

Acid-sensing (proton-gated) ion channels (ASICs) in GtoPdb v.2025.4

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Abstract

Acid-sensing ion channels (ASICs, **nomenclature as agreed by NC-IUPHAR [52, 2, 3]**) 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 *Caenorhabditis elegans*, channels in *Drosophila melanogaster* and the mammalian bile acid-activated ion channel BASIC [94], previously known as BLINaC [75] and INaC [77]. ASIC subunits contain 2 TM domains and a large extracellular part whose shape resembles that of a hand, as shown by high-resolution structures of chicken and human ASIC1a [49, 43, 7, 101, 100, 81]. They assemble as homo- or heterotrimers to form proton-gated, voltage-insensitive, Na⁺ permeable, channels that are activated by levels of acidosis occurring in both physiological and pathophysiological conditions with ASIC3 also playing a role in mechanosensation (reviewed in [48, 93, 52, 74, 23]). Splice variants of ASIC1 [termed ASIC1a (ASIC, ASIC α , BNaC2 α) [88], ASIC1b (ASIC β , BNaC2 β) [19] and ASIC1b2 (ASIC β 2) [83]; note that ASIC1a is also permeable to Ca²⁺], ASIC2 [termed ASIC2a (MDEG1, BNaC1 α , BNC1 α) [70, 89, 42] and ASIC2b (MDEG2, BNaC1 β) [60]] differ in the first third of the protein. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H⁺-gated currents. A third member, ASIC3 (DRASIC, TNaC1) [87] is one of the most pH-sensitive isoforms (along with ASIC1a) and has the fastest activation and desensitisation kinetics, however can also carry small sustained currents. ASIC4 (SPASIC) evolved as a proton-sensitive channel but seems to have lost this function in mammals [62]. Mammalian ASIC4 does not support a proton-gated channel in heterologous expression systems but is reported to downregulate the expression of ASIC1a and ASIC3 [1, 47, 35, 58, 24]. ASICs channels are primarily expressed in central (ASIC1a, -2a, 2b and -4) and peripheral neurons including nociceptors (ASIC1-3) where they participate in neuronal sensitivity to acidosis. Humans express, in contrast to rodents, ASIC3 also in the brain [28]. ASICs have also been detected in photoreceptors and retinal cells (ASIC1-3), cochlear hair cells (ASIC1b), testis (hASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC1a and -3), urothelial cells, adipose cells (ASIC3), vascular smooth muscle cells (ASIC1-3), immune cells (ASIC1,-3 and -4) and bone (ASIC1-3) (ASIC distribution is reviewed in [59, 29, 46]). A neurotransmitter-like function of protons has been suggested, involving postsynaptically located ASICs of the CNS in functions such as learning and fear perception [36, 54, 104] and of the PNS in mechanoreceptor-neurite transmission [98, 97]. ASIC activation also contributes to cell damage in focal ischemia [95, 73] and autoimmune inflammation (arthritis and multiple sclerosis) [41, 96], as well as neuron activation during seizures and pain [93, 30, 31, 13, 33]. Heterologously expressed heteromultimers form ion channels with differences in kinetics, ion selectivity, pH- sensitivity and sensitivity to blockers that resemble some of the native proton activated currents recorded from neurones [60, 5, 39, 11]. In general, the known small molecule inhibitors of ASICs are non-selective or partially selective, whereas the venom peptide inhibitors have substantially higher selectivity and potency. Several clinically used drugs are known to inhibit ASICs, however they are generally more potent at other targets (*e.g.* [amiloride](#) at ENaCs, [ibuprofen](#) at COX enzymes) [72, 67]. The information in the tables below are for the effects of inhibitors on homomeric channels, for information of known effects on heteromeric channels see the comments below.

Contents

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Database links

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

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=118>

Channels and Subunits

ASIC1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=684>

ASIC2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=685>

ASIC3

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=686>

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