

Acid-Sensing Proton-Gated Ion Channels (ASICs) and Epithelial Sodium Channels (ENaC)

Key References

- Askwith, C.C., et al., Neuropeptide FF and FMRFamide potentiate acid-evoked currents from sensory neurons and proton-gated DEG/ENaC channels., *Neuron*, **26**, 133-141 (2000).
- Escoubas, P., et al., Isolation of a tarantula toxin specific for a class of proton-gated Na⁺ channels., *J. Biol. Chem.*, **275**, 25116-25121 (2000).
- Garty, H., et al., Epithelial sodium channels - function, structure, and regulation., *Physiol. Rev.*, **77**, 359-396 (1997).
- Hong, K., et al., *In vivo* structure-function analyses of *Caenorhabditis elegans* MEC-4, a candidate mechanosensory ion channel subunit., *J. Neurosci.*, **20**, 2575-2588 (2000).
- Kellenberger, S., et al., Epithelial sodium channel/degenerin family of ion channels: A variety of functions for a shared structure., *Physiol. Rev.*, **82**, 735-767 (2002).
- Krishtal, O., The ASICs: Signaling molecules? Modulators?, *Trends Neurosci.*, **26**, 477-483 (2003).
- Mano, I., et al., DEG/ENaC channels: a touchy superfamily that watches its salt., *Bioessays*, **21**, 568-578 (1999).
- Rossier, B.C., The epithelial sodium channel (ENaC): new insights into ENaC gating., *Pflugers Arch.*, **446**, 314-316 (2003).
- Sluka, K.A., et al., Chronic hyperalgesia induced by repeated acid injections in muscle is abolished by the loss of ASIC3, but not ASIC1., *Pain*, **106**, 229-239 (2003).
- Thomas, C.P., et al., New insights into epithelial sodium channel function in the kidney: site of action, regulation by ubiquitin ligases, serum- and glucocorticoid-inducible kinase and proteolysis., *Curr. Opin. Nephrol. Hypertens.*, **13**, 541-548 (2004).
- Waldmann, R., et al., H⁺-gated cation channels - neuronal acid sensors in the NaC/DEG family of ion channels., *Curr. Opin. Neurobiol.*, **8**, 418-424 (1998).
- Xiong, Z.G., et al., Neuroprotection in ischemia: Blocking calcium-permeable acid-sensing ion channels., *Cell*, **118**, 687-698 (2004).

Overview

The recently discovered ENaC/degenerin gene family encodes sodium channels involved in various cell functions in metazoans. The subfamilies include the degenerins, which are part of a mechanosensory complex in the nematode *C. elegans*, the FMRFamide peptide-gated sodium channel FaNaC present in snails, and the mammalian subfamilies ENaC and ASICs. This entry focuses on the mammalian channels.

Structurally, functional ENaC and ASICs are composed of several homologous subunits that are arranged around the central channel pore. Analysis of the functional ENaC or FaNaC complex suggests that they form tetramers. ENaC has a fixed subunit stoichiometry with two α and one each of β and γ subunits. ASICs can form hetero- and homomultimeric channels. ENaC subunits have a predicted mass of 73-76 kDa; ASIC subunits are somewhat smaller with 58-63 kDa. ENaC and ASIC subunits have intracellular N- and C-termini, two transmembrane domains and a large extracellular loop. This topology has been experimentally verified for α ENaC and for ASIC2a. Structure-function studies in ENaC identified the region immediately preceding the second transmembrane domain as important for ion permeation and selectivity and for binding of the pore blocker amiloride.

ENaC is highly selective for sodium over potassium ($pNa/pK \geq 100$), while ASICs are less selective with a pNa/pK ratio of ~ 10 . ENaC and ASICs do not conduct divalent cations except for ASIC1a that has a low but significant permeability to calcium that may be physiologically important. All members of the ENaC/degenerin family are inhibited by amiloride, which acts as a pore blocker. The IC_{50} for current block on cloned ENaC and ASICs is 0.1 μM and

10-100 μM respectively for amiloride, and 0.01 μM and $\sim 10 \mu M$ for the amiloride derivative benzamil. ENaC is a constitutively active channel. ASICs are normally closed channels that are transiently activated by extracellular acidification and subsequently inactivate in the continued presence of the extracellular acidic stimulus. The mechanism of pH-gating of ASICs is currently not known. For ASIC3 it has been suggested that acidification removes a tonic channel block by extracellular calcium.

