

Acid-sensing Ion Channels in Sensory Perception*

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Acid-activated currents blocked by amiloride have been reported for a long time in most neurons of the mammalian brain as well as in sensory neurons (1). A decade ago, Waldmann and colleagues (2) were the first to clone the ion channels underlying these currents, which have been called acid-sensing ion channels (ASICs).² ASICs are neuronal voltage-insensitive cationic channels activated by extracellular protons. They belong to the ENaC/DEG (epithelial amiloride-sensitive Na⁺ channel and degenerin) family of ion channels (3). ASICs share the same overall structure with other members of this family, which is characterized by two hydrophobic transmembrane regions flanking a large extracellular domain representing more than 50% of the protein and comprising many conserved cysteines (Fig. 1). Functional ASICs probably assemble as tetramers, as proposed for two other channels of the ENaC/DEG family, *i.e.* ENaC and FaNaC (the invertebrate FMRF-amide-activated Na⁺ channel). The ASIC family in mammals (ASICs) have also been cloned from toadfish, lamprey, shark, and zebrafish) comprises four different genes encoding seven isoforms (4, 5) (Fig. 1). ASICs are widely expressed in neurons of both the central and the peripheral nervous system but have also been detected in non-neuronal tissues including testis (human ASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC3), and bone (ASIC1–3) (Table 1).

ASICs Are Extracellular pH Sensors

The only known activator of ASICs is extracellular proton. ASIC1b2 and ASIC2b are not activated by acidic pH on their own but are able to associate with other isoforms to modulate their properties (Table 1). ASIC4 has a particular status because it is not activated by proton and remains so far the least understood isoform. ASICs are voltage-independent, low conductance channels that mainly conduct Na⁺ ($g_{\text{Na}} \sim 10\text{--}15$ picosiemens). ASIC1a has the unique property among ASICs to be permeable to Ca²⁺ in its homomeric form, providing a novel pathway for Ca²⁺ entry into neurons. Extracellular Ca²⁺ also

regulates these channels with a dual inhibitory and stimulatory effect. It has been proposed for ASIC3 that H⁺ ions would activate the channel by displacing Ca²⁺ from a high affinity binding site involved in the Ca²⁺ block and located on the extracellular side of the open pore (6). However, this model does not fully explain the activation of other ASICs by protons as shown for ASIC1a. The sensitivity to external protons, the activation and inactivation kinetics, and the pharmacology vary according to the ASIC subtypes and the subunit composition of the channel complex, with $\text{pH}_{0.5}$ for activation ranging from 4.0 to 6.8 and activation thresholds as high as pH 7.2 (Table 1). Most ASICs are therefore activated by pH variations in the physiological range. Protons trigger a transient inward current that desensitizes rapidly (within seconds, Fig. 1). As a result, the properties of ASICs make these channels more suitable to sense dynamic pH fluctuations, but as discussed below they also have the capacity to respond to prolonged or slow acidification.

Roles in Nociception

Almost all ASIC isoforms are present in primary sensory neurons of the trigeminal, vagal, and dorsal root ganglia. ASIC1, ASIC2, and ASIC3 are significantly expressed in the small and medium nociceptive sensory neurons that are able to detect noxious chemical, thermal, and high threshold mechanical stimuli. ASIC2 and ASIC3 are also expressed in large neurons that mostly correspond to low threshold mechanoreceptors (see below). ASIC proteins have been detected in the soma and in the peripheral nerve endings of DRG neurons. The presence of certain ASICs (*e.g.* ASIC1a) on central projections in the dorsal horn of the spinal cord is less clear. Activation of ASICs by protons can depolarize the neurons and generate action potentials. A decrease in pH has been associated with non-adapting pain in human volunteers (7), and the cutaneous acid-induced pain elicited by moderate pH (up to pH 6.0) appears to be largely mediated by ASICs (8, 9). Pain associated with more acidic pH also involves the capsaicin receptor TRPV1, which participates in the DRG response to low range pH (below pH 6.0). ASICs have therefore been proposed to be involved in the perception of pain in conditions associated with tissue acidosis such as ischemia, inflammation, tumors, or lesions. All these situations are associated with prolonged acidification, raising the question of the activation of these channels by slow and/or prolonged acidosis. In fact, ASIC3-containing channels display in addition to the transient current a sustained component that does not inactivate while the pH remains acidic (Fig. 1). This sustained current involves different mechanisms depending on the extent of pH change. It results from the window of overlap between inactivation and activation of the transient current for small extracellular acidification (between pH 7.3 and 6.7) (10) but seems to be independent of the peak current for more acidic pH. The fast reactivation of certain ASICs could also lead to their activation if oscillations of the extracellular pH occur (*e.g.* waves of acidification).

