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THIAZOLIDINEDIONES AS PEROXISOME PROLIFERATOR - ACTIVATED RECEPTOR - γ - ACTIVATOR

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ABSTRACT

Now a day Hyperglycaemia (type 2 diabetes) is a major therapeutic problem. This is moderately because reduced insulin sensitivity and beta cell failure lead to resistant to current therapies. The thiazolidinediones are a new class of drugs that get better insulin sensitivity. Thiazolidinedione structure has been an significant structural domain of research, involving design and development of new drugs for the treatment of type 2 diabetes. Wide research on the mechanism of action and the structural requirements has shown that the intended antidiabetic activity in type 2 diabetes is due to their agonistic effect on peroxisome proliferator-activated receptor (PPAR) belonging to the nuclear receptor super family. Pharmacology and chemistry of thiazolidinediones as PPARγ agonists and the potential of newer analogues as dual agonists of PPARs and other promising targets for the therapy of type 2 diabetes are presented. Thiazolidinediones (TZDs) are five-membered heterocyclic having sulfur, nitrogen, and oxygen atoms in their ring structure and exhibiting potent as well as wide range of pharmacological activities.

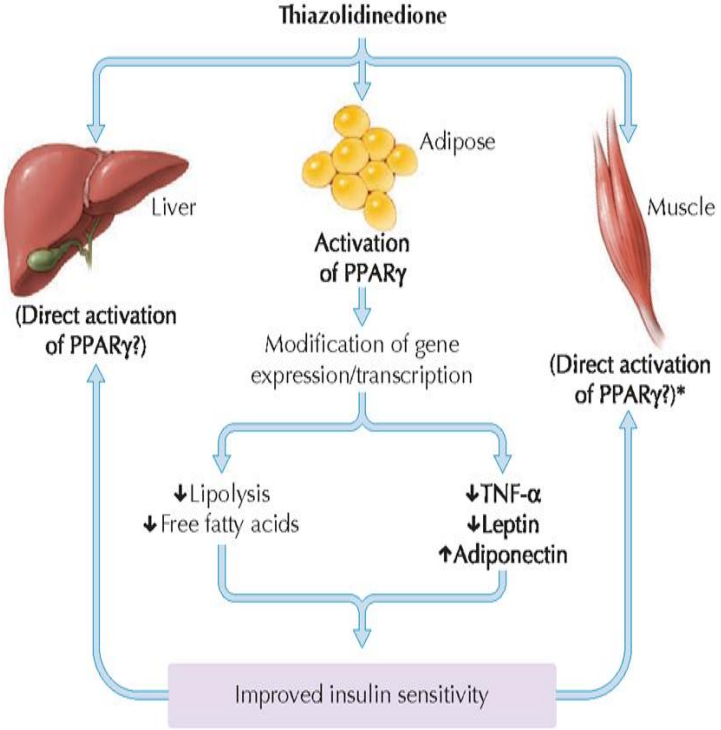
KEYWORDS: Peroxisome Proliferator-Activated Receptor (PPARγ), Thiazolidinediones, Agonist.

