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Acid-Sensing Ion Channels Contribute to Neurotoxicity

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Abstract

Acidosis that occurs under pathological conditions not only affects intracellular signaling molecules, but also directly activates a unique family of ligand-gated ion channels: acid-sensing ion channels (ASICs). ASICs are widely expressed throughout the central and peripheral nervous systems and play roles in pain sensation, learning and memory, and fear conditioning. Overactivation of ASICs contributes to neurodegenerative diseases such as ischemic brain/spinal cord injury, multiple sclerosis, Parkinson's disease, and Huntington's disease. Thus, targeting ASICs might be a potential therapeutic strategy for these conditions. This mini-review focuses on the electrophysiology and pharmacology of ASICs and roles of ASICs in neuronal toxicity.

Keywords

Acid-sensing ion channels; Neurodegenerative diseases; Neurotoxicity

Introduction

Under pathological conditions such as tissue inflammation, infections, ischemic stroke, traumatic brain/spinal cord injury, cancer, and epileptic seizure, lactic acid accumulates because of increased anaerobic glucose metabolism and the release of protons from ATP hydrolysis. These mechanisms cause a profound decrease in tissue pH, termed acidosis. Acidosis has long been considered to aggravate cell injury through intracellular signaling molecule mechanisms [1, 2]. However, it can also activate a unique family of ligand-gated

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ion channels: acid-sensing ion channels (ASICs) [3], which are highly expressed in the central and peripheral nervous system [4–12].

ASICs are members of the epithelial Na^+ channel/degenerin (ENaC/DEG) family of ion channels [13]. At least six different ASIC subunits (ASIC1a, 1b, 2a, 2b, 3, and 4) have been identified so far, which are encoded by four genes (*ACCN1–ACCN4*). The members of this superfamily are largely permeable to Na^+ and, to a lesser degree, to Ca^{2+} in certain subunit(s). ASICs also share the same topology with ENaC/DEG family, consisting of two trans-membrane (TM) domains, a large, cysteine-rich extracellular loop, and short intracellular N- and C-termini [3]. Functional ASICs are trimeric complexes of these subunits [14, 15], and most of these subunits can form homomeric and/or heteromeric channels [16–27]. ASIC2b and ASIC4 cannot form functional channels by themselves, but they can associate with other ASIC subunits to assemble functional channels with different properties [27].

ASICs are widely expressed in brain neurons [28–30], where at least three (ASIC1a, ASIC2a, and ASIC2b) of the six subunits can be found. ASIC1a is the predominant subunit in the brain; this is because deleting ASIC1a gene in mice eliminates majority of the ASIC currents [20, 24–26]. Homomeric ASIC1a and heteromeric ASIC1a/2b channels are permeable to both Na^+ and Ca^{2+} ions [3, 24, 27, 31]. In peripheral sensory neurons, all ASIC subunits exist and different combinations of ASIC subunits contribute to ASIC currents [9].

Although the primary ligand for ASICs is the proton, the large extracellular loop (more than 350 amino acids) of these channels is suitable for other non-proton ligands. For example, 2-guanidine-4-methylquinazoline (GMQ) and MitTx from the venom of the Texas coral snake have been identified as ligands for ASICs [32, 33]. ASICs are inhibited by the diuretic amiloride, a nonselective ASIC blocker [3]. The tarantula toxin psalmotoxin 1 (PcTx1) blocks homomeric ASIC1a [34] and heteromeric ASIC1a/2b [27] channels. Mambalgins, snake toxins from the black mamba, inhibit homomeric ASIC1 and heteromeric ASIC1-containing channels [35]. The APETx2, a sea anemone toxin, inhibits homomeric ASIC3 and ASIC3-containing heteromeric channels [36]. The newly discovered peptide toxin PhcrTx1, a sea anemone *Phymanthus crucifer*, inhibits peak ASIC currents in rat dorsal root ganglion (DRG) neurons [37].

