ABSTRACT

Objective: To study the effects of perindopril on insulin sensitivity and cardiovascular complications in Wistar and spontaneously hypertensive (SH) rats made diabetic with streptozotocin (STZ).

Methods: Streptozotocin (STZ, 45 mg/kg) was given as a single dose tail-vein injection and perindopril in the dose of 1 mg/kg, p.o. daily for six weeks. The serum samples were analyzed for glucose, insulin, cholesterol and triglycerides. Oral Glucose Tolerance Test (OGTT) was done using 1.5 g/kg glucose and area under the curve for glucose (AUC_{glucose}) and area under the curve for insulin (AUC_{insulin}) were determined. Cardiac functions were recorded as per the method of Neely's working heart preparation.

Results: SH rats showed hyperinsulinemia along with hypertension. Injection of STZ produced a decrease in insulin levels and hyperglycemia in both Wistar as well SH rats. Treatment with perindopril prevented STZ-induced hyperglycemia and decreased the elevated blood pressure in both Wistar diabetic and SH diabetic rats. The AUC_{glucose} was found to be significantly higher in Wistar as well as SH diabetic rats whereas, the AUC_{insulin} was significantly decreased. Treatment with perindopril caused a significant decrease in AUC_{glucose} without any alteration in AUC_{insulin}. Injection of STZ also produced hypercholesterolemia, hypertriglyceridemia and decrease in left ventricular developed pressure (LVDP). These changes were prevented by perindopril in both Wistar and SH rats.

Conclusion: Perindopril produces an improvement in insulin sensitivity, prevents dyslipidaemia and cardiac dysfunctions associated with STZ-diabetes in Wistar and SH rats.

KEYWORDS

ACE inhibitor, diabetes mellitus, hyperlipidaemia, hypertension

INTRODUCTION

In the recent years insulin resistance and hyperinsulinemia have been postulated to play a significant role in the etiology of hypertension. It is therefore essential for an antihypertensive therapy not only to lower blood pressure but also improve insulin sensitivity and prevent dyslipidemia and target organ damage. It has been reported from our laboratory that vasodilators like hydralazine, prazosin, angiotensin converting enzyme (ACE) inhibitors enalapril and lisinopril and calcium channel blockers nifedipine and amlodipine prevent STZ-induced cardiomyopathy, cardiac dysfunction and hyperlipidaemia. Cardiodefective beta-adrenoceptor blocker atenolol however did not improve diabetes-induced cardiac dysfunctions, cardiomyopathy, and hyperlipidemia.

There has been a controversy on the use of STZ-diabetic and DOCA hypertensive rats to study the various beneficial effects of an antihypertensive in a diabetic-hypertensive state. Spontaneously hypertensive rats (SHRs) are reported to be hyperinsulinemic with normal blood glucose levels. They develop cardiac hypertrophy and their arterial wall thickness is reported to be greater. The vascular collagen elastin content in SHRs is greater as compared to Wistar Kyoto rats and may be responsible for diminished arterial compliance.

Perindopril is a long acting ACE inhibitor that displays pharmacodynamic properties similar to other agents in this class. Several results from short-term studies have suggested that ACE inhibitors may be advantageous over other conventional antihypertensive agents in reducing albuminuria in both
hypertensive and normotensive diabetics with microalbuminuria or persistent proteinuria. Increasing attention is also being directed towards the effect of antihypertensive drugs on insulin sensitivity in diabetic patients. ACE inhibitors have been shown to improve insulin sensitivity. Taking into consideration all the above facts, the present investigation was undertaken to study the effect of six weeks treatment with perindopril on cardiovascular complications, and insulin sensitivity in Wistar and spontaneously hypertensive (SH) rats made diabetic with STZ.

