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In vivo Evaluation of PPAR-α and PPAR-γ Agonist in Hyperlipidemia Induced Wister Albino Rats

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Abstract: The present study was aimed to find possible role of pioglitazone (PPARγ agonist) and fenofibrate (PPARα agonist) by Triton induced hyperlipidemia Model, Diet induced model and Relative organ weight analysis.. The study revels that, both pioglitazone and fenofibrate has significantly reduced the elevated levels of serum triglycerides and cholesterol in both atherogenic diet and triton induced hyperlipidemia at 3 mg kg^{-1} b.wt. Significant increase in HDL level was observed in animals treated with pioglitazone 3 mg kg^{-1} b.wt. and fenofibrate 3 mg kg^{-1} b.wt. in animals induced hyperlipidemia with atherogenic diet. The liver enzymes reveal that, there was significant reverse in ASAT levels in animals treated with pioglitazone 3 mg kg^{-1} b.wt. and fenofibrate 3 mg kg^{-1} b.wt. Histopathology reports also suggest that, there was a protection to liver and heart against atherogenic and triton induced damage. In combination therapy of both pioglitazone and fenofibrate in atherogenic diet and triton induced hyperlipidemia,there was no potentiation in their activity when they have administered in combination.

Key words: Atherosclerosis, hyperlipidemia, pioglitazone, fenofibrate, triton

INTRODUCTION

Hyperlipidemia is classified into a primary and a secondary type, which indicates the complexities associated with disease. The primary disease may be treated by anti-lipidemic drugs but the secondary type originating from diabetes, renal lipid nephrosis or hypothyroidism demands the treatment of the original disease rather than hyperlipidemia (Suzuki and Suzuki, 2006). Atherosclerotic coronary artery diseases constitute a major cause of death in developed country. Atherosclerosis is now identified as the manifestation of inflammation and hyperlipidemia. Progression of atherosclerosis can be slowed if elevated serum concentration of the lipoprotein and triglycerides are reduced which prevent coronary heart disease. Also, inhibition of inflammatory molecules and growth factors reduce the progression of atherosclerosis, also hyperglycemia and hyperinsulinemia are associated with high fat diet (Hsuch and Law, 2001).

With the next decade health care systems world will face the very real prospect of being overwhelmed by the demands placed on then because of the ever increasing number of individuals diagnosed with type two diabetes mellitus (Zimmet *et al*., 2001; Dunstan *et al*., 2002). The development of insulin resistance is a critical state in the evaluation of this disorder and the increasing prevalence of obesity linked to the shift to more sedentary life styles, has contributed significantly to this prevalence. Macro vascular complications, including ischemic coronary and cerebrovascular disease, are a major cause of morbidity and mortality in this group of patients. When focusing on this diabetic epidemic, it is important, however, not to overlook individuals with so called prediabetes; in woman atherosclerotic vascular events also occur more frequently than in the general population (Saydah *et al*., 2001; Unwin *et al*., 2002). In both groups, the co-existence of other adverse vascular traits (hypertension and dyslipidemia) with insulin resistance undoubtedly fuels the drive towards atherogenic vascular disease.

The past 10 years have seen a new paradigm emerge for the transcriptional regulation of metabolic pathways with the discovery of peroxime proliferation activated receptors PPARs (PPAR-α, PPRA-γ and PPAR-δ), a trio of nuclear receptor activated by lipids. Characterization of PPARs led to the realization that certain nuclear receptors have evolved to recognize specific metabolic intermediates in the pathways that they control. Unlike

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though steroids receptors, which bind a single high affinity ligand, PPARs have the ability to recognize range of structurally diverse molecules. The importance of this property became clear when it was discovered that the physiology activators of these receptors are likely to be native and modified polyunsaturated fatty acids. Thus, PPARs are transcription factors that regulate expression of genes involved in lipid metabolism and the physiologic ligands for these receptors are lipids themselves (Walczak and Tontonoz, 2002).

