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Review Article

Streptozotocin (Streptozocin: STZ) as a diabetic agent: A narrative review and update

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Abstract:

Streptozotocin is a glucosamine nitrosourea chemical with a glucose molecule and methyl group connected at one end. Its chemical name is 2-deoxy-2(methyl nitrosamine) carbonyl) amino)-D-glucose, and it was produced by the bacterial strain Streptomyces achromogenes in a fermentation broth (gram-positive bacterium). Typically, it is a poisonous glucose analogue that causes experimental diabetes.STZ is an ideal agent to induce experimental type 2 diabetes, it has more advantages than alloxan over sustained hyperglycemia and the development of well characterized diabetic complications with a low incidence of ketosis and mortality. Streptozotocin's beta cell toxicity is mostly caused by the pancreas's loss of NAD. Nicotinamide inhibits poly (ADP-ribose) synthetase activity and prevents NAD depletion in pancreatic beta-cells, which reduces the cytotoxicity caused by streptozotocin.

Keywords: STZ, Streptomyces Achromogenes, Nicotinamide, Gram Positive Bacterium.

Introduction

Streptozotocin is a permanent diabees mellitus inducing agent. Streptozotocin is a glucosamine nitrosourea chemical with a glucose molecule and methyl group connected at one end [1]. Its chemical name is 2-deoxy-2(methyl nitrosamine) carbonyl) amino)-D-glucose, and it was produced by the bacterial strain Streptomyces achromogenes in a fermentation broth (gram-positive bacterium). Typically, it is a poisonous glucose analogue that causes experimental diabetes.

The STZ-induced diabetes was originally demonstrated in an animal model by Rakieten *et al* [7]. It is commonly administered as a single intravenous dose between 40 and 60 mg/kg of body weight based on the prior experimental model. Through glucose transporter 2, streptozotocin penetrates the beta cells of the pancreas (GLUT-2). DNA alkylation caused by the methyl nitrosourea moiety is the mechanism by which streptozotocin acts on the beta-cell. DNA is damaged as a result of the streptozotocin's methyl group transfer, which results in DNA fragmentation. [1,2] When DNA is damaged, poly ribosylation is activated, which lowers NAD and ATP levels and eventually may cause beta-cell death.

Malignant insulinomas are treated with it. STZ is transported into the cell by the low affinity

glucose transporter GLUT-2 of Beta-cells, which results in DNA alkylation and the permanent necrosis of cells. The biological effects of streptozotocin, such as its antibacterial, beta-cell (beta)-cytotoxic, oncolytic, and oncogenic actions, reveal that it has four important biological qualities. Using a chromatographic approach, streptozotocin (2-deoxy-2-[3-methyl-3-nitrosourea] 1-D-glucopyranose) can be distinguished into two anomeric forms, and (HPLC). [1,3]

