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New insights into the alternative splicing regulation of the epithelial sodium channel in Dahl rats

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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.

Biography

Dr. Marlene Shehata has received her PhD in Cellular and Molecular Medicine, specializing in Genetics of Cardiovascular Diseases from the University of Ottawa during the period of 2004-2010. Dr. Shehata is also a licensed Ontario Pharmacist practicing in Southwestern Ontario. Currently, she is working as a Clinical Pharmacist Consultant in numerous academic hospitals, nursing homes and community pharmacies in Southwestern Ontario. She has successfully completed her Administrative responsibilities as a Manager for the Pharmacy and Clinical Services Department. She is currently the Editor-in-Chief of the Journal of Pharmacology Research, Associate Editor for the Journal of Ecobiotechnology and The Journal of Biotechnology Applications. She sits on the editorial boards of numerous journals including the African Journal of Biotechnology and Hypertension-Open Access. Dr. Shehata has authored 23 research articles, 2 book chapters and 24 abstracts. She is a member of the Canadian Hypertension Society, Canadian Cardiovascular Society, Ontario Pharmacists Association and Ontario College of Pharmacists. She is the 2011 recipient of the Certificate of Excellence by Hypertension Canada and the 2007 Horizon Award recipient by Memorial University of Newfoundland. She was awarded numerous other awards including the Pfizer Canada, Canadian Hypertension Society (CHS) and the Canadian Institutes of Health Research (CIHR) Doctoral Research Award in 2005, the Ontario Graduate Scholarship in 2005, Merck Frosst Best Basic Science Presentation Award in 2006 and the Ontario Graduate Scholarship for Science and Technology in 2004 and 2006. Marlene was selected as one out of five Canadian pharmacists' finalists in Diabetes Management: Best Practices in Patient Care 2009 Competition; she was recognized on the "Volunteer Wall" on campus the University of Ottawa for sacrificially giving over 180 hours of volunteer work in 2007 academic year. Her motivation, enthusiasm, and perseverance made her an ideal candidate for receiving the 2008 Have a Heart Bursary by the Canadian Cardiovascular Society.