EFFECT OF THIAZOLIDINEDIONE TREATMENT ON RESISTIN LEVELS IN INSULIN RESISTANT SPRAGUE DAWLEY RATS

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INTRODUCTION

Adipose tissue secretes various adipocytokines, including adiponectin, interleukin-6, leptin, resistin, TNF-α, visfatin and resistin which play an important role in pathogenesis of insulin resistance and cardiovascular disease. Resistin is one of the factors which affects peripheral insulin resistance. Serum resistin levels were found to be elevated in two different genetic models of mice and in a diet-induced model of insulin resistance and obesity. In the fructose-fed rat model of insulin resistance, resistin mRNA levels were increased. Mice exhibiting decreased adiposity and improved insulin sensitivity, were found to have decreased serum resistin levels.

Most individuals appear to develop insulin resistance when environmental factors interact with specific genetic predispositions that confer susceptibility. These include abnormalities of nutritional intake, obesity and decreased physical activity. Obesity is one of the key environmental factors responsible for the development of insulin resistance as it leads to increased production of adipocytokines such as resistin. This indicates the role of resistin in regulating insulin sensitivity. If resistin is involved in the pathogenesis of insulin resistance, it can be predicted that insulin sensitizing agents like thiazolidinediones may decrease resistin expression. Resistin mRNA and protein are down regulated by antidiabetic thiazolidinediones (TZDs) in adipocytes. The present study was designed to evaluate resistin levels after treatment with thiazolidinediones and effect on insulin resistant diabetes.

SUBJECTS AND METHODS

The project and relevant regulations governing the study were approved by the committee for postgraduate studies, Army Medical College, Rawalpindi.

The study was conducted from January to July 2010 at Army Medical College, Rawalpindi in collaboration with National Institute of Health (NIH), Islamabad. Ninety healthy Sprague Dawley rats with an average weight of 250±50 gm were procured from animal house of NIH, Islamabad. They were kept in its animal house facility where the temperature was maintained at 22±3 °C. Food and water was available ad libitum. The rooms were well ventilated and 12-hour light-dark cycle was maintained.

By convenient sampling the rats (n=90) were divided into 3 equal groups (n=30 in each group). Weight of the animals was recorded and blood samples for baseline fasting blood glucose and serum resistin levels, triglycerides and HDL were taken by tail bleed. Group I served as control without any intervention and fed on normal diet. Rats in group II and III were fed on a high sucrose diet (Table-1) for 4 weeks to induce insulin resistance. Serum resistin level indicates insulin resistance with decrease in high density lipoproteins (TG/HDL) ratio; being considered as one of the surrogate markers for insulin resistance. Blood sampling was done at the end of 4th week by tail bleed to confirm the presence of insulin resistance. After confirmation of development of
insulin resistance, rats in group III were treated with rosiglitazone injected intraperitoneally, 5 mg/Kg body weight for seven days. At the end of 5th week terminal sampling was done by intra cardiac bleed under ether anesthesia and the animals sacrificed. The plasma and serum samples were stored at -80 °C till assay of plasma glucose, serum triglycerides, HDL, TG: HDL ratio, and resistin levels.

DISCUSSION

Rosiglitazone treatment significantly decreased (p<0.05) at the end of 4 weeks compared to the control (12.43±3.01 ng/ml) after the intake of high sucrose diet for four weeks as statistical significance. Therefore, potential complications of PPARγ activation in vivo may be avoided by making resistin the target of insulin resistance therapy if regulation and properties of human resistin are similar to those of rat resistin.

Administration of resistin to mice impairs the glucose tolerance without reducing insulin levels, and decreases sensitivity to the effects of insulin. The demonstration in this study that sucrose feeding produces insulin resistance is comparable to the findings of other studies carried out in high fructose and high sucrose fed rats, in which different techniques were used to assess insulin resistance. Serum resistin levels were increased in insulin resistant rats due to the increase in adipose tissue mass and body weight. It is well known that adipocytes secrete resistin. It is possible that resistin could lead to insulin resistance.

According to Curat et al11, resistin expression in vivo is specific to white adipose tissue, and it is found in the serum of normal mice. Resistin is an adipocyte derived factor that contributes to the development of insulin resistance in vivo and has been supported by the studies on adipocytes, where neutralization with resistin antiserum enhanced insulin-stimulated glucose uptake. Administration of resistin to mice impairs the glucose tolerance without reducing insulin levels, and decreases sensitivity to the effects of insulin. Our study supported these findings that resistin is a hormone having effects on glucose metabolism which is antagonistic to those of insulin and thiazolidinediones improve insulin resistance by decreasing resistin levels. A significant correlation does exist between fasting glucose and serum resistin level. These findings are comparable to the previous study by Lazar et al12 on the rodent model in which fasting blood glucose level was higher in resistin transgenic mice than in their non-transgenic littermates, and glucose tolerance was impaired in the hyper-resistinemic mice.

Thiazolidinediones represents an important breakthrough in the therapy of insulin resistance, and their ability to down regulate resistin level suggests that there exists a link among resistin, insulin resistance and the mechanism of action of thiazolidinediones. Therefore, potential complications of PPARγ activation in tissues13 may be avoided by making resistin the target of insulin resistance therapy if regulation and properties of human resistin are similar to those of rat resistin.

RESULTS

Serum resistin levels in groups II and III were found to be significantly increased (p<0.05) at the end of 4 weeks (Table-2), after the development of insulin resistance by high sucrose diet. Serum resistin levels increased to 21.75±2.92 ng/ml in group II. In group III the serum resistin level increased to 20.94±2.29 ng/ml(p<0.05) after the intake of high sucrose diet for four weeks as compared to the control (12.43±3.01 ng/ml). Rosiglitazone treatment significantly decreased (p<0.05) resistin levels in group III from 20.94±2.29 ng/ml to 14.48±2.19 ng/ml.

Table-2: Serum resistin at end of 4th and 5th week (ng/ml)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I n=30</th>
<th>Group II n=30</th>
<th>Group III n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum resistin 4th week</td>
<td>12.11±3.01</td>
<td>21.75±2.92</td>
<td>20.94±2.29</td>
</tr>
<tr>
<td>Serum resistin 5th week</td>
<td>12.11±3.01</td>
<td>21.71±2.88</td>
<td>14.48±2.19</td>
</tr>
</tbody>
</table>

DISCUSSION

The relationship between obesity, insulin resistance, and cardiovascular diseases has been recognized since long but the mechanisms for their interrelationship are indistinct. Feeding of high sucrose diet for a period of 4 weeks led to the increased body weight, hyperglycemia and increased TG:HDL ratio in insulin resistant model as compared to the healthy control. A decrease in insulin sensitivity accompanied the hyper triglyceridemia in Sprague Dawley rats after 4 weeks of high sucrose diet. Adipose tissue mass increased due to high sucrose diet. Adipocytes are the source of adipocytokines including resistin. Resistin has been documented to antagonize the actions of insulin. The demonstration in this study that sucrose feeding produces insulin resistance is comparable to the findings of other studies carried out in high fructose and high sucrose fed rats, in which different techniques were used to assess insulin resistance. Serum resistin levels were increased in insulin resistant rats due to the increase in adipose tissue mass and body weight. It is well known that adipocytes secrete resistin. It is possible that resistin could lead to insulin resistance.

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REFERENCES

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