources, mostly in the same way as human insulin. Human insulin and analogs both have the same activities except for their duration of action. For example, in the US, they only use analogs, and bovine and porcine insulin are not commercially available. Human insulin is only produced when bacteria are introduced into yeast cells in the human insulin manufacturing code. Human insulin analogs are the altered form of insulin and, unlike human insulin, are still used. There are some examples of insulin analogs like Apidra, Novolog, and Humalog. Exogenous insulin can be used in type I diabetes mellitus or supplemented to a sufficient extent in type II diabetes mellitus. These insulin preparations vary based on so many factors, namely dose, blood supply and temperature, site of administration, physical activity, and onset and duration of action.

INSULIN MEDICATIONS

Insulin medical preparations are nothing but insulin mixed in water. Clinical insulins are made up of mixtures of normal insulin with some other constituents like preservatives that can be used. These help to prevent rapid action or protein denaturing, delay insulin absorption, reduce the prophylaxis at the site of administration adjusts the pH solution and so many others. Insulin analogous is minor variations of the molecules of human insulin, (technically "insulin receptor ligands"). They are called so because they are not insulin technically, but those which hold on to the glucose management functionalities of hormones. They have absorption activity characteristics that are not presently possible in subcutaneous insulin properly. They are firstly absorbed in to mimic actual beta cells insulin, or slowly absorbed after injection after a rapid insulin decline action all while holding on glucose-lowering action of insulin in the individual body. In 2015, the Collaboration of Cochrane various kinds of meta-analyses was done. In 2007, GIQCS and CADTH have not proved any unambiguous advantages of these analogous. It is essential to choose an experienced person to choose the type, dose, and timings of insulin medication in diabetic people.

THE MOST COMMON INSULIN ARE

FAST-ACTING INSULIN

Insulin analogs such as lispro, glulisine, and as part begin to act within 5-15 minutes and remain active for 3-4 hours. Most insulins form hexamers, which enter the bloodstream in an active form with a delay; however, these insulin analogs do not have normal insulin activity. New varieties of insulin analogs are pending regulatory approval in the United States that are designed to be fast acting but have genetic structures that are the same as regular human insulin.

SHORT-ACTING INSULIN

Short-acting insulins include regular insulins and show effect within 30 minutes and work actively for 5-8 hours.

INTERMEDIATE-ACTING INSULIN

Intermediate-acting analogs like NPH insulin start to work within 1-3 hours and they are active for 16-24 hours.

LONG-ACTING INSULIN

Long-acting insulins include insulin glargine U 100 and detemir, both of which start working after a few hours and are continuously active for almost 24 hours, although this can vary in different patients.

ULTRA-LONG-ACTING INSULIN

These insulins include the Analogues Insulin Glargine and Degludec and they begin to show effect in 30-90 minutes and actively work for more than 24 hours.

ADMINISTRATION OF INSULIN

Unlike many other medicines, insulins cannot currently be taken orally. Like all other proteins administered in our GIT, they are mostly reduced to single amino acids, after which all their activities are shifted. There is some ongoing research to improve the stability of insulin in the digestive tract to achieve oral administration of insulin.

Fig: Administration of Insulin

SYRINGE OR PEN

Bot of the Syringe and the insulin pen administer insulin through the needle. Pens are found more convenient and comfortable than that syringes, and children may find pens more convenient.

Fig: Syringe or Pen

INSULIN PEN

Cartridges are used in some pens. These cartridges can be inserted into these already-filled pens. Once all the insulin has been used, the cartridges should be discarded. The insulin dose is put into the pen and the insulin is injected through a needle. The advantages of insulin pens are that they require less training to inject, they cost less than a pump and they are more travel-friendly.

Fig: Insulin pen

INSULIN PUMP

Insulin pumps are the size of a small cell phone. The dose can be administered using the pump. The dose can be calculated during high glucose levels and while the patient is eating. The pump helps deliver the insulin into the bolus by pumping it through a thin plastic tube that can be placed under the patient's skin. The site of administration is mainly the abdominal area and the back of the upper arm.

INSULIN INHALER

Insulin is inhaled using an oral inhaler, and the ultra-fast-acting insulin is delivered before meals. Inhaled insulin is used in conjunction with long-acting insulin injections.