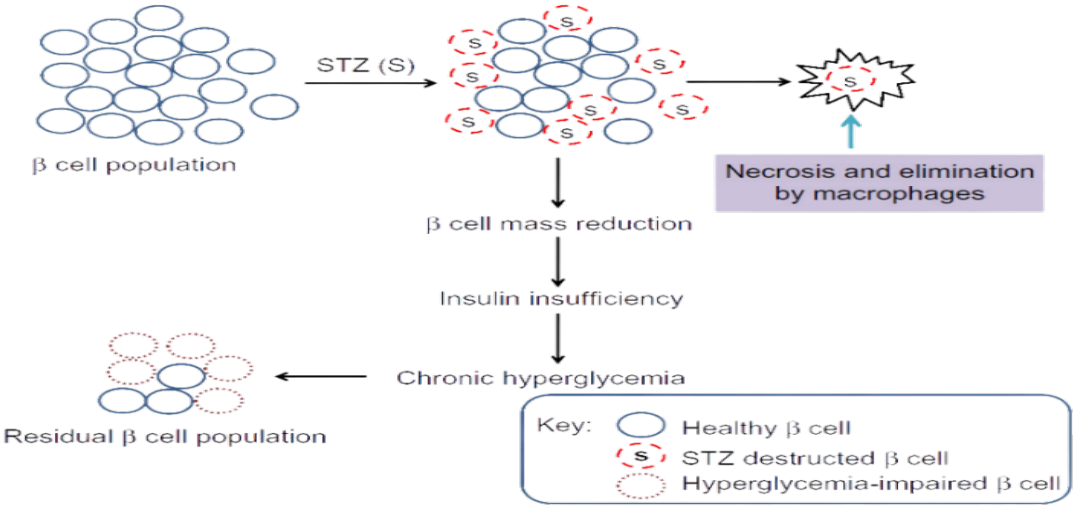

Figure 1: Mechanism of action of STZ
(Source: https://doi.org/10.2147/DMSO.S82272.)

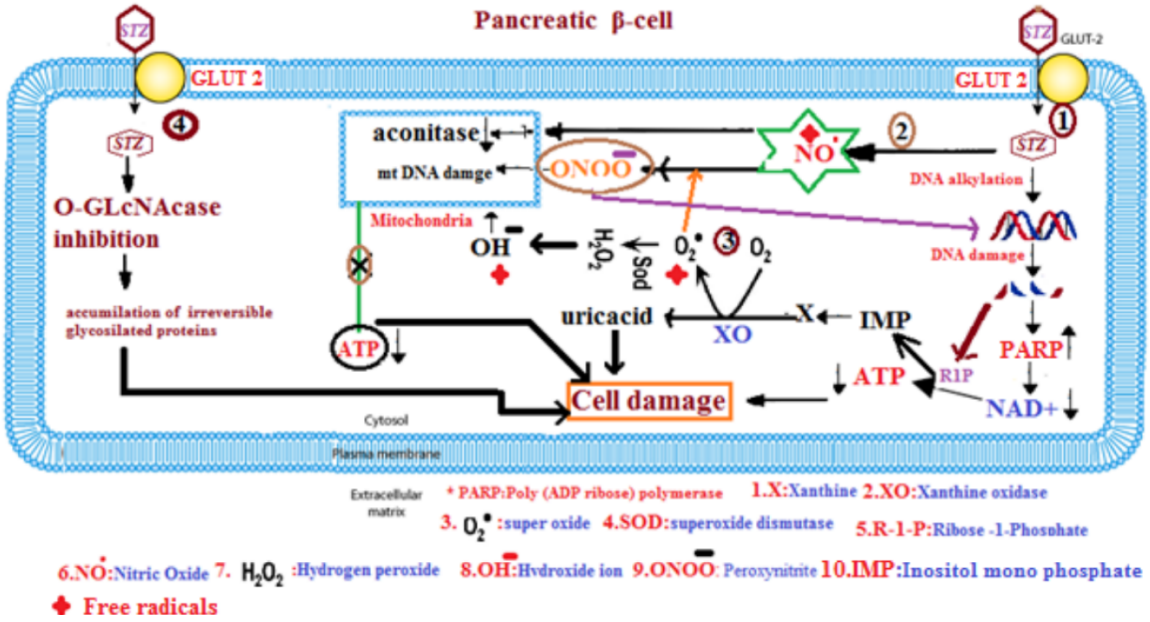

Figure 2: Induction of diabetes by STZ
(**Source:** Busineni Jayasimha Goud *et al*. Ijppr. Human, 2015; Vol. 3 (1): 253-269)

In terms of solubility, STZ is largely soluble in polar organic solvents, but only to a limited level in water, ketones, and lower alcohols. This disintegrates in water at a rate of 50 mg/mL and produces a light-yellow, clear to slightly cloudy solution. Rapid mutarotation to an equilibrium blend of alpha- and beta-anomers occurs in aqueous STZ solutions. At pH 4, STZ solution is most stable, with stability rapidly dropping at higher or lower pH. Solutions that have just been made are transparent and have a faint straw tint. According to many research associations, the streptozotocin solution (in citrate or acetate buffer, pH 4.5) should be supplied "immediately" and no later than 15 to 20 minutes after dissolution.[4,5]

