Acid-sensing (proton-gated) ion channels (ASICs)

Overview: Acid-sensing ion channels (ASICs, provisional nomenclature; see Wemmie *et al*., 2006; Lingueglia, 2007) are members of a Na^+ channel superfamily that includes the epithelial Na^+ channel (ENaC), the FMRF-amide-activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabitis elegans,* channels in *Drosophila melanogaster* and 'orphan' channels that include BLINaC (Sakai *et al*., 1999) and INaC (Schaefer *et al*., 2000). ASIC subunits contain two putative TM domains and assemble as homo- or hetero-trimers (Jasti *et al*., 2007; Gonzales *et al*., 2009) to form proton-gated, voltage-insensitive, Na^+-permeable, channels. Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASICα, BNaC2α) (Waldmann *et al*., 1997a), ASIC1b (ASICβ, BNaC2β) (Chen *et al*., 1998) and ASIC1b2 (ASICβ2) (Ugawa *et al*., 2001); note that ASIC1a is also permeable to Ca^{2+}] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1α, BNC1a) (Price *et al*., 1996; Waldmann *et al*., 1996; Garcia-Anoveros *et al*., 1997) and ASIC2b (MDEG2, BNaC1β); (Lingueglia *et al*., 1997)] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H^+-gated currents. A third member, ASIC3 (DRASIC, TNaC1) (Waldmann *et al*., 1997b), has been identified. A fourth mammalian member of the family (ASIC4/SPASIC) does not support a proton-gated channel in heterologous expression systems and is reported to down-regulate the expression of ASIC1a and ASIC3 (Akopian *et al*., 2000; Grunder *et al*., 2000; Donier *et al*., 2008). ASIC channels are primarily expressed in central and peripheral neurons including nociceptors where they participate in neuronal sensitivity to acidosis. They have also been detected in taste receptor cells (ASIC1–3), photoreceptors and retinal cells (ASIC1–3), cochlear hair cells (ASIC1b), testis (hASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC1a and –3), vascular smooth muscle cells (ASIC1–3), immune cells (ASIC1, –3 and –4) and bone (ASIC1–3). The activation of ASIC1a within the central nervous system contributes to neuronal injury caused by focal ischemia (Xiong *et al*., 2007) and to axonal degeneration in autoimmune inflammation in a mouse model of multiple sclerosis (Friese *et al*., 2007). However, activation of ASIC1a can terminate seizures (Ziemann *et al*., 2008). Further proposed roles for centrally and peripherally located ASICs are reviewed in Wemmie *et al*. (2006) and Lingueglia (2007). The relationship of the cloned ASICs to endogenously expressed proton-gated ion channels is becoming established (Escoubas *et al*., 2000; Sutherland *et al*., 2001; Wemmie *et al*., 2002; 2003; 2006; Diochot *et al*., 2004; 2007; Lingueglia *et al*., 2006; Lingueglia 2007; Hattori *et al*., 2009). Heterologously expressed heteromultimers form ion channels with altered kinetics, ion selectivity, pH-sensitivity and sensitivity to blockers that resemble some of the native proton-activated currents recorded from neurones (Lingueglia *et al*., 1997; Babinski *et al*., 2000; Escoubas *et al*., 2000; Baron *et al*., 2008).

Nomenclature	ASIC1	ASIC2	ASIC3
Other names	ASIC; BNaC2	BNC1; BNaC1; MDEG	DRASIC, TNaC1
Ensembl ID	ENSG00000110881	ENSG00000108684	ENSG00000213199
Endogenous activators	Extracellular H^+ (ASIC1a, pEC_{50} ~ 6.2–6.8; ASIC1b, pEC_{50} ~ 5.1–6.2)	Extracellular H^+ (pEC_{50} ~ 4.1–5.0)	Extracellular H^+ (transient component pEC_{50} ~ 6.2–6.7) (sustained component pEC_{50} ~ 3.5–4.3)
Blockers (IC_{50})	ASIC1a: psalmotoxin 1 (PcTx1) (0.9 nM), Zn^{2+} (~7 nM), A-317567 (~2 μM), Pb^{2+} (~4 μM), Ni^{2+} (~0.6 mM), amiloride (10 μM), EIPA, benzamil (10 μM), ibuprofen/ flurbiprofen (350 μM) ASIC1b: amiloride (21–23 μM), Pb^{2+} (~1.5 μM)	Amiloride (28 μM), A-317567 (~30 μM), Cd^{2+} (~1 mM)	APETx2 (63 nM) (transient component only), amiloride (16–63 μM) (transient component only – sustained component enhanced by 200 μM amiloride at pH 4), A-317567 (~10 μM), aspirin/ diclofenac (92 μM – sustained component), salicylic acid (260 μM – sustained component), Gd^{3+} (40 μM)
Functional characteristics	ASIC1a: γ ~ 14 pS; P_{Na}/P_K = 5–13, P_{Na}/P_{Ca} = 2.5; rapid activation rate (5.8–13.7 ms), rapid inactivation rate (1.2–4 s) at pH 6.0, slow recovery (5.3–13 s) at pH 7.4 ASIC1b: γ ~ 19 pS; P_{Na}/P_K = 14.0; $P_{Na}>>P_{Ca}$; rapid activation rate (9.9 ms), rapid inactivation rate (0.9–1.7 s) at pH 6.0, slow recovery (4.4–7.7 s) at pH 7.4	γ ~ 10.4–13.4 pS; P_{Na}/P_K = 10, P_{Na}/P_{Ca} = 20; rapid activation rate, moderate inactivation rate (3.3–5.5 s) at pH 5	γ ~ 13–15 pS; biphasic response consisting of rapidly inactivating transient and sustained components; very rapid activation (<5 ms) and inactivation (0.4 s); fast recovery (0.4–0.6 s) at pH 7.4, transient component partially inactivated at pH 7.2
Probes	[^{125}I]-PcTx1 (ASIC1a K_D = 213 pM)		