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² The abbreviations used are: ASIC, acid-sensing ion channel; DRG, dorsal root ganglion; ENaC/DEG, epithelial amiloride-sensitive Na⁺ channels and degenerins; TRPV1, transient receptor potential vanilloid 1; CaMKII, calmodulin-dependent protein kinase II; NPAF, neuropeptide AF; NPFF, neuropeptide FF; NPSF, neuropeptide SF.

ASIC3 thus appears as a good candidate for perception of non-adapting pain caused by acids and for modulation of nociceptive neuron excitability by low pH. In cardiac afferents, ASIC3 has been proposed to be the sensor of myocardial acidity that triggers angina during cardiac ischemia (11). Interestingly, lactate and arachidonic acid, both released during ischemia, up-modulate ASIC1 and ASIC3. Data from the knock-out mouse support a role for ASIC3 but not ASIC1 in the sensing of tissue acidosis in muscle

in models of secondary mechanical hyperalgesia induced by inflammation or by repeated acid injection into the muscle (12, 13). Chronic inflammation actually induces the expression of most ASICs at a transcriptional level (14), and the ASIC3 current is potentiated by pro-inflammatory mediators such as serotonin, bradykinin, and arachidonic acid, suggesting a contribution of ASICs to the peripheral sensitization of nociceptors (Fig. 2). However, the available data obtained by gene inactivation and transgenic expression of a dominant-negative subunit in mice do not allow definite conclusions to be drawn concerning the precise roles of ASIC3 in acidic pain sensing and more generally in nociception (15–17). For instance, data in mice models suggest an increased sensitivity to some painful stimuli in the absence of ASIC3. It is interesting to note that the phenotypes observed might be influenced by specific local environments (e.g. expression of different ASIC-associated proteins), differences between the territories innervated (e.g. the ASIC3 protein is more expressed in muscle *versus* skin nociceptors in rat (18)), or species differences (e.g. the prevalence of ASIC-like currents is smaller in mouse *versus* rat skin nociceptors (19)).

A direct participation of central ASICs in pain processing could make the analysis even more complex. The expression of ASIC1a and ASIC2 in neurons of the spinal cord, where they are up-regulated by peripheral inflammation (20), may, for instance, contribute to the transmission and modulation of noxious information and participate in central sensitization associated with prolonged pain. Interestingly, this process shares significant similarities with hippocampal long term potentiation, which is impaired in ASIC1-inactivated mice (21). These mice also have defects in hippocampus-dependent spatial learning, cerebellum-dependent eye-blink conditioning, and amygdala-dependent fear conditioning (4). A large body of evidence suggests the presence of ASIC1a and probably ASIC2a in the synaptic membranes of central neurons (4). It has been

