Research paper www.ijcps.com

International Journal of
Chemical and Pharmaceutical Sciences
2012, Mar., Vol.3 (1)

ISSN: 0976-9390
IJCPS

Effect of Telmisartan and Rutin in Alcohol Plus High Fructose Diet Induced Metabolic Dysfunction in Rats

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ABSTRACT

Metabolic effectcomparision of rutin and telmisartan on high fructose diet induced metabolic dysfunction.SpraugueDawly rats was determined in this study. The metabolic syndrome was induced by feeding the animals with high fructose diet (HFD). Effect of telmisartan and rutinand HFD induced metabolic syndrome for a period of 28 days. During the study period the weekly body weight variation was determined. At the end of the study the animals were fasted for 24 h and blood sample was collected through retro orbital sinus. The plasma samples were used to estimate the biochemical parameters such as blood glucose, AST, ALT, urea, uric acid, creatinine, total cholesterol, triglyceride and HDL levels. At the day of the termination, the experimental animals were sacrificed, organs were removed and absolute organ weight was measured.In this present work we studied the effect of telmisartan on both vascular and metabolic parameters. Administration of alcohol at this condition further increases the risk. Combination of HFD and alcohol may increase reactive oxygen species this will damage the liver. Rutinis a Flavonoid glycoside having powerful anti oxidant as well as powerful anti-inflammatory property.In this study rutin and telmisartan were used to prevent the hepatic damage as well as metabolic dysfunction in rats.This study with support from ongoing clinical studies would be useful to standardize the standard dosage regimen or development of new selective PPAR γ modulators in metabolic dysfunction patients, for whom the treatment options are not satisfactory.Rutin shows promising effect on reactive oxygen species.

Keywords: Rutin, Telmisartan and High fructose diet.

1. INTRODUCTION

Metabolic syndrome is a set of risk factors that includes: abdominal obesity, a decreased ability to process glucose (increased blood glucose and/or insulin resistance), dyslipdemia, and hypertension [1] Patients who have this syndrome have been shown to be at an increased risk of developing cardiovascular disease and/or type 2diabetes. Metabolic syndrome is a common condition that goes by many names (dysmetabolic syndrome, syndrome X, insulin resistance syndrome, obesity syndrome, and Reaven's syndrome) [2].

All of the factors associated with metabolic syndrome are interrelated. Obesity and lack of exercise tend to lead to insulin resistance. Insulin resistance has a negative effect on lipid production, increasing VLDL (very low-density lipoprotein), LDL (low-density lipoprotein – the "bad" cholesterol), and triglyceride levels in the bloodstream and decreasing HDL (high-density lipoprotein – the "good" cholesterol). This can lead to fatty plaque deposits in the arteries which, over time, can lead to cardiovascular disease and strokes. Insulin resistance also leads to increased insulin and glucose levels in the blood. Excess insulin increases sodium retention by the kidneys, which increases blood pressure and can lead to hypertension [3,4].

Metabolic syndrome is thought to be caused by adipose tissue dysfunction and insulin resistance. Dysfunctional adipose tissue also plays an important role in the pathogenesis of obesity-related insulin resistance.Both adipose cell enlargement and infiltration of macrophages into adipose tissue results in the release of pro-inflammatory cytokines and promotes insulin resistance [5].

Insulin resistance appears to be the primary mediator of metabolic syndrome.PPAR- γ agonists such as telmisartan had shown promising improvement in the metabolic abnormalities associated with insulin resistant. In addition to its effect on metabolic parameters the vascular protective nature has been demonstrated in several experiments, these agents performing the vascular protection through anti oxidative, anti-

inflammatory and ant proliferative mechanisms [6].

2. MATERIALS AND METHODS

2.1. Animals

Experimental study was carried out using adult Male Sprague Dawly (SD) rats weighing between 140-160g. The animals were housed in polypropylene cages of dimension 16"×9"×7". The cages were maintained under clean and hygienic conditions. Animals were acclimatized to light and temperature with a 12h-12h dark-light cycle. The rats were fed with normal rodent pellet diet and high fructose diet (HFD) induced insulin and water *ad libitum.*The study protocol was approved by the Institute Animals Ethics Committee, IAEC (UCP/IAEC/2009/042) and all the animal experiments were carried out in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India [7].

2.2. Metabolic syndrome inducing agents

HFD containing fructose-624 g/kg (62%), fats as vegetable oils 5 g/kg, protein 223 g/kg (22%), necessary amino acids, vitamins 1.25% and minerals [8].The weight gain of t the animals are in associated with hyperplasia, enhance feeding efficiency, adiposity and altered loco motor activity and satiety signaling in 14 days [9, 10]. In present study alcohol plus HFD diet administered for the duration of 28 days used to induce obesity in SD rats.

