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저칼륨혈증 콩팥에서 세포주기 조절 단백질의 발현

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Expression of Cell Cycle-regulating Proteins in the Hypokalemic Rat Kidney

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Hypokalemia causes cell proliferation and hypertrophy in the kidney collecting duct. Cell proliferation requires orderly progression through the cell cycle. Especially, D-type cyclins, cyclin dependent kinases (CDK) and CDK inhibitors play a central role in the regulation of cell cycle. However, the mechanism of the cell cycle has not yet been clearly defined in the hypokalemic kidney.

Sprague-Dawley rats received either K^+-free or control diets for 2 week. Kidney tissues were processed for immunocytochemistry and immunoblot analysis. Rats receiving the K^+-deficient diet developed hypokalemia (2.5±0.61 vs 4.4±0.54 mmol/l, $p<0.05$) and showed typical histopathology including hyperplasia and hypertrophy in the outer medullary collecting ducts (OMCD). Hypokalemia significantly increased the expression of proliferating cell nuclear antigen (PCNA), cyclin D1 and D3, CDK 2, 4, and 6 in the OMCD. In contrast, expression of p18 (INK4c), p21 (WAF1/Cip1), and p27 (Kip1) was significantly decreased in the OMCD. In the cortex, there was also a slight increase in expression of CDK2 and p18. The collecting duct consists of two different cell types, the principal cell and intercalated cell. To identify the cell type that proliferates, double immunolabeling with AQP2 (principal cell marker) and H^+-ATPase (intercalated cell marker) were performed. The relative number and proportion of H^+-ATPase-positive intercalated cells significantly increased, while the number and proportion of AQP2-positive principal cells decreased. Interestingly, the CDK2 immunoreactivity remarkably increased mainly in the nucleus of AQP2-positive, H^+-ATPase-negative principal cells in the OMCD. In contrast, strong p27 immunolabeling of the nucleus dramatically decreased in principal cells in the OMCD. These findings suggest that cell proliferation occurs mainly in principal cells in response to chronic hypokalemia and CDKs and CDK inhibitors may play a critical role in the regulation of principal cell cycle. The mechanisms behind the paradoxical increase in the number and proportion of intercalated cells remain to be established.
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Hypokalemia, Cell cycle, Collecting duct