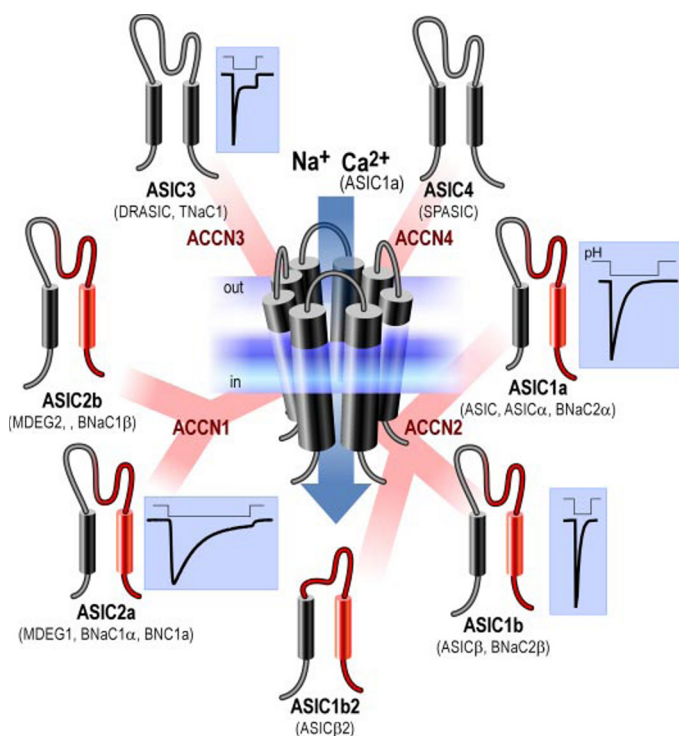


FIGURE 1. **The ASIC family of ion channels.** Regions shared by the splice variants are highlighted in red. Typical current traces of homomeric channels are shown.

TABLE I

Properties of ASIC channels

n/a, not applicable.

Isoform	Tissue distribution	pH _{0.5 act}	Blockers	Modulators	Physiology	Pathology
ASIC1a	PNS, brain, spinal cord, retina, taste cells, bone	6.2–6.8	amiloride, NSAIDs, A-317567, PcTx1	RFa peptides, lactate, spermine, AA, proteases	visceral mechanoperception, visual transduction, synaptic plasticity, fear conditioning, nociception? (PNS and CNS)	upregulated by inflammation in DRG and spinal cord, tissue damage after brain ischemia, downregulated in a rat model of neuropathic pain, downregulated in a rat model of epilepsy, detected in gliomas
ASIC1b	PNS, taste cells, cochlear hair cells	5.1–6.2	amiloride	PcTx1, spermine, proteases	nociception?	upregulated by inflammation in DRG
ASIC2a	PNS (including specialized mechanoreceptors), brain, spinal cord, retina, cochlear spiral ganglion, taste cells (rat), bone	4.1–5.0	amiloride, A-317567	zinc	ASIC1a modulation in the CNS, visual transduction, cutaneous and visceral mechanoperception, suprathreshold hearing, taste	upregulated by inflammation in spinal cord, protects against light-induced retinal degeneration, upregulated in rat brain during ischemia, detected in gliomas
ASIC2b	PNS, brain, spinal cord, retina, taste cells	n/a	n/a		ASIC2a and ASIC3 modulation	upregulated by inflammation in DRG, downregulated in a rat model of epilepsy
ASIC3	PNS (including specialized mechanoreceptors), taste cells, retina, testis, lung epithelial cells, inner ear, bone	6.2–6.7	amiloride, NSAIDs, A-317567, APETx2	RFa peptides, lactate, AA, amiloride	nociception, cutaneous and visceral mechanoperception, hearing	upregulated by inflammation in DRG, acid sensing and inflammatory and non-inflammatory mechanical hyperalgesia in muscle, possible role in angina
ASIC4	PNS (low), brain, spinal cord, retina, pituitary gland, inner ear	n/a	?	?	?	?

