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TELMISARTAN EFFECT IN HYPERTENSION ASSOCIATED WITH DYSLIPIDEMIA

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Abstract:

Hypertension and dyslipidemia are two major risk factors for cardiovascular diseases and commonly occur together. Dyslipidemia is a primary,widely established as an independent major risk factor for coronary heart disease. Management of dyslipidemia in hypertension patients significantly decreases the total cardiovascular risk. Peroxisome proliferator-activated receptors [PPARs] belong to the nuclear family of ligand activated transcriptional factors and comprise three different isoforms, PPAR-α, PPAR-β/δ, and PPAR-γ. The main role of PPARs is to regulate the expression of genes involved in lipid and glucose metabolism. Several studies have demonstrated that PPAR agonists improve dyslipidemia and glucose control in animals, supporting their potential as a promising therapeutic option to treat diabetes and dyslipidemia. PPAR-γ, the best characterized of the PPARs, plays a crucial role in adipogenesis and insulin sensitization.Telmisartan, an angiotensin receptor blocker [ARB] that is highly selective for AT1 receptor has been found to be a PPAR-α agonist and a selective PPAR-G modulator. This unique action of telmisartan on PPAR leads to favourable effects on lipid and carbohydrates metabolism which is independent of BP lowering effect. This provides additional benefit in treatment of dyslipidemia.

Keywords: *Telmisartan, Hypertension, Dyslipidemia, PPAR.*

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INTRODUCTION:

Hypertension

Hypertension is defined by persistent elevation of arterial blood pressure [BP]. Patients with diastolic blood pressure [DBP] values <90 mm Hg and systolic blood pressure [SBP] values ≥140 mm Hg have isolated systolic hypertension.[1]

Hypertension remains the most prevalent cardiovascular disease [CVD] risk factor and is present in ever-growing numbers worldwide.[2,3] In the United States hypertension affects over 30% of adults or approximately 76,400,000 [2008 data] men and women age 20 years. Data from the National Health and Nutrition Examination Survey indicate that approximately 8% of adults in the United States have undiagnosed hypertension, and of those diagnosed only three-quarters use antihypertensive medications. Among those taking medication, blood pressure [BP] is controlled in only half.[4] The societal and financial burden of hypertension is not likely to reverse soon as projections suggest a 10% increase in hypertension prevalence by the year 2030.[5] These statistics are especially troubling when one considers the consequences of hypertension; elevated BP [140/90 mmHg] precedes myocardial infarction [MI], stroke, or congestive heart failure in 69% of cases.[6]

In hypertensive individuals, there is a high prevalence of decreased level of high density lipoprotein [HDL], increased total cholesterol and elevated triglyceride [TG] levels as compared to normotensive individuals.[7] Hypertension is a common cardiovascular disease and coexists with conditions like dyslipidemia and ischemic heart disease. Elevated total cholesterol [TC] levels increase the risk of cardiovascular disease associated with hypertension and dyslipidaemia. When these two conditions coexist, it demands a strict emphasis on dietary and pharmacological therapy to achieve control on both successfully. Contrary to the goal, it is reported that only in 32% of hypertensive patients; lipid profile is improved, while this percentage falls to eleven for control of both blood pressures [BP] and lipids.[8]

DYSLIPIDEMIA:

Disorders of lipoprotein metabolism together with high fat diets, obesity and physical inactivity have all contributed to the current epidemic of atherosclerotic disease seen in developed countries. Disorders of lipoprotein metabolism that result in elevated serum concentrations of total cholesterol [TC] and low-density lipoprotein cholesterol [LDL-C] increase the risk of an individual developing cardiovascular disease [CVD]. In contrast, high-density lipoprotein cholesterol [HDL-C] confers protection against CVD, with the risk reducing as HDL-C increases. It is, therefore, clear that the term hyperlipidaemia, which was formerly used to describe disorders of lipoprotein metabolism, is inappropriate. It is more appropriate to use the term dyslipidaemia, which encompasses both abnormally high levels of specific lipoproteins, for example, LDL-C, and abnormally low levels of other lipoproteins, for example, HDL-C, as well as disorders in the composition of the various lipoprotein particles. It is particularly appropriate when considering the individual at risk of CVD with a normal or high TC and low HDL-C [total cholesterol:HDL-C ratio].[9]

