

Review Article

Novel Insights into Acid-Sensing Ion Channels: Implications for Degenerative Diseases

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ABSTRACT: Degenerative diseases often strike older adults and are characterized by progressive deterioration of cells, eventually leading to tissue and organ degeneration for which limited effective treatment options are currently available. Acid-sensing ion channels (ASICs), a family of extracellular H⁺-activated ligand-gated ion channels, play critical roles in physiological and pathological conditions. Aberrant activation of ASICs is reported to regulate cell apoptosis, differentiation and autophagy. Accumulating evidence has highlighted a dramatic increase and activation of ASICs in degenerative disorders, including multiple sclerosis, Parkinson's disease, Huntington's disease, intervertebral disc degeneration and arthritis. In this review, we have comprehensively discussed the critical roles of ASICs and their potential utility as therapeutic targets in degenerative diseases.

Key words: acid-sensing ion channel (asic), calcium (ca²⁺), degenerative diseases, therapeutic target

Degenerative diseases are characterized by massive cell loss, ultimately leading to deterioration in quality or function of tissues or organs and possible failure of vital organs [1, 2]. Although the etiology and pathogenesis of these diseases remain unclear, recent advances indicate that the processes of organ deterioration share common core features, including cell injury and dysfunction that contribute to functional and morphological impairment of cells. Despite considerable progress in understanding the molecular mechanisms of degenerative diseases, current therapeutic options are limited and no effective treatment drugs have emerged to date. Elucidation of both the common and unique mechanisms of deterioration may therefore facilitate the identification and development of effective anti-degenerative targets and drugs.

Acid-sensing ion channels (ASICs) belonging to the

degenerin/epithelial sodium channel (DEG/ENaC) superfamily are widely distributed within mammalian nervous systems as well as non-neural tissues, such as cancer cells [3], articular chondrocytes [4] and intervertebral disc cells [5], where they play significant pathophysiological roles. ASICs are proton-gated cation channels activated by acidosis, lactate and arachidonic acid, which are involved in Na⁺ and Ca²⁺ flux [6]. Intracellular Ca²⁺ ([Ca²⁺]_i) is a ubiquitous second messenger in signal transduction pathways that modulates diverse physiological functions. Under pathological conditions, a robust increase in [Ca²⁺]_i usually occurs through various extracellular Ca²⁺ influx and intracellular Ca²⁺ release mechanisms [7]. Ca²⁺ influx into cells is commonly mediated through activating channels or receptors, such as voltage-gated Ca²⁺ channels, α -amino-

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3-hydroxyl-5-methyl-4-isoxazole-propionate receptors, transient receptor potential channels, and *N*-methyl-D-aspartate receptors [8]. Interestingly, ASICs have been shown to play crucial roles in modulating cell behavior via regulation of intracellular Ca^{2+} accumulation, including apoptosis [4, 9], differentiation [10], and autophagy [11]. Multiple lines of evidence suggest that aberrant expression and activation of ASICs contribute to the progression of various degenerative diseases, including multiple sclerosis, Parkinson's disease, Huntington's disease, intervertebral disc degeneration and arthritis. This review provides a summary of the properties of ASICs and their functional roles in the degenerative processes of several diseases, with further focus on their potential utility as novel pharmacological and therapeutic targets for degenerative diseases.

Structure and characteristics of ASICs

ASICs are voltage-independent, proton-gated cation channels that can be blocked by amiloride. To date, at least seven different ASIC isoforms (ASIC1a, ASIC1b,

ASIC1b₂, ASIC2a, ASIC2b, ASIC3, ASIC4) encoded by four separate genes (*Accn1*, *Accn2*, *Accn3* and *Accn4*) have been identified in mammals [12-14]. All members of the ASIC family share the same topology as the DEG/ENaC family, comprising two hydrophobic transmembrane domains (TM1 and TM2), short intracellular N- and C- termini, and a large cysteine-rich extracellular loop [15, 16] (Fig.1A). The extracellular domain of ASICs has a highly negative cavity, designated 'acidic pocket', which is located distant from the transmembrane domain [17]. This acidic pocket, considered an ASIC pH sensor, contains several pairs of acidic amino acids and is responsible for acid-dependent gating, desensitization as well as response to specific extracellular modulators [18]. The functional channel of ASICs is a trimer of these subunits [17] (Fig.1B). The majority of homomeric and/or heteromeric trimers have different properties. Interestingly, however, ASIC2b and ASIC4 cannot form functional homomeric proton-gated channels by themselves [19, 20].