The functional roles of ASICs in the nervous system are still under active investigation. ASIC1a channels localize at cell bodies, dendrites, and postsynaptic dendritic spines and participate in synaptic plasticity, learning and memory, and fear conditioning [19, 20, 38]. However, a recent study from the Lien group suggests that ASIC1a is not necessary for normal hippocampal long-term potentiation (LTP) and spatial memory [39]. Normal LTP is observed in ASIC1a conditioning knockout mice, and disrupting the ASIC1a gene in mice does not impair hippocampal spatial memory [39]. Therefore, the role of ASIC1a in learning and memory remains controversial. Activation of Ca^{2+}-permeable homomeric ASIC1a and heteromeric ASIC1a/2b channels contributes to acidosis-mediated ischemic brain injury [24, 27, 40–43]. Moreover, ASIC1a channels play critical roles in neurodegenerative diseases such as multiple sclerosis [44–46], Parkinson's [47] and Huntington's [48] disease, seizure

disorder [49], and depression [50]. Thus, controlling their activation might ameliorate acidosis-mediated CNS disorders [11, 41–43]. This mini-review summarizes recent progress in the electrophysiology and pharmacology of ASICs and roles of ASICs in neuronal toxicity.

Electrophysiology of ASICs

As shown in Tables 1 and 2, homomeric and heteromeric ASICs display different pH sensitivities that allow them to detect changes in pH under either physiological or pathological conditions [5–7]. The electrophysiological properties of ASICs have been extensively studied in heterologous expression systems [3, 22, 51, 52] and in neurons from different brain regions, such as hippocampus [17, 21], cortex [22–24, 53], cerebellum [54], striatum [26], retinal ganglion [55], and spinal cord [18, 56].

ASIC1a is a critical subunit of ASICs and widely expressed in central as well as peripheral sensory neurons [3, 7, 8]. Homomeric ASIC1a channels have a pH for half-maximal activation (pH_{50}) between 6.2 and 6.8 [16, 26, 30, 51, 57]. Although the precise configuration of ASICs in native neurons is uncertain, homomeric ASIC1a and heteromeric ASIC1a/2 channels are believed to be the major components in brain neurons [19, 21, 24, 26, 30]. For instance, rapid drops in extracellular pH from 7.4 to lower levels (e.g., 6.0, 5.0, and 4.0) trigger transient inward currents in cultured medium spiny neurons (MSNs) of the mouse striatum [26]. The dose–response curve for the activation of ASICs reveals a pH_{50} value of 6.25. This pH_{50} value of ASICs in MSNs is comparable to that of homomeric ASIC1a channels [3]. The ASIC currents in MSNs have a linear current–voltage relationship with a reversal potential close to +60 mV, suggesting that ASICs in MSNs are Na^+ selective.

Unlike homomeric ASIC1a channels, channels that contain rodent homomeric ASIC1b differ in that (1) although the final two thirds of the amino acid sequences of the ASIC1a and ASIC1b proteins are identical, there are significant differences in the first 172 amino acids beginning at the N terminal; this sequence includes the intracellular N-terminus, the TM1 domain, and the proximal part of the ectodomain [58, 59]; (2) expression of ASIC1b in the nervous system is limited to peripheral sensory neurons, while ASIC1a is also expressed in the CNS; (3) rodent ASIC1b is impermeable to Ca^{2+} while ASIC1a channels have significant Ca^{2+} permeability. Interestingly, a recent study has shown that human ASIC1b channels are permeable to Ca^{2+} [60]; (4) the threshold for activation of ASIC1b currents is lower than ASIC1a (~6.5 for ASIC1b and ~7.0 for ASIC1a) and it has lower pH_{50} (5.9); and (5) ASIC1b is potentiated by PcTx1 [61], which is a selective inhibitor of ASIC1a.

ASIC2a and ASIC2b are expressed in the brain [21, 27]. Different from brain ASIC1a subunit, brain ASIC2a and 2b subunits are not critical for acid-evoked currents [21]. Homomeric ASIC2a channels are relatively insensitive to protons, with a pH_{50} of 4.4 [62–64]. However, ASIC2a sub-units associate with ASIC1a to form heteromeric ASIC1a/2a channels in the brain [21–24] and with ASIC3 to assemble heteromeric ASIC2a/3 channels in peripheral sensory neurons [66]. Different from homomeric ASIC2a subunits, homomeric ASIC2b subunits do not form functional channels by themselves, but associate with other ASIC subunits to form heteromultimeric channels [27, 52, 64]. For example, ASIC2b can

associate with ASIC1a to form functional ASIC1a/2b channels with Ca^{2+} permeability, which is involved in acidosis-induced neuronal injury [27]. Therefore, ASIC2a and ASIC2b subunit can interact with other ASIC subunits and reveal different pH sensitivity, desensitization kinetics, and ion selectivity of ASICs [22, 27, 52].