Efficacy over Alloxan

The majority of animal research uses chemicals or medications to artificially induce diabetes. Alloxan is a well-known chemical substance that has been utilized in research on diabetes; it is poisonous and causes the pancreatic beta cells to die. In earlier studies, the drug alloxan was used to cause type 1 diabetes in rats, mice, and rabbits. Due to its toxicity and instability, Types 1 and 2 diabetes are now induced using streptozotocin rather than alloxan. STZ is an ideal agent to induce experimental type 2 diabetes, it has more advantages than alloxan over sustained hyperglycemia and the development of well characterized diabetic complications with a low incidence of ketosis and mortality.[2,6]

1. The range of the STZ dose is not as narrow as in the case of alloxan.
2. In compared to alloxan, STZ's higher chemical stability and lower toxicity allow for better manipulation and more flexible dosing.
3. In addition, STZ administration is preferred to alloxan treatment due to a larger proportion of successfully inducing diabetes and lower mortality rates in experimental animals.

Route of administration

The two most usual ways to administer STZ are intraperitoneally (IP) or intravenously (IV), though rodents have also received the medication via subcutaneous, intracardiac, and intramuscular routes.

Dose of STZ

A single 100 mg/kg intraperitoneal dose causes severe islet destruction and results in insulin-dependent diabetes. The dosing range for inducing experimental type 2 diabetes is 35–65 mg IP.[7,9]

Diabetogenic action of STZ

1) Alkylation of DNA by STZ causing DNA damage, PARP activation, leading to depletion of NAD+ and ATP stores that causes pancreatic beta cell death

2) Spontaneous release of NO by STZ, impairment of mitochondria by NO, inhibition of APT synthesis ultimately leading to beta cell death.

3) Generation of free radicals like superoxide (O2◦-), hydroxide (OH◦-), peroxynitrite (ONOO), causing beta cell damage.

4) Inhibition of O-GlcNAcase by STZ, formation of irreversible glycosylated proteins that damage pancreatic beta cell. [10,12,13]

Disadvantages of Streptozotocin Model[11-15]

1. STZ is a pancreatic cell chemical toxin that induces prompt and irreversible necrosis of pancreatic cells.
2. STZ-induced diabetic rats demonstrated severe hyperglycemia (FBG≥250) associated with a depletion of pancreatic insulin content/action. After a month they need insulin for survival.
3. Residual beta cell tries to overcome the insulin depletion by development of functional insulinoma.
4. STZ is a DNA alkylating substance and my lead to liver and kidney tumors in rats.

When used as an antineoplastic treatment for various cancers, STZ has been shown to be cytotoxic to pancreatic beta-cells even at

therapeutic dosages (up to 15 mM), and at these concentrations, STZ causes apoptosis in pancreatic beta-cells. Recent research has demonstrated that STZ is toxic to the neuroendocrine cells of the gut as well as other organs that express GLUT 2, including the brain, liver, and kidneys. The selective uptake of STZ, its metabolic activation, and detoxification in particular cell types, as well as on the redox homeostasis and mitochondrial bioenergetics in these cells, may be associated with the differential cytotoxicity by STZ in different cellular systems because STZ competes with glucose uptake and is thought to be dependent upon the specific expression of selective GLUT transporters.

Experimental model of T2DM[11-18]

For the purpose of improving our understanding of the numerous facets of its pathophysiology and ultimately discovering new treatments and a cure, experimental production of diabetes mellitus in animal models is crucial. Various techniques have been employed with varying degrees of effectiveness to cause diabetes mellitus in lab animals. The pancreas can be surgically removed, but at least 90–95 percent of the pancreas must be removed in order to cause diabetes. A less reliable method of inducing diabetes has been anterior hypophysis extract injection.

For reversible diabetes induction, an alloxan-induced diabetic animal is used. On the other hand, this model has a high mortality rate. Another method which is more uniformly effective and widely used is the injection of Streptozotocin nicotinamide model.

