Epithelial Sodium Channel (ENaC)

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Abstract: The epithelial sodium channel (ENaC) is a cell membrane-bound ion-channel that is permeable for Na^+, Li^+ and H^+, and it is a major regulator of salt and water reabsorption in a number of epithelial tissues. Abnormalities in ENaC function have been directly linked to several human disease states including Liddle's syndrome, psuedohypoaldosteronism, and cystic fibrosis and may be implicated in states as diverse as salt-sensitive hypertension, nephrosis, and pulmonary edema. ENaC activity in epithelial cells is highly regulated both by open probability and number of channels. In animal kidney, ENaC plays a crucial role in controlling sodium reabsorption to keep the normal blood pressure. The expression of ENaC is abnormally regulated by dietary sodium in salt-sensitively hypertensive rats, and that this abnormal expression would be one of the factors causing salt-sensitive hypertension. [Journal of American Science 2009; 5(6):62-69]. (ISSN: 1545-1003).

Keywords: epithelial sodium channel (ENaC); Aldosterone: pioglitazone; Thiazolidinedione; serum- and glucocorticoid-inducible kinase (SGK); angiotensin-converting enzyme (ACE); inhibitor; hypertension; chronic heart failure. Renal; kidney

1. Introduction

The epithelial sodium channel (ENaC), also named sodium channel non-neuronal 1 (SCNN1) or amiloride sensitive sodium channel (ASSC), is a cell membrane-bound ion-channel that is permeable for Na^+, Li^+ and H^+, and it is a major regulator of salt and water reabsorption in a number of epithelial tissues. Abnormalities in ENaC function have been directly linked to several human disease states including Liddle's syndrome, psuedohypoaldosteronism, and cystic fibrosis and may be implicated in states as diverse as salt-sensitive hypertension, nephrosis, and pulmonary edema. ENaC activity in epithelial cells is highly regulated both by open probability and number of channels. Open probability is regulated by a number of factors, including proteolytic processing, while ENaC number is regulated by cellular trafficking. It is important to understand apical membrane delivery, cell surface stability, endocytosis, retrieval, recycling of ENaC, the molecular partners that have so far been shown to participate in these processes, and sites and mechanisms of hormonal regulation of trafficking by aldosterone, vasopressin, and insulin (Butterworth et al., 2009).

ENaC activity is limiting for sodium reabsorption in the distal nephron. Humans regulate blood pressure by fine-tuning sodium balance through control of ENaC. ENaC dysfunction causes some hypertensive and renal salt wasting diseases. According to the recent report, ENaC is sensitive to phosphatidylinositol 4,5-bisphosphate (PIP2), the target of phospholipase C-mediated metabolism, and phosphatidylinositiol 3,4,5-trisphosphate (PIP3), the product of phosphatidylinositide 3-OH kinase (PI3-K). PIP2 is permissive for ENaC gating possibly interacting directly with the channel. Activation of distal nephron P2Y receptors tempers ENaC activity by promoting PIP2 metabolism. This is important because gene deletion of P2Y2 receptors causes hypertension associated with hyperactive ENaC. Aldosterone, the final hormone in a negative-feedback cascade activated by decreases in blood pressure, increases ENaC activity. PIP3 sits at a critical bifurcation in the aldosterone-signaling cascade, increasing ENaC open probability and number. PIP3-effectors mediate increases in ENaC number by suppressing channel retrieval. PIP3 binds ENaC, at a site distinct from that important to PIP2 regulation, to modulate directly open probability (Pochynyuk et al., 2008).

The renal epithelial sodium channel (ENaC) is of fundamental importance in the control of sodium reabsorption through the distal nephron. ENaC is an important component in the overall control of sodium balance, blood volume and thereby of blood pressure. This is clearly demonstrated by rare genetic disorders of sodium channel activity (Liddle's Syndrome and Pseudohypoaldosteronism type 1 associated with contrasting effects on blood pressure). Subtle dysregulation of ENaC however may also be important in essential hypertension - a common condition and a major cause of cardiovascular morbidity and mortality.

