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Acid-sensing ion channels in pain and disease

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Abstract

Why do neurons sense extracellular acid? In large part, this question has driven increasing investigation on acid-sensing ion channels (ASICs) in the CNS and the peripheral nervous system for the past two decades. Significant progress has been made in understanding the structure and function of ASICs at the molecular level. Studies aimed at clarifying their physiological importance have suggested roles for ASICs in pain, neurological and psychiatric disease. This Review highlights recent findings linking these channels to physiology and disease. In addition, it discusses some of the implications for therapy and points out questions that remain unanswered.

Acid-evoked currents were first observed in neurons in the early 1980s[1,2]. In 1997, a protein producing a similar acid-gated current was cloned and identified as an acid-sensing ion channel (ASIC)[3]. This protein was closely related to a previously cloned member of the degenerin–epithelial Na^+ channel family (DEG–ENaC family; also called BNC1, MDEG or BNaC1 by three separate groups)[4–6]. This and other related channel family members were subsequently found to be pH-sensitive[7] and renamed ASICs to reflect their related structure, function and pH sensitivity[8]. We now know that the ASIC family of channel subunits (TABLE 1) is largely responsible for the acid-evoked currents previously observed in neurons[1,2].

A number of excellent reviews have focused on ASIC structure, function and physiology[9–17]. Many studies on ASICs have focused on their potential physiological roles.

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Much of this work has been guided by channel subunit localization in peripheral and central neurons (TABLE 1). In peripheral sensory neurons, ASICs have been found on cell bodies and sensory terminals, where they have been suggested to be important for nociception and mechanosensation[18,19]. In central neurons, ASICs have been found on the cell body, dendrites and at dendritic spines and have been suggested to contribute to synaptic plasticity[20–22]. The aim of this Review is to update readers on recent progress on ASICs in the context of disease. Increasing evidence supports roles for ASICs in rodent models of pain, neurological disease and psychiatric disease.

ASICs: a brief background

ASICs are permeable to cations and are activated by extracellular acidosis. They are subject to modulation by extracellular alkalosis[23,24], intracellular pH[25,26] and various other factors (TABLE 2). Much of what we know about these channels' properties comes from expressing recombinant ASIC subunits in heterologous cells[7,13,27–29]. Channels are formed by combinations of ASIC subunits in homotrimeric or heterotrimeric complexes (FIG. 1a), with different subunits conferring distinct properties (TABLE 1). The amino acid sequences of ASIC subunits are well conserved between species. For example, the mouse ASIC1A and the human ASIC1A share over 99% of their amino acid sequence identity. The recently described crystal structure of the chicken ASIC1 homomultimeric channel has shed light on the subunit interactions[30,31] (FIG. 1a) and, along with sequence homology analyses, has driven numerous structure–function experiments that are revealing how the channels respond to pH and other stimuli. Interestingly, in addition to the non-covalent inter-subunit interactions, disulphide bonds between trimers may also create higher-order complexes and alter channel function[32].

At sensory neuron terminals, protons and other endogenous (or exogenous) chemicals are thought to activate ASICs[12,13] (FIG. 2; TABLE 2). It has also been suggested that ASICs respond to mechanical stimuli at these terminals, a hypothesis that stems from the close structural relationship between ASICs and the mechanosensitive channels in *Caenorhabditis elegans*[33]. Findings from a number of studies are consistent with the possibility that ASICs contribute to mechanosensation[13,18,19]. For example, ASIC2 was found in mechanosensitive structures in rodent skin and was implicated in touch sensation[18]. More recently, ASIC2 was implicated in blood pressure regulation by aortic baroreceptors[34]. In another recent study, genetically disrupting or pharmacologically inhibiting ASIC3 impaired the ability of light skin pressure to recruit cutaneous blood flow, which increased vulnerability to pressure ulcers[35]. Such observations suggest that ASICs may have a mechanosensory role. However, the molecular mechanisms underlying these responses are not yet clear[35]. Not all studies investigating the role of ASICs in mechanosensation have detected ASIC-dependent effects[36]. Furthermore, unlike pH, mechanical stimulation has not been shown to directly gate any of the ASICs. Thus, unlike the related mechanosensitive channels, which can directly be gated by pressure[33], the precise roles of ASICs in mechanosensation continue to be debated.

In CNS neurons, disrupting the gene encoding ASIC1A in mice eliminated most of the current evoked by extracellular acid, suggesting that ASIC1A is a critical channel

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subunit[20,37,38] (FIG. 1b). At the subcellular level, ASIC1A was detected in the cell body, in dendrites and in postsynaptic dendritic spines[20,39], suggesting that it has a role in synaptic physiology (FIG. 3). Supporting this possibility, whole-animal ASIC1A-knockout mice had reduced long-term potentiation, reduced acid-evoked Ca^2 entry at dendritic spines and reduced dendritic spine number in hippocampal slices[20,39]. Also, in cultured hippocampal neurons from ASIC1A-knockout mice, an increase in presynaptic vesicle release was observed[40]. Consistent with these observations, a number of learning and memory-related phenotypes have been reported in ASIC1A-knockout mice[20,21,38,41,42], in mice overexpressing human ASIC1A[43] and in mice overexpressing mouse ASIC3 in the brain[44]. These phenotypes include differences in cued and contextual fear conditioning[21,38,41–44], reduced eyeblink conditioning[20] and a mild deficit in Morris water maze learning that was normalized with a more intensive training protocol[20]. In contrast to these observations, when murine ASIC1A expression in the CNS was disrupted by CRE-mediated excision via the nestin promoter, no deficits in Morris water maze learning or in hippocampal long-term potentiation were detected; however, deficits in fear conditioning were reported[38]. The reasons for the apparent differences in results with this cell-restricted knockout versus mice with unconditional ASIC1A disruption are not yet clear.

Compared with ASIC1A, much less is known about the other ASIC subunits in the brain. For example, ASIC2A and ASIC2B are expressed in the brain, but unlike ASIC1A these subunits are not required for acid-evoked currents in central neurons. However, in the absence of ASIC1A, ASIC2 subunits produced a small amount of current in brain neurons in response to very acidic pH (pH 4.0)[45]. Additionally, ASIC2A and ASIC2B interact with ASIC1A and can shift the pH sensitivity, desensitization kinetics and ion selectivity of acid-evoked currents[27,28,45,46]. Furthermore, unlike ASIC1A, ASIC2A can interact with postsynaptic density 95 (REF. 47), and ASIC2A was found to deliver ASIC1A-containing channel complexes to dendritic spines in cultured hippocampal slices[47]. Altering channel properties may produce significant behavioural effects. For example, expressing ASIC3 in the brain of transgenic mice increased the desensitization rate of acid-evoked currents and impaired fear conditioning[44].

