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DIABETES AND METHODS TO INDUCE EXPERIMENTAL DIABETES

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Review Article

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ABSTRACT

Diabetes mellitus has become a problem of great magnitude and a major public health concern. Studies have demonstrated that, in some countries, diabetes affects up to 10% of the population aged 20 years and older. The disease develops if the pancreas does not make enough insulin or the cells in the muscles, liver and fat do not use insulin properly, or both. Several experimental models of human disease are used to study pathophysiological factors involved in diabetes and to assess antihyperglycemic agents. Today different strains of rats are available and in most laboratories, therapeutic studies on diabetes are carried out on these models.

KEYWORDS: Antihyperglycemic, Diabetes, experimental models.

Introduction

Diabetes is a disease in which levels of blood glucose, also called blood sugar, are above normal. Over the passage of time, high blood glucose, also called hyperglycemia, damages nerves and blood vessels, which can lead to complications such as heart disease, stroke, kidney disease, blindness, nerve problems, gum infections, and amputation. It is a fast growing medical problem in affluent societies and critically attacks the metabolic activity of patient. It is a major crippling disease in the world leading to huge economic losses (Harsh M., 2005; Goodman and gilman, 2006). In recent years, developed nations have witnessed an explosive increase in the prevalence of diabetes mellitus (DM) predominantly related to lifestyle changes and the resulting surge in obesity. In India, this disorder is on alarming condition as compared to most of the developed countries. Despite advances in understanding of the disorder and the management, the mortality and morbidity due to this disease is increasing (Dhanbal S.P., 2004).

DIFFERENT MODELS TO INDUCE EXPERIMENTAL DIABETES MELLITUS:

The various animal models for inducing diabetes are:

a) Alloxan induced diabetes

b) Streptozotocin induced diabetes

c) Other diabetogenic compounds

d) Pancreatectomy in dogs

e) Hormone induced diabetes

f) Insulin deficiency due to insulin antibodies

g) Virus induced diabetes

ALLOXAN INDUCED DIABETES:

Surveys on chemically induced diabetes in animals were given by Frerichs and Creutzfeldt (1968, 1971). Hyperglycemia and glucosuria after administration of alloxan has been described in several species by different researchers, such as in dogs (Brunschwig et al.

1943; Tasaka et al. 1988), in rabbits (Baily and Baily 1943), in rats (Dunn and McLetchie 1943; Goldner and Gomori 1944) and in other species (Frerichs and Creutzfeldt 1968, 1971). Dosage and treatment regimen have been elaborated for the most frequently used species. In most species a triphasic time course is observed: an initial rise of glucose is followed by a decrease, probably due to depletion of islets from insulin, again followed by a sustained increase of blood glucose. Rats, rabbits and dogs are mostly employed for alloxan induced diabetes model.

PROCEDURE:

Rabbits weighing 2.0 to 3.5 kg are infused via the ear vein with 150 mg/kg alloxan monohydrate (5.0 g/100 ml, pH 4.5) for 10 min resulting in 70% of the animals to become hyperglycemic and uricosuric. The rest of the animals either die or are only temporarily hyperglycemic (Baily and Baily 1943; Pincus et al. 1954; Bander et al. 1969). Rats of Wistar or Sprague-Dawley strain weighing 150–200 g are injected subcutaneously with 100–175 mg/ kg alloxan (Blum and Schmid 1954; Katsumata and Katsumata 1990; Katsumata et al. 1993). Male Beagle dogs weighing 15–20 kg are injected intravenously with 60 mg/kg alloxan. Subsequently, the animals receive daily 1000 ml 5% glucose solution with 10 IU Regular insulin for one week and canned

food ad libitum. Thereafter, a single daily dose of 28 IU insulin (Ultratard HM®) is administered subcutaneously (Brunschwig at al 1943; Geisen 1988).

STREPTOZOTOCIN INDUCED DIABETES

Rakieten et al. (1963) reported the diabetogenic activity of the antibiotic streptozotocin. The compound turned out to be specifically cytotoxic to beta-cells of the pancreas.

PROCEDURE:

Male Wistar rats weighing 150–220 g fed with a standard diet are injected with 60 mg/kg streptozotocin (Calbiochem) intravenously. As with alloxan, three phases of blood glucose changes are observed. Initially, blood glucose is increased, reaching values of 150–200 mg% after 3 hours. Six–eight hours after streptozotocin administration, the serum insulin values are increased up to 4 times, resulting in a hypoglycemic phase which is followed by persistent hyperglycemia. Severity and onset of diabetic symptoms depend on the dose of streptozotocin. After the dose of 60 mg/kg i.v., symptoms occur already after 24–48 hours with hyperglycemia up to 800 mg%, glucosuria and ketonemia. Histologically, the beta-cells are degranulated or even necrotic. A steady state is reached after 10–14 days allowing the use the animals for pharmacological tests.

OTHER DIABETOGENIC COMPOUNDS:

A number of other compounds have been found to induce symptoms of diabetes and/or obesity, such as dithizone (Maske and Weinges 1957; Frerichs and Creutzfeldt 1971; Hansen et al. 1989; Goldberg et al. 1991) or goldthioglucose (Stauffacher et al. 1967; Caterson et al. 1988; Silva and Hernandez 1989; Heydrick et al. 1995) or monosodium glutamate (Sartin et al. 1985). Rabbits, cats, golden hamsters and mice can be employed for this model.

