The Role of PPAR Agonists in Diabetes Mellitus

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Abstract

Diabetes mellitus is a complex metabolic disorder characterized by hyperglycemia due to inadequacy of insulin secretion and/ or insulin action. The major symptoms include polydypsia, polyphagia, polyuria, blurred vision and weight loss. The world wide prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.PPAR agonists are drugs which act on the peroxisome proliferator-activated receptor. They are used for the treatment of the metabolic syndrome, diabetes mellitus, mainly for lowering triglycerides and blood sugar. There are four classes of PPAR agonists (alpha, gamma, delta, pan and dual). The peroxisome proliferatoractivated receptor (PPAR) alpha and gamma isoforms of the family of nuclear transcription factors are pharmaceutical targets for therapeutic intervention because they can potentially ameliorate not only the hyperglycemia of diabetes, but also the dyslipidemia that is characteristic of this disorder (low high-density lipoprotein cholesterol, high triglycerides, small, dense low-density lipoprotein particles).

Keywords- hyperglycemia, PPAR agonist, dyslipidemia, polydypsia, polyphagia

INTRODUCTION

Diabetes mellitus is a chronic, lifelong condition that increases the body's blood glucose levels. There are three major types of diabetes namely Type 1 diabetes, Type 2 diabetes and gestational diabetes. Type 1 diabetes (insulin dependent) occurs when the body's immune system affects or kills the beta cells of the pancreas. Approximately 10% of all diabetes cases are Type 1. Studies suggest that insulin- dependant diabetes tag along with microvascular, microvascular and neurological complications (1). Type 2 diabetes occurs when the body cannot properly use the released insulin (insulin resistance or insulin insensitivity) or does not produce enough insulin. Approximately 90% of all cases are of Type 2. Gestational diabetes is a condition that occurs in women who weren't previously diagnosed with diabetes exhibit high blood glucose levels during pregnancy. This occurs due to pregnancy related factors such as human placental lactogen that affects the susceptible insulin receptors. Some symptoms of diabetes include polydypsia, polyphagia, polyuria, kussmauls breathing etc.

The number of individuals suffering with diabetes has risen from 108 million in 1980 to 422 million in 2014 (2). The world wide prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.

The risk factors associated with type 1 diabetes include family history, illness and pancreatic disease and that of type 2 diabetes include obesity, gestational diabetes, impaired glucose tolerance, increasing age, unhealthy diet and physical inactivity. The complications of diabetes mellitus include diabetic retinopathy, neuropathy and nephropathy. Patients with diabetes mellitus encounter with more adverse effects after myocardial infarction compared to non-diabetic patients. This occurrence may be due to to an accelerated atherosclerotic process, diastolic left ventricular dysfunction related to diabetic cardiomyopathy or other undetectedunfavourable processes(3).

The main aim in the management of diabetes mellitus is to lower the blood glucose levels as close to normal. Measures to control blood pressure and cholesterol levels is essential because diabetes increase the risk of heart disease and peripheral arterial disease. Involvement in physical activities and modifying eating habits are the first steps in reducing the blood glucose levels. Insulin therapy is given to diabetes of all types(4). Insulin therapy is required permanently for patients with type 1 diabetes unless they receive a whole organ- pancreas transplant. Patients with type 2 diabetes also require insulin treatment as their beta cell function declines over time. But the most commonly used treatment for type 2 diabetes include treatment with metformin, sulfonylureas, meglitinides, thiazoledinediones, DPP-4 inhibitors, SGLT-2 inhibitors and insulin therapy. PPAR agonists are used increasingly to counteract the effects of diabetes.

PPAR agonists

PPAR agonists are drugs which activate peroxisome proliferator-activated receptor. Each isoform controls different activities. Agents that activate individual PPARs have different effects(5).They are used for treating the symptoms of Diabetes by lowering the triglycerides and blood sugar. PPAR agonists are ligand-regulated transcription factors that control gene expression by binding to specific response elements (PPREs) which is present within promoters(6).

There are four classes of PPAR-agonists namely PPAR-alpha, PPAR-gamma,PPAR-delta,dual and pan PPAR agonists.These receptors function as lipid sensors that regulate the expression of large gene arrays and modulate the important metabolic events(7). PPAR-alpha is the main target of fibrate drugs (clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate). They are indicated for cholesterol disorders and disorders characterised by high triglyceride levels. PPAR-alpha, is produced in the skeletal muscles and the liver, where it is involved in the body's breakdown and transport of fatty acids. PPAR-alpha play a vital role in reducing inflammation both in the vascular wall and the liver (8).
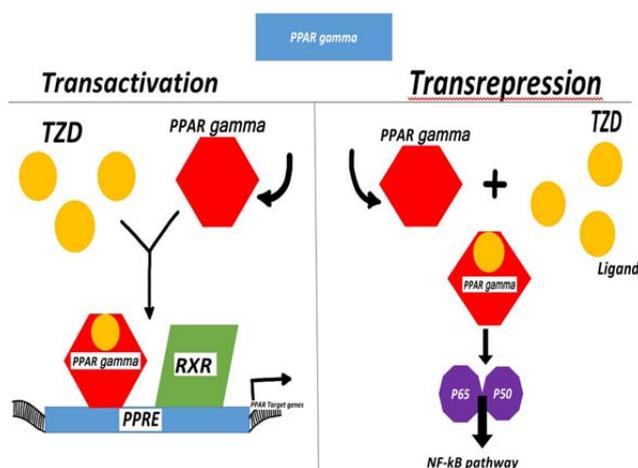
PPARγ are members of the nuclear hormone receptor family of ligand-activated transcription factor.They play a key role in regulating the insulin sensitivity, adipocyte differentiation, inflammation and cell growth (9). PPAR gamma is the main target of thiazolidinediones used in diabetes mellitus characterised by insulin resistance.