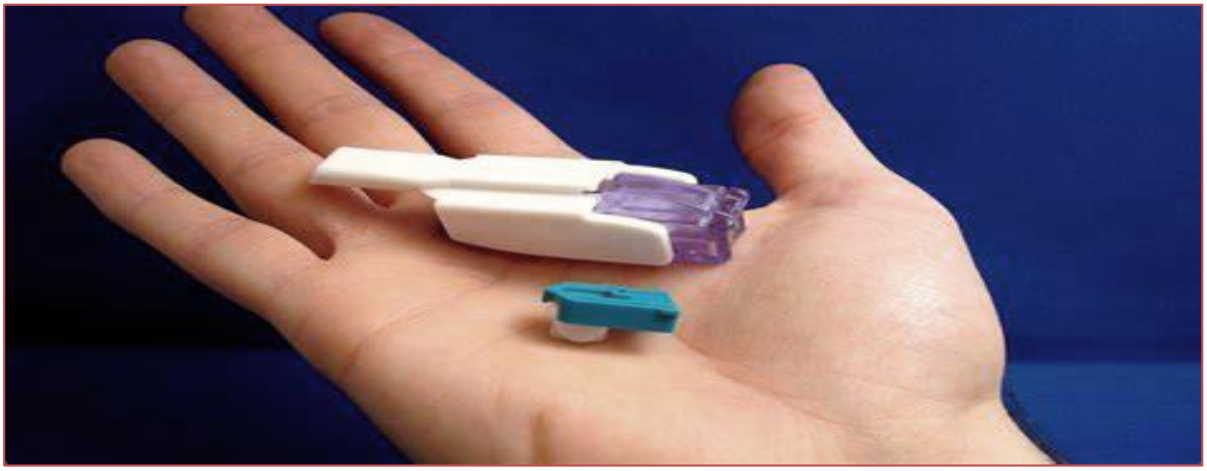

Fig: Insulin Inhaler

DETECTION OF INSULIN IN PLASMA, BLOOD, AND SERUM

Insulin is usually measured in plasma, serum, and blood to monitor therapy in diabetics, to protect against cases of poisoning in hospitalized persons, or to support a medical-legal clarification of doubtful deaths. The explanation of the result of insulin concentrations is complex, there are different types of insulin and different types of routes of administration, anti-insulin antibodies are present in insulin-dependent diabetics, and the drugs are unstable ex vivo. Another potentially surprising factors are the widespread cross-reactivity of commercial insulin immunoassays for biosynthetic insulin analogs. As an antidote to hypertension drug overdose, high-dose intravenous insulin is used, and within the human body post-mortem, it is used for insulin redistribution. In some cases, it may be preferable to use the chromatographic technique of the insulin assay to avoid cross-reactivities that affect the quantitative results and also help to identify the specific insulin types found in the sample.

MEDICINAL USES

Several diseases are treated with insulin, including diabetes and the acute complications of diabetes such as hyperosmolar hyperglycaemic states and diabetic ketoacidosis. Hyperkalaemia is also treated by insulin with glucose. Insulin is also safe for the fetus during pregnancy. It is a fact that insulin cannot be given orally because it is not properly absorbed in the GI. There is some ongoing research to improve the stability of insulin in the digestive tract to achieve oral administration of insulin. There are numerous insulin analogs available on the US market. The structure of this analog is related to the structure of human insulin. Biosynthetic analog insulins have been synthesized for clinical uses during meals. Subcutaneous administration of Humalog shows faster absorption than regular insulin. Other analogs such as Apidra and Novo Rapid also possess a profile similar to Humalog. All of these are quickly absorbed due to their amino acid sequence. This does not require an injection before eating.

There is a long-acting insulin. The first long-acting insulin was Lantus. Insulin is administered subcutaneously. Away with the help of a needle, a syringe, and an insulin pump.

INSULIN RESISTANCE AND ALZHEIMER'S DISEASE

In Alzheimer's disease, the earliest diagnostic features are physiological and anatomical compromises. In recent years these have been recognized as an integral part of the pathology of Alzheimer's disease. Elevated glucose levels and sensitivity to insulin puts insulin resistance at risk for age-related abnormalities, including Alzheimer's disease. The hippocampus is critical for sensing and understanding various biomolecular signaling pathways. These pathways underlie learning, and cognition can facilitate the development of various therapeutics. Several risk factors have been observed for developing insulin resistance, such as arthritis, education, physical and social activity, diet, and stress. Examples include cardiovascular disease, high cholesterol and increasingly appreciated vascular damage, and memory impairment associated with Alzheimer's disease. In recent years, various metabolic diseases such as glucoregulatory diseases and insulin-resistant type 2 diabetes contribute to risks. Inflammatory diseases are a very common denominator in various diseases such as insulin resistance and dementia. In addition, aging is an insulin sensitivity that drives insulin resistance and depends on various factors such as lifestyle. Brain injury results in stimulation and production of A and causes insulin resistance, with the sensitizer providing relief and support found in animal models such as amyloidosis, as an abnormal production of A can cause insulin resistance, which contributes to various cognitive-related defects. Human genetics such as ethnicity also play an important role in contributing to insulin resistance, which increases the risk of Alzheimer's. Furthermore, the mechanism for this has not been clearly understood, and most physiological abnormalities have combined risks such as environmental and genetic.