The epithelial sodium channel is formed from three partly homologous subunits. In this review we deals firstly with current views of structural and functional features of the renal epithelial sodium channel with particular emphasis on mechanisms and processes involved in the control of sodium channel activity at the biochemical and cellular levels. We then focus on genetic aspects with reference to the significance of genetic variation in the sodium channel genes in relation to blood pressure. In particular, we review recent investigations on the potential clinical significance of mutations within the genes encoding ENaC subunits in individuals with high blood pressure. Lastly, we also examine the potential value of pharmacological targeting of the renal epithelial sodium channel with the sodium channel inhibitor amiloride for the treatment of hypertension (Sagnella and Swift, 2006).

Lithium is used commonly to treat bipolar mood disorders. In addition to its primary therapeutic effects in the central nervous system lithium has a number of side effects in the kidney. The side effects include nephrogenic diabetes insipidus with polyuria, mild sodium wasting, and changes in acid/base balance. These functional changes are associated with marked structural changes in collecting duct cell composition and morphology, likely contributing to the functional changes (Nielsen et al., 2008).

The apical membrane of many tight epithelia contains sodium channels that are primarily characterised by their high affinity to the diuretic blocker amiloride. These channels adjust the sodium reabsorption for the maintenance of body salt and water homeostasis. In vertebrate animals, ENaC is involved in the reabsorption of sodium in kidney, colon, lung and sweat glands; they also play a role in taste perception.

Amiloride was originally described in 1967 as a potassium-sparing diuretic, the mechanism of action of which is to block the ENaC within the distal tubule of the kidney. In addition, higher doses of amiloride were found to be capable of inhibiting the Na(+)/H(+) exchangers (NHE) and the Na(+)/Ca(2+) exchangers. In time, several amiloride analogs have been synthesized to have a marked increase in their specificity to inhibit the ENaC, the NHE or the Na(+)/Ca(2+) exchangers. Although the NHE inhibitors have received the most recent attention, large-scale clinical trials using NHE inhibitors in ischemic cardiac states have shown them to be either ineffective or associated with an unacceptable risk profile. Aldosterone excess in animal models is known to cause cardiovascular injury, and blockade of mineralocorticoid receptors in human beings with heart disease improves outcomes. However, the exact mechanisms of aldosterone injury in animal models of hypertensive disease and protection with mineralocorticoid receptor antagonists in human trials of heart failure remain unknown. These effects are unexplained by changes in BP, potassium, or sodium balance. An additional possibility is that aldosterone action and mineralocorticoid receptor blockade is conferred by alterations in ENaC activity. Emerging experimental evidence suggests the possibility that systemic or central ENaC inhibition or both may be an alternative to the treatment of hypertension and cardiovascular disease states. Clinical trials to evaluate further the potential beneficial cardiovascular effects of ENaC blockade are needed. This article reviews the case for ENaC inhibition as a potential target for cardiovascular and renal protection in human beings (Teiwes and Toto, 2007).

The ENaC has a central role in sodium transport across membranes. It is expressed on the apical cell surface of renal tubular epithelia and also on other aldosterone-responsive epithelial cells. In the kidney, ENaC contributes to the regulation of blood pressure via changes in sodium balance and blood volume. Rare monogenetic disorders associated with hypertension have been described, such as Liddle syndrome, which gives rise to increased sodium reabsorption in the kidney via increased ENaC activity. There are many other variants in the genes encoding ENaC subunits, some of which occur with sufficient frequency as to be termed polymorphic variants. The Thr594Met polymorphism of the ENaC beta-subunit gene SCNN1B occurs exclusively in Black individuals, with a frequency of 6-8% in those with hypertension. It increases cAMP mediated ENaC sodium current in affected B lymphocytes, and has been associated with hypertension in a Black South London population.There is preliminary evidence that amiloride is effective as monotherapy in hypertensive individuals with the Thr594Met polymorphism and in patients with resistant hypertension, who have evidence of increased amiloride-sensitive sodium channel activity. If these preliminary studies are corroborated in larger studies, then amiloride may provide an important new strategy for blood pressure control in selected individuals (Swift and MacGregor, 2004).

The epithelial sodium channel (ENaC) is a membrane protein made of three different but homologous subunits (a, b, and g) present in the apical membrane of epithelial cells of, for example, the distal nephron. This channel is responsible for salt reabsorption in the kidney and can cause human diseases by increasing channel function in Liddle's syndrome, a form of hereditary hypertension, or by decreasing channel function in pseudohypoaldosteronism type I, a salt-wasting disease in infancy. This review briefly discusses recent

advances in understanding the implication of ENaC in Liddle's syndrome and in pseudohypoaldosteronism type I, both caused by mutations in the SCNN1 (ENaC) genes. Furthermore, it is still an open question to which extent SCNN1 genes coding for ENaC might be implicated in essential hypertension. The development of Scnn1 genetically engineered mouse models will provide the opportunity to test the effect of environmental factors, like salt intake, on the development of this kind of salt- sensitive hypertension (Hummler, 2003).

