DIFFERENT MODELS USED TO INDUCE DIABETES: A COMPREHENSIVE REVIEW

VINEETA TRIPATHI, JANESHWER VERMA*
ITS Paramedical College, Muradnagar, Ghaziabad, Uttar Pradesh India.
Email : Vineeta.tripathi05@gmail.com
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ABSTRACT
Diabetes mellitus is a group of heterogeneous metabolic disorders. A large number of pharmacological agents and animal models are used in study of diabetes for understanding the pathogenesis, complications, genetic and environmental influences. Animal models for type 1 diabetes range from animals with spontaneously developing autoimmune diabetic to chemical ablation of the pancreatic beta cells and Type 2 diabetes is studied in both obese and non-obese animal models with varying degrees of insulin resistance and beta cell failure. In recent years, a large number of new genetically modified animals, chemical agents, surgical manipulations, viruses and diabetogenic hormones have been engineered for the study of diabetes.

Keywords: Diabetes Mellitus, Chemical Agents, Surgical Manipulation, Diabetogenic Hormones.

INTRODUCTION
Diabetes mellitus is group of metabolic disorders characterised by hyperglycemia, glycosuria and hyperlipaemia. Diabetes was affected approximately 177 million people worldwide in year 2000 and it is expected to increase up to 300 million till year 2025 [1]. Diabetes is not a single disease it's group of heterogeneous syndromes such as heart attack, stroke and peripheral vascular disease [2]. Diabetes mellitus is divided into four categories –

Type-1 diabetes
Type-1 diabetes is also called insulin dependent diabetes mellitus because this disease is characterised by an absolute deficiency of insulin. Beta cells are destructed due to invasion by virus, action of chemical toxins or due to action of autoimmune antibodies. This beta cell necrosis is causes insulin deficiency and caused Type-1 diabetes [3].

Type-2 diabetes
Non-insulin dependent diabetes mellitus or Type-2 diabetes is frequently accompanied by target organ insulin resistance that limits responsiveness to both endogenous and exogenous insulin [4].

Type-3 diabetes
This type of diabetes is caused by chronic pancreatitis or chronic drug therapy with glucocorticoids, thiazides diuretics, diazoxide, growth hormone and with some protease inhibitors (e.g. saquinavir).

Type-4 diabetes
This type of diabetes is observed in approximately 4-5% of all pregnancies, due to placental hormones that promotes insulin resistance [5].

For more study about diabetes, rodents such as rat, mouse, hamster, guinea pigs and the rabbits are suitable models. They are used for natural development of study. At present time best and quickest way to induce diabetes is with use of chemicals (alloxan, streptozotocin, dithizone, monosodium glutamates etc.), viruses and genetically diabetic rats. In recent years, scientists and technologists have worked toward refining techniques that have led to the discovery of chemical agents that pharmacologically alter the function of the pancreas. The main advantage of using such chemicals is that body changes during and after the induction of diabetes can be observed. The five major diabetogenic agents are chemicals, biological agents, peptides, potentiators, and steroids but most commonly used chemicals agents are alloxan and streptozotocin [6].

Chemical Causes of Diabetes
Alloxan
Alloxan is most prominent chemical compound used in diabetogenic research. In research it is used for induction of Type 1 diabetes. Alloxan is a ura derivative which causes selective necrosis of the β-cells of pancreatic islets [7]. It has been widely used to induce experimental diabetes in animals such as rabbits, rats, mice and dogs with different grades of disease severity by varying the dose of alloxan used [8].

Chemical Properties
• The chemical name of alloxan is 2,4,5,6 tetraoxypyrimidine; 2, 4, 5, 6- pyrimidinetrone, which is an oxygenated pyrimidine derivative which is present as alloxan hydrate in aqueous solution [9].
• Alloxan was prepared by the oxidation of uric acid by nitric acid and the monohydrate form is simultaneously prepared by oxidation of barbituric acid by chromium trioxide. The drug has been noted to its diabetogenic action when administered parenterally, i.e., intravenously, intraperitoneally or subcutaneously. The dose of alloxan required for inducing diabetes depends on the animal species and route of administration [10]. Moreover, alloxan has been demonstrated to be non-toxic to the human beta-cells, even in very high doses, because humans have different glucose uptake mechanisms as compared to rodents [11,1,12].

Phases of diabetes induction
Alloxan induces triphasic blood glucose response when injected into experimental animals. The first phase that comes within the first minutes after alloxan administration is transient hypoglycemic phase that lasts maximally for 30 minutes [13,14]. In this little phase hypoglycemic response has been noted to be result of stimulation of insulin secretion that increases the concentration of insulin in plasma. The mechanism behind the first phase of this hyperinsulinemia may be a temporary increase in ATP availability due to inhibition of glucose phosphorylation through glucokinase inhibition [15].

The second phase appears after 1 hour of administration of alloxan and leads to rise in blood glucose concentration. Moreover, the plasma insulin concentration decreases at the same time. This is the first hyperglycemic phase for 2-4 hours, after the first contact of the pancreatic beta cells with the toxin. This hyperglycemic phase is result of inhibition of insulin secretion from the pancreatic beta cells, due to their beta cell toxicity [16,17].

