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Evaluation of the Key Mechanism Justifying the High Sensitivity of Obese Rodents to Streptozotocin (STZ)

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Abstract

Diabetes mellitus (DM) is a metabolic disease caused by the absence or dysfunction of insulin; a hormone secreted by the pancreatic beta cell (β-cell) whenever blood glucose exceeds the normal physiological value. The long-term effects of the disease on the body's organs are one of the leading causes of death in the world. To alleviate this global burden of DM, a number of studies have been conducted to lower blood glucose levels in patients. For genetic and ethical reasons, humans are far from being appropriate subjects in such investigations and the use of animal models has therefore been the way forward. Streptozotocin (STZ) is a glucosamine-nitrosourea compound that selectively destroys β-cells and has been widely used to induce Type I diabetes in several animal species. Recent literature has shown that a non-diabetic dose of STZ, combined with a high-fat diet (HFD), can mimic Type II diabetes. Yet, researchers seldom provide data to corroborate the high sensitivity of STZ on these animal models. In addition, there are few reports of potentially fatal effects of the use of STZ as a supplement in obese HFD animals when attempting to induce Type II diabetes. The present review article highlights the parameters that could be at the origin of the extreme sensitivity and vulnerability of obese animals to STZ.

Keywords

Streptozotocin, High-Fat Diet, Obesity, Sensitivity

1. Introduction

A large number of species have been used in diabetes studies, including primates

[1] [2] Rodents have the highest recorded use, especially for studies engaged in testing natural compounds and pharmaceuticals; this is due to their small size, ease of availability, short generation interval and economic considerations [3]. Diabetic animal models have been developed by a number of methods ranging from genetic [4] [5] chemical [6], spontaneous autoimmune [7], viral [8] [9], surgical (pancreatectomy) [9] to diet-associated [3] [10] [11]. The induction method to be considered depends on the type of DM to be developed and the objectives of the research [6]. Diabetes induced by means of chemical methods have been shown to be most effective for various research purposes and provide the most cost effective and easiest DM models [12]. Streptozotocin (STZ), a chemical compound that resembles glucose and selectively accumulates in the pancreatic β-cells via the glucose transporter 2 (GLUT2) is one of the diabetogenic agents of choice in this process [13] [14] [15].

In the cell, STZ causes a number of synergetic molecular mechanisms leading to β-cell death [16] [17]. Beta cells are more active in the glucose uptake than other cell (hepatocyte) in the body and therefore are more vulnerable to STZ toxicity [18]. Significant depletion of insulin-secreting cells ultimately induces hyperglycaemia.

Until recently, STZ was primarily involved in the induction of Type I DM in non-genetically modified adult animal species [19]. The development of a true Type II diabetic model in which insulin resistance precedes the onset of the disease, remains a challenge. This challenge was partly overcome by Reed [20] who successfully developed a Type II DM rodent model (Sprague Dawley rats) by combining a HFD diet with a single dose of STZ (50 mg/kg body weight). To obtain similar results, minor to major modifications of the Reed's protocol followed in subsequent years, the most notable being the significant reduction of STZ dose (to 30 - 35 mg/kg body weight) [3] [11] [21] [22]. The reasons these changes have occurred over time while keeping other parameters according to Reed's work are not clearly explained in the literature.

Animals subjected to different diet regimens express different degree of susceptibility to STZ at a given treatment dose [11] [23]. The HFD induces obesity, insulin resistance [20] [24] [25] [26] and sensitivity to STZ [27]. The molecular mechanisms that justify the hypersensitivity and vulnerability (unpublished work) of obese rodents exposed to a dose of STZ that normally does not induce DM in animals fed a standard diet, is yet to be elucidated. Understanding the pathway that describes how HFD/obesity improves the diabetogenic effect of STZ can shed light on the cause(s) of the inconsistency of the results seen when the drug is used to induce diabetes, and thus help to include new parameters during the protocol design.

Here we review the adverse effects of obesity in non-adipose tissue (islets of Langerhans) and discuss the main models of STZ mechanism in β-cell toxicity. The literature will be used to explore the different factors that underlie the association between the islet microenvironment in HFD animals and the intense action of STZ.