**MATERIALS AND METHODS**

**Induction of diabetes in rats and treatment protocol:** Healthy albino rats of Wistar (normotensive) and Okomoto Okai strain (SH) rats 12-15 weeks old were used in the experiments. Initial blood pressure was recorded by tail-cuff, non-invasive method using Harvard blood pressure monitor (Kent, U.K.) as per the method described by Gokhale et al. Diabetic was induced by a single tail-vein injection of STZ (45 mg/kg). Animals showing glucosuria (> 2 %) 48 h after injection of STZ were considered as diabetic. The animals were divided into 2 groups of 8 animals each viz. Normotensive (Wistar strain) and Hypertensive (SH with blood pressure above 150 mm Hg). Animals from each group were subdivided into 4 groups, viz. Control, Control treated, Diabetic control and Diabetic treated. Perindopril was given in the dose of 1 mg/kg, p.o. daily for six weeks. All the animals were observed throughout the study period for changes in their behavioral patterns, water intake, food intake, changes in body weight, and mortality. Blood pressure and heart rate measurements were done using the Harvard blood pressure monitor (Kent, U.K.) at the interval of 10 days as per the method described by Gokhale et al.

**Blood sampling and serum analysis:** Blood samples were collected from the tail vein and allowed to clot for 30 min at room temperature. The blood samples were then centrifuged at 3000 rpm for a period of 20 min. Supernatant clear serum was then separated and stored at -20°C until analysis was done. Serum samples were then analyzed for glucose, cholesterol, and triglycerides spectro-potometrically using enzymatic kits from Bayer Diagnostics, Vadodara, India. Serum insulin was analyzed by radioimmunoassay method using the kit obtained from Bhabha Atomic Research Center (BARC), Mumbai, India.

**Oral glucose tolerance test (OGTT):** After 18 hours fasting, rats were given 1.5 g/kg of glucose orally. Then samples of blood were collected from the tail vein at 0, 10, 20, 30 and 60 min of glucose administration. The serum was separated and the glucose and insulin levels were estimated using the methodology as described before. The integrated area under the curve (AUC) for glucose and insulin was calculated by the trapezoid rule (AUC = \(\frac{C_1 + C_2}{2} \times (t_1 - t_2)\)) and changes in glucose and insulin concentrations during OGTT were expressed as AUC_{glucose} (mg/dl/min) and AUC_{insulin} (\(\mu U/ml/min\)) respectively.

**Recording of cardiac function:** One day after collection of blood samples the animals were sacrificed by cervical dislocation and hearts were quickly dissected out and placed in Chenoweth Koele solution maintained at 37±1°C. They were mounted as per the modified Neely’s Working Heart model. The aortic outflow was connected to a compliance chamber containing 2 to 3 ml of air. Hearts were subjected to an after load of 75 cmH\textsubscript{2}O and allowed to stabilize for 10 min at the perfusion pressure of 10 cmH\textsubscript{2}O. The left ventricular developed pressure (LVDP) was then recorded at different atrial filling pressure (5 cm H\textsubscript{2}O to 20 cm H\textsubscript{2}O) changed in 2.5 cm H\textsubscript{2}O steps.

**Statistical analysis:** Data were evaluated statistically with two-way ANOVA followed by Tuckey’s test. Values of P less than 5% (P<0.05) were considered significant.

**RESULTS**

Induction of diabetes with STZ produced a significant loss in body weight, polydipsia and polyphagia. The loss in body weight was not prevented by perindopril treatment in Wistar diabetic or SH diabetic animals (Table 1). The STZ-induced polydipsia was found to be prevented by perindopril treatment in Wistar diabetic animals. In SH rats however, treatment with perindopril failed to prevent STZ-induced polydipsia (Table 1). There was a 20% mortality in STZ untreated diabetic rats. There was no mortality in STZ-diabetic rats treated with perindopril.
Cardiovascular parameters: Mean blood pressure in SH rats were found to be significantly higher as compared to Wistar rats. Injection of STZ produced significant increase in blood pressure not only in Wistar, but also in SH rats (Table 2). Treatment with perindopril produced significant reduction in blood pressure after 45 days in Wistar as well as SH rats. After 15 days of induction of diabetes, a significant decrease in heart rate was found in Wistar diabetic animals. This bradycardia was significantly prevented by pretreatment with perindopril in Wistar diabetic animals (Table 2).