The epithelial sodium channel (ENaC) is of fundamental importance in the control of sodium fluxes in epithelial cells. Modulation of sodium reabsorption through the distal nephron ENaC is an important component in the overall control of sodium balance, blood volume and thereby of blood pressure. This is clearly demonstrated by rare genetic disorders of sodium-channel activity (Liddle's syndrome and pseudohypoaldosteronism type 1), associated with contrasting effects on blood pressure. The mineralocorticoid aldosterone is a well-established modulator of sodium-channel activity. Considerable insight has now been gained into the intracellular signalling pathways linking aldosterone-mediated changes in gene transcription with changes in ion transport. Activating pathways include aldosterone-induced proteins and especially the serum- and glucocorticoid-inducible kinase (SGK) and the small G-protein, K-Ras 2A. Targeting of the ENaC for endocytosis and degradation is now emerging as a major mechanism for the down-regulation of channel activity. Several proteins acting in concert are an intrinsic part of this process but Nedd4 (neural precursor cell expressed developmentally down-regulated 4) is of central importance. Other mechanisms known to interact with ENaC and affect sodium transport include channel-activating protease 1 (CAP-1), a membrane-anchored protein, and the cystic fibrosis transmembrane regulator. The implications of research on accessory factors controlling ENaC activity are wide-ranging. Understanding cellular mechanisms controlling ENaC activity may provide a more detailed insight not only of ion-channel abnormalities in cystic fibrosis but also of the link between abnormal renal sodium transport and essential hypertension (Gormley et al., 2003).

The activity of epithelial sodium channels (ENaC) is increased by phosphatidylinositides, especially phosphatidylinositol 4,5-bisphosphate (PI(4,5)P(2)) and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P(3)). Stimulation of phospholipase C by either adenosine triphosphate (ATP)-activation of purinergic P2Y receptors or epidermal growth factor (EGF)-activation of EGF receptors reduces membrane PI(4,5)P(2), and consequently decreases ENaC activity. Since ATP and EGF may be trapped in cysts formed by the distal tubule, it is possible that ENaC inhibition induced by ATP and EGF facilitates cyst formation in polycystic kidney diseases (PKD). However, some results suggest that ENaC activity is increased in PKD. In contrast to P2Y and EGF receptors, stimulation of insulin-like growth factor-1 (IGF-1) receptor by aldosterone or insulin produces PI(3,4,5)P(3), and consequently increases ENaC activity. The acute effect of aldosterone on ENaC activity through PI(3,4,5)P(3) possibly accounts for the initial feedback for blood volume recovery after hypovolemic hypotension. PI(4,5)P(2) and PI(3,4,5)P(3), respectively, interacts with the N terminus of beta-ENaC and the C terminus of gamma-ENaC. However, whether ENaC selectively binds to PI(4,5)P(2) and PI(3,4,5)P(3) over other anionic phospholipids remains unclear (Ma et al., 2007).

The appropriate regulation of sodium (Na(+)) absorption in the aldosterone-sensitive distal nephron (ASDN) is essential to precisely match urinary Na(+) excretion to dietary Na(+) intake whilst taking extra-renal Na(+) losses into account. There is increasing evidence that Na(+) transport in the connecting tubule (CNT) is of particular importance for the maintenance of body Na(+) balance and for the long-term control of extra-cellular fluid volume and arterial blood pressure. Na(+) transport in the CNT critically depends on the activity and abundance of the amiloride-sensitive epithelial sodium channel (ENaC) in the luminal membrane of the CNT cells. As a rate-limiting step for transepithelial Na(+) transport, ENaC is the main target of hormones (e.g. aldosterone, angiotensin II, vasopressin and insulin/insulin-like growth factor 1) to adjust transepithelial Na(+) transport in this tubular segment (Loffing and Korbmacher, 2009).