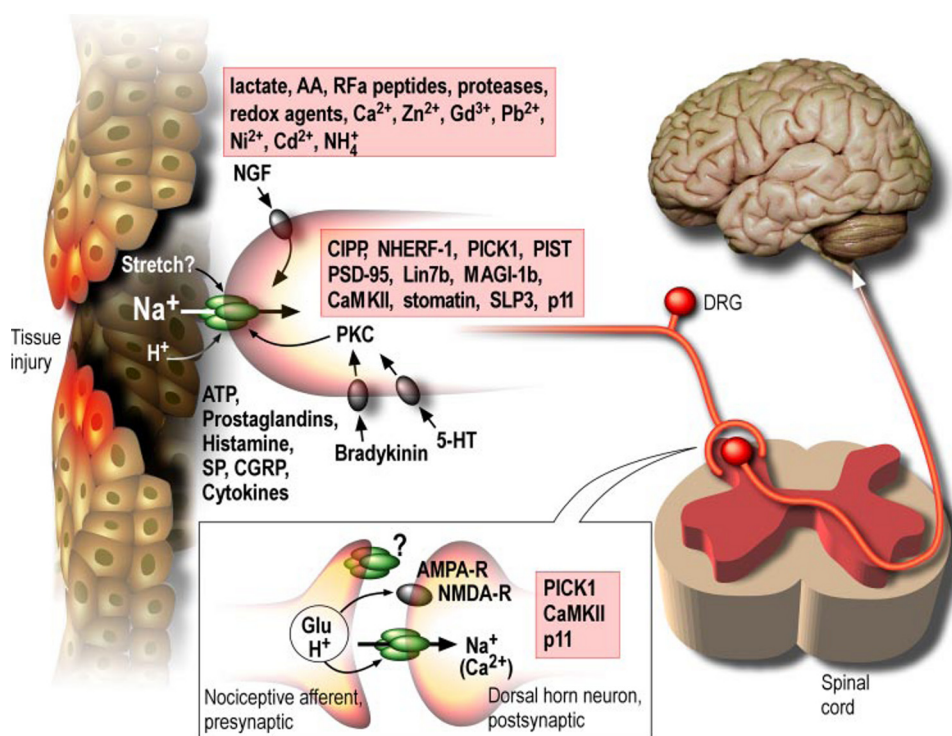


FIGURE 2. **ASICs (green) in primary afferent nociceptors and second order spinal cord neurons.** ASIC3 and ASIC1 are the most important ASICs in the peripheral nervous system and the central nervous system, respectively. Interacting proteins and extracellular modulators are shown. ASIC3 activity is up-regulated by activators of the protein kinase C pathway released during inflammation. Peripheral inflammation also increases the ASIC transcript levels in DRG and spinal cord. ASICs may be present in interneurons and descending fibers in the dorsal horn of the spinal cord (not shown). Synaptically released protons could activate ASICs in the postsynaptic and, possibly, the presynaptic membrane (*inset*). AA, arachidonic acid; NGF, nerve growth factor; PKC, protein kinase C; SP, substance P; CGRP, calcitonin gene-related peptide; 5-HT, 5-hydroxytryptamine or serotonin.

proposed that synaptically released protons may activate ASICs (Fig. 2) although no direct evidence of a participation of these channels in synaptic transmission could be provided so far. This hypothesis is based on the low pH of synaptic vesicles and on the observation that exocytosed protons can modulate synaptic ion channels as shown for the presynaptic Ca^{2+} channel mediating vesicle release in the ribbon synapses of mammalian cone photoreceptors (22). However, it remains to be established if the pH changes in the vicinity of synaptic cleft during chemical transmission in “classical” synapses are compatible with an activation of ASIC channels.

Roles in Mechanotransduction

Several members of the ENaC/DEG family of ion channels have been proposed to participate in mechanosensation, the most famous being the *Caenorhabditis elegans* degenerins (23). ASIC2a and ASIC3 are expressed in mechanoreceptors, including specialized cutaneous mechanosensory structures like Meissner corpuscles, Merkel nerve endings, and palisades of lanceolate nerve endings surrounding the hair shaft (16, 24, 25). Mice with targeted deletion of ASIC2 and ASIC3 were reported to display subtle alterations in both normal (ASIC2 and -3) and painful (ASIC3) cutaneous mechanical sensitivity (16, 25), although knock-out mice for ASIC1 did not. Some sensory modalities are increased whereas other are decreased, depending on the type of mechanoreceptors and on the isoform of ASIC involved. ASIC1, ASIC2, and ASIC3 also contribute to visceral mechanosensation (26, 27), and the con-