ASIC3 is expressed primarily in peripheral sensory neurons and is very sensitive to pH drops [56, 64–67]. For example, a decline of 0.2 pH units (e.g., a fall in pH from 7.4 to 7.2) can trigger inward currents in CHO cells expressing homomeric ASIC3 channels [68]. In contrast to other subunits of ASICs, homomeric ASIC3 channels can respond to a large drop of extracellular pH with a transient inactivating current followed by a sustained component [65, 68, 69]. The transient currents are highly sensitive to protons, with a pH_{50} of around 6.5 [65, 69]. Electrophysiological studies have shown that ASIC3 subunits function as homomeric or heteromeric channels in sensory neurons [16, 70–75]. They can sense extracellular acidification occurring under physiological or pathological conditions, such as cutaneous touch, pain perception, inflammation, and ischemia [70, 74, 76–82]. For example, ASIC3 channels expressed in cardiac sensory neurons can respond to myocardial ischemia [70, 75, 82]. Furthermore, cutaneous sensory neurons from rats display large ASIC3-like currents when stimulated by moderate acidosis [72]. More recently, ASIC3 is identified as an essential neuronal sensor for the vasodilation response to direct pressure in both humans and rodents and for protecting against pressure ulcers in mice [74].

ASIC4 subunits are expressed in pituitary gland. Similar to ASIC2b, they do not seem to form functional homomeric channels [83, 84]. Interestingly, perfusion of ASIC4-expressing oocytes with acidic solutions of a pH down to 4.0 does not elicit any channel activity. Based upon its high expression in pituitary gland, ASIC4 might modulate the release of pituitary hormones [84].

Pharmacology of ASICs

The pharmacological profiles of ASICs have been listed in Tables 1 and 2.

Amiloride

Amiloride, a nonspecific blocker of ASICs, is a potassium-sparing diuretic agent and commonly used in the management of hypertension and congestive heart failure. It inhibits ASIC currents and acid-induced increases in intracellular Ca^{2+} ($[Ca^{2+}]_i$) with an IC_{50} of 10–60 μM [3, 18, 24, 26]. Unlike currents mediated by other homomeric ASICs, however, the sustained current mediated by homomeric ASIC3 channels is insensitive to amiloride and it can be potentiated by amiloride [82]. Based on the studies of ENaC, it is believed that amiloride inhibits ASICs by a direct blockade of the channel [85–87]. The pre-TM II region of the channel is critical for the effect of amiloride. Mutation of Gly-430 in this region, for example, dramatically changed the sensitivity of ASIC2a current to amiloride [88]. Consistent with its inhibition on the ASIC current, amiloride has been shown to reduce acid-induced pain in the peripheral sensory system [89–92] and acidosis-mediated injury of CNS neurons [24, 31]. Despite its clinical availability, amiloride has affinity for other ion channels (e.g., ENaC and T-type Ca^{2+} channels) and ion exchange systems (e.g., Na^+/H^+ and Na^+/Ca^{2+} exchanger). Based upon this modest specificity for ASICs, there is limited

enthusiasm for evaluating the use of amiloride as a future neuroprotective agent in humans. It is worth mentioning that the normal activity of Na^+/Ca^{2+} exchangers, for instance, is critical for maintaining the cellular Ca^{2+} homeostasis and the survival of neurons against delayed calcium deregulation caused by glutamate receptor activation [93]. Inhibition of Na^+/Ca^{2+} exchangers by amiloride may therefore compromise normal neuronal Ca^{2+} handling, thereby, potentiating excitotoxicity [93].

A-317567

A-317567, a small molecule structurally unrelated to amiloride, is another nonselective ASIC blocker [92]. It inhibits the ASIC1a, ASIC2a, and ASIC3-like currents in rat DRG neurons with an IC_{50} of 2–30 μM. Unlike amiloride which has no effect on the slow component of the ASIC3 current, A-317567 blocks both fast and sustained ASIC3 currents. Also different from amiloride, A-317567 does not show diuresis or natriuresis activity [92], suggesting that it is more specific for ASICs than amiloride. Its inhibition of sustained ASIC3 currents suggests that it might be potent in reducing acidosis-mediated chronic pain. Indeed, A-317567 has been shown to be effective in suppressing pain in a rat model of thermal hyperalgesia at a dose tenfold lower than amiloride [92]. Based upon this observation, it would be interesting to know the effects of this small molecule on nociceptive behavior in humans.

