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Review

A step ahead of PPARγ full agonists to PPARγ partial agonists: Therapeutic perspectives in the management of diabetic insulin resistance

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ABSTRACT

Described since long as a member of the nuclear receptor superfamily, peroxisome proliferator-activated receptors (PPARs) regulate the gene expression of proteins involved in glucose and lipid metabolism. PPARs indeed regulate several physiologic processes, including lipid homeostasis, adipogenesis, inflammation, and wound healing. PPARs bind natural or synthetic PPAR ligands do function as cellular sensors to regulate the gene transcription. Dyslipidemia, and type 2 diabetes mellitus (T2DM) with insulin resistance are treated using agonists of PPARα and PPARγ, respectively. The PPARγ is a key regulator of insulin sensitization and glucose metabolism, and therefore is considered as an imperative pharmacological target to combat diabetic metabolic disease and insulin resistance. Of note, currently available PPARγ full agonists like rosiglitazone display serious adverse effects such as fluid retention/oedema, weight gain, and increased incidence of cardiovascular events. On the other hand, PPARγ partial agonists are being suggested to devoid or having less incidence of these undesirable events, and are under developmental stages. Current research is on the way for the development of novel PPARγ partial agonists with enhanced therapeutic efficacy and reduced adverse effects. This review sheds lights on the current status of development of PPARγ partial agonists, for the management of T2DM, having comparatively less or no adverse effects to that of PPARγ full agonists.

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1. Introduction

The fundamental cellular events like lipid metabolism, glucose metabolism, cell proliferation, and inflammation are regulated by peroxisome proliferator-activated receptors (PPARs), which are ligand-dependent transcription factors (Brown and Plutzky, 2007). PPARs are the transcriptional factor primarily involved in the regulation of glucose and lipid homeostasis and they are the

Abbreviations: DIO mouse, diet-induced obesity mouse; LBD, ligand-binding domain; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; SGK-1, serum/glucocorticoid-regulated kinase-1; T2DM, type 2 diabetes mellitus; ZDF rat, Zucker Diabetic Fatty rat

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Table 1
Adverse effects of thiazolidinediones.

Assessments	Adverse effects of thiazolidinediones
Body weight	Weight gain and increased adipogenesis (*mainly with rosiglitazone*)
Fluid volume	Fluid retention and peripheral oedema (*mainly with rosiglitazone*)
Cardiovascular events	Increased incidence of cardiovascular events like cardiac hypertrophy, heart failure and myocardial infarction (*mainly with rosiglitazone*)
Skeletal abnormalities	Bone loss and fractures
Urinary bladder pathology	Bladder cancer (*mainly with pioglitazone*)
Liver	Liver toxicity (*mainly with troglitazone*)

molecular pharmacological targets for improvement of metabolic disorders like diabetes mellitus (Cho et al., 2011). Three isoforms such as PPARα, PPARγ and PPARβ/δ have been identified (Brown and Plutzky, 2007). These nuclear receptors regulate several physiologic and pathologic processes that influence lipid homeostasis, inflammation, adipogenesis, reproduction, wound healing, and carcinogenesis (Abbott, 2009; Balakumar and Mahadevan, 2012). The PPARγ has been the most intensively investigated one among three subtypes of PPARs. The PPARγ is abundantly expressed in both white and brown adipose tissue. It plays a key role in adipocyte differentiation and insulin sensitivity (Kubota et al., 1999; Balakumar et al., 2007). PPARγ is also expressed in non-adipose tissues, including heart, kidney, spleen, and components of the vasculature like endothelial and smooth muscle cells (Chetty and Sharma, 2006). PPARγ forms heterodimers with the retinoid X receptor (RXR) that transactivate PPAR-responsive elements (PPREs) of target genes involved in insulin sensitivity, glucose metabolism and immune response (Burgermeister et al., 2006).

Thiazolidinedione class of drugs (*e.g.* rosiglitazone, pioglitazone) activates PPARγ and subsequently improves insulin sensitivity to achieve a persuasive antidiabetic action in patients afflicted to type 2 diabetes mellitus (T2DM) with insulin resistance (Balakumar et al., 2009; Balakumar and Jagadeesh, 2012). The first thiazolidinedione, troglitazone, was approved by the US Food and Drug Administration (FDA) in 1997 and was withdrawn from the market in 2000 due to liver toxicity issues (Bilik et al., 2010; Liao et al., 2010). Other thiazolidinediones, rosiglitazone and pioglitazone were approved by the US FDA in 1999 (Starner et al., 2008; Bilik et al., 2010).