Cholesterol levels were found to be significantly higher in Wistar diabetic and SH diabetic rats and treatment with perindopril produced considerable reduction in these levels (Table 2).

LVDP was reduced significantly at higher filling pressures in hearts from diabetic animals, both Wistar (Figure 1) as well as SH rats (Figure 2) as compared to their respective controls. Perindopril treatment prevented this reduction in LVDP (Figure 1). Hearts from diabetic hypertensive animals showed higher LVDP

Table 1. Effect of perindopril treatment on the general parameters (at the end of six weeks) of experimental animals.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>% Change in body weight</th>
<th>Water intake (ml/day/rat)</th>
<th>Food intake (g/day/rat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar control</td>
<td>14.2 ± 2.1</td>
<td>25 ± 2</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Wistar treated</td>
<td>17.6 ± 0.8</td>
<td>27 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>SH control</td>
<td>17.4 ± 3.1</td>
<td>25 ± 2</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>SH treated</td>
<td>16.9 ± 2.0</td>
<td>31 ± 5</td>
<td>35 ± 5</td>
</tr>
<tr>
<td>Wistar diabetic</td>
<td>-4.0 ± 1.1*</td>
<td>110 ± 2*</td>
<td>55 ± 3*</td>
</tr>
<tr>
<td>Wistar diabetic treated</td>
<td>0.9 ± 2.0@#</td>
<td>68 ± 9@#</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>SH diabetic</td>
<td>1.3 ± 0.8*</td>
<td>98 ± 6@#</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>SH diabetic treated</td>
<td>1.7 ± 1.2*</td>
<td>51 ± 5@#</td>
<td>45 ± 2</td>
</tr>
</tbody>
</table>

Two-way F (7, 56) 22.1 51.31 3.6
ANOVA P < 0.001 < 0.001 < 0.01

Each value represents mean ± SEM of 8 experiments
*Significantly different from Wistar control (P<0.05) (Tukey's Test)
*Significantly different from SH control (P<0.05) (Tukey's Test)
@Significantly different from diabetic control (P<0.05) (Tukey's Test)

Figure 1. Effect of treatment with perindopril on LVDP of heart taken from Wistar rats. Each point and the bar represent the mean±SEM of 6 experiments.

*Significantly different from Wistar control (P<0.05); ** Significantly different from diabetic control (P<0.05).
as compared to diabetic animals but lower than Wistar animals (Figure 2). Treatment with perindopril in non-diabetic hypertensive group did not show any alteration in cardiac functions (Figure 1 & 2).

Index of hypertrophy was calculated as the ratio of wet heart weight to the body weight was found to be significantly higher in Wistar diabetic and diabetic hypertensive animals. Index of hypertrophy was also higher in SH rats as compared to the normotensive Wistar rats. Perindopril treatment prevented the STZ-induced hypertrophy in both normotensive and hypertensive animals (Table 2).

**Serum glucose, insulin and oral glucose tolerance test (OGTT)**

Serum glucose levels in Wistar and SH rats were not found to be significantly different from each other, but insulin levels in SH rats were found significantly higher (Table 3). Injection of STZ produced a significant elevation in serum glucose levels in SH as well as Wistar rats. Treatment with perindopril in Wistar and SH diabetic rats significantly reduced the serum glucose levels. However, the serum glucose levels still remained high as compared to the Wistar controls. STZ produced significant decrease in insulin levels in both Wistar and SH diabetic rats. Treatment with perindopril did not affect the insulin levels in any of the groups (Table 3).

Glucose tolerance was found to be decreased significantly in both Wistar diabetic and SH diabetic rats and perindopril was found to increase partially this glucose tolerance. There was a marked increase in glucose levels after oral administration of glucose to STZ diabetic rats in both Wistar and SH rats. In control Wistar and SH rats, there was an increase in glucose upto 60 minutes. Oral administration of glucose to Wistar control and SH control rats produced a significant increase in insulin levels at

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**Figure 2.** Effect of treatment with perindopril on LVDP of heart taken from SH rats. Each point and the bar represent the mean±SEM of 6 experiments.

