Acid-sensing ion channels (ASICs): therapeutic targets for neurological diseases and their regulation

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Extracellular acidification occurs not only in pathological conditions such as inflammation and brain ischemia, but also in normal physiological conditions such as synaptic transmission. Acid-sensing ion channels (ASICs) can detect a broad range of physiological pH changes during pathological and synaptic cellular activities. ASICs are voltage-independent, proton-gated cation channels widely expressed throughout the central and peripheral nervous system. Activation of ASICs is involved in pain perception, synaptic plasticity, learning and memory, fear, ischemic neuronal injury, seizure termination, neuronal degeneration, and mechanosensation. Therefore, ASICs emerge as potential therapeutic targets for manipulating pain and neurological diseases. The activity of these channels can be regulated by many factors such as lactate, Zn²⁺, and Phe-Met-Arg-Phe amide (FMRFamide)-like neuropeptides by interacting with the channel’s large extracellular loop. ASICs are also modulated by G protein-coupled receptors such as CB₁ cannabinoid receptors and 5-HT₂. This review focuses on the physiological roles of ASICs and the molecular mechanisms by which these channels are regulated.

INTRODUCTION

Tissue acidosis is a common feature in pain-generating pathological conditions such as inflammation, ischemic stroke, infections, and cancer. Tissue injury leads to the release of inflammatory mediators, including substance P, bradykinin, histamine, 5-hydroxytryptamin (5-HT or serotonin), glutamate, ATP, interleukin-1, nerve growth factor (NGF), and proton (1). Application of an acidic solution on human skin induces pain (2, 3). It is well known that the extracellular pH levels drop to 5.4 in acute inflammation (4). Severe ischemia also induces the reduction of pH to 6.3 or even lower (5, 6). In the central nervous system (CNS), the pH of the synaptic cleft can fall during neurotransmission, as the synaptic vesicles are acidic (7, 8). Recently, local pH changes during normal brain activity were detected in mouse and human brains, although the extent of pH fluctuations still needs to be clarified (9).

Acid-sensing ion channels (ASICs) play a critical role in the perception of a wide range of pH changes in conditions related to tissue acidosis. ASICs are voltage-insensitive, proton-gated cation channels which are activated by extracellular pH fall. These channels are expressed throughout the central and peripheral nervous system. ASICs belong to the ENaC (Epithelial Na⁺ Channel)/DEG (Dегенерин)/ASIC (Acid-sensing ion channel) superfamily of ion channels. The members of ENaC/DEG/ASIC (EDA) superfamily share the same topology, consisting of two hydrophobic transmembrane domains, a large cysteine-rich extracellular loop, and short intracellular N- and C-termini (Fig. 1A).

Four genes, including ACCN2, ACCN1, ACCN3, and ACCN4, encode at least six different ASIC subunits, ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4 (Table 1). ASIC1a and ASIC1b are protein products of alternative splicing from the ACCN2 gene, and ASIC2a and ASIC2b are products of the alternative spliced ACCN1 gene. The CNS primarily expresses ASIC1a, ASIC2a, and ASIC2b, while all subunits are expressed in the peripheral nervous system (PNS) (6). In 2007, Eric Gouaux et al. first showed the tridimensional structure of a chicken ASIC1 channel (10). They found that three subunits are required to form a functional channel (Fig. 1B). All ASIC subunits assemble to form homo- or hetero-trimeric channels, except for ASIC2b and ASIC4. ASIC2b and ASIC4 may only contribute to forming heteromeric channels with other ASIC subunits, and modulate the expression or properties of the channels (11, 12). Although the canonical ligand for ASICs is the proton, the large extracellular loop of these channels allowed the possibility of the existence of other non-proton ligands (6, 7). Some examples include 2-hydroxy-4-methylquinazoline (GMQ) (13) and MitTx from the venom of the Texas coral snake (14) (Table 1). Moreover, amiloride, a non-specific blocker of ASICs, paradoxically triggered the sustained currents of ASIC3 at normal pH through binding to the non-proton ligand sensing domain of channels (15). Therefore, one possibility is that homomeric ASIC2b and ho-
Fig. 1. ASIC subunits and activation of ASICs by extracellular acidification. (A) Each subunit has two hydrophobic transmembrane domains, a large cysteine-rich extracellular loop, and short intracellular N- and C-termini. (B) Three subunits assemble to form a functional homo- or hetero-trimeric channel. (C) ASIC currents evoked by extracellular pH fall in tsA cells. ASIC1a, ASIC2a, and ASIC3 were activated by application of pH 6.0, 4.5, and 5.0 solution, respectively. The membrane potential was clamped to −70 mV. The dashed line indicates zero current level.

