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Review

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Diabetic Complications in Experimental Models

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Abstract: In this review, the aim is to focus on diabetic complications in experimental models of diabetis. For this purpose, complications, chiefly seen in log-term periods in various systems of animals, such as cardio vascular and nervous systems, gastrointestinal, urogenital and respiratory tracts, etc., have been stated. Furthermore, novel and conventional therapeutic approaches in their management have also been briefly discussed.

Key Words: Diabetes, diabetic complications, animal models, insulin

Introduction

As a metabolic disease affecting a large population in various countries, mortality rate of diabetes mellitus have been largely reduced through the control of hyperglycemia by the development of potent antidiabetic substances (1), ultrapure recombinant human insulin (2) and new methods for insulin delivery (3). Consequently, mean life expectancy of diabetic patients has been increased especially in well developed countries (4). Despite these significant developments in antidiabetic therapy, diabetic complications chiefly seen in the long term are persistently deleterious to a large extent. While some of these complications are closely related to a lack of compliance during antidiabetic therapy, are apparant even with an optimal therapeutic regimen. Novel approaches in antidiabetic therapy are aimed not only to decrease high blood glucose levels, but also to eradicate long-term diabetic complications which may cause a diminished life expectancy and/or a poor quality of life.

Animal models of diabetes are increasingly being used in the investigation of etiopathogenesis of diabetes and long-term diabetic complicatins seen in clinical studies (5,6). to common models of diabetes used in biomedical studies have been established on chemically-induced and spontaneous (genetically-induced) diabetic animals. Both models with certain advantages and disadvantages have been used almost equally in the investigation of diabetic complications. Streptozotocin (STZ) (7) and alloxan (ALX) are the chemicals used to induce experimental diabetes, mostly in rodents. Administration of the chemicals to adult rats or mice results in a state resembling insulin-dependent (type 1) diabetes in human beings (7,8), whereas intraperitoneal injections of STZ (9,10) or ALX (11,12) produce a model for non-insulin-dependent (type 2) diabetes. BB (Bio Breed) (13), Cohen (14), Zucker (6) rats, ob/ob(db/db) (6,15), C57Bl/KsJdb(16) mice and Chinese hamsters (6) are among the mutant animals having various characteristics of human diabetes used for the investigation of diabetic complications. The main purpose of this review is to focus on diabetic complications in experimental models of diabetes and on the novel and conventional modalities used in their management.

Experimental Diabetic Complications

As in the case of clinical diabetes, experimental diabetic complications may be subdivided into the following classes: A) Neurological complications, B) Cardiovascular complications, C) Gastrointestinal complications, D) Urological complications, E) Respiratory complications, F) Ophthalmic complications, G) Reproductive complications, H)Haematological and biochemical complications, I) Complications related to Drug metabolism and pharmacokinetics. Most of these complications are closely related to the impairment in

smooth muscles as a result of experimental diabetes (17).

A) Neurological Complications

One of the most prevalent diabetic complications is neuropathy seen in 21% of diabetic patients (18). Diabetic neuropathy has also been observed in animal models. Diabetes may affect the autonomic, sensory and motor nerves and the central nervous system (19-22). Both morphological and functional changes due to experimental diabetes have been observed in the autonomic nervous system (19). Neuropathy is detectable in chemically-induced (19) and spontaneous (20,23) diabetes models. Development of this diabetic complication highly significant, since it causes various neuropsychiatric deficits and behavioural changes (24) and accelerates the development of complications such as cardiovas cular, gastrointestinal and urogenital complications (25-28). Changes in certain neurotransmitters have been reported in various animal models of diabetes. For example, altered β-endorphin, Met-and Leu-enkephalin levels in the pituitary (20) and changed noradrenaline and dopamine levels in adrenergic nerves (28,29) have been demonstrated in experimental diabetes. Impaired axoplasmic transport of noradrenaline in the sciatic nerve of spontaneously diabetic mice (30) and lower activities of monoamine oxidase and tyrosine hydroxlase in diabetic rat brains (31,32) seem to be closely related to the changes in neurotransmitter levels. The function of the sensory nerves is also impaired in experimental diabetes. STZ-induced diabetes attenuates opiate receptor mediated nociceptive reactions in mice (33). The potential for morphine dependence also seems to be lower in STZ-diabetic rats and spontaneously diabetic C57BL/ksjdb mice (34). Cellular ethiopathogenesis of diabetic neuropathy is not fully understood. There is however, a high likelihood that the causes such as lower Na, K-ATPase activities, impaired sorbitol metabolism, lower myo-inositol levels, neural ischaemia etc. may be involved in this pathology (21).

