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Effectiveness of Diabetogenic Agent Streptozotocin in Inducing Diabetes Mellitus in Experimental Animals: A Literature Review

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ABSTRACT

Background: Diabetes mellitus is one of the serious diseases due to its chronicity which can cause complications to various organs. Various animal studies on complications of Diabetes mellitus are needed. Research on animal studies of Diabetes mellitus is very diverse in terms of the studies studied and the variants of diabetogenic agents that induce Diabetes mellitus. ***Objective***: This literature review compares and reviews several studies related to the use of streptozotocin as a diabetogenic agent that induces diabetes mellitus in experimental animals and highlights the effectiveness of streptozotocin in causing the incidence of diabetes mellitus in experimental animals. ***Method***: The method that the researcher used in this study is a non-systematic review that uses database sources from journal publications in ScienceDirect, PubMed, and Google Scholar. ***Result***: Streptozotocin is able to effectively cause hyperglycemia and induce diabetes mellitus in experimental animals. In previous studies, it was found that intraperitoneal injection of low-dose streptozotocin is able to maintain a state of hyperglycemia for a long time, making it easier to observe complications of diabetes.

Keywords: streptozotocin; diabetes mellitus; experimental animal.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by increased blood glucose levels (hyperglycemia) due to insulin insufficiency either due to impaired insulin secretion or function [1]. Insulin insufficiency can be caused by a deficiency or disruption of insulin production by pancreatic beta cells in the islets of Langerhans or caused by a decrease in the sensitivity and responsiveness of body cells to the insulin hormone so that the body cannot use insulin effectively. According to WHO, the term diabetes describes a group of chronic metabolic disorders characterized and identified by the presence of hyperglycemia that has serious impacts on various organ functions such as the heart, blood vessels, eyes, kidneys, and nerves [2]. According to the International Diabetes Federation (IDF), the global prevalence of diabetes in the 20-79 age group in 2021 is estimated to be 10.5% (536.6 million people) and will increase to 12.2% (783.2 million) in 2045. Riskesdas 2018 data shows the prevalence of diabetes in Indonesia is 8.5%, an increase compared to Riskesdas 2013 which was 6.9%. Epidemiologically, it is estimated that in 2030 the prevalence of Diabetes mellitus (DM) in Indonesia will reach 21.3 million people (Diabetes Care, 2004). This shows that Diabetes mellitus is still a major health problem in Indonesia [3].

Research on experimental animals for Diabetes mellitus is very diverse in terms of the studies studied and the variants of diabetogenic agents that induce Diabetes mellitus. Experimental research on Diabetes mellitus using experimental animals is based on the pathogenesis of the disease in humans which is chronic. Currently, research has been conducted using animal models that are pathologically made to suffer from Diabetes mellitus. Pathological conditions in the experimental animal model are made to prevent, determine the pathogenesis of the disease, and determine the diagnosis, and therapy used in the treatment of Diabetes mellitus [4].

This literature review aims to explain the effectiveness of streptozotocin as a diabetogenic agent inducing diabetes mellitus through various recent studies. By knowing how effective streptozotocin is in causing hyperglycemia or long-term diabetes in experimental animal models, it is hoped that this review can help further researchers in choosing diabetes-inducing agents to observe the chronic effects of diabetes itself.

METHOD

This study seeks references that can support theories that are relevant to the problem being studied.

According to Winoto, the process of conducting a literature review involves searching for relevant textual sources related to the problem or topic being studied, including books and journals [5]. Data sources come from scientific articles from various journal databases, such as Google Scholar, PubMed, and Science Direct. Article searches are conducted using keywords such as "Streptozotocin," "Diabetes Mellitus," and "Animal Models." This literature can be accessed in full text in PDF format and in peer-reviewed journals. The data collection strategy used was to collect several journals from the internet and highlight a few sentences from each journal found. From these highlights, we organized them into points.

RESULT AND DISCUSSION

Diabetes Mellitus

- ***Definition of Diabetes***

Diabetes mellitus is a metabolic disorder characterized by increased blood glucose levels due to due to impaired insulin secretion or function [1]. Hyperglycemia is a condition in which there is an increase in blood sugar levels caused by impaired glucose metabolism in the body, one of which is caused by Diabetes mellitus. Chronic hyperglycemia in patients with Diabetes mellitus is associated with long-term damage or dysfunction of several vital organs of the body, especially the eyes, kidneys, nerves, heart, and blood vessels [9]. Based on several explanations above, Diabetes mellitus is a metabolic disorder characterized by increased blood sugar levels (hyperglycemia) which can cause damage to various important organs and systems of the human body.

- ***Classification and Pathophysiology of Diabetes Mellitus***

According to the ADA (American Diabetes Association) 2013, Diabetes mellitus is grouped into 4 types. Namely, Diabetes mellitus type 1, Diabetes mellitus type 2, other specific types of Diabetes mellitus, and gestational Diabetes mellitus [13].

(a) Diabetes mellitus type 1

Diabetes mellitus type 1 is a systemic glucose metabolism disorder characterized by chronic hyperglycemia due to inadequate insulin levels due to the destruction of pancreatic beta cells. This condition occurs due to an autoimmune process that destroys pancreatic beta cells so that insulin production is greatly reduced or even stopped so that sufferers will require exogenous insulin intake [14].

