

Abstract

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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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