

Epithelial sodium channel (ENaC) in GtoPdb v.2021.2

Israel Hanukoglu¹

1. Ariel University, Israel

Abstract

The epithelial sodium channels (ENaC) are located on the apical membrane of epithelial cells in the kidney tubules, lung, respiratory tract, male and female reproductive tracts, sweat and salivary glands, placenta, colon, and some other organs [9, 13, 22, 21, 42]. In these epithelia, Na⁺ ions flow from the extracellular fluid into the cytoplasm of epithelial cells via ENaC. The Na⁺ ions are then pumped out of the cytoplasm into the interstitial fluid by the Na⁺/K⁺ ATPase located on the basolateral membrane [36]. As Na⁺ is one of the major electrolytes in the extracellular fluid (ECF), osmolarity change initiated by the Na⁺ flow is accompanied by a flow of water accompanying Na⁺ ions [6]. Thus, ENaC has a central role in regulating ECF volume and blood pressure, primarily via its function in the kidney [37]. The expression of ENaC subunits, hence its activity, is regulated by the renin-angiotensin-aldosterone system, and other factors involved in electrolyte homeostasis [37, 30].

In the respiratory tract and female reproductive tract, large segments of the epithelia are composed of multi-ciliated cells. In these cells, ENaC is located along the entire length of the cilia that cover the cell surface [15]. Ciliary location greatly increases ENaC density per cell surface and allows ENaC to serve as a sensitive regulator of osmolarity of the periciliary fluid throughout the whole depth of the fluid bathing the cilia [15]. In contrast to ENaC, CFTR (ion transporter defective in cystic fibrosis) is located on non-ciliary cell-surface [15]. In the vas deferens segment of the male reproductive tract, the luminal surface is covered by microvilli and stereocilia projections with backbones composed of actin filament bundles [42]. In these cells, both ENaC and the water channel aquaporin AQP9 are localized on these projections and also in the basal and smooth muscle layers [42]. Thus, ENaC function is also essential for the clearance of respiratory airways, transport of germ cells, fertilization, implantation, and cell migration [15, 22].

Contents

This is a citation summary for Epithelial sodium channel (ENaC) in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

GtoPdb is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [7].

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

[Epithelial sodium channel \(ENaC\)](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=122>

[Introduction to Epithelial sodium channel \(ENaC\)](#)

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=122>

Channels and Subunits

Complexes

ENaC $\alpha\beta\gamma$

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=742>

Subunits

ENaC α

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=738>

ENaC β

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=739>

ENaC γ

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=741>

ENaC δ

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=740>

References

1. Anand P, Puranik A, Aravamudan M, Venkatakrishnan AJ and Soundararajan V. (2020) SARS-CoV-2 strategically mimics proteolytic activation of human ENaC. *Elife* **9** [PMID:32452762]
2. Baconguis I, Bohlen CJ, Goehring A, Julius D and Gouaux E. (2014) X-ray structure of acid-sensing ion channel 1-snake toxin complex reveals open state of a Na(+) -selective channel. *Cell* **156**: 717-29 [PMID:24507937]
3. Bize V and Horisberger JD. (2007) Sodium self-inhibition of human epithelial sodium channel: selectivity and affinity of the extracellular sodium sensing site. *Am J Physiol Renal Physiol* **293**: F1137-46 [PMID:17670907]
4. Bogdanović R, Kuburović V, Stajić N, Mughal SS, Hilger A, Ninić S, Prijović S and Ludwig M. (2012) Liddle syndrome in a Serbian family and literature review of underlying mutations. *Eur J Pediatr* **171**: 471-8 [PMID:21956615]
5. Boggula VR, Hanukoglu I, Sagiv R, Enuka Y and Hanukoglu A. (2018) Expression of the epithelial sodium channel (ENaC) in the endometrium - Implications for fertility in a patient with pseudohypoaldosteronism. *J Steroid Biochem Mol Biol* **183**: 137-141 [PMID:29885352]
6. Bourque CW. (2008) Central mechanisms of osmosensation and systemic osmoregulation. *Nat Rev Neurosci* **9**: 519-31 [PMID:18509340]
7. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
8. Butterworth MB, Weisz OA and Johnson JP. (2008) Some assembly required: putting the epithelial sodium channel together. *J Biol Chem* **283**: 35305-9 [PMID:18713729]
9. Canessa CM, Merillat AM and Rossier BC. (1994) Membrane topology of the epithelial sodium channel in intact cells. *Am J Physiol* **267**: C1682-90 [PMID:7810611]
10. Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD and Rossier BC. (1994) Amiloride-sensitive epithelial Na⁺ channel is made of three homologous subunits. *Nature* **367**: 463-7 [PMID:8107805]
11. Chang SS, Grunder S, Hanukoglu A, Rösler A, Mathew PM, Hanukoglu I, Schild L, Lu Y, Shimkets RA and Nelson-Williams C et al.. (1996) Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. *Nat Genet* **12**: 248-53 [PMID:8589714]
12. Collier DM and Snyder PM. (2011) Identification of epithelial Na⁺ channel (ENaC) intersubunit Cl⁻ inhibitory residues suggests a trimeric alpha gamma beta channel architecture. *J Biol Chem* **286**: 6027-32 [PMID:21149458]
13. Duc C, Farman N, Canessa CM, Bonvalet JP and Rossier BC. (1994) Cell-specific expression of epithelial sodium channel alpha, beta, and gamma subunits in aldosterone-responsive epithelia from the rat: localization by in situ hybridization and immunocytochemistry. *J Cell Biol* **127**: 1907-21 [PMID:7806569]
14. Edelheit O, Ben-Shahar R, Dascal N, Hanukoglu A and Hanukoglu I. (2014) Conserved charged residues at the surface and interface of epithelial sodium channel subunits--roles in cell surface expression and the sodium self-inhibition response. *FEBS J* **281**: 2097-111 [PMID:24571549]
15. Enuka Y, Hanukoglu I, Edelheit O, Vaknine H and Hanukoglu A. (2012) Epithelial sodium channels (ENaC) are uniformly distributed on motile cilia in the oviduct and the respiratory airways. *Histochem Cell Biol* **137**: 339-53 [PMID:22207244]
16. Gentzsch M and Rossier BC. (2020) A Pathophysiological Model for COVID-19: Critical Importance of Transepithelial Sodium Transport upon Airway Infection. *Function (Oxf)* **1**: zqaa024 [PMID:33201937]
17. Giraldez T, Rojas P, Jou J, Flores C and Alvarez de la Rosa D. (2012) The epithelial sodium channel δ -subunit: new notes for an old song. *Am J Physiol Renal Physiol* **303**: F328-38 [PMID:22573384]

