Review Article

Current Pharma Research

ISSN: 2230-7842

CPR 3(2), 2013, 846-854.

PPAR Dual Agonist: In Treatment of Type II Diabetes.

***[1]Kishan Patel, [1]R. N. Sharma, [1]L. J. Patel, [2]G. M. Patel**

[1]S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana-Gozaria Highway, Kherva, Gujarat, India, [2]K. B. Institute of Pharmaceutical Education and Research, Gandhinagar, Gujarat, India.

Abstract

Peroxisome proliferator-activated receptors (PPARs) are central regulators of lipoprotein metabolism and glucose homeostasis that are considered particularly useful for improving glycemic control and co morbidities in patients with type II diabetes mellitus. Clinical trials of PPAR-α agonists have demonstrated efficacy in reducing cardiovascular events; however, these benefits have been confined to subgroups of patients with low levels of high-density lipoprotein cholesterol or high levels of triglycerides. While activators of PPAR-γ reduce early atherosclerotic lesions and reduce cardiovascular events, these agents have the effect of increasing fluid retention in patients, which results in more hospitalizations for congestive heart failure. The PPAR α / γ dual agonists are developed to increase insulin sensitivity and simultaneously prevent diabetic cardiovascular complications. Such compounds are under clinical trials and proposed for treatment of type II diabetes with secondary cardiovascular complications. However, PPAR α / γ dual agonists such as muraglitazar, tesaglitazar and ragaglitazar have been noted to produce several cardiovascular risks and carcinogenicity, which raised number of questions about the clinical applications of dual agonists in diabetes and its associated complications. Therefore future studies of PPAR-γ agonists or dual PPAR-α/γ agonists will require further delineation of the risk profile to avoid adverse outcomes in susceptible patients.

Key Words

Peroxisome proliferated-activated receptors, Type II diabetes, Dual agonist.

Introduction

Identification of molecular mechanisms of the transducer proteins involved in metabolic and anabolic pathways is crucial for understanding the energy homeostasis in the human body and to develop new therapeutic agents for the treatment of chronic metabolic disorders such as, atherosclerosis and diabetes. Cardiovascular disorders are the most common cause of morbidity and mortality in diabetes and their prevalence is increasing constantly in developing countries. Diabetes is a metabolic disorder characterized by insulin resistance and reduced secretion of insulin and is associated with cardiovascular pathologies such as atherosclerosis, hypertension,

***Corresponding Author:**
kishan_birju@yahoo.com

endothelial dysfunction, cardiac dysfunction and myocardial infarction. The peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes[1]. PPARs play essential roles in the regulation of cellular differentiation, development, and metabolism (carbohydrate, lipid, protein), and tumorigenesis[2] of higher organisms[3, 4].

Types of PPAR

To date, three major types of PPAR, encoded by separate genes, have been identified; they are PPAR- α (NR1C1), PPAR- δ/ β (NR1C2) and PPAR-γ (NR1C3). Functions of PPARs and conditions that are the targets of PPAR agonists are summarized in Table 1.

Like other nuclear receptors, PPARs are modular in structure and contain the following functional domains:

- (A/B) N-terminal region
- (C) DBD (DNA-binding domain)
- (D) flexible hinge region
- (E) LBD (ligand binding domain)
- (F) C-terminal region

The DBD contains two zinc finger motifs, which bind to specific sequences of DNA known as hormone response elements when the receptor is activated. The LBD has an extensive secondary structure consisting of 13 alpha helices and a beta sheet[5]. Natural and synthetic ligands bind to the LBD, either activating or repressing the receptor.

PPARs (PPARα, PPARγ, PPARβ/δ) are transcription factors that regulate gene transcription by binding to specific DNA response elements upon ligand activation and heterodimerization with the 9-cis retinoic acid receptor. Ligand-induced conformational changes induce the recruitment of coactivators that transmit transcription activation signals to basal transcriptional machinery[6]. Depending upon the activating ligand, different receptor conformations are adopted, leading to differential coactivator recruitment and subsequent downstream effects on gene expression (Figure 2). Selective modulation has been described both for PPARα (selective peroxisome proliferator-activated receptor α modulator [SPPARαM])[7] and PPARγ [SPPARγM][8], and could explain the differences seen in biological activity of ligands, even those belonging to the same pharmacological class. Thus, the selective modulator concept provides a molecular approach to develop ligands devoid of adverse effects, while maintaining the desirable biological efficacy[9]. The gene transcription mechanism is identical in all PPAR subtypes. Important biological effects of each individual PPAR isoform are shown in Figure 3.