Table 1. Properties, inhibitors, and regulators of ASICs

| Gene | Protein Alternative name | pH0.5 activation | Non-proton ligand | Inhibitor | Regulator | Distribution | Physiology |
|------|--------------------------|------------------|------------------|-----------|-----------|-------------|------------|
| ACCN2 | ASIC1a | 6.2-6.8 (6, 11, 17, 100-104) | MitTx (14) | Amiloride (102), Mambalgin (28), PeTx1 (16, 24), A-317567 (27), NSAIDs (26), Pb2+ (30), Ni2+ (31), Ca2+ (33), Zn2+ (34) | GMQ (43), Dynorphin A (39), Big dynorphin (39), FMRFamide-like neuropeptides (41, 42), Lactate (36), Spermine (38), Nitric oxide (40) | PNS/CNS | In the CNS: Synaptic plasticity (47), Learning and memory (47) in the CNS: Fear (44), Central sensitization (104), PNS: Visual transduction (105) |
| | ASIC2b | MDEG2, BNaC2β | 3.8-5.0 (6, 11, 100, 103, 104) | MitTx (14) | Amiloride (102), A-317567 (27), Ca2+ (33), Cysteine oxidase (40) | Zn2+ (35), Nitric oxide (40) | PNS/CNS | In the CNS: Visual transduction (107), PNS: Mechanosensation (65), Perception of sour taste (108) |
| | ACCN3 | ASIC1a | 6.2-6.7 (6, 11, 100, 101, 103) | GMQ (13), MitTx (14), Amiloride (15) | A-317567 (27), NSAIDs (26), Cysteine oxidase (31), Hypertonicity (62) | FMRFamide-like neuropeptides (41, 42), Lactate (36), Arachidonic acid (37), Spermine (38), Nitric oxide (40) | PNS | In the CNS: Acute and primary inflammatory pain (62), Cardiac pain (101), Secondary mechanical hyperalgesia (60) |
| | ACCN4 | ASIC4 | N/A | | | | PNS | |

memonic ASIC4 have their own specific ligands (6).

**BIOPHYSICAL PROPERTIES OF ASICs**

All ASIC subunits have different pH sensitivities that enable them to detect a wide range of physiological pH. ASIC1a and ASIC3 are sensitive to slight extracellular acidosis, whereas ASIC2a requires more acidic pH value for activation. The pH values for half maximal activation (pH0.5 activation) of each subunit are described in Table 1. A slight discrepancy is apparent in the pH0.5 activation values depending on different studies. This discrepancy may be due to the different species and heterologous expression systems used by the various researchers. In addition, each subunit shows different biophysical properties in kinetics and ion selectivity. ASICs are mainly permeable to Na+ ion. However, ASIC1 homomeric channels, human ASIC1b homomeric channels, and ASIC1a/2b heteromeric channels are also permeable to Ca2+ ion (6, 16, 17). Activation of ASIC1a increased intracellular Ca2+ concentration in hippocampal, cortical, and dorsal root ganglion (DRG) neurons (18-20). Although Ca2+ permeability of ASICs is very low, the increase of intracellular Ca2+ through ASICs can induce neuronal injury during brain ischemia accompanied by prolonged acidosis (19, 21, 22).

A rapid drop in the extracellular pH from 7.4 to 6.0 for 10 seconds evoked transient ASIC1a inward currents that inactivated within seconds (Fig. 1C). ASIC2a homomers were activated by more acidic pH values, and displayed slow activat-
ing and slow inactivating currents. ASIC3 homomers have bi-
phasic currents, a rapidly activating transient current followed
by a sustained current that does not fully inactivate during pro-
longed acidosis. The increase in cation conductance that allows
fluxes of K\textsuperscript{+}, Cs\textsuperscript{+}, and Na\textsuperscript{+} ions contributes to the sus-
tained currents of ASIC3. This plays a role in the perception of
non-adapting pain. ASIC1a homomeric channels have the unique
property of tachyphylaxis. Tachyphylaxis means that the cur-
cent amplitude is gradually reduced to successive acid
stimuli, even though the time interval between repetitive acid
stimulations is sufficient for recovery from desensitization (23).
Tachyphylaxis occurs due to proton permeation through
ASIC1a channels, and it is attenuated by the extracellular Ca\textsuperscript{2+}
ion (23).