Up to 60% of the variability in cholesterol fasting lipids may be genetically determined, although expression is often influenced by interaction with environmental factors. The common familial [genetic] disorders can be classified as:

- The primary hypercholesterolaemias such as familial hyper-cholesterolaemias in which LDL-C is raised.
- The primary mixed [combined] hyperlipidaemias in which both LDL-C and triglycerides are raised.
- The primary hypertriglyceridaemias such as type III hyperlipoproteinaemia, familial lipoprotein lipase deficiency and familial apoC-II deficiency.[9]

Hypertension and hyperlipidemia commonly coexist. In hypertensive individuals, there is a high prevalence of decreased level of high density lipoprotein [HDL], increased total cholesterol and elevated triglyceride [TG] levels as compared to normotensive individuals.[10] Elevated total cholesterol [TC] levels increase the risk of cardiovascular disease associated with hypertension and dyslipidaemia. When these two conditions coexist, it demands a strict emphasis on dietary and pharmacological therapy to achieve control on both successfully. Contrary to the goal, it is reported that only in 32 % of hypertensive patients; lipid profile is improved, while this percentage falls to eleven for control of both blood pressures [BP] and lipids.[11] The antihypertensive drugs primarily affect the increased blood pressure without affecting the disordered lipid metabolism that often accompanies hypertension. Angiotensin II receptor blockers [ARBs] are efficient antihypertensive agents that act through inhibition of AT1 receptors.[12]

ANGIOTENSIN II RECEPTOR BLOCKERS

Angiotensin II receptor antagonists [angiotensin receptor blockers [ARBs]] are widely used clinically as antihypertensive agents. In addition to reducing blood pressure [BP], ARBs attenuate cardiovascular risk via suppression of the reninangiotensin system [RAS] mediated by antagonism of the angiotensin II [AT1] receptor.[13] There are eight ARBs currently on the market for hypertension and in different cardiovascular indications, ie, losartan, valsartan, candesartan, eprosartan, irbesartan telmisartan, olmesartan, and azilsartan, All ARBs are approved for the treatment of hypertension. In addition, irbesartan and losartan are approved for diabetic nephropathy, losartan is approved for stroke prophylaxis, and valsartan and candesartan are approved for heart failure and to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction. ARBs also demonstrated effectiveness in preventing atheromas, decreasing endothelial dysfunction, increasing fibrinolysis, reducing proteinuria, and preserving kidney function in diabetic patients.[14]

TELMISARTAN

Telmisartan is licensed for the treatment of essential hypertension. Telmisartan, a nonpeptide AT-II-receptor antagonist, gained FDA approval for use in the treatment of hypertension in 1998. Peak plasma levels are obtained 0.5-1 hour after oral administration, and the plasma t1/2 is ~24 hours. Oral bioavailability of ARBs generally is low [<50%, except for irbesartan, with 70% available], and protein binding is high [>90%]. Telmisartan is cleared from the circulation mainly by biliary secretion of intact drug. The plasma clearance of telmisartan is affected by hepatic but not renal insufficiency.[15] The recommended oral dosage of telmisartan is 40-80 mg once daily. When further blood pressure reduction is needed [beyond that achieved with 80 mg/day], the addition of hydrochlorothiazide has been found to produce incremental reductions.[16]

DRUG INTERACTIONS

No interactions with drugs that inhibitor are metabolized by CYP isoenzymes would be expected, given that CYP isoenzymes are not involved in telmisartan's metabolism, with the possible exception of interference with the metabolism of drugs metabolized by CYP2C19. When telmisartan is administered with digoxin, peak and trough plasma concentrations of digoxin are increased 49% and 20%, respectively. When telmisartan is given with warfarin there is no evidence of any change in the International Normalized Ratio.