PPAR-α and PPAR-γ regulate vascular and inflammatory cell functions. PPAR-α and PPAR-γ are expressed in endothelial cells, monocytes/macrophages and in the vascular smooth muscle cells of both medial and initimal layers. PPAR-α ligands inhibit smooth muscle cell production of inflammatory products and causes macrophage apoptosis. PPAR-γ ligands, (1) inhibits smooth muscle cell migration process, (2) inhibits monocyte/macrophage production of inflammatory enzymes, cytokines, (3) induce monocyte/macrophage differentiation and uptake of oxidized LDL and (4) induce monocyte and endothelial cell apoptosis (Walczak and Tontonoz, 2002). In this direction, the present study is designed to find the possible role of fenofibrate (PPAR-α agonist) and pioglitazone (PPAR-γ agonist) in hyperlipidemia.

MATERIALS AND METHODS

Chemicals: E-Coline diagnostic kits for cholesterol, triglyceride, ASAT, ALAT purchased from E-Merck India Ltd., Mumbai. Triton wr-1339 (Tyloxapol), Fenofibrate, purchased from Sigma chemicals, USA. Cholesterol, purchased from S.D. Fine Chemicals, Mumbai, India. Pioglitazone purchased from Wockhardt Ltd., Aurangabad, India on March 2008.

Animals: Healthy adult, male albino rats of Wister strain, weighing 100-150 g were obtained from central animal house, Ooty, India. The animal house was well maintained at temperature between 22±1°C, humidity 60±10%, with 12 h light/dark cycle. The animals were housed in large, spacious, hygienic cages during the course of experimental period. The animals were fed with water and pallet diet *ad libitum*, supplied by M/S Hindustan Lever Ltd., Bangalore, India and for antihyperlipidemic studies animals were fed with prepared atherogenic diet throughout the experimental period.

Experimental design

Triton induced hyperlipidemia model (Gandhi and Mulky, 1993): The rats were divided into five groups (each group contains 8 animals).

Group 1 received only 1 mL saline for 44 h, group 2 received only triton (sham control) at 350 mg kg^{-1}, group 3 received triton+pioglitazone (3 mg kg^{-1} orally), group 4 received triton+fenofibrate (3 mg kg^{-1} orally), group 5 received triton+pioglitazone (3 mg kg^{-1} orally)+fenofibrate (3 mg kg^{-1} orally), 40 albino rats of Wister strain weighing about 180-200 g divided in to 5 groups each contain 8 animals as mentioned above. Drugs were administered immediately and 24 h after the administration of triton. After 44 h of the triton administration animals were euthanized with excess dose of thiopental sodium and blood was collected. Serum was separated by centrifugation and estimated for cholesterol and triglycerides.

Experimental design (diet induced model): The rats were divided into five groups (weighing 100-150) each group contains 6 animals. Group 1: received drug vehicle only (0.3% CMC) for 60 days with normal diet (20 g/day/rat), group 2: received atherogenic diet (sham control) (20 g/day/rat) only for 60 days, group 3: received AD (20 g/day/rat) for 60 days. After 45 days, animals were treated with Pioglitazone (3 mg/kg/day orally) for 15 days along with AD, group 4: received AD (20 g/day/rat) for 60 days. After 45 days animals were treated with Fenofibrate (3 mg/kg/day, orally) for 15 days along with AD. Group 5: received AD (20 g/day/rat) for 60 days. After 45 days animals were treated with combination of Pioglitazone (3 mg/kg/day)+Fenofibrate (3 mg/kg/day orally) for 15 days along with AD.

Animals were divided into five groups and animals in group 2 to 5 were fed with atherogenic diet for 60 days. Drugs were administered to animals in group 3 to 5 for last fifteen days as described above. During this period body weight was observed on day -0, 45 and 60. On day 60 animals were euthanized with excess dose of thiopental sodium and blood was collected and stored for 10 min at room temperature without an anticoagulant. Coagulated blood was centrifuged at 2500-3000 rpm for 15 min and serum was separated and stored at 4°C to estimate the following parameters:

- Serum lipid parameters
- Biochemical's parameters

The liver, heart and kidney were excised, cleaned with water, dried with filter paper and weighed. Further, the liver and heart were stored in 10% neutral formalin buffer for histopathology studies.

