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COMPARATIVE EVALUATION OF DIFFERENT RAT MODELS WITH CO-EXISTING DIABETES-MELLITUS AND HYPERTENSION

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Abstract : We have evaluated the suitability of different rat models for the study of effects of antihypertensives on cardiovascular and metabolic complications of diabetes mellitus and hypertension. IDDM was induced in Wistar and spontaneously hypertensive (SH) rats by single tail vein injection of STZ (45 mg/kg, i.v.). Neonatal STZ-diabetes (nSTZ) was induced by administering STZ, 70 mg/kg (i.p.) to 5 day old Wistar rat pups. DOCA-hypertension was induced in Wistar and STZ-diabetic rats using deoxycorticosterone acetate (DOCA, 5 mg/kg, s.c.) and NaCl (2%) in drinking water. Intravenous injection of STZ produced cardinal signs of diabetes mellitus including hyperglycemia, loss of body weight, polyphagia and polydipsia. STZ-diabetic rats also showed hyperlipidemia and hypoinsulinemia. STZ-treated rats developed hypertension and bradycardia. nSTZ rats were found to have mild hyperglycemia and were hypertensive and hyperinsulinemic. The OGTT and ITT revealed that nSTZ rats are insulin resistant. SH rats were also found to be hyperinsulinemic and hypertensive. Although, these rats were found to be insulin resistant, they did not demonstrate hyperglycemia. DOCA-treated STZ-diabetic rats were found to have milder hyperglycemia when compared to STZ-diabetic rats not treated with DOCA. Although, DOCA treatment was not found to alter serum levels of glucose and insulin, results of OGTT revealed enhanced glucose disposal in DOCA-treated Wistar rats, suggesting that DOCA probably produces some effect on glucose homeostasis in rats. The present data also suggest that STZ-diabetic rat may be considered a suitable model for IDDM. On the other hand, nSTZ and SH rats were hyperinsulinemic and insulin resistant and may be used as models to study insulin sensitivity. DOCA-hypertensive rat may not be a suitable model for studying the effects of various drug interventions on glucose homeostasis and insulin sensitivity as DOCA itself appears to influence these factors.

Key words : diabetes-mellitus streptozotocin hypertension hyperinsulinemia DOCA-hypertension

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INTRODUCTION

It has been reported that the combination of elevated blood pressure, glucose intolerance, obesity, low HDL cholesterol, and elevated serum triglycerides 'cluster' in diabetic patients (1, 2). A concept that has emerged linking diabetes mellitus and hypertension is the existence of hyperinsulinemia and associated insulin resistance (3, 4). Increasing epidemiological data points to a striking association of hypertension with hyperinsulinemia and insulin resistance in diabetic subjects (4, 5, 6, 7). There are several reports suggesting that there is a subnormal response to insulin on glucose uptake in the peripheral tissues leading to a compensatory hyperinsulinemia. This in turn causes hypertension and cardiovascular complications through its effects on kidneys (7, 8) via activation of sympathetic nervous system (9) and vascular hypertrophy and remodeling (10, 11) that cause hypertension. Insulin is known to stimulate the sympathetic nervous system activity resulting in significant elevation of plasma catecholamine levels (8). Various control trials have confirmed that blood pressure reduction by antihypertensives can decrease the incidences of stroke but not that on coronary heart disease (CHD), which remains a major cause of hypertensive mortality in hypertensive patients (12, 13). While treating hypertension in the patients with diabetes mellitus, metabolic effects of antihypertensives require a special consideration as some antihypertensive agents may produce undesirable metabolic effects in the long-term treatment. Hence, there is a need of well-defined animal models having both diabetes mellitus and hypertension to study antihypertensive agents better. In the light of these, we investigated a few rat models of diabetes mellitus and hypertension with the aim of assessing their suitability in the study of effects of antihypertensives on the cardiovascular and metabolic complications of diabetes mellitus and hypertension.