Characteristics of the experimental model (Streptozotocin-nicotinamide)[19-21]

Streptozotocin's beta cell toxicity is mostly caused by the pancreas's loss of NAD. Nicotinamide inhibits poly (ADP-ribose) synthetase activity and prevents NAD depletion in pancreatic beta-cells, which reduces the cytotoxicity caused by streptozotocin. In India, Shirwaikar A *et al*. (2000), Nayak Y (2014), and many others used a single intraperitoneal injection of 60 mg/kg STZ 15 minutes following a 120 mg/kg nicotinamide injection to induce type 2 NIDDM. This dosage effectively produced the moderate fasting hyperglycemia with a blood glucose range of 180–250mg. In order to obtain moderate and sustained hyperglycemia with 40% conservation of pancreatic insulin stores, Pellegrino Masiello and his team administered several dosages of nicotinamide (100-350 mg/kg body wt.) intra-peritoneally 15 min before STZ delivery (65 mg/kg i.v.). This unique NIDDM syndrome, which is identical to human NIDDM in terms of diminished pancreatic insulin storage.

It has been suggested that the administration of nicotinamide (NA) plus streptozotocin (STZ) will cause experimental diabetes in rats. Rats are given NA to partially protect insulin-secreting cells from STZ, but STZ is known to harm pancreatic B-cells. The glucose transporter GLUT2 allows STZ to enter B-cells where it damages DNA and increases the activity of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP-1). However, excessive activity of this enzyme causes the cells that secrete insulin to necrotize and deplete intracellular NAD (+) and ATP. NA's protective effects result from its suppression of PARP-1 activity. Inhibiting this enzyme stops cells exposed to STZ from losing NAD (+) and ATP. Additionally, because NA is a precursor to NAD (+), it raises intracellular NAD (+) levels. The STZ and NA doses that are administered to the experimental rats have a significant impact on how severe their diabetes is.

As a result, as compared to control animals, diabetic rats' blood glucose levels might vary greatly, from mild hyperglycemia to severe hyperglycemia. The level of blood insulin may also only slightly decrease or significantly increase. The insulin-secretory response to glucose is slowed down in STZ-NA-induced diabetic rats compared to control animals,

according to in vitro investigations. This results from decreased beta-cell bulk as well as metabolic issues in the cells that secrete insulin. Numerous test's findings have shown that this diabetes model is helpful in investigations of several elements.

Animal models in type 2 diabetes

Classification of Type 2 diabetes in Animals:

Table 1

Model category	Obese	Non obese
Spontaneous or genetically derived diabetic animals	-ob/ob mouse - db/db mouse - KK mouse -KK/A^{y} mouse - NZO mouse - NONcNZO10 mouse - TSOD mouse -M16 mouse -Zucker fatty rat - ZDF rat -SHR/N-cp rat -JCR/LA-cp rat -OLETF rat -Obese rhesus monkey	- Cohen diabetic rat -GK rat - Torri rat Non obese C57BL/6 - (Akita) mutant mouse - ALS/Lt mouse
Diet/nutrition induced diabetic animals	Sand rat C57/BL 6J mouse Spiny mouse	
Chemically induced experimental animals	GTG treated obese mice	-Low dose ALX or STZ adult rat, mice etc. -Neonatal STZ rat
Surgical diabetic animals	VMH lesioned dietary obese diabetic rat	Partial pancreatectomized animals *e.g.,* dog, primate, pig & rats
Transgenic/knock-out diabetic animals	-B_3 receptor knockout mouse -Uncoupling protein (UCP1) knock-out mouse	Transgenic or knock out mice involving genes of insulin and insulin receptor and its components of downstream insulin signaling *e.g.* IRS-1, IRS-2,GLUT-4, PTP-1B and others PPAR-γ tissue specific knockout mouse Glucokinase or GLUT 2 gene knockout mice Human islet amyloid polypeptide overexpressed rat (HIP rat)

(KK, Kuo Kondo; KK/Ay, yellow KK obese; VMH, ventromedial hypothalamus; ZDF, Zucker diabetic fatty; NZO, New Zealandobese; TSOD, Tsumara Suzuki obese diabetes; SHR/N-cp, spontaneously hypertensive rat/NIH-corpulent; JCR, James C Russel;OLETF, Otuska Long Evans Tokushima fatty; GTG, gold thioglucose; ALX, alloxan; STZ, streptozotocin; GLUT-, glucose transporter;IRS, insulin receptor substrate; GK, Goto-Kakizaki; PPAR, Peroxisome proliferator activated receptor, PTP, phosphotyrosinephosphotase; ALS, alloxan sensitive)

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