2.3. Effect of telmisartan and rutin in alcohol plus high fructose diet induced metabolic syndrome

Induction of insulin resistant in the experimental animals was carried out by feeding alcohol plus high fructose diet. The animals were divided into the ten groups each contains six animals as follows.

Group 01: Control (fed with normal pellets chows)

Group 02: HFD (10% v/v *p.o.*) with normal pellets)

Group 03: Alcohol (20% v/v p.o) with normal pellets

Group 04: HFD(10% v/v) + Alcohol (20% v/v) with normal pellets

Group 05: HFD + telmisartan (5mg/kg) p.o with normal pellets

Group 06: Alcohol + telmisartan (5mg/kg) p.o with normal pellets

Group 07: HFD + alcohol + telmisartan (5mg/kg) p.o with normal pellets

Group 08: HFD + rutin (50mg/kg) p.o with normal pellets

Group 09: Alcohol + rutin (50mg/kg) p.o with normal pellets

Group 10: HFD + alcohol + rutin (50mg/kg) p.o with normal pellets.

The doses of Rutin (50mg/kg B.wt) and Telmisartan (5mg/kg B. Wt) [11] were selected for this study is based on previous reports. The standard drug and investigational products were administered orally or 28 days. At morning time treatment drugs curcumin and telmisartan were administered to animals. The metabolic syndrome was induced by feeding the experimental animals with high fat diet. During the study period the weekly body weight variation was determined. End of the study the animals were fasted for 24 h and blood sample was collected through retro orbital sinus [12].The blood samples were collected in a in a sodium EDTA tubes, centrifuged at 3000 RPM for 20 min and subjected to biochemical analysis. The plasma samples were used to estimate the biochemical parameters such as blood glucose, AST, ALT, urea, uric acid, creatinine, total cholesterol, triglyceride and HDL levels were analyzed. The LDL levels were calculated using Frieldwann's formula [10,13]. After terminating the daily dosing the animals were sacrificed by cervical dislocation [7] and the organ such as heart, liver, kidney, spleen and fat pads (mesenteric, left and right perirenlnd uterine fat pads) were removed and the absolute organ weight was measured and relative organ weight was calculated.

2.4. Statistical Analysis

All results are expressed as mean±SEM. Statistical analysis was performed using the Graph pad prism 5, Graph pad software. One-way ANOVA followed by Dunnett's test was performed.

3. RESULT AND DISCUSSION

Effect of telmisartan and rutin on body weight in alcohol plus HFD induced metabolic dysfunction in rats was presented in Table-1. End of the study the high fructose diet group, and alcohol plus HFD treated groups were showed a significant ($P<0.001$) increase in body weight when compared to control group. At the same time, rutin and telmisartan was significantly ($P<0.001$) inhibited the HFD and alcohol plus HFDinduced increase in body weight respectively. Same like the HFD and alcohol plus HFD +rutincombined group and HFD and alcohol plus HFD + telmisartan combined group also significantly ($P<0.001$) reduced the body weight when compare to the HFD fed group.

Effect of rutin and telmisartan on biochemical and lipid profiles was presented in Table-2 and 3. High fructosediet, alcohol group and alcohol plus HFD groups were showed a significantly increase in blood glucose level, AST, ALT, urea, uric acid, creatinine and lipid profile when compared to control group.Rutin and telmisartan was significantly inhibited the HFD and alcohol plus HFD induced biochemical changes when compare to the HFD group and alcohol group respectively. Same like the alcohol plus HFD+ curcumin combined group and HFD and alcohol plus HFD + telmisartan combined group also significantly (P<0.001) inhibited the biochemical changes when compare to the HFD fed group.

Table-1: Effect of rutin and telmisartan on body weight in HFD and alcohol plus HFD induced insulin resistance and metabolic syndrome

Groups	Mean ± Sem
Group-I	181.0 ± 0.91
Group-II	228.2 ± 3.32***
Group-III	216.6 ± 0.91***
Group-IV	244.0 ± 1.82***
Group-V	209.15 ± 0.85&&&
Group-VI	213.0 ± 1.29&&&
Group-VII	215.5 ± 0.64&&&
Group-VIII	207.0 ± 1.47$$$
Group-IX	206.25 ± 1.54$$$
Group-X	212.5 ± 1.04$$$

Values are mean ± SEM (N=6). ***P<0.001 as compare to control; &&&P<0.001 as compare to HFD and alcohol control,$$$P<0.001 as compare toHFD and alcohol control. One way ANOVA followed by Dunnett's multiple comparison tests.

