BENEFICIAL EFFECTS OF VARIOUS PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS ON LIPID PROFILES AND OBESITY: A REVIEW

Shahad W. Ahmed* and Nada N. AL-Shawi

*Department of Clinical and Laboratory Sciences, College of Pharmacy, University of Baghdad, Baghdad, Iraq. 
2 Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Peroxisome proliferator-activated receptors are family of nuclear receptors and are set of three receptor sub-types encoded by distinct genes: PPAR-α is also known also known nuclear receptor subfamily 1, group C, member 1 (NR1C1) and it is highly expressed in liver, skeletal muscle, kidney, heart and the vascular wall, PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3) and it is predominantly detected in adipose tissue, intestine and macrophages.

Such family of receptors acts as lipid sensors and regulates a broad range of genes in many metabolically-active tissues; where, such receptors family can regulate lipid and lipoprotein metabolism, glucose homeostasis, weight gain associated with insulin resistance in type 2 diabetic patients, cell proliferation, fibrogenesis and differentiation.

The peroxisome proliferator-activated receptors are activated by fatty acid derivatives and pharmacological agents such as fibrates and thiazolidinediones (glitazones) which are specific for PPAR-α and PPAR-γ respectively. Furthermore, PPAR-β/δ is also called fatty acid-activated receptor; and its activation in skeletal muscle cells can increase the uptake and catabolism of fatty acids through β-oxidation.

The dual peroxisome proliferator-activated receptor agonist activate both alpha and gamma isoforms; and the pan PPAR agonist can activate all of alpha, beta/delta, and gamma isoforms. The current review illustrates the effect of various PPAR agonists on obesity.

Key words: Peroxisome proliferator-activated receptors, natural agonists, synthetic agonists, lipid profile, obesity.

Introduction

General Considerations

Peroxisome proliferator activated receptors (PPARs) are a group of nuclear receptor proteins which can act as transcription factors that play important roles in the regulation of genes that essential for cell differentiation, growth and various metabolic processes such as carbohydrates, lipids, and proteins metabolism (Michalik et al, 2006). Moreover, PPARs also known as insulin and lipid sensors (Grygiel-Gorniak,2014).

Such receptors subtypes are ligand-activated transcription factors consisting of an N-terminal DNA binding domain and a C-terminal Ligand Binding Domain (LBD) (Lagana et al, 2016). Furthermore, the family of PPARs consists of three isoforms: PPAR-α (NR1C1), PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3); where, PPAR-α is highly present in the metabolically-active tissues; moreover, the PPAR-γ, which has three forms: PPARγ1, PPARγ2 and PPARγ3 are primarily expressed in white and brown adipose tissue; and the third isoform (PPARβ/δ) is practically-found in all tissues (Xu et al.,2018). All the three PPARs forms have natural agonists, such as variety of polyunsaturated long-chain fatty acids and arachidonic acid derivatives; in addition, each form of PPAR can be activated by synthetic agonists (Fan et al, 2018).

Peroxisome proliferator activated receptors (PPARs) types:

Peroxisome proliferator activated receptor-
alpha (PPAR-α)

Peroxisome proliferator activated receptor-alpha (PPAR-α) is widely expressed in tissues with elevated fatty acid (FAs) catabolism level; where, such receptor form can regulate genes that control FA uptake; and it can play a major role in the oxidation of FAs in the liver; moreover, PPAR-α is highly-expressed in tissues that oxidize FAs at a rapid rate; while, such receptor form is expressed in low levels in small and large intestine, adrenal gland, and skeletal muscle (Braissant et al,1995). Furthermore, the activation of PPAR-α can reduce the quantities of available FAs for synthesis of triglyceride and very low density lipoprotein (VLDL) in liver; in addition, its activation can promote FA oxidation in fasting (Sander et al,1999).

The physiological role of PPAR-α receptor form is to detect the overall flux of dietary FAs; where, it can raise the apo-lipoproteins production such as apo-AV, apo-CIII, resulting in reduced of triglycerides (TGs) level in circulation; and the activation of PPAR-α can decrease the levels of TGs in the liver and the circulation; furthermore, some of the PPAR-α agonists can mildly-increase high density lipoprotein-cholesterol (HDL-C) level in humans (Ide et al,2003); for example, fenofibrate increased HDL-C levels by 10% to 25%, to a degree directly dependent of baseline TG and HDL-C levels (Michel et al,2008).

The PPAR-α binds to number of ligands, for example, arachidonic acid (AA) metabolites such as leukotrienes (LTs), prostaglandins (PGs), and to a class of lipid lowering drugs that primarily mediate their clinical effects by activating PPAR-α such as synthetic fibrate drugs (bezafibrate, fenofibrate, clofibrate and gemfibrozil) (Sher et al,1993).

Peroxisome proliferator activated receptor-gamma (PPAR-γ)

Two distinct N-terminal isoforms named as PPARγ1 and PPARγ2 have been found in mice and humans (Mukherjee et al,1997).

