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Modeling Diabetes Mellitus Using Streptozotocin: Review Approach For Future Diabetic Research

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Abstract
Globally, diabetes mellitus (DM), a chronic metabolic disease marked by persistent hyperglycemia, causes a considerable amount of morbidity and mortality. To test treatment approaches and clarify illness causes, animal models are crucial.With its specific cytotoxicity targeting pancreatic β-cells through GLUT2-mediated uptake, streptozotocin (STZ), a glucosamine-nitrosourea combination, is frequently used to induce experimental diabetes in mice. STZ triggers DNA alkylation, oxidative stress, and β-cell death, leading to insulin insufficiency and hyperglycemia.Different diabetic phenotypes can be modeled by STZ, depending on the dosage and administration method. For example, a single high dose can quickly cause type 1 diabetes (T1D), while several low doses can mimic the slow death of β-cells that occurs in autoimmune processes. Additionally, STZ in conjunction with high-fat diet feeding allows for the modeling of late-stage type 2 diabetes (T2D), which includes both β-cell loss and insulin resistance.The lack of progressive autoimmune characteristics, inter-strain variability, and off-target organ damage are some of the drawbacks of STZ-induced models, despite their excellent cost-effectiveness and reproducibility. Targeted medication delivery and genetic manipulation are two recent improvements that try to increase model accuracy. Enhancing STZ protocols improves their translational value, which speeds up the creation of novel treatment interventions and promotes a deeper comprehension of diabetes pathogenesis.This study reviews the methodology, mechanisms, applications, limitations, and future perspectives of STZ-induced diabetes models in mice, offering guidance for standardized protocol optimization.

Keywords: *Streptozotocine (STZ), diabetes mellitus, mice model, Type 2 diabetes, hyperglycemia, Pancreatic β-cells.*

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I. Introduction

Chronic hyperglycemia is a defining feature of diabetes mellitus (DM), a metabolic disorder caused by deficits in either insulin action or secretion, or both. Diabetes affects over 537 million people globally, and its prevalence continues to rise, putting substantial strain on economies and healthcare systems. [1]. Its increasing prevalence throughout the world makes it imperative to comprehend the underlying mechanisms and create novel treatments. To better understand the underlying causes of diabetes and develop effective treatment strategies, we need trustworthy animal models that accurately mimic the features of human illness. Deciphering the intricacies of diabetes has been made possible by animal models, especially mouse models. [2]**.** Chemical agents are one of the various ways to induce diabetes in animal models, and they have proven to be highly effective and reproducible. Animal models of diabetes are induced using STZ, alloxan, vactor, dithizone, 8-hydroxyquinolone, and gold thioglucose [3]. Because of its simplicity, reproducibility, and high specificity for pancreatic β-cells, streptozotocin (STZ) is considered the gold standard among the several agents available for experimentally causing diabetes [4]. It has a high affinity for pancreatic β-cells because it shares the same structure as glucose and is absorbed by the GLUT2 transporter [4]. Once internalized, STZ causes β-cell necrosis or apoptosis, which causes DNA alkylation, reactive oxygen species (ROS), and nitric oxide production, ultimately leading to insulin insufficiency and hyperglycemia [5]. STZ is an effective method for creating diabetic animal models, especially in mice, due to its selective β-cell cytotoxicity. To use STZ to induce various types of diabetes, a number of dosing methods have been devised. A single high-dose injection of STZ (≥150 mg/kg) simulates the acute onset of type 1 diabetes (T1D) and quickly kills β-cells [6]. However, the slow autoimmune death of β-cells seen in human T1D is more accurately simulated by several low-dose STZ regimens (e.g., 40–60 mg/kg over 5 days in a row) [7]. Furthermore, a high-fat diet (HFD) combined with STZ treatment causes insulin resistance and β-cell dysfunction, simulating some features of type 2 diabetes (T2D) [8]**.**

Although STZ-induced models of diabetes are very useful for studying the disease, they have drawbacks. Careful experimental design and interpretation are required due to the non-physiological nature of β-cell death, potential off-target toxicities (especially hepatotoxicity and nephrotoxicity), and variation in mouse strain sensitivity [4, 9]**.** To address these issues and enhance the translational applicability of STZ-induced diabetes models, innovations including genetic mouse models and nanoparticle-mediated STZ delivery have been developed [10, 11]**.**

This review paper covers in detail the mechanisms of STZ action, mouse diabetes induction methods, diabetes research applications, model limitations, and future objectives. By impartially assessing the benefits and drawbacks of STZ-induced diabetes models, we intend to help researchers select and improve models that are appropriate for their specific research goals.