Table -2: Effect of rutin and telmisartan on lipid profile in HFD andalcohol plus HFD induced insulin resistance and metabolic syndrome

Groups	Total cholesterol	Liver Weight	HDL Levels	LDL levels
Group-I	50.16± 1.66	2.57 ± 0.02	30.33± 0.76	25.66 ± 1.17
Group-II	76.83 ± 1.60***	3.28 ± 0.12***	23.50 ± 0.88***	32.66 ± 1.85a***
Group-III	82.00 ± 1.23***	3.18 ± 0.26***	21.35 ± 0.88***	28.00 ± 0.57 a***
Group-IV	90.83 ± 1.24***	3.92 ± 0.17***	18.66 ± 0.76***	37.50 ± 0.76a***
Group-V	43.00 ± 0.89&&&	2.90 ± 0.08&&&	36.16± 1.10&&&	18.83 ± 0.74b&&&
Group-VI	47.83 ± 1.42&&&	2.92 ± 0.09&&&	27.33 ± 0.86&&&	18.66 ± 0.71&&&
Group-VII	45.33 ± 1.66&&&	2.79 ± 0.10&&&	27.83 ± 0.86&&&	19.50 ± 0.84&&&
Group-VIII	57.50 ±1.54$$$	2.83 ± 0.06$$$	29.00 ± 0.89$$$	19.16 ± 0.60$$$
Group-IX	44.00 ± 1.29$$$	2.87 ± 0.02$$$	33.66 ± 1.26$$$	19.00 ± 0.51$$$
Group-X	56.66 ± 1.25$$$	2.80 ± 0.06$$$	32.83 ± 0.79$$$	18.16 ± 0.70$$$

Values are mean ± SEM (N=6). ***P<0.001 as compare to control; &&&P<0.001 as compare to HFD and alcohol control,$$$P<0.001 as compare toHFD and alcohol control. One way ANOVA followed by Dunnett's multiple comparison tests.

Table -3: Effect of Rutin and telmisartan on biochemical parameters in HFD and alcohol plus HFD induced insulin resistance and metabolic syndrome

Groups	Blood glucose	AST	ALT
Group-I	91.16 ± 1.35	25.29 ± 0.19	36.68 ± 0.97
Group-II	157.66± 1.47***	82.56 ± 1.06***	85.36 ± 0.45***
Group-III	138.16 ± 2.58***	87.20 ± 0.60***	90.55 ± 0.76***
Group-IV	168.00 ± 0.96***	98.20 ± 0.67***	110.25 ± 1.25***
Group-V	112.83 ± 2.08&&&	52.86 ± 2.16&&&	67.32 ± 1.53&&&
Group-VI	114.0 ± 2.43&&&	42.26 ± 0.54&&&	55. 12 ± 0.89&&&
Group-VII	131.5 ± 2.17&&&	47.13 ± 0.70&&&	60.26 ± 0.77&&&
Group-VIII	117.50 ± 2.86$$$	46.48 ± 0.58$$$	56.12 ± 0.52$$$
Group-IX	104.66 ± 1.54$$$	35.56 ± 0.07$$$	47.86 ± 0.26$$$
Group-X	115.2 ± 1.96$$$	40.06 ± 0.74$$$	52.16 ± 1.58$$$

Values are mean ± SEM (N=6). ***P<0.001 as compare to control; &&&P<0.001 as compare to HFD and alcohol control,$$$P<0.001 as compare toHFD and alcohol control. One way ANOVA followed by Dunnett's multiple comparison tests.

Our study demonstrated the beneficial effects of Telmisartan and rutin on both abnormal metabolic characters and vascular dysfunction in insulin resistant rats.Initially we have validated the predaibetic metabolic syndrome rat model by feeding high fructose diet to the male Sprague Dawley rats [14].Development of metabolic syndrome and glucose intolerance was assessed by performing the plasma biochemical analysis such as plasma glucose, triglyceride, insulin and total cholesterol levels [15].

Development of hypertension in insulin resistance links the relation between metabolic syndrome and cardiovascular disorders, indicating the potential role of obesity and other components of metabolic syndrome in the development of hypertension and other CVDs.

Improvement in the abnormal biochemical profile and glucose intolerance in HFD fed and alcohol plus HFD + Telmisartan treated animals.It will be showing clearly the beneficial effects of Telmisartan in metabolic syndrome and type II diabetes [16].

The metabolic syndrome rats showed a significant increase in the activity of serum LDL VLDL levels.The increased blood levels of total cholesterol, LDL, VLDL as well as lowered levels of HDL in high fructose diet rat have been identified in the development of hypercholestremia, which is one of the risk factors for CAD. Administration of telmisartan and rutin produces a significant decrease in the activity of LDL VLDL Our findings showed that obese rats treated with the telmisartan and rutin exhibited significant decreases in LDL VLDL activity, The telmisartan and rutin could prevent the development of atherosclerosis through regulating vascular inflammatory processes in rats fed with an high fructose diet [17].