A number of pharmacological tools can be used for inves-
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vation during multiple sclerosis. Multiple sclerosis, which is an autoimmune inflammatory disease accompanying tissue acidosis in inflammatory lesions, leads to axonal degeneration in the CNS (58). Excessive accumulation of Ca\(^{2+}\) ion through ASIC1a activation during multiple sclerosis contributes to induce axonal degeneration. Disrupting the ASIC1a gene attenuates axonal degeneration during multiple sclerosis. Amiloride, a non-specific blocker of ASICs, has also displayed neuroprotective effects against axonal degeneration (58). These results suggest that ASIC1a could be an effective neuroprotective target for the treatment of neuronal degeneration.

In the PNS

Nociception: Noxious stimuli is mainly carried by the thin nerve fibers, such as thin myelinated Aβ-fibers and unmyelinated C-fibers, and the neurons participating in nociception are mostly small (59). Almost all ASIC subunits are abundantly expressed in the small and medium nociceptive sensory neurons, which are responsible for pain perception. Among the ASIC subunits, ASIC3, which is the most essential for pain, is specifically localized in nociceptive fibers innervating the skeletal and cardiac muscles, joints, and bone (1, 11, 60). In these tissues, anaerobic metabolism during severe exercise or tissue injury induces the accumulation of lactate and protons, resulting in the activation of nociceptors. In addition, inflammation and tissue injury increase the expression levels of ASIC1a, ASIC2b, and ASIC3 mRNA in DRG neurons (26). Activation of ASICs, which is important for sensitizing cutaneous nociceptors, is upregulated by inflammatory mediators such as bradykinin, arachidonic acid (37, 61), and nitric oxide (40). ASIC3-like currents were activated by tissue acidification in rat cutaneous sensory neurons, and acidosis-induced pain was suppressed by APETx2, a specific blocker of ASIC3, or knockdown of ASIC3 with siRNA (62).

Mechanosensation: ASICs have also been found in large mechanosensitive neurons (mechanoreceptors), which are responsible for the perception of mechanical stimuli or proprioception. It was initially proposed that ASICs have a role in mechanotransduction, since their phylogenetic homologues in the nematode *Caenorhabditis elegans* (C. elegans) (the mechanosensory abnormality 4- or 10- (MEC-4/MEC-10) proteins, which are expressed in touch receptor neurons in C. elegans), is important for touch sensation (63). ASIC subunits are localized in specialized nerve endings of skin and muscle spindles, and cutaneous mechanosensory structures such as Meissner corpuscles, Merkel cell neurite complexes, and Pacinian corpuscles (11, 64). Therefore, ASICs have been considered to participate in neurosensory mechanotransduction, although the role of ASICs in mechanosensation is still controversial. The role of ASICs in mechanotransduction has been investigated in behavioral studies by using mice with the targeted gene deleted. Disrupting the ASIC2 gene significantly reduced the firing rates of Aβ-fibers in response to low-threshold mechanical stimuli. Thus, ASIC2 was proposed to be involved in the perception of light touch (65). However, disrupting the ASIC2 gene had no effect on the current amplitude or kinetics in response to mechanical stimuli in large DRG neurons (66). These conflicting results could be generated from the compensatory effects of multiple mechanosensitive ion channels (e.g. TRP channels) or receptors in ASIC knockout mice (64). The role of ASICs in mechanosensation remains elusive.

**REGULATION OF ASICs**

Lactate: During brain ischemia, the concentration of lactate has been reported to increase up to 15 mM from the resting level of below 1 mM (36). It is well known that the buildup of lactic acid accompanying acidosis contributes to neuronal injury. Lactate significantly potentiated the amplitude of ASIC currents in rat sensory neurons innervating the heart (36). Potentiation of ASICs by lactate was also observed in excised outside-out membrane patches, indicating that the effect of lactate is not mediated by receptor activation or signaling cascade (36). One hypothesis suggested that lactate may potentiate ASIC currents by chelating extracellular divalent ions such as Ca\(^{2+}\) and Mg\(^{2+}\) ions, which in turn modulate the activities of membrane receptors and ion channels (49). The effect of lactate on ASICs was mimicked by reducing the concentration of Ca\(^{2+}\) and Mg\(^{2+}\) ions in the extracellular solution, even without treating lactate. Moreover, potentiation of ASIC currents by lactate was diminished by increasing the concentration of divalent ions (36). These results suggest that lactate potentiates the activity of ASICs by chelating extracellular divalent ions.