When expressed in heterologous cells, ASIC2A can form homomultimeric channels independently of ASIC1A; however, a role for ASIC2A or ASIC2B that is independent of ASIC1A has not yet been identified. Because the pH sensitivity of ASIC2A is outside what is considered physiological (for example, effector concentration for half-maximum response (EC_{50}) ~ pH 4.5–4.9)[27,28], ASIC2 homomers may be activated by something besides pH *in vivo*. A recent study found that an exogenous peptide, MitTx, greatly increased the pH-sensitivity of ASIC2A[48], suggesting that it could act as a ‘coincidence detector’ that responds to pH in combination with other modulators[48]. Thus, a better understanding of ASIC2 localization and function vis-à-vis ASIC1A could be very informative.

The precise mechanisms by which ASICs are activated in the brain remain uncertain. One potential mechanism might involve protons released during neurotransmission by acidic (~pH 5.5) neurotransmitter-containing vesicles[49] (FIG. 3). However, thus far, postsynaptic ASIC-dependent currents have not been detected during neurotransmission[20,22,38]. Protons generated by other sources, such as localized energy metabolism, might also contribute to

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ASIC activation[50,51], as might the growing list of ASIC modulators[10] (TABLE 2). The downstream mechanisms by which ASIC1A activation produces its effects also remain poorly defined. ASICs most probably influence neuronal function through membrane depolarization[52,53], Ca^{2+} entry[39] and through a number of downstream signalling cascades[54] (FIG. 1c). Future studies should help to clarify the roles of ASICs in synaptic plasticity, learning, memory and behaviour.

ASICs and pain

A number of pain-causing stimuli, such as inflammation, lower extracellular pH. This observation hints at the existence of pH-sensitive receptors on nociceptive neurons and suggests that their activation causes pain. Possible candidate receptors include ASICs, which produce acid-evoked cation currents and are present both in the cell body and at terminals of peripheral nociceptive neurons (FIG. 2). Interestingly, ASIC1 and ASIC2 subunits are also present in areas of the CNS that are important in pain processing (FIG. 3). These findings have led investigators to hypothesize that ASICs contribute to pain. Support for this hypothesis has been gathered by genetically disrupting ASIC expression in mice and using pharmacological inhibitors[12,13]. However, early results were mixed. For example, ASIC3-knockout mice and mice with simultaneous disruption of ASIC1A, ASIC2 and ASIC3 showed increased pain-related behaviours[55,56]. By contrast, pharmacological blockade using the sea anemone peptide APETx2 and genetic knockdown of *Asic3* decreased pain-related behaviours[57]. In addition, ASIC1A-knockout mice showed changes in some pain behaviours but not in others[58,59]. Furthermore, inhibiting ASIC1A in the CNS, but not the peripheral nervous system (PNS) reduced pain behaviours[60,61]. Such mixed results have raised important questions. Do ASICs really promote pain? If so, which subunits transmit the nociceptive signals? Do ASICs contribute to pain pathways in the CNS or the PNS, or both? A series of recent studies address these questions.

Strong evidence that activating ASIC3 is sufficient to cause pain was provided by a small molecule, 2-guani-dine-4-methylquinazoline (GMQ). GMQ was found to bind ASIC3 at a site that is distinct from its acid-sensing domain and to open the channel at neutral pH. Importantly, injecting GMQ into the mouse paw triggered pain behaviours in wild-type but not *Asic3*$^{-/-}$ mice (FIG. 2). GMQ is a synthetic molecule, but the authors demonstrated that agmatine, a related endogenous polyamine, binds to the same site on ASIC3 and causes pain behaviour[62]. Interestingly, agmatine also interacted with other inflammatory signals to increase ASIC3-dependent currents and pain[63]. These data indicate the existence of non-proton ASIC3 activators and suggest that endogenous molecules may activate ASICs to cause pain (TABLE 2). It is not yet clear whether any endogenous polyamines reach the high levels (~10 mM) that would be necessary to activate ASIC3. Polyamines are known to accumulate in synaptic and dense core vesicles, raising the possibility that these molecules might activate ASIC3 during synaptic transmission[62].

Experiments with a peptide component (MitTx) in the venom of the Texas coral snake *(Micrurus tener tener)* further indicated roles for ASIC1, ASIC2 and ASIC3 in pain. MitTx triggered persistent activation of ASIC1A and ASIC1B homomultimers in cultured somatosensory neurons, and at higher concentrations it also activated ASIC3 (REF. 48).

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Interestingly, although MitTx did not activate ASIC2A at neutral pH, it potentiated its proton sensitivity more than 100-fold, suggesting that a similar, as-yet-unidentified endogenous compound might facilitate ASIC2A responses to physiological changes in pH. The authors speculated that ASIC2A might function as a co-incidence detector for pH and some as-yet-unidentified modulator. Injecting purified MitTx into the hind paw of mice elicited pain behaviours that were significantly diminished by ASIC1A disruption (FIG. 2). Disrupting ASIC3 also attenuated the pain response when higher MitTx concentrations were injected. These findings indicated that MitTx elicits pain through ASIC1A, and to a smaller degree ASIC3, in peripheral nociceptive neurons[48].

Recent evidence also points to roles for ASICs in pain processing in the CNS. A peptide (psalmotoxin 1 (PcTx1)) in the venom of the Trinidad chevron tarantula (*Psalmopoeus cambridgei*) inhibits ASIC1A homomultimeric channel activity[64]. Intrathecal injection of PcTx1 reduced thermal, mechanical, chemical, inflammatory and neuropathic pain in rodents[60,61]. Interestingly, this peptide also raised endogenous Met-enkephalin levels in cerebrospinal fluid[60]. However, a mechanistic link between ASIC1A and Met-enkephalin has not yet been elucidated.

In the spinal cord, ASIC1A and ASIC2A levels were increased by peripheral inflammation, suggesting a role for ASICs in central sensitization of pain[61,65]. Consistent with this possibility, brain-derived neurotrophic factor (BDNF) promoted ASIC1A cell surface expression via phosphorylation at Ser-25 through the phosphoinositide 3-kinase–protein kinase B (also known as AKT1) pathway[66]. Furthermore, genetically disrupting ASIC1A reduced mechanical hyperalgesia elicited by intrathecal BDNF injection[66]. Taken together, these studies suggest that ASICs in the CNS contribute to pain processing. Although the mechanisms of ASIC action in central pain circuits are not yet clear, it is possible that ASICs may alter neuron excitability or synaptic plasticity.