PPAR Ligands:

Chemical structures of some PPAR ligands are given below (Figure 4):

PPARα AND PPARγ AS A DUAL AGONIST:

PPARα/γ dual agonists are new class of drugs, which have been developed to target both PPARα and PPARγ simultaneously in order to produce synergistic anti diabetic and cardio

protective effects. Simultaneous activation of PPARα and γ activators might, through a complementary mechanism of action, alter the tissue distribution of fatty acids by stimulating their uptake and utilization in adipose tissue, liver and skeletal muscle (Figure 5). The recently investigated PPARα/γ dual agonists are naveglitazar, netoglitazone, muraglitazar, ragaglitazar, tesaglitazar, imiglitazar, MK 767, LY 929 and LSN862[10]. The PPARα/γ dual agonists are noted to reduce triglycerides, raise cardioprotective HDL levels and consequently improve insulin sensitivity[6,11–13]. Treatment with ragaglitazar significantly reduced blood pressure in spontaneously hypertensive rats and improved endothelial function in Zucker diabetic fatty (ZDF) rats when compared with pioglitazone treatment[14]. Moreover, it has been reported that treatment with DRF 2519, a PPAR α/γ dual agonist has resulted in better lipid profile and enhanced aortic smooth muscle relaxation in ZDF rats when compared with rosiglitazone treatment[15]. These results exemplify the beneficial effects of dual PPAR α/γ dual agonist in improving the cardiovascular risk factors. The PPARγ agonists are shown to increase adipogenesis and body weight, whereas PPARα agonists counteract these effects by decreasing food intake and fat deposits in animals[11, 16]. Thus, increase in body weight observed with PPARγ treatment may not be associated with PPARα/γ dual agonists. However, such effects are not clear in human situation. The muraglitazar has efficiently reduced hemoglobin A_1C and improved the lipid profile in diabetic patients[13]. However, the clinical study with muraglitazar was discontinued recently due to higher incidence of edema and heart failure[17]. Tesaglitazar has been shown to reduce atherosclerosis in the LDL receptor deficient mice probably by its direct actions on the vessels[18]. Further, tesaglitazar has been suggested to have beneficial effects on both hyperglycemia and dyslipidemia[19]. However its development has been terminated due to the elevated serum creatinine and associated decreases in glomerular filtration rate[20]. These discouraging results with muraglitazar and tesaglitazar have raised a number of questions about the role of PPARα/γ dual agonists in diabetic complications. The balanced binding affinity of PPARα/γ dual agonists towards both the receptor subtypes is necessary to give optimal biological effects of both PPARα-mediated and PPARγ-mediated actions. Supra therapeutic activation of PPARα or PPARγ may be associated with adverse effects such as carcinogenesis, renal dysfunction, fluid retention and heart failure[21–23]. The muraglitazar has high affinity towards PPARγ and tesaglitazar possesses more affinity towards PPARα[20]. Thus, the lack of balance in binding affinity may lead to supra-therapeutic expression of the stronger agonist which may cause adverse effects. The clinical study in which dual PPARα/γ stimulation by means of concomitant administration of fenofibrate and rosiglitazone

improved atherogenic dyslipidemic profile in patients with good tolerability[24]. Hence, the future development of dual agonists with selective and balanced PPARα/γ activity may be appropriate and sensible option. One of the challenges of the development of PPAR dual agonists is that one single molecule has to cause the appropriate pharmacological profile by interaction with two or more different receptors that are expressed in two or more different sites of action.

Conclusion

Cardiovascular complications are known to alter the life style and reduce the life time of patients with diabetes. PPAR agonists have emerged as a promising group of agents for treating Type II diabetes and associated cardiovascular risk factors. The dual agonists have been proposed to reduce hyperglycemia, hyperlipidemia and simultaneously prevent the progression of cardiovascular complications. Unfortunately, the clinical development of few PPARα/γ dual agonists such as muraglitazar and tesaglitazar etc. has been discontinued due to their undesirable pharmacological effects. The side effects of these agents may be due to their imbalanced and supra-therapeutic activity on PPARγ and PPARα. Therefore, the dual agonists with selective and balanced agonistic activity on PPARα/γ could be an appropriate therapeutic option. The PPARα/δ dual agonists and PPARα/γ/δ pan agonists are currently under development to prevent the diabetic cardiovascular complications.