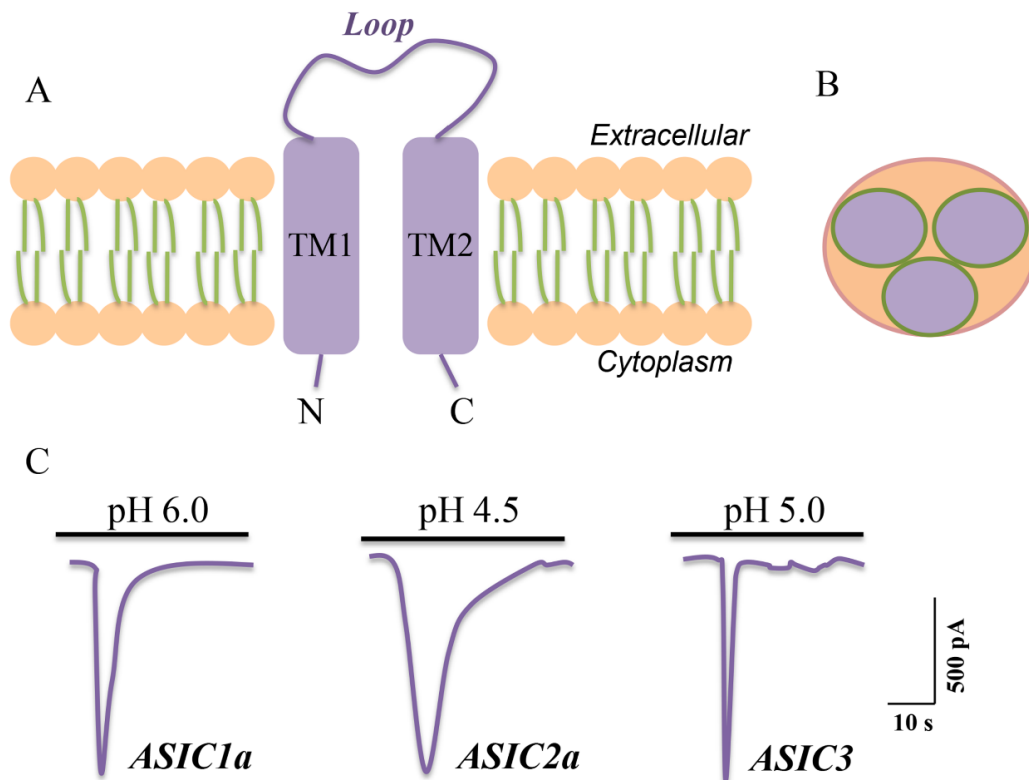


Figure 1. The structure and electrophysiological properties of ASICs. (A) Structure of individual ASIC subunits. (B) Three subunits assemble to form a functional homo- or heterotrimeric channel. (C) Electrophysiological properties of ASICs: representative traces of ASIC1a, ASIC2a, and ASIC3 in pH 6.0, 4.5, and 5.0 solutions, respectively. The membrane potential was clamped to -60 mV.

Table 1. Properties of ASIC channels

Gene	Protein	Alternative name	pH ₅₀ activation	Inhibitor	References
Accn2	ASIC1a	ASIC α BNaC2 α	6.2-6.8	Amiloride PcTx1 Mambalgins Benzamil; A-317567	[6, 15-17, 21, 36]
	ASIC1b	ASIC β BNaC2 β	5.9	Amiloride Mambalgins	
Accn1	ASIC2a	MDEG1 BNaC1 α BNC1	4.35	Amiloride A-317567	[15, 22, 38, 39]
	ASIC2b	MDEG2 BNaC1 β	N/A	N/A	
Accn3	ASIC3	DRASIC TNaC	6.2-6.7	Amiloride APETx2; A-317567	[15, 36, 43, 44]
Accn4	ASIC4	SPASIC	N/A	N/A	[15]

N/A, not applicable

ASIC subunits are abundantly expressed in central and peripheral neurons and non-neural tissues [21], but show variable distribution. All the isoforms are expressed in the peripheral nervous system [22], while ASIC1a, ASIC2a and ASIC2b subunits are primarily localized in the central nervous system (CNS) [19, 23]. ASIC1a is widely expressed throughout the cerebral cortex, hippocampus, cerebellum, pineal gland, amygdala, dorsal root ganglion, and bone [24-27]. ASIC1b is almost exclusively expressed in sensory neurons. In contrast, ASIC3 is predominantly expressed in dorsal root ganglia neurons, especially nociceptive sensory neurons [28]. ASIC4, a new member of this ion channel group, exists within inner ear neurons, adenohypophysis, and intervertebral disc [29, 30].