*Arachidonic acid:* Arachidonic acid (AA), a polyunsaturated fatty acid with a 20-carbon chain and four double bonds, is involved in cellular signaling activities as a lipid second messenger (37, 61). AA is liberated from membrane phospholipids by the activation of phospholipase A\(_2\) (PLA\(_2\)). The increase of intracellular Ca\(^{2+}\) concentration during brain ischemia leads to the activation of PLA\(_2\), resulting in increased production of AA. AA is also one of the proinflammatory factors playing a critical role in pathological conditions such as inflammation and neurological disorders including ischemic neuronal injury (67). Moreover, AA has been known to regulate the functions of various types of potassium channels, L-type and N-type Ca\(^{2+}\) channels (68), and transient receptor potential (TRP) channels (69). The activity of ASICs is also regulated by AA (37, 61) (Fig. 2). The effects of AA can be mediated either by the direct action of AA or by the AA metabolites (70). However, inhibition of AA metabolism has no significant effects on AA-mediated potentiation of ASIC currents (37). Moreover, the regulation of ASICs by AA was not attributed to cell swelling or membrane stretch, both of which were induced by the bath application of hypotonic solution (37). These results suggest that AA increases the activity of ASICs by a direct action, and not by AA metabolism or membrane stretch.

FMRFamide-like neuropeptides: FMRFamide and structurally re-
ASICs are regulated by signal transduction pathways. 5-HT$_2$ receptors activate PLC\(\beta\) through the heterotrimeric G$_{q/11}$ proteins. PLC\(\beta\) hydrolyzes membrane PI(4,5)P$_2$ to two second messengers, IP$_3$ and DAG. IP$_3$ releases Ca$^{2+}$ from the internal Ca$^{2+}$ stores in ER. DAG activates PKC, which enhances the activity of ASICs by interaction with PICK1. CB$_1$ receptors inhibit ASICs via suppression of AC/cAMP pathway. AC is inhibited by the heterotrimeric G$_{i/o}$ proteins, and inhibition of AC leads to reduction of the cAMP levels, which in turn inhibits binding of PKA to AKAP150. TrkB activates PI3-K, and enhances the membrane expression of ASICs through Akt proteins. Arachidonic acid directly potentiates the amplitude of ASIC currents. Abbreviations: ASICs: Acid-sensing ion channels, 5-HT$_2$R: 5-HT$_2$ receptor, CB$_1$R: Cannabinoid-1 receptor, PLC\(\beta\): phospholipase C\(\beta\), PI(4,5)P$_2$: phosphatidylinositol 4,5-bisphosphate, PI(3,4,5)P$_3$: phosphatidylinositol 3,4,5-trisphosphate, IP$_3$: inositol 1,4,5-trisphosphate, IP$_3$R: inositol 1,4,5-trisphosphate receptor, DAG: diacylglycerol, PKC: protein kinase C, PICK1: protein interacting with C-kinase, ER: endoplasmic reticulum, AC: adenylyl cyclase, cAMP: cyclic AMP, PKA: protein kinase A, AKAP150: A-kinase anchoring protein 150, TrkB: tropomyosin-related kinase B, BDNF: brain-derived neurotrophic factor, PI3-K: phosphatidylinositol 3-kinase, Akt: protein kinase B, AA: arachidonic acid.