II. Streptozotocin: An Overview And Mechanism Of Action

Streptozotocin (STZ) is a naturally occurring nitrosourea derivative that was first isolated from the bacterium Streptomyces achromogenes in 1959 by Vavra and colleagues [12, 13]. Initially identified for its antimicrobial properties, STZ soon gained prominence for its selective cytotoxic effects on pancreatic β-cells, making it a pivotal tool in diabetes research [13, 14] Chemically, STZ is composed of a glucose moiety linked to a highly reactive nitrosourea group, allowing it to exploit the glucose transport pathways for cellular entry [4, 15]**.** The selective uptake of STZ by pancreatic β-cells is mediated through the GLUT2 (glucose transporter 2) protein, which is highly expressed in rodent β-cells [4, 5, 16]**.** This specificity explains the preferential β-cell targeting observed during STZ administration. Upon cellular entry, STZ exerts its toxic effects through multiple mechanisms. One primary mechanism is DNA alkylation, whereby STZ transfers its methyl group to DNA bases, causing extensive DNA damage and triggering β-cell death via necrosis or apoptosis [5, 17, 18] Concurrently, STZ induces the generation of reactive oxygen species (ROS), exacerbating oxidative stress within the β-cells and contributing to mitochondrial dysfunction [16, 19]**.** Another critical mechanism involves the release of nitric oxide (NO), a reactive nitrogen species that enhances DNA strand breaks and inhibits DNA repair enzymes such as poly (ADP-**ribose**) polymerase (PARP), further promoting β-cell apoptosis [5] **.** The cumulative effects of DNA damage, oxidative stress, and nitrosative stress ultimately result in rapid and irreversible β-cell destruction, leading to insulin deficiency and persistent hyperglycemia — hallmarks of diabetes mellitus [7]. The β-cell specificity of STZ is species-dependent, largely due to variations in GLUT2 expression levels. For example, rodents exhibit high GLUT2 expression in β-cells, making them highly susceptible to STZ, whereas in humans, β-cell GLUT2 expression is much lower, limiting the direct translational application of STZ-induced diabetes models [4, 5]. The efficacy of STZ is also influenced by its pharmacokinetics. Because of its short plasma half-life (less than 15 minutes in rodents) and quick clearance from the circulation, it requires careful dose timing to ensure effective β-cell targeting [6]**.** Because it has a substantial impact on the severity and repeatability of diabetes induction, the dosage and mode of administration of STZ (intraperitoneal versus intravenous) need to be carefully standardized in experimental methods [9]. The injection of STZ is linked to off-target toxicities, such as nephrotoxicity, hepatotoxicity, and neurotoxicity, despite its excellent efficacy in simulating diabetes. This is indicative of its nonspecific DNA-damaging characteristics [9]**.** While highly effective in modeling diabetes, STZ administration is associated with off-target toxicities, including nephrotoxicity, hepatotoxicity, and neurotoxicity, reflecting its nonspecific DNA-damaging properties when administered at high doses [4, 6, 7, 20, 21]. To improve its selectivity and reduce systemic adverse effects, attempts are being made to improve STZ distribution by the use of nanoparticles, slow-release formulations, or β-cell-specific targeting agents.

Therefore, comprehending the complex mechanism of action of STZ is crucial for both optimizing experimental diabetes models and evaluating the pathological results and limitations of this commonly employed technique.

Methods of STZ Administration

Different routes of administration of streptozotocin (STZ) in mice affect the degree of β-cell death, consistency, and efficiency. Subcutaneous delivery, intravenous injection, and intraperitoneal injection are common techniques. Because oral delivery has a low bioavailability, it is rarely used. The decision is based on the intended diabetic phenotype, strain sensitivity, and research objectives. For reliable outcomes, timing, dosage precision, and adherence to preparation guidelines are essential.

