Are partial PPAR gamma agonists a rational therapeutic strategy for preventing abnormalities of the diabetic kidney ?

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ABSTRACT :

Diabetes mellitus is probably the single most important metabolic disease and is widely recognized as one of the leading causes of death and disability. Up to a third of people with diabetes mellitus suffer end-stage renal failure due to diabetic nephropathy. Diabetic nephropathy strategies to delay progression of diabetic nephropathy- including glycemic and blood pressure control, modification of the rennin-angiotensin system and management of lipid levels with statins-have been effective, but development of new strategies is essential if the ever-increasing burden of this disease is to be minimized. Peroxisome proliferator-activated receptors (PPAR) are members of the nuclear hormone receptor superfamily of ligand- activated transcription factors. PPAR-γ is the key regulator of lipid metabolism and energy balance implicated in the development of insulin resistance. The identification of putative natural and synthetic ligands and activators of PPAR-γ has helped to unravel the molecular basis of its function, including molecular details regarding ligand binding, conformational changes of the receptor and cofactor binding leading to the emergence of the concept of selective PPAR-γ modulators .No satisfactory therapeutic option is currently available to treat patients with nephropathy except for fewer agents like angiotensin converting enzyme inhibitors, angiotensin AT1 receptor blockers and few antioxidants, which have been shown to improve the function of diabetic kidney to some extent. Thus, tremendous efforts are being made to explore promising therapeutic interventions to treat diabetic nephropathy. This review discussed various presently employed and recently developed pharmacological interventions to treat diabetic nephropathy and to improve the function of diabetic kidney. In addition, the recently identified potential target sites involved in the pathogenesis of diabetic nephropathy have been delineated.

Keywords:- Diabetes, nephropathy, Peroxisome proliferator-activated receptors

INTRODUCTION:

Diabetes causes profound disturbances of carbohydrate, protein and lipid metabolism that leads to pathological changes in the organs and subsequent vascular complications [1].Diabetes mellitus is a chronic metabolic disease, which occurs mainly due to insulin deficiency or insulin resistance. Uncontrolled diabetes mellitus often leads to various serious complications such as retinopathy, neuropathy, nephropathy and cardiomyopathy [2]. Preventative strategies are of paramount importance in reducing the incidence of nephropathy in patients with type 2 diabetes mellitus [3]. Glycemic and blood pressure control, specific modulation of the rennin-angiotensin system and smoking cessation [4] have only a modest impact on progression of diabetic nephropathy. Evidence from animal models indicates that reduction of serum lipid levels has a renoprotective effect [5]. In humans there is increasing, but as yet only circumstantial, data to support the hypothesis that lipid lowering statin therapy slows deterioration of renal function in both diabetic and nondiabetic populations [6, 7]. There is no care for diabetic nephropathy; hence, alternative strategies to attenuate the progressive decline in renal function are essential.

Diabetic nephropathy is structurally associated with mesangial cell expansion, thickening of glomerular and tubular basement membrane, glomerular hypertrophy, glomerulosclerosis [8, 9, 10], it is now recognized that tubulointerstitial inflammation and fibrosis, tubular dilation and atrophy are ultimately more predictive of renal outcome [11]

ROLE OF PPARs IN DIABETIC NEPHROPATHY

PPARs are the nuclear receptor superfamily consists of several ligand-regulated transcription factors that include the steroid and thyroid hormone recetors, Vitamin D3 receptors, retinoic acid receptors, and of peroxisome proliferator–activated receptors (PPARs), among other [12,13,14,15]. PPAR-γ is a member of the NRIC sub group, which includes PPAR- alfa and beta. These receptors form heterodimers with the retinoid X receptor and modulate the transcription of genes. PPAR- γ is predominantly expreesed in white and brown adipose tissue, with lower expression in liver, muscle and other tissues [24]. PPAR-γ ligands include a surprisingly diverse set of natural ligands

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[25]. Such as linolenic, eicosapentaenoic,docohexaenoic, arachidonic acid and synthetic ligands such as the TZDs, L-tyrosine-based compounds,several nonsteroidal anti-inflammatory drugs and a variety of new chemical classes. [26,27]. Originally identified as a regulator of adipogenesis, PPAR-γ was thought to mediate the action of TZDs solely through its actions in adipose tissue. However, subsequent studies utilizing tissue-specific PPAR-γ gene knockouts have demonstrated a complex role for PPAR-γ in whole-body insulin sensitivity involving multiple tissues, including liver and muscle.[28].

Type of PPARs

1. To date, three receptor subtypes have been identified: PPAR α, PPAR β/δ, PPARγ.[16]. PPAR- γ is further of four sub types. i.e. PPAR-γ 1, PPAR-γ 2, PPAR-γ 3 and PPAR-γ 4 [16,17].

