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Review Article

ADDITIONAL PHARMACOLOGICAL ACTIVITIES OF PIOGLITAZONE: A RETROSPECTIVE REVIEW

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ABSTRACT

Glitazones are the antihyperglycemic agents used in the treatment of Type-II diabetes mellitus (T2DM) as monotherapy or in combination with metformin, insulin and sulfonylureas. The drugs - Rosiglitazone and Pioglitazone under this class exert their pharmacological action by directly stimulating the nuclear Peroxisome Proliferator Activated Receptor (PPAR-**γ**) and thereby regulating peripheral insulin resistance. Pioglitazone, the PPAR- **γ** agonist apart from exerting its hypolipidemic effects and anti-hyperglycaemic effect also has positive pleiotropic effects such as anti-Parkinson's, anti-bacterial, anti-hypertensive, antiinflammatory actions etc. Renal and hepatic cyst growth inhibition, learning and memory enhancement, blockade of L-type calcium channels in vascular smooth muscles are other effects influenced by pioglitazones. The present review throws light on the additional pharmacological effects of pioglitazone other than its positive effect on glucose metabolism.

Keywords: Pioglitazone**,** Thiazolidinediones(TZDs), Troglitazone, Type-II Diabetes mellitus.

INTRODUCTION

Glitazones are a newer class of antihyperglycemic agents which include rosiglitazone and pioglitazone that are currently in use in the treatment of Type II Diabetes. Pioglitazone has been shown to act as potent and selective agonist for the nuclear receptor Peroxisome Proliferator Activated Receptor-gamma (PPAR-γ) and activation of PPAR-γ promotes transcription of insulin responsive genes and thereby regulate glucose and lipid metabolism. Pioglitazone action leads to improvement in insulin sensitivity in target tissues through increased membrane expression of GLUT-4 glucose transporters in skeletal muscle and adipose tissue, and by decreased hepatic glucose output through inhibition of gluconeogenesis. Pioglitazone also enhance HDL cholesterol and lower triglyceride levels (Sharma HL and Sharma KK). Pioglitazone, apart from its well-known antihyperglycaemic and hypolipidemic effects, has been reported to exert its positive effects in several debilitating diseases and hold promise in the treatment of many such diseases. In this review, we summarize the additional pharmacological activities of Pioglitazone more than its effects on lipid and carbohydrate metabolism.

PIOGLITAZONE-DRUG HISTORY

Troglitazone the first glitazone was launched in USA by march 1997 but was withdrawn on grounds of liver toxicity in march 2000 (Rishi Shukla and Sanjay Karla, 2011). Rosiglitazone and Pioglitazone reached the US market in 1999 as first line agents to be used alone or in combination with metformin or sulfonyureas in the treatment of for diabetes mellitus (Gale, 2001).

PIOGLITAZONE-CURRENT STATUS

Pioglitazone in addition to its glucose lowering effect also benefits cardiovascular parameters such as lipids, blood pressure, endothelial function, inflammatory biomarkers and fibrinolytic status. Other activities like anti-parkinsonism (Quinn *et al.,* 2008), anti-bacterial (Masadeh *et al.,* 2011), hypolipidemic also have been studied (Francis *et al.,* 2003; de Souza *et al.,* 2001; Bhosale *et al.,* 2012). Additionally

pioglitazone also influences learning and memory (Searcy *et al.,* 2012), oxidative stress (Kadiiska *et al.,* 2012) blockade of L type Ca^{++} channels in vascular smooth muscles (Zhang *et al.,* 1994; Song *et al.,*1997; Nakamura *et al.,* 1998; Asano *et al.,* 1999), renal and hepatic bile duct cyst growth inhibition (Blazer-Yost *et al.,* 2010) etc.

In spite of its beneficial effects, an emerging issue regarding pioglitazone use concerned with the fluid retention and congestive heart failure have been reported (Patel *et al.,* 2005; Patel *et al., 2006)*.Association of bladder cancer with antidiabetic treatment have also been reported in a study made by FDA adverse event reporting system database (Rishi Shukla and Sanjay Karla, 2011).