Preparation of Streptozotocin Solution

STZ is unstable in aqueous solutions, hence must be prepared fresh before administration [4].

STZ powder should be stored at –20°C to prevent degradation.

STZ is typically dissolved in cold citrate buffer (0.1 M, pH 4.5) [5].

STZ solution is prepared at a concentration appropriate to deliver the desired dose in a volume of 10 mL/kg body weight [2].

Solutions should be kept on ice and used within 15–30 minutes after preparation.

Dosing Regimens.

1. Single High-Dose Protocol: A single intraperitoneal (IP) injection of STZ at 150–200 mg/kg body weight induces rapid and irreversible diabetes This method produces extensive β-cell destruction within 48–72 hours [6]**.**
2. Multiple Low-Dose Protocol: Mice receive daily IP injections of STZ at 40–60 mg/kg for five consecutive days to gradually induce diabetes This protocol better simulates autoimmune-mediated β-cell destruction, resembling human type 1 diabetes [7]**.**
3. Neonatal STZ Model: STZ administration at a dose of 80–100 mg/kg in 2-day-old neonatal mice leads to partial β-cell destruction and results in type 2 diabetes-like phenotypes in adulthood [2].
4. High-Fat Diet + Low-Dose STZ Model: Combining a high-fat diet (HFD) with a single low-dose STZ (30–60 mg/kg) creates a model of type 2 diabetes featuring both insulin resistance and β-cell dysfunction [22]. Table 1 & 2 clearly describe comparasion of different methods of STZ administration

Table No 1. Comparative description of different methods of STZ administration

Protocol / Method	Dose & Procedure	Type of Diabetes Induced	Key Features	Reference
Single High-Dose STZ	150–200 mg/kg, single IP injection	Type 1 Diabetes (T1DM)	Rapid, massive β-cell destruction; insulin deficiency; minimal immune involvement	[4, 6, 7]
Multiple Low-Dose STZ	40–60 mg/kg for 5 consecutive days (IP)	Autoimmune Type 1 Diabetes	Gradual β-cell destruction; T-cell mediated insulitis; autoimmune-like diabetes	[7]
High-Fat Diet (HFD) + Low-Dose STZ	HFD for 4–6 weeks + 30–60 mg/kg STZ (IP)	Type 2 Diabetes (T2DM)	Insulin resistance + partial β-cell dysfunction; mimics human T2DM	[22] [23]
Neonatal STZ Model	80–100 mg/kg STZ at 2 days old	Type 2 Diabetes-like (T2DM-like)	Mild β-cell damage in early life; progressive insulin resistance with aging	[2]

III. Critical Factors Influencing Stretozotocin Induced Diabetes

Streptozotocin (STZ) is frequently used to cause diabetes in mice, however the results of administering STZ can differ greatly depending on a number of important variables. For research on diabetes in humans to be accurate, reproducible, and relevant, these factors must be understood and controlled.

Dose and Mode of STZ administration

One of the main factors influencing the degree of diabetes induction is the STZ dosage. The rapid, near-total death of β-cells usually occurs with a single high dose (≥150 mg/kg), causing severe hyperglycemia that mimics type 1 diabetes (T1DM) [4, 6, 24]. According to Like and Rossini (1976), on the other hand, several low dosages (e.g., 40–60 mg/kg for 5 days in a row) simulate the autoimmune course of type 1 diabetes by causing minor insulitis and gradual β-cell impairment. Additionally, the route of administration (intraperitoneal versus intravenous) affects reproducibility, systemic toxicity, and absorption rate [5, 25, 26].

Mouse Strain and Genetic Background

Different mouse strains are susceptible to STZ in different ways. To induce diabetes, for example, C57BL/6 mice are often resistant and require higher dosages than DBA/2 and ICR mice, which are very sensitive [2]. Genetic determinants that impact GLUT2 expression, antioxidant capacity, and β-cell mass are responsible for these strain-dependent differences [27].