Nomenclature

Three types of PPARs have been identified; alpha, gamma and delta(beta).

. α (alpha) – expressed in liver,kidney, heart, muscle, adipose tissue and other

. γ (gamma) – although transcribed by the same gene, this PPAR exists in four forms;

1. γ1- expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas and spleen
2. γ2 – expressed mainly in adipose tissue (30 amino acids longer)
3. γ3 – expressed in macrophages, large intestine, white adipose tissue.
4. γ4 – expressed in endothelial cells.

δ (delta) – expressed in many tissue but markedly in brain, adipose tissue and skin.

Mechanism of action

PPARs are the transcription factors i.e. they regulate the transcription of genes in response to ligand binding [18,19] . After ligand binding, PPARs undergo specific conformational change that allow for the recruitment of one coactivator protein or more. Ligand differ in their ability to intract with coactivators, which explains the various biologic responses observed. PPARs regulate gene transcription by two mechanisms i.e. tranactivation and transrepression [18]. In transactivation, which is DNA-dependent mechanism, PPAR form a heterodimer complex with the retinoid X recptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results in transcription of PPAR-γ target genes which ultimately involved in diverse biological processes such as adipocytes proliferation, glucose and lipid metabolism [20]. In transrepression, PPARs can repress gene transcription by negatively interfering with other signal- transduction pathways, such as the NF-κB singling pathway, in a DNA-Binding – independent manner [21].

ADRs of PPARs

The thiazolidinedione (TZD) class of peroxisome proliferator–activated receptor gamma (PPAR-γ) ligands such as rosiglitazone (Avandia) and pioglitazone (Actos) have been introduced into clinical practice for treating hyperglycemia and insulin resistance in patients with type 2 diabetes[22]. However, these approved agents are associated with adverse drug reactions such as plasma volume expansion, hemodilution, and edema [23]. In addition; it has been shown that PPAR-γ agonists can cause substantial cardiac hypertrophy and peripheral adiposity in several preclinical studies[17] . pioglitazone is associated with an increased risk of bladder cancer, liver failure, and heart failure. 95% confidence intervals for bladder cancer associated with the use of pioglitazone compared with no thiazolidinedione use [36]. It has been shown that these adverse drug reactions (ADRs) are due to selective and activation complete of PPAR-γ in the affected tissues.

Partial PPAR gamma agonists

The partial PPAR gamma may act to improve whole body glucose disposal without increasing adipose mass. An interesting difference between PPAR and Partial PPAR was revealed by the observation that in adipocytes partial PPAR was more effective than PPAR in preventing insulin resistance induced by TNFα [29]. PPAR possess a number of deleterious side effect, including significant weight gain and peripheral edema[30]. Weight gain is likely due to both increased adiposity and fluid retention. Edema is particularly a problem in patients who are also taking insulin or sulfonylureas and TZD treatment has been linked to increased incidence of congestive heart failure [30]. Accordingly, efforts have been mounted to generate novel PPAR-γ modulstors that retain the beneficial clinical effects while avoiding these side effects. A variety of new PPAR-γ ligands that possess differential pharmacological affinities for PPAR-γ and have been termed selective PPAR-γ modulators (SPPAR-γ MS) have been reported[31]. SPPAR-γ Ms are believed to bind in distinct manners to the ligand binding pocket of PPAR-γ leading to altered receptor conformational stability and resulting in distinct pattern of gene expression [31]. The molecular basis of this effect is thought to involve differential cofactor displacement and recruitment that regulate gene and tissue specific manner [32]. Further characterization of SPPAR-γ Ms will ideally yield agents for the treatment of diabetes, which are as effective as current therapies but reduce or eliminate the more deleterious side effects.

A partial PPAR-γ agonist, which bind to PPAR-γ partially and show desirable pharmacological activity of the full agonist rosiglitazone and avoid of its ADRs. Significant decreases in glucose were also observed with partial PPAR-γ monotherapy [33]. Partial PPAR-γ lowered glucose levels in diabetic, but not normoglycemic subjects and that the time course of the beneficial glycemic effects was similar to that of the insulin-sensitizing TZDs which possess glucose and insulin-lowering properties mediated via activation of PPAR-γ. Accumulating data indicate that partial PPAR-γ improves hyperglycemia in streptozotocin (STZ)-induced diabetes in rats [34].

Conclusion

Furthermore, partial PPAR-γ appears to enhance insulin sensitivity in a manner that leads to less weight gain than the currently marketed compounds. Gene expression regulation in 3T3-L1 adipocytes has been described for one PPAR-γ partial agonist compared with several full agonists. Partial PPAR-γ modulated the expression of fewer genes and often showed attenuated regulation of genes regulated by full agonists[35].

Conflict of Interest

No conflict of interest has been declared.

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