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COMMUNICATION

A Brief Report on Some Physiological Parameters of Streptozocin-Diabetic Rat

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ABSTRACT

Several biological changes occur when streptozocin is given to experimental animals. The rat streptozocin (STZ) model is extensively used in diabetic experiments. In this brief report, the main physiological characteristics of rats injected with streptozocin are presented. These characteristics are manifested by weight loss, organ weight reduction, serum glucose elevation, decrease in serum insulin level, and other enzyme and hormonal changes. A collection of these parameters may be helpful in establishing a database to describe this model.

Key Words: *Diabetes; Diabetic rat model; Insulin; Physiological parameters; Streptozocin.*

INTRODUCTION

Streptozocin (STZ) is a nitrosourea derivative ($C_8H_{15}N_3O_7$) anticancer drug that was first discovered as a by-product of the fermentation process of *Streptomyces achromogenes*. However, the current production of STZ is through chemical synthesis. STZ is used clinically in the management of β-cell islet cancer. Its effectiveness is due to the presence of a D-glucosamine moiety that promotes its accumulation in Langerhans islets. STZ is also used in biomedical research as an agent to induce diabetes in experimental animals (1).

The STZ-diabetic rat is used extensively as a model system for diabetes research. The biological profile of this model in terms of its biochemical and biophysical parameters is not yet fully developed. This report provides a database on some physiological characteristics of the STZ-diabetic rat model.

PHYSIOLOGICAL EFFECTS

Effect on Body and Organ Weight

Following a 55–65 mg/kg intravenous dose of STZ, there is a significant reduction in the whole body weight of both Sprague-Dawley and Wistar rats (2–7). This effect is observed as early as 4 days following the injection (4) and is maintained for the remainder of life without

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treatment (7). Rats could lose more than 25% of their original weight over 2 to 3 months (7). This effect is seen in both sexes of Sprague-Dawley and Wistar rats. Male Wistar rats experienced on average greater body weight loss than female rats (8). The toxic effect on organ weight is also significant. There appears to be an increase in kidney weight (7,9,10). A decrease in liver (2,5), prostate (3), testicle (3), and heart (7) weights was noted. Most authors believe that these effects may be related to swelling or general tissue damage.

Effect on Blood Glucose Level

The average blood glucose level in healthy Sprague-Dawley or Wistar rats can range from 74 to 168 mg/dl (10,11). Following an intravenous administration of STZ (50–75 mg/kg), blood glucose concentration increases dramatically. This rise in blood glucose is seen as early as 2 to 4 days after the injection (4,12,13) and is maintained for the remainder of life in untreated rats. The blood glucose concentration range in STZ-diabetic rats is expected to be from about 250 to more than 700 mg/dl (10,11,13). Following a 50 mg/kg intravenous dose of STZ to Wistar male rats (5–6 weeks old), the blood glucose daily concentrations stabilized to an average of 424, 358, 283, 380, and 456 mg/dl at 1:00 A.M., 4:00 A.M., 7:00 A.M., 7:00 P.M., and 10:00 P.M., respectively (11). This effect is an obvious outcome of the toxic effect of STZ on Langerhans islets; this pancreatic damage following STZ administration is documented by an increased production of nitric oxide and prostaglandins in isolated pancreatic tissue obtained from STZ-diabetic rats (14).

Effect on Insulin Blood Level

Intravenous injection of STZ destroys pancreatic β-cells and results in a reduction in insulin blood level. When STZ is given in doses of 50–60 mg/kg i.v., insulin levels decrease significantly from baseline values (6,11,15,16). On average, the decrease in insulin level is about 45%. This toxic effect is manifested as a rise in blood sugar. However, these findings suggest that significant residual activities of insulin exist in the diabetic rat even after 42 days postinjection (6). Such activity should be taken into account when this rat model is used in diabetic research. It should be noted also that there is an up-regulation in the insulin surface receptors in the liver following an intravenous STZ injection of 65 or 75 mg/kg in Wistar and Sprague-Dawley rats (5,12). The total body clearance of insulin in STZ-diabetic rats is significantly higher than that of controls (5). In addition, STZ increased significantly the hepatic plasma flow rate of circulating insulin (5). Insulin uptake by brain tissue increases in STZ-diabetic mice (17), an increase that is not related to changes in serum glucose concentration, serum insulin level, or altered vascular space (17).

