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Dissertations-Kurzfassung

Inhibition of Comt with Tolcapone slows disease progression in two substrains of the Han:SPRD rat with autosomal dominant polycystic kidney disease

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Polycystic kidney disease (PKD) is the most frequent hereditary renal disease. Modifier genes seem to influence the course of cystic kidney diseases in both humans and animals. Two substrains originating from the former Han:SPRD rat strain, PKD/Mhm and PKD/US, were inbred after they were separated approximately 20 years ago. A difference in the phenotype of the two substrains was observed with PKD/Mhm animals being more severely affected. In order to locate and identify modifier genes for PKD, gene expression profiles of the two substrains were analyzed. For this study, animals were sacrificed at the age of 36 d. Body and kidney weights were determined and biochemical parameters analyzed including plasma creatinine and urea. Upon analysis of the gene expression profiles a marked increase in expression levels of the enzyme catechol-O-methyltransferase (Comt) was found in PKD/Mhm rats compared to PKD/US rats. The results obtained in the microarray experiments were confirmed using both quantitative RT-PCR and Western blot analysis. Comt was presumed as putative modifier gene influencing the course of cystic kidney disease. The presumptive PKD modifying function of Comt is emphasized by the fact that Comt lies within the modifier of polycystic kidney disease locus 2 (MOP2) in the pcy mouse model of PKD. Furthermore, it was hypothesized that if the different degrees of fibrosis in the two substrains could be attenuated by downregulating the activity of Comt, the enzyme might have a PKD modulating function and influence the severity and progression of the diseases. Using an antagonist having an influence on the phenotype could prove that Comt is a modifier gene. In a feasibility study, we investigated such effects of the selective and reversible Comt inhibitor Tolcapone. We treated six to eight female and male animals of both substrains with oral doses of the drug (30 mg/kg/d) for five weeks beginning at their 21st day of life. Treated animals were compared to their respective untreated control counterparts. Biochemical analysis of standard plasma and urine parameters did not reveal significant differences in kidney function after only five weeks of therapy except for a decrease in plasma urea in PKD/Mhm males. Likewise, the degree of cyst formation (cyst score) between the different treatment groups did not differ significantly. Comparing histological sections of treated and untreated animals, however, showed a promising effect on of the fibrotic scaring in the kidney. Obviously, after only five weeks of therapy and only one oral dose, Tolcapone therapy induced a trend towards a decline of fibrotic alterations in the kidney. The subsequent three month (30 mg/kg/d) therapeutic trial started at the tenth day of life with three oral doses until weaning and then was continued through drinking water. Ten to twelve female and males animals of both substrains were investigated along with their respective control groups. Biochemical analysis of standard plasma and urine parameters revealed significant difference in kidney function between PKD/Mhm males and PKD/US males. The degree of cyst formation (cyst grading) did not significantly differ between any of the treatment and control groups. The cyst size distribution was significantly influenced by three months of Tolcapone treatment in all treatment and control group pairs. Tubular epithelial proliferation characterizes ADPKD and inflammation accompanies the course of renal failure. Tolcapone treated animals had significantly less proliferating (Ki-67), apoptotic, and inflammatory (CD43) cells than did their control groups. The areas affected by fibrosis were significantly smaller in Tolcapone treated animals. In summary, three months Tolcapone treatment remarkably delayed the loss of renal function, inhibited renal enlargement, and retarded inflammation, cell proliferation, apoptosis, and fibrosis development, and markedly reduced renal cAMP levels in the rat model of ADPKD. With these findings it is demonstrated that Comt is a modifier of PKD.