Role of Nicotinamide in Streptozotocin Induced Diabetes in Animal Models

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Abstract

Diabetes mellitus (DM) is a metabolic disease with abnormal glucose homeostasis, due to defects in secretion or action of insulin. It is a potentially morbid condition with high prevalence worldwide and has become a major medical concern. Animal models play an important role in understanding such type of diseases. Diabetes in experimental animal develops either spontaneously or by using chemical, surgical, genetic or other techniques, and depicts many clinical features or related phenotypes of the disease. Streptozotocin (STZ) is a widely used chemical for the induction of experimental diabetes in animals. In this review, we have provided the evidences related to the fact that Nicotinamide play a protective role against destruction of pancreatic β- cells in STZ induced diabetes model in experimental animals..

Keywords: Diabetes mellitus; STZ; Nicotinamide

Introduction

Diabetes mellitus (DM) is mainly characterized by hyperglycemia [1] with an imbalance of carbohydrate, protein and fat metabolism due to reduced production of insulin from pancreas (defects in insulin secretion), or when insulin cannot be used efficiently by the body (defect in insulin action), or both [1,2]. Two major forms of diabetes are Type I DM (TIDM) and Type II DM (TIIDM). TIDM is also termed as insulin dependent DM (IDDM) and TIIDM as non insulin dependent DM (NIDDM). TIDM is immune mediated and is characterized by destruction of pancreatic β-cells and requires daily administration of exogenous insulin [3]. TIIDM is the most prevalent form of diabetes, mainly characterized by partial destruction of pancreatic β-cells, which results in relative insulin deficiency/ resistance [2,4]. About 5-10% diabetic patients have TIDM as it affects 3 in 1000 children whereas TIIDM is considered to be the most prevailing form of diabetes, which accounts for about 90% of diabetic cases [5].

Animal models have been used widely to obtain knowledge of various pathological conditions related to diseases such as diabetes. STZ induced diabetes is considered to be the most reliable method. STZ induced structural, functional and biochemical alterations observed are similar to those which appear with diabetes in human [6]. Therefore STZ-induced diabetes represents a clinically relevant model to study the pathogenesis of diabetes and associated complication.

Streptozotocin (STZ)

STZ (2-deoxy-D-glucose derivative of N-methyl-N-nitrosylurea) is a glucosamine nitrosourea, hydrophilic compound which was first isolated from a soil microorganism Streptomyces acromogenes and showed broad spectrum antibiotic activity [7,8].

The diabetogenic action of STZ is related to its selective destruction of pancreatic β-cells, which are the only source of insulin in body. As STZ is glucose derivative, the blood glucose moieties enables STZ to be selectively transported to pancreatic β-cells via the low-affinity GLUT2 glucose transporter in the plasma membrane [9,10].

Exposure of STZ to pancreatic β-cells results in damage via different pathways:

a. STZ destructs β-cells by damaging the major macromolecule i.e. DNA by alkylating. Alkylation of DNA results in fragmentation of DNA in β-cells [10,11]. DNA injury by STZ leads to overstimulation of PARP-1 [(poly(ADP-ribose) polymerase-1] in the insulin-secreting cells and is harmful to the cell as a result of a substantial depletion of the intracellular PARP-1 substrate, NAD+. NAD+ is an important molecule implicated in energy metabolism at the cellular level [12,13].

b. STZ also decreases the activity of islet mitochondrial aconitase, reduces oxygen consumption by mitochondria and decreases the mitochondrial membrane potential [14].

c. Generation of nitric oxide may play a role in the cytotoxic action of STZ on insulin-secreting cells. This assumption is supported by results demonstrating that scavengers of nitric oxide (NO) attenuate early DNA-strand breaks induced by STZ [15].

d. STZ generates low amounts of ROS in pancreatic β-cells. These effects may partially contribute to β-cells damage induced by STZ because of a weak antioxidant defense in these cells [16,17].

e. It has also been revealed that c-Jun N-terminal kinase (JNK) is also involved in the cytotoxicity of STZ. Increased activity of this enzyme is observed in the case of cellular stress leading to cell death. Studies on insulin-secreting cells exposed to STZ demonstrated increased activity of JNK, whereas inhibitors of this enzyme attenuated the cytotoxic action of STZ. Activation of JNK by STZ is supposed to be preceded by increased activity of PARP-1 since PARP-1 inhibitors are able to decrease the activity of both PARP-1 and JNK [18].
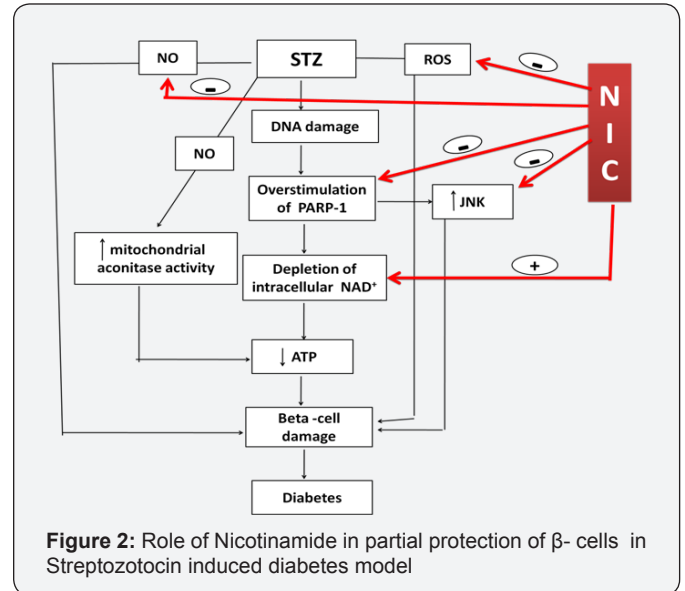
Nicotinamide (NIC)

