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Mechanism of Streptozotocin while causing Diabetes Mellitus

SAZEDUR RAHMAN AKANADA, Imruj Rahman, Sourodeep Das, Dr.Mohibul Hoque

Abstract

The field of diabetic mellitus (DM) research now has access to a variety of genotypic and phenotypic choices that would otherwise be unavailable thanks to the rapid and cost-efficient Streptozotocin (STZ)-induced diabetes mellitus (DM) approach. Despite the fact that STZ is frequently utilised in small animal models, the information available about preparation, dose, and administration, as well as the timing and severity of DM, as well as any associated morbidity and mortality, are frequently constrained and inconsistent. Streptozotocin (STZ) is used to induce diabetes in different animal species. Animals treated with STZ develop symptoms that resemble those seen in people with diabetes. This is why STZ-treated animals are often used to study diabetes mechanisms and for preclinical evaluation of new antidiabetic therapies.

Introduction

Diabetes mellitus (DM) is a continual sickness characterised by hyperglycemia ensuing in insulin resistance and/or insulin secondary deficiency as a result of the failure of beta- (β)pancreatic cells. Diabetes may be categorised into 4 clinical categories, type 1 diabetes (because of autoimmune destructionof the β cells, normally main to absolute insulin deficiency),type 2 diabetes (because of a innovative insulin secretory defect in the historical past of insulin resistance), gestational diabetes mellitus (GDM) and different precise sorts of diabetes because of different causes, for example, genetic defects in mobilcelular feature or insulin action, drug- or chemical-inducedalterations and any sicknesses of the exocrine pancreas characterised via way of means of a procedure that diffusely injures the pancreas can motive diabetes. Diabetes is normally diagnosedbased on plasma glucose criteria.

Streptozotocin (STZ) was first isolated from the soil microorganism *Streptomyces acromogenes* and exhibited broad-spectrum antibiotic activity. Since its discovery in 1959, STZ has been widely used to induce diabetes in laboratory animals and in preclinical studies. Of the many chemicals available to induce diabetes, STZ is the most convenient for modeling human diabetes in animals. The structural, functional and biochemical changes observed in STZ-induced diabetes are similar to those commonly seen in human diabetes. Therefore, STZ-induced diabetes is a clinically relevant model to study the pathogenesis of diabetes and its complications in experimental animals. It has a short biological half-life of only 5-15 minutes.STZ accumulates mainly in pancreatic β-cells via

the GLUT2 transporter system and causes β-cell cytotoxicity.The diabetic effect of STZ was first revealed in 1963. Since then, it continued to be the agent of choice for inducing diabetes in experimental animals.

STRUCTURAL FEATURES OF STZ

Streptozotocin (2-deoxy-2-[3-methyl-3-nitrosourea] 1-D-glucopyranose) exists in two anomers,α and β forms that can be separated by chromatographic methods .It is a pale yellow to off-white crystalline powder. The molecular weight of streptozocin is265 g/mol, chemical formula is C8H15N3O7. The molecular structure of STZ is familiar to2-deoxy-D-glucose substituted at C2 with an N-methyl-N-nitrosourea group. This is the cytotoxic portion of STZ in beta-cell damage. Streptozotocin is a nitrosourea compound of glucosamine with a methyl group at one end and a glucose molecule at another end.