(O) SH control, (□) SH treated, (●) SH diabetic, (■) SH diabetic treated.
* Significantly different from SH control (P<0.05); **Significantly different from SH diabetic control (P<0.05).
Table 2. Effect of perindopril treatment on cardiovascular parameters and lipid levels of the experimental animals after six weeks of treatment with perindopril.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Index of hypertrophy</th>
<th>Cholesterol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar control</td>
<td>105 ± 4</td>
<td>370 ± 10</td>
<td>3.4 ± 0.14</td>
<td>58.6 ± 8.6</td>
<td>185 ± 14</td>
</tr>
<tr>
<td>Wistar treated</td>
<td>95 ± 3</td>
<td>390 ± 13</td>
<td>3.2 ± 0.2</td>
<td>66.4 ± 1.1</td>
<td>156 ± 21</td>
</tr>
<tr>
<td>SH control</td>
<td>163 ± 4*</td>
<td>420 ± 15</td>
<td>4.8 ± 0.2*</td>
<td>63.7 ± 7.5</td>
<td>190 ± 13</td>
</tr>
<tr>
<td>SH treated</td>
<td>142 ± 1*#</td>
<td>380 ± 15</td>
<td>4.2 ± 0.3#</td>
<td>69.7 ± 12.7</td>
<td>163 ± 9</td>
</tr>
<tr>
<td>Wistar diabetic</td>
<td>141 ± 2*</td>
<td>300 ± 18*#</td>
<td>4.3 ± 0.2*</td>
<td>140.3 ± 14.6*</td>
<td>427 ± 33*#</td>
</tr>
<tr>
<td>Wistar diabetic treated</td>
<td>115 ± 6*@#</td>
<td>345 ± 10</td>
<td>3.9 ± 0.1@#</td>
<td>57.3 ± 6.6*@#</td>
<td>234 ± 25@</td>
</tr>
<tr>
<td>SH diabetic</td>
<td>182 ± 3*#</td>
<td>380 ± 17</td>
<td>5.9 ± 0.5*#</td>
<td>87.0 ± 3.2</td>
<td>489 ± 38*#</td>
</tr>
<tr>
<td>SH diabetic treated</td>
<td>128 ± 3*@#</td>
<td>385 ± 35@#</td>
<td>4.3 ± 0.3@#</td>
<td>78.5 ± 0.5@#</td>
<td>203 ± 18@</td>
</tr>
</tbody>
</table>

Two-way F (7, 56) 69.07 3.8 9.8 10.56 30.04
ANOVA P < 0.001 < 0.001 < 0.001 < 0.001 < 0.001

Each value represents mean ± SEM of 8 experiments
*Significantly different from Wistar control (P<0.05) (Tukey’s Test)
#Significantly different from SH control (P<0.05) (Tukey’s Test)
@Significantly different from diabetic control (P<0.05) (Tukey’s Test)