ADVERSE EVENTS

The overall frequency of adverse events with telmisartan 20-160 mg/ day was reported to be similar to that with placebo. Rates of upper-respiratory-tract infection [7%], dizziness [5%], back pain [3%], sinusitis [3%], and diarrhea [3%] were similar to the rates for placebo [6%, 6%, 1%, 3%, and 2% respectively]. The rate of cough with telmisartan [15.6%] was comparable to that with placebo [9.6%] and significantly less than with lisinopril [60%].[16]

Numerous studies have demonstrated that the peroxisome proliferator–activated receptor-γ [PPAR-γ] plays an important role in regulating carbohydrate and lipid metabolism and that ligands for PPAR-γ can improve insulin sensitivity, reduce triglyceride levels, and decrease the risk for atherosclerosis.[17]

Peroxisome proliferator-activated receptors [PPAR] are nuclear hormone-activated receptors and transcription factors. To date, three different PPAR subtypes have been cloned and characterized: PPAR-α, PPAR-β and PPAR-γ [18-21]. The ligands for PPAR have been demonstrated to include structurally diverse compounds that vary from industrial chemicals and pharmaceutical drugs to endogenous fatty acids. These ligands can induce enormous molecular and cellular changes, including peroxisome proliferation, adipogenesis, β-oxidation enhancement, and cell-cycle regulation. After a decade of intense study, much has been learned regarding the molecular mechanisms by which PPAR activation results in its biologic consequences. PPAR have been shown to be critical factors in regulating diverse biologic processes, including lipid metabolism, adipogenesis, insulin sensitivity, immune response, and cell growth and differentiation.[18-21] and participate in the pathogenesis of a cluster of human diseases designated the metabolic syndrome, which includes insulin resistance, glucose intolerance, obesity, dyslipidemia, hypertension, atherosclerosis, and micro-albuminuria.[22-24]

Importantly, the fibrate class of PPAR-α agonists including fenofibrate and clofibrate are clinically proven lipid-lowering drugs [25], whereas the thiazolidinedione [TZD] class of PPAR-γ ligands such as rosiglitazone [Avandia] and pioglitazone [Actos] have recently been introduced into clinical practice for treating hyperglycemia and insulin resistance in patients with type 2 diabetes [26].

TISSUE EXPRESSION OF PPAR

In general, PPAR-α is highly expressed in tissues that possess high mitochondrial and β-oxidation activity, including liver, renal cortex, intestine mucosa, and heart. Lower expression of PPAR-α is also observed in several other tissues. PPAR-γ is highly enriched in adipose tissue, but lower expression levels have also been reported in urinary bladder, intestine, kidney, spleen, adrenal, heart, liver, lung, brain, and vasculature. Unlike PPAR-α and PPAR-γ, PPAR-β/δ seems to be ubiquitously expressed at low levels in almost every tissue examined. In the kidney, PPAR-α is highly abundant in the proximal tubules and medullary thick ascending limbs with much lower levels in glomerular mesangial cells [27,28].

MODE OF PPAR ACTION

Upon binding their cognate ligands, the transcriptional activity of PPAR is altered. A conformational change in the PPAR/retinoid X receptor-A [RXR-A] dimer allows the heterodimer to bind to PPAR-response elements [PPRE] to activate gene transcription. PPRE generally consist of a directrepeat of hexameric core recognition elements spaced by 1 bp [DR1, 5'AGGTCANAGGTCA-3'] located in the promoter regions of target genes [Figure 1] [18]. After activation of the PPAR/RXR heterodimer at the PPRE, the PPAR/RXR-A complex can recruit diverse nuclear receptor co-factors that modulate transcriptional activity of PPAR and RXR-A receptor heterodimer. These coactivators include cAMP response element- binding protein, PPAR-γ coactivators, cAMP response element-binding protein binding protein, and steroid receptor coactivator-1. Co-repressors such as nuclear receptor co-repressor and silencing mediator of retinoid acid and thyroid hormone receptor can modulate the transcriptional activity of PPAR by remodeling chromatin and establishing physical contacts with transcription initiation machinery. Therefore, multiple mechanisms are involved in controlling the transcription of PPAR target genes in a given cell or tissue. The expression level of PPAR receptors, the chemical properties and local concentrations of PPAR-specific ligands, and the availability of these co-factors all contribute to the biologic effect of PPAR activation or inactivation. [20,29].