2. Obesity and Insulin Resistance

Obesity has a high prevalence in the world today; and is defined as an excessive accumulation of fat in the body [28]. A person is declared obese when their body mass index (BMI), defined as the ratio of a person's weight in kilograms to the square of their height in meters is greater than 25 [29]. Traditionally considered as an imbalance between the amount of food consumed, and the body's energy expenditure, obesity is also strongly associated with the genetic context of an individual's metabolism [28].

Scientists engaged in the study of obesity have been challenged to identify factors, molecules and pathways that lead to the development of obesity in the hope that these parameters could be targeted for therapeutic intervention [30] [31] [32]. A gene region, known as fat mass and obesity-related gene (FTO) is found to be strongly associated with obesity; and has been extensively studied since its discovery in 2007 [29]. However, previous studies have not found the mechanism that explains how gene differences in this region lead to obesity [11]. Numerous studies have attempted to link the FTO region with brain areas concerned with appetite or propensity to exercise, but have found that the region acts primarily on adipocyte progenitor cells independently of the brain [11] [33] [34]. Whether obesity is caused by an imbalance between dietary intake and energy expenditure, genetic factors, or a combination of both, it typically leads to the organism's inability to effectively regulate nutrient metabolism [34] [35]. Normally in healthy humans, while excess fat is stored in the adipose tissue during positive caloric balance, excess glucose accumulates in the liver and muscle tissue in the form of glycogen [36]. Whenever the glycogen store is full, lipogenesis may occur mainly in the liver and sometimes in the adipocytes [35]. To compensate for, and maintain normoglycemia, the β-cell of the pancreas becomes very active especially in individuals with insulin resistance, although the molecular signals inducing this functional adaptation remain unknown [37] [38]. Increased insulin secretion, insulin gene expression, and an increase of the β-cell mass successfully keeps the body healthy for some time, and possibly even for life in some individuals [37]. In individuals with certain genetic predispositions, β-cell compensatory activity fails, leading to a condition known as glucolipotoxicity, the main cause of β-cell dysfunction [11]. The first stage of an individual's transition from a healthy state to a prediabetic state is characterised by the presence of an impaired fasting glucose, impaired glucose tolerance; or both, and resistance to insulin signalling [39]. Nevertheless, metabolically healthy obese individuals and metabolically lean and diseased individuals are present in the population, indicating that obesity does not automatically cause Type II DM [40] [41].

Despite the evidence of the major role obesity plays in the development of DM, factors causing the disease syndrome in these individuals are not yet defined in the literature [42]. However, Skovsø, 2014 [42] has demonstrated that obesity is always associated with a dramatic increase in the regulation of many

inflammatory genes and specific macrophages in white fat cells. Adipose tissue dysfunction causes ectopic fat to accumulate in non-adipose tissues such as liver, muscle, and pancreas [11] [23]. The accumulation of triglyceride in the pancreatic β-cell causes a chain of biochemical reactions leading to an increase in lipogenesis [43]. The alteration of the chemistry of the internal environment thus created facilitates the development of biological interactions putting the β-cell in a total imbalance [44]. It is estimated that a 50 to 60% reduction in β-cell function is established twelve to several years before the diagnosis of diabetes [44] [45] [46].

Many studies have been conducted to determine the exact mechanism governing the glucolipotoxicity process [35]. Unfortunately, of all these studies, no mechanisms have been identified in attempting to mimic the human biological environment [34]. In addition, palmitic acid (PA) and oleic acid (OA) are fatty acids (FAs) usually used in these studies but at widely varying concentrations, and at least 3 times higher than those found in the blood plasma of lean individuals [47] [48]. Therefore, results obtained from in-vitro studies using FAs should be interpreted with caution. Although apoptosis is induced in-vitro by a high concentration of FAs [48], to our knowledge, no in-vivo study has clearly demonstrated the direct effect of a high concentration of FAs on β-cell death.

Zucker rats developed by mutation of the glutamate-269 (Glu-269) to proline (Pro) substitution in the extracellular portion of the leptin receptor are well used in the study of Type II DM and considered for the analysis of adverse effects of glucolipotoxicity [49]. As in humans, this animal model becomes diabetic as it ages, but does not depend on exogenous insulin to live [50]. Zucker rats' β-cells initially compensate for the progression of obesity and associated insulin resistance by increasing insulin secretion, insulin mRNA levels, and insulin content, but can no longer lift this challenge, and animals eventually become hyperglycaemic [35] [50] [51]. Factors such as the metabolism of leptin in the body may be associated with a human genetic predisposition to Type II DM because leptin is important in maintaining the plasma level of triglycerides. The following emphasises the key role of the hormone leptin, in fat metabolism.