Thiazolidinediones, acting via PPARγ, influence free fatty acid flux and thus reduce insulin resistance and blood glucose levels (10). PPARγ agonists are therefore used to treat type 2 diabetes.They are used for treating hyperlipidemia in atherosclerosis. Animal studies have shown that they play a major role in the amelioration of pulmonary inflammation, especially in asthma (11). The PPAR gamma agonists express anti fibrotic effects on the renal cells subjected to elevated glucose levels (12). Therapeutic approach to retard thedevelopmentof diabetic nephropathy is essential in the treatment of diabetes mellitus.Activation of PPAR gamma receptors decreases theeffect of diabetic nephropathy (13).The investigations shown to alleviate the delay of the development of diabetic nephropathy include glycemic control, blood pressure control (14,15), and some underlying mechanisms in the renin angiotensin system (16,17,18) and lipid lowering therapy (19,20).Activation of PPARδ receptor enhances the lipoprotein metabolism and hence lowers the triglyceride levels and alleviates macrophage inflammatory responses (21).Studies reveal that activation of PPARδ in the liver represses the hepatic glucose output which contributes to improved glucose homeostasis (22).

The adverse effects of PPAR agonists include fluid retention, macular edema, cardiac failure and myocardial ischemia (23).

Action of PPAR gamma agonists-Thiazolidinediones (TZD's)

The thiazolidinediones binds to the nuclear PPARγ receptor. PPARγ is a nuclear receptor. The receptor upon activation regulates the transcription and expression of specific genes. Together with the isoforms PPAR-α and PPAR-δ, is a member of a family of nuclear hormone receptors that includes the retinoid X receptor (RXR), the vitamin D receptor and the thyroid hormone receptor. PPARs play an important role as lipid sensors and regulators of lipid metabolism (24).

PPAR's regulate the gene transcription by two mechanisms. The first mechanism is by transactivation which is DNA dependant. The second mechanism is by transrepression which is DNA independent.

Transactivation

The PPAR's on binding to the TZD's forms a heterodimer with the RXR. They bind to specific peroxisome proliferators response elements (PPRE) on many key target genes which are involved in the carbohydrate and lipid metabolism. The main objective of expression of specific genes is toalleviate the storage offatty acids in adipose tissue, reducing the systemic circulation of fatty acids. Hence the cells become dependant on oxidation of glucose to produce energy for other cellular mechanisms.

Transrepression

The PPAR's on binding to the endogenous ligands (long unsaturated fatty acids) forms causes ligand activation. This leads to the formation of a heterodimer p50/p65 which activates NF-kB. NF-kB controls many genes involved in inflammation.The NF-κB pathway hence regulates the proinflammatory cytokine production, leukocyte recruitment, or cell survival, which are important contributors to the inflammatory response (25).

TZDs have shown to selectively stimulate lipogenic activities in fat cells resulting in greater insulin suppression and regulation oflipolysis (26).They decrease free fatty acids available for infiltration into the other tissues; thus TZDs treatment target the insulin-desensitizing effects of free fatty acids in muscle and liver (27). Finally, TZDs have shown to alter the expression and release of adipokines. Resistin and TNF-α, which have the potential to reduce insulin sensitivity, are reduced following incubation with TZDs (28, 29, 30).

Advances in treatment

Newer PPAR agonists are being researched upon for their use in humans to reduce elevated glucose levels. One such compound is Bavachinin, a natural pan PPAR agonist. It has effectively reduced glucose levels without inducing hepatotoxicity or weight gain.It exhibits distinctive synergistic effects in association with synthetic PPAR-γ and PPAR-α agonists upon carbohydrate and lipid metabolism in db/db and diet-induced obese mice (31). Certain Angiotensin type-1 blockers have been found to decrease the occurrence of type- 2 diabetes mellitusby an unspecified molecular mechanism. This promotes the PPAR-gamma dependant differentiation in adipocytes (32).

CONCLUSION

PPARs are effective in treating diabetes by lowering the triglycerides and blood glucose levels. PPARα agonists are used for treating dyslipidemia especially low HDL cholesterol and increased triglyceride levels. It is also effective in reducing cardiovascular problems. PPARγ agonists are used for treating type 2 diabetes. PPAR gamma agonists regulates thefatty acid catabolism and energy uncoupling which in turn decreases the triglyceride stores and enhances the cardiac contractility. The activation of PPARδ in the liver suppresses the hepaticglucose output which is responsible for improved glucose homeostasis.PPARδ receptor activation regulatelipoprotein metabolism to reduce the triglyceride levels.

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