Effect on Enzymes, Proteins, Hormones, and Lipids

Several toxic effects are seen in Holtzman M, Sprague-Dawley, or Wistar rats following STZ dosing of 50–100 mg/kg. The hepatic concentration of cytochrome is elevated in Sprague-Dawley rats (9). Subsequent treatment of these rats with insulin returned values to normal. The conjugation process (i.e., glucuronidation and sulfation) was significantly reduced (substrate: 4-nitrophenol) in Sprague-Dawley rats (18). Alteration in protein composition of P-450 proteins is also observed in Wistar rats (4). A significant increase in concentration of hepatic cAMP concentration is seen in Holtzman rats after an intraperitoneal injection (19). A significant increase in protein excretion is also observed following STZ treatment (20). Urinary albumin excretion is more than fourfold higher in STZ-diabetic female Wistar rats than in control rats (21).

The effect of STZ on other major enzyme systems has also been studied. There is no effect observed on monooxygenase enzyme in the kidneys or adrenal [substrate: benzo(a)pyrene] (9) nor is there any difference between control and STZ groups in the activity of hydroxylase enzyme in the kidneys [substrate: benzo(a)pyrene] (4).

Enzyme activity changes as a response to STZ toxicity may vary from organ to organ and even within the same organ. STZ increases the activity of *o*-de-ethylase in the liver and intestine; however, a decrease in activity is found in the lungs (2). Higher activity of protein kinase C is observed in the membrane fraction of the heart, but less activity is seen in the cytosolic fraction (6). No change in platelet cAMP-phosphodiesterase in Wistar rats is found, while a significant decrease in soluble cGMP-phosphodiesterase enzyme activity is observed (22).

The activity of enzymes in response to STZ injury may also vary between sexes. A decrease in hydrogenase enzyme activity on testosterone is seen in female Wistar rats and not in male rats (4).

The dose of STZ may also play a role in the effect on an enzyme's activity. For example, methionine metabolism decreases with an increase in STZ dose from 55 to 75 mg/kg i.p. (23). This is reflected by a proportional increase in plasma methionine concentration with STZ

dose. STZ-induced diabetic rats experience an increase in liver Na+/K+-ATPase activity that can be attributed to an enhanced expression of the beta 1 subunit of the enzyme (24).

Plasma cholesterol concentration did not change after 2 weeks postinjection of STZ; however, a significant increase in the concentration occurs after 28 days (16). In contrast, STZ causes a significant elevation in triglyceride concentration in plasma 2 weeks after treatment. This effect is maintained for more than 28 days (16). A significant elevation in serum phospholipids (>30%), free fatty acids (>225%), and triglycerides (>35%) is seen 10-weeks postinjection in STZ-diabetic rats (25). Testosterone levels decrease in male Wistar rats after STZ injection (3). STZ did not affect the hematocrit readings in male Wistar rats (5). In rats treated with STZ, platelets are more sensitive to aggregation when adenosine diphosphate (ADP) is present in a high concentration (2.5 μM) (16). The release of serotonin from platelets, as is induced with thrombin, significantly increases in STZ-treated rats (22).

Effects on Electrolytes and Creatinine Clearance

In Wistar and Sprague-Dawley rats, no effect in serum sodium, potassium, or chloride after STZ treatment occurs (20). However, increases in levels of potassium and chloride in urine are seen in STZ-treated rats, while the urinary excretion of sodium ions remains unaffected (20).

Although there is no significant effect on creatinine clearance after STZ administration, serum creatinine is higher than that in the control group (20). Serum creatine phosphokinase (CPK) is higher (>25%) in STZ-diabetic Wistar albino rats compared to control rats (26). Thus, serum creatinine may not be a good predictor for creatinine clearance in STZ-diabetic rats.

CONCLUSION

The overall biologic profile of STZ-diabetic rats consists of hyperglycemia, reduction in circulating insulin, weight loss, changes in organ weight, and alteration in the quantity and function of proteins, enzymes, and electrolytes.

The STZ-diabetic rat provides an experimental model for studying diabetes. Knowledge of the physiological parameters of this model is essential in explaining experimental findings obtained from it.

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