PIOGLOTAZONE AND PARKINSONISM

The pathogenesis of Parkinson's disease involve glial activation and inflammatory processes (McGeer *et al.,* 1988; Hunot *et al.*, 1997; Hirsch, 2000; Ouchi *et al.*, 2005; Gerhard *et al.,* 2006; Kurkowska-Jastrzebska *et al.,* 1999; Langston *et al.,* 1999; Mc Geer *et al.,* 2003). The neuroprotective properties of pioglitazone has been reported in MPTP induced Parkinson's disease in C57BL6/J mice where chronic dietary administration of pioglitazone (20mg/kg/day) attenuated the MPTP-induced glial activation, striatal dopamine depletions and dopaminergic cell loss in the substantia nigra (Breidert *et al.,* 2002; Dehmer *et al.,* 2004). The neuroprotective effect of pioglitazone has been shown to be mediated by inhibition of MAO-B and thereby blocking the conversion of MPTP to its active toxic metabolite, MPP^+ in mice. The protective effect of pioglitazone pretreatment was evident from its action in preventing reduction in dopaminergic nigral cell count and depletion in the striatal dopamine and striatal dopamine metabolites such as DOPAC and HVA. Pioglitazone pretreatment caused improvement in behavioural, neurochemical and immunohistological deficits in MPTP mouse model and this effect is attributed to its inhibitory activity on the enzyme MAO-B (Quinn *et al.,* 2008). In another study, amelioration of neuro-inflammation was observed in Parkinsonian monkeys that received a dose of 5mg/kg p.o of pioglitazone along with higher CSF levels of pioglitazone. This observation confirmed the ability of pioglitazone to cross the blood brain barrier and support the concept of PPAR-**γ** as viable target against neuro-degeneration in early Parkinsonism (Swanson *et al.,* 2011).

PIOGLITAZONE AND ALZHEIMER'S DISEASE

Alzheimer's disease is the most widespread cause of dementia and its incidence will increase rapidly with aging (Kochanek *et al.,* 2009). However, the underlying causes leading to the progressive decline in cognitive function in Alzheimer's disease are still poorly understood (Searcy *et al.,* 2012). A potentially important observation in the pathogenesis of Alzheimer's disease has emerged from studies showing that the risk of Alzheimer's disease and mild cognitive impairment (MCI) is increased in subjects with metabolic syndrome and Type-II diabetes mellitus (Hartmann *et al.,* 2001; Luchsinger *et al.,* 2008;Whitmer *et al.,* 2008; Biessels *et al.,* 2008; Messier *et al.,* 2009). As a result, it is suggested that the drugs used in treating Type II diabetes mellitus might be efficacious in eliciting potential therapeutic effect of improving learning and memory defecits in Alzheimer's disease. In particular, the thiazolidinediones (TZDs) have been shown to exert multiple beneficial effects on age-related cognitive decline (Abbatecola et al., 2010; Risner *et al.,* 2006; Ryan *et al.,* 2006; Watson *et al.,* 2005; Sato *et al.,* 2011). It is also reported that pioglitazone exert their positive effects on cognitive and functional outcomes in patients with mild cognitive impairment and diabetes (Sato *et al.,* 2011). In addition, factors related to lipid metabolism also appear to play an important role in determining sensitivity to the possible cognition enhancing effects of TZDs.

The beneficial effects of TZDs in several murine models of Alzheimer's disease have been noticed with reduction in inflammatory cytokines (Heneka *et al.,* 2005; Feinstein *et al.,* 2003; Lacombe *et al.,* 2004; Landreth *et al.,* 2001), oxidative stress (Nicolakakis et al., 2008), Aβ deposits (Heneka *et al.,* 2005; To *et al.,* 2011; Escribano *et al.,* 2010), glial activation (Heneka *et al.,* 2005, Nicolakakis *et al.,* 2008) tau phosphorylation (To *et al.,* 2011; Escribano *et al.,* 2010).

The effect of pioglitazone on learning and memory was studied by using wide range of biomarkers such as cognitive decline, synaptic impairment, elevated Aβ peptides and neuritic plaques, as well as hyperphosphorylated tau proteins and neurofibrillary tangles (Oddo *et al.,* 2003).

Long term treatment of pioglitazone caused improved performance in triple transgenic mice model in active avoidance task, increased short and long term hippocampal plasticity, reduced Aβ and tau staining, and altered expression of several known pharmacologically-relevant gene targets such as TNF-α, NFκB and interleukin-related genes. In addition, microarray analysis

also revealed several targets of pioglitazone to be associated with cognition and establish the efficacy of pioglitazone in treating Alzheimer's disease (Searcy *et al.,* 2012)**.**

PIOGLITAZONE AND ANTI-BACTERIAL ACTIVITY

Pioglitazone has been shown to possess a dose dependent antibacterial activity against some important Gram-positive micro-organisms like *Streptococcus pneumoniae*_ and gram negative micro-organisms like *Escherichia coli* and *Klebsiella pneumonia*. Furthermore, pretreatment of bacterial cultures with pioglitazone has been shown to enhance the antibacterial activity of amoxicillin, cephalexin and ciprofloxacin (Masadeh *et al.,* 2011). These data encourages the possibility of pioglitazone as an anti-bacterial agent and however ongoing studies are aiming at in finding out the appropriate mechanism by which this anti-bacterial effect is brought out.

