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Molecular Pathogenesis of Hyperkalemic Distal Renal Tubular Acidosis

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Hyperkalemic distal renal tubular acidosis (dRTA) is a uniquely heterogeneous disorder characterized by the combined impairment of distal tubular potassium (K^+) and hydrogen (H^+), in contrast to classic hypokalemic dRTA with an isolated defect in H^+ secretion. It is distinguished from the other hyperkalemic form of RTA, so-called selective aldosterone deficiency (SAD) or type IV RTA, by the inability to acidify urine (pH<5.5) in response to challenge (sodium sulfate or loop diuretics) and aldosterone resistance (pseudohypoaldsteronism). Hyperkalemic dRTA can be further divided into two categories: one with a primary voltage defect in sodium (Na^+) transport and the other with a generalized defect of both distal tubular K^+ and H^+ secretion, caused by inherited (genetic mutation in epithelial sodium (Na^+) channel (ENaC), mineralocorticoid receptor (MR) for PHAI, and WNK4, WNK1, cullin 3 and KLHL3 for PHAII) or acquired diseases (drugs blocking ENaC, obstructive uropathy, sickle cell tract or disease, calcineurin inhitor (cyclosporine and tacrolimus), diabetes mellitus). In addition to the effect of hyperkalemia to diminish urine ammonium (NH_4^+) excretion through the reduced ammonia production and transfer, an enhanced upstream NaCl reabsorption in the distal convoluted ducts (DCT) or impaired ENaC function that lead to voltage-dependent defects to drive K^+ secretion through ROMK in principle cells and H^+ secretion through H^+ATPase in the α intercalated cells are also responsible for hyperkalemia and metabolic acidosis. Recent studies have shown that WNK-SPAK/OSR/NCC and mTOR pathway in distal tubules as well as the regulation of pendrin (bicarbonate secretion) in β intercalated cells are also involved in hyperkalemic dRTA. Clinical cases and animal models of hyperkalemic dRTA are presented to provide new insight into the understanding of its molecular mechanism.