METHODS

Induction of STZ-diabetes and hypertension in adult rats:

STZ-diabetes was induced by a single tail vein injection of 45 mg/kg STZ intravenously into Wistar rats. Control Wistar rats received saline alone. In addition to Wistar rats spontaneously hypertensive (SH) rats of Okamoto Oki strain were also used. STZ was also injected to SH rats in the dose of 45 mg/kg, intravenously. Animals showing glucosuria, 48 hours after STZ injection were considered diabetic. Although STZ-induced diabetic (Wistar) rats exhibited hypertension, DOCA was used to induce hypertension in Wistar (DOCA group) as well as STZ-diabetic rats (DOCA-DIA group). DOCA (5 mg/kg) was administered subcutaneously every day to rats. These animals were also given 2.5% NaCl in drinking water. Treatment with DOCA was initiated 7 days after STZ treatment. Animals showed development of hypertension ten days after initiation of DOCA treatment.

Induction of neonatal STZ-diabetes in rats:

STZ (70 mg/kg, i.p.) was administered to 5-day old Wistar rat neonates (14). Control animals received saline alone. Animals were reared under standard conditions and those

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Induction of neonatal STZ-diabetes in rats:

STZ (70 mg/kg, i.p.) was administered to 5-day old Wistar rat neonates (14). Control animals received saline alone. Animals were reared under standard conditions and those

showing serum glucose levels greater than 150 mg/dl at 16 weeks of age were considered as diabetic.

Experimental protocol and serum analysis

The experimental animals were maintained under, standard conditions with food and water *ad libitum* for a period of six weeks. Blood pressure and heart rate were measured initially and at the end of six weeks by the indirect tall cuff method using the Harvard blood pressure monitor cum oscillograph (Kent, UK). At the end of six weeks blood samples, were collected from the retro-orbital plexus and analyzed for glucose, total cholesterol, triglycerides, glutamate pyruvate translocase (GPT) and creatinine spectrophotometrically using diagnostic kits (Bayer Diagnostics, Vadodara, India). Serum levels of insulin and T_3 were analyzed by radioimmunoassay using diagnostic kits (BRIT, India).

The animals were also subjected to oral glucose tolerance test (OGTT) and insulin tolerance test (ITT) at the end of six weeks. Area under the curves (AUC) for glucose and insulin were calculated from the results of OGTT. K_{ITT} was obtained from results of ITT to express insulin sensitivity. At the end of six weeks the liver and gastrocnemius muscle were dissected out and the glycogen content was estimated spectrophotometrically by the method of Seifter et al (15).

Statistical analysis

All data are presented as mean ± SEM. The rat models were compared with Wistar control rats using one-way analysis of variance (ANOVA). The computed F-ratio was used for the Tukey's multiple range test. The computed Q values were compared with the tabulated Q values at 5% level.

RESULTS

General and cardiovascular parameters

Intravenous injection of streptozotocin (STZ) was found to produce loss of body weight in Wistar, DOCA-hypertensive and SH rats (Table I). The percentage change in body weight of other rat models over a period of 6 weeks was not significantly different from Wistar control (Table I).

TABLE I: General characteristics and cardiovascular parameters in the experimental rat models.

Parameters	*WS CON (n=6)*	*STZ-DIA (n=5)*	*nSTZ (n=7)*	*SH (n=5)*	*SH-DIA (n=5)*	*DOCA (n=6)*	*DOCA-DIA (n=6)*
% Change in body weight	20±2.5	−24.9±1.5*	18±2	19±3	−20±4*#	19.5±1.2	−23.3±2.53*#
Food intake (mg/rat/day)	25±3	40±8*	28±5	18±5	48±4*#	21±1	35±3*#
Water intake (ml/rat/day)	30±5	79±5*	33±4	30±3	72±1*#	33±8	70±3*#
Blood Pressure (mm Hg)	99±8	155±2*	157±6*	183±9*	204±3*#	218±12*	155±3*#
Heart rate (b/m)	380±11	305±8*	370±10	370±11	345±22*	372±27	301±11*

*Significantly different from Wistar control ($P<0.05$)
#Significantly different from respective control ($P<0.05$)

STZ-induced diabetes was also found to produce polyphagia and polydipsia. Injection of STZ to neonatal rat pups did not alter the food or water intake (Table I). The food and water intake of SH and .DOCA-hypertensive rats was however comparable to that of Wistar control rats (Table I).