PIOGLITAZONE AND HYPOLIPIDEMIC ACTIVITY

Dyslipidaemia is common among patients with diabetes mellitus which is characterised by increased level of triglycerides, modest elevations of LDL and lower levels of HDL cholesterol leading to increased risk of cardiovascular disease (St-Pierre *et al.,* 2005). A head-to-head clinical trial conducted by Goldberg *et al., (*2005), has revealed that pioglitazone decreased and rosiglitazone increased the triglyceride concentrations with a net lipid effect of slightly lowered LDL/HDL ratio. This implies that both pioglitazone and rosiglitazone are involved in altering the HDL and LDL levels. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in type-II diabetes mellitus patients have been demonstrated with significant changes in triglycerides and HDL level without causing significant changes in total cholesterol and LDL levels (Rosenblatt *et al.,* 2001). Pioglitazone administration was found to be effective in improving the lipid profile and controlling the blood glucose levels by reducing the serum glucose, glycosylated heamoglobin (HbA1c), Total Cholesterol (TC), Triglycerides (TG) and High density lipoprotein (HDL) against Streptozotocin-Nicotinamide induced diabetes mellitus (Kakadiya *et al.,* 2010). More data revealed the overall beneficial effect of TZDs by lowering the atherogenic index of plasma (Chiquette *et al.,* 2004). It has been reported that pioglitazone treatment in high fructose diet fed rats resulted in a partial reversal of disturbed lipid profile with significant reduction in triglycerides and an improvement in HDL level in a dose dependent manner (Biswas *et al.,* 2012). Furthermore, pioglitazone administration in high fat diet induced hyperlipidemic animals caused significant reduction in total serum triglycerides and VLDL levels along with increase in HDL level whereas no significant decrease in serum cholesterol and LDL level (Bhosale *et al.,* 2012).

PIOGLITAZONE AND HYPERTENSION

Accumulated data depicts that TZDs in general, attenuates the presser response to norepinephrine and angiotensin II and thereby preventing the development of hypertension in animal models (Yoshioka *et al.,* 1993; Kaufman *et al.,* 1995; Zhang *et al.,* 1994). The possible mechanism of anti hypertensive effect of TZDS might be blockade of voltage-gated (L-type) calcium channels, by which mechanism, dihydropyridine calcium channel blockers acts (Zhang *et al.,* 1994). Several papers have shown that thiazolidinediones, such as troglitazone and pioglitazone, can reduce peripheral resistance and exert hypotensive effects (Dubey *et al.,* 1993; Pershadsingh *et al.,* 1993; Ogihara *et al.,* 1995; Buchanan *et al.,* 1995; Kotchen *et al.,* 1996). A meta analysis even reported about the efficacy of TZDs in reducing blood pressure of diabetes mellitus patients with and without hypertension (Chiquette *et al.*, 2004; Dormandy *et al.,* 2005).

Another study conducted in human volunteers also have shown that administration of pioglitazone in hypertensive patient s(with or without DM) have decreased Systolic Blood Pressure and diastolic Blood Pressure and the potential mechanisms behind it includes peripheral vasodilatation, decreased sympathetic activation via improved insulin sensitivity or down-regulation of Renin-Angiotensin system (RAS) (Kelly *et al.,* 2007). Moreover, a dose dependent anti-hypertensive effect of pioglitazone has been reported with a significant increase in systolic blood pressure was induced (Biswas *et al.,* 2012) in high fructose diet (HFD) (Yadav *et al.,* 2004) fed rats. These studies strengthen the possiblity of pioglitazone as an effective anti-hypertensive agent.

PIOGLITAZONE AS CALCIUM CHANNEL BLOCKER AND ANTI- PROLIFERATIVE AGENT

Troglitazone and pioglitazone by themselves inhibits the voltage dependent L-type Ca^{2+} channels present in vascular smooth muscle cells (Zhang *et al.,* 1994; Song *et al.,* 1997; Nakamura *et al.,* 1998).The vasoactive agents such as epidermal growth factor, insulin and

basic fibroblast growth factor eliciting cell proliferation was effectively inhibited by the administration of troglitazone and pioglitazone (Dubey *et al.,* 1993; Law *et al.,* 1996). Despite several mechanisms of TZDs, the underlying mechanism behind their action on inhibition of cell proliferation is unclear (Lehmann *et al.,* 1995). Reports are available on the involvement of calcium in the growth-regulatory control for number of cell types since DNA synthesis and cell proliferation requires calcium ions. A reduction in calcium entry through calcium channels might be the underlying mechanism for the antiproliferative effects of thiazolidinediones (Berridge, 1995).