Relative organ weight analysis: On day 60 animals were euthanized with excessive dose of thiopental sodium and Liver, heart and kidneys were excised, washed with water, dried with filter paper and weighed.

$$\text{Relative organ weight} = \left(\frac{\text{Weight of the organ (g)}}{\text{Weight of the body (g)}}\right) \times 100$$

RESULTS AND DISCUSSION

Effect of pioglitazone, fenofibrate and combination of both on lipid profile in triton induced rats: The results reveal that, the rats treated with triton showed highly significant ($p<0.001$) increase in serum cholesterol and triglycerides levels when compared with control animals. Whereas, animals in group 3 (Triton+ pioglitazone), group 4 (Triton+ fenofibrate) and group-5 (Triton+pioglitazone+ fenofibrate) reversed significantly ($p<0.001$) the elevated levels of serum cholesterol and triglycerides when compared with group 2 (triton induced hyperlipidemia). However, the animals treated with combination of pioglitazone and fenofibrate not showed potentiation in their activity when compared with their individual treatment in triton induced hyperlidemia as shown in Table 1.

Effect of pioglitazone, fenofibrate and combination of both on body weight in rats fed with atherogenic diet: The present study shows that, there was a significant increase in body weight in all the groups when compared with control. Whereas, no significant change in body weight was observed in group 3, group 4 and group 5 when compared with group 2 (AD treated) as shown in Table 2 and 3.

Table 1: Effect of pioglitazone, fenofibrate and combination of both on serum lipid parameters in triton induced rats

Treatment/dose (mg kg^{-1} b.wt.)	Serum cholesterol (mg dL^{-1})	Serum triglycerides (mM)
Vehicle control	41.62±1.3	45.25±2.04
Triton 350 mg	295.12±20.7^{+++}	307.75±30.20^{+++}
Triton + pioglitazone	85.00±6.1***, $^{+}$	76.00±7.1***
Triton + fenofibrate	80.25±3.4***	72.00±8.9***
Triton + pioglitazone + fenofibrate	105.00±4.05***$^{+++}$	82.50±7.4***

Values are expressed as Mean±SEM (n = 8), vehicle (normal saline), CMC: carboxy methyl cellulose $^{+++}p<0.001$, $^{++}p<0.01$, $^{+}p<0.05$ compared with control, ***p<0.001, **p<0.01, *p<0.05 compared with triton

Table 2: Effect of pioglitazone, fenofibrate and combination of both on body weigh in rats fed with atherogenic diet

Treatment/dose (mg kg^{-1} b.wt.)	Body weight (g)
Vehicle control	201.66±6.5
Sham control (AD)	286.00±9.3^{+++}
Atherogenic diet + pioglitazone 3 mg	283.67±10.3^{+++}
Atherogenic diet + fenofibrate 3 mg	279.50±7.6^{+++}
Atherogenic diet + pioglitazone 3 mg + fenofibrate 3 mg	281.16±13.3^{+++}

Values are expressed as Mean±SEM (n = 6), vehicle (normal saline), AD: atherogenic diet. $^{+++}p<0.001$, $^{++}p<0.01$, $^{+}p<0.05$ compared with vehicle control, **p<0.001, **p<0.01, *p<0.05 compared with atherogenic diet

Effects of pioglitazone, fenofibrate and combination of both on lipid profile in rats fed with atherogenic diet: The effect of atherogenic diet in animals showed significant ($p<0.001$) increase in ASAT level when compared with vehicle control. In group 3 (Atherogenic diet +pioglitazone), group 4 (Atherogenic diet +fenofibrate) and group-5 (Atherogenic diet + pioglitazone + fenofibrate) showed significant ($p<0.001$) reduction in ASAT levels when compared with group 2 (atherogenic diet). However, no significant change in ALAT level was observed in all treated animals when compared with control as shown in Table 4.

The study reveals that, there was a significant ($p<0.001$ vs. control) increase in serum cholesterol, triglyceride and decrease in HDL-C in atherogenic treated animals. Whereas, significant ($p<0.001$) decrease in serum cholesterol and triglyceride and increase in HDL-C levels were observed in group 3 (Atherogenic diet + pioglitazone), group 4 (Atherogenic diet +fenofibrate) and group-5 (Atherogenic diet + pioglitazone + fenofibrate) when compared with group 2 (AD treated). However, combination of pioglitazone and fenofibrate not showed any synergistic effect when compared with their individual treatment as shown in Table 5.