Table 3. Effect of perindopril treatment on serum glucose, insulin, AUC_{glucose} and AUC_{insulin} after six weeks of treatment with perindopril.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Serum glucose (mg/dl)</th>
<th>Serum insulin (µU/ml)</th>
<th>AUC_{glucose} (mg/dl/min)</th>
<th>AUC_{insulin} (µU/ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar control</td>
<td>143.6 ± 9.2</td>
<td>27.4 ± 3.6</td>
<td>7.3 ± 0.14</td>
<td>1038.6 ± 103.4</td>
</tr>
<tr>
<td>Wistar treated</td>
<td>126.4 ± 2.3</td>
<td>28.4 ± 3.9</td>
<td>4.9 ± 0.2*</td>
<td>1257.4 ± 188.1</td>
</tr>
<tr>
<td>SH control</td>
<td>108.6 ± 4.9</td>
<td>50.7 ± 2.8*</td>
<td>6.8 ± 0.16</td>
<td>1675.3 ± 116.6*</td>
</tr>
<tr>
<td>SH treated</td>
<td>104.1 ± 12.4</td>
<td>46.7 ± 3.2*</td>
<td>4.7 ± 0.25*#</td>
<td>1579.4 ± 12.7</td>
</tr>
<tr>
<td>Wistar diabetic</td>
<td>535.3 ± 36.9*</td>
<td>11.8 ± 0.8*#</td>
<td>16.3 ± 0.9*#</td>
<td>440.4 ± 54.6</td>
</tr>
<tr>
<td>Wistar diabetic treated</td>
<td>427.8 ± 24*@#</td>
<td>14.6 ± 4.2*#</td>
<td>11.9 ± 0.1*@#</td>
<td>527.3 ± 56.6</td>
</tr>
<tr>
<td>SH diabetic</td>
<td>540.2 ± 11.0*</td>
<td>14.5 ± 1.7*#</td>
<td>21.6 ± 0.8*#</td>
<td>607.5 ± 88.6</td>
</tr>
<tr>
<td>SH diabetic treated</td>
<td>369 ± 18*@#</td>
<td>12.6 ± 1.38*#</td>
<td>13.3 ± 0.3*@#</td>
<td>524.5 ± 56.5</td>
</tr>
</tbody>
</table>

Two-way F (7, 56) 113.7 27.85 171.4 0.334
ANOVA P < 0.0001 < 0.001 < 0.0001 < 0.001 >0.05

Each value represents mean ± SEM of 8 experiments
* Significantly different from Wistar control (P<0.05) (Tukey’s Test)
# Significantly different from SH control (P<0.05) (Tukey’s Test)
@ Significantly different from diabetic control (P<0.05) (Tukey’s Test)
10 minutes which declined by the end of 30 minutes to normal. In STZ-treated Wistar or SH rats, administration of glucose failed to elicit the release of insulin. Treatment with perindopril failed to alter the insulin release or levels in any of the groups. However, glucose levels were found to be decreased in diabetic and SH diabetic animals. The AUC_{glucose} was found to be significantly higher in STZ-diabetic Wistar as well as SH diabetic rats whereas, the AUC_{insulin} was considerably decreased in these animals. Treatment with perindopril caused a significant decrease in AUC_{glucose} without any alteration in AUC_{insulin} (Table 3).

DISCUSSION

STZ produced a significant loss in body weight in diabetic group over the period of six weeks. The maximum loss in body weight was observed within first ten days. This loss in body weight was not prevented by perindopril treatment. Polyphagia, and polydipsia accompanied the loss in body weight in Wistar diabetic animals. These findings were consistent with those reported earlier. The STZ-induced polydipsia was found to be prevented by perindopril treatment in Wistar diabetic animals. In SH rats there was a significant loss of body weight and polydipsia. Treatment with perindopril failed to prevent STZ-induced changes in SH rats.

Blood pressure of SH rats was found to be significantly higher than that in Wistar rats. This elevation in blood pressure in SH rats was associated with an increase in insulin levels. Accumulated evidence indicates that hyperinsulinemia is associated with high blood pressure. In other studies, it has been reported that insulin, via its action on insulin like growth factor receptors, causes an increase in vascular smooth muscle cell growth in vitro. Therefore, it is possible that chronic hyperinsulinemia cause hypertrophy and lead to narrowing of lumen of resistant vessels, consequently raising vascular resistance and blood pressure.

While hyperinsulinemia appears to be associated with hypertension, there is a report that contradicts this hypothesis. Insulin when infused intravenously, caused a dose dependent increase in leg blood flow in humans and this effect was independent of plasma glucose concentration. It was also revealed that although insulin caused both systemic and peripheral vasodilation, the increase in blood flow in skeletal muscle exceeded the increment at the systemic level.

In continuation to these reports, we found that injection of STZ into Wistar or SH rats decreases insulin levels. However, these animals develop a significant hypertension after 2-3 weeks. Such an increase in blood pressure has also been reported from other laboratories. The possible explanation for the development of hypertension, despite of STZ-induced hypoinsulinemia could be the development of insulin resistance. Insulin resistance has been postulated to be one of the important factors in the etiology of hypertension. STZ has been reported to produce insulin resistance in rats.

