Rosiglitazone: A PPAR-γ Full Agonist of the Thiazolidinedione Class for Management of Type II Diabetes

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Abstract

Type II diabetes mellitus (DM) is a condition of decreased sensitivity to insulin. Medications like Rosiglitazone, classified as Thiazolidinediones (TZDs), have been used for type II DM-associated conditions including hyperglycemia, insulin resistance, and obesity. Rosiglitazone targets peroxisome proliferator active receptor gamma (PPAR- γ) to promote transcription of genes that control glucose and lipid metabolism when insulin is present. TZDs have proven to help improve insulin sensitivity, but complications have resulted in post-market surveillance of these medications. Development of a drug that targets PPAR- γ without severe adverse reactions could be the next step in diabetic treatment.

Case Synopsis

- A 73-year-old, obese female patient was admitted to the emergency department with fatigue, pink frothing phlegm, cyanosis, and dyspnea.
- The patient had a medical history of type II diabetes, hypertension and congestive heart disease for almost 10 years
- Four weeks after initiation of rosiglitazone, her cardiovascular system examination revealed that her heart rate was rhythmic, but tachycardic. There was pretibial edema (4+) on the lower extremities bilaterally.
- Based on clinical and laboratory findings, the physician diagnosed acute pulmonary edema probably due to rosiglitazone use.
- Rosiglitazone was discontinued.

Introduction

Rosiglitazone acts as a full PPAR-γ agonist and may be utilized by patients with type II diabetes mellitus. Rosiglitazone targets PPAR- γ, a nuclear hormone receptor that initiates transcription. It decreases insulin resistance by increased transcription of GLUT4 transporters in adipose and skeletal tissues. This improves utilization of glucose[1] and may help treat type II diabetes.

An important part of the PPAR- γ structure is its ligand binding pocket (LBP) in which agonists bind, creating a conformational change in the receptor. This change makes the binding site more favorable for co-activators, which activates transcription.

PPAR-γ binds:
- Thiazolidinediones, such as rosiglitazone, when insulin is present.
- Natural lipophilic molecules such as fatty acid chains and products originating from arachidonic acid and prostaglandins[9].

PPAR- γ full agonist pharmacophore:
- Tertiary amine
- 2-6 Carbon linker between tertiary amine and ether
- Glitazone group (thiazolidine-2,4-dione, and benzene ring)

Adverse Effects of PPAR- γ full agonists:
- Adipogenesis
- Fluid retention
- Increase risk of heart failure

Molecular Story

The ligand binding region of PPAR- γ is defined by three natural fatty acids that bind in three different arms of the binding site[2]. Each arm has different interactions that give an agonist effect. Rosiglitazone binds to two of the three arms. One of the natural fatty acids forms two hydrogen bonds with two different histidine residues, 323 and 449, seen below in figure 2. There is also a tight pocket that separates the middle arm from the arm with two hydrogen bonds. The tight pocket is formed by a methionine and cysteine residues, numbered 364 and 285 respectively, which can also be seen in figure 2.

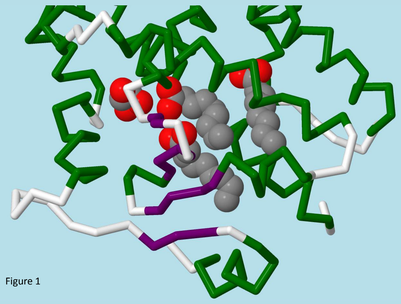

Figure 1

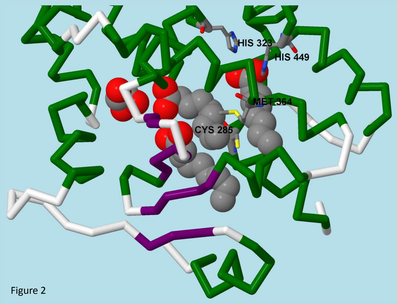

Figure 2

Rosiglitazone fits into two different arms of the binding site in PPAR-γ, occupying about 52% of the ligand binding domain, which gives it a full agonist effect[1]. Rosiglitazone forms the same two hydrogen bonds with histidine residues 323 and 449, but it forms two additional hydrogen bonds with a tyrosine and lysine residue. These four hydrogen bonds give the TZD head of rosiglitazone a fixed position in the binding pocket of PPAR-γ. Unlike the natural fatty acids that bind to PPAR-γ, rosiglitazone is able to reach into another arm of the binding site through the tight pocket between the cysteine and methionine residues. This tight pocket is seen in figure 4. The central benzene ring of rosiglitazone fits right between the pocket into the other arm.