INTERODUCTION

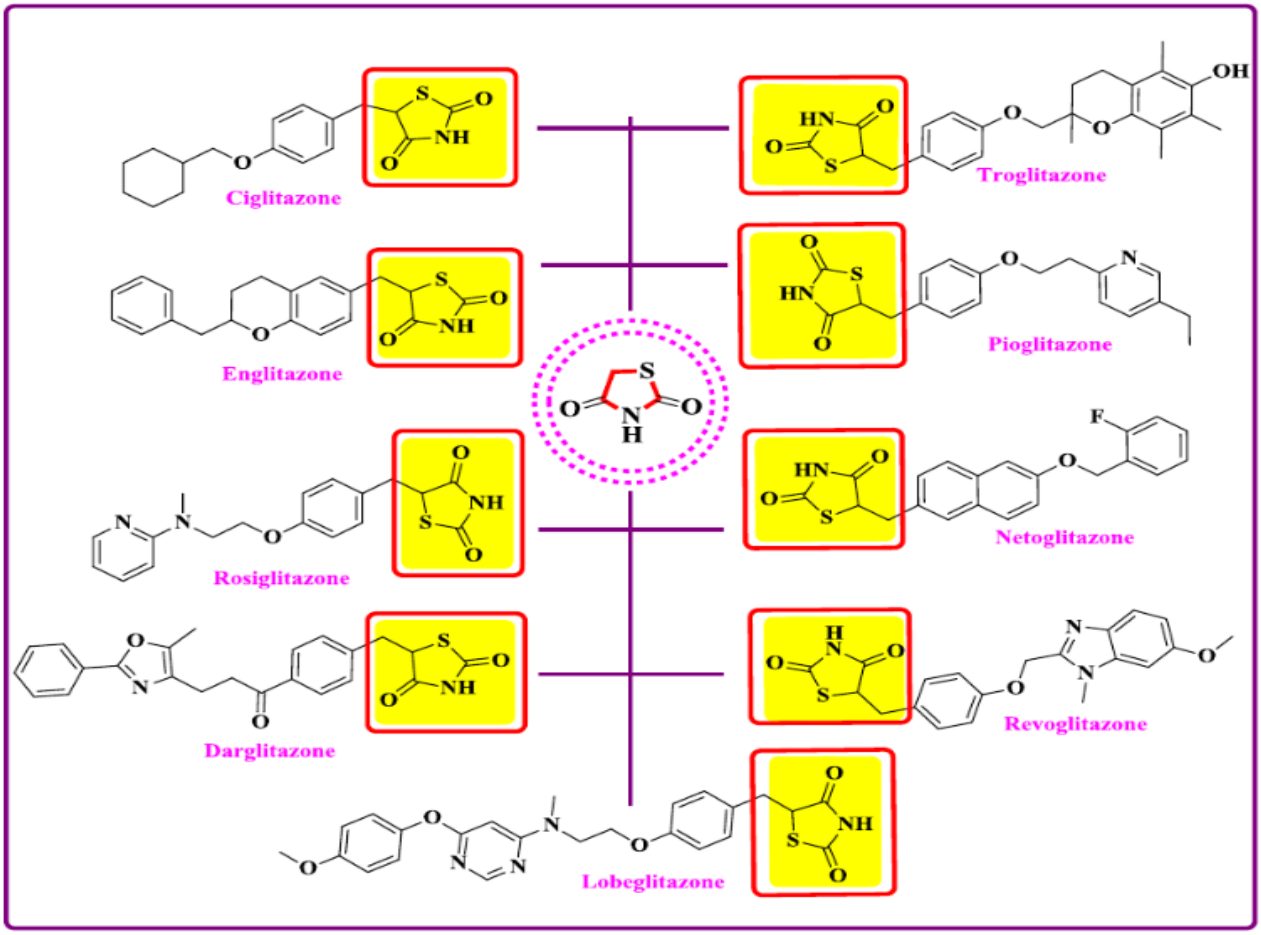
Diabetes Mellitus is one of the major disease to human health worldwide and it is be the seventh leading cause of death.[1] A report by World Health Organization (WHO) is of observe that the number of people above eighteen years of age have been affected by diabetes has rapidly increased.[2] Type 2 diabetesis the major form of diabetes and contributes to 90% of people with diabetes. around the world. Hypoglycemic drugs like sulfonylureas, biguanides, glinides, and glitazones are used for the treatment of type 2 diabetes but all of them suffer from unintended effects like hypoglycemia and obesity.[3–6] Thiazolidinediones (TZDs) or glitazones are important group of drugs which are active orally in the treatment of type 2 diabetes. TZDs bind avidly to Peroxisome proliferator-activated receptor gamma (PPARγ agonists) and the activation of PPARγ by these drugs influences a number of genes expressed which are involved in lipid and glucose metabolism and preadipocyte differentiation. They enhance the sensitivity to insulin (insulin sensitizers) and promote the consumption of glucose by peripheral tissues.[7] As the thiazolidinediones (or 'glitazones') develop insulin sensitivity through actions whichare completely different from those of other oral hypoglycaemic drugs, there has been a lot of interest in their potential role in type 2 diabetes.

