

Streptozotocin Induced Diabetic Rat Model

Introduction

Type 1 diabetes is an autoimmune disorder that affects nearly 347 million people worldwide. The autoimmune disorder is characterized by the destruction of insulin-producing beta cells in the pancreas by the patient's immune system. Because insulin regulates the metabolism of glucose, its absence results in dangerously elevated glucose levels in the blood. Patients are thus dependent on insulin injections to regulate their blood glucose level which must be constantly monitored throughout the day to avoid hypo- or hyperglycemia. Even with careful management, type 1 diabetes patients face the constant risk of the disease's serious side effects which include kidney failure, blindness, nerve damage, heart attack, stroke, and pregnancy complications. While management with insulin can allow patients to live a full life, it is not a cure and requires constant attention. Thus, animal models of diabetes are imperative for the development of more effective diabetes management and treatment.

Streptozotocin (STZ) is a synthetic antineoplastic agent and is used clinically for the treatment of metastatic islet cell carcinoma of the pancreas. STZ is a highly selective cytotoxic agent to insulin producing pancreatic islet β -cells and is shown to induce diabetes in various animal models including mice and rats.

Noble Life Sciences has optimized an STZ-induced model of diabetes in the rat. This is the model of choice for preclinical development of therapeutic agents for diabetes because:

- The STZ-induced diabetes model in rats has been extensively studied and characterized
- This is a simple and relatively cost-effective model of diabetes
- STZ causes complete eradication of pancreas beta cells when administered at a single high dose and can thus be used as a model for type 1 diabetes where insulin production can be completely eliminated

Applications

- Diabetes treatment/management for lowering blood glucose in a non-beta-cell-dependent manner
- Testing cell and gene therapies and other transplantation therapies where the end point is lowering of blood glucose
- Develop treatments to diabetes induced chronic wounds
- Diabetes pathophysiology
- Study of diabetes side effects

Model Read-Outs

- Blood glucose level
- Body weight
- Insulin tolerance test
- Serum insulin levels

Methodology

Adult Nude female rats ranging from 365-430 g were divided into two groups: **1)** No-STZ control (1 rat), **2)** STZ-diabetic (3 rats). On day 0, group 2 rats were injected intravenously with 60 mg/kg STZ. Blood glucose levels and body weights were recorded every two to three days beginning one day before STZ

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treatment. Serum was collected from all rats immediately prior to STZ injection and 14 days post STZ injection to confirm the absence of insulin in diabetic rats.

On days 43 and 50, an insulin tolerance test was performed. All rats were fasted overnight, and two diabetic rats were injected with 0.75 U/kg human recombinant insulin intraperitoneally. One normal and one diabetic rat were not injected with insulin to control for normal glucose fluctuations over time. Glucose was measured in all rats immediately prior to insulin injection and at 20, 40, and 60 minutes post injection. Serum was collected at 60 minutes post injection. All measurements and injections were performed between 10:30 am-12:00 pm.

Results

STZ injection resulted in elevated blood glucose to levels of 400-500 mg/dl, over 2-3 times the normal level (normal approximately 100-150 mg/dl) (**Figure 1**). This was maintained for the entire duration of the 50-day study. There was a slight decrease in blood glucose by day 43, though still over twice the normal level. The loss of the ability of the pancreatic beta cells to produce insulin in diabetic rats was confirmed by ELISA (**Figure 2**).

Figure 1. STZ injection induces diabetes in nude rats. Nude rats (n=1 control; n=3 STZ) were injected with 60 mg/kg STZ IV on day 0. Blood glucose of STZ-treated rats rose to over 350 mg/dl and remained at this level for the duration of the 50-day study. Normal rat remained approximately constant in blood glucose level. Mean +/- standard error is shown for STZ treated rats.