B) Cardiovascular Complications

As a long-term complication, cardiovascular diseases may be apparent in both diabetic patients and experimental animals. These complications are the most serious and commence one of the major causes of mortality causes due to diabetes. In log-term diabetic patients, cardiomyopathy and congestive heart failure may develop as a result of the impaired left ventricular function (35,36). The function of the coronary arteries in diabetic patiens is also impaired depending on the calcification of the arterial wall (37).The exact cause of the impaired left ventricular function is not known. However, animal experiments have revealed changes in myocardial β-adrenergic responsiveness. Both insulin-dependent 538-40) and noninsulin-dependent diabetes (12) may cause a decrease in myocardial contractility induced by adrenergic agonists. ınsulin replacement therapy of insulin-dependent diabetic rats corrects these changes (39,40). It has been suggested that thyroid hormones mediate the beneficial effect of insulin (39). In vitro insulin treatment is ineffective on the lower myocardial β-adrenergic responses (40). Treatment of non-insulin-dependent diabetic rats with the oral antidiabetic drug glyburide, also normalizes the reduced β-adrenergic responsiveness in the myocardium which may be a collective reason for the congestive heart failure seen in diabetes mellitus. α1-Adrenergic responsiveness of rat myocardium has been reported to be higher due to experimental diabetes (43,44) and partly reversed by insulin treatment (44). This increase may serve as a compensatory mechanism for the lower β-adrenergic responsiveness in this organ. A supersensitivity to muscarinic agonists has been also demonstrated in the myocardium in STZ-diabetic rats. This supersensitivity may be due to higher cholineacetyltransferase activity and choline concentration and lower cholinesterase activity in the myocardium (45,46). Inotropic responses of the myocardium to calcium have also been reported to be lower presumably due to a deficient calcium uptake of sarcoplasmic reticulum (387). Purinergic responses of rat atria seem to be higher in STZ-diabetes (47). The smooth muscles of blood vessels may be also affected depending on the experimental diabetes. The influence of diabetes on the catecholamine-induced vasopressor activity is contradictory. A lower responsiveness of the rat aorta to roradrenaline and phenylephrine has been noted in STZ diabetes and this change is reversed by insulin treatment (48,49). This observation has not been confirmed in the aorta of dibetic rabits (49) and, moreover, higher α-adrenergic responsiveness of the rat aorta has been reported in experimentally-induced diabetes (50,51). A lower prostacylin release in response to adrenaline has been observed in the aorta of STZ diabetic rats (52). Lower responsiveness of rat aorta to serotonin has been reported as well (49,53). Calcium and potassium-induced contractions of diabetic rat aorta are also lower suggesting a lower activity of calcium channels and/or a lower calmodulin level in this tissue (50,53-55). However, no change has been reported in the calcium channel activity of the aorta of STZ-diabetic rats (56)

and lower calmodulin levels in the aorta of long-term diabetic rats have been reported (57). Changes in the endothelial functions of arteries may also be significant in the development of vascular diabetic complications. Changes in the production of EDRF (Endothelium derived relaxing factor) have been reported to be in the arteries of both insulin-dependent and non-insulin-dependent diabetic rats (11,58,59). These changes are possibly the result of endothelial destruction which may be due to both atherosclerosis (60) and hyperglycemia (61). In addition, contractile responses of the aorta of diabetic rats to endothelin-1 (ET-1) have been found to be lower (55). Most of the changes described above may play a role as a compensatory mechanism rather than a pathological cause of the cardiovascular complications. In contrast, the increase in circulating endothelin levels (62), plasma angiotensin converting enzyme activity (63) and the decrease in circulating prostacyclin levels (64) have been reported. These changes seem to be the mechanisms responsible for diabetic cardiovascular complications. In addition, hypotensive responses of diabetic rats to isoprenaline (64) and the isoprenaline effect on the cerebral circulation of STZ diabetic rats (66) have been found to be lower.

