Abstract


Aldosterone potentiates 1,25-dihydroxyvitamin D3 action in renal thick ascending limb via a nongenomic, ERK-dependent pathway.

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BACKGROUND: Recently, we demonstrated that aldosterone inhibits HCO3- absorption in the rat medullary thick ascending limb (MTAL) via a nongenomic pathway blocked by inhibitors of extracellular signal-regulated kinase (ERK) activation.

OBJECTIVE AND METHODS: Here we examined the effects on the MTAL of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], which regulates cell functions through nongenomic mechanisms in nonrenal systems.

RESULTS: Addition of 1 nM 1,25(OH)2D3 to the bath decreased HCO3- absorption by 24%, from 15.0 +/- 0.3 to 11.4 +/- 0.5 pmol. min-1. mm-1 (P < 0.001). This inhibition was maximal within 60 min and was eliminated by pretreatment with actinomycin D, cycloheximide, or inhibitors of protein kinase C. In MTAL bathed with 1 nM aldosterone [added 15-20 min before 1,25(OH)2D3], the absolute (5.6 +/- 0.3 vs. 3.6 +/- 0.3 pmol. min-1. mm-1) and fractional (49 +/- 2 vs. 24 +/- 2%) decreases in HCO3- absorption induced by 1,25(OH)2D3 were significantly greater than those in the absence of aldosterone (P < 0.05). The effect of aldosterone to potentiate inhibition by 1,25(OH)2D3 was not affected by spironolactone but was eliminated by the MAPK kinase/ERK inhibitor U-0126. U-0126 did not affect inhibition of HCO3- absorption by 1,25(OH)2D3 alone. Aldosterone induced rapid activation of ERK via a transcription-independent pathway. We conclude that 1) 1,25(OH)2D3 inhibits HCO3- absorption in the MTAL via a genomic pathway involving protein kinase C, which may contribute to 1,25(OH)2D3-induced regulation of urinary net acid and/or Ca2+ excretion and 2) aldosterone potentiates inhibition by 1,25(OH)2D3 through an ERK-dependent, nongenomic pathway.

CONCLUSION: These results identify a novel regulatory interaction whereby aldosterone acts via nongenomic mechanisms to enhance the genomic response to 1,25(OH)2D3. Aldosterone may influence a broad range of biological processes, including epithelial transport, by modifying the response of target tissues to 1,25(OH)2D3 stimulation.

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