PcTx1

PcTx1, a peptide toxin isolated from venom of the South American tarantula *Psalmopoeus cambridgei*, is a potent inhibitor for homomeric ASIC1a and heteromeric ASIC1a/2b channels [27, 34]. This toxin contains 40 amino acids cross-linked by three disulfide bridges. In heterologous expression systems, PcTx1 inhibits the acid-activated currents mediated by homomeric ASIC1a subunits with an IC_{50} of 0.7 nM [34]. At concentrations that effectively inhibit the homomeric ASIC1a current, it has no effect on the currents mediated by other configurations of ASICs such as ASIC2a and ASIC3 [34] or known voltage-gated Na^+, K^+, and Ca^{2+} channels as well as several ligand-gated ion channels (NMDA and GABA-mediated currents) [24]. Therefore, PcTx1 was thought to act as a specific inhibitor of homomeric ASIC1a prior to 2011, but now, this concept has been changed. Recently, heteromeric ASIC1a/2b channels expressed in oocytes are also inhibited by PcTx1 with an IC_{50} of 2.64 nM, which is similar to its inhibition of homomeric ASIC1a channels expressed in oocytes with an IC_{50} of 3.64 nM [27]. Unlike amiloride which directly blocks the ASICs, PcTx1 acts as a gating modifier. When binding to ASIC1a, it shifts the channel from its resting state toward the inactivated state by increasing its apparent affinity for protons [59]. In contrast to ASIC1a, PcTx1 binds most tightly to the open state of the ASIC1b, promoting opening of the channel and potentiating the ASIC1b channel [61]. Therefore, selective concentrations of PcTx1 inhibit and potentiate ASIC1a and 1b channels, respectively. Also, we should keep in mind that PcTx1 is a selective, but not specific inhibitor of ASIC1a channel.

APETx2

APETx2, a peptide toxin isolated from the sea anemone *Anthopleura elegantissima*, is a potent and selective inhibitor for homomeric ASIC3 and ASIC3-containing channels [36].

The toxin contains 42 amino acids, which are cross-linked by three disulfide bridges. It inhibits transient peak acid-evoked currents mediated by homomeric ASIC3 channels and ASIC-like currents in DRG neurons [36]. In contrast to the peak ASIC3 current, the sustained component of the ASIC3 current is insensitive to APETx2. In addition to homomeric ASIC3 channels (IC_{50} =63 nM for rat and 175 nM for human), APETx2 inhibits heteromeric ASIC3/1a (IC_{50} =2 μM), ASIC3/1b (IC_{50}=900 nM), and ASIC3/2b (IC_{50}=117 nM). Homomeric ASIC1a, ASIC1b, ASIC2a, and heteromeric ASIC3/2a channels, on the other hand, are not sensitive to APETx2 [36].

Mambalgins

Mambalgins are peptides isolated from black mamba that belong to the family of three-finger toxins and have no sequence homology with either PcTx1 or APETx2. They inhibit homomeric ASIC1a and heteromeric ASIC1a/2a or ASIC1a/2b channels that are expressed in the CNS, with the IC_{50} values between 50 and 250 nM. Mambalgins also inhibit ASIC1b and ASIC1a/1b channels that are specific for sensory neurons with IC_{50} values of 192 and 72 nM, respectively. Mambalgins potently inhibit native ASIC currents in spinal cord, hippocampal, and sensory neurons and have no effect on ASIC2a, ASIC3, ASIC1a/3, and ASIC1b/3 channels, as well as on TRPV1, P2X2, 5-HT_{3A}, Nav1.8, Cav3.2, and Kv1.2 channels [35]. Mambalgins induce a strong shift of the pH-dependent activation of ASIC1a channel towards more acidic pH, with only a minor effect on the steady-state inactivation that is shifted towards more alkaline pH. Moreover, mambalgins bind more tightly to the closed state and to a much lesser extent the inactivated/desensitized state of the ASIC1a channel, promoting closure of the channel at any pH [35].

