International Journal of Pharmacological Research
ISSN: 2277-3312 (Online)
Journal DOI: https://dx.doi.org/10.7439/ijpr **Review Article**

Streptozotocin is more convenient than Alloxan for the induction of Type 2 diabetes

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***Article History:**
Received: 31/12/2016
Revised: 14/01/2017
Accepted: 14/01/2017
DOI: https://dx.doi.org/10.7439/ijpr.v7i1.3790

Abstract

Alloxan as well as Streptozotocin tend to be toxic glucose analogues which preferentially build up in pancreatic beta tissue via the actual GLUT2 glucose transporter. Alloxan as well as Streptozotocin would be the most notable diabetogenic chemical substances in diabetes investigation. Both tend to be cytotoxic glucose analogues. Even though their cytotoxicity is actually achieved by way of different paths, their systems of beta cellular selective motion are similar. In 1838, Wohler as well as Liebig synthesized the pyrimidine type, which these people later known as alloxan. Within 1943, alloxan grew to become of curiosity about diabetes investigation when Dunn as well as McLetchie reported it could stimulate diabetes within animals due to the particular necrosis from the pancreatic beta tissue. The ensuing insulinopenia causes a situation of fresh diabetes mellitus known as 'alloxan diabetes. Streptozotocin (STZ) was isolated through *Streptomyces achromogenes* within 1960, Streptozotocin is definitely an antimicrobial agent and it has also already been used like a chemotherapeutic alkylating agent. In 1963, Rakieteneting reported which Streptozotocin is actually diabetogenic. Once again, this insulinopenia affliction, called 'Streptozotocin diabetes' is brought on by the particular necrosis from the pancreatic beta tissue and Streptozotocin may be the agent of preference for the actual induction associated with diabetes mellitus within animals since. STZ is actually preferred compared to Alloxan in order to induce diabetic rat because of its higher inductive price and reduce toxicity. STZ is much better especially whenever inducing DM2, STZ as well as nicotinamide may be used within recent functions. The fatality rate associated with alloxan is actually high and result in a high reduction in bodyweight. In this short article we may demonstrates using STZ is actually more security and handy than using Alloxan for that induction associated with diabetes mellitus 2.

Keywords: Type 2 diabetes, Streptozotocin diabetes, Alloxan diabetes.

1. Introduction

Type 2 diabetes is growing in prevalence worldwide which is strongly associated with being overweight and insulin resistance [1]. You will find 95 percent of those individuals belonging to type 2 diabetes. Therefore, it is excellent urgency to find much better treatments and novel prevention techniques for type 2 diabetes. To do this goal, appropriate experimental models are thought as essential tools with regard to understanding the molecular foundation, pathogenesis of the vascular as well as neural lesions, actions associated with therapeutic agents, and genetic or environmental influences that boost the risks of type two diabetes. Many studies have reported how the rats fed with higher fat diet (HFD) develop insulin resistance although not frank hyperglycemia or diabetes. It is suggested how the HFD might be an easy method to initiate the insulin resistance which is among the important features of type 2 diabetes [2]. Simultaneously, Streptozotocin (STZ) is popular to reproducibly induce each insulin-dependent and noninsulin dependent diabetes mellitus at present by inducing β cellular death through alkylation associated with DNA. Although high-dose STZ seriously impairs insulin secretion mimicking type 1 diabetes, low-dose STZ has already been known induce a moderate impairment of insulin secretion which is comparable to the feature of the actual later stage of type 2

diabetes. Therefore, investigators have begun to develop a rat design by feeding.

The animal with high-fat diet following low-dose STZ that would closely mimic the natural history of the disease events (from insulin resistance to β cell dysfunction) as well as 2 Experimental Diabetes Research metabolic characteristics of human type 2 diabetes [3]. On the other hand, Alloxan cannot be used to induce T2DM. Some available models include fructose-fed, high fat diet fed followed by a low dose of STZ and STZ/Nicotinamide. It is also understood that alloxan-induced diabetic model does not exactly simulate the human type 2 diabetes mellitus [4].

2. Streptozotacin

Streptozotocin is actually naturally occurring chemical; accustomed to produce Type- 1 diabetes within animal design and Type- 2 diabetes along with multiple low doses. It's also used within medicine with regard to treating metastatic most cancers of islets associated with Langerhans.