ASICs are extremely susceptible to reduction of extracellular pH. Under pathological conditions, such as inflammation, ischemia and hypoxia, decrease in extracellular pH from ~7.5 to 4 triggers activation of ligand-gated cation channels, including ASICs [31, 32]. Despite similar topological structures, different subunits display distinct sensitivities to additional decreases in extracellular pH (Fig.1C). For instance, ASIC1a and ASIC3 are the most sensitive to H⁺ channel proteins of these subunits than other ASIC members, which are activated by pH levels below 7.0 [33]. In contrast to ASIC1a homomers, ASIC2a shows low sensitivity to reduced extracellular pH (pH₅₀=4.35) and slow channel inactivation [34, 35]. Moreover, homomeric ASIC2a displays slower kinetics of desensitization than ASIC1a homomers [36, 37]. ASIC2b does not form functional ion

channels by itself, distinct from homomeric ASIC2a subunits [19]. On the other hand, ASIC2b associates with other ASIC subunits to form heteromultimeric channels with unique functional properties [19, 35]. ASIC3 is primarily expressed in peripheral sensory neurons and plays an important role in pain perception, particularly high-intensity pain stimulation and acid-induced hyperalgesia [38]. The current of homomeric ASIC3 consists of instantaneous and steady-state components, which differ significantly in sensitivity to extracellular hydrogen ions [39]. The electrophysiological characteristics of ASIC4 remain largely unknown and require further study (Table 1).

ASICs and Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the CNS affecting both the brain and spinal cord, which leads to axonal degeneration [40]. Although the etiology of MS is unclear, new insights suggest oligodendrocyte apoptosis as one of the critical events in physiological and pathophysiological processes [41]. Several studies have revealed that cytokine and ionic imbalance are the most important factors in axonal degeneration through inducing neuron mitochondrial dysfunction, alteration of ion exchange mechanisms and energy failure [42]. Recent histological analyses and *in vivo* studies have confirmed that undue accumulation of Ca²⁺ and Na⁺ ions contributes to axonal degeneration during MS, and activation of ASIC1 plays a crucial role in accumulation of Na⁺ and Ca²⁺ ions [43, 44]. Disruption

of the *ASIC1* gene in mice markedly attenuated clinical deficits and axonal degeneration in an experimental autoimmune encephalomyelitis (EAE) mouse model of MS. Moreover, pH measurements showed that the pH dropped from ~7.4 to ~6.5 in inflammatory CNS lesions, indicating that tissue acidosis is sufficient to open the ASIC1 channel in the spinal cord of EAE mice. Inhibition of ASICs by the non-specific blocker, amiloride, led to neuroprotective effects against axonal degeneration [40]. Another recent study revealed enhanced expression of ASIC1 in spinal cord, optic nerve tissues and axons within lesions from patients with active MS and mice with acute EAE [45]. Increased ASIC1 expression was additionally observed via co-localization with the axonal damage marker, β -amyloid precursor protein, and associated with axonal injury. Remarkably, amiloride exerted protective effects against myelin and neuronal injury in the acute model, and ameliorated disability in mice with chronic-relapse EAE. In addition, 4-aminopyridine influenced the symptoms of MS as well as the course of the disease via inhibitory actions on ASIC and voltage-gated potassium channels [46]. These findings collectively support the potential efficacy of ASIC1 as a protective target for axon degeneration associated with active MS.

