International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 2, Suppl 2, 2010

Review Article

ROSIGLITAZONE-A JOURNEY THAT NEVER COMPLETED

ANJALI GOPALA[1], VIVEK KUMAR SHARMA[2] AND SUBRAHMANYA SARMA GANTI[1]

[1]Deptt. of Pharmacy, ISF College of Pharmacy, Moga, Punjab-142001, India, [2]Govt. College of Pharmacy, Rohru, Distt. Shimla (HP) - 171207, India. Email: ssganti2010@rediffmail.com

Received: 08 Jan 2010, Revised and Accepted: 27 Jan 2010

ABSTRACT

Diabetes is the major cause of mortality and morbidity leading to cardiovascular and other related complications. Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor super family comprising of three subtypes such as PPARα, PPARβ and PPARγ. Activation of PPAR α reduces triglycerides and involves in regulation of energy homeostasis. Activation of PPARγ causes insulin sensitization and enhances glucose metabolism, whereas activation of PPARβ enhances fatty acid metabolism. Several basic and clinical studies have exemplified the beneficial effects of PPARγ ligands in preventing the cardiovascular risks and diabetes related complications.

The PPARγ agonists are developed to increase insulin sensitivity and simultaneously prevent diabetic cardiovascular complications. Rosiglitazone was developed for treatment of Type II diabetes with secondary cardiovascular complications. Rosiglitazone was used with a good rate of success. Unfortunately recent research has linked Rosiglitazone with several of cardiovascular risks and complications including increase risk of myocardial infarction. Present review is an effort to critically justify the status and use of Rosiglitazone in treatment of diabetes.

Key words: Rosiglitazone, Diabetes, PPAR, Pioglitazone

INTRODUCTION

Diabetes is a metabolic disorder characterized by insulin resistance and reduced secretion of insulin and is associated with cardiovascular pathologies such as atherosclerosis, hypertension, endothelial dysfunction, cardiac dysfunction and myocardial infarction[1].

Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy and the risk of cardiovascular disease is increased. Type 1 diabetes is a chronic disease characterized by hyperglycaemia due to absolute deficiency of insulin secretion which is caused by autoimmune destruction of the pancreatic beta cells. Evidence of autoimmunity is provided by the appearance of autoantibodies prior to the onset of clinical disease. The clinical presentation ranges from mild nonspecific symptoms or no symptoms to coma. Although type 1 diabetes usually develops before 30 years of age, it can occur at any age. At presentation, most patients are thin and have experienced weight loss, polyuria, polydipsia, fatigue, and diabetic ketoacidosis.

In type 2 diabetes mellitus, the actions and secretion of insulin are impaired, as opposed to the absolute deficiency of insulin that occurs with type 1 diabetes mellitus. Type 2 diabetes is characterized by two major pathophysiologic defects: (1) insulin resistance, which results in increased hepatic glucose production and decreased peripheral glucose disposal, (2) impaired β cell secretory function[2].

Insulin resistance is an impaired biological response to the effects of exogenous or endogenous insulin. Insulin resistance in the hepatic and peripheral tissues, particularly skeletal muscle, leads to unrestrained hepatic glucose production and diminished insulin-stimulated peripheral glucose uptake and utilization[3]. Insulin secretion by the pancreatic beta cell is initially sufficient to compensate for insulin resistance, thereby maintaining normal blood glucose levels. Hyperinsulinaemia, which accompanies insulin resistance, can maintain sufficiently normal glucose metabolism as long as pancreatic β cell function remains normal. However, in patients who may develop type 2 diabetes, insulin secretion eventually fails, leading to hyperglycaemia and clinical diabetes[4]. Individuals with type 2 diabetes may have few or no classic clinical symptoms of hyperglycaemia[5]. The difficulty in maintaining metabolic control, for example measured by hemoglobin A1c (HbA1c) over time may be related to several behavioral factors (for example difficulties with healthy eating, exercise, medication regimens) but primarily reflects the underlying progressive decline in β cell function. Type 2 diabetes has traditionally been treated in a stepwise manner, starting with life style modifications[6,7,8,] exercise[9] and later on pharmacotherapy with oral agents. Several classes of oral agents are available for clinical use. These mainly include insulin secretagogues (drugs that delay the absorption of carbohydrates from the gastrointestinal tract) and insulin sensitizers (Thiazolidinediones)[10].