Fig. 2. ASICs are regulated by signal transduction pathways. 5-HT$_2$ receptors activate PLC\(\beta\) through the heterotrimeric G$_{q/11}$ proteins. PLC\(\beta\) hydrolyzes membrane PI(4,5)P$_2$ to two second messengers, IP$_3$ and DAG. IP$_3$ releases Ca$^{2+}$ from the internal Ca$^{2+}$ stores in ER. DAG activates PKC, which enhances the activity of ASICs by interaction with PICK1. CB$_1$ receptors inhibit ASICs via suppression of AC/cAMP pathway. AC is inhibited by the heterotrimeric G$_{i/o}$ proteins, and inhibition of AC leads to reduction of the cAMP levels, which in turn inhibits binding of PKA to AKAP150. TrkB activates PI3-K, and enhances the membrane expression of ASICs through Akt proteins. Arachidonic acid directly potentiates the amplitude of ASIC currents. Abbreviations: ASICs: Acid-sensing ion channels, 5-HT$_2$R: 5-HT$_2$ receptor, CB$_1$R: Cannabinoid-1 receptor, PLC\(\beta\): phospholipase C\(\beta\), PI(4,5)P$_2$: phosphatidylinositol 4,5-bisphosphate, PI(3,4,5)P$_3$: phosphatidylinositol 3,4,5-trisphosphate, IP$_3$: inositol 1,4,5-trisphosphate, IP$_3$R: inositol 1,4,5-trisphosphate receptor, DAG: diacylglycerol, PKC: protein kinase C, PICK1: protein interacting with C-kinase, ER: endoplasmic reticulum, AC: adenylyl cyclase, cAMP: cyclic AMP, PKA: protein kinase A, AKAP150: A-kinase anchoring protein 150, TrkB: tropomyosin-related kinase B, BDNF: brain-derived neurotrophic factor, PI3-K: phosphatidylinositol 3-kinase, Akt: protein kinase B, AA: arachidonic acid.
to phosphoinositides. Supplementing PI(4,5)P₂ analogue in the pipette solution had no effects on the activity of ASIC1a (86). Furthermore, activation of muscarinic receptors that hydrolyze endogenous membrane PI(4,5)P₂ did not affect the amplitude of ASIC1a currents (86). This result conflicts with the previous study. The bath application of muscarinic receptor agonists strongly inhibited the amplitude of ASIC1a currents in Chinese hamster ovary (CHO) cells (87). Therefore, PI(4,5)P₂ sensitivity of ASIC1a still needs to be clarified.

**Phosphatidylinositol 3-kinase:** Activation of tropomyosin-related kinase B (TrkB) by brain-derived neurotrophic factor (BDNF) induces pain hypersensitivity, although the underlying mechanism is not understood. A recent study found that TrkB activation increases the surface expression and the activity of ASIC1a via the phosphatidylinositol 3-kinase (PI3-K)/protein kinase B (PKB or Akt) pathway (88) (Fig. 2). BDNF-induced forward trafficking of ASIC1a is crucial for secondary mechanical hyperalgesia (88). Phosphorylation of Serine-23 at the N-terminus of ASIC1a is critical for BDNF-induced ASIC1a trafficking. Enhancement of ASIC1a surface expression by BDNF was abolished by the mutation of Serine-23 of ASIC1a to alanine (88). Therefore, ASIC1a could be a potent analgesic target for pain hypersensitivity.

**MODULATION OF ASICs BY GPCRs**

**G<sub>qi</sub> protein-coupled receptors**

**Cannabinoid-1 receptor:** Cannabinoid-1 (CB₁) receptors, which modulate nociceptive pain, are highly expressed in nociceptive primary sensory neurons (89, 90). Activation of CB₁ receptors, which belong to the G<sub>qi</sub> protein-coupled receptor family, induces the inhibition of adenylyl cyclase (AC) leading to the reduction of cyclic AMP (cAMP) level. WIN55,212-2, an agonist of CB₁ receptors reversibly inhibited ASIC currents in rat primary sensory neurons (91). Furthermore, the mean number of action potentials induced by acid stimulus decreased following activation of CB₁ receptors (91). Suppression of ASIC currents by CB₁ receptors was abolished by the application of cAMP analogue or the AC activator forskolin (91). These results indicate that analgesic effects of cannabinoids are mediated by the inhibition of AC/cAMP-dependent pathway through CB₁ receptors. A-kinase anchoring protein 150 (AKAP150) has been reported to be co-localized with ASIC1a and ASIC2a in rat cortical neurons, and regulates the activity of these channels. It has also been reported that the inhibition of protein kinase A (PKA) binding to AKAP150 reduces the amplitude of ASIC currents, suggesting that AKAP150 mediates the PKA-dependent phosphorylation of ASICs (92). Therefore, the reduction of PKA activity may be involved in the CB₁ receptor-mediated analgesic effects of cannabinoids (Fig. 2).