Consistent with the pivotal role of ASIC1 in the animal model of MS, studies by Arun et al. [47] showed that amiloride exerts a neuroprotective effect in patients with primary progressive MS. The normalized annual rate of whole-brain volume during the amiloride treatment phase (3 years) was significantly reduced, compared to the pretreatment phase. Similarly, changes in diffusion indices of tissue damage within primary clinically relevant deep grey matter and white matter structures were markedly alleviated during the treatment phase. A significant association between polymorphisms in MS and ASIC2 was revealed in a genome-wide study, further confirming the theory that ASIC2 is involved in the pathogenesis of MS [48]. Taken together, these findings suggest that blockade of ASICs may provide an alternative therapeutic approach to attenuate axon degeneration associated with MS. Nevertheless, the mechanisms by which ASICs regulate related cellular processes involved in MS, such as inflammation, remain to be established.

ASICs and Parkinson's disease

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by the degeneration of midbrain dopaminergic neurons, resulting in motor dysfunction and disability [49, 50]. The underlying mechanisms of neuronal loss associated with PD processes are currently unclear. A number of cell death pathways have been described in PD. Programmed cell

death is a mechanism underlying cell demise in numerous pathologies, including progressive neurodegenerative disorders [51]. Midbrain dopamine neurons are vulnerable to toxic damage, which leads to disorders, such as PD. The pathologic process is associated with cerebral lactic acidosis. A previous report focused on the presence and characteristics of ASICs in mesolimbic dopamine neurons [52]. More recent studies have provided direct evidence that amiloride not only protects substantia nigra neurons from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced degeneration but also preserves dopaminergic cell bodies in the substantia nigra [53]. Additionally, administration of PcTX venom, a specific blocker of ASIC1a, had a modest effect, reducing loss in striatal dopamine active transporter binding and dopamine uptake. Interestingly, a deficit in the ubiquitin E3 ligase, parkin, significantly promoted the protein kinase C-evoked potentiation of native ASIC-like currents in hippocampal neurons. ASIC signaling may play a pivotal role in defects in parkin-mediated monoubiquitination of protein interacting with C kinase 1 that contribute to dopamine neuron degeneration in PD [54]. Paeoniflorin (PF), a monoterpene glycoside extracted from the root of Chinese herb *Radix Paeoniaealba*, is traditionally used to treat neurodegenerative disorders, especially PD. Both amiloride and PF protected PC12 cells against acid-induced injury and apoptosis by reducing Ca^{2+} influx, possibly through inhibition of ASIC1a channels [55]. Notably, the neuroprotective effects of amiloride and PF were associated with upregulation of autophagy-related protein light chain 3 (LC3)-II. Furthermore, PF enhanced the autophagic degradation of α -synuclein via modulating protein expression and activity of ASICs, subsequently leading to protective effects against acidosis-induced cytotoxicity [11]. These findings collectively support blockade of ASICs as a potential therapeutic strategy for PD. Further studies focusing on the effects of application of ASIC inhibitors to patients with PD are necessary to accurately define the specific roles of ASICs in this neurodegenerative disorder.

ASICs and Huntington's disease

Huntington's disease (HD) is a rare, progressive and fatal hereditary neurodegenerative disease characterized by movement and personality disorders and progressive cognitive decline [56], for which no completely effective treatments in human patients are currently available. A common and widely reported phenomenon of energy metabolism impairment in HD is accumulation of lactic acid in the CNS and possible subsequent acidosis in both animal models and human patients [57, 58]. Wong et al. [59] showed that the amiloride derivative, benzamil, a potent blocker of epithelial sodium channels, significantly

decreases huntingtin-polyglutamine (htt-polyQ) aggregation *in vitro*. The therapeutic effect of benzamil was confirmed in the R6/2 animal model of HD. Administration of benzamil additionally ameliorated inhibition of ubiquitin-proteasome system (UPS) activity, promoting degradation of soluble htt-polyQ specifically in its pathological range. Furthermore, blockage of activity and/or expression of ASIC1a via RNA interference enhanced UPS activity and reduced htt-

polyQ aggregation in the striatum of R6/2 model mice.

The results suggest that ASICs play a pivotal role in the polyQ aggregating process and pathogenesis of HD, and may therefore present an effective therapeutic target for progressive HD and other polyQ-related disorders. However, it is essential to establish the validity of ASIC inhibitors as HD treatment agents in preliminary preclinical studies.