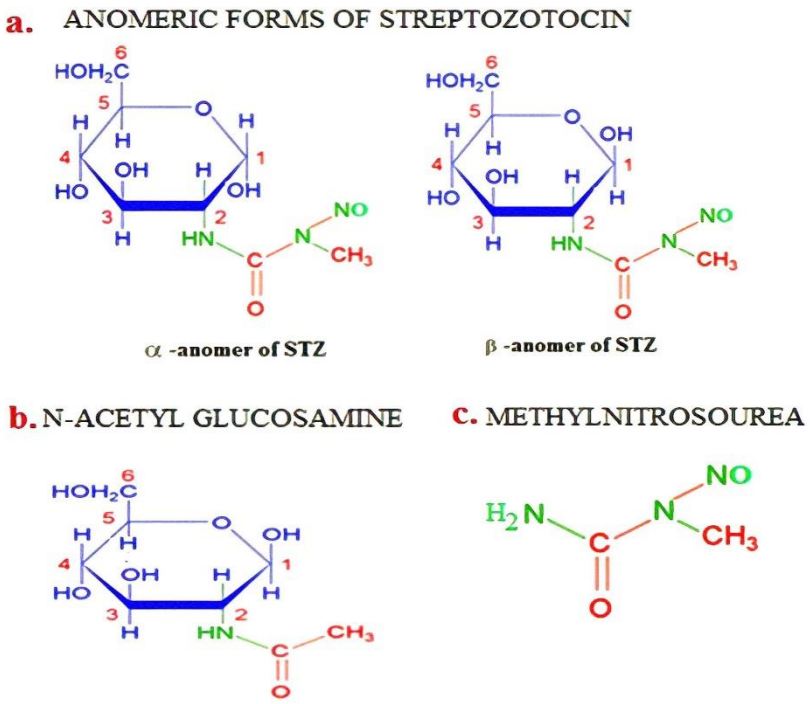

Figure 1 :-Chemical Structure of STZ (a. α and β Anomeric forms of STZ b.Structuralanalog of STZ – N-acetyl glucosamine C. cytotoxic moiety of STZ- N-methyl-N-Nitrosourea)

Dose and Route of administration of STZ

The two most common administration protocols are single high-dose or multiple low-dose intraperitoneal injections. For induction of diabetes with a single high-dose regimen, reported doses range from 40 mg/kg to 220 mg/kg. The low-dose protocol typically consists of 5 consecutive intraperitoneal doses of 40 mg/kg streptozotocin daily, but 4 (35 mg/kg) and 6 daily doses, and 5 doses of 40 mg/kg of two separate coursesis beingreported.

There have been numerous reports of using different dosing regimens and administration methods to cause diabetes in rats. The two most popular ways to administer STZ are intraperitoneally (IP) and intravenously (IV), though rodents have also received the medication via subcutaneous, intracardiac, and intramuscular routes.

Mechanism of Action of STZ

Although STZ has been used for many years to develop animal models of diabetes, its exact mechanism of action is still unknown. The preferential absorption of STZ by pancreatic cells and its toxic effector mechanism in the animal body to produce a diabetic model are two of the mode of action of STZ cellular toxicity which as a result helps to induce diabetes.

In both mammalian and bacterial cells, streptozotocin prevents DNA (Deoxyribonucleic Acid) synthesis. In Bacterial cells, it causes a special reaction with cytosine groups that leads to DNA degeneration and Destruction. Via the glucose transporter GLUT2, streptozotocin enters the pancreatic cell and causes DNA to be alkylated. By activating poly adenosine diphoshateribosylation and nitric oxide release, STZ also causes pancreatic cells to die through necrosis, which leads to the development of insulin-dependent Diabetes.