There was a significant decrease in the heart rate in STZ-treated Wistar, DOCA-treated and SH rats (Table I). STZ treated Wistar, DOCA treated and SH rats also showed lower serum levels of T_3 (Table II). On the other hand, neonatal STZ-diabetic rats that received STZ on day 5 of life had heart rate comparable to Wistar control rats (Table I). These rats had serum T_3 levels comparable to Wistar control rats (Table II). DOCA and hypertensive rats showed serum T_3 levels comparable to Wistar control rats (Table II). Serum total cholesterol and triglyceride levels were found to be significantly higher in STZ-diabetic Wistar, DOCA-hypertensive and SH rats (Table II). Neonatal STZ-diabetic and SH rats were found to have serum total cholesterol and triglyceride levels comparable to Wistar controls (Table II). The triglyceride levels in SH rats were significantly lower as compared to Wistar control rats. In DOCA-hypertensive rats also serum levels of both cholesterol and triglycerides were lower when compared to Wistar control rats (Table II).

Serum GPT and creatinine

Serum GPT and creatinine levels were significantly higher in STZ-diabetic Wistar, DOCA-hypertensive and SH rats (Table II). In neonatal STZ diabetic and DOCA-hypertensive rats serum GPT and creatinine levels were comparable to control Wistar rats (Table II). SH rats were found to have elevated GPT levels, however, serum creatinine levels in SH rats were comparable to control Wistar rats (Table II).

TABLE II: Biochamical parameters in the experimental rat models.

Parameters	*WS CON (n=6)*	*STZ-DIA (n=5)*	*nSTZ (n=7)*	*SH (n=5)*	*SH-DIA (n=5)*	*DOCA (n=6)*	*DOCA-DIA (n=6)*
T_3 (ng/ml)	1.4±0.07	0.7±0.03*	1.46±0.02	1.34±0.02	0.99±0.06*	1.33±0.06	0.8±0.04*
Total cholesterol (mg/dl)	75.5±6.1	162.9±14.6*	85.4±8.3	64.8±8	110.8±13.8*	53.5±6.2*	143.5±7.9*
Triglycerides (mg/dl)	76.4±10.9	139.7±20.3*	101.9±12.9	50.1±0.6*	122±6.1*	33±5.3*	143.8±19.4*
SGPT (U/ml)	25.3±0.9	55.1±2.5*	27.7±1.3	41.9±4*	117.2±23*#	27±1.3	56.2±2.8*
Creatinine (mg/dl)	0.8±0.1	1.4±0.23*	0.9±0.3	0.7±0.1	1.8±0.05*	0.7±0.1	1.9±0.1*
Glucose (mg/dl)	101.5±5.8	359±13.9*	161.2±13.7*	96.1±16	481.4±33.1*#	112.7±5.2	232±20.6*#
Insulin (μU/ml)	28.8±0.5	14.7±0.3	118.8±11.4*	73±4.9*	45.1±0.9*#	24.4±1.4	18.7±0.4*#

*Significantly different from Wistar control ($P<0.05$)
#Significantly different from respective control ($P<0.05$)

Glucose and insulin levels

Injection of STZ to adult or neonatal Wistar rats and SH rats was found to produce hyperglycemia (Table II). Hyperglycemia in STZ-diabetic rats treated with DOCA and neonatal STZ-diabetic rats was milder as compared to hyperglycemia in STZ-diabetic Wistar rats (Table II). Non-diabetic DOCA-hypertensive and SH rats were found to have serum glucose levels comparable to Wistar control rats (Table II).

STZ treatment in Wistar, and DOCA-hypertensive rats was found to produce significantly lower levels of insulin when compared to control Wistar rats (Table II). SH rats were found to have elevated serum levels of insulin (Table II). STZ treatment to SH rats was found to significantly lower the serum insulin levels, however, they were still higher than Wistar control rats (Table II). STZ treated neonatal rat pups were also found to be hyperinsulinemic at 16 weeks of age (Table II).