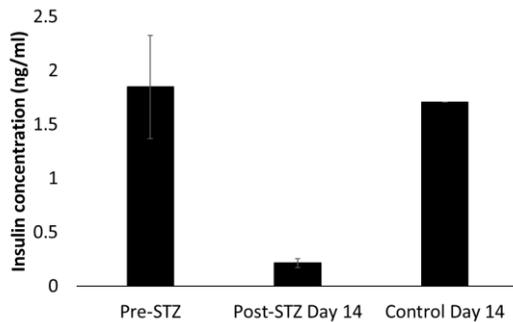
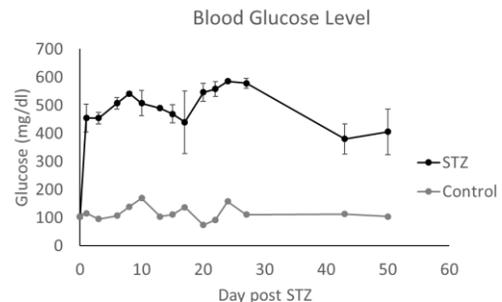


Figure 2. Diabetic rats lose the ability to produce insulin. A rat insulin ELISA on collected serum confirmed the absence of insulin production in diabetic rats. There was no change in insulin production by the control (no STZ) rat. Pre-STZ n=4; Post STZ Day 14 n=3; Control Day 14 n=1. Mean +/- standard error is shown for Pre-STZ and Post-STZ Day 14 groups.

On days 43 and 50 post-STZ injection, an insulin tolerance test (ITT) was performed. Serum collected prior to insulin administration and 60 minutes post insulin administration confirmed the presence of human insulin in the treated rats (**Figure 3a**). Blood glucose of the treated rats decreased steadily over the course of 60 minutes post insulin injection and reached a minimum of an approximate 60% decrease (**Figure 3b**). Control normal and diabetic rats not treated with insulin maintained steady, slightly increasing, blood glucose levels over the course of 60 min.

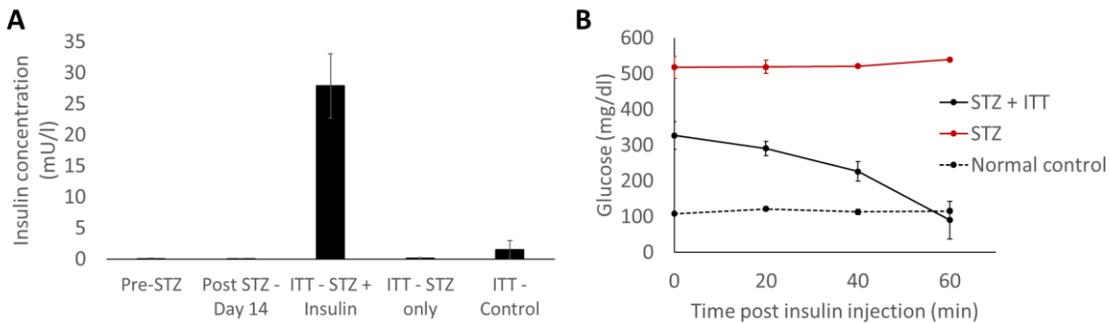


Figure 3. Insulin tolerance test demonstrates diabetic rats are responsive to insulin injection. **A)** A human insulin ELISA on collected serum confirmed the presence of insulin in diabetic insulin-treated rats only. **B)** Insulin administration decreases blood glucose levels approximately 60% in 60 min. Non-insulin- treated control and diabetic rats maintain steady glucose levels. Mean +/- standard error of n=2 experiments is shown.

Induction of diabetes due to the cytotoxic effect of STZ on insulin producing pancreatic β -cells is further confirmed by gross organ examination and histology of liver and pancreas. STZ treated rats showed reduction in the size of islets with less cytoplasm in the pancreas and hepatic steatosis in the liver. Both tissues showed signs of chronic inflammation with lymphocytes, macrophages, and mast cells.

Summary

The results herein demonstrate successful induction of diabetes in nude rats within days of a single high-dose administration of STZ. STZ injection causes degeneration of the pancreatic beta cells and thus a decrease or absence of endogenously produced insulin. Diabetes is confirmed by both an absence of insulin and increase in blood glucose levels. Diabetic rats are responsive to intraperitoneal insulin injection which decreases blood glucose to normal levels within 60 min. This relatively simple and quick model is a great choice for the preclinical analysis of non-beta cell dependent treatments for type 1 diabetes.