Troglitazone and pioglitazone have been found to inhibit the calcium entry elicited by vasopressin and PDGF (Platelet Derived Growth Factor) in aortic smooth muscle cells. They also inhibit vasopressin-mediated calcium permeable nonselective cation channels (Icat) as well as voltage-dependent L-type Ca^{2+}channels. It has been reported that troglitazone and pioglitazone inhibit cell proliferation induced by vasopressin and PDGF in a concentration-dependent manner (Asano *et al.,* 1999). These findings conclude that troglitazone and pioglitazone restrain proliferation of vascular smooth muscle cells by inhibiting the calcium entry in an agonist (vasopressin and PDGF) dependent manner.

PIOGLITAZONE IN POLYCYSTIC KIDNEY AND LIVER DISEASE

In general, it has been proposed that cyst expansion occurs chiefly due to the secretion of ions and fluids by the epithelial cells and even some studies indicate that renal cyst formation in polycystic kidney disease are usually driven by the secretion of anions like Cl^{-}or HCO_3^{-}(Ye and Grantham,1993; Davidow *et al.,* 1996; Mangoo-Karim *et al.,*1995). Inhibitor studies and electrophysiological analysis performed also confirm that cystic fibrosis transmembrane conductance regulator is the Cl^- channel responsible for anions secretion in both kidney and biliary cysts (Davidow *et al.,* 1996;Muchatuta *et al.,* 2009). Studies performed in cell culture (Nofziger *et al.,* 2009) and with freshly isolated bile duct epithelia (Muchatuta *et al.,* 2009) depicts that PPARγ agonists inhibit the cAMP-stimulated anion transport and mRNA expression of the cystic fibrosis transmembrane conductance regulator (CFTR).

The efficacy of pioglitazone was shown in PCK rodent model with 7 weeks of pioglitazone treatment after the embryonic or neonatal period treatment showed a decrease in the liver cyst burden in female animals and decrease in renal cyst burden in the male animals. A 14 weeks of pioglitazone treatment resulted in a significant reduction in kidney and liver cysts in both sexes and its crosssectional kidney images also showed a decrease in cyst burden in the presence of pioglitazone (Blazer-Yost *et al.,* 2010)

PIOGLITAZONE AS ANTI-INFLAMMATORY AND NEURO-PROTECTIVE AGENT

Pioglitazone has been shown to regulate the activation of peroxisome proliferator activated receptor-**γ**(PPAR-**γ**)would modulate inflammatory responses *in vitro* and *in vivo* protecting cells from death and toxicity(Jiang *et al.,*1998;Ricote *et al.,*1998;Combs *et al.,*2000;Heneka *et al.,*1999;Heneka *et al.,*2000;Kim *et al.,*2002;Inestrosa *et al.,*2005;Luna-Medina *et al.,* 2005;Storer *et al.,*2005).Some evidences suggests the vital role of glial cells and inflammatory processes in pathogenesis of parkinson's disease. Also a microglial activation has been demonstrated in substantia nigra of PD patients and in human patients exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(Langston *et al.,*1999),in an MPTP-induced mouse model of parkinson's disease(Kurkowska-Jastrzebska *et al.,*1999).Thus the activated microglia is believed to contribute to neurodegeneration through the release of cytotoxic compounds including reactive oxygen intermediates, nitric oxide, proteases and pro-inflammatory cytokines(Chao *et al.,*1992;Hunot *et al.,*1996;Bal-Price and Brown 2001;Le *et al.,*2001).

A new role for PPAR-γ receptors in the regulation of inflammation has also been described(Delerive *et al.,*2001)and PPAR-**γ** agonists have been shown to inhibit inflammatory processes in a variety of cell types in vitro, including monocytes/macrophages (Jiang *et al.,*1998;Ricote *et al.,*1998),microglial cells(Combs *et al.,*2000) and *in-vivo* modulation of inflammatory responses in brain(Heneka *et al.,*2000).