2. Structure

ENaC consists of 4 subunits that are named α-, β-, γ-, δ-ENaC. Each of the subunits consists of two transmembrane helices and an extracellular loop. The amino- and carboxy-termini of all polypeptides are located in the cytosol. One subunit consists of about 510 to 920 amino acid residues, which is made of an intracellular N-terminus region followed by a transmembrane domain, a large extracellular loop, a second transmembrane segment and a C-terminal intracellular tail.

Human ENaC-alpha subunit sequence (669 amino acid):

```
      1 megnkleeqd ssppqstpgl mkgnkreeqg lgpepaapqq ptaeeealie fhrsyrelfe
     61 ffcnnttihg airlvcsqhn rmktafwavl wlctfgmmyw qfgllfgeyf sypvslninl
    121 nsdklvfpav tictlnpyry peikeeleel driteqtlfd lykyssfttl vagsrsrrdl
    181 rgtlphplqr lrvpppphga rrarsvassl rdnnpqvdwk dwkigfqlcn qnksdcfyqt
    241 yssgvdavre wyrfhyinil srlpetlpsl eedtlgnfif acrfnqvscn qanyshfhhp
    301 mygncytfnd knnsnlwmss mpginnglsl mlraeqndfi pllstvtgar vmvhgqdepa
    361 fmddggfnlr pgvetsismr ketldrlggd ygdctkngsd vpvenlypsk ytqqvcihsc
    421 fqesmikecg cayifyprpq nveycdyrkh sswgycyykl qvdfssdhlg cftkcrkpcs
    481 vtsyqlsagy srwpsvtsqe wvfqmlsrqn nytvnnkrng vakvniffke lnyktnsesp
    541 svtmvtllsn lgsqwslwfg ssvlsvvema elvfdllvim flmllrrfrs rywspgrggr
    601 gaqevastla ssppshfcph pmslslsqpg papspaltap ppayatlgpr pspggsagas
    661 sstcplggp
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Reference:

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  AUTHORS   Chow,Y.H., Wang,Y., Plumb,J., O'Brodovich,H. and Hu,J.
  TITLE     Hormonal regulation and genomic organization of the human
            amiloride-sensitive epithelial sodium channel alpha subunit gene
  JOURNAL   Pediatr. Res. 46 (2), 208-214 (1999)
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Human ENaC-beta subunit sequence (640 amino acid):

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      1 mhvkkyllkg lhrlqkgpgy tykellvwyc dntnthgpkr iicegpkkka mwflltllfa
     61 alvcwqwgif irtylswevs vslsvgfktm dfpavticna spfkyskikh llkdldelme
    121 avlerilape lshanatrnl nfsiwnhtpl vlidernphh pmvldlfgdn hngltsssas
    181 ekicnahgck mamrlcslnr tqctfrnfts atqaltewyi lqatnifaqv pqqelvemsy
    241 pgeqmilacl fgaepcnyrn ftsifyphyg ncyifnwgmt ekalpsanpg tefglklild
    301 igqedyvpfl astagvrlml heqrsypfir degiypmsgt etsigvlvdk lqrmgepysp
    361 ctvngsevpv qnfysdyntt ysiqaclrsc fqdhmirncn cghylyplpr gekycnnrdf
    421 pdwahcysdl qmsvaqretc igmckescnd tqykmtisma dwpseasedw ifhvlsqerd
    481 qstnitlsrk givklniffq efnyrtiees aannivwlls nlggqfgfwm ggsvlclief
    541 geiiidfvwi tiiklvalak slrqrraqas yagppptvae lveahtnfgf qpdtaprspn
    601 tgpypseqal pipgtpppny dslrlqpldv iesdsegdai
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Reference:

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  AUTHORS   McDonald,F.J., Price,M.P., Snyder,P.M. and Welsh,M.J.
  TITLE     Cloning and expression of the beta- and gamma-subunits of the human
            epithelial sodium channel
  JOURNAL   Am. J. Physiol. 268 (5 PT 1), C1157-C1163 (1995)
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Human ENaC-gama subunit sequence (649 amino acid):

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      1 mapgekikak ikknlpvtgp qaptikelmr wyclntnthg crrivvsrgr lrrllwigft
     61 ltavalilwq callvfsfyt vsvsikvhfr kldfpavtic ninpykystv rhlladleqe
    121 trealkslyg fpesrkrrea eswnsvsegk qprfshripl lifdqdekgk ardfftgwkr
    181 kvggsiihka snvmhieskq vvgfqlcsnd tsdcatytfs sginaiqewy klhymnimaq