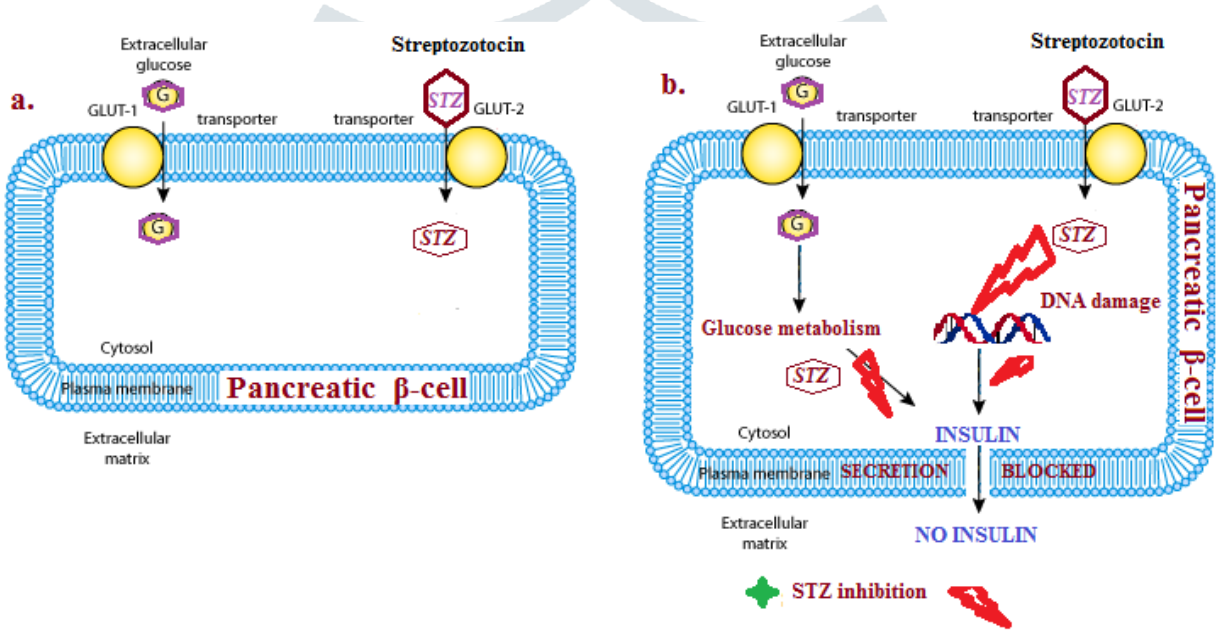

Figure 2. Selective uptake of stz by β cells of pancreas

Rodents (rats, mice, hamsters) and other mammals (monkeys and rabbits) are susceptible to STZ-induced diabetes. The toxic effects of STZ include selective uptake into β-cells via its low-affinity plasma membrane glucose transporter GLUT2. Unlike the general lipophilicity of its group of compounds – the nitrosoureas – STZ is inherently hydrophilic due to the substitution of the glucose moiety. The hydrophilicity of STZ limits its free diffusion across the cell's phospholipid bilayer plasma membrane as it is hydrophobic. The 2-deoxyglucose moiety of STZ is structurally similar to glucose, allowing selective uptake into β-cells by the glucose transporter (GLUT)-2. Hepatocytes and renal tubular cells also express the GLUT-2 transporter and are sensitive to STZ. This leads to normal kidney and liver damage in STZ-induced diabetes models. STZ is diabetogenic because it selectively destroys insulin-producing beta cells by inhibiting insulin production and inducing necrosis. Endocrine non-β-cells in pancreatic islets, such as α-cells and δ-cells, and extra pancreatic parenchyma remained intact after STZ challenge, indicating the selective properties of STZ over β-cells. STZ also causes cardiac and adipose tissue

damage, enhances oxidative stress, inflammation, and endothelial dysfunction, and concentrations of the drug or its metabolites are more consistent in liver, kidney, intestine, and pancreas than in plasma higher. When STZ enters cells, it inhibits glucose metabolism and insulin secretion from beta cells and affects the pancreas.

Conclusion

Streptozotocin is a naturally occurring diabetes inducing agent which is a pale yellow to off-white crystalline powder. It was first isolated from *Streptomycesacromogenes* .The molecular weight of streptozocin is 265 g/mol, chemical formula is C8H15N3O7. The molecular structure of STZ is familiar to 2-deoxy-D-glucose substituted at C2 with an N-methyl-N-nitrosourea group. This is the cytotoxic portion of STZ in beta-cell damage.

Streptozotocin prevents DNA synthesis and causes DNA degeneration and destruction, leading to insulin-dependent Diabetes, With the help of glucose transporter.

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