Peroxisome proliferator activated receptors (PPARs) belong to the nuclear receptor superfamily[11] and three isoforms of PPARs, encoded by different genes, have been identified such as PPARα, PPARβ and PPARγ[12]. The fibrate class of hypolipidemic drugs acts through PPARα [13], thiazolidinedione class of anti-diabetic agents acts through PPARγ[14] whereas clinical implications of PPARβ agonists as hypolipidemic agents are under investigation [15].

PPARα, PPARβ and PPAR display differential tissue distribution with PPARα, being expressed mainly in the liver, skeletal, and cardiac muscle and in the endothelial cells and smooth-muscle cells of the vascular wall. It regulates genes that influence lipoprotein metabolism and fatty acid uptake and oxidation as well as production of inflammatory markers. Fibrates such as fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil act as full or partial PPARα, agonists[16]. PPARβ is expressed in many tissues, with the highest expression in the skin, brain, and adipose tissue. PPARγ is expressed most abundantly in adipose tissue but is also found in pancreatic beta cells, vascular endothelium, and macrophages[17.] PPARγ was originally identified as a central regulator of gene expression and differentiation in adipose cells[18].

Because traditional agents have a limited impact on insulin resistance and β-cell function, thiazolidinediones may be an appropriate choice especially for combination therapy in patients achieving poor glycaemic control with initial monotherapy. By improving insulin sensitivity, thiazolidinediones may exert beneficial effects on cardiovascular risk factors. The excess cardiovascular risk in type 2 diabetes cannot be attributed to classic risk factors alone (mainly hypertension, hypercholesterolaemia and smoking), but if present, these risk factors are at least as important as in patients without diabetes [19].

The thiazolidinediones consist of rosiglitazone and pioglitazone. These substances decrease insulin resistance in muscle and adipose tissue by activating the peroxisome proliferator-activated receptor (PPARγ) which increases production of proteins involved in glucose uptake.

They also decrease hepatic glucose production by improving hepatic insulin sensitivity[20].

Rosiglitazone is an extremely selective and potent agonist of the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, these receptors are located in key target tissues for insulin action such as adipose tissue, skeletal muscle, and the liver. The activation of PPAR nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, utilization and regulation of fatty acid metabolism. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the experimental animal through increased sensitivity to insulin's action in the insulin dependent tissues. Part of this action is mediated by an increase in the insulin-regulated glucose transporter GLUT-4 in the adipose tissue. Rosiglitazone is predominantly metabolized by Cytochrome P450 and is more than 99% bound to plasma proteins, primarily albumin [21].

Rosiglitazone is marketed by the pharmaceutical company GlaxoSmithKline as a stand-alone drug (Avandia) and in combination with metformin (Avandamet) or with glimepiride (Avandaryl). Annual sales peaked at approx $2.5bn in 2006. The drug's patent expires in 2012.When Rosiglitazone entered; market was under the unfortunate legacy of its predecessor, Troglitazone (Rezulin), which the FDA withdrew due to unwanted hepatic side effects on 08-08-03 [22].

Oral antidiabetic agents are most often used to treat type 2 diabetes mellitus in its initial stages if lifestyle modifications have failed. The thiazolidinediones, rosiglitazone and pioglitazone offer new oral treatment options and affect many tissues and parts of the body.

One explanation for the beneficial effects of thiazolidinediones is their unique mechanism of action as selective and potent inhibitors of PPARγ . PPARγ receptors are present in many tissues like adipose, hepatic and skeletal muscle tissue and control insulin-responsive genes, which have a wide-ranging influence. Thiazolidinediones appear to improve markers of inflammation and fibrinolysis, exert beneficial effects on vascular reactivity, improve the lipid profile and fat distribution, and decrease pancreatic β cell injury.