Thiazolidinediones (TZDs) are potent therapeutic agents that have proven successful in the treatment of type-2 diabetes in rodents and in human (Spiegelman, 1998). These compounds, including troglitazone, rosiglitazone and pioglitazone, are believed to exert their benefit as high affinity agonists of peroxisome proliferators-activated receptor-γ(PPAR-γ), whose subsequent activation of multiple nuclear genes

Table 3: Effect of pioglitazone, fenofibrate and combination of both on (%) relative organ weight in rats fed with atherogenic diet

Treatment/dose (mg kg^{-1} b.wt.)	Heart (%)	Liver (%)
Vehicle control	0.230	2.76
Sham control (AD)	0.249	3.48
Atherogenic diet + pioglitazone 3 mg	0.287	3.41
Atherogenic diet + fenofibrate 3 mg	0.286	3.36
Atherogenic diet + pioglitazone 3 mg+ fenofibrate 3 mg	0.287	3.39

Values are expressed as Mean±SEM (n = 6), vehicle (normal saline), AD: atherogenic diet

Table 4: Effect of pioglitazone, fenofibrate and combination of both on serum biochemical parameters in rats fed with atherogenic diet

Treatment/dose (mg kg^{-1} b.wt.)	ASAT ($IU\ L^{-1}$)	ALAT ($IU\ L^{-1}$)
Vehicle control	156.00±2.4	36.50±1.3
Sham control (AD)	183.50±2.1^{+++}	70.83±0.6^{+++}
Atherogenic diet + pioglitazone 3 mg	160.00±3.05***	67.16±0.4^{+++}
Atherogenic diet + fenofibrate 3 mg	167.16±3.7**	70.16±0.4^{+++}
Atherogenic diet + pioglitazone 3 mg+ fenofibrate 3 mg	164.50±2.4***	67.83±0.5^{+++}

Values are expressed as Mean ± SEM (n=6), vehicle (normal saline), AD: Atherogenic diet. $^{+++}p<0.001$, $^{++}p<0.01$, $^{+}p<0.05$ compared with vehicle control, ***p<0.001, **p<0.01, *p<0.05 compared with atherogenic diet

Table 5: Effect of pioglitazone, fenofibrate and combination of both on serum lipid profile in rats fed with atherogenic diet

Treatment/dose (mg kg^{-1} b.wt.)	Serum cholesterol (mg dL^{-1})	Serum triglycerides (mM)	HDL-C (mg dL^{-1})
Vehicle control	45.67±1.8	53.30±2.07	32.30±0.7
Sham control (AD)	106.83±1.92^{+++}	183.83±15.7^{+++}	38.83±0.3^{+++}
Atherogenic diet +pioglitazone 3 mg	74.67±1.69^{+++}	73.16±4.7***	50.30± 0.5^{+++},***
Atherogenic diet +fenofibrate 3 mg	81.17±2.41^{+++}, ***	77.83±6.5***	42.67±0.5^{+++},**
Atherogenic diet +pioglitazone 3 mg+ fenofibrate 3 mg	84.00±6.3^{+++}, ***	69.67±6.9***	49.67±0.3^{+++}, ***

Values are expressed as Mean±SEM (n = 6), vehicle (normal saline), AD: atherogenic diet. $^{+++}$p<0.001, $^{++}$p<0.01, $^{+}$p<0.05 compared with control, **p<0.001, **p<0.01, *p<0.05 compared with sham control atherogenic diet

reduces hyperlipidemia and hyperglycemia and improves insulin sensitivity. Included among the many actions of TZDs are shifts in systemic lipid profiles, with decreases in serum lipid concentrations.

Our present reports reveal that pioglitazone (PPARγ agonist) and fenofibrate (PPARα agonist) has showed a significant decrease in elevated serum triglycerides and cholesterol and increase in HDL cholesterol in atherogenic diet and decrease in elevated serum triglycerides and cholesterol in triton induced hyperlipedemia. It shows that PPARγ agonists are improve insulin sensitivity, could be expected in lowering circulating triglycerides and cholesterol and raise in HDL cholesterol levels. PPARγ agonists promote the trapping and storage of free fatty acids within adipocytes ,a circumstance bound to both increase fat mass and improve insulin sensitivity and dyslipidemia by reducing fatty acid flux to liver and skeletal muscles and also by induction of glycerol kinase expression and activity in rat adipocytes.