The results of the effects of STZ on glucose and insulin levels and OGTT also support the hypothesis that STZ may cause insulin resistance. Serum glucose levels in Wistar diabetic as well as SH diabetic rats were found to be significantly higher as compared to control animals. Glucose levels were not altered significantly in either Wistar or SH rat with perindopril treatment; however, in diabetic animals, perindopril treatment produced a significant decrease in glucose levels. This was not associated with any alteration in insulin levels in either of the groups i.e. diabetic and non-diabetic. Treatment with perindopril failed to alter the insulin release or levels in any of the groups when compared with their respective controls. AUC_{glucose} was found to be significantly higher in STZ-diabetic Wistar as well as SH diabetic rats whereas, the AUC_{insulin} was considerably decreased in these animals. Treatment with perindopril caused a significant decrease in AUC_{glucose} without any alteration in AUC_{insulin}. Perindopril is reported to cause improvement in insulin sensitivity. This explains the decrease in glucose level by perindopril in spite of low levels of insulin. The mechanism of improvement of insulin sensitivity by ACE inhibitors is not known. The possible explanation could be the association between insulin mediated glucose disposal and vasodilator effect of these drugs. Angiotensin converting enzyme is responsible for the inactivation of bradykinin. It has been reported that ACE inhibitors may augment the activity of kallikrein kinin prostaglandin system.
Treatment with perindopril prevented STZ-induced elevation in blood pressure not only in Wistar rats but also SH rats. The blood pressure was found to be significantly reduced in diabetic SH rats by the treatment with perindopril. The reduction in blood pressure and serum glucose levels with no change in insulin levels suggests that treatment with perindopril causes an increase in insulin sensitivity, nullifying insulin resistance seen in STZ diabetic rats. Bradycardia has been frequently observed in STZ diabetic rats. The development of STZ-induced bradycardia has been attributed to a down regulation of myocardial beta adrenoceptors, hypothyroidism, depression of myocardial calcium metabolism, reduced uptake of calcium by the sarcoplasmic reticulum and concomitantly depression of SR-calcium ATPase activity. In the present study, Wistar diabetic rats were found to have significantly bradycardia as compared to the control animals. The mechanism of bradycardia appears to be STZ-induced hypothyroidism. Perindopril treatment prevented STZ-induced bradycardia in Wistar diabetic animals. However, in SH rats, STZ failed to produce bradycardia, and treatment with perindopril caused no change in heart rate in hypertensive and hypertensive diabetic group. It is possible that changes in calcium metabolism and/or metabolism of other ions contribute to the bradycardia induced by STZ in rats.

Index of cardiac hypertrophy was found to be significantly higher in STZ-diabetic and STZ diabetic SH rats. Elevated blood pressure should be considered as the most important factor in developing hypertrophy as it imposes the work overload on diabetic heart. Cardiomyopathy may also be thought to be involved. In the present investigation, the index of hypertrophy was found to be significantly higher in the Wistar diabetic and in the SH diabetic rats with respect to their corresponding control groups. Perindopril treatment significantly prevented this increase in index of hypertrophy.

Increase in the left atrial filling pressure produced a gradual rise in the LVDP, which was found to be significantly lower especially at higher filling pressure in diabetic rats. Treatment with perindopril significantly prevented the STZ-induced cardiac depression in both diabetic and hypertensive diabetic rats. Because rats are relatively resistant to atherosclerosis, the involvement of cardiomyopathy seems to be the possible mechanism in the cardiac depression, but the underlying biochemical changes are still unclear. Since both contraction and relaxation of cardiac muscle is affected by diabetes, a great deal has been focused on the ability of the cardiac muscle to handle calcium. In STZ diabetic rats the ability of the sarcoplasmic reticulum to take up and release calcium is depressed. Similarly reports for decreases in Na+K+ATPase and adenyl cyclase accompanied by decreases in sodium/calcium exchanges and calcium pump activity have been documented in diabetes. In addition to cardiomyopathy, alteration in the lipid metabolism seems to be another factor involved in cardiac depression. Perindopril treatment significantly reduced the lipid levels in diabetic rats. Thus it is possible that this may be one of the reasons responsible for improvement in cardiac dysfunction in perindopril treated diabetic rats.