2.1 Streptozotocin: mechanism of action

Streptozotocin prevents insulin release and causes a situation of insulin-dependent diabetes mellitus. Each effect could be attributed in order to its particular chemical qualities, namely its alkylating strength. As along with alloxan, its beta cellular specificity is principally caused by selective mobile uptake as well as accumulation. ROS regarding alloxan as well as DNA alkylation regarding Streptozotocin mediate the actual toxic motion.

2.2 Beta cell selectivity of Streptozotocin:

Streptozotocin is really a nitrosourea analogue where the N-methyl-N-nitrosourea (MNU) moiety is actually linked towards the carbon-2 of the hexose. Nitrosoureas are often lipophilic as well as tissue uptake with the plasma membrane layer is quick, Streptozotocin is actually less lipophilic as well as selectively gathered in pancreatic beta tissue via the actual low-affinity GLUT2 sugar transporter within the plasma membrane [5,6]. Therefore, insulin-producing cells that not convey this sugar transporter tend to be resistant in order to Streptozotocin [7,8]. This declaration also explains the higher toxicity associated with Streptozotocin in contrast to N-methyl-N-nitrosourea within cells which express GLUT2, despite the fact that both ingredients alkylate DNA to some similar degree [9-11]..

2.3 Beta cell toxicity of Streptozotocin

It's generally assumed how the toxicity associated with streptozotocin depends upon the DNA alkylating exercise of its methyl nitrosourea moiety. The transfer of methyl group from Streptozotocin towards the DNA molecule leads to damage, fragmentation from the DNA [12]. Within the attempt to correct DNA, poly (ADP-ribose) polymerase (PARP) is actually over stimulated. This particular diminishes mobile NAD+, as well as subsequently ATP, stores [13]. The depletion from the cellular power stores ultimately leads to beta cellular necrosis. Even though Streptozotocin additionally methylate's meats, DNA methylation is actually ultimately accountable for beta cellular death, but chances are that proteins methylation plays a role in the practical defects from the beta tissue after contact with Streptozotocin [14,15]. The system of poisonous action is a result of alkylation, along with methylation associated with DNA angles being much more toxic compared to ethylation [16].

3. Alloxan

Alloxan is actually most notable chemical compound utilized in diabetogenic investigation. In research it's used with regard to induction associated with Type 1 diabetes. Alloxan is really a urea derivative which in turn causes selective necrosis from the β- tissue of pancreatic islets. It's been widely accustomed to induce fresh diabetes within animals for example rabbits, rodents, mice as well as dogs along with different levels of illness severity through varying the actual dose associated with alloxan utilized. Alloxan was made by the oxidation of uric acid by nitric acid and also the monohydrate form is simultaneously prepared by oxidation of barbituric acid by chromium trioxide. The drug may be noted in order to its diabetogenic motion when given parenterally, i.e., intravenously, intraperitoneally or even subcutaneously. The dosage of alloxan necessary for inducing diabetes depends upon the animal as well as route of supervision.

3.1 Beta cell toxicity and diabetogenicity of alloxan

Alloxan may generate reactive oxygen species (ROS) inside a cyclic reaction using its reduction item, dialuric acidity. In the actual beta tissue the poisonous action associated with alloxan is actually initiated through free radicals formed with this redox response. Autoxidation associated with dialuric acidity generates superoxide radicals as well as hydrogen peroxide and within the Fenton reaction within the presence of the suitable steel catalyst (typically iron) hydroxyl radicals. The autoxidation associated with dialuric acidity involves the actual intermediate formation from the alloxan revolutionary. The reduction of alloxan in order to dialuric acid within the cell demands the presence of the suitable thiol, often the tripeptide glutathione (GSH) to create the redox cycling partner, dialuric acidity, and oxidized glutathione[17,18].