Perhaps the strongest evidence to date that inhibiting ASICs in either the CNS or the PNS reduces pain was obtained using black mamba (*Dendroaspis polylepis polylepis*) venom, which contains a three-finger peptide (mambalgin-1) that blocks ASIC currents. Mambalgin-1 inhibited current from ASIC1A and ASIC1B homomers as well as from heteromers of ASIC1A–ASIC2A, ASIC1A–ASIC2B or ASIC1A–ASIC1B. Importantly, mambalgin-1 inhibited pain in mice when injected either centrally or peripherally. Intrathecal or intracerebroventricular injection reduced pain responses in acute thermal and inflammatory pain models (carrageenan and formalin), and injecting mambalgin-1 peripherally into the paw reduced acute thermal pain (FIG. 2) and inflammatory hyperalgesia. Interestingly, the central analgesic effects were dependent on ASIC1A and ASIC2A, whereas the peripheral analgesic effects were dependent on ASIC1B. Importantly, unlike opioid analgesics and PcTx1, mam-balgin-1 elicited minimal analgesic tolerance, suggesting that there is potential for more long-lasting analgesia. Also, unlike opioids, mambalgin-1 produced no respiratory suppression. These observations suggest that mambalgin-like ASIC antagonists may have distinct advantages over opioids for pain alleviation[67].

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These studies highlight the possibility that the PNS and CNS use different combinations of ASIC subunits to mediate pain. Optimum signalling through ASICs at different anatomical sites may require different channel properties, and channel activity might be optimized through different combinations of ASIC subunits and ASIC modulators. Importantly, these studies identify ASICs as potential targets for new pain medications. The ASIC inhibitor amiloride (which also affects a number of non-ASIC targets) is approved for use in humans, and a few small translational experiments have demonstrated its potential for reducing cutaneous pain and migraine[68–70].

ASICs, neurotoxicity and neurological diseases

A number of neurological diseases involve acidosis, arising from several possible sources, including ischaemia, inflammation, metabolism and synaptic transmission[50] (FIG. 4). Extreme or prolonged acidosis kills neurons, and there is growing evidence that ASICs mediate acid-induced toxicity in the CNS. Some of the earliest evidence for ASICs in acidosis-induced injury came from cell culture and mouse models of ischaemia[37,71]. Disrupting ASIC1A or inhibiting ASICs with amiloride or PcTx1 reduced acidosis-induced cell death in cultured neurons[37,71]. Moreover, these ASIC manipulations substantially reduced infarct volume in rats and mice after middle cerebral artery occlusion[37,72].

Subsequent studies have suggested that a number of other neurodegenerative diseases lead to localized acidosis and that disrupting ASICs pharmacologically or genetically may be protective. In addition to ischaemic stroke, ASICs have now been implicated in multiple sclerosis[73], Huntington's disease[74], Parkinson's disease[75] and spinal cord injury[76]. TABLE 3 lists these studies, many of which have been previously reviewed[14,15]. Below, we review some recent advances in understanding how different ASIC subunits and ASIC modulators might contribute to neurotoxicity.

Much of the previous work on ASICs and neurotoxicity focused on ASIC1A homomultimeric channels and their ability to conduct Ca^{2+} and induce Ca^{2+}-mediated toxicity[37,39,71]. Building on these observations, a recent paper observed that constitutive endocytosis of ASIC1A in a clathrin- and dynamin-dependent manner protected cells against acid-induced cell death[77]. Potential roles of the other ASICs, particularly ASIC2B, have been uncertain, as ASIC2B homomers do not form pH-sensitive channels[7,27]. A recent study suggested an important role for ASIC2B in acidosis-induced neuron death[78]. This study found that heteromultimeric channels composed of ASIC2B–ASIC1A were Ca^{2+}-permeable and sensitive to PcTx1, similar to ASIC1A homomeric channels. Ba^{2+} was subsequently shown to inhibit these ASIC2B–ASIC1A channels and attenuate acidosis-induced cell death[78], suggesting that targeting ASIC2B, as well as ASIC1A, may prevent acid-induced neurotoxicity.

In addition to causing acidosis, brain injury results in the release of a number of endogenous chemicals that can modulate ASICs, including lactate, arachidonic acid and dynorphin (TABLE 2). These and other factors may boost ASIC currents and their associated toxicity[54,79–81]. Several studies have highlighted the importance of ASIC modulators in

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neurotoxicity and identified potential new leads for therapeutic compounds that may target ASICs.

The abundance of the endogenous polyamine spermine in the CNS and its interaction with ASICs could have important consequences for neurotoxicity[82,83]. In a recent study, exogenous spermine was delivered to the brain through an intracerebroventricular cannula before middle cerebral artery occlusion[84]. As predicted, spermine increased infarct volume, but this toxicity-promoting effect was significantly reduced in ASIC1A-knockout mice. Consistent with this result, blocking the production of endogenous spermine also protected against ischaemic damage in an ASIC1A-dependent manner. These observations suggest that the toxic effects of spermine, agmatine and other ASIC modulators might be due to their effects on ASICs and highlight the possibility that ASIC modulators might be valuable therapeutic targets.

Interestingly, several traditional Chinese medicines were suggested to produce their neuroprotective effects through ASICs[85–88]. Three such compounds (puerarin, sophocarpine and ginsenoside-Rd), which were previously known to protect against damage caused by middle cerebral artery occlusion, all interfered with ASIC1A function by reducing current amplitude, increasing channel desensitization or decreasing ASIC1A expression[85–88]. It will be interesting to see whether the neuroprotective effects of these compounds depend on ASICs, whether they are effective in other models of neurotoxicity and whether they have additional analgesic or behavioural effects depending on the ASIC subtype they target. They might also be valuable lead compounds, as their safety has largely been established already.

ASICs and glioblastoma

Glioblastoma cells exhibit constitutively active amiloride- and PcTx1-sensitive cation currents. These currents are thought to be mediated by hybrid channels comprised of ASIC1A and other DEG– ENaCs[89–92]. Recently, the potential role of ASICs in glioblastoma was probed by targeting ASIC1A in cultured human glioma cells. The ASIC inhibitor PcTx1 inhibited cell migration and cell cycle progression. Similarly, the amiloride analogue benzamil caused cell cycle arrest[93]. These results suggest the possibility that pH and ASIC1A activity may be crucial in glioblastoma pathophysiology. They further suggest the intriguing possibility that targeting pH and ASICs might inhibit the growth and spread of some cancers.