3. Role of Leptin in Fatty Acid Metabolism

Leptin, also known as the "obesity hormone", was discovered in 1994 [50] [51] and considered a potential treatment for exceptional weight loss. Secreted by adipocytes, the role of the hormone is to up-regulate the oxidation of long chains of FAs via the sympathetic nerve-α-adrenergic receptor [52] and, in doing so, prevent non-adipose tissue from accumulating triglycerides [50] [51] [53] (**Figure 1**). Triglycerides are normally maintained in a very narrow range in these tissues (less than 150 milligrams per decilitre) [54], making the molecule (triglyceride) the most useful index for overall non-oxidative metabolism [50] [51] [55]. When leptin is absent or its receptor non-functional, excess FAs (up to 1000 ng/islet) [43] in non-adipose tissues enter a toxic metabolic pathway in

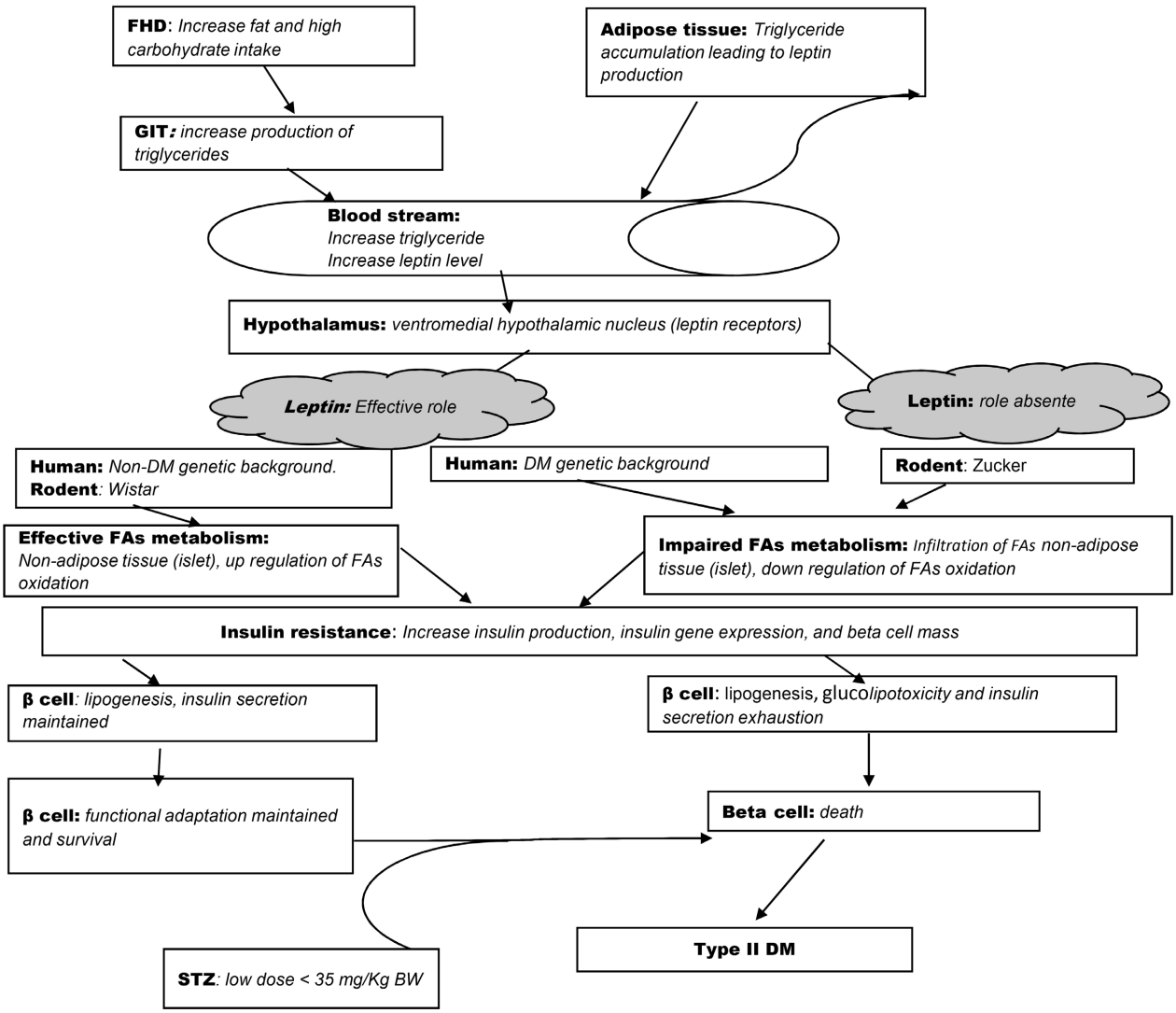

Figure 1. Role of leptin in fatty acid metabolism and management of lipid and glucose overload in non-adipose tissues (islets) leading to insulin resistance in humans and unmodified rodents. Normally, each time an adipose tissue accumulates an excess of triglycerides, it begins to secrete leptin. Leptin acts on the leptin receptor in the hypothalamus, resulting in stimulation of fatty acid oxidation and glucose uptake via the sympathetic pathway thus preventing lipotoxicity in non-adipose tissues such as the pancreas. In the absence or dysfunction of leptin, as in the obese Zucker rat, lipotoxicity develops leading to DM. A condition, however, that occurs in certain groups of people with the effective functional leptin hormone, but is believed to be genetically predisposed to the disease.

which ceramide is produced [56], followed by cellular lipotoxicity and lipoapoptosis [50] [51] [55]. For example, the accumulation of FAs in heart tissue causes cardiac dysfunction, insulin resistance in the muscle, and lipotoxicity; and in the pancreatic islet, lipoapoptosis occurs (55). Also, the toxic consequences of lipid overload would depend on the duration and the magnitude of the imbalance between the fat input and fat output in a specific tissue [53].

In congenital human disorders characterised by the absence of adipocytes, the fat storage, and leptin production site, lipotoxicity is severe, and begins early in life [55]. In rodents genetically modified by the leptin receptor mutation, lipo-