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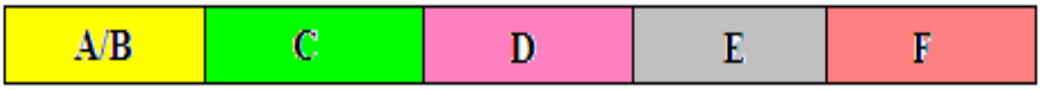

Fig. 1: Schematic representation of the functional domains of PPARs.

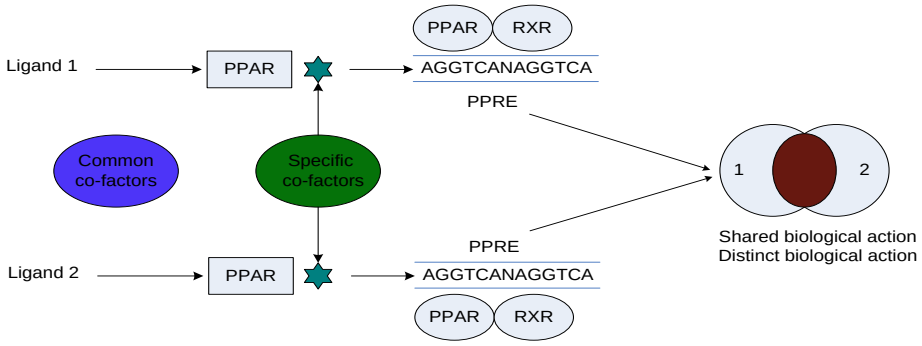

Fig. 2: Ligands interact with the PPAR receptor to induce ligand-specific conformational changes.

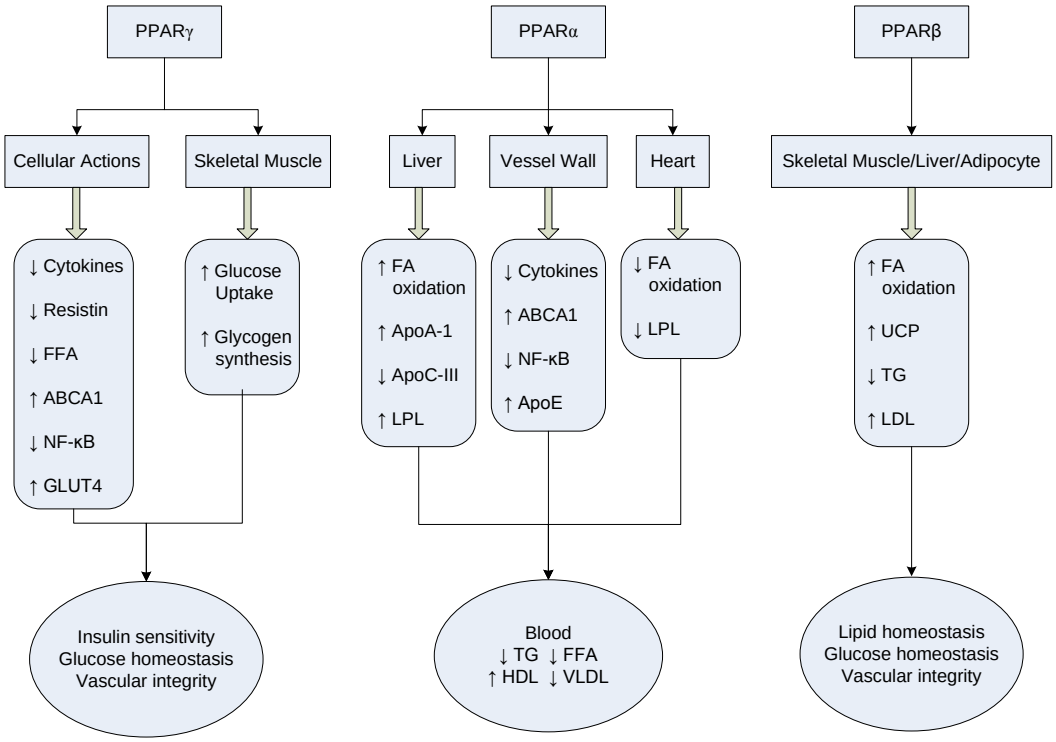

Fig. 3: PPARs gene transcription mechanisms and their biologic effects in different organs.