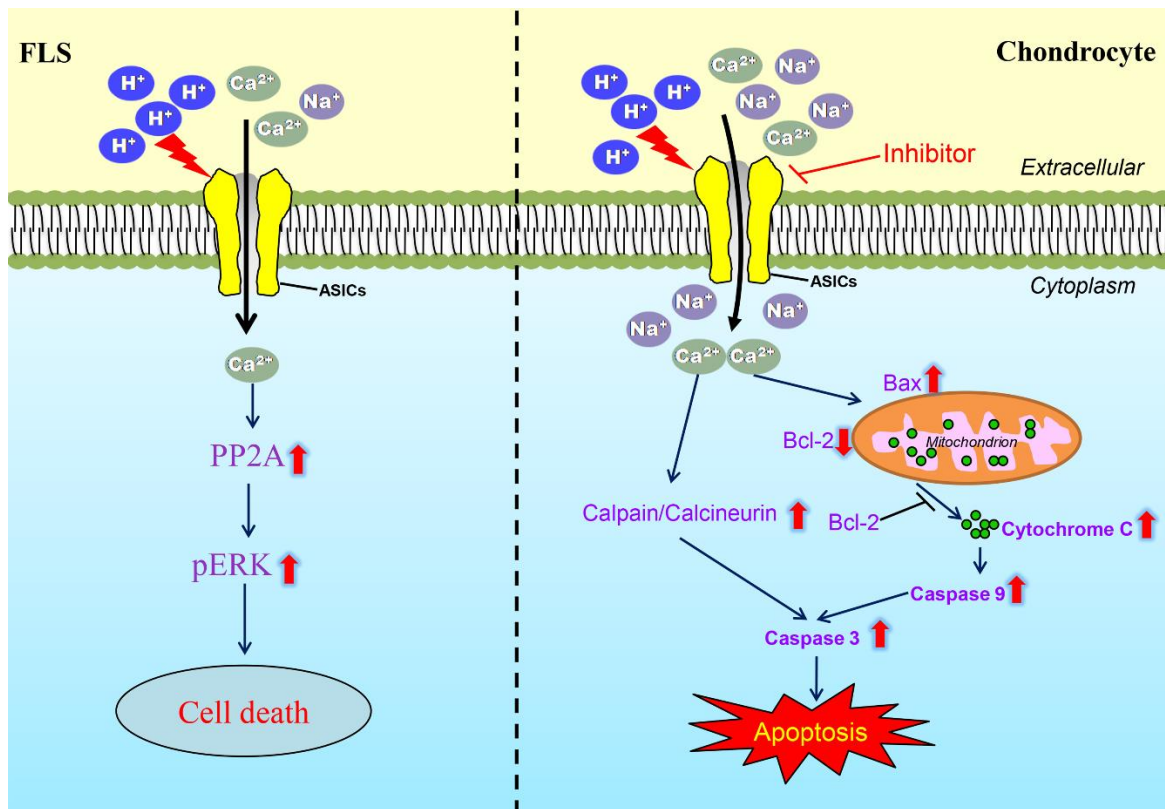


Figure 2. Roles of ASICs in arthritis fibroblast-like synoviocytes and chondrocytes. ASICs were activated by extracellular low pH to positively regulate $[Ca^{2+}]_i$, inducing activation of PP2A and pERK to mediate cell death in FLS. Simultaneously, activated ASICs triggered intracellular Ca^{2+} accumulation in articular chondrocytes and subsequently upregulated Calpain, Calcineurin, Bax, Cytochrome c and Caspase 3/9, ultimately leading to chondrocyte apoptosis in arthritis.

ASICs and Intervertebral Disc Degeneration

Intervertebral disc degeneration (IVDD) is characterized by chronic excessive destruction of the extracellular matrix (ECM), leading to low back pain [60, 61]. Although disc cell death through apoptosis is closely associated with development of IVDD, the underlying mechanisms are not fully elucidated. Under hypoxic

conditions, disc cell metabolism is partially anaerobic, resulting in high concentrations of lactic acid and an acidic environment that is enhanced by the presence of cytokines [62, 63]. Matrix acidity has a potentially negative effect on gene expression, proliferation and viability of disc cells [64]. A recent study reported a significant increase in ASIC1 and ASIC4-positive cells in the annulus fibrosus of degenerated IVD and marked

upregulation of ASIC1, ASIC2 and ASIC3 in the nucleus pulposus [30]. More importantly, Li et al. [65] demonstrated that acid-induced $[Ca^{2+}]_i$ elevation via ASIC1a is involved in endplate chondrocyte apoptosis. Moreover, inhibition of ASIC1a using psalmotoxin 1 (PcTx1) or specific small interfering RNA (siRNA) suppressed acid-induced apoptosis and elevation of $[Ca^{2+}]_i$ in endplate chondrocytes of IVDs. Another recent study by Yuan et al. [66] demonstrated that ASIC1a activation by extracellular acid induces ECM metabolism via increasing matrix metalloproteinases activity and expression through the nuclear factor- κ B (NF- κ B)

signaling pathway in rat endplate chondrocytes.