C) Gastrointestinal Complications

Diabetic gastroenteropathy is one of the primary autonomic syndromes related to diabetes (67). Asymptomatic dilatation of the stomach (68) and impaired gastric acid secretion (69) in diabetic patients have been reported. In ALX diabetic rats, lower basal and histamine-induced gastric acid secretion has been demonstrated (70,71). By the application of advanced biostatistical methods (72,73), it has been establishad that both direct and indirect (vagally-induced) components of histamine-induced gastric acid secretion is lower in ALX diabetic rats (71). This observation confirms the dyspepsia seen in diabetic subjects. Attenuated responses of rat stomach fundus to serotonin has been observed (74-76). The lower responses to serotonin in rat stomach fundus may be an explanation for the asymptomatic dilatation of the stomach observed in diabetic patients. Another gastrointestinal diabetic complication is lower β-adrenergic responsiveness in this tract. Both ALX-and STZ-induced diabetes causes a decrease in β-adrenergic responses of rat duodenum (74). This decrease in β-adrenergic responses may be apparent not only in insulin-dependent diabetes but also in non-insulin-dependent diabetes(77). Lower β-adrenergic responses may be seen in almost every segment of the gastrointestinal tract (77,78). Similarly, contractile responses of jejunum to bradykinin and neurotensin in STZ diabetic rats have been found to be lower, while neurokinin A and B-induced contractions in this tissue have been shown to be higher due to diabetes (78). Contractile responses of gastrointestinal tract to acetylcholine and substance P have been reported to be lower in experimentally diabetic rats, as well (79). Calcium-irduced contractions of the intestine of ALX-diabetic rats have been shown to be lower (80). This lower responsiveness of rat intestine to calcium is attributable to a decrease in the calmodulin level in the smooth muscle (57,81). α-Adrenergic, but not cholinergic and purinergic responses of isolated ceacum of STZ diabetic rats have been reported to be higher (82). Megacolan (83) and increase in gastrointestinal motility (84) have been observed in STZ-diabetic rats. This increased absorption may be due to an enhancement in the glucose transporter capacity of intestinal villi (86). In the intestine of experimentally diabetic rats, the activity of phosphofructokinase, an important enzyme in the utilization of glucose, has been reported to be lower (87).

D) Urological Complications

Nephropathy is one of the most significant complications seen in diabetes mellitus (88). The signes of nephropathy such as proteinuria (89), albuminuria (90), glomerulopathy (91) have been observed in STZ diabetic rats. The excretion pattern of urinary proteins is also altered in experimental diabetes(92). Urinary retention resulting from an atony in the urinary bladder is another significant complication in diabetic patients (93). Similar changes have also been indicated in experimental models of diabetes. Enlargement of the urinary bladder, increases in the amount of urine and in the threshold urine volume necessary for trigering micturation have been reported in STZ diabetic rats (94,95). Urinary bladders of diabetic rats are hypertrophic having a two fold increase in weight, and its collagen content is also increased (96,97). In the in vitro experiments, contractile responses of urinary bladder muscle to electrical stimulation, ATP, bethanecol, prostaglandin F2 and KCI have been found to be higher in rats with 8 and 16 week diabetes. These diabetic changes in the bladder contractility have been reported to be normalized to some extent following insulin therapy (98). Similar changes in the bladder muscle have been seen in spontaneously diasetic BB rats (99,100). In the urinary bladder from STZ-diabetic rats, an increase in muscranic receptor medi-

ated biosynthesis of prostacyclin has been observed (52).

E) Respiratory Complications

In diabetes mellitus, long-term complications related to the respiratory tract may occur and these complications may be apparent in animal models. Morphological and biochemical abnormalities have been indicated in the lungs of STZ-diabetic rats (101,102). Responsiveness of tracheal segments to carbachol has been reported to be higher due to a vagal neuropathy in experimentally diabetic rats (103). While this observation has been confirmed by the observation of lower acetylcholine responsiveness in the tracheal smooth muscle from both insulin-dependent (Type I) diabetic and non-insulin-dependent (Type II) diabetic rats exhibit a decrease in the contractile responses to acetylcholine and these changes are normalized by insulin treatment for 10 days (105). Furthermore, higher contractile responses to KCl have been demonstrated in the tracheal muscle of 12-13 week diabetic rats (104).