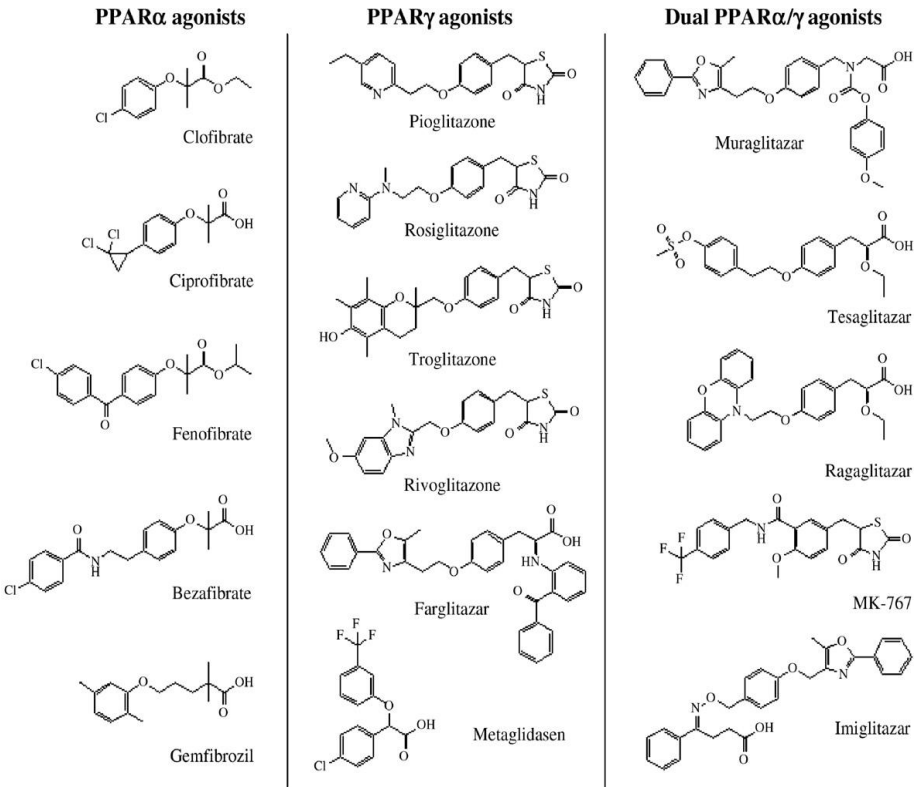

Fig. 4: Chemical structures of PPAR ligands.

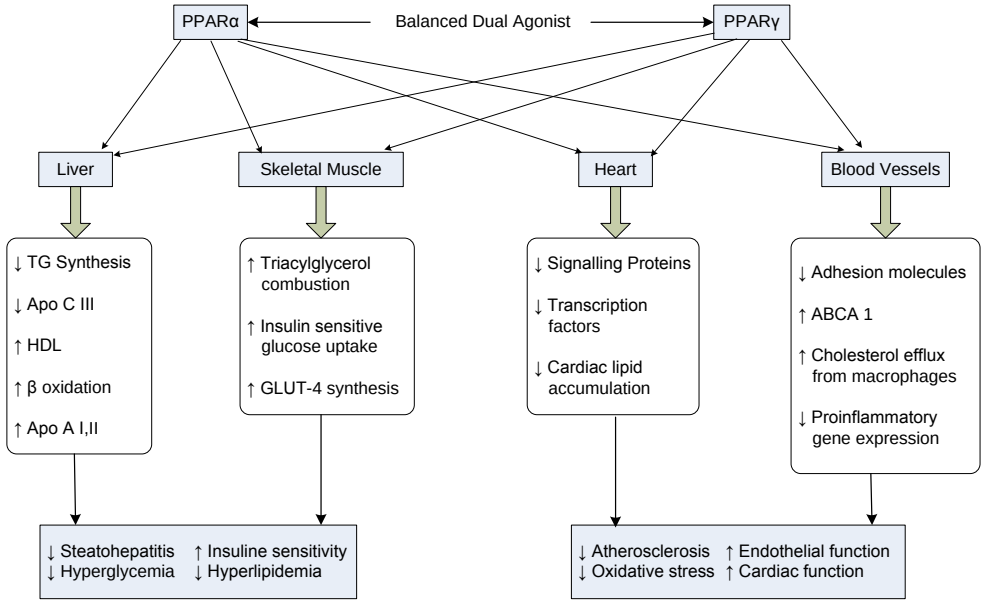

Fig. 5: The synergistic beneficial actions of balanced PPARα/γ dual agonists.

