

Regulation of Na/H exchanger by steroid hormoens

Shigeaki Muto, Satoru Ebata, Yukio Miyata

Department of Nephrology, Jichi Medical School

Summary

In vascular smooth muscle cells (VSMC), Na/H exchange (NHE) plays an important role in intracellular pH (pHi) regulation. Recently, nongenomic effect of aldosterone (ALDO) on NHE activity has been suggested in VSMC. The effects of short (3 hr)- and long (24 hr)-term exposure to ALDO on NHE activity were examined in cultured VSMC from rat thoracic aortae by using a pH-sensitive fluorescent dye (BCECF). The NHE activity was calculated from the initial rate of Na-dependent pHi recovery after acid load. The NHE activity significantly increased after short- and long-term exposure of VSMC to ALDO. The inhibitors of mRNA transcription (actinomycin D) and of protein synthesis (cycloheximide) had no effect on the short-term ALDO effect, but inhibited the long-term ALDO effect. The antagonists of mineralocorticoid receptor (MR)(spironolactone) and of glucocorticoid receptor (GR)(RU 38486) caused no effect on the short-term ALDO effect, but inhibited the long-term ALDO effect. Two protein kinase C (PKC) inhibitors (staurosporine A, calphostin C) and PKC downregulation (24 hr preexposure to phorbol 12-myristate 13-acetate, PMA) inhibited both the short- and long-term ALDO effects. Exposure to PMA for 3 hr mimicked the short-term ALDO effect. The short-term ALDO effect was inhibited by disruptors of microtubule (colchicine) and of filamentous actin (cytochalasin B).

We conclude: (1) the short-term effect of ALDO on NHE activity is not mediated through either MR or GR, occurs independent of gene transcription and protein synthesis, and involves in the structural elements of cytoskeleton, (2) the long-term effect of ALDO on NHE activity occurs through both MR and GR and requires gene transcription and protein synthesis. Both short- and long-term effects of ALDO are mediated through PKC activation. Therefore, ALDO activates NHE by nongenomic and genomic mechanisms in VSMC.