Diabetes is associated with hypertriglyceridaemia, which is due to increase in adipose tissue lipolysis in absence of insulin a decrease in lipoprotein lipase activity and reduced carnitine levels. In a normal heart, cardiac muscle derives 60-70% of its ATP from oxidation of fatty acids. In diabetic state due to absence of insulin sensitivity there is mobilization of fatty acid from adipose tissue and proteins leading to increase in free fatty acids. In the present investigation, we have observed an increase in lipid levels with simultaneous decrease in insulin levels in diabetic rats. Because of this increase in the FFA there is a shift to the predominant fatty acid oxidation, which may account for over 90% of the energy production. As this process takes place in the mitochondria, fatty acids must first be transported to the mitochondria from cytoplasm, which occurs via carnitine dependent system.

It has been well documented that diabetes mellitus is associated with changes in lipid metabolism. Rats treated with STZ have increased plasma level of triglycerides, and cholesterol. In the present investigation we observed significant increase in cholesterol levels in diabetic and diabetic hypertensive animals. SH diabetic animals showed an elevation in triglyceride levels as compared to the SH control animals. Perindopril treatment significantly reduced cholesterol levels in diabetic normotensive and diabetic hypertensive animals. Triglyceride levels were
however, not found to be decreased by perindopril in SH diabetic rats.

In conclusion, our data suggest that perindopril improves insulin sensitivity and prevents some of the complications like elevation of blood pressure, hyperglycemia, hypercholesterolemia, and cardiac depression. It may thus be useful as yet another preferred drug in hypertension associated with diabetes mellitus.

ACKNOWLEDGEMENTS

This study was supported financially by the Council for Scientific and Industrial Research, New Delhi. We are also grateful to the Cardiovascular Division, I.R.I.S. France for supply of perindopril as a gift.

REFERENCES


RUSSIAN REMEDIES TAKE ON THE CHALLENGE OF THE WEST

Russian remedies could take out hardy US bacteria. Long-abandoned by Western medicine, viruses that naturally kill microbes are being imported as a potential substitute for antibiotics.

The emergence of multi-drug-resistant bacteria is intensifying the search for antibiotic replacements. Bemoaning the problem, clinician Glenn Morris of the University of Maryland in College Park got an idea from a colleague from the former Soviet republic of Georgia. Morris explains: "He said, 'why don't you use 'phage therapy?'; I said, 'what's 'phage therapy?''."

'Phages - more properly, bacteriophages - are viruses that are harmless to humans but kill bacteria. They were widely researched as a means to tackle disease until the 1940s. When potent antibiotics appeared on the scene, the West discarded them. Eastern Europe and the former Soviet Union pursued 'phage therapy, so 'phage creams, pills and plasters are commonly available there. Now Morris and his colleagues are carrying out basic tests to update the treatments for US product licenses. Worktops contaminated with the foodborne bacteria Listeria are clean within 24 hours of 'phage treatment, he told the Experimental Biology 2002 meeting in New Orleans on Sunday. Salmonella and Escherichia coli are similarly wiped out. 'Phages could be used in food production or packaging, Morris suggests.

Unlike antibiotics, 'phages kill only a specific bacterial type, leaving other, beneficial bugs intact. For example, antibiotic resistant strains of the gut bacteria Enterococcus, which can cause dangerous infections after surgery or in chemotherapy patients, are also being tackled. We are naturally surrounded by 'phages. The type that Morris is using attack and multiply inside bacteria then split them apart to escape. The 'phages keep killing until their victims run out, and then quietly die.

"US science tends to have a prejudice against Soviet science," adds Morris, who now collaborates with the Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi, Georgia. Bringing down the "scientific cold wall" will lead to a productive association and help develop newer means of combating drug resistance.

(www.nature.com/nsu/020422/020422-4.html)