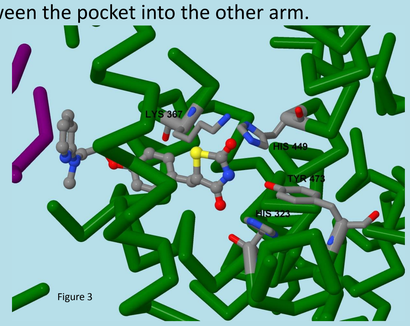

Figure 3

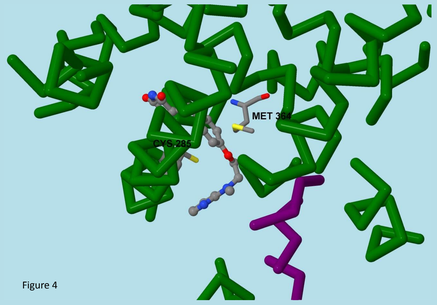

Figure 4

Aside from hydrogen bonds, there are also some areas of hydrophobic interactions within the binding site. The sulfur atom in the TZD ring of rosiglitazone fits within the hydrophobic pocket of two phenylalanines, one glutamine, and one lysine residue. These hydrophobic interactions can be seen in figure 5. All these interactions hold rosiglitazone in it's U shape in the binding site[3], which can be seen in the distal view of figure 6.

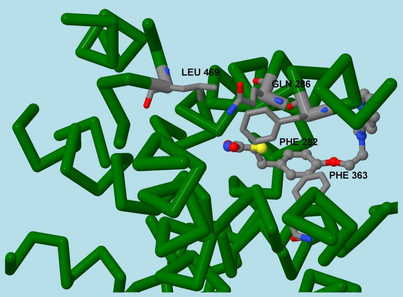

Figure 5

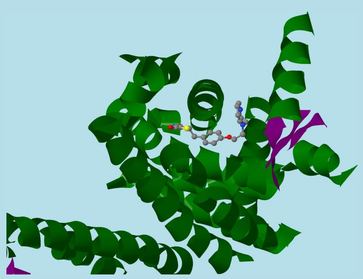

Figure 6

The Next Question

- Adverse effects are attributed to rosiglitazone being a PPAR-γ full agonist
- The natural ligands of PPAR-γ that influence insulin sensitivity in adipocytes are MCFAs.
- These MCFAs are partial agonists and do not cause the adverse effects of a full agonist [2].
- Development of a partial agonist drug similar to MCFAs may be an ideal solution to eliminate adverse reactions related to TZDs.
- Restructuring the molecule so only partial binding occurs at the current binding site could be another alternative solution to resolve the adverse effects.
- More research is necessary if partial agonists are to be used for type II diabetes.

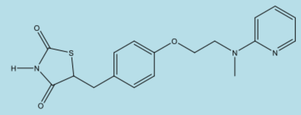

Figure 7

Summary

- Rosiglitazone acts as a full PPAR-γ agonist
- Some of Rosiglitazone`s adverse effects include: adipogenesis, fluid retention, and increased risk of heart failure
- An important part of the PPAR- γ structure is its ligand binding pocket (LBP) in which agonists bind, creating a conformational change in the receptor.
- Further exploration into the development of a drug that targets PPAR- γ but doesn't cause severe adverse reactions could be the next step in diabetic treatment.

Acknowledgements

We would like to acknowledge the following:
- Dr. Daniel Sem for preparing and guiding us through this project
- Dr. Frank Dailey for his contributions as our team mentor.
- Dr. Margaret Franzen for providing knowledge and insight for this project.
- Dr. Katie Reinke for contributing insight on drug interactions linked to rosiglitazone use.
- Dr. Beth Bennin for contributing insight on drug interactions linked to rosiglitazone use.

References

1. Nolte RT, Wisely GB, Westin S, et al. Ligand Binding and Co-Activator Assembly of the Peroxisome Proliferator-Activated Receptor-Gamma. Nature. 1998;395(6698):137–143. http://www.ncbi.nlm.nih.gov/pubmed/9744270. Accessed December 3, 2014.
2. Liberato MV, Nascimento AS, Ayers SD, Lin JZ, Cvoro A, et al. (2012) Medium Chain Fatty Acids Are Selective Peroxisome Proliferator Activated Receptor (PPAR) Activators and Pan-PPAR Partial Agonists. PLoS ONE 7(5): e36297. Doi: 10.1371/journal.one.0036297. Accessed December 3, 2014.
3. Rosiglitazone Maleate. IN: Micromedex 2.0 [database online]. Truven Health Analytics Inc. http://0-www.micromedexsolutions.com.topcat.switchinc.org/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch Updated periodically. Accessed December 1, 2014.

The CREST Program is funded by NSF-DUE grants #1022793 and #1323414.