NIC (pyridine-3-carboxamide) also known as niacinamide, is an active and water soluble form of vitamin B3 (niacin). Niacine converted into NIC in the body and is a food additive. NIC is essential to the coenzymes NADH and NADPH and consequently for numerous enzymatic reactions in the body including formation of ATP. NIC has neuro-protective and antioxidant functions and is given to animals to partially protect pancreatic β-cells against STZ [19,20].

Figure 1: Modulation of Streptozotocin consequences by Nicotinamide
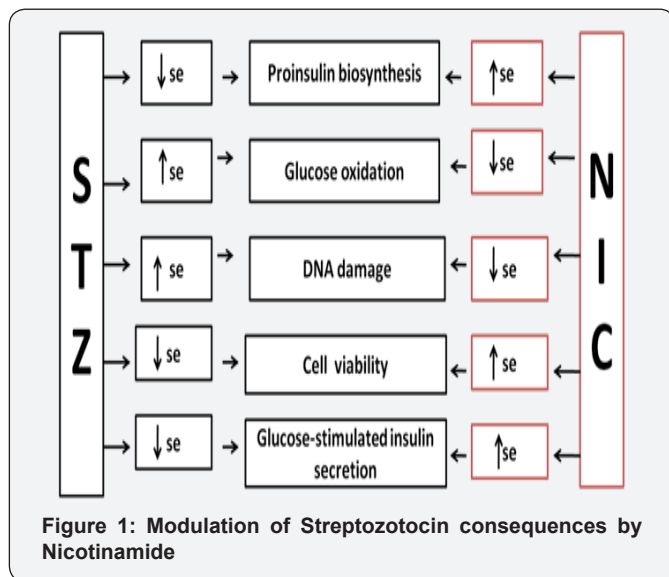
Numerous in vitro experimental studies conducted on isolated rat pancreatic islets have revealed that effects of STZ

like reduction of pro-insulin biosynthesis, inhibition of glucose-stimulated insulin secretion etc. were modulated by NIC [21-24] (Figure 1).

NIC shows its partial protection against STZ induced destruction of β-cells by two major mechanisms i.e. either by inhibiting PARP-1 [13,25] or by increasing the concentration of NAD+ (by reducing utilization of NAD+ or by increasing its biosynthesis) [26] (Figure 2).

Figure 2: Role of Nicotinamide in partial protection of β- cells in Streptozotocin induced diabetes model

Type of Diabetes Induced by STZ

The single intravenous dose between 40 and 60mg/kg body weight in adult rats can induce TIDM [27], but higher doses are also used. STZ is also efficacious after intraperitoneal administration of a similar or higher dose [28]. STZ may also be given in multiple low doses. Such treatment is used predominantly in the mouse and the induction of IDDM is mediated by the activation of immune mechanisms. The nonspecific activation of the immune system via complete Freund's adjuvant prior to STZ injections allows to reduce its diabetogenic dose even in the rat [29,30].

NIDDM can easily be induced in rats by intravenous or intraperitoneal treatment with 100mg/kg body weight STZ on the day of birth. This method of NIDDM induction was described for the first time by Portha et al. [31]. At 8-10 weeks of age and thereafter, rats neonatally treated with STZ manifest mild basal hyperglycemia, an impaired response to the glucose tolerance test and a loss of β-cells sensitivity to glucose [32]. But in adult rats, if NIC is administered at a dose range of 100-500mg/kg prior to the administration of STZ it leads to cytoprotective effect. It should be emphasized that the effects induced in rats by STZ and NIC vary depending on the doses of these two compounds, the age of the animals and the time of NIC administration in relation to the administration of STZ [19,20]. Factors, such as the administration route of STZ and the nutritional state of rats may also have some influence. In the case of relatively low doses of NIC given to rats, its protective action is negligible. Conversely,

high doses of NIC may provide total protection [8,27]. The age of rats is also of major importance since β-cells of younger animals are less sensitive to STZ and are better protected by NIC. It is also known that the protective action of NIC on β-cells decreases with the time elapsed after administration of STZ to rats. This decrease is supposed to result from ATP depletion since the uptake of NIC by β-cells is ATP-dependent. In the majority of experiments, NIC is given to rats 15min before STZ [32].

Conclusion

STZ-induced diabetes is a clinically important animal model and most extensively used to mimic human diabetic condition. STZ can produce both types of DM i.e., TIDM and TIIDM depending on the dose and route of administration but couldn't be affective every time. But the role of NIC is worth considering which can modulate the occurrence of type of DM via its cytoprotective action against the toxic effect of STZ at a particular dose.

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