    241 vplekkinms ysaeellvtc ffdgvscdar nftlfhhpmh gncytfnnre netilstsmg
    301 gseyglqvil yineeeynpf lvsstgakvi ihrqdeypfv edvgteieta mvtsigmhlt
    361 esfklsepys qctedgsdvp irniynaays lqiclhscfq tkmvekcgca qysqplppaa
    421 nycnyqqhpn wmycyyqlhr afvqeelgcq svckeacsfk ewtlttslaq wpsvvsekwl
    481 lpvltwdqgr qvnkklnktd lpkllifykd lnqrsimesp ansiemllsn fggqlglwms
    541 csvvcvieii evffidffsi iarrqwqkak ewwawkqapp cpeaprspqg qdnpaldidd
    601 dlptfnsalh lppslgtqvp gtpppkyntl rlerafsnql tdtqmldel
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Reference:

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  AUTHORS   McDonald,F.J., Price,M.P., Snyder,P.M. and Welsh,M.J.
  TITLE     Cloning and expression of the beta- and gamma-subunits of the human
            epithelial sodium channel
  JOURNAL   Am. J. Physiol. 268 (5 PT 1), C1157-C1163 (1995)
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Human ENaC-delta subunit sequence (704 amino acid):

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      1 maflsrtspv aaasfqsrqe argsillqsc qlppqwlste awtgewkqph ggaltsrspg
     61 pvapqrpchl kgwqhrptqh naackqgqaa aqtpprpgpp sappppkeg hqeglvelpa
    121 sfrelltffc tnatihgair lvcsrgnrlk ttswgllslg alvalcwqlg llferhwhrp
    181 vlmavsvhse rkllplvtlc dgnprrpspv lrhlelldef arenidslyn vnlskgraal
    241 satvprhepp fhldreirlq rlshsgsrvr vgfrlcnstg gdcfyrgyts gvaavqdwyh
    301 fhyvdilall paawedshgs qdghfvlscs ydgldcqarq frtfhhptyg scytvdgvwt
    361 aqrpgithgv glvlrveqqp hlpllstlag irvmvhgrnh tpflghhsfs vrpgteatis
    421 iredevhrlg spyghctagg egvevellhn tsytrqaclv scfqqlmvet cscgyylhpl
    481 pagaeycssa rhpawghcfy rlyqdlethr lpctsrcprp cresafklst gtsrwpsaks
    541 agwtlatlge qglphqshrq rsslakiniv yqelnyrsve eapvysvpql lsamgslcsl
    601 wfgasvlsll ellellldas altlvlggrr lrrawfswpr aspasgassi kpeasqmppp
    661 aggtsddpep sgphlprvml pgvlagvsae eswagpqple tldt
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Reference:
AUTHORS Yamamura,H., Ugawa,S., Ueda,T., Nagao,M., Joh,T. and Shimada,S.
TITLE Epithelial Na+ channel delta subunit is an acid sensor in the human oesophagus
JOURNAL Eur. J. Pharmacol. 600 (1-3), 32-36 (2008)

3. Location and function

ENaC is located in the apical membrane of polarized epithelial cells particularly in the kidney, lung and colon. It is involved in the transepithelial Na^+ transport that accomplishes with Na^+/K^+-ATPase. ENaC plays a major role in the Na^+ and K^+ homeostasis of blood, epithelia and extraepithelial fluids by resorption of Na^+. The activity of ENaC in colon and kidney is modulated by the mineralcorticoid aldosterone. It can be blocked by either triamterene or amiloride, which are used medically to serve as diuretics.

ENaC exists in taste receptor cells also, where it in involved in salt taste perception. In rodents the entire salt taste is mediated by ENaC, whereas in human about 20% taste comes from the ENaC.

Units β and γ are associated with Liddle's syndrome. Amiloride and triamterene are potassium-sparing diuretics which act as epithelial sodium channel blockers.

4. Interaction with Cystic fibrosis transmembrane conductance regulator