PhcrTx1

This newly discovered peptide toxin has been isolated from the sea anemones *P. crucifer* [37]. PhcrTx1 inhibits peak ASIC currents in rat DRG neurons with an IC_{50} of 0.1 μM, without affecting the sustained component of the current or its desensitization rate. Furthermore, the toxin reveals its effect in a closed rather than open state of the ASICs. PhcrTx1 also inhibits voltage-gated K^+, but not voltage-gated Na^+, currents in rat DRG neurons with an IC_{50} of 3.4 and 3.5 μM, for peak and steady-state component, respectively. PhcrTx1 inhibits voltage-gated K^+ currents in DRG neurons, but with significantly lower potency and efficacy than the inhibition on ASIC currents. Thus, PhcrTx1 represents the first member of a new structural group of sea anemone toxin acting on both ASICs and K_v channels, with high and low potency, respectively [37].

Activation of ASICs Triggers Membrane Depolarization and Increases Intracellular Ca^{2+} in Brain and Spinal Cord Neurons

Membrane depolarization is often caused by influx of cations, e.g., Na^+ or Ca^{2+} influxes through voltage-gated or ligand-gated ion channels. ASICs as ligand-gated and Na^+-selective cation channels have a reversal potential close to Na^+ equilibrium potential (+60 mV), and activation of ASICs by pH drop at resting membrane potentials triggers exclusively inward currents which result in membrane depolarization and the excitation of neurons [17, 26, 56]. For instance, a minor drop in extracellular pH from 7.4 to 6.8 elicits a

profound membrane depolarization, which is accompanied by trains of action potentials [26]. This acid-mediated membrane depolarization is significantly inhibited by selective or nonselective ASIC blockers, suggesting involvement of ASICs in membrane depolarization. Tetrodotoxin, a voltage-gated Na^+ channel inhibitor, has little effect on the membrane depolarization but completely diminishes the action potentials triggered by a drop in pH from 7.4 to 6.8. In addition, the ASIC-mediated membrane depolarization may facilitate the activation of voltage-gated Ca^{2+} channels and NMDA receptor-gated ion channels [19, 25], further promoting neuronal excitation and $[Ca^{2+}]_i$ accumulation. The Ca^{2+} permeability of ASICs in CNS neurons has been characterized using fluorescent Ca^{2+} imaging and ion substitution protocols [24, 27, 31, 94]. In rodent cortical, striatal, hippocampal, and spinal neurons, activation of ASICs by reduction of extracellular pH induces increases in $[Ca^{2+}]_i$. This acid-induced increase in $[Ca^{2+}]_i$ could be recorded in the presence of a cocktail blocking other voltage-gated and ligand-gated Ca^{2+} channels [24, 26, 94], indicating a Ca^{2+} entry directly through ASICs. The acid- induced increase in $[Ca^{2+}]_i$ is eliminated by selective ASIC1a and ASIC1a/2b inhibitor PcTx1 or by deleting ASIC1a gene [24, 26, 27, 31]. Thus, homomeric ASIC1a and heteromeric ASIC1a/2b channels constitute additional and important Ca^{2+} entry in neurons [3, 24, 27, 31, 51].

Neurotoxicity Triggered by Activation of ASICs in Neurodegenerative Diseases

ASICs in Ischemic Brain and Spinal Cord Injury

Acidosis has long been recognized to play a critical role in ischemic brain and spinal cord injury [1, 2]; however, the cellular and molecular mechanisms underlying this effect remain uncertain. Acidosis directly triggers intracellular molecule and/or signaling, which contributes to cell death. The hypothesis of that activation of ASICs is responsible for acidosis-mediated neuronal injury is based on the following evidence: (1) ASICs, especially type 1a, are expressed at high levels in the brain and spinal cord; (2) falls in pH to levels commonly seen in ischemia also activate ASICs; and (3) the demonstrated role of ASICs in $[Ca^{2+}]_i$ accumulation is widely accepted as a mediator of cell death [24]. To support this hypothesis, recent studies from many groups have shown that both ASIC1a and ASIC1a/2b channels contribute to acidosis-mediated neuronal injury [24, 27, 31, 40, 94–99]. For instance, in cultured mouse, rat, and human cortical or spinal neurons, activation of ASICs by acidosis induces glutamate receptor-independent neuronal injury, which is inhibited by pretreatment with PcTx1, which selectively inhibits ASIC1a and ASIC1a/2b and/or by disrupting ASIC1a gene in mice [24, 27, 40, 94, 98]. In rodent models of brain ischemia, intracerebroventricular injection of PcTx1 can reduce infarct volume produced through transient or permanent focal ischemia by up to 60 % [24, 40]. Similarly, deleting the gene encoding ASIC1 in mice shows significant neuroprotection [24]. The neuroprotection by PcTx1 has a time window of efficacy of up to 5 h, and the protection persists for at least 7 days [40]. These data suggest that homomeric ASIC1a and heteromeric ASIC1a/2b channels play a critical role in acidosis-mediated neuronal death and implicate the ASIC1a and ASIC1a/2b channels as novel pharmacological targets to prevent neuronal injury after stroke [24, 27, 40].