18. Hanukoglu A. (1991) Type I pseudohypoaldosteronism includes two clinically and genetically distinct entities with either renal or multiple target organ defects. *J Clin Endocrinol Metab* **73**: 936-44 [PMID:1939532]
19. Hanukoglu A, Edelheit O, Shriki Y, Gizewska M, Dascal N and Hanukoglu I. (2008) Renin-aldosterone response, urinary Na/K ratio and growth in pseudohypoaldosteronism patients with mutations in epithelial sodium channel (ENaC) subunit genes. *J Steroid Biochem Mol Biol* **111**: 268-74 [PMID:18634878]
20. Hanukoglu A and Hanukoglu I. (2018) In systemic pseudohypoaldosteronism type 1 skin manifestations are not rare and the disease is not transient. *Clin Endocrinol (Oxf)* **89**: 240-241 [PMID:29702750]
21. Hanukoglu I, Boggula VR, Vaknine H, Sharma S, Kleyman T and Hanukoglu A. (2017) Expression of epithelial sodium channel (ENaC) and CFTR in the human epidermis and epidermal appendages. *Histochem Cell Biol* **147**: 733-748 [PMID:28130590]
22. Hanukoglu I and Hanukoglu A. (2016) Epithelial sodium channel (ENaC) family: Phylogeny, structure-function, tissue distribution, and associated inherited diseases. *Gene* **579**: 95-132 [PMID:26772908]
23. Horisberger JD and Chraïbi A. (2004) Epithelial sodium channel: a ligand-gated channel? *Nephron Physiol* **96**: p37-41 [PMID:14988660]
24. Jasti J, Furukawa H, Gonzales EB and Gouaux E. (2007) Structure of acid-sensing ion channel 1 at 1.9 Å resolution and low pH. *Nature* **449**: 316-23 [PMID:17882215]
25. Kashlan OB and Kleyman TR. (2012) Epithelial Na(+) channel regulation by cytoplasmic and extracellular factors. *Exp Cell Res* **318**: 1011-9 [PMID:22405998]
26. Kellenberger S, Gautschi I and Schild L. (2003) Mutations in the epithelial Na⁺ channel ENaC outer pore disrupt amiloride block by increasing its dissociation rate. *Mol Pharmacol* **64**: 848-56 [PMID:14500741]
27. Kellenberger S and Schild L. (2015) International Union of Basic and Clinical Pharmacology. XCI. structure, function, and pharmacology of acid-sensing ion channels and the epithelial Na⁺ channel. *Pharmacol Rev* **67**: 1-35 [PMID:25287517]
28. Kleyman TR and Eaton DC. (2020) Regulating ENaC's gate. *Am J Physiol Cell Physiol* **318**: C150-C162 [PMID:31721612]
29. Kleyman TR, Kashlan OB and Hughey RP. (2018) Epithelial Na⁺ Channel Regulation by Extracellular and Intracellular Factors. *Annu Rev Physiol* **80**: 263-281 [PMID:29120692]
30. Knepper MA, Kwon TH and Nielsen S. (2015) Molecular physiology of water balance. *N Engl J Med* **372**: 1349-58 [PMID:25830425]
31. Lingueglia E, Voilley N, Waldmann R, Lazdunski M and Barbry P. (1993) Expression cloning of an epithelial amiloride-sensitive Na⁺ channel. A new channel type with homologies to *Caenorhabditis elegans* degenerins. *FEBS Lett* **318**: 95-9 [PMID:8382172]
32. Lu M, Echeverri F, Kalabat D, Laita B, Dahan DS, Smith RD, Xu H, Staszewski L, Yamamoto J and Ling J et al.. (2008) Small molecule activator of the human epithelial sodium channel. *J Biol Chem* **283**: 11981-94 [PMID:18326490]
33. Noreng S, Bharadwaj A, Posert R, Yoshioka C and Baconguis I. (2018) Structure of the human epithelial sodium channel by cryo-electron microscopy. *Elife* **7** [PMID:30251954]
34. Noreng S, Posert R, Bharadwaj A, Houser A and Baconguis I. (2020) Molecular principles of assembly, activation, and inhibition in epithelial sodium channel. *Elife* **9** [PMID:32729833]
35. Palmer LG, Patel A and Frindt G. (2012) Regulation and dysregulation of epithelial Na⁺ channels. *Clin Exp Nephrol* **16**: 35-43 [PMID:22038262]
36. Pirahanchi Y, Jessu R and Aeddula NR. (2021) Physiology, Sodium Potassium Pump *StatPearls* [PMID:30725773]
37. Rossier BC, Baker ME and Studer RA. (2015) Epithelial sodium transport and its control by aldosterone: the story of our internal environment revisited. *Physiol Rev* **95**: 297-340 [PMID:25540145]
38. Rossier BC and Stutts MJ. (2009) Activation of the epithelial sodium channel (ENaC) by serine proteases. *Annu Rev Physiol* **71**: 361-79 [PMID:18928407]
39. Rotin D and Staub O. (2011) Role of the ubiquitin system in regulating ion transport. *Pflugers Arch* **461**: 1-21 [PMID:20972579]
40. Saxena A, Hanukoglu I, Saxena D, Thompson RJ, Gardiner RM and Hanukoglu A. (2002) Novel mutations responsible for autosomal recessive multisystem pseudohypoaldosteronism and sequence variants in epithelial sodium channel alpha-, beta-, and gamma-subunit genes. *J Clin Endocrinol Metab* **87**: 3344-50 [PMID:12107247]
41. Saxena A, Hanukoglu I, Strautnieks SS, Thompson RJ, Gardiner RM and Hanukoglu A. (1998) Gene structure of the human amiloride-sensitive epithelial sodium channel beta subunit. *Biochem Biophys Res Commun* **252**: 208-13 [PMID:9813171]
42. Sharma S, Kumaran GK and Hanukoglu I. (2020) High-resolution imaging of the actin cytoskeleton and epithelial sodium channel, CFTR, and aquaporin-9 localization in the vas deferens. *Mol Reprod Dev* **87**: 305-319 [PMID:31950584]

