Effects of Lysophosphatidic Acid (LPA) and Antidiuretic Hormone (ADH) on Cl^- Secretory Responses in Polycystic Kidney Disease (PKD)

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Polycystic kidney disease (PKD) is a genetic disease that causes the formation of fluid-filled cysts in the kidney and other organs such as the liver and pancreas. Kidney function is seemingly unaltered despite substantial cyst development over the first four to six decades of life, but then the decline in renal function is precipitous often leading to complete renal failure in 5 years. Antidiuretic hormone (ADH) causes an increase in Cl^- secretion into the cyst lumen, and one of the drugs in human clinical trials for treatment of PKD is an ADH receptor antagonist. The hormone works by stimulating cAMP production, which leads to the Cl^- secretion. Interestingly, we have found that cyst fluid from human patients also causes a secretory Cl^- flux that can lead to the growth of the remaining intact cysts. The active component of the cyst fluid is LPA, a phospholipid that acts as an extracellular signaling molecule. This secretion is important in late stage disease when large cysts are likely to leak or burst contributing to the rapid decline in renal function. Electrophysiological techniques were implemented to compare the ion fluxes stimulated by ADH and LPA. In the mpkCCD_{c14} (mouse principal cells of the cortical collecting duct clone 4) cell line we found that the Cl^- secretory pathways stimulated by the two factors are separate and independent. Further indication of this separation is our finding that LPA stimulation does not increase cAMP levels. Therefore we have identified an additional target for potential pharmaceutical intervention in the treatment of PKD.

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