There was a significant increase in the activity of enzymes AST and ALT in the metabolic syndrome rats compared with control rats. Liver is bombarded by the free fatty acids (FFA) that pour out of the adipose tissue into the portal blood. This can directly cause inflammation within the liver cells, which then release further pro-inflammatory cytokines, leading to more hepatocyte injury and affecting the integrity of liver cells. The present results demonstrate that the telmisartan and rutin showed a significant decrease in the activity of both AST and ALT and showing a hepatic protective action.

Histopathological studies of Liver were conducted.The regenerative changes were observed in the group of animals treated with the telmisartan and rutin the tissue elements lost due to the induction of disease condition namely metabolic syndrome and alcohol induced liver toxicity, the cardiovascular co-morbidity were regenerated and restored in the treated animals.

4. CONCLUSION

The investigation undertaken to study the effects of telmisartan and rutin were found to be very effective in countering high fructose diet and alcohol induced changes in lipid profile /metabolic disturbances and improving the lipid profile, liver function.

Telmisartan and Rutinwere found to be effective in countering high fructose diet and alcohol induced changes in tissue elements of Liver. Telmisartan showed decrease in weight gain, indicating the beneficial role of partial PPAR-γ agonist in obesity and metabolic syndrome.Further studies are needed to explore the underlying mechanisms.

This study with support from ongoing clinical studies would be useful to standardize the standard dosage regimen or development of new selective PPAR γ modulators in metabolic dysfunction patients, for whom the treatment options are not satisfactory.Rutin shows promising effect on reactive oxygen species.

5. REFERENCES

1. Olufadi R and Byrne CD. Clinical and laboratory diagnosis of the metabolic syndrome, **J** ClinPathol., 2008; 61(6): 697-706.
2. Lann D and LeRoith D. Insulin resistance as the underlying cause for the metabolic syndrome. Med Clin North Am., 2007; 91(6):1063-77.
3. Hsieh PS. Reversal of fructose-induced hypertension and insulin resistance by chronic losartan treatment is independent of AT2 receptor activation in rats. **J** Hypertens., 2005; 23: 2209–2217.
4. Hwang IS, Ho H, Hoffman BB and Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension., 1987; 10: 512–516.
5. Gustafson B, Hammarstedt A and Andersson CX. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis, ArteriosclerThrombVasc Biol., 2007; 27(11): 2276-83.
6. Yamagishi S, Nakamura K and Matsui T. Potential utility of telmisartan, an angiotensin II type 1 receptor blocker with peroxisome proliferator-activated receptor-gamma (PPAR-gamma)-modulating activity for the treatment of cardiometabolic disorders, CurrMol Med., 2007; 7(5): 463-9.
7. CPCSEA Guidelines for laboratory animal facility, Indian **J** Pharmacol., 2003; 35:257-274.
8. Kurtz TW. Treating the metabolic syndrome: telmisartan as a peroxisome proliferator-activated receptor-gamma activator. ActaDiabetol., 2005; 42(1): S9-16.
9. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI,

Block ER, Herrera-Acosta J, Patel JM and Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome, Am **J** Physiol Renal Physiol., 2006; 290: F625-31.

10. Tanner M and Link N. Hyperlipidemia: Part 1. Evaluation and dietary management, West **J** Med., 2001; 175: 246-50.
11. Yamana A, Arita M, Furuta M, Shimajiri Y and Sanke T. The angiotensin II receptor blocker telmisartan improves insulin resistance and has beneficial effects in hypertensive patients with type 2 diabetes and poor glycemic control, Diabetes Res ClinPract., 2008; 82:127-31.
12. Parasuraman S, Raveendran R and Kesavan R. Blood sample collection in small laboratory animals, **J** PharmacolPharmacother., 2010;1: 87-93.
13. Adeneye AA, Adeyemi OO and Agbaje EO. Anti-obesity and antihyperlipidaemic effect of Hunteriambellata seed extract in experimental hyperlipidaemia, **J** Ethnopharmacol., 2010; 20(130) :307-14.
14. Elliott SS, Keim NL, Stern JS, Teff K and Havel PJ. Fructose, weight gain, and the insulin resistance syndrome, Am **J** ClinNutr., 2002; 76: 911–922.
15. Hwang LC, Bai CH and Chen CJ. Prevalence of obesity and metabolic syndrome in Taiwan, **J** Formos Med Assoc., 2006; 105(8): 626-35.
16. Smith DH: Treatment of hypertension with an angiotensin II-receptor antagonist compared with an angiotensin-converting enzyme inhibitor: a review of clinical studies of telmisartan and enalapril. ClinTher., 2002; 24(10): 1484-501.
17. Metodiewa. Evidence for antiradical and antioxidant properties of four biologically active N,N-Diethylaminoethyl ethers of flavaoneoximes: A comparison with natural polyphenolic flavonoid rutin action, IUBMB Life, 1997; 41(5): 1067–1075.