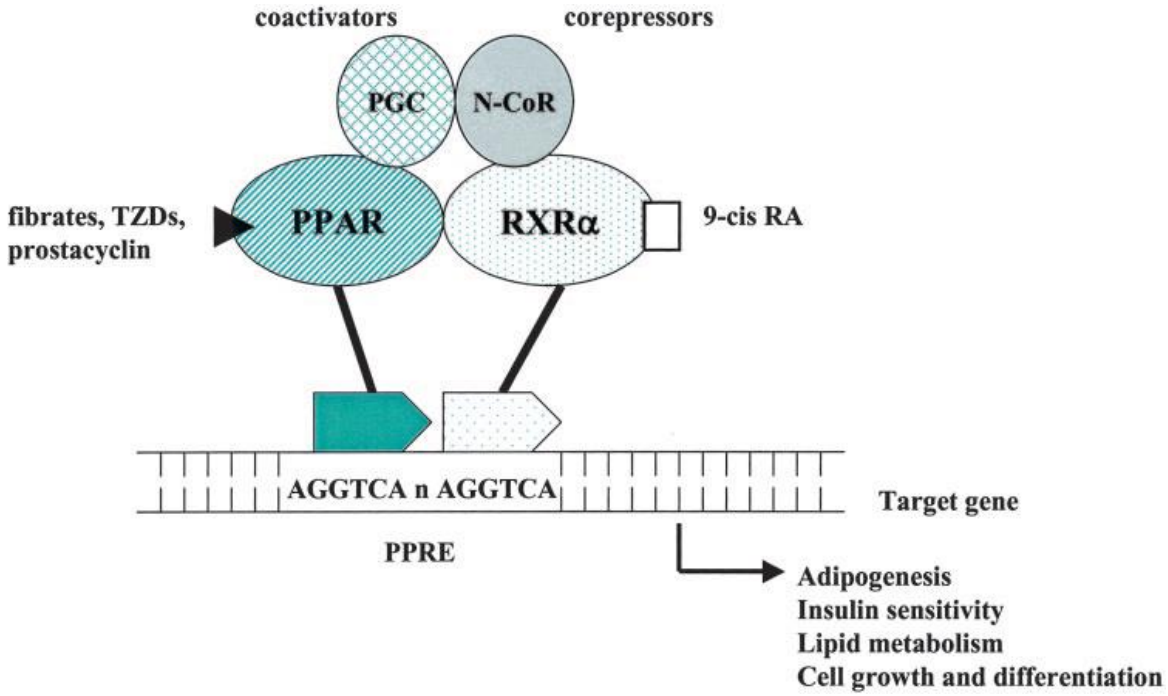

Fig.1: Mode of PPAR Action

Unlike natural fatty acids, which are good substrates for P-oxidation, substituted fatty acids, which are not a substrate for P-oxidation, are more potent PPAR activators, suggesting that the degree of PPAR activation is inversely correlated with the rate of fatty acid P-degradation. Although these studies demonstrate that exogenous fatty acids activate PPAR, it is not clear whether the active form is the acid or the acyl-CoA thioester, the production of which is controlled by the enzyme acyl-CoA synthetase. These acyl-CoA derivatives are either stored as an intracellular acyl-CoA ester pool complexed with the acyl-CoA binding protein or utilized in various intracellular enzymatic pathways. The direct involvement of acyl-CoA derivatives in intracellular lipid metabolism [in contrast to free fatty acids], together with the finding that xenobiotic peroxisome proliferators also form acyl-CoA esters , suggests that acyl-CoAs may be PPAR activators and/or ligands.[30]

Peroxisome proliferator-induced acyl-CoA synthetase activity generates acyl-CoA esters that are used predominantly for P-oxidation [31,32]. Due to the pronounced increase of peroxisomal P-oxidation, associated with a more moderate induction of mitochondrial P-oxidation, after treatment with peroxisome proliferators, less acyl-CoA esters should be available to be utilized for TG synthesis. A reduction in acetyl-coA carboxylase [33-35] and fatty acid synthase [36] activities will inhibit de novo fatty acid synthesis, further diminishing the intracellular fatty acid levels available for TG synthesis [37]. Moreover, peroxisome proliferators not only increase poxidation and decrease TG synthesis [38], but also decrease apoB and VLDL production and secretion [35, 39-40].