ASICs and epilepsy

Another neurological disease in which ASICs have been suggested to play a part is epilepsy[94]. Seizures reduce brain pH, and it has been known for decades that acidosis inhibits seizures. Thus, one potential reason that most seizures are self-limited is because of feedback inhibition mediated by low pH (FIG. 4). ASIC1A has been implicated in this feedback mechanism[52], as deleting the gene encoding ASIC1A in mice increased the duration of chemoconvulsant-induced seizures, although it did not affect seizure threshold. Conversely, overexpressing ASIC1A in mice, produced the opposite effect and inhibited seizures. Consistent with a role in terminating seizures, loss of ASIC1A reduced postictal depression, which has been thought to underlie seizure termination. The ability of acidic pH

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to suppress seizure-like activity was reduced in hippocampal slices from the ASIC1A-knockout mice. Furthermore, the ability of CO_2 inhalation and associated acidosis to inhibit seizure-induced lethality was lost in these ASIC1A-knockout mice. Following high-dose pentylenetetrazol administration, wild-type mice survived when breathing 10% CO_2, whereas the ASIC1A-knockout mice did not. These studies suggest that the prolonged seizures of status epilepticus and the associated increase in seizure-related mortality might result from ASIC1A dysfunction[52]. Thus, ASIC1A might be a novel target for treating epilepsy or status epilepticus.

It is still unclear how ASIC1A inhibits seizure activity. The acid-evoked current in inhibitory neurons might be responsible (FIG. 4), as in the hippocampus, ASIC1A is more abundant in GABAergic neurons than in glutamatergic neurons[52,95,96]. It is also puzzling that other studies have raised the possibility that ASIC1A might have the opposite effect and increase seizure activity[15]. For example, amiloride inhibited seizures in several animal models, although it is not clear whether those effects were due to amiloride's inhibition of ASICs or of other molecules such as the Na^+/H^+ exchanger[15,97–99].

More work is needed to determine whether the effects of ASIC1A on seizures in rodents also occur in humans. A step in this direction was recently taken by a human genetic study that suggested an association between single nucleotide polymorphisms (SNPs) in *ASIC1* and temporal lobe epilepsy[100].

ASICs and psychiatric disease

Psychiatric illnesses are extremely common, with an estimated half of all Americans surveyed experiencing at least one psychiatric illness during their lifetime[101]. However, our understanding of the molecular, physiological and neuroanatomical bases of these disorders is remarkably limited. Advances in psychiatric genetics have drawn increasing attention to the possibility that psychiatric illness might result from synaptic dysfunction. The synaptic localization of ASICs and their prominent expression in brain structures underlying emotion, cognition and behaviour (including the amygdala, bed nucleus of the stria terminalis, habenula, nucleus accumbens and periaqueductal grey (FIG. 3)), suggest that ASICs are well positioned to influence psychiatric symptoms[20,21,39,102]. The possibility that ASICs have a role in brain function and behaviour is supported by initial studies of the effects of ASIC1A disruption in mice on synaptic plasticity, neurophysiology and models of anxiety and depression. ASIC1A-knockout mice exhibited deficits in cued and contextual fear conditioning as well as in unconditioned fear behaviours, such as predator odour-evoked freezing, open-field centre-avoidance and acoustic startle responses[20,21,102].

Another role for ASICs in fear-related behaviours was recently identified, which linked ASIC1A more closely to brain pH changes *in vivo*. CO_2 inhalation rapidly lowers pH in the brain and has long been known to trigger fear and panic attacks in humans[42,103]. Paralleling the CO_2 effects in humans, CO_2 inhalation also triggered fear-like behaviours in mice[42]. Importantly, eliminating or inhibiting ASIC1A markedly reduced these responses. Likewise, buffering the acidosis with bicarbonate reduced CO_2-evoked freezing behaviour. At least one anatomical site of ASIC1A action in these behaviours was the amygdala; localized

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ASIC1A expression in the amygdala restored CO_2-induced freezing in ASIC1A-knockout mice to near wild-type levels. Moreover, the freezing induced by CO_2 was reproduced by injecting acidic solution directly into the amygdala of wild-type but not ASIC1A-knockout mice. These observations provide some of the clearest evidence so far that ASIC activation in the brain depends on pH. From these data, one might also speculate that ASICs in the amygdala might help to prevent suffocation by inducing active defence responses. Rising CO_2 heralds the potential threat of suffocation. Thus, the ability to detect CO_2 and elicit prompt defensive action could be life-saving. From an evolutionary perspective, it is interesting to imagine that this might be a key role for ASICs.

In addition to its role in fear behaviour, ASIC1A was found to contribute to depression-related behaviours in mice. Genetically or pharmacologically disrupting ASIC1A reduced depression-related behaviours in the forced swim test, tail suspension test and after experiencing unpredictable mild stress[104]. Interestingly, the antidepressant-like effect of inhibiting ASIC1A was independent of serotonin depletion and also independent of several currently used antidepressants, including fluoxetine, desipramine and bupropion. These findings raise the possibility that inhibiting ASIC1A might reduce depression through a novel mechanism of action — a potentially exciting possibility, given that standard antidepressants are ineffective for many patients. More studies linking ASICs to depression and clarifying the mechanisms may mitigate some of the barriers to developing ASIC inhibitors for depression therapy.

So far, only a handful of genetic studies have evaluated the potential link between ASICs and human psychiatric illness. The largest of these studies examined the relationship between SNPs in *ASIC1* with anxiety disorders and depression. In this twin-pair study that included 589 cases versus 539 controls, no statistically significant association was identified. The data did suggest a possible link to depression, but it was not significant when corrected for multiple comparisons[105]. In another study, a quantitative trait locus for anxiety-related behaviours in mice was found to be homologous to the human chromosomal region 12q13, which contains *ASIC1*. Interestingly, this same region was linked to panic disorder in humans[106].

Besides these notable examples, a few small genome-wide association studies have suggested associations between SNPs in *ASIC2* with panic disorder, lithium-response in bipolar disorder and citalopram-response in major depressive disorder[107–109]. In addition, the *ASIC2*-containing locus has been associated with autism[110]. Although these initial genetic findings are encouraging, they are not definitive. Stronger genetic associations to human illness might come from high-throughput, genome-wide sequencing or from other rapidly progressing technological advances in human genetics research. Expanding the search to include genes that regulate pH or modulate ASIC function might also be beneficial to the search for genetic variations affecting ASICs.

Together, these studies suggest the possibility that abnormal ASIC function might contribute to psychiatric illness and that targeting ASICs may be therapeutically beneficial. The prominent behavioural effects of ASIC1A raise questions about the role of brain pH in behaviour. For example, does pH change in the brain while conducting normal cognitive

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tasks? Might these pH changes produce important behavioural or cognitive effects? Moreover, might targeting brain pH provide a novel therapeutic approach? Better methods for measuring brain pH in animals and in humans may help to answer some of these questions. Recently, an MRI study using T1 relaxation in the rotating frame (T1ρ) suggested that the visual cortex may become acidic in response to a visual stimulation with a flashing checkerboard pattern[111]. This initial example is consistent with the possibility that pH may fluctuate during routine brain activity. Tools such as this could greatly improve our understanding of the roles of pH in the brain in behaviour and disease.