The PPAR-γ primarily exists in adipose tissue, intestine and macrophages. Two isoforms of PPAR-γ are observed in the humans and mouse: PPAR-γ1, which present in almost all tissues except muscle, and PPAR-γ2, which mainly present in adipose tissue and the intestine (Park et al,2017). The PPAR-γ has been involved in the pathology of many diseases like diabetes, and atherosclerosis; where, it has been shown that such form of receptor be an active regulator of target genes associated in lipid and glucose metabolism; and the PPAR-γ agonists are effective antidiabetic agents such as most insulin-sensitizing medications [(i.e., the thiazolidinediones) (glitazones)]; where, such group of drugs can activate PPAR-γ and is associated with enhanced insulin sensitivity as a way of lowering glucose serum level without increasing pancreatic insulin secretion (Willson et al,2000); furthermore, PPAR-γ agonists may also have beneficial effects in treatment of other disorders such as atherosclerosis, inflammation and cancer (Kim et al,2015); moreover, PPAR-γ agonists have been used in the treatment of hyperlipidemia (Burdick et al,2005) and increase HDL-C levels (Willson et al,2000); additionally, activation of PPAR-γ can reduce the inflammatory response of certain cells, especially endothelial cells (Hamblin et al,2009).

Peroxisome proliferator activated receptor-delta/beta (PPAR δ/β)

Peroxisome proliferator-activated receptor-delta [(PPAR-δ), also known as PPAR-β] is a member of the PPAR subgroup in the nuclear receptor superfamily. Although PPAR-δ is widely expressed, its level of expression in different tissues differs depending on the type of cell and the state of the disease (Xu et al,2013).

The essential feature of PPAR-δ is modulation of cellular energy consumption; and in muscle cells, activation of PPAR-δ by ligands can shift energy production to FAs oxidation from glycolysis as an alternative energy source, which increase muscle endurance (Fan et al,2017). The PPAR-δ is also called fatty acid-activated receptor (FAAR); and its activation in skeletal muscle cells can increase the uptake and catabolism of FAs through β-oxidation (Holst et al,2003).

In addition to its role on fatty acid oxidation, PPAR-δ is highly found in pancreatic islet beta cells and its activation can stimulate insulin secretion which in turn can lead to enhance blood glucose homeostasis through a number of mechanisms (Iglesias et al,2012). Researchers reported that PPAR-δ agonists may have beneficial effects in the metabolic syndrome via increasing FAs consumption in the adipose tissue and skeletal muscle and weight loss could be expected as well (Luquet et al,2005).

A potent ligand, GW501516, can cause a significant dose-dependent rise in HDL-C while it can reduce low density lipoprotein-cholesterol (LDL-C), triglycerides (TGs) and insulin levels in the insulin resistant middle-aged obese rhesus monkeys; furthermore, GW501516 was also reported to enhance expression of the reverse cholesterol transporter ATP-binding cassette A1 and it can induce apolipoprotein A1-specific cholesterol efflux (Oliver et al,2001).
Dual peroxisome proliferator-activated receptor (PPAR) agonists:

Dual PPAR Alpha/Gamma

The dual peroxisome proliferator-activated receptor alpha and gamma isoforms of the family of nuclear transcription factors are considered as medical targets for therapeutic action of drugs that treat not only the hyperglycemia of diabetes, but also the dyslipidemia (Ahmed et al,2007); where, such isoforms have been shown to improve obesity and diabetes symptoms. Fibrates can enhance lipid profiles; and TZDs (glitazones) can reduce blood glucose and inflammation; furthermore, it has been shown that fibrates can act synergistically with TZDs to improve obesity-induced insulin resistance (Tsuchida et al,2005).

Since PPARs have key roles as energy homeostasis and as regulators of inflammation; thus, much research has been directed towards developing synthetic PPAR ligands. It was realized that in the 1990s the lipid-modifying properties of the fibrates were attributable to selectively activate PPAR-α; moreover, TZDs, which are structural analogs of fibrates, were eventually shown to activate PPAR-γ; furthermore, synthetic PPAR-γ agonists have been established, and preclinical research is clarifying this receptor’s role; additionally, agents that activate multiple PPAR isoforms are being developed such as dual PPARα/γ and pan-PPAR α/γ/δ agonists (Bart et al,2005).

Therapeutic effect of PPAR agonists:

Thiazolidinediones (TZDs) (Glitazones)

Thiazolidinediones (TZDs) (glitazones) is a class of heterocyclic compounds composed of a five-membered C3NS ring. Such family of medications is used for the treatment of diabetes mellitus type 2 that which introduced in late 1990s (Hulin et al,1996).

The TZDs or glitazones are family of antidiabetic drugs and the first compounds known as high affinity PPAR-γ agonists, are rosiglitazone, pioglitazone, and troglitazone (Henke et al,1998;Cobb et al,1998). Also, TZDs (glitazones) have potent anti-inflammatory, antithrombotic effects that may improve glucose tolerance and the long-term cardiovascular (CV) risk associated with atherosclerosis in type-2 diabetes patients (Staels,2005). Additionally, it has been reported that the beneficial effects of TZDs on glucose metabolism are regulated by binding to PPAR-γ, and induction of adipogenesis, which is considered as the mechanism of weight loss by TZDs (glitazones) (Spiegelman,1998).