Rosiglitazone belonging to thiazolidinedione group which also encompasses troglitazone (withdrawn due to hepatic toxicity) and pioglitazone. It increases the sensitivity of skeletal muscle, liver and adipose tissue to insulin without directly stimulating insulin secretion from pancreatic ß-cells, thereby reducing plasma glucose levels and endogenous glucose production[23]. Differences in the side chain on the main thiazolidine-structure in comparison to pioglitazone are thought to be responsible for the distinct bioavailability, metabolism and antihyperglycaemic

potency of rosiglitazone. Although rosiglitazone appears to be associated with some effects that are not mediated by PPARγ,[24] binding of rosiglitazone to this receptor seems to be the important component of its mechanism of action. Rosiglitazone has several pharmacodynamic properties

which could ameliorate the increased risk of cardiovascular disease in type 2 diabetes mellitus. In clinical studies in patients with type 2 diabetes mellitus, rosiglitazone has been associated with reductions in the levels of small dense low density lipoprotein-cholesterol (LDL-C) – despite overall increases in total LDL-C - and increase in the levels of high density lipoprotein-cholesterol (HDL-C). Diastolic and systolic blood pressures are thought to be decreased after rosiglitazone treatment. Some other surrogate parameters indicating especially cardiovascular risk were reported to be positively influenced by rosiglitazone therapy.

Since the discovery of PPARs by Isselman and Green in 1990, these molecules have been shown to play a major role in a diverse group of processes and pathological conditions associated with aging, inflammation, immunity, obesity, cancer, and fertility [25,26].

PPARs regulate gene transcription by two mechanisms namely transactivation and transrepression. In transactivation, which is DNA-dependent, PPARγ forms a heterodimer with the retinoid X receptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results in transcription of PPARγ target genes. In transrepression, PPARs can repress gene transcription by negatively interfering with other signal-transduction pathways, such as the nuclear factor-κB (NFκB) signaling pathway, in a DNA-binding-independent manner.

Apart from its role during transcriptional regulation, which requires DNA-binding, PPAR can also function in a DNA-binding-independent manner to transrepress different target genes. PPAR may exert anti-inflammatory effects by negatively regulating the expression of pro-inflammatory genes induced during macrophage differentiation and activation The activated PPAR/RXR heterodimer reduces the availability of co-activators required for gene induction by other transcriptional factors. Thus, without distinct cofactors, transcriptional factors, such as activated protein-1 (AP-1), nuclear factor-κB (NF-κB), nuclear factor of activated T cells (NFAT) or signal transducer and activator of transcription (STAT), cannot cause gene expression. In lipopolysaccharide (LPS)/interferon-γ (IFN-γ) stimulated macrophages, attenuation of inducible nitric oxide synthase (iNOS) expression in response to PPAR activation [27,28].

Both nondiabetic subjects and those with type 2 diabetes mellitus (T2DM) show increased insulin-stimulated glucose uptake in peripheral tissues as well as increased hepatic insulin sensitivity (the ability of insulin to suppress endogenous glucose production) and insulin sensitivity in adipose tissue (measured from the ability of insulin to suppress free fatty acid concentrations)[29].