Summary and future directions

There is now a substantial and growing body of research in animal models that implicates ASICs in various diseases. However, it will be important to determine how our current knowledge of ASICs translates to humans. One path to translation would be to find genetic associations between ASICs and human traits or diseases. Another path is to determine whether ASIC inhibitors produce effects in humans; along this line, several beneficial effects of amiloride have been recently reported[68–70,112]. More knowledge of brain pH dynamics is also needed and may require improved methods to measure and manipulate pH *in vivo*[111]. Last, a better understanding of the molecular mechanisms of ASIC action will help to clarify how inhibiting or potentiating these channels affects physiology, pathophysiology and behaviour. This knowledge will help to develop new therapies targeting ASICs and ASIC modulators.

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Glossary

Degenerin–epithelial Na^+ channel family	(DEG–ENaC family). A family of ion channels that includes acid-sensing ion channels and is characterized by two transmembrane domains, a relatively large cysteine-rich extracellular domain and several highly conserved amino acid sequence motifs
Nociception	Refers to detection of painful and injurious stimuli and translation into a neuronal signal
Mechanosensation	Refers to detection of mechanical stimuli and translation into a neuronal signal
Acidosis	A physiological state characterized by acidic pH (high H^+ concentration)
Alkalosis	A physiological state characterized by basic pH (low H^+ concentration)
Baroreceptors	Receptors that are sensitive to changes in blood pressure

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Long-term potentiation	A long-lasting, activity-dependent strengthening of synaptic transmission
Postictal depression	The reduction in electroencephalographic activity that occurs immediately after a seizure
Pentylenetetrazol	A GABA receptor antagonist used to elicit seizures

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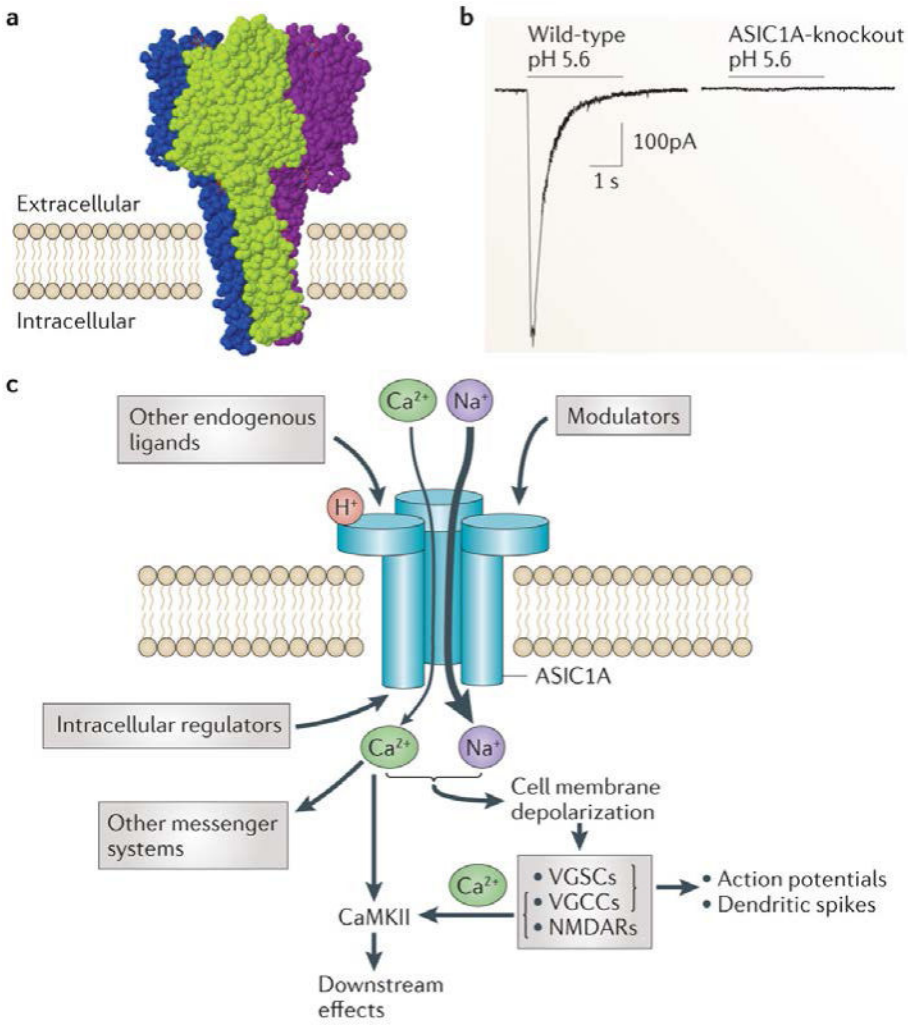

Figure 1. Structure and function of ASIC1A

a| The crystal structure of the chicken acid-sensing ion channel 1 (ASIC1) indicates that three subunits combine into a trimeric channel complex (different colours represent distinct ASIC1 subunits)[30] **b**| Whole-cell voltage-clamp recordings from neurons in acute amygdala slices showing an absence of pH 5.6-evoked current in neurons lacking ASIC1A. **c** | ASICs are activated by extracellular protons (H^+) and possibly other yet-to-be identified ligands, and are modulated by a number of other factors (TABLE 2). ASIC1A, schematized here, is permeable to cations, primarily Na^+ and to a lesser degree Ca^{2+}. Upon activation, an inward current depolarizes the cell membrane, which activates voltage-gated Ca^{2+} channels (VGCCs) and voltage-gated Na^+ channels (VGSCs) and may contribute to NMDA receptor (NMDAR) activation through the release of the voltage-dependent Mg^{2+} blockade. Thus, Na^+ and Ca^{2+} influx contributes to membrane depolarization, the generation of dendritic spikes and action potentials, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activation and possibly influence other second-messenger pathways. In addition, a number of intracellular proteins have been suggested to regulate ASICs (see REF. 17 for recent review).

