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Inhibition of Comt using Tolcapone slows disease progression in three different animal rat models of polycystic kidney disease

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Polycystic kidney diseases (PKDs) are not only one of the most frequent disorders among hereditary renal diseases in humans, but also one of the leading causes of end-stage renal failure. Although common features of PKD including proliferation and apoptosis of epithelial cells, aberration of cell polarity, matrix deposition, interstitial inflammation, and fibrosis have been demonstrated to be responsible for cyst formation and loss of renal function, the pathogenesis of the disease is still incompletely understood. Although a number of agents have progressed to clinical trials, and many others have shown promising preclinical results, an effective therapy does not yet exist and thus to date treatment has been limited to renal replacement therapy. The recent identification of Comt as a putative modifier of PKD severity and the effectiveness of its selective antagonist Tolcapone in previous experimental treatment studies in heterozygously (cy/+) affected male PKD/Mhm animals have provided a new approach for therapeutic intervention in PKD.

With a view to confirm the previous results of Comt inhibition, three months of Tolcapone treatment was investigated not only in already analysed PKD/Mhm (resembling the autosomal dominant polycystic kidney disease) rats, but also in PKD2 mutant transgenic rats (TGR (CMV-hPKD2(1-703)) (resembling a mutation in humans) and PCK (resembling the autosomal recessive polycystic kidney disease) rats, and also in healthy Sprague Dawley rats (a general model for the study of human toxicology and pharmacology). Male animals of all these strains were randomly assigned to both Tolcapone treatment groups and vehicle control groups with 12 animals per group, respectively. After weaning the therapy was initiated at the 28th day of life. The drug was supplied via the drinking water in treatment groups and control animals obtained the drug vehicle alone. After three months of Tolcapone therapy the experiment was terminated.

All morphologic and immunohistochemical assessments were performed in paraffin sections of kidneys and livers. After three months of Tolcapone treatment significantly less proliferative (Ki-67), apoptotic (TUNEL) and inflammatory (CD43) cells were present in the kidneys of treated rats compared to the respective untreated control animals. Cystic and fibrotic areas were measured on Azan stained kidney and liver sections and the correlation to total kidney/liver area was calculated. The areas affected by fibrosis in the renal cortex and the medulla were significantly decreased by the long term Tolcapone treatment. In addition, Tolcapone treatment resulted in a decrease of both the average of total renal cyst number and the percentage of cyst areas of the total kidney area in all analysed animal models of PKD comparing treated and control groups. Biochemical parameters of plasma and urine samples were determined by standard laboratory methods. After therapy merely a trend towards lower levels of plasma creatinine and plasma urea became obvious comparing treated and control groups. The total kidney weight and the kidney mass index as indicators of renal volume were significantly reduced by Tolcapone treatment only in males of one animal model. The Tolcapone therapy was generally well tolerated without any side effects or mortalities. In summary, in three animal models of PKD three months Tolcapone treatment remarkably inhibited cell proliferation, apoptosis and inflammation, slowed cyst enlargement and fibrosis, and resulted in an obvious trend towards lower levels of plasma creatinine and plasma urea. Therefore, in comparison to the previous Tolcapone treatment study our mainly results are rather on the morphological side than on the functional side of analysed parameters. In consideration of the differences in study design compared to the previous Tolcapone treatment, our data confirm the previous conclusion that Comt is a modifier of polycystic kidney disease and Comt inhibition using Tolcapone could provide an alternative promising therapeutic strategy in order to slow down PKD progression.