The mechanisms by which insulin sensitization occurs are thought to involve either direct action on fatty acid uptake and storage in adipose tissue (also known as the fatty steal hypotheses) or indirectly via its action adipokines such adiponectin[30]. The free fatty acid storage in adipose tissue as opposed to liver and skeletal most likely exerts a protective effect on these tissues. In addition, advantageous effects on the beta cells of the pancreas may occur by inhibiting glucolipotoxicity[31]. Taken together, the mechanisms of action are complex and multifold and the many effects of TZDs in various tissues make it impossible to define all the exact mechanisms underlying their insulin sensitizing effects in vivo in humans[32].Adipose tissue is no longer considered as a passive storage depot for triglycerides and fatty acids, but rather an active metabolic organ that produces various biologically active molecules (referred to as adipocytokines) which act as autocrine, paracrine or endocrine regulators of many physiological and patophysiological processes in the organism. Among them, a special attention and scientific interest has been lately focused on adiponectin, which is thought to be the molecular link between adiposity and the insulin resistance. Adiponectin is a protein of 30 kD and is exclusively produced in the adipose tissue. Adiponectin possesses antidiabetic, anti-atherogenic and anti-inflammatory characteristics. Plasma concentrations of adiponectin are decreased in the metabolic syndrome; therefore therapeutic strategies that increase adiponectin levels could be potentially useful for the treatment of the metabolic syndrome, as well as prevention and/or delaying the development of manifest type 2 diabetes and atherosclerotic coronary vascular disease [33,34,35]. Continuing loss of b-cell function is the underlying cause of deteriorating metabolic control in people with type 2diabetes. Fatty acids could play a role in the reduction of b-cell insulin secretion. The failure of β-cell function is believed to be attributable to the apoptosis of β-cells in response to increased FFA or to an accumulation of triglycerides in the b-cells [36,37]. The FFA excess in b-cells increases the novo ceramide synthesis[38] and nitric oxide formation[39] ,while reducing the antiapoptotic protection of b-cells[40].

The turning point of the fortune of Rosiglitazone was the publication of the data from the metanalysis by Niessen in 2007.[41] Niessen and Wolski in their paper conclude that "Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and in the risk of death from cardiovascular causes with borderline significance".

REFERENCES

1. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American heart association. Circulation1999; 100:1134– 46.