Neonatal STZ-diabetic rats were found to have significantly higher $AUC_{glucose}$ (Table III). This was associated with comparable $AUC_{insulin}$ and lower K_{ITT} value as compared to Wistar control rats (Table III). The glycogen content in liver and skeletal muscle in neonatal STZ-diabetic rats was comparable to Wistar control rats (Table III).

SH rats were found to be hyperinsulinemic (Table II). This was associated with low K_{ITT} value when compared to Wistar controls suggesting that SH rats are probably insulin resistant. In SH rats $AUC_{insulin}$ was unaltered, whereas, $AUC_{glucose}$ was significantly higher when compared to Wistar control rats (Table III). It was interesting to note that there was a significant increase in skeletal muscle glycogen (Table III) in SH rats. DOCA treatment was not found to alter serum insulin or glucose (Table II) levels in Wistar rats. In DOCA-hypertensive rats the $AUC_{insulin}$ was lower, although the difference was not significant as compared to Wistar controls (Table III). Further, despite comparable K_{ITT} value, there was enhanced

TABLE III: Parameters related to insulin sensitivity in the experimental rat models.

Parameters	*Wistar control (n=6)*	*nSTZ (n=7)*	*SH (n=6)*	*DOCA (n=6)*
$AUC_{GLUCOSE}$ (mg/dl/min)×10^4	49.78±0.16	184.91±10.78*	67.05±6.17*	29.43±3.85*
$AUC_{INSULIN}$ (μU/dl/min)×10^4	49.14±4.31	51.43±6.65	34.11±7.89*	37.80±6.53
K_{ITT}	4.2±0.13	3.45±0.21*	2.55±0.16*	4.02±0.48
Liver glycogen (μg/100 tissue weight)	841.6±332	2488.2±791	803±330	420.6±16*
Muscle glycogen	73.0±19.6	75.4±11.6	150.4±19.5*	120.2±1.3*

*Significantly different from Wistar control ($P<0.05$)

glucose disposal as indicated by the significantly lower $AUC_{glucose}$ (Table III) in DOCA-hypertensive rats when compared to Wistar control rats suggesting that DOCA may have an action on glucose metabolism. DOCA treatment was also found to produce a decrease in liver glycogen and increase in skeletal muscle glycogen again suggesting that DOCA probably has some effect on glucose metabolism in Wistar rats (Table III).

DISCUSSION

In the present study STZ-diabetes was associated with a rise in blood pressure in Wistar rats. Measurement of blood pressure, directly and indirectly in our laboratory has revealed that STZ-diabetic Wistar rats develop hypertension. STZ not only induces diabetes but also hypertension in rats (16, 17). Alternations of the prostaglandin and/or the kallikrein-kinin systems, impaired renal prostaglandin E_2 synthesis and altered hypothalamamic pressor responses have been suggested to be involved in the pathogenesis of hypertension in STZ-diabetes in rats (18–21). Elevation of blood pressure in STZ-diabetic rats could also be due to increased ACE activity in serum and other tissues and a decrease in plasma renin activity (PRA) (22). However, there are other reports that do not support the existence of hypertension in STZ-diabetic rats (20). Rodgers et al (23) measured blood pressure indirectly and reported that STZ induces a depressor effect in SH rats and has no effect in Wistar-Kyoto rats. Further, Kusaka et al (24) reported similar findings and suggested that measuring blood pressure by the indirect tail-cuff method may result in higher blood pressure values due to emaciation of the rat tail in diabetic rats that may result in structural changes that require extra pressure above the maximum to occlude the tail artery. This controversy led us to select a rat model of simultaneously occurring diabetes mellitus and hypertension where diabetic animals were also made hypertensive by subcutaneous administration of DOCA.

