Epithelial sodium channels (ENaC)

Overview: Epithelial sodium channels (ENaC) are responsible for sodium reabsorption by the epithelia lining the distal part of the kidney tubule and fulfil similar functional roles in some other tissues such as the airways and the distal colon. This reabsorption of sodium is regulated by aldosterone, vasopressin and glucocorticoids and is one of the essential mechanisms in the regulation of sodium balance, blood volume and blood pressure. ENaC expression is also vital for lung fluid balance (Hummler *et al.*, 1996). Sodium reabsorption is suppressed by the 'potassium-sparing' diuretics amiloride and triamterene. The first ENaC subunit (α) was isolated by expression cloning, using a cDNA library derived from the colon of salt-deprived rats, as a current sensitive to inhibition by amiloride (Canessa *et al.*, 1993). Two further subunits (β and γ) were identified by functional complementation of the α subunit (Canessa *et al.*, 1994). A related δ subunit was later identified (Waldmann *et al.*, 1995) that has a wider tissue distribution. ENaC subunits contain two putative TM domains connected by a large extracellular loop and short cytoplasmic amino- and carboxy-termini. The stoichiometry of the ENaC in the kidney and related epithelia is thought to be predominantly a heterotetramer of 2α:1β:1γ subunits (Firsov *et al.*, 1998).

Nomenclature	Epithelial sodium channel (ENaC)
Ensembl ID	Human α subunit, ENSG00000111319; human β subunit, ENSG00000168447; human γ subunit, ENSG00000166828; human δ subunit, ENSG00000162572
Activators (EC_{50})	S3969 (1.2 μM) (Lu *et al.*, 2008)
Blockers (IC_{50})	Amiloride (100–200 nM), benzamil (~10 nM), triamterene (~5 μM) (Canessa *et al.*, 1994; Kellenberger *et al.*, 2003)
Functional characteristics	γ ~ 4–5 pS, $P_{Na}/P_K > 20$; tonically open at rest; expression and ion flux regulated by circulating aldosterone-mediated changes in gene transcription. The action of aldosterone, which occurs in 'early' (1.5–3 h) and 'late' (6–24 h) phases, is competitively antagonized by spironolactone and its active metabolites. Glucocorticoids are important functional regulators in lung/airways and this control is potentiated by thyroid hormone; but the mechanism underlying such potentiation is unclear (Barker *et al.*, 1990; Sayegh *et al.*, 1999; Richard *et al.*, 2004). The density of channels in the apical membrane, and hence G_{Na}, can be controlled via both serum- and glucocorticoid-regulated kinases (SGK1, 2 and 3) (Debonneville *et al.*, 2001; Friedrich *et al.*, 2003) and via cAMP/PKA (Morris and Schafer, 2002). ENaC is constitutively activated by serine peptidases, such as furin, prostasin (CAP1), plasmin and elastase (Planes and Caughey, 2007; Rotin and Schild, 2008; Kleyman *et al.*, 2009; Rossier and Stutts, 2009). The activation of ENaC by proteases is blocked by a protein, SPLUNC1, secreted by the airways and which binds specifically to ENaC to prevent its cleavage (Garcia-Caballero *et al.*, 2009). Pharmacological inhibitors of proteases (e.g. camostat acting upon prostasin) reduce the activity of ENaC (Maekawa *et al.*, 2009). Phosphatidylinositides such as PtIns(4,5)P_2 and PtIns(3,4,5)P_3) stabilize channel gating probably by binding to the β and γ ENaC subunits, respectively (Ma *et al.*, 2007; Pochynyuk *et al.*, 2008), while C-terminal phosphorylation of β and γ ENaC by ERK1/2 has been reported to inhibit the withdrawal of the channel complex from the apical membrane (Yang *et al.*, 2006). This effect may contribute to the cAMP-mediated increase in sodium conductance.

Data in the table refer to the 2αβγ heteromer. There are several human diseases resulting from mutations in ENaC subunits, or their regulation, most of which lead to overexpression or under-expression of the channel in epithelia. The best known of these is Liddle's syndrome, usually associated with gain of function mutations that result in decreased down-regulation of ENaC through impaired binding of the ubiquitin ligase, Nedd4-2 (Staub *et al.*, 1996; Rotin and Schild, 2008). Pseudohypoaldosteronism type 1 (PHA-1) can occur through either mutations in the gene encoding the mineralocorticoid receptor, or mutations in genes encoding ENaC subunits (see Bonny and Hummler, 2000). Regulation of ENaC by phosphoinositides may underlie insulin-evoked renal Na^+ retention that can complicate the clinical management of type 2 diabetes using insulin-sensitizing thiazolidinedione drugs (Guan *et al.*, 2005).

Abbreviation: S3969, (*N*-(2-hydroxyethyl)-4-methyl-2-(4-methyl-1*H*-indol-3-ylthio)pentanamide

Further Reading

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