toxicity also occurs very early [57]. However, in diet-induced obesity, non-adipose tissues are overprotected by hyperleptinemia; but only for a limited period of time before tissue resistance to leptin of unknown aetiology develops; the time that, excess fat begins to penetrate the non-adipose tissue and resulting in lipotoxicity.

4. Lipotoxicity

The accumulation of triglyceride is not the direct cause of islet cells destruction in genetically modified obese animals (Zucker rats) [58] (**Figure 1**). In-vitro studies reveal that ceramide formation is the main step in this process. Ceramide is a condensation of serine and palmitol (FA), a reaction catalysed by pamitol transferase [56]; the level of which is strongly elevated in prediabetic obese Zucker rat models [59] [60]. The increase in ceramide level enhances the activation of nitric oxide synthase (iNOS), that of the formation of nitric oxide (NO) [61]; the direct cause of cell apoptosis (discussed later in the review).

In non-genetically modified obese HFD rodents, the glucolipotoxicity hardly develops or never develops in DM, and can be suspended before the death of the β-cells. This suggests that factors mediating the conversion of the prediabetic state to a complete Type II DM in humans may be absent or altered in non-genetically modified rodents. However, a few days of HFD diet are sufficient to transform the internal metabolic milieu of these animals to the threshold of a healthy state with significant insulin resistance but never become diabetic. Thus, to trigger the onset of the final stage of the metabolic syndrome as to mimic the typical human pathophysiology of Type II DM [61], these animals are usually administered a single non-diabetes inducible dose of STZ (30 - 35 mg/kg body weight) which may be the additional factor to insulin resistance that finally causes the development of Type II DM. It raises the questions as to what is, or are, the cumulating factors that enhance the β-cell death under this condition? These observations aroused our curiosity about the striking difference between the diabetogenic doses of STZ administered to the rats and mice. How does STZ work in the model of HFD-induced obesity?