Schematic representation of the toxic effects of the glucose analogues alloxan and Streptozotocin in beta cells, which produce chemical diabetes [19]

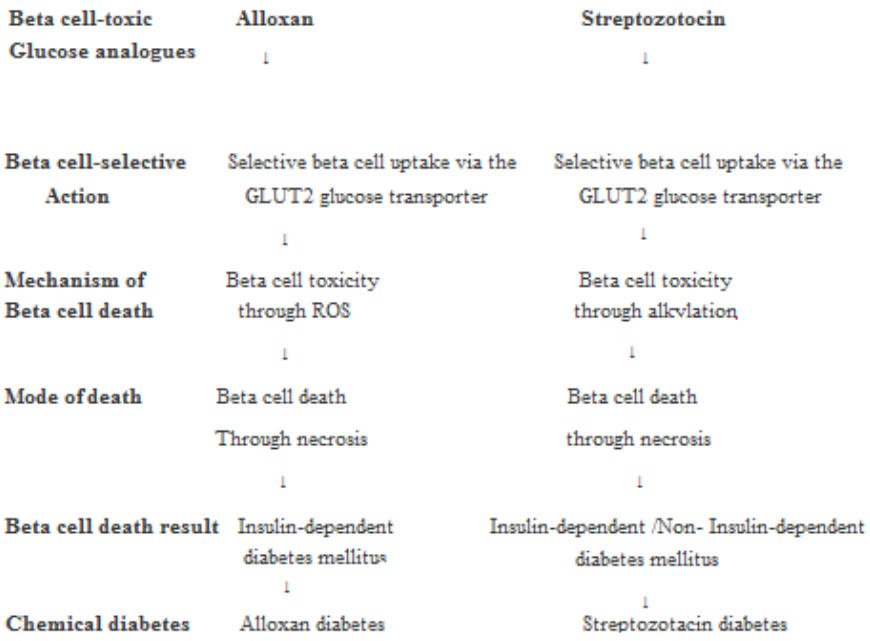

Table 1: Comparison of the chemical properties of Alloxan and Streptozotacin

	Alloxan	Streptozotocin
Chemical name	2,4,5,6-Tetraoxypyrimidine; 2,4,5,6-pyrimidinetetrone	2-Deoxy-2-([(methylnitrosoamino)carbonyl]amino)-D-glucopyranose
Chemical structure	Oxygenated pyrimidine derivative; barbituric acid derivative (5-ketobarbituric acid)	Cytotoxic methylnitrosourea moiety (*N*methyl-*N*-nitrosourea) attached to the glucose (2-deoxyglucose) molecule; glucosamine derivative
Chemical properties	Very hydrophilic, beta cell-toxic glucose analogue (partition coefficient –1.8); weak acid	Hydrophilic, beta cell-toxic glucose analogue
Chemical reactivities	Thiol reagent that is reduced to dialuric acid in the presence of GSH and other thiols	DNA alkylating agent
Mode of toxicity	Generation of ROS	DNA alkylation

4. Streptozotacin is more convenient than alloxan for the induction of diabetes

STZ is actually preferred chemical agent to stimulate experimental diabetes because it has a few advantages more than ALX for example, longer half-life (15 min), sustained hyperglycemia with regard to longer duration and also the development associated with well characterized diabetic problems with less incidences associated with ketosis in addition to mortality [20]. Alloxan not just has poisonous effects upon islets associated with Langerhans, but additionally affect additional body internal organs. It generally produces serious diabetes. Streptozotocin is actually more particular to beta cells instead of alloxan. STZ is much better especially whenever inducing DM 2, STZ as well as nicotinamide may be used within recent functions. Rats along with T1DM caused by ALX offered biochemical modifications in bloodstream and morphological as well as ultra-structural lesions within the liver which largely was similar to chronic lean meats disease within humans. Liver modifications ranged in the fatty deterioration of lean meats cells in order to steatohepatitis as well as periportal fibrosis. ALX altered the standard pathways associated with cellular metabolic process, including the actual inactivation associated with certain nutrients, which resulted in liver harm and passing away [21].

