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DIABETOGENIC POTENTIAL OF STREPTOZOTOCIN IN THE GENERATION OF DIABETES MELLITUS IN ALBINO MICE

Biological Science

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ABSTRACT

BACKGROUND: Streptozotocin is toxic to beta cells and therefore used to produce animal model for diabetes mellitus. The Streptozotocin induces diabetes mellitus by the selective inhibition of glucose-stimulated insulin secretion and the formation of reactive oxygen species (ROS) which promotes death of beta cells. Both these effects result in a pathophysiological state of insulin-dependent diabetes mellitus in animals.
AIM: Generation of streptozotocin-induced mice diabetic models.
OBJECTIVES: To study the production of diabetes in albino mice.
METHODS: Diabetogenic albino mice were developed using intraperitoneal injection of different concentrations of streptozotocin (50-250 mg/KgBW) so that the hypoglycaemic efficacy of plant extracts can successfully be performed.
RESULTS: Streptozotocin induced a multiphasic plasma glucose response when injected intraperitoneally in albino mice. At 150 mg/kg BW of streptozotocin concentration the hyperglycaemic activity was noticed only after 35 hours of exposure (209.0 mg/dL of blood). At this concentration streptozotocin caused significant increase in plasma glucose level to 270 mg/dL after 50 hours of exposure.
CONCLUSIONS: It can be concluded that the streptozotocin is a diabetogenic agent when administered to albino mice.

KEYWORDS

Streptozotocin, Albino Mice, Diabetes Mellitus, Ros

INTRODUCTION

Streptozotocin (STZ) is a glucosamine-nitrosourea, alkylating antineoplastic agent. It is toxic to insulin-producing beta cells of pancreas and is used to treat certain cancers of pancreatic islets of Langerhans and also to produce animal model for diabetes mellitus. DNA damage caused by STZ induces the production of a transcription factor known as the peroxisome proliferator-activated receptor-γ (PPARγ). This transcription factor is involved in adipogenesis and in the regulation of adipocyte gene expression and glucose metabolism[1]. PPARγ is thus important for diabetes induction[2].It enhances glucose transport to cells through glucose transporter protein (GLUT2) only, but not recognized by other glucose transporters. STZ thus shows relative toxicity to beta cells because these cells have high levels of GLUT2[3,4].

For induction of diabetes this drug can be administered to experimental animals through different routes viz. intraperitoneal, intravenous and subcutaneous with single or multiple doses. The genetic strains, route of administration and nutritional status of experimental animals play an important determining role for induction of diabetes[5].

Streptozotocin induces diabetes mellitus in experimental animals by partial degradation of the beta (β) cells of islet of Langerhans in pancreas and subsequent compromise in the quality and quantity of insulin produced by these cells. The Streptozotocin induces two distinct pathological effects. First, the selective inhibition of glucose-stimulated insulin secretion, and second the formation of reactive oxygen species (ROS) which promotes death of beta cells. Both these effects result in a pathophysiological state of insulin-dependent diabetes mellitus in animals[6]. The former is associated with specific inhibition of a pancreatic glucose sensor enzyme, glucokinase by streptozotocin whereas the latter is rather connected with the redox cycling ability of STZ which results in the generation of ROS.

Materials and Methods

Diabetogenic albino mice were developed using different concentrations of streptozotocin (50-250 mg/KgBW). Adult albino mice weighing around 250-300 gram with 7.5 ± 0.5 cm length were selected and mice were housed in shoe-box type cages under good hygienic conditions in animal house during experimental period. The mice were acclimatized for 15 days in an environmentally controlled room under standard conditions (21±2°C, 55±5% humidity, 12 hr Light: Dark cycle).

Streptozotocin solution in 0.05M sodium citrate at pH 4.5 at the dose of 35 mg/kg body weight was administered by multiple intra-peritoneal injections. The mice were then allowed to access the respective food and water *ad libitum*. Mice with fasting blood glucose level of 200 mg/dl (7.8 mmol/l) or higher were considered to be diabetic and were used in the study. A parallel set of control mice (non-diabetic) were injected with citrate buffer only.

The mice were fed on diet pellet consisted of wheat grains, choker wheat, maize grains, soybean grains, sun drop oil, milk powder and jaggery and water *ad libitum* to ensure proper growth. One pellet of feed per mice was given. Data were expressed as the mean ± S.E and analysed by ANOVA. The results obtained have been presented in Table-1 and Figure-1.

Table-1: Plasma Glucose Level In Mg/dl Of Albino Mice After Administration Of Different Concentration Of Streptozotocin At Different Time Intervals

Plasma glucose level in reference range (mg/dL)	Plasma glucose level in control mice (mg/dL)	Concentration of Streptozotocin administered (mg/kgBW)	Exposure time intervals in hours									
70-110	72.15 ±1.02		5	10	15	20	25	30	35	40	45	50
		50	77.00 ±1.17	86.00 ±1.75	100.50 ±1.63	107.00 ±1.16	110.00 ±0.65	113.00 ±1.66	115.00 ±0.74	117.00 ±1.52	119.00 ±0.67	120.00 ±0.84
		100	78.00 ±1.12	88.00 ±1.75	97.20 ±1.15	105.50 ±1.25	110.35 ±1.26	113.00 ±1.37	117.00 ±1.25	120.00 ±1.12	121.00 ±0.71	122.00 ±1.15
		150	85.00 ±1.11*	99.00 ±1.65*	114.50 ±1.35*	142.20 ±1.17*	167.50 ±1.35*	188.20 ±1.35*	209.00 ±1.61*	220.00 ±1.64*	242.00 ±1.63*	270.00 ±1.35*