The clinical use of thiazolidinediones like rosiglitazone has been restricted in several countries, including Malaysia (http://www.diabetes.org.my/article.php?aid=837, 2014). In spite of their very potent antidiabetic action, the clinical uses of PPARγ full agonists (thiazolidinediones) are associated with several serious adverse effects (Table 1), including weight gain, increased adipogenesis, fluid retention, peripheral oedema, increased incidence of cardiovascular events like cardiac hypertrophy and heart failure, and bone loss and fractures (Hernandez et al., 2011; Henriksen et al., 2011; Kouskoumvekaki et al., 2013; Jones et al., 2009). Of note, thiazolidinedione-treated diabetic hypertensive patients were at a high risk for angina, congestive heart failure, cerebral vascular accident and myocardial infarction (Wang et al., 2011). These major safety concerns have not only restricted the clinical use of PPARγ full agonists; but also have led to the developmental failure of PPAR full agonists. Intriguingly, however, several PPARγ partial agonists in bench studies are shown devoid or having less incidence of adverse effects that are associated with rosiglitazone-like PPARγ full agonists (Balakumar and Kathuria, 2012; Taygerly et al., 2013; de Groot et al., 2013; Wang, 2014). Worthy of note that PPARγ partial agonist like balaglitazone has been demonstrated clinically exerting good antidiabetic action with reduced adverse effects that are associated with PPARγ full agonist, pioglitazone (Henriksen et al., 2011). In an effort to identify novel PPARγ ligands with an improved pharmacological profile and less adverse effects, current research interest has been shifted towards to the development of potential PPARγ partial agonists. This review will discuss recently identified novel PPARγ partial agonists and their unique pharmacological actions.

2. Undesirable effects associated with the use of PPARγ full agonists: clinical evidences

The clinical use of PPARγ full agonists such as rosiglitazone and pioglitazone has been associated with ominous adverse effects (Nissen and Wolski, 2007; Balakumar and Jagadeesh, 2012). Among patients with impaired glucose tolerance or T2DM, rosiglitazone use for at least 12 months was noted to be associated with a significantly increased risk of myocardial infarction and heart failure (Singh et al., 2007). The Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD) clinical trial assessed cardiovascular outcomes after addition of rosiglitazone to either metformin or sulfonylurea compared to the combination of the two over 5–7 years of follow-up (Home et al., 2009). In this study, addition of rosiglitazone to glucose-lowering therapy in T2DM patients was confirmed increasing the risk of heart failure and of some fractures, largely in women (Home et al., 2009). Meta-analyses of clinical trials suggested that the use of rosiglitazone in T2DM patients might increase the risk of myocardial ischemic events by 30–40% (Schernthaner and Chilton, 2010). Also the use of thiazolidinediones for the T2DM management has been associated with an increased risk of peripheral edema (Berlie et al., 2007). A meta-analysis suggested at least a two-fold increase in the risk for developing edema with a thiazolidinedione agent, while the risk appeared to be greater with rosiglitazone than pioglitazone (Berlie et al., 2007). Of note, in a retrospective cohort analysis, myocardial infarction was suggested to be more common in rosiglitazone users than pioglitazone users, while the incidence of a combined end point of myocardial infarction and/or sudden death in patients receiving rosiglitazone was not significantly different from that of patients receiving pioglitazone (Ziyadeh et al., 2009). However, in a recent clinical study, higher risks for death overall and due to cardiovascular disease, and heart failure were found for rosiglitazone compared to pioglitazone, whereas these excess risks were noted to be a largest in patients aged 65 years or older (Gallagher et al., 2011). Of note, the European regulatory decision suspending rosiglitazone was supported by this study (Gallagher et al., 2011). This study report is akin to a population based cohort study, which reported that among older diabetic patients, pioglitazone was associated with a significantly lower risk of heart failure and death than rosiglitazone (Juurlink et al., 2009). Likewise, a recent meta-analysis of observational studies suggest that among T2DM patients, the use of rosiglitazone is associated with significantly higher odds of congestive heart failure, myocardial infarction, and death compared to pioglitazone use (Loke et al., 2011).

In addition to peripheral edema and prominent cardiovascular risks, a possible association between long-term use of thiazolidinediones and fractures, particularly of the hip and wrist, in diabetic patients was highlighted (Meier et al., 2008). In T2DM patients, thiazolidinediones had detrimental effects on bone

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