5. Multiple Low-Doses Streptozotocin Induced Type 2 Diabetes Rat Model

Numerous studies possess reported how the rats given with high fat diet plan (HFD) create insulin resistance although not frank hyperglycemia or even diabetes [22-24]. It is actually suggested how the HFD may be an easy method to start the insulin opposition which is among the important options that come with type two diabetes. Simultaneously, Streptozotocin (STZ) is popular to reproducibly stimulate both insulin-dependent as well as non-insulin resistant diabetes mellitus at present by causing β cellular death via alkylation associated with DNA. Even though high-dose STZ seriously impairs insulin release mimicking kind 1 diabetes, low-dose STZ may be known in order to induce the mild disability of insulin release which is comparable to the feature from the later phase of kind 2 diabetes [25,26]. Consequently, investigators have begun to develop the rat design by feeding your pet with high-fat diet plan following low-dose STZ that could closely imitate the organic history from the disease occasions (from insulin opposition to β cellular dysfunction) in addition to metabolic features of human being type two diabetes. The objective of the existing study would be to develop a suitable, stable pet model that is analogous towards the human kind 2 diabetes mellitus through a mix of high-fat diet plan with several low-dose STZ shots. As an effect, we give a suitable pet model to comprehend the feasible cellular as well as molecular systems of kind 2 diabetes.

Table 2: The doses of various chemical diabetogens (Alloxan and STZ) in different species

Chemicals	Species	Dose (s) (in mg/kg)	References
Alloxan	Rat	40-200 (iv or ip)	[27-30]
	Mice	50-200 (iv or ip)	[27, 29, 31]
	Rabbit	100-150 (iv)	[27, 32]
	Dog	50-75 (iv)	[25, 33]
Streptozotocin	Rat	35-65 (iv or ip)	[27, 29,34,35]
	Mice	100-200 (iv or ip)	[27,29,34,38]
	Hamst	50 (ip)	[39
	Dog	20-30 (iv)	[29, 38]
	Pig	100-15(iv)	[38, 40, 41]
	Pmates	50-150(iv)	[38, 41, 42]
IV intravenous; IP, Intraperitoneal			

Table 3: Classification of type 2 diabetes in animals

Animals Model category	Obese	Non obese
Spontaneous or Genetically derived diabetic animals	ob/ob mouse db/db mouse KK mouse NGO mouse NONcNZO10 mouse TSOD mouse M16 mouse Zucker fatty rats ZDF rats SHR/N-cp rats JCR/LA-cp rats OLETF rats Obese rhesus monkey	Cohen diabetic rat GK rats ALS/Lt mouse
Diet/nutrition induced diabetic animals	Sand rats C57/BL 6J mouse Spiny mouse	
Chemically induced diabetic animals	GTG treated obese mice	Low dose ALX or STZ adult rats, mice, *etc*. Neonatal STZ rat
Surgical diabetic Animals	VMH lesioned dietary obese diabetic rat	Partial pancreatectomized animals *e.g.* dog, primate, pig & rats
Transgenic/knock-out involving diabetic animals	B3 receptor knockout mouse Uncoupling protein (UCP1) knock-out mouse	Transgenic or knockout mice genes of insulin and insulin receptor and its components of downstream insulin signaling *e.g.* IRS-1, IRS-2, GLUT-4, PTP-1B and others. PPAR-γ tissue specific Knock out mouse. Glucokinase or GLUT 2 gene knockout mice. Human iselts amyloid polypeptide rat

KK, Kuo Kondo; KK/Ay, yellow KK obese; VMH, ventromedial hypothalamus; ZDF, Zucker diabetic fatty; NZO, New Zealandobese; TSOD, Tsumara Suzuki obese diabetes; SHR/N-cp, spontaneously hypertensive rat/NIH-corpulent; JCR, James C Russel; OLETF, Otuska Long Evans Tokushima fatty; GTG, gold thioglucose; ALX, alloxan; STZ, Streptozotocin; GLUT-, glucose transporter; IRS, insulin receptor substrate; GK, Goto-Kakizaki; PPAR, Peroxisome proliferator activated receptor, PTP, phosphotyrosinephosphotase; ALS, alloxan sensitive

6. Conclusion

Each alloxan as well as Streptozotocin stimulate insulin insufficiency. While the actual mechanisms associated with beta cell-selective motion through uptake via the actual GLUT2 glucose transporter as well as beta cellular death by way of necrosis tend to be identical, ROS regarding alloxan as well as DNA alkylation regarding Streptozotocin mediate the actual toxic action of those glucose analogues. Type 2 diabetes mellitus precisely simulate the actual human type 2 diabetes mellitus. Nevertheless, n-STZ rat versions have a number of advantages within the other versions as referred to above and it is regarded as one from the suitable fresh animal types of Type two diabetes mellitus [43].

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