Hebden et al (25) have reported that the DOCA-hypertensive STZ diabetic rat may be a useful model to study the effects of different pharmacological agents on atherosclerosis and hyperlipidemia. We found that DOCA-hypertensive STZ diabetic rats developed hypertension that was significantly less severe than that induced by STZ diabetes or DOCA saline treatment alone. This suggests that DOCA probably produces a sort of counteraction to STZ-induced hypertension. STZ-diabetic produced hyperglycemia and hypoinsulinemia in Wistar and DOCA-hypertensive rats. Hyperglycemia in STZ treated DOCA-hypertensive rats was milder. Dai and McNeill (26) also reported a similar counteraction by DOCA to STZ diabetes induced myocardial dysfunction in rats. Further, DOCA was also found to alter glucose-homeostasis in STZ-diabetic rats. The mechanism by which DOCA treatment increases blood pressure may involve sodium retention and a subsequent volume expansion (27, 28). Some studies have indicated that the involvement and altered activity of the brain renin-angiotensin system (29, 30) leading to increased sympathetic activity (31), vasopressin release (32) and baroreceptor attenuation (33) may also be involved in the development and maintenance of DOCA-NaCl hypertension.

The SH rats have a genetic predisposition towards hypertension and closely resembles essential hypertension in humans. The pathogenesis of hypertension in this rat model is not well understood. This model has been characteristics contribute to the elevation of blood pressure (35, 36, 37). High insulin levels may produce hypertension by one or a combination of the following mechanisms, like insulin-induced natriuresis (38), activation of sympathetic activity by insulin (39), trophic effects of insulin on vascular smooth muscle (40), and insulin-mediated increase in intracellular sodium levels which could sensitize the arteriolar smooth muscle cells to the pressor effects of catecholamines and angiotensin II (41, 42). Injection of STZ to SH rats was found to further elevate blood pressure. Similar findings have been reported earlier (19). STZ-treated SH rats were found to develop severe apoplexy and showed a high mortality. This could be due to severe stress caused by simultaneous presence of diabetes and high blood pressure.

Neonatal administration of STZ has been reported to produce destruction of beta cells resulting in hypoinsulinemia and severe hyperglycemia in this rat pups (14). However, as the rats grow there appears to be partial regeneration of pancreatic beta cells along with development of characteristics of NIDDM such as hyperinsulinemia and mild hyperglycemia (43). Bonora et al (44) have reported hyperinsulinism with low hepatic extraction and hypersecretion of beta cells in mild glucose intolerance and in obese subjects. In our studies, rats treated with STZ on day 5 of life were found to be hypertensive at 16 weeks of age. Hyperinsulinemia associated with insulin resistance observed may be postulated as one of the mechanisms for the development of hypertension in these animals. We also found normal beta cell secretion (as indicated by AUC insulin after a glucose load) in neonatal STZ-diabetic rats which suggests that the peripheral hyperinsulinemia in neonatal STZ-diabetic rats be probably not due to increased beta cell secretion. Therefore, the high insulin concentration found in neonatal STZ-diabetic rats need not be pancreatic in origin. It could also be due to metabolic alterations at extra pancreatic levels. The presence of hyperinsulinemia, higher AUC glucose and low K_{ITT} values in neonatal STZ-diabetic rats indicates insulin resistance in these rats.

Like nSTZ-diabetic rats, SH rats exhibited hyperinsulinemia and lower insulin sensitivity index when compared to Wistar controls. It was interesting to note that while $AUC_{Insulin}$ was unaltered, $AUC_{glucose}$ was significantly higher in SH rats when compared to Wistar controls. These findings further support insulin resistance in SH rats. There was a significant increase in skeletal muscle glycogen in SH rats suggesting a better uptake of glucose peripherally.

DOCA treatment was not found to alter serum insulin levels in female Wistar rats. The $AUC_{insulin}$, $AUC_{glucose}$ and K_{ITT} in DOCA-hypertensive rats were comparable to Wistar controls. The AUC glucose revealed enhanced glucose disposal in DOCA-hypertensive rats when compared to Wistar controls suggesting that DOCA may have an action on glucose metabolism, either directly inhibiting the assimilation or

production and/or increasing the utilization of glucose or indirectly enhancing the metabolic effects of insulin. Similar findings have been reported by Dai and McNeill (34). DOCA treatment was also found to produce a decrease in liver glycogen and increase in skeletal muscle glycogen again suggesting that DOCA probably has some effect on glucose metabolism in Wistar rats.