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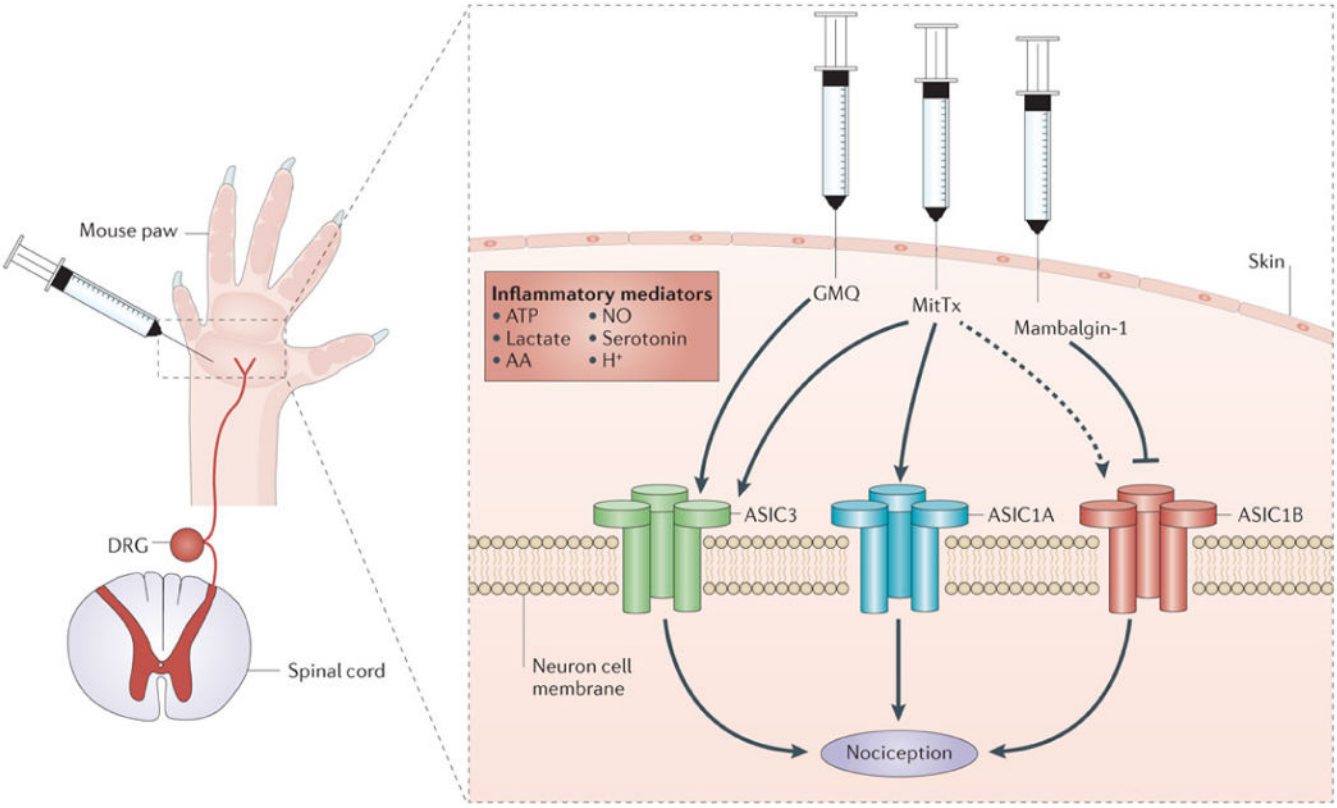

Figure 2. Roles for peripheral ASICs in pain

Recent studies have taken advantage of acid-sensing ion channel (ASIC) agonists (2-guanidine-4-methylquinazoline (GMQ) and MitTx) and an antagonist (mambalgin-1) to clarify the roles of ASICs in pain. When injected into the mouse paw, the synthetic compound GMQ, which activates ASIC3, induced pain behaviours that were absent in ASIC3-knockout mice. These behaviours were not affected by ASIC1A disruption[62]. The Texas coral snake toxin, MitTx, evoked pain-related licking behaviour that depended on ASIC1A and, to a lesser degree, ASIC3 (REF. 48). ASIC1B was also activated by MitTx (dashed line), but its role in MitTx-evoked pain was not investigated. Mambalgin-1, a toxin from black mamba venom, blocked several combinations of ASIC subunits, and when it was injected into the mouse paw, it inhibited flick latency to heat through ASIC1B-containing channels[67]. In addition, another recent study indicated a role for the inflammatory mediator serotonin. Serotonin increased acid-evoked currents through ASIC3 and increased acid-evoked pain-behaviour in the mouse paw, which was attenuated by ASIC3 disruption[113]. A number of other inflammatory mediators have been suggested to modulate ASICs in pain, including arachidonic acid (AA), nitric oxide (NO), ATP and lactate (TABLE 2). DRG, dorsal root ganglion.

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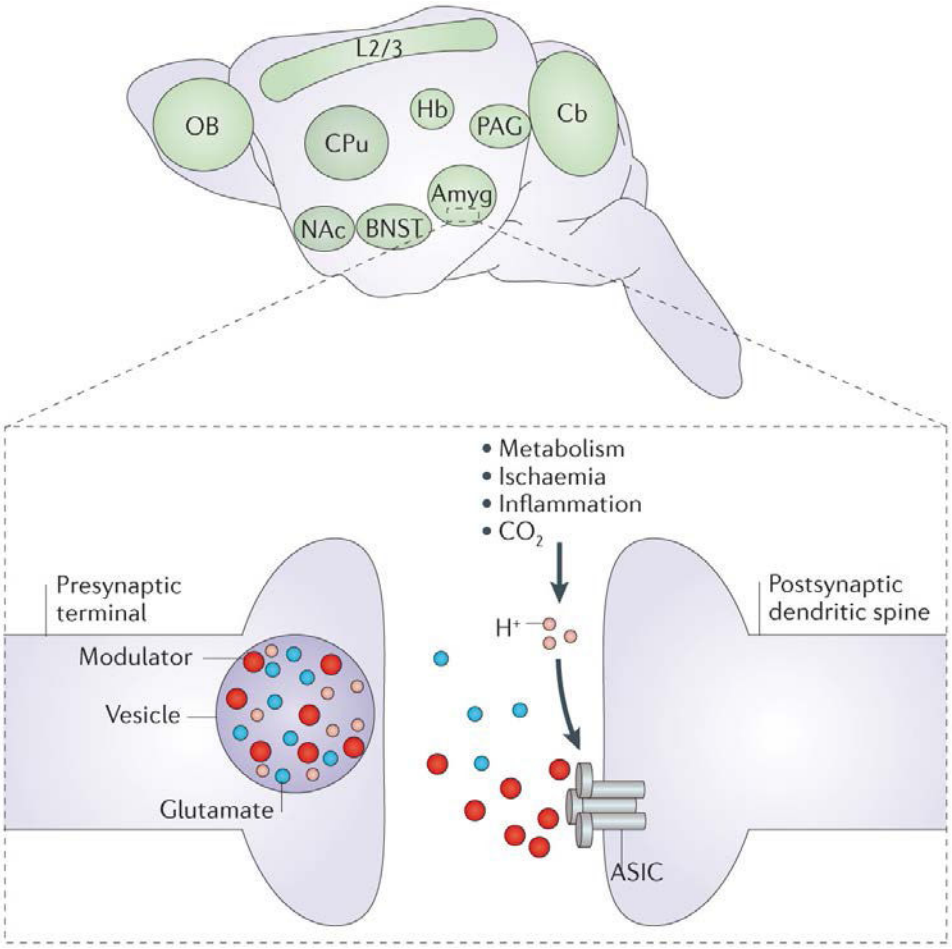