Table No. 2 Comparison of different routes for STZ administration

Method	Procedure	Advantages	Considerations	References
Intraperitoneal (IP) Injection	- Inject STZ into the lower right or left abdominal quadrant using a 26–30 gauge needle. - Deliver at 10 mL/kg volume per mouse (Furman, 2021).	Quick, technically easy.	Risk of bowel puncture; requires proper restraint.	[5, 6]
Intravenous (IV) Injection	- Inject into the lateral tail vein using a 27–30 gauge needle. - Warming mice under a lamp helps dilate veins (Lenzen, 2008).	Precise dosing, rapid systemic absorption.	Technically demanding; stress-prone.	[4]
Subcutaneous (SC) Injection	- Inject under the skin between the shoulders.	Less invasive, slower absorption.	Less used for diabetes induction; delayed effect.	[5]
Oral (Gavage)	- Administer via oral gavage.	Non-invasive gastrointestinal route.	Poor bioavailability; rarely used.	[6]

Sex and Hormonal Status

The susceptibility to STZ is strongly influenced by sex differences. According to Ganda et al. (1976) and Like & Rossini (1976), estrogens protect mice from oxidative stress and β-cell apoptosis, which is why male mice typically acquire more severe diabetes than female mice. For consistent diabetes modeling, most researchers prefer to use male mice, unless they are looking at sex-specific effects.

Age and Weight of Mice

The age of the mice should be taken into account when administering STZ. Younger mice (6–8 weeks old) exhibit more consistent responses and β-cell vulnerability than older mice, whose comorbidities or regenerative capacities may complicate results [6]. Underweight and overweight mice may react differently to STZ in terms of stress and have altered pharmacokinetics, which may affect how severe their diabetes is.

STZ Stability and Preparation

Since STZ is highly unstable in aqueous solutions, it should be freshly dissolved in cold citrate buffer (pH 4.5) just before use to maintain its diabetogenic potential [5]. Degradation can occur even with short durations between preparation and administration, increasing variability among tests and decreasing efficacy.

Environmental and Experimental Conditions

External factors such as housing conditions, nutritional composition, stress management, and infection status may influence the onset and progression of diabetes after STZ treatment [27]**.** For instance, after taking STZ, animals given a high-fat diet who previously had insulin resistance show worsening hyperglycemia.

Batch-to-Batch Variability of STZ

Results may vary depending on the activity and purity of STZ from one commercial source to another, and even from batch to batch [4]**.** Each time a new batch of STZ is produced, researchers conduct pilot dosing trials to adjust their models appropriately.

Health and Immune Status of Mice

Animals' β-cell sensitivity to STZ can be influenced by their immunological status. Variable responses can be seen in mice with reduced immunity or inflammatory illnesses, particularly in autoimmune-based protocols like the multiple low-dose STZ paradigm [7]**.**

IV. Streptozotocin: Differential Induction Of Diabetes Mellitus

Streptozotocin is a naturally occurring antibiotic and diabetogenic substance that causes hyperglycemia by attacking pancreatic β-cells. In order to better understand disease causes and assess treatment options, it is used in experimental research to imitate various forms of diabetes in mice and rats. Table 3 provides information on the delivery of streptozotocin (STZ) and the prevalence of different types of diabetes. Preclinical research on disease processes and drug testing can benefit greatly from the various diabetic models that are produced by different STZ delivery techniques.

Table No. 3. STZ induced different types of Diabetes

STZ Protocol	Dose/Administration	Diabetes Type Modeled	Features	References
Single High Dose	150–200 mg/kg, intraperitoneal (i.p.)	Type 1 Diabetes (T1DM)	Rapid, massive β-cell destruction; severe hyperglycemia	[7, 24, 28]
Multiple Low Doses	40–60 mg/kg/day for 5 consecutive days, i.p.	Type 1 Diabetes (Autoimmune-like)	Gradual β-cell loss, simulating autoimmune β-cell destruction	[29, 30]
Low-Dose STZ + High-Fat Diet (HFD)	HFD for 4 weeks + STZ (30–40 mg/kg, i.p.)	Type 2 Diabetes (T2DM)	Insulin resistance + partial β-cell dysfunction	[23, 27, 31, 32]
Very Low Dose STZ	20–30 mg/kg, single or multiple injections	Mild Hyperglycemia / Prediabetes	Partial β-cell impairment; for studying complications	[2]
STZ during Pregnancy	Low-dose STZ before or early pregnancy	Gestational Diabetes Model	Hyperglycemia during gestation; fetal effects studied	[33]
Delayed Onset (Adult Autoimmune Diabetes)	Low-dose STZ + immune adjuvants	Latent Autoimmune Diabetes of Adults (LADA) Model	Slow progression to insulin dependency	[34, 35]

