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Review Article

DIFFERENT MODELS USED TO INDUCE DIABETES: A COMPREHENSIVE REVIEW

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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 2diabetes 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 disese 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 –1diabetes is also called insulin dependent diabetes mellitus because this disese 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, thiazids 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 physiologically 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 urea 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-pyrimidinetetrone, 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 [11,12].

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 sulfhydryl (-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 dialuric 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 Ca^{2+} 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 Ca^{2+} 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 nitrosourea 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 carcinomas and other gastrointestinal cancers, but severe toxicity and myelosuppression were observed in most of the patients[31,32,33].
- Streptozotocin has broad spectrum antibiotic activity[34].

Mechanism of Action

Streptozotocin prevents DNA (Deoxyribonucleic acid) synthesis in mammalian and bacterial cells, in the bacterial cells; it renders special reaction with cytosine 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 diphoshate ribosylation 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 organosulfur 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 1diabetes [38].

Mechanism of Action

Zinc-chelating agent such as dithizone is causes diabetes in laboratory animals. Dithizone has abilities to permeate membranes and to complex zinc inside liposomes with the release of protons, that can enhance diabetogenicity. When such complexing agents are added to lipid vesicles at pH 6 containing entrapped zinc ions, they acidify the contents of these vesicles. Such proton release occurs within the zinc-containing insulin storage granules of pancreatic beta-cells; solubilisation of insulin would be induced which leads to osmotic stress and eventually the granule rupture and finally diabetes is induced [39].

Gold thioglucose

Gold thioglucose is diabetogenic compound, which is induced hyperphagia and severe obesity induced Type -2 diabetes.

Chemical Properties

- It is derivative of sugar glucose.
- Gold thioglucose is precipitated with methanol and recrystallized with water and methanol.

Mechanism of Action

Gold thioglucose developed obesity induces diabetes in genetically normal mouse strains. Gold thioglucose treated DBA/2 (Dilute Brown Non- Agouti), C57BLKs, and BDF1 mice gained weight rapidly and significantly increase non fasting plasma glucose level within 8-12 weeks. These mice showed impaired insulin secretion, mainly in early phase after glucose load and reduced insulin content in pancreatic islets [40]**.**

Monosodium glutamate

Monosodium glutamate induces Type -2 diabetes without polyphagia.

Chemical Properties

- It is most abundant naturally occurring non- essential amino acid.
- Freely soluble in water.

Mechanism of Action

Monosodium glutamate causes a very large insulin response after ingestion. It is developed glycosuria in both male and female mice but not induced polyphagia. Within 29 weeks level of glucose concentration in blood, total cholesterol and triglyceride were higher [41].

Virus Induced Diabetes

Juvenile- onset diabetes mellitus may be due to virus infections and beta- cell specific autoimmunity [42]. In 1960s Gamble and co –workers reported newly diagnosed juvenile- onset diabetes (Type-1) due to viral infections. At present time two viruses are reported first is D- variant of encephalomyocarditis (EMC-D) and another is Coxsackie virus [43].

D- Variant Encephalomyocarditis

EMC- D virus can infect and destroy pancreatic beta cells in certain inbred strains of mice and produce insulin dependent hyperglycemia [44]. Pre-treatment with a potent immunosuppressive drug, cyclosporine-A increases severity and incidence of diabetes in ICR Swiss mice [45]. In 1992 Utsugi et al demonstrated the clone of EMC-D virus known as NDK25. Intraperitoneal injection of NDK25 develops non- insulin dependent diabetes mellitus [46].

Coxsackie Viruses

Coxsackie viruses are also a possible cause of diabetes in mice; it can infect and destroy pancreatic acinar cells while leaving the adjacent islets of Langerhans intact. Coxsackie B4 virus is strongly associated with the development of insulin-dependent diabetes mellitus in humans. Diabetes induced by Coxsackie virus infection is a direct result of local infection leading to inflammation, tissue damage, and the release of sequestered islet antigen resulting in the re-

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 dexamathasone. 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 reduce this data, many antidiabetic drugs are used and research is going on for more effective anti-diabetic drugs. For study on diabetes, many diabetic models, chemicals and diabetogenic hormones are used at research level. In this review we give an overview of models used to induce diabetes, their chemical properties and mechanism of action. Conclusively many animal models are used to induce diabetes, which further help in the study of development and screening of new anti- diabetic drugs.

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