sequences of ASIC disruption are, in general, greater for visceral mechanoreceptor function than for cutaneous mechanoreceptors. ASIC1a contributes negatively in all classes of visceral afferents. Disruption of ASIC2 has a mixed effect whereas ASIC3 knock-out mice have a markedly decreased mechanosensitivity in almost all classes of visceral afferents, indicating a clear positive effect (26). Recently, a protein indispensable for the function of a subset of cutaneous mechanoreceptors in mouse, the stomatin-like protein 3 (SLP3), has been shown to associate *in vitro* with ASIC2a, ASIC2b, and ASIC3 and to inhibit the endogenous proton-gated currents in HEK-293 cells and in sensory neurons (28). All these data strongly suggest a participation of ASICs in mechanotransduction. However, a role as direct peripheral mechanoreceptors is not clear regarding the lack of evidence for mechanical gating of these channels (29, 30).

Participation in Other Sensory Modalities

ASICs are expressed in rat and mouse taste receptor cells, and

ASIC2 has been proposed to be a mammalian sour taste receptor (31). However, taste cells from ASIC2 knock-out mice respond normally to acid stimuli (32), and these mice show a normal behavioral response to acid taste stimuli. ASICs are therefore probably not acting as general mammalian sour receptors. Almost all ASICs have also been detected in rodent retina (33–36). pH fluctuations play an important role in the retina, where acidic transients are involved in the fine-tuning of visual perception. ASIC2, which is present both in neurons and photoreceptors, is a negative modulator of rod phototransduction (34), whereas ASIC1a is a positive modulator of cone phototransduction and adaptation (35). Inactivation of the ASIC2 gene in mouse also sensitizes the retina toward light-induced degeneration (34). ASIC1, ASIC2, and ASIC3 are also expressed in the mouse inner ear (37, 38). ASIC2 is mainly expressed in spiral ganglion neurons in the adult cochlea. ASIC2 knock-out mice show no significant hearing loss (29, 38), but ASIC2 contributes to suprathreshold hearing functions (38). ASIC3 knock-out mice have normal hearing at 2 months of age but develop hearing losses in the mild-to-moderate range at 4 months (37).

Modulation by Interacting Proteins

The importance of associated proteins to control the surface expression, the subcellular distribution, and the function of ASICs has become evident in recent years (Fig. 2). ASICs contain a PDZ binding motif at their C termini (type II for ASIC1,

-2, and -4 and type I for ASIC3) and interact with several PDZ-containing proteins. PICK1 (protein interacting with C-kinase 1) co-localizes with ASICs in the nervous system and associates with ASIC1 and ASIC2 (39, 40). PICK1 participates in the protein kinase C up-regulation of ASIC2a and ASIC3 (via its association with the ASIC2b subunit) *in vitro* (41). CIPP (42), NHERF-1 (43), PSD-95, Lin-7b, MAGI-1b, and PIST (44) associate with ASIC3 and modulate the current amplitude in heterologous expression systems by increasing (all the proteins but PSD-95) or decreasing (PSD-95) the surface expression of the channel without important modification of its properties. However, the particularly strong effect of NHERF-1 on the ASIC3-sustained current probably reflects a direct modification of the channel activity (43). Most of these proteins are present in DRG neurons and display some degree of co-localization with ASIC3, suggesting an association *in vivo*. ASICs also bind to non-PDZ proteins. The annexin II light chain p11 is expressed in sensory neurons and brain and interacts with the N terminus of ASIC1a to enhance the cell-surface expression of the channel without altering its properties (45).

The integral membrane protein stomatin is also expressed in sensory neurons and has been shown to associate with ASIC1a, ASIC2a, and ASIC3 *in vitro* and to potentially reduce ASIC3 current and accelerate the rate of desensitization of the ASIC2a, ASIC1a+3, and ASIC2a+3 channels (46). As previously mentioned, SLP3, a stomatin-related protein indispensable for the function of a subset of cutaneous mechanoreceptors in mouse, associates *in vitro* with ASIC2a, ASIC2b, and ASIC3 (28). An association between CaMKII and ASIC1a has been described in brain, which is enhanced by ischemia and leads to an increase of the ASIC1a current by CaMKII phosphorylation (47). The activation of ASIC1a during the metabolic acidosis accompanying experimental stroke has been proposed to contribute to neuronal death associated with brain ischemia (48). An interaction between ASIC3 and CFTR has also been described in airway epithelial cells (49), suggesting a putative unexpected functional link between these channels. The physiological relevance of most of these interactions, however, remains to be clarified.