V. Advantages Of Streptozotocin Induced Models

STZ provides a rapid and accurate method for studying diabetes by targeting and killing insulin-producing β-cells via GLUT2 glucose transporters. Because it constantly results in hyperglycemia, it is ideal for studying diabetes. Shorter experimental regimens are made possible by the rapid and reliable induction of diabetes by one or more low-dose injections. STZ can simulate several kinds of diabetes, including gestational diabetes, Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), and moderate hyperglycemia for complications research. It requires only the most basic animal facilities and minimal specialized equipment, making it both technically simple and cost-effective. Study results are more similar due to the widespread acceptance and established nature of STZ procedures. Because STZ-induced chronic hyperglycemia mimics chronic diabetes in people, it is useful for studying nephropathy, retinalopathy, neuropathy, and cardiomyopathy.

VI. Streptozotocin Compare To Other Diabetes-Inducing Agents

Understanding the pathophysiology of the illness and assessing treatment options depend heavily on the research of diabetes in mice. Because of its simplicity, repeatability, and specificity, streptozotocin (STZ) is the most commonly utilized agent. By entering pancreatic β-cells through GLUT2 transporters, STZ causes DNA alkylation, oxidative stress, and cell death, which in turn causes diabetes. Alternative methods for simulating type 1 and type 2 diabetes include genetic modifications, high-fat diet models in conjunction with low-dose STZ, and other agents like alloxan. Like STZ, alloxan produces reactive oxygen species, which results in less reliable results and increased toxicity off-target. Low-dose STZ in conjunction with high-fat diets produces models that are more representative of type 2 diabetes's insulin resistance and β-cell malfunction. Mouse models that have undergone genetic engineering are expensive and time-consuming. Comparing Streptozotocin (STZ) with Other Agents that Cause Diabetes in Mice is explained in Table 4.

Table No. 4. Streptozotocin (STZ) vs Other Diabetes-Inducing Agents in Mice

Agent/Method	Mechanism	Diabetes Type	Advantages	Disadvantages	Reference
STZ	DNA alkylation, ROS, β-cell destruction	Type 1 (autoimmune or toxin-induced); Type 2 (with HFD)	Rapid, controllable, widely used	Toxicity, variability, requires fresh preparation	[4, 6, 36]
Alloxan	ROS-mediated β-cell death	Type 1 (toxin-induced)	Fast induction	Unstable, reversible diabetes, narrow dosing window	[4, 36, 37]
High-Fat Diet (HFD)	Induces insulin resistance	Mild Type 2 (prediabetes)	Non-invasive, models metabolic syndrome	Incomplete β-cell dysfunction alone	[38, 39]
NOD mice	Autoimmune attack on β-cells	Autoimmune Type 1	Mimics human T1DM	Expensive, slow onset	[40-42]
ob/ob and db/db mice	Genetic mutation of leptin/leptin receptor	Obese Type 2	Models human obesity-linked diabetes	Expensive, mutation-specific phenotype	[43, 44]

VII. Streptozotocin Induced Pathologies: Beyond Hyperglycemia

Despite being primarily employed to induce diabetes, streptozotocin (STZ) has been widely used to model secondary consequences, including diabetic cardiomyopathy, diabetic neuropathy and diabetic nephropathy [45-47]. Additionally, insulin resistance is induced in the brain by low-dose STZ given intracerebroventricularly, providing a good model for sporadic Alzheimer's disease [48, 49]**.** At high dosages, STZ can potentially mimic hepatic fibrosis and pancreatitis, according to recent studies [4, 50]. The ability of STZ treatment to imitate different diseases was summarized in Table 5.