Pioglitazone administered orally at a dose of 20mg/kg was found to be effective in eliciting neuro-protective actions and thereby inhibits the iron-induced α-synuclein aggregation, interleukin-1β,interleukin-6 mRNA elevated levels as well as oxygenase-1,cyclo-oxygenase II, nitric oxide synthase and ED-1 protein increased levels which are the indicators of activated microglia. Moreover, iron-induced DNA laddering as well as activation of ER and mitochondrial pathways were also attenuated by pioglitazone. In addition, pioglitazone has decreased the iron-induced elevation of lipid

peroxidation in the infused SN and striatal dopamine level depletion.The inhibition of α-synuclein aggregation and neuro-inflammation sturdily contributes to the pioglitazone-induced anti-inflammatory action and neuroprotection in central nervous system(Yu *et al.*,2010).

PIOGLITAZONE AS CARDIO-PROTECTIVE AGENT IN MYOCARDIAL INFARCTION

Though there is a concern regarding the adverse effects of pioglitazone in eliciting fluid retention (Tang *et al.*,2003) and congestive heart failure (Patel *et al.*,2005), beneficial cardio-protective activity of pioglitazone have also been reported. Previous studies have suggested that PPAR-**γ** activation inhibits TNF production in cardiomyocytes after stimulation with lipopolysaccharides (Takano *et al.*,2000) since TNF activation is linked to congestive heart failure (Frantz *et al.*,2004). Some experimental studies have postulated the protective effects of TZDs in reducing the production of mediators like endothelia (Buchanan *et al.*,1995) and pro-inflammatory cytokines (Sidhu and Kaski,2001) which are involved in the progression of heart failure whereas some other studies have reported that pioglitazone at a dose of 3mg /kg in an average 20mg /kg body weight mice with left ventricular dilatation and heart failure in CD-1 mice model of chronic murine MI has produced protective effects with extensive MI when treatment is started early after MI (Shiomi *et al.*,2002).

PIOGLITAZONE IN ATHEROSCLEROSIS

TZDs were proven as potent inhibitors of cellular migration and proliferation in many *ex-vivo* preparations of animal and human vascular smooth muscle and endothelial cells and are said to be an important contributor to atherosclerosis (Marx *et al.*,1998, Fukunaga *et al.*,2001).

Still, some prediction arises from reports of certain experimental studies which indicate that PPARs may have a preventive role in the pathogenesis of atherosclerosis in regulating the cytokine production, adhesion molecule expression on endothelial cells, brinolysis, modulation of monocyte-derived macrophages, and proliferation of vascular smooth muscle cells (VSMC) (Law *et al.*,2000; Loviscach *et al.*,1999).

Marx *et al.*,(2000), have shown that PPAR-**γ** agonists inhibits the expression of gamma interferon inducible protein10 (IP-10), (Mig) i.e monokine induced by IFN- **γ** and inducible T-cell alpha-chemoattractant (I-TAC) from human vascular endothelial cells and also inhibits the production of MCP-1 monocyte chemotactic protein-1(MCP-1) in cytokine treated human vascular endothelial cells (Murao *et al.*,1999) since these are the major inflammatory cytokines involved in artherogenesis mediated chemotactic attraction of inflammatory cells into the vessel wall.

Though *in-vivo* reports on anti-atherogenic role of pioglitazone is incomplete, evidences for the anti-atherogenic role of PPARs are still mounting. TZDs produced a significant reduction in carotid wall thickness, a marker of early stages of atherosclerosis when tested in Type II diabetes patients (Minamikawa *et al.*,1998). The effect of troglitazone when examined in rat aorta induced with baloon catheter injury resulted in inhibition of growth of vascular smooth muscle and intimal hyperplasia after 14 days of treatment (Law *et al.*,1996). Also troglitazone effects were observed in an atherosclerotic model of a LDL-receptor deficient mouse which resulted in the inhibition of vascular lesions with a concomitant decrease in macrophage content (Collins *et al.*,2000).These findings support the notion that PPAR-**γ** agonist pioglitazone as anti-atherogenic.

CONCLUSION

Some of the adverse effects and complications linked with pioglitazone usage includes fluid retention, cardio-vascular risks, bladder cancer, etc. but clinical study reports reveal that the amount of complications with fluid retention is almost negligible and the risk of bladder cancer occurs only with higher doses of pioglitazone and most clinicians in India had even brought down the dose of pioglitazone to a level of 7.5mg instead of approved dose 15mg. Over and above the manufacturers had even prompted to include a caution regarding the use of TZDs in the product labeling of pioglitazone. In conclusion, the beneficial effects of pioglitazone overweigh the risks associated with its use.

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