MOLECULAR MECHANISMS OF INFLAMMATION-MEDIATED INSULIN RESISTANCE

An increase in blood sugar levels leads to inflammation and accelerates insulin resistance. Proinflammatory cytokines such as IL1-, IL-6, and TNF-. These create an inflammatory environment that decreases insulin sensitivity through feedback inhibition of receptors and impaired mitochondrial function, which stimulate ROS generation and further inflammation. The inflammatory environment can increase NIK, affecting mitochondrial physiology to further promote insulin resistance. Inflammation can be triggered by peripheral immune cells and pro-inflammatory cytokines in the bloodstream during hyperglycemia, which can cross the BBB in addition to inflammation in the immune system.

ALTERNATIVE APPROACHES

Lifestyle factors and environment are the active areas that can improve decreased cognition and reduce pathology. NSAIDs have been tested for Alzheimer's disease. Various natural compounds such as biloba, cerebrospinal, and resveratrol.

DISEASE STAGE-SPECIFIC THERAPEUTIC WINDOWS

An increase in glucose requirements and sensitivity to insulin in the brain confers an increase in resistance to insulin-related diseases and aging. Progression can be elucidated by observing treatment with an insulin sensitizer that showed no improvement in cognition while others did not respond to this treatment. Likewise, continuing treatment to the therapeutic goal is no longer considered appropriate. An increase in the need for glucose and the sensitivity of insulin to the brain leads to an increase in insulin resistance with age and various types of disorders. These progressions can be illustrated by the observation that one month's treatment with a sensitizer produces no improvement in response to any treatment. Similarly, other treatments provide cognitive protection, indicating that intervention continues disease progression where the therapeutic target is inappropriate. In therapeutic widows, suppression of calcineurin has been found to reverse cognition. Surprisingly, calcineurin suppression improves insulin sensitivity in normoglycemia but impairs resistance in diabetes. All of this supports the observation that Alzheimer's disease can correspond to prediabetes condition, which can be elevated without dyshomeostasis, which can ultimately increase the risk of memory impairment. The observation was that PPAR was upregulated while the window for the intervention of PPAR agonism was downregulated. Therefore, it should be discussed that the intervention may increase the likelihood of targets such as AMPK. AMPK may apply to cognitive performance. The main focus of this review was insulin medication and the molecular processes and overall memory associated with Alzheimer's disease. The role of insulin resistance accompanies type 2 diabetes and age is the main risk factor associated with Alzheimer's disease. Insulin signaling is a critical factor in brain homeostasis, memory, metabolism, and synaptic plasticity.

SUMMARY AND CONCLUSION

It is crucial to overcome the one-dimensional prevention and therapy approaches, which have mostly failed to treat AD as a diverse clinical picture that develops from progressive degenerative changes in dynamic organism systems. The most important regulators of life expectancy and physical aging are undoubtedly biological systems related to insulin metabolism. In some subsets of AD patients, it is possible that certain nodes in the insulin network are defective or that non-insulin-related pathway play an important role in the pathogenesis of some subsets. These subgroups can be found using novel techniques from systems network analysis, which will be essential for the development of specialized prevention and treatment plans. From a public health perspective, the simultaneous increase in population aging and the prevalence of insulin resistance increases the risk of a sharp increase in the incidence of dementia. Fortunately, it is possible to detect insulin resistance and associated variables before the onset of AD, when there is still time for lifestyle changes or therapeutic interventions to be most effective.

FUTURE PERSPECTIVE

The failure of amyloid-amyloid techniques has also been reported, suggesting that more avenues need to be explored in the search for disease-modifying drugs for Alzheimer's disease. The pathophysiological link between AD and DM, as well as the efficacy of several antidiuretics already shown in preclinical studies to have a potentially beneficial effect on a variety of neurodegenerative diseases, strongly suggest that these drugs warrant

further research in AD. Insulin is a prospective treatment for AD due to the positive results of numerous clinical trials of intranasal insulin administration in AD, which also showed no significant side effects. The discovery of numerous ongoing studies on the use of antidiabetic drugs in AD and MCI is expected in the coming years.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ABBREVIATIONS

AD: Alzheimer's disease;

SC: Subcutaneous;

DM: Diabetes Mellitus;

MCI, Mild Cognitive Impairment;

ROS: Reactive Oxygen Species;

Ampk: Adenosine Monophosphate-Activated Protein Kinase;

NSAID: Non-Steroidal Anti-Inflammatory Drugs;

BBB: Blood-brain barrier;

US: United State;

GIT: Gastrointestinal tract;

NPH: Neutral Protamine Hagedorn;

HSA: Human Serum Albumin;

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