The administration of fenofibrate (PPARα agonist) induced modifications of plasma lipid levels, with a significant decrease in triglycerides and cholesterol and an increase in HDL. The decrease in circulating triglycerides has been attributed to a stimulation of the degradation of triglycerides through increased expression and activity of lipoprotein lipase and to a decrease of hepatic synthesis and secretion of triglycerides (Staels *et al*., 1998). These results strongly suggest that the modifications of the expression of several key genes of liver fatty acids metabolism observed in fenofibrate treated hamsters (Guo *et al*., 2001), i.e., due to inhibition of acetyl -CoA carboxylase and fatty acid synthase and stimulation of acyl-CoA oxidase expression.

Fatty acids taken up by the liver originate mainly from non-esterified fatty acids carried by serum albumin and from the hydrolysis of triglycerides. Triglycerides are hydrolyzed extracellulary in glycerol and fatty acids by the lipoprotein lipase (LPL), whose gene is stimulated by PPARs . Once imported into hepatocytes, fatty acids are activated into acyl-CoA thioesters by various acyl-CoA synthetases (ACS), one of which, the long-chain fatty acid ACS, is regulated by PPAR-α at the transcriptional level (Schoonjans *et al*., 1995). Acyl-CoA may then either be esterified or alternatively, enter the pathway of β-oxidation. All three enzymes involved in the peroxisomal β-oxidation pathway, e.g., Acyl-CoA oxidase (ACO), enoyl-CoA hydratase/dehydrogenase bifunctional enzyme (HD) and Keto-Acyl-CoA thiolase, are direct PPAR-α target genes (Drayer *et al*., 1992; Lee *et al*., 2001). Long (C14 to 20) and medium-chain (C8 to C12) fatty acids can be oxidized either in peroxisomes or in mitochondria. The flux of fatty acids in to mitochondria is controlled by a carnitine-dependent facilitated transport system. Interestingly, one of its critical components, carnitine palmitoyl transferase-1 (CPT-1), is strongly induced by peroxisome proliferators and fatty acids (Brady *et al*., 1989). Thus the gene encoding CPT-1probably represents another PPAR-α target gene. PPAR-α further directly regulates the mitochondrial β-oxidative spiral by stimulating the expression of the medium-chain acyl-CoA dehydrogenase (MCAD) gene, the promoter of which contains a functional PPRE. Finally, in liver, most of the acetyl-CoA derived from fatty acid β-oxidation is converted into ketone bodies (mainly acetoacetate and 3-hydroxybutyrate). The rate limiting enzyme of this last pathway, the hydroxymethylglutaryl-CoA synthatase, is controlled by PPAR-α (Rodriguez *at al*., 1994). The levels of PPAR-α mRNA and proteins are stimulated in liver by glucocorticoid, resulting in a potentiation of the efficiency of PPAR-α signaling pathway (Lefebvre *et al*., 1997). In contrast, insulin counteracts the stimulatory action of glucocorticoids. Accordingly, PPAR-α expression is stimulator during the stress situation, mainly by elevated circulating glucocorticoid levels and after fasting, probably by means of both increased glucocorticoid and increased insulin levels. Hence, the regulatory action PPAR-α appears to be reinforced precisely according to the physiological situation that involves fatty acid mobilization and possibly, PPAR-α receptor activation.

PPARs were proposed to play an important role in energy homeostasis early after the identification of ACO as a target gene and fatty acids as activators. Indeed, PPAR-α and PPAR-γ appear to regulate the two arms of lipid homeostasis, fatty acid oxidation and triglyceride accumulation, respectively. Specifically, PPAR-α stimulates fatty acid catabolism I several tissues known for their high rates of fatty acid oxidation such as liver,

kidney and brown adipose tissue, whereas PPAR-γ favors fatty acid storage by simulating triglyceride accumulation in adipocytes. The differential expression of both PPAR subtypes would largely explain their differential physiological actions. In brown adipose tissue, the two subtypes could be expected to stimulate preferentially a different subset of target genes involved in the oxidative and lipogenic pathways, respectively. When specific activators of PPAR subtypes become available, it should be possible to test whether PPAR-α and PPAR-γ differentially regulate the two opposite metabolic pathways in a single cell type.

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