PROCEDURE:

Goldberg et al. (1991) injected various chelators, such as dithizone, 8-(p-toluene-sulfonylamino)-quinoline (8-TSQ), and 8-(benzenesulfanylamino)-quinoline (8-BSQ) in a single i.v. dose of 40–100 mg/kg to cats, rabbits, golden hamsters and mice. Dithizone injection causes a triphasic glycemic reaction in rabbits. A phase of initial hyperglycemia is

detected after 2 hours, followed by a normoglycemic phase after 8 h and a secondary permanent hyperglycemic phase after 24–72 hours. Histologically, complete and partial degranulation of beta cells is observed.

PANCREATECTOMY IN DOGS:

Dysfunction of the visceral tract has been considered for a long time to be the cause of diabetes mellitus. Bomskov (1910) reported severe diabetic symptoms in dogs after cannulation of the ductus lymphaticus. This observation, however, could not be confirmed in later experiments (Vogel 1963). The technique was similar to that described by Gryaznova (1962, 1963) for ligation of the thoracic duct in dogs. Von Mehring and Minkowski (1890) noted polyuria, polydipsia, polyphagia, and severe glucosuria following removal of the pancreas in dogs. The final proof for the existence of a hormone in the pancreas was furnished by Banting and Best (1922) who could reduce the elevated blood sugar levels in pancreatectomized dogs by injection of extracts of the pancreatic glands. The role of the pituitary gland in development of diabetes has first been elucidated by Houssay (1930, 1931) in pancreatectomized dogs (Survey by Beyer and Schöffling 1986).

PROCEDURE:

Male Beagle dogs weighing 12–16 kg are used. The animal is anesthetized with an intravenous injection of pentobarbital sodium (50mg/ kg) and placed on its back. After removal of the fur and disinfection of the skin a midline incision is made from the xyphoid process reaching well below the umbilicus. Bleeding vessels are ligated and the abdomen is entered through the linea alba. The falciform ligament is carefully removed and the vessels ligated. A self-retaining retractor is applied. By passing the right hand along the stomach to the pylorus, the duodenum with the head of the pancreas is brought into the operating field. First, the mesentery at the unicate process is cut and the process itself is dissected free. The glandular tissue is peeled off from the inferior pancreatico-duodenal artery and vein. The vessels themselves are carefully preserved.

HORMONE INDUCED DIABETES:

Growth hormone induced diabetes:

Cotes et al. (1949) described the diabetogenic action of pure anterior pituitary growth hormone in cats. In intact adult dogs and cats the repeated administration of growth hormone induces an intensively diabetic condition with all symptoms of diabetes including severe ketonuria and ketonemia. Rats of any age subjected to a similar treatment do not become diabetic but grow faster (Young 1945) and show striking hypertrophy of the pancreatic islets.

Corticosteroid induced diabetes:

Ingle (1941) described hyperglycemia and glucosuria in forced fed rats treated with cortisone. In the guinea pig and in the rabbit, experimental corticoid diabetes could be obtained without forced feeding (Hausberger and Ramsay 1953; Abelove and Paschkis 1954). In the rat, the adrenal cortex, stimulated by corticotrophin, has the capacity to secrete amounts of steroids which induce steroid diabetes (Ingle et al. 1946).

INSULIN DEFICIENCY DUE TO INSULIN ANTIBODIES:

Bovine insulin, dissolved in acidified water (pH 3.0), is incorporated in a water-oil emulsion based on complete Freund's adjuvant or a mixture of paraffin oil and lanolin. A dose of 1 mg insulin is injected in divided doses subcutaneously to male guinea pigs weighing

300–400 gm. Injections are given at monthly intervals and the guinea pigs are bled by cardiac puncture two Weeks after the second and subsequent doses of antigen. It is possible to get 10 ml blood from every animal once a month. Intravenous injection of 0.25–1.0 ml guinea pig antiinsulin serum to rats induces a dose-dependent increase of blood glucose reaching values up to 300 mg%. This effect is unique to guinea pig anti-insulin serum and is due to neutralization by insulin antibodies of endogenous insulin secreted by the injected animal. In this way a state of insulin deficiency is induced. It persists as long as antibodies capable of reacting with insulin remain in the circulation. Slow rate intravenous infusion or intraperitoneal injection prolongs the effect for more than a few hours. However, large doses and prolonged administration accompanied by ketonemia, ketonuria, glucosuria, and acidosis are fatal to the animals. After lower doses, the diabetic syndrome is reversible after a few hours (Moloney and Coval 1955; Wright 1968).

VIRUS INDUCED DIABETES:

Juvenile-onset (type I) diabetes mellitus may be due to virus infections and β-cell specific autoimmunity (Craighead 1978). The D-variant of encephalomyocarditis virus (EMC-D) selectively infects and destroys pancreatic β-cells in susceptible mouse strains similar to human insulin-dependent diabetes (Yoon et al. 1980; Giron and Patterson 1982; Giron et al. 1983; Vialettes et al. 1983). Adult, male ICR Swiss mice are susceptible to the diabetogenic effect of the D-variant of encephalomyocarditis virus in contrast to adult C3H/HeJ male mice which are relatively resistant. Pretreatment with cyclosporin A, a potent immunosuppressive drug, results in increased severity and incidence of diabetes in susceptible ICR Swiss mice and induction of diabetes in resistant C3H/HeJ mice (Gould et al. 1985).

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