VIII. Streptozotocin In Diabetes Research: Pitfalls, Constraints, And Experimental Variability

Although streptozotocin is frequently used to cause experimental diabetes in mice, it has some significant drawbacks. Nephrotoxicity, hepatotoxicity, and general systemic stress are among the off-target consequences that frequently accompany its dose-dependent β-cell toxicity [5]. Different mouse strains, ages, sexes, and delivery methods have different reactions to STZ, which can result in uneven hyperglycemia induction [28, 41]**.** Furthermore, STZ does not fully replicate the autoimmune pathology of human Type 1 diabetes nor the multifactorial nature of Type 2 diabetes. [2, 27]. Furthermore, high-dose regimens can cause systemic stress and increased mortality **[7]**. These drawbacks emphasize the necessity of rigorous standardization and careful interpretation when employing STZ in diabetes research. When employing STZ in diabetes research, these difficulties call for cautious model construction and interpretation.

Table No. 5. Potential of Streptozotocin (STZ) administration in mimicking various diseases

Disease Model	How STZ Induces It	Notes	References
Diabetic Nephropathy	Chronic hyperglycemia caused by STZ damages renal glomeruli, mimicking human diabetic kidney disease.	Used widely to study renal fibrosis and proteinuria.	[47]
Diabetic Neuropathy	STZ-induced diabetes leads to oxidative stress and microvascular damage in nerves.	Models peripheral nerve dysfunction, loss of pain sensation.	[45]
Diabetic Cardiomyopathy	Chronic STZ diabetes causes cardiac fibrosis, hypertrophy, and dysfunction.	Useful for testing cardioprotective agents.	[46]
Cognitive Dysfunction ("Diabetic Alzheimer's")	Intracerebroventricular (ICV) injection of low-dose STZ induces insulin resistance in the brain.	Used to model sporadic Alzheimer's disease (type 3 diabetes concept).	[48, 49]
Hepatic Fibrosis	Long-term hyperglycemia from STZ can also trigger non-alcoholic fatty liver disease and hepatic fibrosis.	Emerging use in metabolic disease research.	[50, 51]
Pancreatitis (At High Dose)	Overdose of STZ can cause direct acinar cell toxicity leading to inflammation and pancreatitis-like symptoms.	Rare and usually an accidental model.	[4]

The provided table 6. summarizes quickly to show STZ limitiation as diabetic inducer as well as flaws. Thus , Streptozotocin (STZ) can cause non-specific toxicity, inconsistency between mouse strains, high dose toxicity, short-term diabetes induction, and insulin resistance in type 2 diabetes models. High doses can cause severe systemic toxicity and side effects.

Table No.6. limitations of STZ as Diabetic Inducer

Loophole / Disadvantage	Explanation	Reference
Non-specific Toxicity	STZ not only damages pancreatic β-cells but also has toxicity toward liver, kidney, and other organs at high doses.	[4, 28]
High Mortality at High Dose	A single high dose can cause severe systemic toxicity leading to early death in mice.	[6]
Variability Between Strains	Different mouse strains (e.g., C57BL/6 vs BALB/c) show different sensitivity to STZ; results are not universally reproducible.	[4, 6]
Sex Differences	Male mice are more sensitive to STZ; females are relatively resistant, complicating gender-based studies.	[24][[53]
Immune System Involvement is Limited	Single-dose STZ-induced diabetes lacks an autoimmune component, unlike true human type 1 diabetes.	[7, 24, 54]
β-Cell Recovery Possible	Low-dose STZ sometimes leads to partial β-cell regeneration over time, especially in young mice.	[6, 55]
Need for Fresh Preparation	STZ is unstable in aqueous solution and must be prepared fresh immediately before injection, complicating large experiments.	[4, 6]

Lessons Learned

Dosage Precision: One of the most important takeaways from STZ-based research is the importance of precise dosage and delivery methods. Standardized techniques are essential since strain-specific reactions or even minor adjustments to the STZ dose can significantly affect the outcomes [4].

Long-term effects must be taken into account: Although STZ-induced diabetes induces hyperglycemia fast, long-term study on sequelae (such as neuropathy and nephropathy) is critical for determining the disease's progression and treatment efficacy [45, 52].