Figure 3. ASIC1A expression in the mouse brain

Acid-sensing ion channel 1A (ASIC1A) is widely expressed in the mouse brain and is enriched in the amygdala (Amyg), bed nucleus of the stria terminalis (BNST), periaqueductal grey (PAG), nucleus accumbens (NAc), caudate putamen (CPu), habenula (Hb), olfactory bulb (OB), cerebral cortex layer 2/3 (L2/3) and molecular layer of the cerebellum (Cb)[21,102]. ASIC1A localization in these brain regions has driven hypotheses about the behavioural roles of ASICs. At the subcellular level, ASIC1A has been detected in postsynaptic dendritic spines (inset), where, in one model, channel activation is caused by protons (H^+) coming from acidic neurotransmitter-containing vesicles. Other pH changes, which are due to metabolism or disease, might also activate ASICs in the CNS. In addition, recent studies have highlighted the possibility that various endogenous factors, including neuropeptides and polyamines, modulate and/or activate ASICs (TABLE 2).

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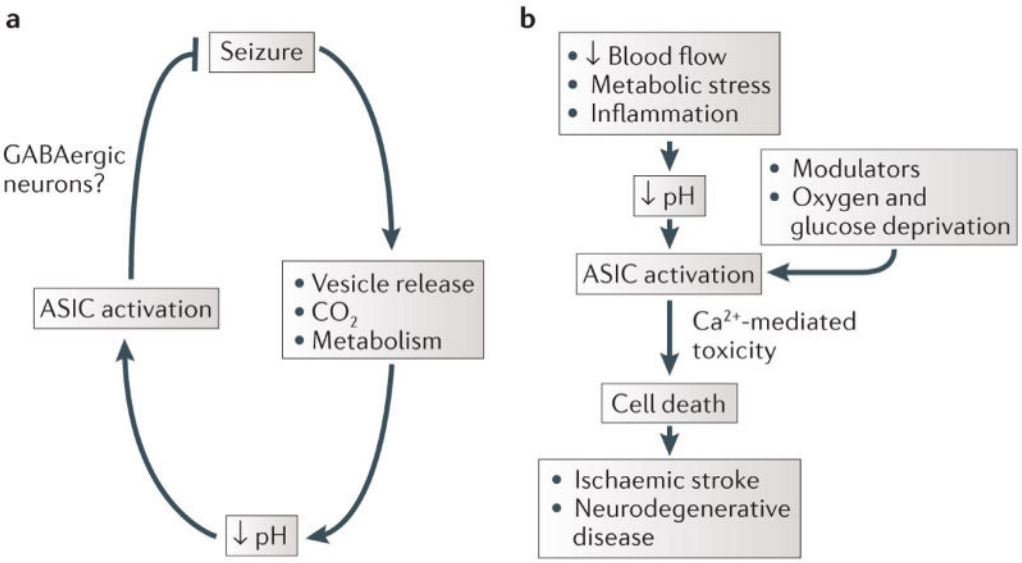

Figure 4. Contrasting roles of brain pH and ASICs in seizures and neurotoxicity

Reduced brain pH can be protective or damaging. **a** | The ability of acidosis to inhibit seizures is thought to be acid-sensing ion channel 1A (ASIC1A)-mediated, possibly owing to abundant ASIC1A expression in GABAergic neurons[52,95,96]. **b** | Accumulating evidence suggests that acidosis potentiates cell death, which contributes to ischaemic stroke and neurodegenerative disease and that this depends on ASIC1A. Other factors, such as oxygen and glucose depletion, inflammation and other modulators are likely to play important parts in these processes.

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Table 1

ASIC subunits and properties

ASIC subtype	pH sensitivity of homomeric channel (pH_{50})	Localization
ASIC1A	5.8–6.8	CNS and PNS
ASIC1B	6.1–6.2	PNS, not yet identified in the CNS
ASIC2A	4.5–4.9	CNS and PNS
ASIC2B	Does not form pH-sensitive homomeric channels, associates with other ASICs to form pH-sensitive channels	CNS and PNS
ASIC3	6.4–6.6	Predominately PNS, detected in mesencephalic trigeminal neurons in the CNS[114]
ASIC4	Does not form pH-sensitive homomeric channels	CNS

Four acid-sensing ion channel (ASIC) genes (*ASIC1*, *ASIC2*, *ASIC3* and *ASIC4*) and six ASIC subunits (ASIC1A, ASIC1B, ASIC2A, ASIC2B, ASIC3 and ASIC4) have been identified. pH sensitivity varies widely across ASIC subtypes. Various pH_{50} values have been seen across studies, reflecting differences in cell type, species and technique. A representative range of pH_{50} values from two studies[27,28] that used consistent methods to evaluate all channel subtypes is given in the table. Heteromeric channels comprised of combinations of the above subtypes have unique channel properties[17]. Various ASIC subtypes have been detected in both the CNS and peripheral nervous system (PNS).