		200	163.00 ±1.16*	208.00 ±1.41*	248.10 ±1.15*	279.50 ±1.31*	301.00 ±1.25*	324.20 ±1.16*	345.00 ±1.25*	352.00 ±1.42*	361.30 ±1.26*	364.00 ±1.66*
		250	183.00 ±1.21*	226.00 ±1.25*	267.00 ±1.31*	297.60 ±1.15*	318.30 ±1.21*	380.00 ±1.41*	428.0 ±1.35*	489.20 ±1.71*	510.00 ±1.63*	527.00 ±1.25*

*Significant at P<0.05 as compared with control

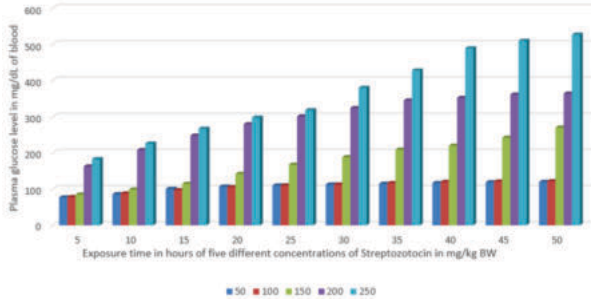

Figure-1: Plasma Glucose Level Of Albino Mice After Administration Of Five Different Concentrations Of Streptozotocin (50, 100, 150, 200 And 250 Mg/ Kg Bw) At Different Exposure Time

RESULTS

Streptozotocin induced a multiphasic plasma glucose response when injected intraperitoneally in albino mice. It was observed that 50 mg/kgBW and 100 mg/kg BW of STZ caused a very slow rise in plasma glucose level up to 50 hours of exposure. After 50 hours of exposure STZ at the concentrations of 50 mg/kg/BW and 100 mg/kgBW caused a rise in the plasma glucose level to 120.0 mg/dL and 122.0 mg/dL respectively that was within the normal reference range (Table-1; Fig-1). The glycaemic values of albino mice increased on increasing the concentration of STZ and time of exposure. At 150 mg/kg BW of streptozotocin concentration the hyperglycaemic activity was noticed only after 35 hours of exposure (209.0 mg/dL of blood). At this concentration streptozotocin caused significant increase in plasma glucose level to 270 mg/dL after 50 hours of exposure (Table-1; Fig-1). The 150 mg/kg BW of streptozotocin could therefore be considered as mild diabetogenic. The streptozotocin at concentrations of 200 mg/kgBW and 250 mg/kgBW was found to be potent inducer of diabetes mellitus after any exposure time. At concentrations of 200 mg/kgBW and 250 mg/kgBW the streptozotocin caused a rise in plasma glucose level to 163.0 mg/dL and 183.0 mg/dL respectively only after 5 hours of exposure. The plasma glucose level increased on increasing the exposure time of streptozotocin. After 50 hours of exposure the streptozotocin at concentration of 200 mg/kgBW and 250 mg/kgBW caused 364.0 mg/dL and 527.0 mg/dL of plasma glucose level (Table-1; Figure-1).

DISCUSSION

The present findings are in accordance with the work of Lenzen[7], Federiuk *et al*[5], Szkudelski[2], Misra *et al*[8], Baidyanath Kumar *et al*[9]. They observed more or less similar results on plasma glucose level response to alloxan in rats. Lenzen[7] observed that the plasma glucose multiphasic response to streptozotocin injection begins in the first few minutes with a transient hypoglycaemic phase that lasts maximally for 30 min. This is considered to be a transient hyperinsulinemia which may be due to a momentary increase in ATP level resulting from the temporary effects of streptozotocin inhibition of glucokinase. The second phase is characterized by upsurge in blood glucose concentration and concomitant decrease in plasma insulin concentration. This occurs one hour after streptozotocin administration. This represents the first hyperglycaemic effect of streptozotocin and it lasts for a period of 2-4 hours. Streptozotocin induced diabetic hyperglycaemia (blood glucose ≥200 mg/dL or 11.1 mmol/ L) in albino mice which occurred only after ten intraperitoneal injection at concentrations 200 mg/kgBW and 250 mg/kgBW. Inhibition of insulin secretion from the pancreatic beta cells due to ROS attack accounts for this phase of streptozotocin diabetogenicity[10,2].

As uptake of streptozotocin by the beta cells of the pancreas reaches its maximum,its toxicity via ROS increases. This leads to induced rupture of the secretary granules and cell membrane of the beta cells[7, 2, 11, 12] leading to flooding of the circulation with insulin. This represents a pathophysiological condition that results in a severe transitional hypoglycaemic phase. The hypoglycaemic phase in streptozotocin diabetogenicity has also been associated with the ability of streptozotocin to cause significant influx of free Ca^{2+} into the cytosol of pancreatic islet beta cells, thereby compromising the intracellular calcium homeostasis. The process involves the depolarization of the pancreatic beta cells, which facilitates further calcium entry into pancreatic cells via voltage dependent calcium channels.

The last phase of the blood glucose response to STZ administration is the permanent diabetic hyperglycaemia that takes place 20 to 50 hours of administration. In this phase there is complete degranulation and loss of structural integrity of the beta cells of pancreatic islets of Langerhans[7,13,14]. Streptozotocin is known to stimulate Type-1 diabetes mellitus.

CONCLUSIONS: It can be concluded that the streptozotocin is a diabetogenic agent when administered to albino mice. The diabetogenic efficacy of streptozotocin is concentration dependent. The 150 mg/kg BW of STZ can be considered as mild diabetogenic, but 200 mg/kg BW and 250 mg/kg BW of STZ as potent inducer of diabetes mellitus.

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