5. Streptozotocin

5.1. Chemical Properties of Streptozotocin

Streptozotocin (STZ) (2-deoxy-2-({[methyl(nitroso) amino] carbonyl} amino)-β-D-glucopyranose) (Zanosar) [16] [62] is a broad-spectrum antibiotic [63] [64]. First identified in 1960 from the soil bacterium Streptomyces Achromogenes, the compound has been used in the treatment of human pancreatic neoplasms [65] and for the induction of diabetes in animals [66]. Very soluble in water, lower alcohols, and ketones [67], STZ is a white or a pale-yellow crystalline powder resulting from a mixture of α and β stereoisomers [62]. The drug has the chemical formula $C_8H_{15}N_3O_7$ (**Figure 2**) with a molecular weight of 265 g/mol [62]. Streptozotocin is also a glucosamine-nitrosourea compound structurally

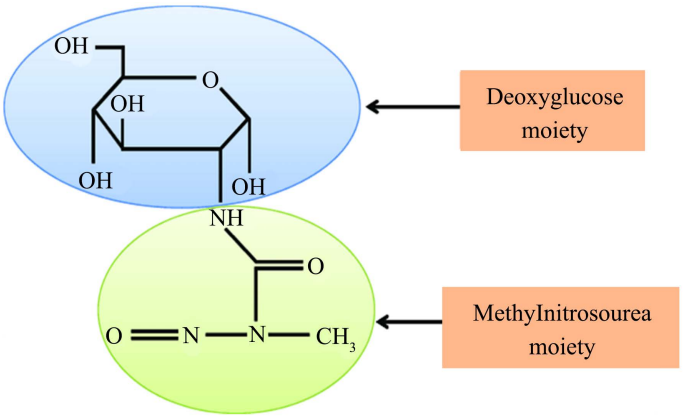

Figure 2. Chemical structure of streptozotocin (Wu and Yan, 2015).

composed of a molecule of glucose at one end and a methyl group at the other end (**Figure 2**) [43] The methyl nitrosourea fraction appears to be responsible for the toxicity of STZ while the deoxyglucose fraction recognises the GLUT2 glucose transporter receptor, which is abundant on the plasma membrane of β-cells and thus remains the best target cell of the drug. However, GLUT2 is also found in liver, and kidney cells to a lesser extent. Streptozotocin has a biological half-life of 5 - 15 minutes and is relatively unstable: working solutions should be prepared immediately before injection [68].

5.2. Dose and Method of Administration of Streptozotocin

Streptozotocin is administered to animals either intraperitoneally (IP) [69], subcutaneously [70] or intravenously (IV) [23] Regardless of mode of administration, the drug seems to have the same metabolic pathway and does not appear to be dose-dependent. A single high dose (40 - 60 mg/kg body weight or multiple low doses can be used to induce Type I DM in rats) [71]; a condition that initially creates a partial pancreatic β-cell damage leading to an inflammatory response. The inflammatory process, in turn, trigger further loss of insulin-producing cells followed by a significant reduction of insulin secretion and ultimately hyperglycaemia. In rats, a dose of STZ less than 40 mg/kg body weight may not be effective [3] [23]. While the highest single dose for the induction of diabetes in rat is only 65 mg/kg body weight [3], up to 200 mg/kg of STZ is administered (Dekel *et al*., 2009), in mice for the same purpose [16] [23] [72]. In addition, even within a single rodent strain, the dose of STZ administered for diabetes induction depends on many other factors; such as animal sex (male or female) [16] [72], diet, circadian rhythm [16]. These factors constituted the biggest challenge in terms of transferring a well-established protocol from one strain to another [73]. Unfortunately, there is no detail on the molecular pathway that justifies this inconsistency. A better understanding of the logical flow of this scenario will pave the way for new avenues in diabetic research using animal models, but most importantly, the genetic-environmental condition associated with the selective onset of diabetes in some individuals may be revealed.

5.3. Streptozotocin across the Target Cell Membrane

Once introduced into the body, the STZ molecule approaches the target cells through the bloodstream. The compound is internalised in the target cell via the low-affinity GLUT2 (also called facilitated glucose transporter) [14] [68] [74]. Glucose transporter 2 membrane receptors are bidirectional glucose transporters restricted to cells of organs involved in glucose homeostasis such as hepatocytes and pancreatic β-cells [75]. The receptor distributes glucose molecules between the extracellular and the intracellular space which is rapidly maintained under physiological conditions and in diseases such as diabetes. The transporter is highly expressed in β-cell membranes and also transports fructose [76] and drug molecules such as STZ [75] [77] in the cells. However, unlike glucose that is also transported by other glucose transporters, several studies have shown that STZ's sole gateway into targeted cells is via the GLUT2 transporter [78].