Possibility of Improvement: While STZ is an essential tool for diabetes research, efforts must be made immediately to enhance repeatability, reduce animal suffering, and imitate the chronic, progressive nature of human diabetes

IX. Future Thoughts Of Streptozotocin-Based Diabetes Research

The future of research using streptozotocin (STZ) in mice will focus on refining its delivery to β-cells via targeted systems like nanoparticles to minimize systemic toxicity [5]**.** Combining STZ with genetically modified models (e.g., immune-deficient or knockout strains) could produce more accurate representations of human diabetes [6, 56] Chronic low-dose regimens, adjusted for sex and age differences, will improve modeling of slow disease progression [7, 57]**.** Furthermore, STZ-induced models will continue to serve as vital platforms for testing β-cell regenerative therapies and studying the molecular basis of diabetic complications [6, 28]. Table 7 explain future research using STZ as diabetes inducer.

Table No. 7. Prospects for Diabetes Research in Mice Using Streptozotocin

Future Research Area	Description
Precision Dosing and Delivery Systems	Development of nanoparticle- or hydrogel-based delivery to target STZ specifically to β-cells, reducing off-target toxicity.
Combination with Genetic Models	Combining STZ with genetically engineered mice (e.g., NOD, knockout mice) to better mimic human diabetes mechanisms.
Chronic Low-Dose Regimens	Exploration of chronic low-dose protocols to model slow β-cell decline similar to human prediabetes and T2DM.
Sex- and Age-Specific Protocols	Designing STZ protocols that account for sex- and age-based differences in susceptibility to improve translational relevance.
Use in Regenerative Medicine Studies	Using STZ-induced models to test β-cell regeneration therapies, stem cell therapies, and gene editing (e.g., CRISPR).
Modeling Diabetic Complications	Inducing diabetes with STZ to study long-term complications like nephropathy, neuropathy, and retinopathy in more standardized ways.
Alternative β-Cell Toxins and Comparisons	Research on other β-cell toxins (e.g., alloxan) and newer agents to compare safety and effectiveness with STZ.

Thus, we may assume that future STZ research would concentrate on targeted delivery methods, new medicines, and the integration of genetic and environmental models to develop full models of diabetes and its consequences. It can also be utilized to investigate associated conditions such as diabetic cardiomyopathy, cognitive impairment, and hepatic fibrosis.

X. Conclusion

The establishment of diabetes mellitus in mice with streptozotocin (STZ) remains a fundamental technique in experimental diabetology due to its affordability, reliability, and ease of use. Type 1 and type 2 diabetes can be modeled with STZ, depending on dosage, frequency, and correlation with dietary modifications [4, 6]. Researchers can reproduce the pathophysiology of human diabetes by selectively killing insulin-producing cells via GLUT2 transporters, which are highly specific to pancreatic β-cells [5]. However, there are certain disadvantages to the STZ approach. Its mode of β-cell destruction, which is mostly mediated through DNA alkylation and oxidative stress, is fundamentally distinct from the autoimmune-driven destruction observed in human type 1 diabetes [7, 9]. Furthermore, STZ-induced animals may exhibit off-target toxicities as hepatotoxicity and nephrotoxicity, especially at larger dosages [4]. Response varies by age, sex, mouse strain, and even STZ batch purity, which further complicates reproducibility across studies [2, 58, 59]. Considering these limitations, future research should focus on enhancing STZ-based models. Better delivery methods like nanoparticle-mediated STZ targeting and the development of hybrid models that combine STZ with genetic or immunological alterations could close the gaps that currently exist between experimental models and clinical disease [10, 11]. Additionally, by standardizing dosage protocols and more precisely characterizing long-term issues in mice treated with STZ, these models will have greater translational significance.

To sum up, even though STZ-induced diabetes in mice has led to many advancements in the field of diabetes research, more work is still needed to improve the precision, safety, and applicability of these models for usage in human disease scenarios. With cautious application and ongoing improvement, the STZ model can help identify new treatment targets and further our knowledge of the pathophysiology of diabetes. Despite being widely accepted worldwide, STZ, a medication used in preclinical research, has not been used in clinical trials and has not received official WHO approval.

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