These results provide evidence that the effects of ASIC1a on IVDD are attributable to its role in modulating cell apoptosis and ECM synthesis. However, gaps still exist in unraveling the precise regulatory mechanisms associating IVDD with different isoforms of ASICs. While these findings suggest considerable promise for inhibition of ASICs as a unique strategy for treatment of IVDD, further research is warranted to determine the biological role of ASICs in IVDD *in vitro* as well as *in vivo*.

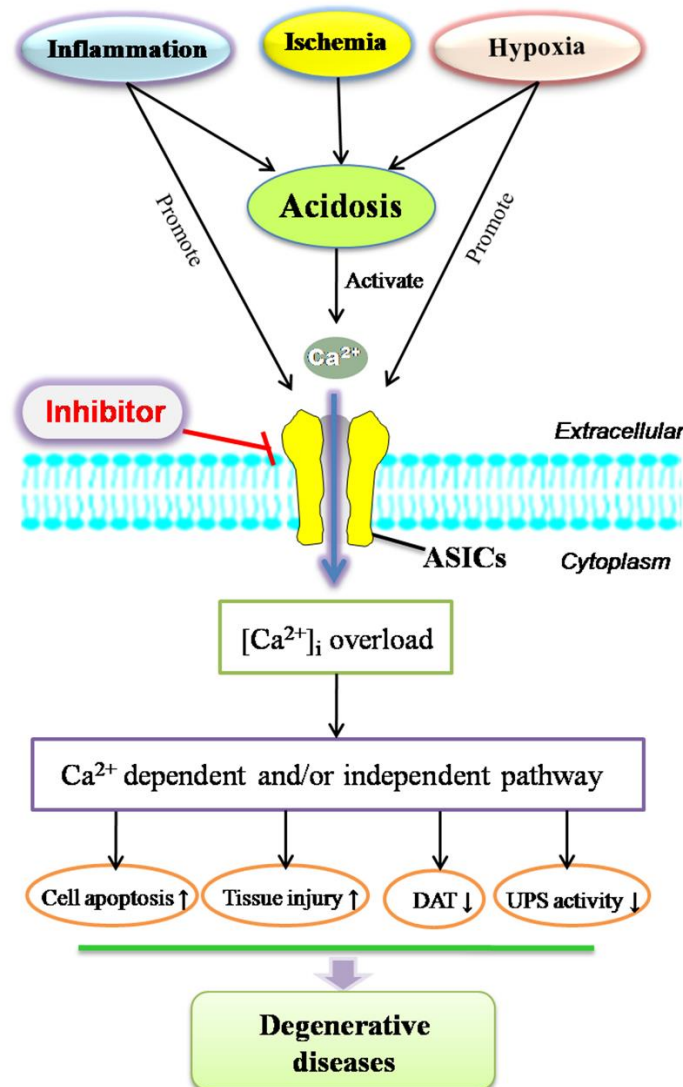


Figure 3. Schematic diagram summarizing the involvement of ASICs in cellular functions. Ischemia, inflammation and hypoxia give rise to tissue acidosis. ASICs are activated by extracellular H⁺ and mediate Ca²⁺ influx. $[Ca^{2+}]_i$ overload in various cell via ASICs leads to the development of degenerative diseases.