(b) Diabetes mellitus type 2

Diabetes mellitus type 2 is a metabolic disorder due to body cell resistance to insulin, resulting in hyperglycemia, and can cause chronic complications in the form of macroangiopathy and microangiopathy [15]. Diabetes mellitus type 2 is a manifestation of progressive insulin secretion disorders that are the background to insulin resistance or ineffectiveness of insulin in the body. Diabetes mellitus is the type of diabetes most commonly experienced by most people in various parts of the world and is most often caused by excess weight (obesity) and lack of physical activity [16].

(c) Other specific types of Diabetes mellitus

Other specific types of diabetes mellitus are diabetes caused by genetic disorders, disorders of the pancreas, disorders of the antibody system, infections, and other pathological disorders. Other specific types of diabetes mellitus can also be caused by genetic disorders that cause changes in insulin function, genetic disorders in insulin function, endocrine disorders, disorders of the exocrine pancreas, the effects of long-term use of certain drugs (glucocorticoids), and the effects of the use of chemicals [17]

(d) Gestational Diabetes mellitus

Gestational diabetes mellitus is a condition of glucose intolerance that can occur at various stages of gestation [18]. Gestational diabetes occurs during pregnancy and disappears after delivery [19].

- ***Diagnostic Criteria of Diabetes Mellitus***

According to Perkeni (2019), Diabetes Mellitus is diagnosed based on blood glucose level examination. Based on the 2019 Diabetes Mellitus diagnostic guidelines by PERKENI, the diagnostic criteria for Diabetes Mellitus consist of:

(a) Fasting blood sugar examination ≥126 mg/dl. Fasting is defined as no calorie intake for at least 8 hours, or

(b) Plasma glucose examination ≥200 mg/dl is performed 2 hours after the Oral Glucose Tolerance Test (OGTT) with a glucose load of 75 grams, or

(c) Random plasma glucose examination ≥200 mg/dl accompanied by typical symptoms (polyuria, polydipsia, polyphagia, and weight loss without an obvious cause), or

(d) The method standardized by the National Glycohemoglobin Standardization Program (NGSP) is used to detect HbA1c ≥6.5%.

Experimental Animals

- ***Experimental Animal in General***

Experimental animals are any animals used in biological and biomedical research that are selected based on the basic requirements or standards required in the research. Experimental animal models are used as a substitute for research samples and not all models are identical to the model subjects.

Therefore, selecting the right laboratory animal model is very important in researching a disease. The ideal laboratory animal model has similarities in mimicry, is easy to grow, is able to produce many offspring, is able to provide blood and tissue samples with just one tail, has low maintenance costs, its genetic composition is known and its disease status can be known and explained [10]. Rats and mice are one of the experimental animals that are often used by researchers to conduct experiments in the laboratory.

Experimental Animals for Diabetes Mellitus

Based on research conducted by Szkudelski in 2001, streptozotocin induction is ideal for producing animal models of diabetes because it can support long-term hyperglycemia, helping to more easily observe the pathophysiology and complications of diabetes [7]. Streptozotocin induction can cause type 1 and type 2 diabetes, depending on the type of treatment given and the dose given to laboratory animals. High-dose streptozotocin injection has been associated with several deaths in the first week after onset, complete destruction of pancreatic beta cells, and increased blood glucose levels. On the other hand, at low doses, pancreatic beta cells of the animal model are partially destroyed, allowing animals to survive longer and be more observable [11].

Streptozotocin

- ***Definition of Streptozotocin***

Streptozotocin (STZ) is a glucosamine nitrosourea compound derived from soil bacteria and was initially developed as an anti-cancer agent in 1963. Streptozotocin is able to cause diabetes mellitus in experimental animals so systemic application of streptozotocin as an experimental material for type 1 diabetes mellitus and type 2 diabetes mellitus is often used [6].

- ***Mechanism of Action of Streptozotocin in Inducing Diabetes Mellitus***

Streptozotocin is able to induce diabetes mellitus by entering pancreatic beta cells through glucose transporter 2 (GLUT 2) and causing alkylation, which is preceded by the formation of free radicals, increased xanthine oxidase enzymes, and restrictions on the formation of adenosine triphosphate in mitochondria by inhibiting the Krebs cycle [7]. Streptozotocin plays a role in the formation of reactive free radicals that can damage cell membranes, proteins, and deoxyribonucleic acid (DNA), as well as reducing insulin production by pancreatic beta cells [8].

- ***Effectiveness of Streptozotocin in Inducing Diabetes Mellitus***

Several studies such as those conducted by Saputra, et al show that the Streptozotocin agent is very suitable for use in producing experimental mice in experimental diabetes mellitus conditions [4]. In this study, administration of streptozotocin can cause experimental diabetic hyperglycemia conditions within 3 days. In another study, conducted by Munjiati et al in 2021, it was shown that the induction of a single dose of streptozotocin has an effect on increasing blood glucose levels in Wistar Rats [12]. This is in line with previous research conducted by Szkudelski in 2001. The findings in the study were that the administration of high doses of intraperitoneal streptozotocin (ip) can cause acute high hyperglycemia due to total damage to pancreatic beta cells. The administration of low doses of intraperitoneal streptozotocin (ip) to experimental animals will cause partial destruction of pancreatic beta cells, allowing the experimental animals to survive longer and chronic complications of diabetes become easier to observe [7].

CONCLUSIONS

Streptozotocin is effectively able to cause hyperglycemia and induce diabetes mellitus in experimental animals by destroying pancreatic beta cells. So that insulin production is disrupted or even stopped. Giving high doses of streptozotocin can cause high acute hyperglycemia due to total damage to pancreatic beta cells. While giving low doses of streptozotocin will cause partial damage to pancreatic beta cells.

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