ENaC interaction with **Cystic fibrosis transmembrane conductance regulator** (**CFTR**) is arguably of the most important pathophysiological relevance in cystic fibrosis. CFTR is a membrane bound protein responsible for chloride transport. In a normal sweat gland, CFTR and ENaC are responsible for salt reabsorption from the sweat glands. CFTR has an *stimulatory* effect on ENaC in the sweat glands only. In cystic fibrosis, the CFTR channel does not work, so ENaC is also inhibited. Hence, the sweat of the patient can physically be tasted to be salty. This was a common technique to help diagnose the disease prior to modern methods. In the airway, CFTR has an *inhibitory* effect on ENaC everywhere *except* the sweat glands. Normally, chloride is secreted into the airway mucous and sodium is absorbed. However, in cystic fibrosis, chloride is not secreted and ENaC is not inhibited. Hence, sodium absorption markedly increases. Lower salt in the mucous results in very thick and viscous mucous, containing far less water than normal (recall that salt has a water retaining property via osmosis and a depletion will result in less water retained). This causes many problems from increased difficulty breathing to a predisposition to catching respiratory tract diseases.

5. Families

ENaC includes 4 subfamilies: α (alpha), β (beta), γ (gamma) and δ (delta). The proteins exhibit the same apparent topology, each with two transmembrane spanning segments, separated by an extracellular loop. The extracellular domains are highly conserved and contain numerous cysteine residues, with flanking C-terminal amphipathic transmembrane regions which pays roles in the formation of the hydrophilic pores of the oligomeric channel protein complexes.

Vertebrate ENaC proteins are similar to degenerins of Caenorhabditis elegans deg-1, del-1, mec-4, mec-10 and unc-8. These proteins can be mutated to cause neuronal degradation, and are also thought to form sodium channels.

6. Genes

The exon–intron architecture of the three genes encoding the three subunits of ENaC have remained highly conserved despite the divergence of their sequences.

Human ENaC-alpha subunit gene 2010 bp, mRNA:

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   1 atggagggga acaagctgga ggagcaggac tctagccctc cacagtccac tccagggctc
  61 atgaagggga acaagcgtga ggagcagggg ctgggccccg aacctgcggc gccccagcag
 121 cccacggcgg aggaggaggc cctgatcgag ttccaccgct cctaccgaga gctcttcgag
 181 ttcttctgca acaacaccac catccacggc gccatccgcc tggtgtgctc ccagcacaac
 241 cgcatgaaga cggccttctg ggcagtgctg tggctctgca cctttggcat gatgtactgg
 301 caattcggcc tgcttttcgg agagtacttc agctaccccg tcagcctcaa catcaacctc
 361 aactcggaca agctcgtctt ccccgcagtg accatctgca ccctcaatcc ctacaggtac
 421 ccggaaatta aagaggagct ggaggagctg gaccgcatca cagagcagac gctctttgac
 481 ctgtacaaat acagctcctt caccactctc gtggccggct cccgcagccg tcgcgacctg
 541 cgggggactc tgccgcaccc cttgcagcgc ctgagggtcc cgcccccgcc tcacggggcc
 601 cgtcgagccc gtagcgtggc ctccagcttg cgggacaaca acccccaggt ggactggaag
 661 gactggaaga tcggcttcca gctgtgcaac cagaacaaat cggactgctt ctaccagaca
 721 tactcatcag gggtggatgc ggtgagggag tggtaccgct tccactacat caacatcctg
 781 tcgaggctgc cagagactct gccatccctg gaggaggaca cgctgggcaa cttcatcttc
 841 gcctgccgct tcaaccaggt ctcctgcaac caggcgaatt actctcactt ccaccacccg
 901 atgtatggaa actgctatac tttcaatgac aagaacaact ccaacctctg gatgtcttcc
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1081 tttatggatg atggtggctt taacttgcgg cctggcgtgg agacctccat cagcatgagg
1141 aaggaaaccc tggacagact tgggggcgat tatggcgact gcaccaagaa tggcagtgat
1201 gttcctgttg agaaccttta cccttcaaag tacacacagc aggtgtgtat tcactcctgc
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1381 caggttgact tctcctcaga ccacctgggc tgtttcacca agtgccggaa gccatgcagc
1441 gtgaccagct accagctctc tgctggttac tcacgatggc cctcggtgac atcccaggaa
1501 tgggtcttcc agatgctatc gcgacagaac aattacaccg tcaacaacaa gagaaatgga
