Spironolactone Suppresses NF-κB and AP-1 Inflammatory Signaling Independent of the Mineralocorticoid Receptor

Elinoff JM, Dougherty EJ, Solomon MA, Danner RL
Critical Care Medicine Department, Mark O. Hatfield Clinical Research Center, National Institutes of Health, Bethesda, MD, U.S.A.

Background: Mineralocorticoid receptor (MR) antagonists, including spironolactone and eplerenone, improve morbidity and mortality in diverse patient populations with vascular inflammation. Improvements in endothelial function by MR antagonists are primarily ascribed to direct inhibition of aldosterone-mediated MR activation. However, the molecular basis of spironolactone interference with NF-κB-driven inflammatory responses has not been established.

Methods: The effects of spironolactone and eplerenone were studied using NF-κB and AP-1 reporter gene assays in a human kidney line (HEK293) transfected with the human MR, glucocorticoid receptor (GR), androgen receptor (AR), or progesterone receptor (PR) and challenged with inflammatory stimuli. The effect of spironolactone on NF-κB nuclear translocation and DNA binding was examined by enzyme-linked immunosorbent assay. Primary human pulmonary artery endothelial cells (PAECs) were used to compare the effects of spironolactone and eplerenone on selected inflammatory target genes by quantitative real-time PCR.

Results: In HEK293 cells, spironolactone suppressed both TNFα-induced NF-κB and phorbol ester-induced AP-1 promoter activity independent of MR, GR, AR or PR expression. In contrast, eplerenone had no effect on NF-κB or AP-1 reporter activity at comparable doses in either the absence or presence of nuclear receptor expression. Despite significant suppression of NF-κB promoter activity, spironolactone did not appear to alter TNFα-induced p65/p50 DNA binding. In primary human PAECs, spironolactone inhibited TNFα- and phorbol ester-induced ICAM1, IL-6, IL-8 and CCL-2 mRNA expression, while the effects with eplerenone were minimal.

Conclusions: Spironolactone has anti-inflammatory effects not shared with eplerenone that are independent of not only MR, but also AR and PR. Spironolactone suppression of inflammatory signaling independent of MR and the renin-angiotensin aldosterone system may be beneficial in vascular conditions with an inflammatory component such as pulmonary arterial hypertension.