F) Ophthalmic Complications

Cataracts, retinopathy, keratopathy and thrombotic glaucoma are the common long-term ophthalmic complications in diabetic patients. Diabetic eye complications are the one of major causes of blindness. Similar complications have been also detected in the experimental models of diabetes. Incidence of the development of cataracts in experimentally-diabetic rats has been found to be increased by a high sugar diet, also (106). In particular, a galactose-rich diet may facilitate the development of cataracts in diabetic animals (106,107). In ALX diabetic rats, lens glutathione reductase activity has been found to be higher when compared to non-diabetic animals (108). In addition, lower glucose-6-phosphate dehydrogenase and sorbitol (polyol) dehydrogenase activities in th rat lens have been reported due to ALX diabetes (109). Neuronal and vascular changes have been observed in the retina of Cohen diabetic rats. A striking decrease in the mural, endothelial and rod cells of the retina has been demonstrated in Cohen diabetic rat (110) and STZ diabetic rats (111). The retinal changes in Cohen diabetic rats have been proposed to be closely related to diabetic microangiopathy (112). Similar retinal changes have been observed in spontaneously diabetic Chinese hamsters (113), dogs (114) and BB rats (115). Furthermore, higher permeability of the blood-retina barrier has been reported to be a consequence of higher capillary permeability in the retina of spontaneously diabetic BB rats (116,117).

G) Reproductive Complications

Reproductive complications are seen in both male and female patients suffering from diabetes mellitus. Impotence, retrograde ejaculation and lower fertility have been reported in male diabetic patients (25). Some of the complications in diabetic patients may be seen in experimental models of diabetes. Impaired VIPergic innervation (118) and lower prostacyclin levels (119) have been reported in the penis tissue of rats with STZ diabetes. The smooth muscle of rat vas deferens seems to be affected by experimentally-induced diabets, as well. Increased contractile responses to noradrenaline (120-123), Phenylephrine, clonidine (122), acetyhlcholine (121,122) and KCl (122) have been observed in both STZ and ALX diabetic rats. Most of the studies reported a higher α-adrenergic responsiveness of vas deferens in rats with long-term experimental diabetes, while one report described the higher α-adrenergic responsiveness of rat vas deferens in rats with long-term experimental diabetes, while one report described the higher α-adrenergic responsiveness of rat vas deferens in short-term diabetes (123). Furthermore, this report also demonstrated that long-term experimental diabetes causes a decrease in α-adrenergic responsiveness in rat vas deferens.

H) Haematological and Biochemical Complications

Haematological and biochemical changes have been reported in both diabetic patients and animals. An increase in the thrombin-and ADP-induced platelet aggregation has been reported in STZ-diabetic rats (124,125). In contrast, no change has been observed in the collagen -induced platelet aggregation due to experimental diabetes (215). Similar changes have been observed in spontaneously diabetic BB rats (126) and ALX diabetic rats (127), but not in ALX diabetic rabbits (128). Although the mechanism of diabetic changes in platelets is fully understood, these changes in the platelet aggregation have been accepted as a factor that may increase thrombus formation in blood vessels (129). Another diabetic change having biochemical and haematological significance is the development of nonenzymatic protein glycosylation both in diabetic patients and animals (130). As an important parameter of glycemic control, glycosylated haemoglobin possesses a lower oxygen binding capacity in diabetics (131). As a pathological process, glycosylation has been seen in other proteins having functional significance such as insulin (132) and structural significance such as collagen (133,134). The glycosylation of insulin may also

reduce its biological activity in vivo (132). This process appears to be an irreversible feature, since the glycosylation occurs through the covalent binding of sugar moieties (135). It seems quite possible that the non-enzymatic protein glycosylation contributes to many diabetic complications. Insulin receptor tyrosine kinase activity has been found to be impaired both in STZ diabetic and obese Zucker rats (136,137). Hepatic glusose transporter activity also appears to be altered in STZ diabetic rats (138). Na-K-ATPase activities of skeletal muscle, myocardium and peripheral nerves have been reported to be lower (139). It has been demonstrated that calmodulin levels in fat and liver tissues from spontaneously diabetic BB rats are lower when compared with controls (140,141). In STZ diabetic rats, lower calmodulin levels in smooth muscle have been also observed (57,81).