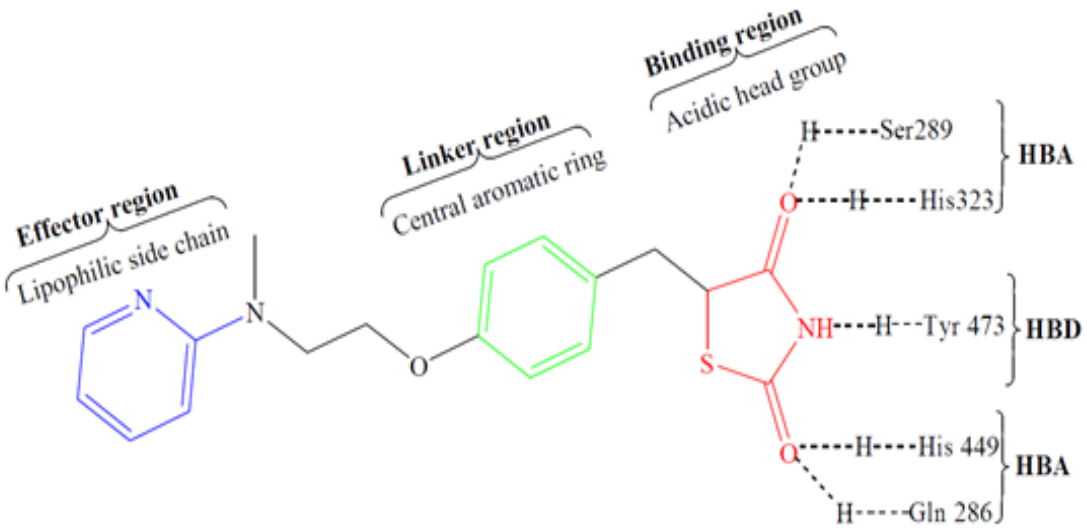
Molecular mechanisms of action

Peroxisome Proliferator-Activated Receptor gamma (PPARγ) is a member of a family of nuclear receptors. peroxisome proliferator-activated receptor alpha (PPARγ), is predominantly expressed in the liver and is thought to mediate the triglyceride lower actions of fibrates.[8] PPARγ is expressed in many tissues, including colon, skeletalmuscle, liver, heart and activated macrophages, but is most abundant in adipocytes. Thiazolidinediones are selective agonists of PPARγ. Whenactivated by a ligand, such as a thiazolidinedione, PPARγ binds to the 9-*cis* retinoic acid receptor to form a heterodimer. This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism.[9]



Thiazolidinediones (TZDs) are a group of pharmacologicalagents that strengthen insulin action (insulin sensitizes) andpromote glucose utilization in peripheral tissues hence act as antidiabetic agents. There was number of thiazolidinedionederivatives act as antidiabetic agents. Few examples are shown in fig,





HBA: Hydrogen bond acceptor HBD: Hydrogen bond donor
Figure: Drug interaction with Peroxisome proliferator-activated receptor gamma.

Development of the Thiazolidinediones

The first compound, ciglitazone, had better glycaemic control in animal models of insulin resistance, but its mechanism of action was poorly understood and toxicity prohibited trials in humans. Other compounds were subsequently developed with less toxicity in animals, and two important findings led to a rapid increase in our understanding of their mode of action. These findings were that thiazolidinediones:

- Binding to peroxisome proliferator-activated receptor gamma (PPARγ)[11]
- Increase insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction incirculating free fatty acids.[12]

Three compounds troglitazone, pioglitazone and rosiglitazone have been passed in clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs. Unfortunately, troglitazone caused uncommon but serious liver toxicity, leading to its withdrawal from use. It seems likely that this toxicity was related to the vitamin E-like part of the molecule. Hepatotoxicity does not seem to be associated with the other two compounds, but regular liver function tests are recommended.[10]

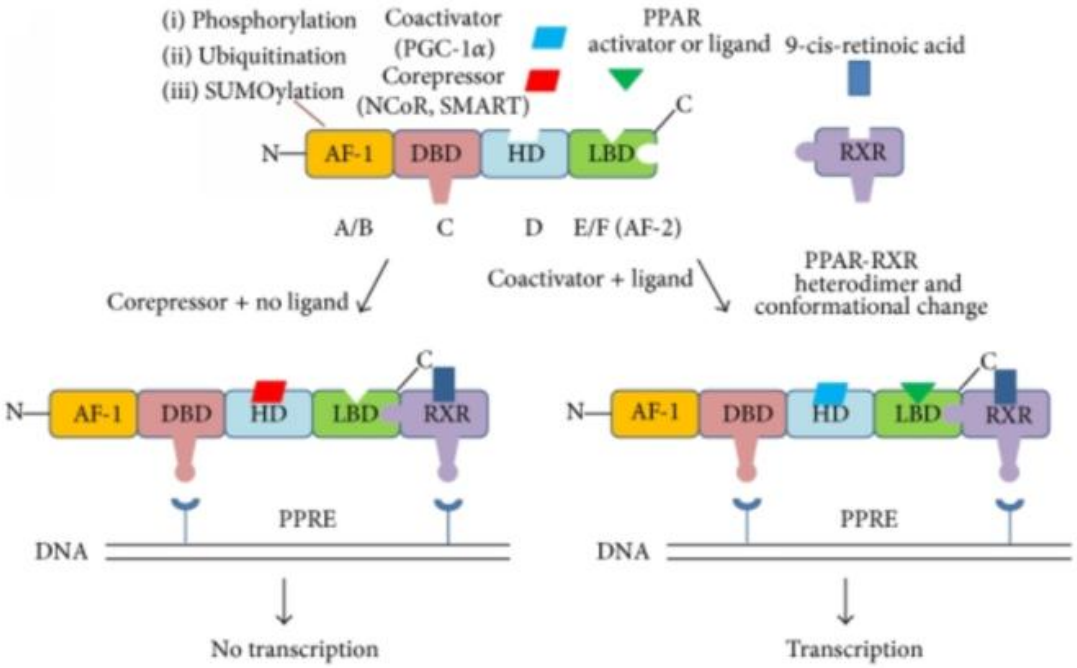
PPARs as a molecular target for antidiabetic drugs

