The TRPP2-dependent channel of renal primary cilia also requires TRPM3

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INTRODUCTION

Primary cilia of renal epithelial cells express several members of the transient receptor potential (TRP) class of cation-conducting channel, including TRPC1, TRPM3, TRPM4, TRPP2, and TRPV4. Some cases of autosomal dominant polycystic kidney disease (ADPKD) are caused by defects in TRPP2 (also called polycystin-2, PC2, or PKD2). A large-conductance, TRPP2- dependent channel in renal cilia has been well described, but it is not known whether this channel includes any other protein subunits.

METHODS

To study this question, we investigated the pharmacology of the TRPP2-dependent channel through electrical recordings from the cilia of mIMCD-3 cells, a murine cell line of renal epithelial origin,

RESULTS

The pharmacology was found to match that of TRPM3 channels. The ciliary TRPP2-dependent channel is known to be activated by depolarization and/or increasing cytoplasmic Ca^{2+}. This activation was greatly enhanced by external pregnenolone sulfate, an agonist of TRPM3 channels. Pregnenolone sulfate did not change the current-voltage relation of the channel. CIM0216, another TRPM3 agonist, modestly increased the activity of the ciliary channels. The channels were effectively blocked by isosakuranetin, a specific inhibitor of TRPM3 channels. Knocking out TRPM3 by CRISPR/Cas9 genome editing eliminated the ciliary channel. After knocking out TRPM3, TRPP2 protein was still evident in the cilia, so it is unlikely that the absence of functional ciliary channels results from a failure of trafficking.

CONCLUSIONS

The channel is both TRPM3-dependent and TRPP2-dependent, suggesting that it may include both types of subunit. The potential of pregnenolone sulfate as a therapeutic for cystic kidney disease should be considered.