Bradycardia has been frequently observed in STZ-diabetic rats (18, 19). The development of STZ-induced bradycardia has been attributed to a down regulation of myocardial beta-adrenoceptors associated with an increase in catecholamines in the circulation and the heart (45) and hypothyroidism (46).

STZ diabetes produced dyslipidemia in Wistar, DOCA-hypertensive and SH rats. It has been well documented that diabetes mellitus is associated with changes in lipid metabolism. Rats treated with STZ have increased plasma levels of triglycerides, total cholesterol, and free fatty acids and phospholipids (47). Neonatal STZ-diabetic and SH rats has serum total cholesterol comparable to control Wistar rats. Serum triglycerides were normal in neonatal STZ-diabetic rats, however, they were significantly low in SH rats. This indicated that these models of diabetes and/or hypertension do not develop dyslipidemia. Interestingly, DOCA-hypertensive rats were found to have low serum total cholesterol and triglycerides when compared to Wistar control rats. Dai and McNeill (26) and Hebden et al (25) have reported that DOCA hypertension is associated with an increase in plasma cholesterol and triglycerides. Although, these workers have suggested that DOCA increases insulin sensitivity they have not specified as to why then there is a disturbance in lipid profile in the DOCA-hypertensive rat. If there was an improvement in insulin sensitivity with DOCA then the lipid levels in DOCA-saline treated rats should have been normal since insulin plays a vital role in lipid metabolism. In the present study DOCA hypertension was associated with significantly lower levels of serum total cholesterol and triglycerides when compared to control Wistar rats. These findings suggest that DOCA probably enhances insulin action on lipid metabolism.

STZ treatment results in changes in various hepatic enzyme systems. Many fundamental alterations in hepatic function related to changes in metabolism also occur following STZ treatment. In the present study serum GPT level in STZ treated Wistar, DOCA-hypertensive and SH rats was found to be elevated. Relative hypoxia is an important factor in the development of tissue change in diabetes (48). Serum GPT levels in neonatal STZ-diabetic and DOCA-hypertensive rats were comparable to control Wistar rats whereas, those in SH rats were higher when compared to control Wistar rats. Long standing hypertension in the genetically hypertensive SH rats probably causes microvascular changes in liver leading to liver damage.

Rats treated with STZ develop changes in renal function including altered renal haemodynamics and structural changes, which can be attributed to the development of diabetes and are relevant when considering cardiovascular control (49). STZ has no significant nephrotoxic potential and

its direct effect on the kidney need not be considered when using the drug in order to study the effect of diabetes on renal function and structure (50). Rise in serum creatinine levels has also been reported in the patients with diabetes mellitus (51). STZ treatment in Wistar, DOCA-hypertensive and SH rats resulted in elevation of serum creatinine levels. Neonatal STZ-diabetic, DOCA-hypertensive and SH rats had normal serum creatinine levels when compared to control Wistar rats.

In the light of the above discussion it may be concluded that although, all the rat models manifested hypertension and a disruption in the 'insulin-glucose' balance to varying degrees, there were differences in the mechanism of induction of such an imbalance. STZ-diabetic rats were hypoinsulinemic, whereas, NIDDM and SH rats were hyperinsulinemic and insulin resistant. The STZ-diabetic, neonatal STZ-diabetic and SH rats may be considered as good animal models for studying the effects of chronic treatment with antihypertensives on metabolic status as they appear to be models for at least some mechanisms leading to hypertension and metabolic disturbances in humans. On the other hand, the DOCA-hypertensive rats may not be a suitable model for studying the effects of antihypertensives on insulin sensitivity as DOCA itself appears to influence insulin and glucose homeostasis.

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