Psalmotoxin 1 (PcTx1) inhibits ASIC1a by modifying activation and desensitization by H^+, but promotes ASIC1b opening. PcTx1 has little effect upon ASIC2a, ASIC3 or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 (Escoubas *et al*., 2000; Diochot *et al*., 2007). Blockade of ASIC1a by PcTx1 activates the endogenous enkephalin pathway and has very potent analgesic effects in rodents (Mazzuca *et al*., 2007). APETx2 most potently blocks homomeric ASIC3 channels, but also ASIC2b + ASIC3, ASIC1b + ASIC3 and ASIC1a + ASIC3 heteromeric channels with IC_{50} values of 117 nM, 900 nM and 2 μM respectively. APETx2 has no effect on ASIC1a, ASIC1b, ASIC2a or ASIC2a + ASIC3 (Diochot *et al*., 2004; 2007). IC_{50} values for A-317567 are inferred from blockade of ASIC channels native to dorsal root ganglion neurones (Dube *et al*., 2005). The pEC_{50} values for proton activation of ASIC channels are influenced by numerous factors including extracellular di- and poly-valent ions, Zn^{2+}, protein kinase C and serine proteases (reviewed by Lingueglia *et al*., 2006). Rapid acidification is required for activation of ASIC1 and ASIC3 due to fast inactivation/desensitization. pEC_{50} values for H^+ activation of either transient, or sustained, currents mediated by ASIC3 vary in the literature and may reflect species and/or methodological differences (Waldmann *et al*., 1997b; de Weille *et al*., 1998; Babinski *et al*., 1999). The transient and sustained current components mediated by rASIC3 are selective for Na^+ (Waldmann *et al*., 1997b); for hASIC3 the transient component is Na^+-selective ($P_{Na}/P_K > 10$) whereas the sustained current appears non-selective (P_{Na}/P_K = 1.6) (de Weille *et al*., 1998; Babinski *et al*., 1999). The reducing agents dithiothreitol (DTT) and glutathione (GSH) increase ASIC1a currents expressed in CHO cells and ASIC-like currents in sensory ganglia and central neurons (Andrey *et al*., 2005; Chu *et al*., 2006) whereas oxidation, through the formation of inter-subunit

disulphide bonds, reduces currents mediated by ASIC1a (Zha *et al*., 2009). ASIC1a is also irreversibly modulated by extracellular serine proteases, such as trypsin, through proteolytic cleavage (Vukicevic *et al*., 2006). Non-steroidal anti-inflammatory drugs are direct blockers of ASIC currents at therapeutic concentrations (reviewed by Voilley, 2004). Extracellular Zn^{2+} potentiates proton activation of homomeric and heteromeric channels incorporating ASIC2a, but not homomeric ASIC1a or ASIC3 channels (Baron *et al*., 2001). However, removal of contaminating Zn^{2+} by chealation reveals a high-affinity block of homomeric ASIC1a and heteromeric ASIC1a + ASIC2 channels by Zn^{2+} indicating complex biphasic actions of the divalent (Chu *et al*., 2004). Nitric oxide potentiates submaximal currents activated by H^+ mediated by ASIC1a, ASIC1b, ASIC2a and ASIC3 (Cadiou *et al*., 2007). Ammonium activates ASIC channels (most likely ASIC1a) in midbrain dopaminergic neurones: that may be relevant to neuronal disorders associated with hyperammonemia (Pidoplichko and Dani, 2006). The positive modulation of homomeric, heteromeric and native ASIC channels by the peptide FMRFamide and related substances, such as neuropeptides FF and SF, is reviewed in detail by Lingueglia *et al*. (2006). Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes, enhance ASIC currents (Mamet *et al*., 2002), and in the case of arachidonic acid directly activate the channel (Smith *et al*., 2007; Deval *et al*., 2008). The sustained current component mediated by ASIC3 is potentiated by hypertonic solutions in a manner that is synergistic with the effect of arachidonic acid (Deval *et al*., 2008).

Abbreviations: A-317567, C-{6-[2-(1-Isopropyl-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-cyclopropyl]-naphthalen-2-yl}-methanediamine; **EIPA**, ethylisopropylamiloride; **FMRFamide**, Phe-Met-Arg-Phe-amide; **neuropeptide FF**, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-amide; **neuropeptide SF**, Ser-Leu-Ala-Pro-Gln-Arg-Phe-amide

Further Reading

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