Table 1: Human PPARs as Targets in the Metabolic Syndrome.

Receptor	Functions	Conditions targeted by Agonists
PPARα	Controls lipid metabolism.	Atherogenic dyslipidemia (elevated serum triglycerides and low HDL). Target of fibrate drugs.
PPARγ	Controls glucose metabolism and adipocyte differentiation.	Insulin resistance in type 2 diabetes. Target of thiazolidinediones.
PPARδ	Appears to control multiple aspects of the metabolic syndrome.	Metabolic syndrome, obesity, atherosclerosis.

Table 2: Current Status of Preclinical and Clinical Progress of PPAR Dual and Pan Agonists[25]

Compound	Nature of agonist	Targeted disease	Status
Muraglitazar	Dual PPARα/γ	Metabolic disorders and Type II diabetes	Discontinued in 2006 due to adverse cardiovascular events (myocardial infarction, stroke, heart failure, and transient ischemic attack)
Tesaglitazar (AZ-242)	Dual PPARα/γ	Type I diabetes, Type II diabetes, cardiac arrhythmia, and lipid metabolic disorder	Discontinued in 2006 due to elevated creatinine, ↓GFR, weight gain, anaemia, and leukopenia
Naveglitazar (Y-818)	Dual PPARα/γ	Cardiovascular disease, lipid metabolism disorder, metabolic disorder, and Type II diabetes	Further development has been stopped
Ragaglitazar (DRF-2725)	Dual PPARα/γ	Type II diabetes	Discontinued in 2004 due to weight gain, oedema, anaemia, and urothelial cancer
Farglitazar	Dual PPARα/γ	Type II diabetes	Discontinued in 2003
KRP-297, MK 767	Dual PPARα/γ	Type II diabetes	Discontinued in 2004 due to Hemangiosarcoma
JTT-501	Dual PPARα/γ	Type II diabetes	Discontinued in 2002 due to oedema
Imiglitazar (TAK559)	Dual PPARα/γ	Type II diabetes	Discontinued in 2004 due to abnormalities in liver enzyme tests
Chiglitazar (CS038)	Dual PPARα/γ	Type II diabetes and metabolic disorders	Phase II clinical trial
MK-0767, KRP-297	Dual PPARα/γ	Type II diabetes	Discontinued
Netoglitazone (MCC-555 or RWJ-241947)	Dual PPARα/γ	Atherosclerosis and Type II diabetes	Phase II clinical trial
Compound 3q	Dual PPARα/γ	Type II diabetes	Discontinued due to tumourogenesity and mild hepatotoxocity
5-Substituted 2-benzoylamino-benzoic acid derivatives: (BVT-142)	Dual PPARα/γ	Type II diabetes	Preclinical
O-arylmandelic acid derivatives	Dual PPARα/γ	Not defined	Preclinical
Azaindole-α-alkyloxy-phenylpropionic acid	Dual PPARα/γ	Not defined	Preclinical
Oxime substituted with α-substituted-β-phenylpropionic acid derivatives with oxime	Dual PPARα/γ	Not defined	Preclinical
Amide substituted with α-substituted-β-phenylpropionic acid derivatives	Dual PPARα/γ	Not defined	Preclinical
2Alkoxydihydro cinnamate derivatives	Dual PPARα/γ	Type II diabetes and atherosclerosis	Preclinical
TZD-18	Dual PPARα/γ	Not defined	Preclinical
α-Aryloxyphenyl acetic acid derivatives	Dual PPARα/γ	Not defined	Preclinical
Tricyclic-α-alkyloxyphenyl propionic acids	Dual PPARα/γ	Atherosclerosis and Type II diabetes	Preclinical
T659 (T913659)	Dual PPARα/δ	Not defined	Preclinical
Halofenate	PPARγ partial agonist	Not defined	Preclinical
PA-082	PPARγ partial agonist	Not defined	Preclinical
Bezafibrate	Pan PPARα/γ/ δ agonist	Not defined	Marketed
Carbazole-derived compounds	Pan PPARα/γ/ δ agonist	Not defined	Preclinical
BPR1H036	Pan PPARα/γ/δ agonist	Cardiovascular diseases, atherosclerosis and Type II diabetes	Preclinical
PLX-204 and GW-625019	Pan PPARα/γ/δ agonist	Pulmonary hypertension and Type II diabetes	Phase I clinical trial
GW-677954	Pan PPARα/γ/δ agonist	Type II diabetes	Phase II clinical trial

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