Streptozotocin sugar moiety is the chemical structural arrangement that allows the drug to identify the target cell membrane receptor and mediate the transfer into the cytoplasm. The receptor thus remains the STZ susceptibility marker and their level of distribution on the β-cell membrane, the expression and state define the degree of toxicity of the drug that may or may not lead to the onset of diabetes [17]. For example, insulin-secreting cells from humans and the Old World monkey are very resistant to STZ because of the very low level of GLUT2 on their cell membrane (1% to 2% of those found in rats) [79] [80]. Recent reports have shown that human β-cells transplanted to rodents are not destroyed when these animals even receive high doses of STZ [17] [81]. Interestingly, human pancreatic islet cancer cells, on the other hand, express high levels of GLUT2 and STZ thus, has been used for many years as an oncogenic agent in the treatment of islet malignancy [82] [83]. On the other hand, rat RINm5f insulinoma cell lines are very insensitive to STZ toxicity because they do not express GLUT2 glucose transporters [84]. These animal models quickly become sensitive once the expression of the transporter is induced [85]. Therefore, if HFD induces susceptibility to STZ in rodents, the properties of GLUT2 may have improved under such conditions.

On the contrary, the impairment of the expression of GLUT2 [81] and its translocation from the cytoplasm to the cell membrane is the early signs of β-cell functional disturbance in HFD/obese animals [86]. These changes are also observed in diabetic Goto-Kakizaki rats [86] [87] and other genetically modified diabetic rodents such as Zucker and Wistar Kyoto rats that are hyperinsulinemia and hyperglycaemic [87] [88]. A prolonged hyperglycaemic clamp at 200 - 250 mg/dl does not alter the expression of GLUT2 in β-cells from standard rat chow-fed rats [89]. This suggests that even a mild hyperglycaemia in HFD fed animals down-regulates the GLUT2 gene expression independent on the level of plasma insulin. Factors suppressing GLUT2 expression in HFD rats are yet to be defined. Nevertheless, even a reduction of more than 90% of the glucose transporter cannot exert any physiological effect on the glucose metabolism in β-cells

[16] and certainly also on STZ action. Glucose transporter 2 is therefore not a contributing factor to the STZ influence. The evidence for the extreme susceptibility of β-cells to STZ in HFD-fed rats appears to depend on their cytoplasmic metabolic byproducts such as nitric oxide (NO) and/or reactive oxygen species (ROS).

5.4. Intracellular Fate of Streptozotocin

Although the exact cytotoxic molecular mechanism of the diabetogenic action of STZ is unclear, the process is well-known to be associated with four major synergistic biochemical pathways via its nitrosourea moiety [90] [91]. Firstly, carbamoylation and alkylation of cellular components, secondly, the release of NO, thirdly, the generation of free radicals, and oxidative stress, and lastly, the inhibition of O-GlcNAcase [19].

Once inside the cell, STZ is able to decompose spontaneously to form an isocyanate molecule and a methyldiazohydroxide molecule [64] [92] (**Figure 3**). Methyldiazohydroxide in turn splits to form a highly reactive carbonium ion (CH3+) which is considered a key player in DNA alkylation induced by STZ. Carbonium ions cause cross-linking of interstrand DNA. Streptozotocin DNA methylation is initiated at the position O6 of guanine, a reaction which interferes with hydrogen bonding and allows guanine to mis-pair with thymine. This replacement of molecules causes a point of mutation leading to DNA damage [18] [93] [94].