2. Kahn SE, Porte D Jr. The pathophysiology of type II (non insulin dependent) diabetes mellitus: implications for treatment.In: Porte D Jr, Sherwin RS editor(s). Ellenberg & Rifkin's Diabetes Mellitus. 5th Edition.1997. Stamford, Conneticut (U.S.A.): Appleton &Lange.
3. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM: a balanced overview. Diabetes Care1992;15:318–68.
4. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of Type 2 diabetes in the offspring of diabetic parents. Annals of Internal Medicine1990;113:909-915.
5. Ruige JB, DeNeeling JND, Kostense PJ, Bouter LM, Heine RJ. Performance of an NIDDM screening questionnaire based on symptoms and risk factors. Diabetes Care1997;20:491-496.
6. Armour T, Norris S, Brown D, Zhang X, Caspersen C. Initiating and maintaining physical activity for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews2004;10:234-237.
7. Gimenez-Perez G, Gonzalez-Clemente JM, Mauricio D. Lifestyle interventions for preventing type 2 diabetes mellitus. Cochrane Database of Systematic Reviews2001;1:290-301.
8. Moore H, Summerbell C, Hooper L, Ashton V, Kopelman P. Dietary advice for the prevention of type 2 diabetes mellitus in adults. Cochrane Database of Systematic Reviews(DOI: 10.1002/14651858.CD005102.pub2)2005.
9. Thomas D, Elliott E.Exercise for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2001, Issue 1. (DOI: 10.1002/14651858.CD002968.)
10. Richter B, Neises G. Human' insulin versus animal insulin in people with diabetes mellitus. Cochrane Database of System- atic Reviews 2005, Issue 1 (DOI: 10.1002/14651858.CD003816)
11. Huss JM, Kelly DP. Nuclear receptor signaling and cardiac energetics. CircRes2004; 95:568–78.
12. Buse JB.Glitazones and heart failure: critical appraisal for the clinician. Circulation2003; 108:57-61.
13. Tenenbaum A, Motro M, Fisman EZ. Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. Cardiovasc Diabetol 2005;4:1–5.
14. Staels B, Fruchart JC(2005)Therapeutic roles of peroxisome proliferatoractivate receptor agonists. Diabetes 54:2460–70
15. Barish GD, Narkar VA, Evans RM.PPAR delta: a dagger in the heart of the metabolic syndrome. J Clin Invest2006; 116:590–7.
16. Raalte DH, Li M, Pritchard PH, Wasan KM. Peroxisome proliferator- activated receptor (PPAR)-alpha: a pharmacological target with a promising future. Pharm Res2004;21(9):1531–1538.
17. Walczak R, Tontonoz P.PPARadigms and PPARadoxes: expanding roles for PPARgamma in the control of lipid metabolism. J Lipid Res2002;43(2):177–186.
18. Rosen ED, Walkey CJ, Puigserver P, Spiegelman BM.Transcriptional regulation of adipogenesis. Genes Dev.2000;14(11):1293–1307.
19. Stamler J, Vaccaro O, Neaton JD, Wentworth D.Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care1993;16: 434–44.
20. Meriden T.Progress with thiazolidinediones in the management of type 2 diabetes mellitus. Clinical Therapeutics2004;26(2):177–90.
21. Tatti P.The Rise and Fall of Rosiglitazone, Clinical Medicine: Therapeutics2009;1:313–319.
22. http://www.fda.gov/ohrms/dockets/98fr/2003n-0350-nwl0001..
23. Wagstaff AJ, Goa KL. Rosiglitazone: A review of its use in the management of type 2 diabetes mellitus. Drugs2002;62(12):1805–37.
24. Yang C, Chang TJ, Chang JC, Liu MW, Tai TY, Hsu WH. Rosiglitazone (BRL 49653) enhances insulin secretory response via phosphatidylinositol 3-kinase pathway. Diabetes2001; 50:2598– 602.
25. Issemann I, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature1990;347(6294):645–650.
26. Badr M. A forum for a highly important and ever-expanding field of study. PPAR Res2001; 61:385.
27. Kodera, Y., Takeyama, K., Murayama, A., Suzawa, M., Masuhiro, Y., Kato, S. Ligand type-specific interactions of peroxisome proliferator activated receptor gamma with transcriptional coactivators, J. Biol.Chem.,2000; 275: 33201– 4.
28. Li, M., Pascual, G., Glass, C.K. Peroxisome proliferator-activated receptor gamma-dependent repression of the inducible nitric oxide synthase gene. Mol. Cell. Biol.2000;20: 4699– 707.
29. Miyazaki Y, Glass L, Triplitt C. Effect of rosiglitazone on glucose and nonesterified fatty acid metabolism in Type 2 diabetic patients. Diabetologia2001;44:2210–2219.
30. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest.2006; 116(7): 1784–1792.
31. Han SJ, Kang ES, Hur KY. Rosiglitazone inhibits early stage of glucolipotoxicity-induced beta-cell apoptosis. Horm Res2008;70:165–173.
32. Yki-Järvinen H.Thiazolidinediones. N Engl J Med2004;351(11):1106–1118.
33. Okamoto Y, Kihara S, Funahashi T.Adiponectin: a key adipocytokine in metabolic syndrome. Clin Sci (Lond)2006;110(3):267-78.
34. 34 Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol2004;24(1):29-33.
35. Havel PJ.Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism.Diabetes2004;53:143-151.
36. Lee Y, Hirose H, Zhou YT, Esser V, McGarry JD, Unger RH.Increased lipogenic capacity of the islets of obese rats: a role in the pathogenesis of NIDDM. Diabetes1997;46:408-13.
37. Pick A, Clark J, Kubstrup C, Levisetti M, Pugh W, Bonner- Weir S. Role of apoptosis in failure of beta-cell mass compensation for insulin resistance and beta-cell defects in the male Zucker diabetic fatty rat. Diabetes1998;47:358-64.
38. Shimabukuro M, Zhou YT, Levi M, Unger RH.Fatty acidinduced beta cell apoptosis: a link between obesity and diabetes. Proc Natl Acad Sci1998a;5: 2498-502.
39. Shimabukuro M, Higa M, Zhou YT. Lipoapoptosis in betacells of obese prediabetic fa/fa rats. Role of serine palmitoyltransferase over expression. J Biol Chem1998b;273: 32487- 490.
40. Shimabukuro M, Wang MY, Zhou YT, Unger RH. Protection against lipoapoptosis of beta cells through leptindependent maintenance of Bcl-2 expression. Proc Natl Acad Sci1998c;95: 9558-61.
41. Niessen S, Wolski K.Effect of Rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. NEJM2007;24:2457.