Researchers also reported that troglitazone was shown to have a dose-response effect in improving ovulation and hirsutism that appeared to be mediated by decreased levels of hyper-insulinemia and decreased levels of free testosterone (Azziz et al,2001). But, it has been published that troglitazone is removed from the worldwide market due to its hepatotoxicity; while, pioglitazone and rosiglitazone are still available today; where, both medications are effective in improving insulin sensitivity, glycemic control, ovulation and menstrual regularity without hepatotoxicity seen in troglitazone(Stout et al,2005).

Fibrates

The class of fibrate medications has been in use since the late 1960s; where, clofibrate is the first member followed by fenofibrate, bezafibrate, gemfibrozil, and ciprofibrate over the next few decades (WHO,1980).

The fibrates are synthetic ligands bind to peroxisome proliferator–activated receptor (PPAR-α) (Berger et al,2002) which clinically minimize TG serum levels, and this depends on PPAR-α pathways that increased FAs uptake (by inducing FAs transport protein), increased FA β-oxidation, and increased transcription of lipoprotein lipase (LPL) and decrease transcription of apolipoprotein (CPU) C-III that block LPL activity (Watts et al,1999). Furthermore fibrates has been shown to decrease serum TGs and increase HDL-c through PPAR-α-mediated action and also such class has anti-inflammatory and anti-atherosclerotic effect (Marx et al,2001). Additionally, fenofibrate, an agonist of PPAR-α can decrease body mass independent of food intake (Rachid et al,2015).

Aleglitazar

Aleglitazar, a dual peroxisome proliferator-activated receptor agonist that has beneficial effects on lipid profiles (Lincoff et al,2014), its agonistic activity for PPAR-α can control lipid levels which in turn improve dyslipidemia; and its agonistic activity for PPAR-γ regulates glucose levels that improve insulin sensitivity in diabetes (Henry et al,2009). Moreover, aleglitazar can improve glycemic control and not only reduce fasting plasma glucose, fasting insulin, and the glycated hemoglobin (HbA1c) levels in monkeys, but it also can improve insulin sensitivity (Barbara et al,2011). In addition to its glycemic and lipid benefits, aleglitazar can minimize PPAR-related weight gain and edema in patients with type 2 diabetes (Bénardeau et al,2009).

Bezafibrate

Bezafibrate (marketed as Bezalip and several other names) is a fibrate drug, an agonist of PPAR-α and also have high-affinity to PPAR-γ and PPAR-β; so it is
considered as a pan-PPAR agonist (Tenenbaum *et al.*,2005). It is used to treat hyperlipidemia; and it helps to reduced serum LDL-C and TGs, and increase HDL-C (Janos *et al.*,2006). Moreover it has been reported that, bezafibrate is more effective in lowering body weight and blood glucose than fenofibrate in overweight-mice fed with high-fat diet (Fernandes-Santos *et al.*,2009); additionally, it can increase HDL-C, decreases TGs, and enhances insulin sensitivity in diabetic patients(Tenenbaum *et al.*,2006).

**Bavachinin (BVC)**

Bavachinin (BVC) is a flavonoid that contained within the seed of *Psoralea corylifolia* Linn. plant, which has been used in traditional Chinese medicines to avoid and treat type 2 diabetes in clinical researches; moreover, BVC has been described as a novel natural pan-PPAR agonist in *vivo* and *in vitro* in metabolic syndrome, BVC does not antagonize, but synergizes with TZDs and fibrates. This synergistic effect is induced by binding of BVC with PPAR-γ or -α (Chen *et al.*,2009).

Authors reported that the combination of PPAR-β/δ and PPAR-γ agonists has been shown to reduce insulin resistance, control glucose metabolism and improve exercise capacity; thus, BVC has glucose-lowering effects without weight gain and hepatotoxicity (Balakumar *et al.*,2007).

**IVA337**

The IVA337 is a next-generation pan-PPAR agonist developed to produce moderate and well-balanced activation of the three PPAR isoforms (α, β/δ, and γ); and it displayed an anti-fibrotic efbisyacy superior to selective PPAR-α, PPAR-γ, or PPARβ/δ agonists; this particular agonist have a good efbisyacy and safety profile with no weight gain in pre-clinical models as well as in clinical phase 1 and 2 studies in patients with type 2 diabetes (Wettstein *et al.*,2017).

**Conclusion**

The peroxisome proliferator-activated receptors (PPARs) are family of nuclear receptors and are set of three receptor sub-types: PPAR-α (NR1C1), PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3) each encoded by distinct genes; and act as lipid sensors and can regulate a broad range of genes in many tissues such as liver, adipose tissue, and skeletal muscles. Each form of the PPARs is a therapeutic target that can be activated by natural and synthetic ligands, which may have beneficial effects on lipid profile and obesity.

**References**


Hamblin, M., L. Chang, Y. Fan, J. Zhang and Y. E. Chen (2009) PPARs and the cardiovascular system. *Antioxidants &
Beneficial effects of various peroxisome proliferator-activated receptor agonists on lipid profiles and obesity

redox signaling. 11(6) : 1415-1452.