Table 2. The roles of ASICs in degenerative diseases

Disease	Experiment model/ cells or Patients	ASICs inhibition	Roles of blocking ASICs	References
MS	EAE	ASIC1 ^{-/-} , amiloride	disease severity↓, axonal loss↓,	[40]
	EAE	ASIC1 ^{-/-} , amiloride	β-APP↑, oligodendrocyte injury↑,	[45]
	Patients	Amiloride	demyelination↑ whole-brain volume↓, diffusion indices of tissue damage↓	[47]
PD	MPTP	Amiloride, PcTX1	SNc neurons degeneration↓, TH↑, DAT↑, DAT radioligand binding↑,	[53]
	PC12 cells	Amiloride, PF	Striatal DAT binding↑, dopamine↑ [Ca ²⁺] _i ↓, LC3-II↑, LAMP2a↓	[55]
HD	R6/2	Benzamil, ASIC1a siRNA	htt-polyQ aggregation↓, UPS↑	[59]
IVDD	endplate chondrocytes	PcTX1, ASIC1a siRNA	apoptosis↓, caspase-9↓, caspase-3↓, MMP-1/9/13↓	[65, 66]
Arthritis	AA	Amiloride	Mankin scores↓, COII↑, aggrecan↑	[25, 72]
	articular chondrocytes	Amiloride, ASIC1a siRNA, PcTX1	[Ca ²⁺] _i ↓, caspase-9↓, caspase-3↓, Bcl- 2↑, Bax↓	[9, 73]
	MIA	APETx2	secondary hyperalgesia↓	[78, 79]
	CAIA	ASIC3 ^{-/-}	inflammation↑, joint destruction↑, [Ca ²⁺] _i ↓	[81-83]

MS, Multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; β-APP, β-amyloid precursor protein; PD, Parkinson's disease; HD, Huntington's disease; IVDD, Intervertebral disc degeneration; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SNc, substantia nigra; TH

ASICs and Arthritis

Arthritis is inflammation of one or more joints resulting in cartilage and bone destruction. The main symptoms are joint pain, swelling and stiffness that are typically exacerbated with age. The most common types of arthritis are osteoarthritis (OA) and rheumatoid arthritis (RA) [67, 68]. Articular cartilage, a thick and highly hydrated biological soft tissue that lines the surfaces of bones in diarthrodial joints such as the knee, is critical for physiological mobility [69]. Under normal conditions, cartilage homeostasis is maintained by the balance between synthesis and degradation of ECM components, including type II collagen and aggrecan, the most abundant proteoglycan in articular chondrocytes [70]. However, in arthritis states, disruption of the matrix equilibrium leads to progressive loss of cartilage tissue and apoptosis of cells. Interestingly, matrix turnover is influenced by changes in chondrocytes exposed to extracellular acidosis [71]. Recently, to determine the potential involvement of ASICs in cartilage injury, our group tested the effects of amiloride both *in vitro* and *in vivo* [72]. We observed a significant increase in intracellular calcium in articular chondrocytes exposed to extracellular pH 6.0. Amiloride diminished this increase in [Ca²⁺]_i and attenuated acid-induced articular

chondrocyte injury. In addition, amiloride induced a significant decrease in Mankin scores, but increased type II collagen and aggrecan mRNA and protein expression in articular cartilage in adjuvant arthritis (AA) rats. Blockade of ASIC1a with PcTX1 or specific siRNA inhibited acid-induced osteoclast differentiation and bone resorption via regulating activation of the transcription factor, nuclear factor of activated T cells c1 [10]. Similarly, the ASIC1a-specific blocker PcTX venom attenuated acid-induced articular chondrocyte damage [25]. Furthermore, blocking ASICs markedly decreased calpain and calcineurin expression levels as well as caspase-3/9 activity, and led to recovery of mitochondrial membrane potential via regulation of B-cell lymphoma-2 family gene expression in acid-induced chondrocytes [9, 73]. A more recent study reported that interleukin-6 promotes acid-induced articular chondrocyte apoptosis to a significant extent by activating the JAK2/STAT3 and MAPK/NF-κB signaling pathways, resulting in upregulation of ASIC1a expression and function [4].

