Cell volume regulation by P-glycoprotein in mouse proximal tubule

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Summary

The role of P-glycoprotein (P-gp) in cell volume regulation was examined in isolated nonperfused proximal tubule S2 segments from wild-type (WT) mice and those in which both *mdr1a* and *mdr1b* genes were knocked out (KO). When the osmolality of the bathing solution was rapidly decreased from 300 to 180 mOsm/kgH_2O, the tubules from both WT and KO mice exhibited regulatory volume decrease (RVD) by a similar magnitude after the initial cell swelling. The peritubular addition of two P-gp inhibitors (verapamil, cyclosporin A) to either group of the tubules had no effect on RVD. When the tubules from the WT mice were rapidly exposed to a hyperosmotic solution (500 mOsm/kgH_2O) including 200 mM mannitol, they abruptly shrank to 82.1% of their control volume but remained in a shrunken state during the experimental period, indicating a lack of regulatory volume increase (RVI). The addition of the two P-gp inhibitors, but not the inhibitor of the renal organic cation transport system, to the tubules from the WT mice resulted in RVI. Surprisingly, when the tubules from the KO mice were exposed to the hyperosmotic solution, they abruptly shrank to 79.9% of their control volume, and then gradually swelled to 97.7% of their control volume, showing RVI. However, exposure of the tubules from the WT mice to the hyperosmotic solution in the presence of the two P-gp inhibitors had no effect on RVI. When the tubules of the WT mice were exposed to the hyperosmotic solution including either of the two P-gp inhibitors, in the absence of peritubular Na or in the presence of peritubular ethylisopropylamiloride (EIPA, the specific inhibitor of Na/H exchanger), they did not exhibit RVI. In the tubules of the KO mice, both removing peritubular Na and adding peritubular EIPA inhibited RVI induced by the hyperosmotic solution. We conclude that 1) in mouse proximal tubule, P-gp modulates RVI during hyperosmotic stress, but not RVD during hyposmotic stress and 2) basolateral Na/H exchange partly contributes to the P-gp-induced modulation of RVI under hyperosmotic stress.