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Table 2

Pharmacology of ASICs

Class	Compound	Effects on ASICs	Site of action
Endogenous modulators			
Neuropeptides	Dynorpin A, big dynorphin	Increase acid-evoked current by limiting steady-state desensitization of ASIC1A[115], ASIC1A–ASIC2B and ASIC1A–ASIC2A heteromers[78]	Extracellular; big dynorphin competes with PcTx1 (REFS [115, 116])
	Phe-Met-Arg-Phe (FMRF) amide and related peptides	Enhance sustained acid-evoked current and slow inactivation of ASIC1A, ASIC1B and ASIC3 (REF. 117)	Extracellular application[117]
Polyamines	Spermine	Increases ASIC1A-, ASIC1B- and ASIC1A–ASIC2A-mediated currents by shifting proton steady-state desensitization[82–84]	Probably extracellular; interrupted by PcTx1 and extracellular mutations[84]
	Agmatine	Activates homomeric ASIC3 and heteromeric ASIC3–ASIC1B channels[62,63]	Extracellular non-proton, ligand-sensing domain[63]
Cations	Ca^{2+}, Mg^{2+}, Cd^{2+}, Cu^{2+}, Gd^{3+}, Ni^{2+}, Pb^{2+}, Zn^{2+}, Ba^{2+}	Inhibit various homomeric and heteromeric ASIC channels[3,78,83,118–124]	Various. For example, Ca^{2+}-dependent inhibition of ASIC1A was affected by mutating transmembrane region 2 and the extracellular domain[123,124]
Other	Arachidonic acid	Increases sustained inward current[80]	Unknown[125]
	Lactate	Potentiates current amplitude in response to acidosis[79]	Indirect, chelates extracellular divalent ions[79]
	Nitric oxide	Nitric oxide donors potentiate ASIC1A, ASIC1B, ASIC2B and ASIC3 homomers[126]	Probably extracellular[126]
	ATP	Increases pH sensitivity of ASIC3 homomers[127]	Probably through purinergic P2X receptors[127]
	Serotonin	Enhances ASIC3-sustained currents[113]	Extracellular; depends on the non-proton, ligand-sensing domain[113]
Exogenous modulators			
Toxins from venoms	PcTx1	Desensitizes ASIC1A homomers[64,128] and ASIC1A–ASIC2B heteromers[78]	Extracellular proton-sensitive acidic pockets[116]
	APETx2	Inhibits ASIC3 and ASIC3-containing heteromers[129]	Unknown, probably extracellular[129]
	MitTx	Activator of ASIC1A and ASIC1B homomers[48] and enhances pH sensitivity of ASIC2A channels[48]	Unknown extracellular binding site[48]
	Mambalgin-1	Inhibits currents mediated by ASIC1A and ASIC1B homomers, and ASIC1A–ASIC2A, ASIC1A–ASIC2B and ASIC1A–ASIC1B heteromers[67]	Unknown[67]
NSAIDs	Flurbiprofen, ibuprofen, aspirin, salicylic acid, diclofenac	Reduce ASIC1A and ASIC3 currents[130]	Unknown
Other	Amiloride (and derivatives such as DMA)	Reduces currents in all ASIC subtypes[3]	Unknown. Several possible binding sites in the extracellular domain and pore[131,132]
	A-317567	Inhibits endogenous acid-evoked ASIC currents in rat DRG neurons[133] and mouse CNS neurons[104]	Unknown
	GMQ	Activates ASIC3 at neutral pH[62]	Extracellular non-proton, ligand-sensing domain[62]

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Class	Compound	Effects on ASICs	Site of action
	Nafamostat	Inhibits ASIC1A and ASIC2A[134] and inhibits ASIC3 initial phase transient current[134]	Extracellular application; site of action unknown[134]
	Arcaine	Agmatine analogue that activates ASIC3 channels[63]	Extracellular non-proton, ligand sensing domain[63]

ASIC, acid-sensing ion channel; DMA, 5-(N,N-dimethyl)-amiloride hydrochloride; DRG, dorsal root ganglion; GMQ, 2-guanidine-4-methylquinazoline; PcTx1, psalmotoxin 1; NSAIDs, non-steroidal anti-inflammatory drugs.

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Table 3

ASICs and neurological disease

Disease	Role of pH	Role of ASICs
Ischaemic stroke	• Ischaemic stroke causes robust acidosis[135] • Buffering this acidosis reduces infarct volume in the MCAO model[136]	• Genetic disruption or pharmacological blockade of ASIC1A reduces acidosis-induced cell death and infarct volume[37] • Some treatments shown to be neuroprotective in the MCAO model were associated with decreased ASIC1A expression and/or increased ASIC2A expression[88,136] • A treatment that attenuated ASIC1A currents was neuroprotective in the MCAO model, whereas a treatment that enhanced ASIC1A currents was neurotoxic[84,86]
Multiple sclerosis	The EAE model induces spinal cord acidosis[73]	• In the EAE model, genetic disruption of *ASIC1* attenuated clinical severity and axonal degeneration[73] • Treatment with amiloride had neuroprotective effects in both animal models and a cohort of human patients[73,112,137] • ASIC1A is upregulated in lesioned areas in EAE[137] • A genome-wide study found an association between a polymorphism in *ASIC2* and multiple sclerosis[138]
Huntington's disease (HD)	Increased levels of lactate in the brain have been shown in patients with HD as well as in an animal model of HD[139,140]	In a mouse model of HD, depletion of ASIC1A or treatment with amiloride or benzamil reduced polyglutamine aggregation[74]
Parkinson's disease	Patients with Parkinson's disease exhibit increased brain lactate levels[141]	• ASIC currents are found in dopaminergic neurons of the substantia nigra[75,142] • Both amiloride and PcTx1 were neuroprotective in a mouse model of Parkinson's disease[75] • Parkin has been shown to regulate PICK1-dependent potentiation of ASIC2A currents[143]
Migraine		• Dural afferents have ASIC-mediated, acid-evoked currents[144] • Amiloride showed efficacy for the reduction of aura and headache symptoms in a small clinical study[68]
Spinal cord injury		• ASIC1A expression is enhanced in the peri-injury zone[76] • Treatment with PcTx1 or amiloride or depletion of ASIC1A reduced lesion volume and ameliorated functional outcomes[76]
Glioblastoma		• Glioblastomas exhibit a constitutively active amiloride- and PcTx1-sensitive cation current, which is thought to be mediated by ENaC and ASIC hybrid channels[89–91,145] • Knockdown of ASIC1,αENaC or γENaC reduces this current and inhibits cell migration[92] • Treatment with PcTx1 or benzamil caused cell cycle arrest[93]
Epilepsy	• Epileptic seizures induce acidosis[146] • Acidosis, which is induced by carbon dioxide, inhibits seizure activity[147,148]	• Pharmacologically induced status epilepticus reduces levels of ASIC1A- and ASIC2B-encoding transcripts in the hippocampus[94] • Disrupting ASIC1A increased seizure severity and duration, whereas overexpression of ASIC1A reduced seizure severity[52] • Seizure termination by acidosis depends on ASIC1A[52] • Amiloride inhibits seizures in multiple rodent models[15,97–99]

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Disease	Role of pH	Role of ASICs
		• An SNP in *ASIC1* was associated with temporal lobe epilepsy[100]

ASIC, acid-sensing ion channel; EAE, experimental autoimmune encephalomyelitis; ENaC, epithelial NA^+ channel; MCAO, middle cerebral artery occlusion; PcTx1, psalmotoxin 1; PICK1, protein interacting with C kinase 1 (also known as PRKCA-binding protein); SNP, single-nucleotide polymorphism.