LOW DOSE PPARγ AGONIST INHIBITION OF CYST GROWTH IN THE PCK RAT MODEL OF POLYCYSTIC KIDNEY DISEASE

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Polycystic kidney diseases (PKD) are genetic disorders characterized by fluid-filled cysts in kidney tubules and liver bile ducts that enlarge during the patient's life commonly progressing to renal failure in midlife. Cyst enlargement is due in part, to Cl^- secretion via the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel. Our previous studies demonstrated that PPARγ agonists, insulin-sensitizing drugs used to treat diabetes, inhibit Cl^- secretion by renal collecting duct principal cells via decreased CFTR synthesis. The dose response curves for Cl^- transport paralleled the EC_{50}'s for receptor transactivation with a leftward shift, suggesting an increased sensitivity for inhibition of Cl^- secretion. Our previous preclinical studies showed that high (20 mg/kg BW) dose pioglitazone, a PPARγ agonist, inhibited cyst growth in the PCK rat model, which is orthologous to a human form of PKD. PCK rats were fed a diet containing 3 doses of rosiglitazone (4, 0.4, and 0.04 mg/kg BW) for 24 weeks starting at weaning. 4.0 mg/kg BW rosiglitazone is analogous to 20 mg/kg BW pioglitazone used in the previous study. At the end of the study, urine, serum, kidney, liver, and heart were collected for analysis. There was a significant decrease in total kidney weight, kidney weight as a percent of body weight, and renal cyst volume in the lowest does (0.04 mg/kg BW). There was no significance difference in the other doses, and the liver and heart were not changed significantly. This showed both pioglitazone and rosiglitazone were effective in inhibiting cyst growth in the PCK rat indicating a class action of PPARγ agonists. Importantly, the rodent data substantiated the previous tissue culture data showing that a very low dose of rosiglitazone is effective in treatment of PKD.

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