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TITLE

New insights into the alternative splicing regulation of the epithelial sodium channel in Dahl rats: Focus on novel drug targets

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The epithelial sodium channel (ENaC) is critical in controlling the rate of renal sodium reabsorption and maintaining long term blood pressure control. ENaC activity is twice as high in kidneys of high salt-fed Dahl salt-sensitive (S) rats versus a sister salt-resistant strain (Dahl R), which might explain the increased blood pressure in high salt-fed Dahl S rats versus R rats. ENaC blockade in the brain by benzamil rescued Dahl S rats from salt-induced hypertension. The aims of the present study were: (i) To test whether Dahl S rats harbor genetic polymorphisms in the ENaC α, β, and/or γ genes that might contribute to their enhanced ENaC activity; (ii) To investigate whether α ENaC in Dahl rats' kidney is associated with alternatively spliced forms, and their corresponding mRNA levels, should they exist, in Dahl S versus R rats on normal and high salt diet; (iii) To examine the putative biological function of α ENaC alternatively spliced forms when co-expressed with α ENaC-wt. The first comprehensive sequence analysis of ENaC genes did not reveal any differences between Dahl S and R rats that were isogenic in the entire coding regions, exon-intron junctions, 3' and 5' flanking regions of ENaC α, β, and γ genes. Two coding (a and b) and two non coding (c and d) α ENaC alternatively spliced forms were identified whose mRNA levels were elevated in Dahl R versus S rats. Among the four α ENaC transcripts, the salt-sensitive α ENaC-b was highly abundant exceeding α ENaC-wt abundance by ~32 fold. The translated α ENaC-b protein sequestered α ENaC-wt and reduced α ENaC-wt expression in a dose-dependent manner. Increased ENaC activity in Dahl S versus R rats might be attributed to the lower abundance of α ENaC-b, a dominant negative expression regulator of α ENaC.