1561 gtggccaaag tcaacatctt cttcaaggag ctgaactaca aaaccaattc tgagtctccc
1621 tctgtcacga tggtcaccct cctgtccaac ctgggcagcc agtggagcct gtggttcggc
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1741 ttcctcatgc tgctccgaag gttccgaagc cgatactggt ctccaggccg agggggcagg
1801 ggtgctcagg aggtagcctc caccctggca tcctcccctc cttcccactt ctgcccccac
1861 cccatgtctc tgtccttgtc ccagccaggc cctgctccct ctccagcctt gacagcccct
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     /translation="MEGNKLEEQDSSPPQSTPGLMKGNKREEQGLGPEPAAPQQPTAE
     EEALIEFHRSYRELFEFFCNNTTIHGAIRLVCSQHNRMKTAFWAVLWLCTFGMMYWQF
     GLLFGEYFSYPVSLNINLNSDKLVFPAVTICTLNPYRYPEIKEELEELDRITEQTLFD
     LYKYSSFTTLVAGSRSRRDLRGTLPHPLQRLRVPPPPHGARRARSVASSLRDNNPQVD
     WKDWKIGFQLCNQNKSDCFYQTYSSGVDAVREWYRFHYINILSRLPETLPSLEEDTLG
     NFIFACRFNQVSCNQANYSHFHHPMYGNCYTFNDKNNSNLWMSSMPGINNGLSLMLRA
     EQNDFIPLLSTVTGARVMVHGQDEPAFMDDGGFNLRPGVETSISMRKETLDRLGGDYG
     DCTKNGSDVPVENLYPSKYTQQVCIHSCFQESMIKECGCAYIFYPRPQNVEYCDYRKH
     SSWGYCYYKLQVDFSSDHLGCFTKCRKPCSVTSYQLSAGYSRWPSVTSQEWVFQMLSR
     QNNYTVNNKRNGVAKVNIFFKELNYKTNSESPSVTMVTLLSNLGSQWSLWFGSSVLSV
     VEMAELVFDLLVIMFLMLLRRFRSRYWSPGRGGRGAQEVASTLASSPPSHFCPHPMSL
     SLSQPGPAPSPALTAPPPAYATLGPRPSPGGSAGASSSACPLGGP"
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Reference:

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  AUTHORS   Bangel,N., Dahlhoff,C., Sobczak,K., Weber,W.M. and Kusche-Vihrog,K.
  TITLE     Upregulated expression of ENaC in human CF nasal epithelium
  JOURNAL   J. Cyst. Fibros. 7 (3), 197-205 (2008)
   PUBMED   17766193
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Human ENaC-beta subunit gene 1923 bp, mRNA:

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   1 atgcacgtga agaagtacct gctgaggggc ctgcatcggc tgcagagggg ccccggctac
  61 acgtacaagg agctgctggt gtggtactgc gacaacacca acacccacgg ccccaagcgc
 121 atcatctgtg aggggcccaa gaagaaagcc atgtggttcc tgctcaccct gctcttcgcc
 181 gccctcgtct gctggcagtg gggcatcttc atcaggacct acttgagctg ggaggtcagc
 241 gtctccctct ccgtaggctt caagaccatg gacttccccg ccgtcaccat ctgcaatgct
 301 agccccttca agtattccaa aatcaagcat ttgctgaagg acctggatga gctgatggaa
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Reference:

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AUTHORS   Bangel,N., Dahlhoff,C., Sobczak,K., Weber,W.M. and Kusche-Vihrog,K.
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JOURNAL   J. Cyst. Fibros. 7 (3), 197-205 (2008)
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7. Discusssion

In animal kidney, ENaC plays a crucial role in controlling sodium reabsorption to keep the normal blood pressure. It was reported that the expression of ENaC mRNA in the kidney of Dahl salt-sensitive (DS) rats was abnormally regulated by aldosterone. The expression of α-ENaC mRNA in DS rats was abnormally increased by high sodium diet in contrast to Dahl salt-resistant (DR) rats, while it was normally increased by low sodium diet in DS rats similar to DR rats. The expression of beta- and gamma-ENaC mRNA in DS rats was also abnormally increased by high sodium diet unlike DR rats. The expression of serum and glucocorticoid-regulated kinase 1 (SGK1) mRNA was elevated by high sodium diet in DS rats, but it was decreased in DR rats. The expression of ENaC and SGK1 mRNA is abnormally regulated by dietary sodium in salt-sensitively hypertensive rats, and that this abnormal expression would be one of the factors causing salt-sensitive hypertension (Aoi et al., 2007).

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