Unlike observations based on ASIC1a, increased ASIC2a expression appears to provide neuroprotection against ischemic brain injury [100]. Increased ASIC2a expression levels are found in hippocampal neurons that survive global ischemia. Double labeling for DNA strand breaks and ASIC2a expression reveal that only cells without DNA damage express ASIC2a. Increased ASIC2a expression may favor the hypothesis that formation of heteromeric ASIC1a/ASIC2a channels behaves reduced acid sensitivity and no Ca^{2+} permeability. Therefore, the activity of ASIC2a channels may serve as both a signal that opposes to ASIC1a and a potential therapy that protects against ischemic insult.

ASIC1 Channels in Multiple Sclerosis (MS)

MS is an autoimmune disease that affects the brain and spinal cord, associated with axonal degeneration. Previous studies have shown that excessive accumulation of Na^+ and Ca^{2+} ions is involved in axonal degeneration, and activation of ASIC1 also triggers accumulation of Na^+ and Ca^{2+} ions [3, 101, 102]. Consistent with this idea, data from the Fugger group has shown that activation of ASIC1 is responsible for inflammatory lesions in the CNS [44]. In an experimental model of autoimmune encephalomyelitis (EAE), deletion of ASIC1 gene in mice attenuates motor deficits and axonal degeneration. Furthermore, pH measurements in the spinal cord of EAE mice display tissue acidosis sufficient to open ASIC1. Moreover, the ASIC1 gene disruption also shows protective effect in nerve explants in vitro. ASIC blockade by amiloride is equally neuroprotective in nerve explants and in EAE. Thus, ASIC1 may serve as a potential target for axon degeneration associated with MS.

To better understand the role of ASIC1 in MS, they further explore ASIC1 activity in spinal cord and optic nerve tissue from patients with MS and mice with acute and chronic EAE [45]. Increased ASIC1 expression is found in axons and oligodendrocytes within lesions from mice with acute EAE and from patients with active MS. Activation of ASIC1 contributes to oligodendrocyte injury in vitro and demyelination in EAE. Moreover, amiloride treatment reduces permanent disability in chronic-relapsing EAE and is effective at later disease stages. Collectively, these findings suggest that blockade of ASIC1 is not only neuro- but also myelo-protective and, therefore, could form the basis for a new treatment of established CNS inflammatory disease such as MS [45].

More recently, a study from the Palace group has shown that amiloride exerts a protective effect in patients with primary progressive MS. After 3 years of treatment with amiloride in MS patients, a significant reduction is found in normalized annual rate of whole-brain volume during the treatment phase compared with the pretreatment phase. Consistent with this reduction, changes in diffusion indices of tissue damage within major clinically relevant white matter and deep grey matter structures are significantly reduced during the treatment phase. These results extend evidence of the contribution of ASIC1 to neurodegeneration in MS and suggest that amiloride may exert a neuroprotective effect in patients with progressive MS. This pilot study is the first translational study on neuroprotection targeting ASIC1 and supports future randomized controlled trials measuring neuroprotection with amiloride in patients with MS [46].

ASICs in Parkinson's Disease (PD)

PD is a neurodegenerative disorder, characterized by the inexorable loss of dopaminergic neurons from the substantia nigra (SNc) [103]. However, the underlying mechanism of neuronal loss is uncertain. Given the findings of lactic acidosis in the brains of PD patients [104] as well as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice [105] and expression of ASICs in dopamine neurons [106], the effects of two ASIC blockers in a mouse model of PD induced by MPTP treatment have been studied [47]. The brain-penetrant small molecule amiloride has protected SNc neurons from MPTP-induced degeneration and also preserved dopaminergic cell bodies in this brain region. Furthermore, central administration of PcTx venom also results in a modest effect, attenuating deficits in striatal DAT binding and dopamine. These findings suggest a potential role for ASICs as a mediator underlying the pathogenesis of PD.