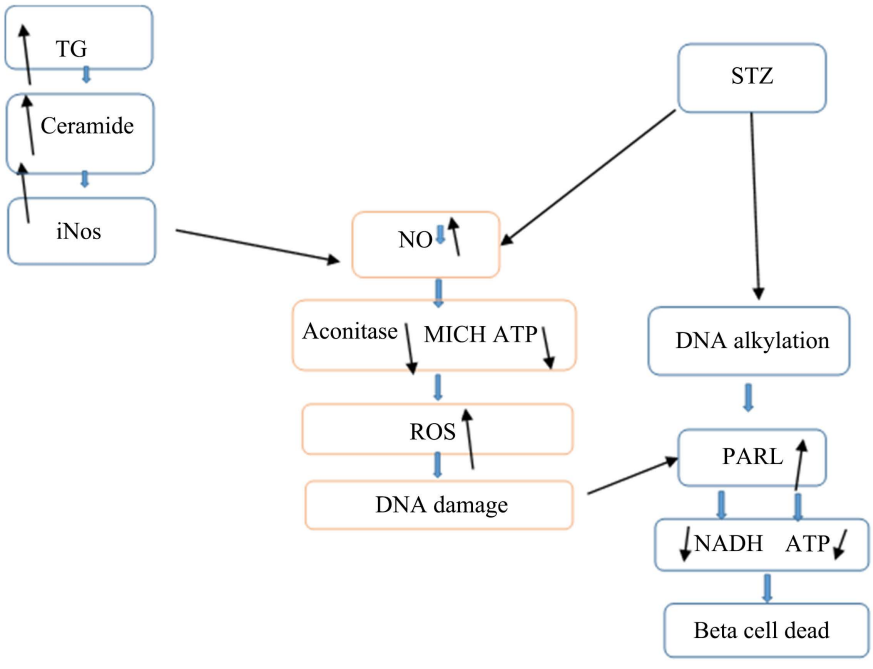

Figure 3. Intracellular metabolic pathways of triglycerides and Streptozotocin (STZ) in pancreatic β cells: both molecules release nitride oxide (NO), which remains the toxic combining element responsible for the rapid beta cells death in obese animals adapted from [16] .

DNA damage caused by STZ-mediated alkylation is repaired by an excision repair process, which requires activation of NAD-dependent enzyme-dependent poly (ADP-ribose) synthetase (PARP) [93]. The over activation of PARP depletes the nicotinamide adenosine dinucleotide (NAD), the main source of intracellular energy and Adenosine triphosphate (ATP) stores leading to pancreatic β-cell necrosis [91] [94]. Although STZ also methylates cytoplasmic proteins, the main cause of β-cell necrosis is in the process of methylation of DNA. A treatment with nicotinamide, also an inhibitor of PARP before the induction of STZ in experimental rats prevents the damage of DNA, and thus protects β-cells from STZ toxicity [94] [95].

The cytoplasmic metabolism of STZ also liberates NO in the targeted cells without the intervention of NO synthase [95] [96]. After two hours of STZ injection, NO release is observed in β-cells of the rat pancreas [16] [97] [98]. Nitric oxide is a free radical discovered in 1772 by Joseph Priestly [95] [96] [99], and is normally synthesised from the enzymatic oxidation of L-arginine to citrulline [95] [99]. Easily transported through biological lipid membranes [95] [100], NO is present in various tissue cells of the body, particularly in endothelial cells (ECs) where its main function is to regulate mitochondrial respiration [98]. In the aqueous medium, NO rapidly binds to oxygen (O_2) and is converted to nitrite [95] [99] [100]. Nitrite acts as a signaling metabolic molecule in several physiological processes [16] [99] [100] [101] [102] and may also participate in cellular toxicity because of its ability to bind to, and inactivate, mitochondrial iron-containing enzymes such as aconitase, involved in the Krebs cycle [103].

The biological action of STZ as a NO donor depends on the amount and duration of NO released [16] [95]. In the presence of a high concentration of NO, as in the case of STZ in the targeted cells, the continuous inactivation of these enzymes (involved in the Krebs cycle) leads to the reduction of intracellular respiration creating a pseudo hypoxia, thus facilitating cell death [16] [81] [95]. Although not the only molecule responsible for β-cell toxicity, NO is said to contribute to DNA damage leading to β-cell death in humans and rodents [21] [81]. It is interesting to note that this process can also be avoided by NO scavengers [21], unfortunately reduced in β-cells [95]. Nitric oxide acting this way contributes in the cascade of cytoplasmic reactions, leading to the formation of free radicals [81]. Streptozotocin reduces the mitochondrial oxygen consumption which in turn reduces ATP mitochondrial production within the β-cells. The reduction of ATP production leads to the depletion NAD [104] [105]. The excessive dephosphorylisation of ATP produces a large amount of substrate to the activity of xanthine oxidase in pancreatic β-cells, causing the formation of uric acid as a by-product of ATP degradation of superoxide anion. Superoxide anion and NO are free radicals carrying unpaired electrons, which for stability, must react with other unpaired electron molecules (other free radicals). The formation of these anions generates hydrogen peroxide and hydroxyl radicals (ROS) [104] [105]. Thus, pre-treatment of β-cells with xanthine oxidase inhibitor allopurinol

limits the toxic effect of STZ on β-cells [104] [105]. Free radical production at the early stages of STZ-induced diabetic rats causes oxidative stress [106] [107].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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