I) Complications Related to Drug Metabolism and Pharmacokinetics

Acute and chronic diabetes mellitus have different effects on the hepatic drug metabolism in rats (142). Sex-dependent changes have been observed in the drug metabolism of certain animal species as a result of diabetes. The hepatic drug metabolism seems to be inhibited in spontaneously diabetic male guinea-pigs, but not in female guinea-pigs (143). Similar changes in the hepatic drug metabolism have been observed in STZ-diabetec rats, as well. Male diabetic rats have a lower aminopyrine metabolism, while females possess an higher aminopyrine metabolism compared with the controls, indicating altered metabolisms due to diabetes (144). It has been suggested that the presence of androgens in male diabetic animals may cause a difference in the capacity of the hepatic drug metabolism (145). The sex hormone metabolism in the liver has been also reported to be different in STZ diabetic rats (146). Changes in the hepatic drug metabolism seem to be closely related to the development of fatty liver (147) and occur as a consequence of altered catalytic activities of cytochrome P-450 (148). Glutathione S-transferase activities of the liver and kidney are also lower and consequently, chloroform toxicity is potentiated in STZ-diabetic rats (149). It has been suggested that experimental diabetes modulates the metabolic activation of chemical carcinogens (150). These changes observed in STZ-diabetic rats may be related to both metabolic and mitochondrial changes in the tissues (151) and there may be differences between male and female animals (152). Similar changes may be seen in animal models of non-insulin-dependent diabetes (153). Interestingly, differences between ALX- and STZ-induced diabetes in rats have been reported in terms of their effects on the hepatic drug metabolism (154). On the other hand, it has been demonstrated that the elimination and excretion kinetics of some drugs, such as gentamycin (155), diflunisal (156), zenarestat (157), etc. are different in various animal models of diabetes.

Therapeutic Modalities

In most cases, antidiabetic therapy with conventional drugs is successful for the clinical management of diabetic complications. There are, however, some diabetic complications which seem to be resistant to antidiabetic drugs even when applied in an optimal dose regimen. Progessive retinopathy is not curable by conventional therapies and may cause blindness when it occurs in diabetic patients (158,159). Diabetic foot may occur in diabetic patients as a complex clinical manifestation following both the development of neuropathy and vascular complication and is not curable by conventional antidiabetic therapies (160). In recent studies in our laboratories, insulin treatment has been found to be ineffective on lower calmodulin levels in smooth muscles of the duodenum, aorta, trachea and vas deferens of STZ-diabetic rats (161,162) In contrast, lower β-adrenergic responsiveness in the myocardium (12,39,40,163-165) and gastrointestinal tract (40,75,163) of insulin-dependent diabetic rats is corrected by insulin replacement therapy. Glyburide or insulin treatment also corrects lower β-adrenergic responsiveness in the myocardium (12) and gastrointestinal tract (166) of non-insulin-dependent diabetic rats. Lithium treatment also has been reported to correct lower β-adrenergic responsiveness in the gastrointestinal tract due to diabetes without improving hyperglycemia (76,167). Vanadium compounds, known as insulinomimetic agents, have been reported to improve the complications related to myocardium (168), blood vessels (169), gastrointestinal (170) and respiratory (104) tracts. Insulin treatment has also been reported to correct the diabetic changes in the urinary bladder (98). In contrast, the decreases in the responsiveness to calcium and calmodulin levels in the smooth muscles of STZ-diabetic rats seem to be resistant to insulin treatment (57,81). Newer therapeutic modalities such as aldose reductase inhibitors seem to be effective against the diabetic myocardial (171), vascular (172) complications and nephropathy (173). Despite of all these observations, novel therapeutic approaches are necessary for the rational treatment of diabetic complications and for the higher quality of life of diabetic patients.

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