The third phase is again a hypoglycemic phase i.e. for 4-8 hours after the alloxan injection, which lasts for several hours. Changes occur during this phase are irreversible [18,19].
Mechanism of action

Alloxan treatment evokes a sudden rise in insulin secretion in the presence or absence of glucose and this insulin release occurs for short duration followed by the complete suppression of the islet response to glucose even when high concentrations of glucose were used [20,21]. Further, important feature of alloxan action in pancreas is preceded by its rapid uptake by pancreatic beta cells. Moreover, in pancreatic beta cells, the reduction process occurs in the presence of reducing agents like reduced glutathione (GSH), cysteine, ascorbate and protein-bound sulphydryl (-SH) groups [22,23]. Alloxan reacts with two -SH groups in the sugar binding site of glucokinase and results in inactivation of the enzyme. As a result diacetyl acid is formed which is then re-oxidized back to alloxan establishing a redox cycle and generates reactive oxygen species (ROS) and superoxide radicals [24,25]. The superoxide radicals liberate ferric ions from ferritin and reduce them to ferrous and ferric ions and also undergo dismutation to yield hydrogen peroxide (H2O2). As a result, highly reactive hydroxyl radicals are formed in the presence of ferrous and H2O2. Another mechanism that has been reported is the effect of ROS on the DNA of pancreatic islets. In the beta cells alloxan causes DNA fragmentation and damage. Antioxidants like superoxide dismutase, catalase and the non enzymatic scavengers of hydroxyl radicals have been found to protect against alloxan toxicity [26]. In addition cytosolic free elevated Ca2+ has also been reported to constitute an important step in the diabetogenic action of alloxan. The calcium influx results from the ability of alloxan to open voltage dependent calcium channels and enhances calcium entry into pancreatic cells. The increased concentration of Ca2+ ion further contributes to supraphysiological insulin release that along with ROS eventually causes damage of beta cells of pancreatic islets [27].

Streptozotocin (STZ)

Streptozotocin is naturally occurring chemical; used to produce Type-1 diabetes in animal model and Type-2 diabetes with multiple low doses. It is also used in medicine for treating metastatic cancer of islets of Langerhans [28].

Chemical Properties

- Streptozotocin is a monofunctional nitrosurea derivative [29].
- First isolated from Streptomyces achromogenes [30].
- It has been used alone or in combination with other chemotherapeutic drugs (vincristine, 5-fluorouracil, methyl-CCNU, procarbazine and 6-thioguanine) for the treatment of colorectal chemotherapeutic drugs (vincristine, 5-fluorouracil, methyl-CCNU, etc.).
- Streptozotocin enters the pancreatic cell via a glucose transporter–GLUT2 (Glucose transporter 2) and causes alkylation of DNA. Further STZ induces activation of poly adenosine diphosphorylation and nitric oxide release, as a result of STZ action, pancreatic –cells are destroyed by necrosis and finally induced insulin dependent diabetes [35,36].

Mechanism of Action

Streptozotocin prevents DNA (Deoxyribonucleic acid) synthesis in mammalian and bacterial cells, in the bacterial cells; it renders special reaction with cystine groups, resulting in degeneration and destruction of DNA. The streptozotocin enters the pancreatic cell via a glucose transporter–GLUT2 (Glucose transporter 2) and causes alkylation of DNA. Further STZ induces activation of poly adenosine diphosphorylation and nitric oxide release, as a result of STZ action, pancreatic –cells are destroyed by necrosis and finally induced insulin dependent diabetes [35,36].

Dithizone

Dithizone induced the symptoms of diabetes in cats, rabbits, golden hamsters and in mice. In dithizonised diabetic animals, the levels of serum zinc, iron, and potassium were found to be higher than normal but copper and magnesium levels were unchanged. After treatment with insulin, most of these serum levels were normal, except for serum potassium and magnesium [37].

Chemical Properties

- Chemical name of dithizone is 8-(p- toluene- sulfonylamino)–quinoline (8-TSQ).
- Dithizone is an organosulphur compound that acts as a chelating agent and forms complexes with lead, zinc and mercury.
- It is used to assess the purity of human pancreatic islet preparations used for transplantation into patients with type 1 diabetes [38].
stimulation of resting auto reactive T cells, further indicating that the islet antigen sensitization is an indirect consequence of the viral infection [47,48].

Hormone Induced Diabetes

Growth hormone induced diabetes

Growth hormone has long distinguished history in diabetes, with possible participation in the development of renal complications [49]. Repeated administration of growth hormone in cats and adult dogs induces diabetes with all symptoms of diabetes including severe ketonuria and ketonemia. More prolonged administration of growth hormone produced permanent diabetes, there was loss of pancreatic islets tissues and of beta cells and only traces of insulin could be extracted from pancreas [50].

Corticosteroid induced diabetes

Corticosteroid used to reduce inflammation can lead to diabetes, which is called steroid diabetes. The most common glucocorticoids which cause steroid diabetes are prednisolone and dexamethasone. Glucocorticoids oppose insulin action and stimulate gluconeogenesis, especially in the liver, resulting in a net increase in hepatic glucose output and induce insulin resistance, hyperglycemia, and hyperlipidemia [51].

CONCLUSION

2.8 % population suffers from diabetes throughout the world. To this end, the study on delayed type 1 diabetes mellitus in human could be extracted from pancreas [50].

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