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Parathyroid hormone regulates Nhe3 gene core promoter: EGR1 and Sp3 might regulate the RNA polymerase II pause?

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The main Na^+ reabsorption mechanism in the renal proximal tubules is the Na^+/H^+ exchanger 3 (NHE3) which is acutely and chronically down regulated by parathyroid hormone (PTH). In rats, continuous administration of PTH to induce hyperparathyroidism reduces the expression of NHE3 both at RNA and protein level with clear decrease of NHE3 at the apical membrane of proximal tubules. Analysis with reporter gene of the rat Nhe3 gene promoterin Opossum Kidney Proximal Tubule (OKP) cells indicated inhibition of transcription by PTH associated to a decrease in NHE3-mRNA stability. We demonstrated that PTH-induced inhibition of Nhe3 gene promoter occurs even in the core promoter. We found that inhibition of the protein kinase A (PKA) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways changed PTH from an inhibitor into an activator of promoter activity as did point mutations in the EGR1, Sp1 and Sp3 binding consensus elements in the promoter. In nuclear extracts of PTH-treated OKP cells, we also observed increased expression of EGR1-mRNA and of some Sp3-protein isoforms. Electrophoretic mobility shift assay showed a super shift of the -61 to -42bp probe with an anti-EGR1 antibody in PTH-treated cells suggesting the EGR1 binding is relevant for the inhibitory activity of PTH. Our results suggest that PTH-induced inhibition of NHE3 transcription is related to higher EGR1 expression to EGR1 binding to the proximal and core promoters and to PKA and JAK/STAT pathway activation. The higher expression of the long isoform (Sp3-li, 90 kDa) and of the short isoform (Sp3-si3) of Sp3 in addition to higher sumoylation of one of the short isoforms of Sp3 induced by PTH could also be related to repression of Nhe3gene expression. As Sp3 was reported to promote RNA polymerase II pause by recruiting phosphatases to the $p21^{CIP1}$ gene promoter, we hypothesize the PTH might increase RNA Pol II pause at the Nhe3 gene promoter.

Biography

Nancy Amaral Reboucas graduated as a medical doctor in 1976 at Federal University of Goias, Brazil. She concluded my medical residence in Nephrology in 1979, and my PhD in Human Physiology at the Institute of Biomedical Science, Department of Physiology and Biophysics, University of Sao Paulo, in 1983. Then, she went on to do post-doctoral fellowship at Yale University for two years, from 1989 to 1991, in the Peter Aronson and Peter Igarashi laboratory, Department of Internal Medicine, section of nephrology. Since then, she coordinates her own laboratory at University of Sao Paulo, in the Department of Physiology and Biophysics, where she teaches renal physiology and membrane physiology to medical students. Her main line of research is transcriptional and functional regulation of the sodium-hydrogen exchanger NHE3 in renal tubules. She is also responsible for a course on Molecular Biology since 1998 that is open to the community. The purpose of this course is introduce graduate students and medical and biomedical professionals to the Molecular Biology of the cell and to the fundamental methods used in a Molecular Biology laboratory.

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