ASICs in Huntington's Disease (HD)

HD is a progressive, fatal neurodegenerative disease that is clinically characterized by a triad of cognitive dysfunction, psychiatric disturbances, and motor impairment. In addition, patients develop weight loss and muscle wasting [107]. Acidosis and deficits in energy metabolism have been observed in both in vitro and in vivo models of HD as well as in the brains of HD patients [107]. Treatments that decrease or enhance activity of the ubiquitin-proteasome system (UPS) may be an attractive strategy against HD and possibly other neurodegenerative disorders. To support this idea, contribution of ASICs in the pathology of HD as well as the effects of amiloride derivative benzamil in HD pathological processes are determined [48]. Treatment with benzamil profoundly alleviates the huntingtin-polyglutamine (htt-polyQ) aggregation in an inducible cellular system. In addition, the effect of benzamil is recapitulated in the R6/2 animal model of HD. Furthermore, benzamil reduces the inhibition of UPS activity, resulting in enhanced degradation of soluble htt-polyQ specifically in its pathological range. Inhibiting the expression of ASIC1a with siRNA also increases UPS activity, resulting in decreased htt-polyQ aggregation in the striatum of R6/2 mice. Therefore, targeting ASIC1a might be an effective approach against HD through modulation of UPS.

Conclusion and Perspective

ASICs are a novel class of ligand-gated ion channels that are expressed primarily in the nervous system and appear as a new receptor both for proton and non-proton ligands. Increasing evidence implicates the involvement of these channels in a variety of physiological and pathological CNS processes. Most importantly, overactivation of Ca^{2+}-permeable ASICs contributes to neurodegeneration. Indeed, several lines of evidence support the hypothesis that ASICs are involved in neurodegenerative diseases such as ischemic stroke. For example, a number of selective and nonselective ASIC inhibitors have been found to exert neuroprotective effects in cerebral ischemia or ischemic stroke. At present, a promising selective ASIC blocker is PcTx1. Because it is a large peptide with no permeability to the blood–brain barrier, it would be difficult to use routinely in stroke patients. Further study will be required to determine the active component of PcTx1, which may be transferable to small molecules, and to validate their use in experimental stroke.

Success of the compounds or agents derived from PcTx1 might, therefore, be valuable for therapeutic purpose in ischemic stroke patients, either alone or in combination with currently approved stroke treatment. Furthermore, development of other potent and specific blockers for individual ASICs may also advance our understanding of the role of these channels in physiological and pathological conditions, leading to novel therapeutic strategies for neurological disorders.

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Table 1

Electrophysiological and pharmacological properties of homomeric ASIC

Gene	Protein	Alternative name	pH_{50} activation	Non-proton ligand	Inhibitor
ACCN2	ASIC1a	ASICα BNaC2α	6.2–6.8	MitTx	Amiloride PcTx1 Mambalgins PhcrTx1 Zn^{2+}
	ASIC1b	ASICβ BNaC2β	5.9	MitTx	Amiloride Mambalgins PhcrTx1 Zn^{2+}
ACCN1	ASIC2a	BNaC1α BNC1a	4.4	MitTx	Amiloride
	ASIC2b	BNaC1β MDEG2	N/A	ND	N/A
ACCN3	ASIC3	DRASIC TNaC	6.2–6.7	GMQ MitTx	Amiloride APETx2 Zn^{2+}
ACCN4	ASIC4	SPASIC	N/A	ND	N/A

N/A not applicable, *ND* not determined

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Table 2

Electrophysiological and pharmacological profiles of heteromeric ASICs

Protein	pH_{50} activation	Non-proton ligand	Inhibitor	Distribution
ASIC1a/2a	5.5–5.8	MitTx	Mambalgins	PNS, CNS
ASIC1a/2b	6.2	ND	PcTx1; Mambalgins	PNS, CNS
ASIC1a/3	6.3	MitTx	APETx2	PNS
ASIC1b/3	6.0–6.2	ND	APETx2	PNS
ASIC2a/3	5.7	MitTx	Amiloride	PNS
ASIC2b/3	6.5	ND	APETx2	PNS
ASIC1a/1b	6.0	ND	Mambalgins	PNS

ND not determined, *PNS* peripheral nervous system, *CNS* central nervous system