

Molecular Modeling Study of PPAR γ Agonists: Dehydro-Di-Isoeugenol, Macelignan, Pioglitazone, Netoglitazone, and Rosiglitazone as Antidiabetic Drugs

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Abstract

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor family. The objective of this study is to analyze the molecular aspects of PPAR γ agonists which used to design of new antidiabetic drugs. The analysis method was comparing the interactions of ligands in the ligand binding domain of the PPAR γ . This analysis showed that most known agonists of PPAR γ interacted via hydrogen bond with Tyr473. Pioglitazone showed three hydrogen bonds with His323 and Tyr473. Netoglitazone showed four hydrogen bonds with Ser289, His323, His449, and Tyr473. Rosiglitazone showed five hydrogen bonds with Ser289, His323, His449, and Tyr473. AZ72, an agonist of PPAR α and γ showed five hydrogen bonds with Ser289, His323, His449, and Tyr473. Molecular modeling was performed by redocking pioglitazone and rosiglitazone using AutoDock Vina. Docking showed that both pioglitazone (Ki 0.22 μ M) and rosiglitazone (Ki 0.70 μ M) occupied their origin sites and interacted with Tyr473. Docking simulation was also performed between dehydro-di-isoeugenol and macelignan to visualize the interaction with PPAR γ . These two compounds are found in nutmeg's seed (*Myristica fragrans* Hout) that have been proven had antidiabetic activity in vitro. It can be concluded that agonists of PPAR γ should have hydrogen bond donor and acceptor groups for interacting with Tyr473. Tyr473 might be a critical site of interaction between the PPAR γ ligand binding domain and its agonists.

Keywords: dehydro-di-isoeugenol, docking simulation, macelignan, netoglitazone, PPAR γ , pioglitazone, rosiglitazon

1. Introduction

Diabetes mellitus (DM) is a group of clinical and genetic disorder that characterized by increasing levels of glucose in the blood. Among the various types of DM, more than 95% of people with diabetes is type 2 diabetes mellitus (T2DM) (American Diabets Association, 2009). T2DM is a combination of insulin resistance and pancreatic β cell insufficiency. One of the receptors target for the treatment of T2DM is peroxisome proliferator-activated receptor γ (PPAR γ).

The peroxisome proliferator-activated receptors (PPARs) γ , β , and α compose a nuclear receptor subfamily that modulates the transcription of a large compendium of genes encoding proteins that regulate lipid metabolism, cell differentiation, and signal transduction in a ligand-dependent manner. PPARs bind as heterodimers with a retinoid X receptor and, upon binding agonist, interact with cofactors so the rate of transcription initiation is increased. The PPARs play a critical physiological role as lipid sensors and regulators of lipid metabolism (Berger & Moller, 2002). PPAR γ has been shown to be a master regulator of adipogenesis and nutrient metabolism in adipocytes where it is highly expressed. PPARs are activated by fatty acids and eicosanoids, which have been identified as natural ligands for the PPARs, hence these receptors are targets for antidyslipidemic drugs and of antidiabetic agents (Cronet et al., 2001; Berger & Moller, 2002). More potent synthetic PPAR ligands, including the fibrates and thiazolidinediones (TZDs), have proven effective in the treatment of dyslipidemia and diabetes (Berger & Moller, 2002). TZDs or glitazones, a class of antidiabetic agents, have been reported as high affinity agonists of PPAR γ (Willson et al., 2000).