Modulation by RF-amide Neuropeptides

FMRF-amide and structurally related peptides lead to a potentiation of the H⁺-gated currents ($EC_{50} \sim 10\text{--}50\text{ }\mu\text{M}$ for FMRF-amide; threshold $\sim 1\text{ }\mu\text{M}$) by increasing the peak amplitude and/or slowing inactivation of ASIC1 and ASIC3 but not ASIC2a (5, 50). The effect seems to be direct on the channel. ASIC3 is the major contributor to the response of DRG neurons (51). FMRF-amide itself is not present in mammals, but NPFF, NPAF, and NPSF are largely expressed in the central nervous system with a high level in the spinal cord where the NPFF expression is enhanced during chronic inflammation. NPFF has also been detected in small and intermediate sized DRG neurons. The modulation of ASICs by endogenous RF-amide peptides has therefore been proposed to play a role in the response to noxious acidosis. However, the modulation of ASICs requires FMRF-amide addition at pH 7.4, *i.e.* when the channel is closed (50), raising questions about how these peptides could affect ASICs *in vivo*.

Pharmacology

ASICs are reversibly blocked by amiloride and its derivatives benzamil and ethylisopropylamiloride at micromolar concentration levels. A paradoxical enhancing effect of amiloride has also been described on the sustained component of ASIC3 (10). ASICs are directly inhibited by therapeutic concentrations of non-steroidal anti-inflammatory drugs ($IC_{50} \sim 92\text{--}350\text{ }\mu\text{M}$) (14). Two toxins that specifically and efficiently block ASICs *in vitro* and *in vivo* have been isolated (52). The tarantula toxin PcTx1 blocks the ASIC1a homomeric channel ($IC_{50} \sim 0.9\text{ nM}$), whereas the sea anemone toxin APETx2 blocks homomeric ASIC3 ($IC_{50} \sim 63\text{ nM}$) as well as ASIC3-containing heteromeric channels ($IC_{50} \sim 0.1\text{--}2\text{ }\mu\text{M}$). PcTx1 also interacts with ASIC1b but does not inhibit the channel and rather promotes its opening (53). A small molecule blocker of ASIC currents (A-317567) was described recently (IC_{50} between 2 and 30 μM on native ASICs in DRG neurons). Interestingly, this compound has an analgesic effect in animal models of inflammatory and post-operative pain (54), confirming the positive role of ASICs in pain associated with these pathological conditions.

Concluding Remarks

Since their discovery a decade ago, ASICs have been shown to participate in a number of different sensory processes. Activation of ASIC3 in sensory neurons by the extracellular acidification induced in conditions such as ischemia, inflammation, tumors, or injury has been proposed to contribute to the generation of pain. TRPV1, another important acid-sensitive cationic channel in DRG neurons, is activated by lower pH values and displays limited overlap of expression with ASIC3 among nociceptors, suggesting complementary roles for these channels in nociception linked to acidosis. ASIC1 and ASIC2 may also contribute to pain processing in central neurons of the spinal cord, in part through a possible role at the synapse. The participation of ASICs in nociception is, however, probably more complex than initially thought and requires further clarification. ASICs also participate in the mechanosensory function, but the molecular basis remains largely unknown. ASICs on their own are not directly activated by mechanical force, but it has been proposed, based on available data for degenerins in *C. elegans*, that ASIC2 and ASIC3 could be able to transduce mechanical signals either directly (with the help of additional proteins) or indirectly. Interestingly, the contribution to mechanotransduction might be independent of pH sensing. This raises the question of the existence of other stimuli than protons for these channels as ASIC4 for instance is not sensitive to pH. ASICs are present in the retina, taste cells, and inner ear. They are important modulators of the visual transduction and have more subtle roles in taste and hearing.

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