- **Structure and Molecular Mechanisms of PPARs**

Peroxisome proliferator-activated receptorsis belonging to nuclear hormone receptor superfamily. They are ligandinducibletranscription factors andcontrol genes important in cell differentiation and various metabolic processes, like lipid and glucose homeostasis, insulin sensitivity, and inflammation.[13] These receptors can be induced by the fatty acids and their metabolites from the diet.[14] PPARs are act as potential targets for the therapies of diabetes, inflammation, atherosclerosis, and hypertension.[15] There are three isoforms, PPARα, PPARβ/δ, and PPARγhave been identified which are encoded bydistinct genes.[16]

- **Structure of DNA Binding Domain of PPARs**

The A/B regions of the PPARs are act as potent transcriptional activators and they get involved in protein phosphorylation, or directly interact with other receptor domains or regulatory proteins. It was observed that the A/B region has not been visualized in any of the crystal structures. Study shown that this region due to its high mobility does not possess significant hydrophobic residues or protected amino acid sequence to provide a meaningfulbinding site. PPARγ ligands did not show any effect on the A/B region.[17] Two zinc-binding sites are seen in the central and highly conserved DNA binding domain, which also contains the architectural elements with the ability for sequence-specific binding to DNA.[18,19]



- **Pharmacological Functions of PPARα**

PPAR$\alpha$is highly expressed in tissues competent of increased fatty acid oxidation, such as liver, skeletal muscle, and heart. Activation of this receptor would result in decreased lipid levels.[20] It is also involved in glucose homeostasis and insulin resistance development.[21]

- **PPARγ Agonists**

Due to their effectiveness as antidiabetic drugs researches have been carried out on this class of compounds. Various chemical scaffolds of natural and synthetic ligands of this group were determined. Literaturereview indicated that diverse, structurally distinct chemical compounds were capable to produce PPARγ activation because the ligand binding domain constitutes a large, flexible pocket able to accommodate the molecules of different size and conformations. Most of the agonists do not occupy the whole binding pocket.[22]

Structure activity relationship studies on thiazolidinediones

Structure of a molecule to its pharmacological activity is an fundamental part of medicinal chemistry. Assessing the pharmacophores and the nature of the binding interactions becomes necessary in development of the potency and selectivity and also is important to discover a molecule with decreased side effects. Attempts to synthesize and screen the analogues of the prototype molecule would be a right method for pharmacophore identification; but it is an old, time consuming method.

Thiazolidinedione interacts by forming hydrogen bonds with His323 (H4), His449 (H11), and Tyr473 residue of helix 12 of PPARγLBD, associated with AF2 domain. It may also form hydrogen bond with Ser289 (H3) and the oxygen; nitrogen atoms of the ring function as both hydrogen bond acceptors and donors. The hydrophobic tail moiety of Rosiglitazone may also interact with helix 3, 5, 6, 7, and the β strand, occupying arm II and arm III of the LBD, throughvan der Waals and hydrophobic interactions which accounts for the efficiency of binding and potency of the molecule. The central phenyl ring is accommodated underneath helix 3 by hydrophobic interactions.[23]

CONCLUSIONS

Structure activity relationship studies have been resulted in a large group of analogues, indicating that thiazolidinediones can accommodate varieties of linkers and lipophilic tails leading to changes in their pharmacodynamic properties, enhanced potency, selectivity, and decreased toxicity. The thiazolidinediones are a new type of therapy for type 2 diabetes. Their action, in large part, is mediated by activation of PPARγ and involves redistribution of surplus fatty acids to peripheral fat. thiazolidinediones possess a large structure which enables them to bind to the polar as well as the big hydrophobic binding pockets of the ligand binding domain of PPAR.

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