Hidden chronic pain is one of the prominent clinical features of arthritis. Although significant progress has been made in terms of elucidating the mechanisms of joint pain at the cellular and molecular level, the data are insufficient to facilitate the development of more effective treatments for arthritic pain. Proton (H⁺) accumulation in

tissues was recently shown to directly cause allodynia and hyperalgesia. ASIC3, a main acid receptor, plays a key role in acid-induced injury and pain [74]. Babinski et al. [75] reported that ASIC3 is activated in the collagen-induced arthritis pain model, which was also verified in AA [76]. Moreover, inflammation led to a decline in pH, and in turn, activation of ASIC3 on primary afferent fibers innervating the knee joint and generation of central pain hypersensitivity. ASIC3 plays an important role in secondary hyperalgesia of the paw, but has a weak influence on primary hyperalgesia [74, 76, 77]. A recent study demonstrated that weight distribution asymmetry and secondary hyperalgesia are inhibited by continuous intra-articular injection of APETx2 through attenuating ASIC3 upregulation in knee joint afferents in a mono-iodoacetate-induced OA model [78]. Furthermore, Deval et al. [79] showed that knockdown of ASIC3 with siRNA and APETx2, a specific blocker of ASIC3, had markedly effective antinociceptive action against primary inflammation-induced hyperalgesia in rat.

Fibroblast-like synoviocytes (FLS) play a vital role in RA pathogenesis, and thus targeting FLS may ameliorate the clinical outcomes of inflammatory arthritis [80]. Interestingly, Kolker et al. [81] found a significantly lower increase in intracellular calcium and hyaluronan release in ASIC3 knockout FLS at pH 5.5, compared to control FLS. Unexpectedly, joint inflammation and destruction were significantly enhanced in ASIC3 knockout mice with collagen antibody-induced arthritis, compared to wild type (WT) mice. Moreover, FLS exposed to pH 6.0 displayed enhanced cell death in the presence of IL-1, which was eliminated in ASIC3^{-/-} FLS [82]. IL-1 β upregulated ASIC3 mRNA and enhanced $[Ca^{2+}]_i$, p-ERK, IL-6 and metalloproteinase mRNA as well as cell death in WT FLS exposed to pH 6.0. Inhibitors of $[Ca^{2+}]_i$ and ERK prevented cell death induced by acidic pH in combination with IL-1 β in WT FLS [83]. Since ASIC3 itself is not Ca²⁺ permeable, the mechanism of ASIC3-mediated regulation of $[Ca^{2+}]_i$ may be as follows: deletion of ASIC3 reduces pH sensitivity of ASICs, release of internal Ca²⁺ stores and secondary activation of other Ca²⁺-permeable channels [84-86]. These findings suggest that ASIC3 plays a protective role in inflammatory arthritis via inhibiting synovial proliferation, which reduces accumulation of inflammatory cytokines and subsequent joint damage (Fig.2).

ASIC1a may therefore promote articular chondrocyte apoptosis as well as osteoclast differentiation. Moreover, elevated levels of ASIC3 in the DRG contribute to arthritic pain, supporting inhibition of ASICs as a potential therapeutic strategy for arthritis. However, ASIC3 has also been shown to play an inhibitory role in synovial proliferation and subsequent accumulation of

inflammatory mediators, indicative of a protective effect in joints. Although several investigators agree that ASICs are involved in the pathogenesis of arthritis, in light of the controversial evidence, the roles of these ion channels in arthritis require further investigation. Clarification of the precise roles of different ASIC subtypes in the pathogenesis of arthritis may aid in the identification of novel pharmacological targets (Table 2).

Conclusion

Acid-alkaline balance is an important factor for maintaining normal physiological activities. However, almost all types of pathological states, such as ischemia, inflammation, hypoxia and cancer, lead to variations in pH. Recent research has focused on the roles of ion channels, such as DEG/ENaC, in diseases. In particular, given that ASICs serve as pivotal acid receptors, multiple lines of evidence support their involvement in the progression of tissue acidosis. Interestingly, this protein family is closely correlated with various degenerative diseases, supporting their potential value as therapeutic targets (Fig.3). The current study showed that amiloride is a classic inhibitor drug of the DEG/ENaC family, but not selective for ASICs. Although several specific ASIC blockers exist, such as PcTx1 and APETx2, their clinical utility remains to be determined. With the advances in biological and molecular techniques, improved knowledge on ASIC function and structure should facilitate the development of a suitable and specific inhibitor for clinical treatment of degenerative disorders. However, the current evidence regarding ASICs in degenerative diseases is relatively limited, the majority of which has been obtained using animal models or *in vitro* systems. Human studies with larger patient populations are required to accurately resolve the mechanisms of action of ASICs in the development of degenerative disorders, which may provide a rationale for developing effective therapeutic interventions targeting ASICs for preventing degenerative disease progression.

Conflicts of interest

The authors declare no conflicts of interest.

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