43. Sheng S, Maarouf AB, Bruns JB, Hughey RP and Kleyman TR. (2007) Functional role of extracellular loop cysteine residues of the epithelial Na⁺ channel in Na⁺ self-inhibition. *J Biol Chem* **282**: 20180-90 [[PMID:17522058](#)]
44. Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, Schambelan M, Gill Jr JR, Ulick S, Milora RV and Findling JW *et al.*. (1994) Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* **79**: 407-14 [[PMID:7954808](#)]
45. Voilley N, Bassilana F, Mignon C, Merscher S, Mattéi MG, Carle GF, Lazdunski M and Barbry P. (1995) Cloning, chromosomal localization, and physical linkage of the beta and gamma subunits (SCNN1B and SCNN1G) of the human epithelial amiloride-sensitive sodium channel. *Genomics* **28**: 560-5 [[PMID:7490094](#)]
46. Waldmann R, Champigny G, Bassilana F, Voilley N and Lazdunski M. (1995) Molecular cloning and functional expression of a novel amiloride-sensitive Na⁺ channel. *J Biol Chem* **270**: 27411-4 [[PMID:7499195](#)]
47. Zennaro MC, Hubert EL and Fernandes-Rosa FL. (2012) Aldosterone resistance: structural and functional considerations and new perspectives. *Mol Cell Endocrinol* **350**: 206-15 [[PMID:21664233](#)]