**G<sub>q/11</sub> protein-coupled receptors**

**5-HT<sub>1A</sub> receptor:** 5-HT (or serotonin), an important proinflammatory mediator, is released from platelets, mast cells, and endothelial cells during tissue injury accompanied by inflammation. 5-HT establishes pain sensation and hyperalgesia through sensitizing nociceptive afferents (93). Proinflammatory mediators such as 5-HT, bradykinin, NGF, and interleukin-1 are known to enhance the activity and the expression levels of ASICs. A mixture of these mediators enhanced the amplitude of ASIC-like currents and the number of neurons expressing ASICs in rat DRG neurons (94). Fourteen mammalian 5-HT receptor subtypes are divided into 7 subgroups of 5-HT receptors (5-HT<sub>1-7</sub>). 5-HT<sub>1A</sub>-induced hyperalgesia is mediated by 5-HT<sub>1A</sub> receptor subtype, which belongs to the G<sub>q/11</sub> protein-coupled receptor family. 5-HT<sub>1A</sub> agonists, excluding the 5-HT<sub>1D</sub> receptor agonists, significantly induced hyperalgesia (95). Another study supported the involvement of 5-HT<sub>1A</sub> receptors in 5-HT-induced hyperalgesia, which was inhibited by 5-HT<sub>1D</sub> antagonists in DRG neurons (96). Moreover, activation of 5-HT<sub>2</sub> receptors potentiated the activity of ASICs in rat DRG neurons via protein kinase C (PKC)-dependent signaling pathways (93). ASICs have a PDZ-binding domain at their C-termini, and interact with PDZ-containing proteins. The combined proteins regulate the surface expression and the activity of ASICs (97). Protein interacting with C-kinase (PICK1), which was shown to co-localize with ASICs, directly interacts with ASICs through the PDZ-binding domain (98). Therefore, the PKC signaling pathway may be involved in the 5-HT<sub>2</sub> receptor-mediated potentiation of ASICs (Fig. 2).

**Neurokinin-1 receptor:** Activation of neurokinin-1 (NK<sub>1</sub>) receptors by substance P, which is released from nociceptive nerve fibers, has an antinoceptive effect in acid-induced chronic muscle pain (99). Mice, lacking substance P and neurokinin A production by disrupting the tachykinin 1 (Tac1) gene or injection of a selective NK<sub>1</sub> receptor antagonist, displayed persistent long-lasting hyperalgesia (99). Substance P significantly reduced ASIC3-mediated currents in muscle afferent DRG neurons. The inhibitory effect of substance P was restrictedly observed in neurons expressing ASIC3. While NK<sub>1</sub> receptor is a G<sub>q/11</sub> protein-coupled receptor, the inhibition of ASIC3-mediated currents by substance P is mediated by the unconventional G protein-independent, tyrosine kinase-dependent pathway (99). Replacing GTP with a non-hydrolysable analog in the internal pipette solution, had no effects on the inhibition of ASIC3-mediated currents by substance P (99). However, ASIC3-mediated currents were significantly diminished by a bath application of genistein, a phosphotyrosine kinase (PTK) inhibitor (99). Furthermore, M channel-like activity is also involved in the antinoceptive effect of substance P. During tissue acidosis in the muscle, ASIC3 channels are activated by protons, and depolarize the muscle afferent neurons, resulting in the firing of action potentials and the release of substance P. Substance P activates NK<sub>1</sub> receptors, and the activation of NK<sub>1</sub> receptors leads to the unconventional pathway, which activates tyrosine kinase and the M channel in the muscle afferent neurons. ASIC3-mediated action potentials are in-
CONCLUSION

Acid-sensing ion channels are pH sensors for detecting a wide range of pH fluctuations during normal physiological processes and pathological conditions. The functions and the properties of ASICs have been investigated using various pharmacological tools and genetic techniques. ASICs are implicated in a number of physiological activities, including pain perception, synaptic plasticity, learning and memory, fear, ischemic neuronal injury, and mechanosensation. However, questions remain about the involvement of ASICs in mechanosensation and learning and memory. Many signaling molecules that regulate the activity of ASICs exist, and ASICs can be modulated by GPCRs. However, the regulation of ASICs remains poorly understood. Further investigation into the regulatory mechanisms of ASICs is necessary for developing effective therapeutic strategies for the treatment of pain and neurological diseases.

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Properties and regulation of Acid-sensing ion channels
Hae-jin Kweon and Byung-Chang Suh

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