ENaC is expressed at the apical membrane of epithelia, where it mediates transepithelial sodium transport in a two-step process that involves entry of sodium via ENaC and extrusion of the intracellular sodium by the basolaterally located sodium/potassium-ATPase. In the kidney and the colon, the transepithelial sodium transport is crucial for sodium and potassium homeostasis and for the control of blood pressure. In the lung or in salivary glands, sodium transport is important for keeping the composition and the volume of the luminal fluid constant. ENaC in the taste buds of the tongue is involved in salt taste sensation. ENaC function in the kidney, the colon and the taste buds is regulated by aldosterone. Mice that are deficient of either ENaC subunit die soon after birth, either from respiratory or metabolic problems. Liddle syndrome, a rare form of hypertension, is caused by hyperactivating ENaC mutations, while pseudohypoaldosteronism type 1, that is accompanied by renal salt loss and hypotension, is caused by loss-of-function ENaC mutations.

ASICs are widely distributed in the central and the peripheral nervous system, where they are thought to induce neuronal depolarization and action potential generation in

response to extracellular acidification. Mice that are deficient of one or several ASIC genes are apparently healthy. Experiments that compared wild type mice with those deficient of certain ASIC genes indicate potential roles of ASICs in learning, fear conditioning, neurodegeneration after ischemia and in pain sensation.

Acid-Sensing Proton-Gated Ion Channels (ASICs) and Epithelial Sodium Channels (ENaC)

SUBFAMILY	ENaC	ASIC
TYPES/SUBTYPES	ENaC is composed of three homologous subunits, α , β , γ	Four genes and splice variants of subunits (ASIC 1-4). Functional ASIC channels are heteromeric or homomultimeric assemblies of subunits
ALTERNATIVE NOMENCLATURE	Amiloride-sensitive Na channel Gene names/data base entry names: SCNN1A/SCAA, (α ENaC); SCNN1B/SCAB, (β ENaC); SCNN1G/SCAG, (γ ENaC)	BNaC2, ACCN2 (= ASIC1a); ASIC β (= ASIC1b); BNaC1, BNC1, MDEG, MDEG1, ACCN1 (= ASIC2a); MDEG2 (= ASIC2b); DRASIC, hTNaC 1 (= ASIC3); SPASIC (= ASIC4)
STRUCTURAL INFORMATION	Subunit contains two transmembrane domains Functional channel is a tetramer α , 669 aa; β , 640 aa; γ , 649 aa (all human)	Subunit contains two transmembrane domains. ASIC1a, 528 aa (human); ASIC1b, 559 aa (rat); ASIC2a, 512 aa (human); ASIC2b, 563 aa (rat); ASIC3, 531 aa (human); ASIC4 539 aa (human)
TISSUE EXPRESSION	Kidney, colon, salivary glands, airway epithelia, skin, taste buds	Central and peripheral nervous system
CONDUCTANCE (Na ⁺)	4-5 pS	10-15 pS
IONIC SELECTIVITY	Li ⁺ > Na ⁺ >>>K ⁺	Li ⁺ = Na ⁺ > K ⁺
CONTROL OF CHANNEL ACTIVITY	Constitutively active channel	Activated by extracellular pH drop
BLOCKERS	Amiloride (A7410), benzamil (B2417), triamteren	Amiloride (A7410), benzamil (B2417), NSAIDs (salicylic acid, (S5922)), acetylsalicylic acid (A2093 , A5376), flurbiprofen (F8514), ibuprofen (I4883 , I7905 , I1892), diclofenac, (D6899), Gd ³⁺ , Psalmotoxin 1 (ASIC1a), the sea anemone peptide toxin APETx3 (ASIC3)
MODULATORS	Proteases (Trypsin; (T1426)) Aldosterone (A9477) (induces cell surface expression)	FMRFamide (P4898) and related peptides Proteases (trypsin (T1426), chymotrypsin (C4129), proteinase K (P6566)) Ca ²⁺ , Mg ²⁺ , Zn ²⁺
PHYSIOLOGICAL FUNCTION	Na ⁺ homeostasis, blood pressure regulation, regulation of airway surface liquid level, taste sensation	Possibly involved in pain sensation, memory functions, fear conditioning, neurodegeneration after ischemia/hypoxia
DISEASE RELEVANCE	Hypertension, Liddle syndrome, pseudohypoaldosteronism type 1	Not known

Abbreviations

NSAIDs: Nonsteroidal anti-inflammatory drugs

APETx3: Anthopleura elegantissima toxin 3

FOOTNOTES