Telmisartan acts as a partial PPAR α agonist and induces PPAR α expression. Thus there is induction of hepatic ACSL1 [acyl coA synthetase long chain] and CPT1A [carnitine palmitoyl trransferase]. This causes significant decrease of triglyceride level. PPAR α in skeletal muscle is not affected by Telmisartan. Hence the myopathy associated with fibrates is not seen with Telmisartan. Thus PPAR α activation by Telmisartan is liver specific because of its specific pharmacokinetic Profile[41] .

DISCUSSION:

Telmisartan is an angiotensin 2 type 1 receptor blocker, originally developed for the treatment of essential hypertension. It was also reported to partially activate the peroxisonme proliferator receptor gamma [PPAR- γ] which may improve insulin sensitivity and dysregulation of adipokine secretion. This activation of Telmisartan through PPAR- γ activation has additional benefit in the treatment of essential hypertension with dyslipidemia. Many animal studies have demonstrated the beneficial effects of telmisartan on obesity, accumulation of visceral adipose tissues, insulin sensitivity and fatty liver.

PPARs are ligand activated transcription factors belonging to the super family of nuclear receptors. PPAR γ is abundantly expressed in adipose tissue and is a major regulator of insulin and glucose metabolism. In contrast, PPAR α is highly expressed in tissues displaying a high metabolic rate of fatty acids, such as the liver and skeletal muscle. PPAR α modulates intracellular lipid metabolism by transcriptional regulation of genes involved in fatty acid uptake, mitochondrial fatty acid oxidation and triglycerides catabolism. PPAR α is the molecular target of fibrates such as Gemfibrozil, etc.

Telmisartan acts as a partial PPAR α agonist and induces PPAR α expression. Thus there is induction of hepatic ACSL1 [acyl coA synthetase long chain] and CPT1A [carnitine palmitoyl trransferase]. This causes significant decrease of triglyceride level. PPAR α in skeletal muscle is not affected by Telmisartan. Hence the myopathy associated with fibrates is not seen with Telmisartan. Thus PPAR α activation by Telmisartan is liver specific because of its specific pharmacokinetic Profile.

It is widely believed that the currently available ARBs are metabolically neutral and have little or no impact on carbohydrate and lipid metabolism when administered in conventional doses used to treat hypertension. However, the current findings suggest that Telmisartan might be an exception in this regard and provide insight into new strategies for developing molecules that could improve many if not all of the biochemical and blood pressure disturbances that compose the metabolic syndrome.

PPAR agonists convey beneficial effects as therapeutic agents for diabetes and atherosclerosis by lowering blood glucose, improving insulin resistance, inflammation, and lipid metabolism; however, adverse side effects limit their clinical use. As such, the future of PPAR-directed agents in cardio-metabolic therapy remains uncertain, although several late-stage molecules may still hold promise. Future directions in PPAR agonist development are likely to focus on optimizing the PPAR subtype interaction profile, maximizing the inhibition of PPAR-γ phosphorylation, and screening against off-target activity. At the present time, clinicians should

keep in mind the risk/benefit ratio of PPAR activators. Intensive research on this therapeutic target will likely lead to the development of safer and more effective PPAR agonists in the near future.

The multiple mechanisms of action of Telmisartan, including AT1 receptor blockade, PPAR γ modulation and hepatic PPAR α activation, characterizes this compound as a therapeutic option for the treatment of patients suffering from multiple cardio metabolic disorders such as hypertension, glucose intolerance, and dyslipidemia.

CONCLUSION:

Clinically, Telmisartan plays a major role in reducing the hypertension by blocking angiotension receptors. Now-a-days a large number of large scale clinical trials had proven that telmisartan not only reduces the blood pressure, but also it shows better improvement on most lipid indices, like increases in HDL and decreases in TC,TG,VLDL, and LDL. One of the possible explanations for such an improvement with telmisartan could be that it acts as a partial PPAR γ agonist. PPAR-γ regulates lipid metabolism and therefore reduces TG and LDL levels.

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