Pioglitazone, an Insulin Sensitizing Drug, Attenuates the Development of Kidney and Liver Disease in the PCK Rodent Model of Polycystic Kidney Disease.

Bonnie L. Blazer-Yost [1], Julie Haydon[1], Tracy Eggelston[2], Jey-Hsin Chen[3], Vicente E. Torres[4] and Vincent Gattone[2]

Affiliations:
1. Department of Biology
Indiana University Purdue University at Indianapolis
Indianapolis, IN 46202

2. Department of Anatomy and Cell Biology
Indiana University School of Medicine
Indianapolis, IN 46202

3. Department of Pathology and Laboratory Medicine
Indiana University School of Medicine
Indianapolis, IN 46202

4. Division of Nephrology and Hypertension
Mayo Clinic
Rochester, MN 55905

Abstract

Polycystic kidney disease is a genetic disorder characterized by growth of fluid-filled cysts predominately in kidney and liver. The only treatment currently available is the removal/aspiration of the largest cysts or organ transplantation. Promising pharmaceutical agents in clinical trials interfere with the action of hormones that increase cAMP thereby inhibiting secretion of Cl^-, and compensatory fluid flux, into the cysts. Other treatments proposed include chemotherapeutic and immunosuppressive drugs that interfere with cellular proliferation as well as with signaling pathways for Cl^- secretion. Long-term use of these agents will have multiple side effects. Based on a recent observation that peroxisome proliferator activated receptor γ agonists such as Actos (pioglitazone) and Avandia (rosiglitazone) decrease mRNA levels of a Cl^- transport protein and the Cl^- secretory response to vasopressin stimulation in cultured renal cells, it is hypothesized that PPARγ agonists will inhibit cyst growth. The current studies show that a 7 or 14 week feeding regimen of 20 mg/Kg BW pioglitazone inhibits renal and hepatic bile duct cyst growth in a rodent model orthologous to human PKD. In addition, the degree of renal cortical fibrosis was diminished in the pioglitazone-treated animals after 14 weeks. These results suggest that PPARγ agonists may be effective in controlling both renal and hepatic cyst growth and renal fibrotic development in polycystic kidney disease.